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# Periodontal Disease and Overall Health: A Clinician's Guide

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Editors  
Robert J. Genco  
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Supported through an educational grant from



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# Periodontal Disease and Overall Health: A Clinician's Guide

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Periodontal Disease and Overall Health: A Clinician's Guide

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# From the Editors

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Dear Colleagues:

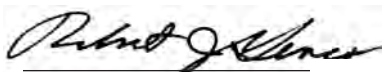
We are very pleased to have had the privilege of assembling and editing this textbook, *Periodontal Disease and Overall Health: A Clinician's Guide*.

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 specific foci of infection 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. 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, Sheila Hopkins, and their 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 eighteen chapters, provide a current and thoughtful perspective on the relationship of periodontal disease to systemic conditions.

It is a pleasure to present 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:

It is with great pride that we present the textbook *Periodontal Disease and Overall Health: A Clinician's Guide*.

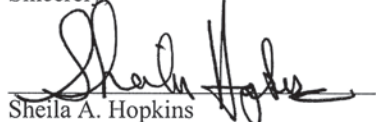
A decade ago, then US Surgeon General C. Everett Koop declared we cannot have good general health without good oral health.<sup>1</sup> This book, the result of a two-year process involving three dozen internationally renowned authors and editors, comprises eighteen chapters of the most contemporary thinking behind what the dental and medical literature suggest is an association between oral and systemic diseases. 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 co-management of the diseases by both dental and medical caregivers.

*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 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 commitment to the project 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. *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 one shining example of our continuing commitment to ensuring the dental professions' education.

Sincerely,



Sheila A. Hopkins  
Vice President and General Manager  
Professional Oral Care



Fotinos S. Panagakos, DMD, PhD  
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Relations and Strategy

1. Oral Health in America: A Report of the Surgeon General. May 2000.



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***"A person can't have good general health without good oral health."***

—Former US Surgeon General C. Everett Koop

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# CHAPTER 1

## Overview

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Robert J. Genco, Ray C. Williams

*“A person can’t have good general health without good oral health.”*

—Former US Surgeon General C. Everett Koop

### INTRODUCTION

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 past 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, the six leading causes of death in the United States in 2005 were heart disease (652,091), cancer (559,312), stroke/cerebrovascular diseases (143,579), chronic lower respiratory disease (130,933), unintentional accidental injuries (117,809), and diabetes (75,119).<sup>1</sup> Five of these chronic diseases are related to periodontal disease. By successfully meeting the challenge to improve oral health and 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 RESEARCH

In the last 50 years, there has been considerable progress 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 Loe and colleagues 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.<sup>2,3</sup> 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 conducted studies showing that specific organisms were associated with periodontal disease (for review see Socransky and Haffajee, 2005).<sup>4</sup> These studies identified several categories of organisms, ranging from early colonizers, which are commensal and relatively nonvirulent, 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.

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 immunopathological actions. Antibodies to these bacteria are formed, which in combination with neutrophils, provide important protection.<sup>5,6</sup> It was seen that if 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 upon triggering by bacterial products such as endotoxin, produces pro-inflammatory cytokines and matrix metalloproteinases that destroy the connective tissues of the periodontium. Inflammatory mediators such as prostaglandin E<sub>2</sub> and interleukin-1 induce alveolar bone resorption. As the role of the host becomes more understood, it is clear that inflammation and the inflammatory response can explain much of the tissue destruction caused by periodontal disease.<sup>7,8</sup>

### **Risk Factor Era**

The second era of discovery brought the identification of risk factors which 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. These risk factors were identified in the late 1980s and early 1990s and include genetic elements, behaviors such as smoking, and acquired disorders such as diabetes mellitus.<sup>9,10</sup> 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 now focused on the relationship of periodontal disease as a risk for certain systemic diseases. Robust studies have shown that periodontal disease is significantly associated with certain systemic diseases such as cardiovascular disease,<sup>11,12</sup> diabetes and complications of diabetes,<sup>13-15</sup> adverse pregnancy outcomes,<sup>16</sup> and respiratory infections.<sup>17</sup> The periodontal disease-systemic disease concept has amassed enough evidence and support that it is now believed that findings about this inter-relationship should be incorporated into the curriculum in schools for health professionals, and should also be made available to enhance the knowledge base of currently practicing healthcare professionals.

The association of periodontal disease with several systemic conditions, such as diabetes and atherosclerotic 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. There are other conditions that also contribute to a systemic inflammatory response including rheumatoid arthritis, psoriasis, and obesity. This chronic systemic inflammatory response in turn increases the risk for atherosclerotic disease, diabetes and complications of diabetes, adverse pregnancy outcomes, and possibly some cancers. The research supporting these associations will be discussed in detail in the following chapters.

### 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 of the chapters in this textbook will review the biologic plausibility for periodontal disease as a risk for systemic conditions. Mechanisms through which periodontal disease can confer this risk will also be presented.

The overall goal of this textbook is to present the 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. 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 the following manner: The initial chapters following this one 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 relationship of periodontal disease to these conditions (Chapters 6 and 8, respectively). The next chapters examine the evidence for periodontal disease as a risk for adverse pregnancy outcomes (Chapter 9), respiratory diseases (Chapter 10), osteoporosis (Chapter 11), rheumatoid arthritis (Chapter 12), and cancer (Chapter 13).

The final section of the textbook discusses comanagement of periodontal disease in diabetes (Chapter 14), cardiovascular disease (Chapter 15), pregnancy (Chapter 16), and other conditions that are 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 inter-relationship.

### Our Hope for This Textbook

It is the hope of the authors and editors that this textbook will provide an up-to-date understanding of the information that details the relationship 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 for dental professionals in general. We also believe this resource will prove valuable to students as well as practicing members of other health professions in the medical community. The integration of medicine and dentistry grows daily, and a common resource such as this textbook could serve as a constructive tool to help the two disciplines work collaboratively.

The editors would like to thank the authors and coauthors for their role in preparing

and presenting current information in a complete, yet concise and readable manner. We are hopeful that this textbook will find broad readership and will be useful to the dental and medical community.

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# CHAPTER 2

## Overview of Periodontal Disease: Causes, Pathogenesis, and Characteristics

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Ying Gu, Maria E. Ryan

### INTRODUCTION

Periodontal diseases are serious chronic infections that involve destruction of the tooth-supporting apparatus, including the gingiva, the periodontal ligament, and alveolar bone. These diseases are initiated by a local accumulation of bacteria adjacent to the tooth. 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 is also one of the most common chronic inflammatory diseases affecting a majority of the population throughout the world. Although plaque is essential for the initiation of periodontal diseases, the majority of the 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, risk factors associated with them, and the etiology, pathogenesis, and management of periodontal diseases.

### TYPES OF PERIODONTAL DISEASE

Periodontal diseases include two general categories based on whether there is attachment or 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.<sup>1</sup>

Periodontitis has been defined as the presence of gingival inflammation at sites where there has been a pathological detachment of collagen fibers from cementum, the junctional epithelium has migrated apically, and bone loss can be detected radiographically. The inflammatory events associated with connective tissue attachment loss lead to the resorption of coronal portions of tooth supporting alveolar bone.<sup>2</sup> The understanding of periodontal disease is continuously changing as new research evidence emerges. Therefore, the classification of periodontal disease has changed since the system developed at the 1989 World Workshop in Clinical Periodontics. The classification presented in this chapter is based on the results developed at the 1999 International Workshop organized by the American Academy of Periodontology (AAP).

The classification of periodontal diseases now includes eight general types<sup>3</sup>:

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.<sup>3</sup> In addition, the above classification is different from case types



**Table 1.** Periodontal Diseases

I. Gingival Diseases
Dental plaque-induced gingival diseases
Nonplaque-induced gingival lesions
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*Adapted from: Ann Periodontol 1999;4:1–6.<sup>3</sup>*

previously developed by the AAP.<sup>4,5</sup> The current case types for periodontal diseases include:

- Gingivitis (Case Type I)
- Mild periodontitis (Case Type II)
- Moderate periodontitis (Case Type III)
- Advanced periodontitis (Case Type IV)
- Refractory periodontitis (Case Type V)

**Gingival Diseases**

Gingival disease is further characterized into plaque-induced and nonplaque-induced categories.<sup>3</sup>

**Plaque-Induced Gingival Diseases**

Gingivitis is gingival inflammation associated with 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; it also occurs in the gingiva of 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) adjacent to the tooth.<sup>6</sup> 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 (PMNLs or neutrophils) to the site. An antibody response to these bacterial antigens is also mounted. Inflammatory cells and their products (e.g., cytokines, enzymes, and antigens) are present at the site of inflammation. Thus, a host immuno-inflammatory 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 changes associated with puberty, menstrual cycle, or pregnancy, as well as with chronic diseases such as diabetes, can alter the host response to dental plaque.<sup>1,7</sup> 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 or with an equivalent bacterial bioburden to a person who does not have these systemic challenges. This 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 immunological function. Patients usually present with gingival enlargement and bleeding associated with spongy gingival tissues and excessive vascularity.

**Medications:** Medications such as anticonvulsant drugs (e.g., dilantin), immuno-

suppressive drugs (e.g., cyclosporine), 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).<sup>8</sup> Medication-associated gingival conditions are often reversed after discontinuation of the offending agents.

**Malnutrition:** The host immune system can be diminished when malnutrition develops, resulting in excessive gingival inflammation. Severe ascorbic acid (vitamin C) deficiencies (i.e., scurvy) can produce bright red, swollen, and bleeding gingival tissues.<sup>1</sup> In the case of 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). Treatment with vitamin C supplements can reverse this condition.

### ***Nonplaque-Induced Gingival Lesions***

These types of lesions usually are rare and mainly due to systemic conditions. Bacteria, viruses, or fungi 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.<sup>9</sup> Primary streptococcal gingivitis is an acute inflammation of the oral mucosa. It is associated with pain and fever, as well as red swollen gingival tissues with bleeding or abscess formation, and can be treated with routine periodontal scaling and root planing in addition to antibiotic therapy. *Herpes simplex* virus Type I is a common virus that can cause gingival lesions.<sup>10</sup> 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, and are 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 one to two weeks. After a primary infection, the herpes virus becomes latent and will be 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.<sup>11</sup> The most common fungal infection is candidiasis, caused by *Candida albicans*, often seen in patients wearing removable prosthetic devices (e.g., 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 that can be removed with a cotton swab or 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, or foreign-body reactions. One of the most common genetic conditions associated with gingival lesions is autosomal-dominant hereditary gingival fibromatosis.<sup>12</sup> It is a benign condition affecting both arches. The gingival tissues are enlarged and asymptomatic. It may be an isolated finding or associated with other syndromes. Treatment is gingivectomy and recurrence is possible. Systemic conditions such as pemphigoid, pemphigus vulgaris, erythema multiforma, and lupus erythematosus can cause desquamative lesions and ulceration.<sup>10,13</sup> Gingival changes due to allergic reactions to certain restorative materials, dentifrices, or mouthrinses are rare, but have been observed.<sup>10</sup> Traumatic lesions are usually produced unintentionally.<sup>10</sup> Aggressive tooth brushing and flossing can

cause gingival damage. Hot foods and drinks can cause minor burns of the gingival tissues. 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. Gingival tissues can also develop localized inflammation when exposed to foreign materials. The most common example is the amalgam remaining in gingival tissues during the placement of restorations or surgical procedures, eventually producing amalgam tattoos.<sup>10</sup>

### PERIODONTITIS

Periodontitis is a chronic infection involving destruction of the tooth-supporting apparatus, including the periodontal ligament and alveolar socket support of the teeth.

Gingivitis may or may not progress to periodontitis, which is associated with attachment and alveolar bone loss. Periodontal disease is initiated by a local accumulation of bacteria (i.e., dental plaque adjacent to the tooth) and their metabolic products (e.g., endotoxin), that stimulate the junctional epithelium to proliferate and produce tissue-destructive proteinases that degrade the basement membrane and allow for the apical migration of the junctional epithelium along the root surface of the tooth, thus deepening the gingival crevice to produce periodontal pockets and associated attachment loss, which is the hallmark lesion of periodontal disease. Some of the clinical signs include bleeding on probing, deep pockets, recession, and tooth mobility. Often, this destructive process is silent and continues for long periods of time without being identified. Eventually, teeth can become loose and may be lost on their own or deemed hopeless, requiring extraction. There are many forms of periodontitis.

### Chronic Periodontitis

Chronic periodontitis (CP) is the most common form of periodontitis and is characterized by pockets with associated attachment 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 exacerbation with rapid progression, or periods of remission can occur. Several studies have addressed the “episodic” nature of periodontitis.<sup>14</sup> The rate of disease progression may be influenced by local and/or systemic conditions that alter the normal host response to bacterial plaque. Local factors such as subgingivally placed fillings or crowns that violate biological width can promote gingival inflammation and clinical attachment loss. Systemic factors such as diabetes can decrease host defenses to bacterial infection. Environmental factors such as smoking and stress can also decrease host immune function, resulting in increased susceptibility to disease. CP can occur as a localized form in which < 30% of the sites are involved, or as a more generalized form in which >30% of existing sites demonstrate increased pocket depth, attachment and bone loss.<sup>4</sup> As mentioned previously, the severity of disease can be described as slight, moderate, or severe, based on the level of destruction.

### Aggressive Periodontitis

This form of periodontitis was previously categorized as Juvenile Periodontitis. Common features include rapid attachment loss and bone destruction in the absence of significant accumulations of plaque and calculus.<sup>15</sup> These forms of periodontitis usually affect young individuals, often during puberty, from 10 to 30 years of age, with a genetic predisposition. The bacteria most often associated with aggressive periodontitis are *Aggregatibacter actinomycetemcomitans* (previously *Actinobacillus actinomycetemcomitans*). Individuals present with hyper-

active inflammatory cells producing high levels of cytokines and enzymes causing rapid, aggressive destruction of periodontal tissues. Aggressive periodontitis can be further characterized as localized and generalized forms. The localized form usually affects first molar and incisor sites. 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.<sup>16</sup> Several hematologic and genetic disorders have also been associated with the development of periodontitis such as acquired, familial, and cyclic neutropenias, leukemias, Down's syndrome, certain types of Ehlers-Danlos syndrome, Papillon-Lefevre syndrome, Cohen syndrome, and hypophosphatasia. The mechanisms by which all of these disorders affect the health of the periodontium are not fully understood and continue to be investigated by many basic and clinical researchers. It is speculated that these diseases can alter host defense mechanisms and up-regulate inflammatory responses, resulting in progressive periodontal destruction.

### **Necrotizing Periodontal Diseases**

These lesions are most commonly observed in individuals with systemic conditions, such as human immunodeficiency virus infection, malnutrition, and immunosuppression. 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 NUP involves clinical attachment and alveolar bone loss.<sup>17</sup>

### **Abscesses of the Periodontium**

Periodontal abscess is a localized purulent infection of the periodontal tissues.<sup>18</sup>

Periodontal abscesses usually develop in periodontitis patients who may have food debris lodged in a pocket, or deep deposits of calculus where drainage from a pocket becomes blocked. 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 due 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 abscess. 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 individuals.<sup>19</sup> In 1986-1987, the National Institute of Dental Research conducted a nationwide survey of oral health in US school children<sup>20</sup> and reported that approximately 60% of children 14 to 17 years of age were found to

have gingivitis. In 1960–1962, the first US national survey of periodontal disease in adults reported that 85% of men and 79% of women have some degree of gingivitis.<sup>21</sup> In the most recent National Health and Nutrition Examination Survey (NHANES III) conducted from 1988 to 1994,<sup>22</sup> more than 50% of adults had gingivitis on an average of three or four teeth, while 63% of 13- to 17-year-old teenagers had gingival bleeding. Both surveys assessed gingival bleeding by a gingival sweep method.<sup>21,22</sup>

### Epidemiology of Periodontitis

Basic clinical measurements for periodontitis are gingival bleeding on probing, clinical attachment loss, 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 the disease may emerge to help better diagnose it. Inflammatory cytokines, enzymes, and bone breakdown products released into 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- $\alpha$ ), interleukin-1 beta (IL-1 $\beta$ ), and others.<sup>23,24</sup> Enzymes such as matrix metalloproteinases (MMPs) and breakdown products such as the collagen telopeptide 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 chairside tool to measure active periodontitis. The development of these markers will also help to facilitate screening for periodontal diseases by medical professionals or even

self-assessment by patients, thereby prompting referrals to the dental office for clinical assessment.

The national data suggest that the milder forms of periodontitis are close to universal.<sup>25</sup> The more severe forms are less prevalent. According to a review of the literature by Brown and L  e<sup>26</sup> focused on a number of epidemiologic studies resulting from a 1981 national probability survey, the prevalence of CP is about 36% for the adult US population as assessed by pocket depth measurements. The prevalence of periodontitis increases with age; 29% in those aged 19 to 44 had CP; this rate increased to 50% for people 45 years or older. In general, moderate periodontitis occurred in 28% of all people while 8% had advanced disease. However, the prevalence of moderate and severe periodontitis increased to 44% in the population older than 45. Based on the presence of periodontal pockets  $\geq 4$  mm, it was determined that 30% of the population has periodontitis on an average of three or four teeth. Severe pockets of  $\geq 6$  mm were found in less than 5% of the population.<sup>22</sup> The prevalence of aggressive periodontitis was low with less than 1%.<sup>27</sup> More recently, NHANES III (1988–1994) reported the prevalence of periodontitis for adults 30 to 90 years old.<sup>28</sup> Attachment loss and probing depths were assessed at two sites per tooth. When assessed by the level of attachment loss, 53% of the population was found to have  $\geq 3$  mm attachment loss. The prevalence of attachment loss increased with age, from approximately 35% for the 30-year-old participants to 89% for the 80-year-old participants. When assessed by probing depth, approximately 64% of the population had probing depths of  $\geq 3$  mm. The prevalence of periodontitis increases with age and was found to be more prevalent in males than females, and in African-Americans and Mexican-Americans than in non-Hispanic Caucasians.

### Risk Factors

There are a number of risk factors associated with periodontal diseases.<sup>29-34</sup> 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. Bacteria are essential for the initiation of the disease, but it is the host response to the bacterial challenge that determines the severity and rate of progression of the periodontitis. Therefore, it is the host's immunologic reaction that determines susceptibility to the disease.

General categories of risk factors associated with the development of periodontitis include genetic, environmental (e.g., tobacco

use), and acquired risk factors (e.g., systemic disease). Risk factors (Table 2) and risk reduction strategies (Table 3) should be considered when assessing each patient.<sup>35</sup> Some risk factors can be modified to reduce a patient's susceptibility. Environmental factors such as tobacco use and stress can be managed with smoking cessation and stress management; for acquired factors such as systemic diseases, medications usually prescribed by the physician can be used to help in the management and control of chronic disorders (Table 3). The use of chemotherapeutic agents specifically designed to improve the clinical outcomes of mechanical treatments for periodontal diseases may be particularly useful in the management of those individuals with single or multiple risk factors. Risk assessment can

**Table 2.** Risk Assessment for Periodontitis

1. Heredity as determined by genetic testing and family history
2. Smoking, including frequency, current use, and history
3. Hormonal variations such as those seen in:
  - a. Pregnancy, in which there are increased levels of estradiol and progesterone that may change the environment and permit 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 (the 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
5. Stress as reported by the patient
6. Nutritional deficiencies and obesity 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

**Sources:** *J Periodontol* 1994;65:260–267.<sup>29</sup> *J Periodontol* 1995;66:23–29.<sup>30</sup> *J Periodontol* 1999;70:711–723.<sup>31</sup> *J Periodontol* 2000;71:1057–1066.<sup>32</sup> *J Periodontol* 2000;71:1215–1223.<sup>33</sup> *J Periodontol* 2000;71:1492–1498.<sup>34</sup>



**Table 3.** Risk Reduction Strategies

1. More frequent visits for those with a genetic predisposition; use of pharmacotherapeutics for the management of periodontitis
2. Smoking cessation using one or more of the six approved regimens; these regimens are rarely 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: <ul style="list-style-type: none"><li>a. Pregnancy, which requires good oral care before conception to prevent complications during pregnancy; treatment during pregnancy may be necessary to prevent adverse pregnancy outcomes</li><li>b. Menopause, which may require hormonal supplements, calcium, and other medications and supplements prescribed by the physician to prevent osteopenia</li></ul>
4. Systemic diseases that require consultation with the physician include: <ul style="list-style-type: none"><li>a. Diabetes (for improved glycemic control)</li><li>b. Osteoporosis (requiring calcium supplements, bisphosphonates)</li><li>c. Immune system and hematologic disorders</li><li>d. Connective tissue disorders</li></ul>
5. Stress management; possible referral to a psychologist or psychiatrist
6. Nutritional supplementation and weight reduction; possible referral to a nutritionist
7. Medications can be changed in consultation with the physician
8. Corrective dentistry
9. Improved oral hygiene (brushing, flossing, use of antiseptics)
10. Occlusal adjustments

**Source:** *Dent Clin North Am* 2005;49:611–636.<sup>35</sup>

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 as 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 plaque,

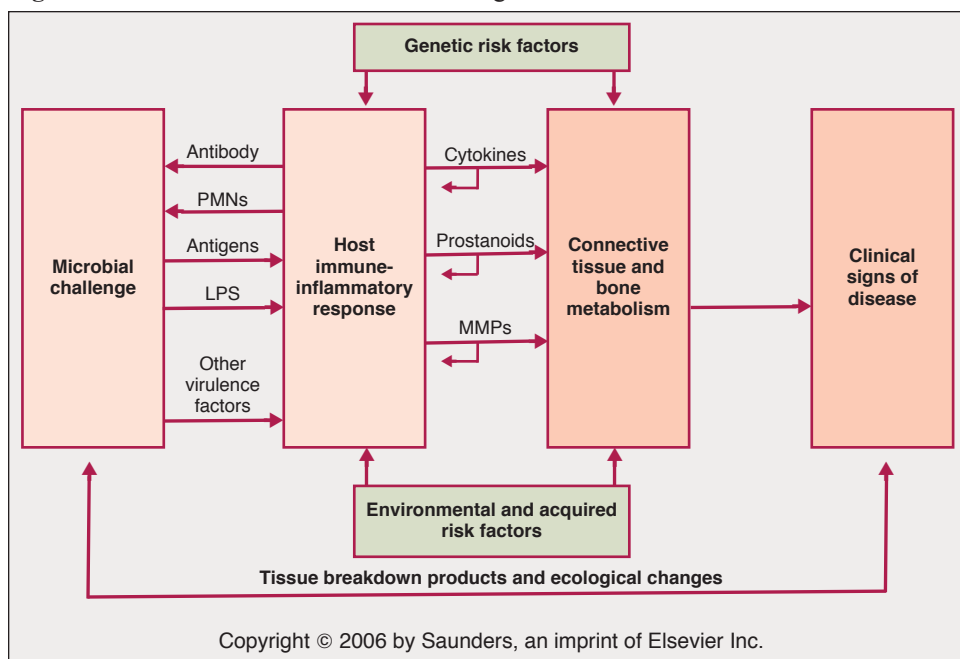
but the severity and progression of the disease is determined by the host response to the bacterial biofilm. People with severe plaque and calculus accumulation will have gingivitis, but not necessarily periodontitis. On the other hand, certain individuals, despite maintaining adequate oral hygiene, find themselves susceptible to aggressive forms of periodontitis, with deep pocketing, tooth mobility, and early tooth loss. Clearly, the response of the periodontal tissues to plaque is different in these two different scenarios. Periodontal disease does not appear to behave as a classic infection, but more as an opportunistic infection.<sup>35</sup> These observations led researchers to realize that the host response to the bacterial challenge, presented by subgingival plaque, is the important determinant of disease severity. Although plaque bacteria are capable of causing direct damage to the periodontal tissues, it is now recognized that

the host immuno-inflammatory response to plaque bacteria produces destructive cytokines and enzymes resulting in periodontal tissue destruction. The host response is essentially protective by intent but can also result in tissue damage, including the breakdown of connective tissue fibers in the periodontal ligament and the resorption of alveolar bone. The host response to the plaque biofilm is modified by genetic factors (helping to explain why aggressive periodontitis tends to have a familial aggregation), as well as systemic and environmental factors (e.g., diabetes, stress, smoking).

To better treat and manage periodontal diseases, we need a more detailed understanding of periodontal pathogenesis (Figure 1).<sup>35-37</sup> 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 that 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 within the tissues. Microbial products also chemotactically attract a constant flux of pro-inflammatory cells migrating from the circulation to the gingival crevice. Neutrophils, or PMNLs, are predominant in the early stages of gingival inflammation. Thus, an immune response is generated in the periodontal tissues and pro-inflammatory cytokines such as IL-1 $\beta$ , TNF- $\alpha$ , and MMPs are produced by inflammatory cells recruited to the lesion site. The functions of PMNLs include phagocytosis and destruction of bacteria. Initially the clinical signs of gingivitis are evident. This response is essentially protective in nature to

**Figure 1.** Schematic Illustration of the Pathogenesis of Periodontitis



**Source:** Carranza's *Clinical Periodontology*, 10th Ed. WB Saunders Company; 2006:275–282.<sup>36</sup> Reproduced with permission.

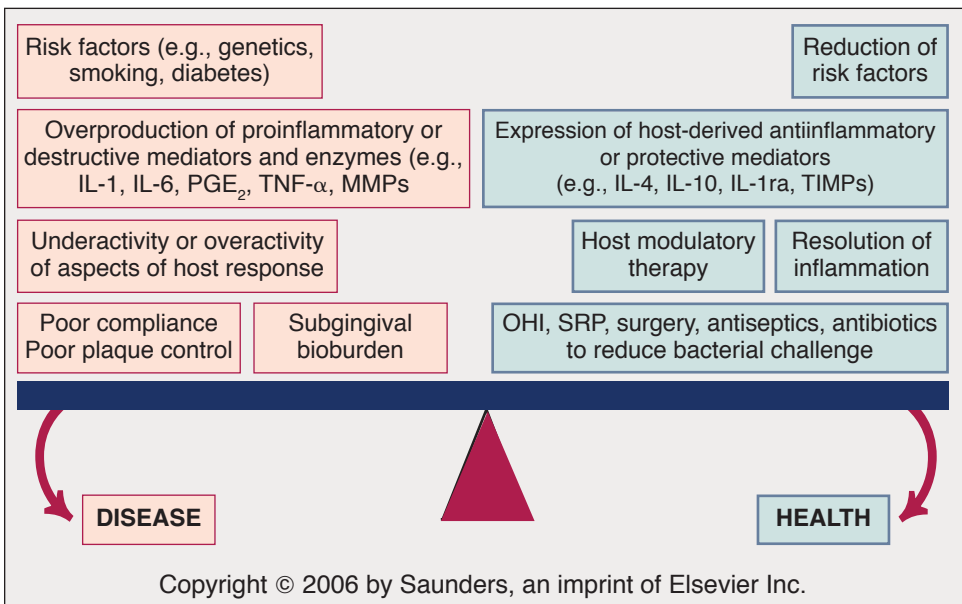


control bacterial infection. In persons who are not susceptible to periodontitis, the primary defense mechanisms control the infection, and chronic inflammation (i.e., chronic gingivitis) may persist. However, in individuals susceptible to periodontitis, the above inflammatory process will eventually extend apically and laterally to involve deeper connective tissues and alveolar bone, recruiting monocytes and lymphocytes to the site of infection at these later stages. These monocytes and macrophages are activated by the bacterial endotoxins leading to the production of high levels of prostaglandins (e.g.,  $\text{PGE}_2$ ), interleukins (e.g., IL-1 $\alpha$ , IL-1 $\beta$ , IL-6), TNF- $\alpha$ , 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 PGs, ILs, and TNF- $\alpha$  in the tissues. The elevated levels of pro-inflammatory 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 MMPs (TIMPs; Figure 2).<sup>36,37</sup> Under normal, healthy conditions, the anti-inflammatory mediators are balanced with inflammatory mediators, thereby controlling tissue destruction. If an imbalance is seen, with excessive levels of the pro-inflammatory mediators, upregulated MMP expression and activity, and insufficient levels of protective anti-inflammatory mediators, loss of periodontal connective tissue and bone will occur.

Thus, plaque bacteria initiate an inflammatory response by the host, resulting in excessive levels of pro-inflammatory mediators and enzymes, leading to the destruction of periodontal tissues. If this inflammation

**Figure 2.** The Periodontal Balance



**Source:** Carranza's *Clinical Periodontology*, 10th Ed. WB Saunders Company; 2006:275–282.<sup>36</sup> Reproduced with permission.

continues and extends further apically, more bone is resorbed, and more periodontal tissue is broken down, leading 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 will eventually enter into the circulation, stimulating the liver to produce acute-phase proteins (notably C-reactive protein, but also fibrinogen, haptoglobin, etc.) which are “biomarkers” of a systemic inflammatory response. The ever-expanding data supporting the fact that this systemic inflammatory response driven by the chronic infection and inflammation associated with periodontitis will eventually increase an individual’s risk for developing a number of systemic diseases, including cardiovascular diseases, adverse pregnancy outcomes, and diabetic complications.

### MANAGEMENT OF PERIODONTAL DISEASES

Periodontal management includes a complete assessment of each individual patient. Medical and dental history, clinical and radiographic examination, as well as an assessment of risk factors are all important to making an accurate diagnosis, prognosis, and developing an optimal treatment plan. There are many treatment options 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, due to a better understanding of the host response, host-modulation therapies have been used as adjunctive approaches to both non-surgical and surgical treatments to aid in reducing probing depths, increasing clinical attachment levels, and in regeneration of

the lost attachment apparatus. It is likely that the most effective therapeutic approaches will 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 the development of periodontal disease and make management of the disease more difficult;<sup>38,39</sup> therefore smoking cessation would benefit all patients with periodontitis. Smoking cessation can be undertaken in the dental office (if staff is appropriately trained) or in a medical setting. There are a variety of medications to aid with smoking cessation, counseling is important as well, and alternative medicine such as acupuncture may be used. Systemic diseases such as diabetes will increase patients’ risk for periodontitis when poorly controlled.<sup>40</sup> When treating people with diabetes, knowing the patient’s level of diabetic control is important to assessing risk, and collaborating with medical colleagues to improve control of diabetes is essential to assure successful periodontal treatment. Periodontitis is also prevalent in patients with cardiovascular disease, and periodontal therapy may have a positive impact on the overall health status of these individuals.

The management of patients with periodontitis can therefore involve the following complementary treatment strategies:<sup>41</sup>

- Patient education, including oral hygiene instruction and explanation of the rationale for any adjunctive treatments
- Risk factor modification and risk reduction
- Reduction of bacterial burden with traditional scaling and root planing
- Intensive periodontal treatment with local delivery systems 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 individualized basis. A combination of treatment approaches (discussed below) for each patient as listed in Figure 3 will provide the ultimate periodontal treatment and result in a better prognosis.<sup>41</sup>

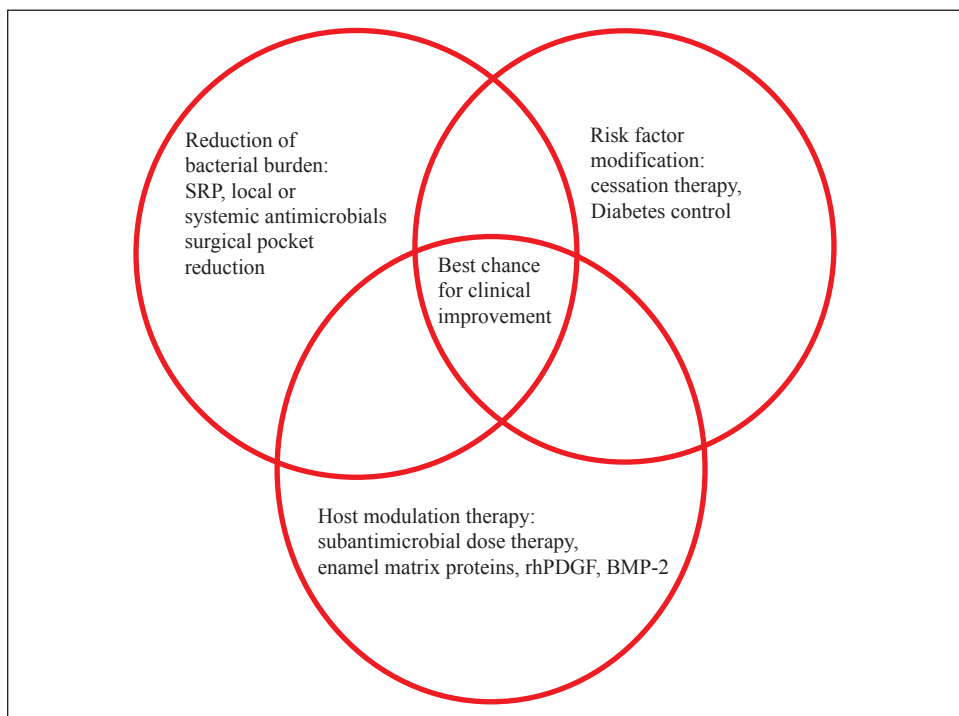
### The Antimicrobial Approach

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

### Mechanical Therapy

A regimen of brushing and flossing, combined with the use of dentifrices and/or mouthrinses containing antiseptics is the most basic approach to microbial reduction and control. 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. Unfortunately, many patients are not compliant, lose motivation, and do not spend a sufficient amount of time brushing or flossing on a daily basis.<sup>42</sup> It is for this reason that dentifrices and mouthrinses containing antiseptics have been developed. Antiseptics have been found to improve plaque reduction, as well as reduce gingival inflammation

**Figure 3.** Complementary Treatment Strategies in Periodontitis



*Adapted from:* Carranza's Clinical Periodontology, 10th Ed. WB Saunders Company; 2006:813–827.<sup>41</sup> Reproduced with permission.

seen with brushing and flossing alone. Therefore, antiseptic-containing dentifrices and mouthrinses have been accepted as adjuncts to the mechanical approach of brushing and flossing.

Routine tooth scaling every six 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 multiple clinical studies demonstrating that it effectively reduces the microbial load and leads to reductions in bleeding on probing and probing depths, and allows for gains in clinical attachment.<sup>43</sup> However, this procedure can be very time-consuming and is operator-dependent.<sup>44</sup> Surgical procedures can be used to visualize the remaining subgingival calculus, and through resective or regenerative procedures will also lead to decreased probing depths that are more manageable for the long-term maintenance of patients with periodontitis. Although nonsurgical and surgical procedures aimed at reducing the bacterial load 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 as significant numbers of micro-organisms may be left behind. In addition, many of the putative pathogens will 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.

### **Mouthrinses and Dentifrices**

#### ***Antiseptic Mouthrinses***

Antiseptic mouthrinses have been used to reduce plaque levels and gingivitis. Two clinically proven American Dental Association-accepted antiseptic mouthrinses are chlorhexidine gluconate (Peridex®) 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.<sup>45</sup>

#### ***Locally Applied Antiseptics***

Periochip® contains the active ingredient chlorhexidine gluconate (2.5 mg) that is released into the pocket over a period of seven to 10 days. It has been found to suppress the bacteria in the pocket for up to 11 weeks post-application.<sup>46</sup> Periochip is the only locally applied antiseptic that is approved by the Food and Drug Administration (FDA) for use as an adjunct to scaling and root planing procedures to aid in the reduction of pocket depths. Other locally applied antimicrobials are antibiotics.

#### ***Dentifrices***

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

There is a large amount of literature on these and other dentifrices containing chlorhexidine and other agents in the control of

gingivitis. A review of the clinical efficacy and safety of a triclosan/copolymer/sodium fluoride dentifrice was carried out by Blinkhorn and colleagues.<sup>47</sup> They found about 200 articles dating from 1998 to 2008 relating to this dentifrice and concluded that twice daily use of this dentifrice will result in clinically significant improvement in plaque control and gingivitis and slower progression of periodontal disease. Further long-term studies extending over several years with these dentifrices are needed to establish whether or not short-term effects seen will be sustained over the long term, and indeed result in preventing the initiation of periodontitis and slowing the progression of already existing periodontitis.

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 reduced with tooth brushing alone, with or without a dentifrice. Interproximal aids such as flossing, interproximal brushing, and to some extent, flushing with effective mouthrinses is often needed for full plaque control on interproximal surfaces of the teeth. As periodontal disease is often initiated and progresses more rapidly in interproximal spaces, it is clear that interproximal cleansing is an important adjunct to toothbrushing with dentifrices.

### Locally Delivered Antimicrobials

#### *Atridox*

Atridox® is an FDA-approved locally delivered tetracycline system. It comes with 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 seven days. This system is applied subgingivally to the base of the pocket through a cannula. Atridox is a resorbable site-specific

locally delivered antibiotic proven to promote clinical attachment gains and reduce pocket depths, bleeding on probing, and levels of pathogenic bacteria for up to six months post-placement.<sup>35</sup> Periodontal disease has been linked to systemic diseases such as diabetes. Research has shown that periodontal treatment with locally delivered doxycycline 10 mg in periodontal pockets produced favorable clinical results in diabetic patients.<sup>48</sup>

#### *Arestin*

Arestin® is an FDA-approved minocycline microsphere system that is bioadhesive and bioresorbable, allowing for sustained release of 1 mg of minocycline up to 19 days. 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<sup>49</sup> and significant reductions in systemic inflammatory biomarkers that are risk factors for cardiovascular disease.<sup>50</sup>

### Systemic Antimicrobials

Systemic antimicrobial therapy is usually reserved for advanced cases of periodontitis: 1) for sites that have not responded to treatment, so-called “refractory periodontitis,” and 2) for patients demonstrating progressive periodontal destruction.<sup>35</sup> Systemic antibiotics can be used as adjuncts to conventional mechanical therapy as strong evidence for their use as a monotherapy has not been developed. For these special situations, randomized double-blinded clinical trials and longitudinal assessments of patients indicate that systemic antimicrobials may be useful in slowing disease progression.<sup>51</sup> Metroni-

dazole can be used to treat acute necrotizing ulcerative gingivitis (NUG),<sup>52</sup> and metronidazole/amoxicillin combination therapy can be used to treat aggressive adolescent periodontitis associated with *A. actinomycetemcomitans*.<sup>53</sup> 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 can be issues.<sup>54</sup> Common antibiotic therapies for the treatment of periodontitis include metronidazole, clindamycin, doxycycline or minocycline, ciprofloxacin, azithromycin, metronidazole/amoxicillin, and metronidazole/ciprofloxacin.<sup>55</sup> 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 (e.g., amoxicillin), azithromycin or clindamycin would be the choice.

Researchers have shown that periodontal treatment can benefit some systemic diseases known to be associated with periodontitis, such as diabetes and preterm delivery. Grossi and colleagues reported that diabetic patients receiving scaling and root planing with systemic doxycycline showed significant reductions in mean HbA1c.<sup>56</sup> Effective treatment of periodontal infection and reduction of periodontal inflammation is associated with a reduction in levels of glycated hemoglobin. Clothier and colleagues also showed that performing scaling and root planing in pregnant women with periodontitis may reduce preterm delivery.<sup>57</sup> However, adjunctive metronidazole therapy did not improve pregnancy outcomes. Two recent studies have not shown improvements in adverse pregnancy outcomes with scaling and root planing.<sup>58</sup> However, the level of periodontal treatment provided may have been very inadequate. More studies are needed in this field to determine the effect of periodontal

treatment on the outcomes of adverse pregnancy and the extent of therapy that may need to be provided in order to have a significant impact.

### Host-Modulation Therapy

Bacteria and the host are two essential factors to the development of periodontitis. Reduction of bacterial load is the conventional approach for the management of periodontal diseases. More recently, periodontal treatment strategies have included host-modulation therapy as an adjunctive treatment option. Host-modulation therapy is treating the host response to either reduce the excess production of cytokines and destructive enzymes so 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 to occur.

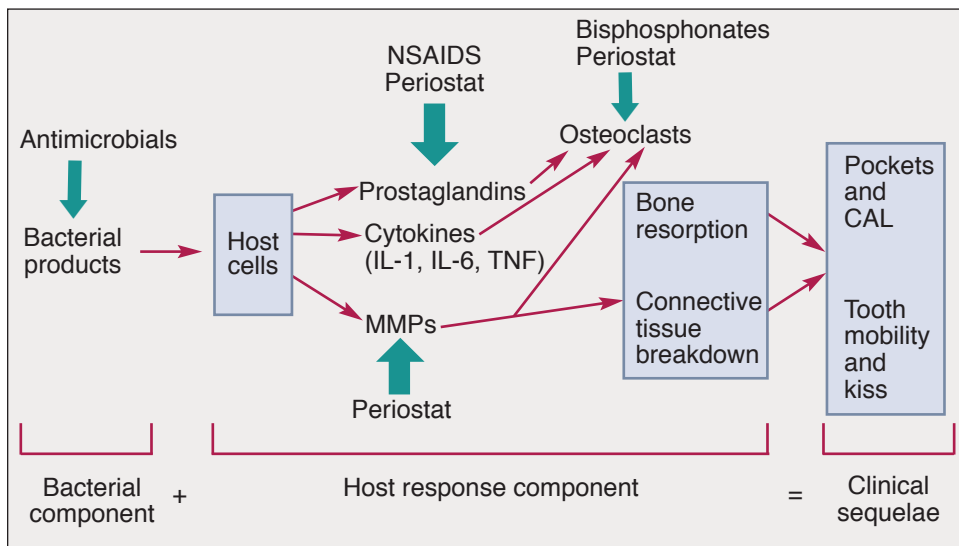
Host modulation was first introduced to dentistry by Williams<sup>59</sup> and Golub and colleagues.<sup>60</sup> Williams stated: "There are compelling data from studies in animals and human trials indicating that pharmacologic agents that modulate the host responses believed to be involved in the pathogenesis of periodontal destruction may be efficacious in slowing the progression of periodontitis."<sup>59</sup> Golub and colleagues discussed "host modulation with tetracyclines and their chemically modified analogues."<sup>60</sup> A variety of different drug classes have been evaluated as host-modulation agents, including the non-steroidal anti-inflammatory drugs, bisphosphonates, tetracyclines (Figure 4),<sup>36</sup> 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-modulation therapy for the



**Figure 4.** Potential Adjunctive Therapeutic Approaches

**Source:** Carranza's *Clinical Periodontology*, 10th Ed. WB Saunders Company; 2006:275–282.<sup>36</sup> Reproduced with permission.

management of periodontitis. SDD is a 20-mg dose of doxycycline (Periostat®) taken twice daily for three months and used in multicenter clinical trials for up to a maximum of 24 months of continuous dosing. SDD is used as an adjunct to scaling and root planing in the treatment of CP. The host-modulation effects of SDD include enzyme inhibition, cytokine reductions, and effects on osteoclast function. Since periodontitis is associated with many systemic diseases (e.g., osteoporosis, diabetes, cardiovascular disease), researchers have investigated the effect of SDD on these systemic conditions. Studies have shown that SDD:

- Can effectively reduce the levels of localized and systemic inflammatory mediators in osteopenic patients, in addition to improving on the clinical measurements of periodontitis<sup>61</sup>
- Has been shown to reduce systemic inflammatory biomarkers in CVD patients<sup>62</sup>
- Decreases HbA1c in patients who are taking normally prescribed hypoglycemic agents<sup>63</sup>

The impact of SDD therapy on periodontitis may be amplified by an independent benefit for other inflammatory diseases; additional studies are being conducted to investigate the impact of this host-modulation therapy.

### 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, and platelet-derived growth factors (PDGF). The initial local host-modulation agent approved by the FDA for adjunctive use during surgery to assist with clinical attachment gain and wound healing was Emdogain; this has been followed by PDGF combined with a resorbable synthetic bone matrix growth-factor enhanced matrix (GEM 21S) to assist in

regenerative procedures approved recently by the FDA, as well as recombinant human bone morphogenetic protein-2 (rhBMP-2) contained within an absorbable collagen sponge to assist with ridge and sinus augmentation. The technology behind GEM 21S has already been marketed for use in wound healing, particularly in people with diabetes, and rhBMP-2 has been used for quite some time by the orthopedic community for the healing of fractures.

The findings discussed with regard to the use of host-modulation therapy to better manage chronic periodontal disease may have applications to other chronic systemic diseases such as arthritis, diabetes, osteoporosis, and cardiovascular disease. In addition, studies utilizing locally delivered antimicrobials as part of an intensive periodontal therapy regimen have shown very promising results. 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 general overall health of the population.

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### Supplemental Readings

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# CHAPTER 3

## Infection and Inflammation

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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 L  e et al. in 1965.<sup>1</sup> Using a novel, now classic, experimental design, it was demonstrated that when students with healthy gingiva abstained from oral hygiene practices for 10–21 days, marginal inflammation of the gingiva (gingivitis) developed as a result of plaque accumulation. Once oral hygiene was reinstated, gingival health returned. Today, *in vitro* and *in vivo* experiments, along with histological 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 although 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 only to periodontal tissues. Bacteria and inflammatory mediators may enter blood circulation to induce systemic inflammation. There is increasing evidence that cardiovascular disease,<sup>2</sup> adverse pregnancy outcomes,<sup>3</sup> and

diabetes mellitus<sup>4</sup> are associated with elevated systemic inflammation, suggesting a common pathway in the pathogenesis of a number of inflammatory diseases.

Depending upon the effectiveness of the innate immune response, bacterial infection may persist and lead to perpetuation of inflammation, which may become chronic with 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 decrease of pro-inflammatory signals as once thought. The ability to manipulate these processes may provide a new treatment paradigm for both local and systemic inflammatory diseases (see Serhan et al.).<sup>5</sup>

### Chapter Goals

This chapter is structured to: (a) provide background information regarding the initiation and orchestration of inflammation at the gingival level after the interaction of the biofilm with host cells; (b) examine the evidence for periodontal disease influencing systemic inflammation and describe the possible biological pathways, as well as the cellular and molecular events that may occur; (c) explore the idea that systemic inflammation may be the link that associates periodontal with other systemic diseases focusing on the potential mechanisms of action; (d) address the role of resolution of inflammation in the pathogenesis of inflammatory diseases; and (e) 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 gingiva initiated by bacteria that leads to the destruction 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 upon the stage of maturation, the biofilm may consist of several hundred different bacterial species, many of which have yet to be identified.<sup>6</sup> Some of these species are associated with health, whereas others are associated with pathology.<sup>7</sup> However, which organisms 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 that perform essential physiologic functions for the bacteria. Variations of these bacterial components may be seen between various species, or even between different strains of the same species. Despite their structural heterogeneity, most of these molecules have conserved motifs known as pathogen-associated molecular patterns (PAMPs) that 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 include LPS, PGN, lipoteichoic acids (LTAs), fimbriae, proteases, heat-shock proteins (HSPs), formyl-methionyl-leucyl-phenyl-alanine (fMLP) and toxins. Host PRRs include the Toll-like receptors (TLRs) and the 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.<sup>8</sup>

#### ***Bacteria and GI Equilibrium***

The oral cavity, as part of the gastrointestinal tract, is naturally colonized by a wide variety of bacteria. This is a physiologic situation that 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 importantly, the phagocytic action of neutrophils that migrate continuously through the junctional epithelium into the gingival sulcus. However, if this equilibrium is disturbed, pathogenic bacteria may overgrow, initiating the pathogenesis of gingivitis and possibly periodontitis. Current understanding of the steps leading to overgrowth of pathogens includes periodontal bacteria attaching to epithelial cells using their fimbriae and PRR recognition of PAMPs, inducing epithelial cell secretion of pro-inflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ , IL-6) and the chemokine IL-8 in the connective

**Table 1.** Summary of Main Effects of Bacterial Virulence Factors on Host Cells

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

Adapted from *J Clin Periodontol* 2005;32(Suppl 6):57–71.<sup>8</sup>

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., *P. gingivalis*, *A. 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.<sup>9</sup>

### **Bacteria in Connective Tissue**

Bacteria and/or their virulence factors found in the connective tissue directly stimulate host cells residing in this area, including leukocytes, fibroblasts, mast cells, endothelial cells, dendritic cells and lymphocytes. Neutrophils, macrophages, fibroblasts and mast cells release more proinflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-12), chemo-attractants (IL-8, MIP-1- $\alpha$ , MIP-2, MCP-1, MCP-5) and PGE<sub>2</sub> in the connective tissue. In addition, degranulation of mast cells results in the secretion of histamine and leukotrienes further amplifying the inflammatory cascade.<sup>10,11</sup>

Mediators that are secreted from activated host cells (e.g., IL-1 $\beta$ , TNF- $\alpha$ , PGE<sub>2</sub>, and histamine) will 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 ICAM-1 and -2).<sup>12</sup> Specifically, P- and E-selectins interact with glycoproteins on leukocytes allowing the cells to adhere reversibly to the vessel wall, 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 conforma-

tional 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. TNF- $\alpha$ , PGE<sub>2</sub> 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 that are produced at the site of infection and bind to proteoglycans of the extracellular matrix, along with bacterial chemo-attractants (fMLP, 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 that 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.<sup>13</sup>

Pro-inflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ , 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



Neutrophils in the 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 pro-inflammatory 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 pro-inflammatory mediators such as TNF- $\alpha$ , IL-1 $\beta$ , 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, that are produced from activated hepatocytes, enter the connective tissue via circulation due to 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.

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.<sup>15</sup> 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: (a) inhibiting the toxic effects or infectivity of pathogens by binding (neutralization); (b) opsonizing the pathogens and promoting phagocytosis; and (c) 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 that 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.<sup>16</sup>

### Summary of Part I

The trigger that causes the shift from tissue homeostasis to pathology remains unclear. The logical extension of L  e’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. Recently, a longitudinal study of periodontal disease progression failed to implicate any single organism or group of organisms in the initiation of periodontal attachment loss.<sup>17</sup> In addition, recent animal studies suggest that the level of host inflammation has a major impact on the composition of the

biofilm. Interestingly, inflammation is a stronger predictor of periodontal attachment loss than the composition or quantity of the oral biofilm.<sup>17</sup> Clearly, the etiology and pathogenesis of periodontitis requires 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 biological 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 inhibits and eliminates penetrating bacteria. Hence, only a small number of bacteria, mostly facultative, 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 initiated after mechanical irritation of the inflamed gingiva during tooth brushing, chewing, oral examination, and scaling and root planing.<sup>18</sup> The microorgan-



isms that gain access to the blood and circulate throughout the body are usually eliminated by the reticulo-endothelial system within minutes (transient bacteremia) and usually there are no other clinical symptoms other than possibly a slight increase in body temperature.<sup>19</sup> 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.<sup>20</sup> 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 pro-inflammatory immune mediators. Moreover, soluble antigens may react with circulating specific antibodies, forming macromolecular complexes. These immune complexes may further amplify inflammatory reactions at sites of deposition.<sup>21</sup>

### ***Pro-Inflammatory Mediators***

A different biological pathway that may explain the systemic inflammation induced by periodontal disease involves pro-inflammatory mediators, such as IL-1 $\beta$ , IL-6, TNF- $\alpha$  and PGE<sub>2</sub> that 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.<sup>22</sup> Moreover, the circulating mediators, due to 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. Pro-inflammatory cytokines may induce leukocytosis, which is an

increase in circulating neutrophils. Moreover, IL-1 $\beta$ , TNF- $\alpha$ , and especially IL-6 may reach the liver and activate hepatocytes to produce acute-phase proteins. The most important acute-phase reactants include 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 multiple pro-inflammatory 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 cardiovascular disease.<sup>23</sup>

Because there is to date no consensus 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 upon 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.<sup>24</sup> Opsonization and phagocytosis are further enhanced by activation of the complement system by CRP. Other pro-inflammatory activities of CRP include the up-regulation of the expression of adhesion molecules, such as ICAM-1 and E-selectin on endothelial cells and the induction of IL-6, IL-1 $\beta$ , and TNF- $\alpha$ , 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 pro-coagulant activity and reduction of fibrinolysis by inducing an increase in the expression of PAI-1, the main inhibitor of fibrinolysis.<sup>25</sup> Finally, CRP mediates proliferation and activation of smooth muscle cells (SMCs) 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.

### **SAA**

SAA proteins are a family of apolipoproteins associated with high-density lipoprotein in plasma. They have several pro-inflammatory 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.

### **PAI-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 physiological process that degrades blood clots.

### **Complement Proteins**

These 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 chemo-attractants to recruit more leukocytes to the site of complement activation. Third, terminal complement components damage certain bacteria by creating pores in the bacterial membrane.<sup>26</sup>

### **LBP and Soluble CD14**

These proteins play an important role in transferring LPS and PGN to the Toll-like receptors. 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 elevated levels of circulating pro-inflammatory cytokines and acute-phase proteins. With the exception of serum antibodies against periodontopathogens, these markers are not specific for periodontal disease, but

could be shared with distant inflammatory processes that have systemic effects. As such, these markers can be affected by other inflammatory diseases that could 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 periodontitis patients, leukocyte counts have been shown to be slightly elevated compared to healthy subjects, although not always significantly.<sup>27</sup> 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.<sup>28</sup> PMNs are the main leukocytes that are increased, and it is possible that these cells are 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 Pro-Inflammatory Cytokines***

In healthy subjects, the levels of circulating pro-inflammatory cytokines are very low or nondetectable. However, in periodontitis patients, several pro-inflammatory cytokines may “spill” into the bloodstream and increase the concentration in the plasma. Of the pro-inflammatory mediators studied, only the levels of IL-6 have been consistently shown to be elevated in the serum. This increase is related to the extent and severity of inflammation in periodontal tissues.<sup>29</sup>

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- $\alpha$  among healthy and periodontitis patients failed to report any differences, and in most cases cytokine levels were not measurable.<sup>30</sup>

### ***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 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 humans, have revealed a positive association between periodontal disease and circulating CRP levels, while a recent meta-analysis limited to human studies has confirmed that plasma CRP is elevated in patients with periodontitis compared to healthy individuals.<sup>31</sup> 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 periodontitis patients compared to healthy individuals.<sup>32</sup> However, to date there is no available evidence to support that periodontal therapy actually reduces the amount of circulating fibrinogen.

### ***Possible Role of Systemic Inflammation in Various Disorders***

During the late nineteenth and early twentieth centuries, the “focal infection” theory dominated the medical world.<sup>33</sup> This theory held that foci of sepsis were responsible

for the initiation and progression of a variety of inflammatory diseases, including 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 finally 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 relationship of periodontal disease to systemic inflammation increased—the idea that periodontal infection may affect the progression of systemic disorders such as cardiovascular disease, adverse pregnancy complications, diabetes mellitus, and other diseases re-emerged.

In this possible association, systemic inflammation seems to play a key role. Specifically, on one hand, periodontal disease may induce systemic inflammation and on the other, there is increasing evidence suggesting that elevated levels of the markers of systemic inflammation are associated with an increased risk for systemic diseases.

### ***Cardiovascular Disease (CVD)***

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.<sup>2</sup> Moreover, studies demonstrate that serum IL-6 levels were significantly elevated in subjects who subsequently experienced an MI compared to age-matched controls.<sup>34</sup> Similarly, plasma levels of soluble P-selectin, soluble CD40L, and macrophage-inhibitory cytokine-1 were all significantly increased in healthy subjects who subsequently developed CVD events compared to matched controls.<sup>35</sup>

Elevated plasma concentrations of TNF- $\alpha$  have also been associated with CVD, and specifically with recurrent nonfatal MI or other CVD events. Moreover, TNF- $\alpha$  levels were persistently higher among post-MI patients at increased risk for recurrent coronary events.

Besides these pro-inflammatory 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.<sup>36</sup> As described already, CRP may contribute to the initiation and development of atherothrombotic lesions not only by up-regulating the expression of pro-inflammatory cytokines, but also by mediating proliferation and activation of SMCs and by activating the pro-coagulant system. This last property may be further enhanced by another acute-phase protein, fibrinogen, which is often found to be elevated in CVD patients.

### ***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 individuals and subjects for which Type 1 diabetes has

been just diagnosed. However, the levels of circulating CRP are significantly higher in individuals with long-term diabetes.<sup>37</sup> 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 pro-inflammatory soluble adhesion molecule, vascular cell adhesion molecule-1 (VCAM-1), have been found in patients with microvascular disease compared to those without.

In 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 individuals who develop Type 2 diabetes later in their lives. Among Pima Indians, a population with a high prevalence of Type 2 diabetes, 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 to those in the lowest tertile. Moreover, in two other studies, healthy individuals demonstrating serum levels of CRP and IL-6 within the highest quartiles were more likely to develop Type 2 diabetes in the next four to seven years compared to subjects in the lowest quartile.<sup>4</sup> Similar results were found with increased levels of another acute-phase protein, PAI-1.

Insulin resistance, which is associated with Type 2 diabetes and usually precedes the development of frank diabetes, may also be affected by pre-existing systemic inflammation since several pro-inflammatory and acute-phase proteins, such as TNF- $\alpha$ , IL-6, MCP-1, PAI-1, and SAA are associated with the induction of insulin resistance.<sup>38</sup>

### Summary of Part II

Based on available evidence, it is possible that systemic inflammation may actually be the link that associates periodontal disease with other systemic diseases. Details of the plausible biological 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 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.<sup>20,39,40</sup> Genetic polymorphisms and other factors may also be responsible for a “hyperinflammatory phenotype” that may further affect the susceptibility of the host to periodontal disease and tissue destruction. Currently, it is believed that in chronic periodontal disease, destruction 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 may remain as gingivitis in some patients and progress to periodontitis in others. Irrespective 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.

### The 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 different pathways can be initiated: (a) the cyclo-oxygenase (COX) pathway that leads to the production of prostaglandins (e.g.,  $\text{PGE}_2$ ), and (b) the lipoxygenase (LO) pathways that lead to the production of a series of hydroxyl acids characterized by the 5-LO products, the leukotrienes (e.g.,  $\text{LTB}_4$ ). 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.  $\text{PGE}_2$  is a potent activator of osteoclast-mediated bone resorption, and with other eicosanoids mediates inflammation and periodontal tissue destruction.  $\text{LTB}_4$  attracts neutrophils, stimulates the release of granule-associated enzymes from neutrophils, and contributes to pro-inflammatory processes and to further tissue damage.

### ***Returning to Homeostasis***

Once the bacteria have been removed by phagocytosis, resolution of inflammation occurs with the reduction or removal of leukocytes and debris from inflamed sites with a return to homeostasis.<sup>5</sup> 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 that is initiated by a newly identified class of receptor agonists that emerge temporally as the inflammatory lesion matures.<sup>5</sup> Although prostaglandins and leukotrienes secreted by neutrophils have pro-inflammatory properties, as inflammation proceeds the same prostaglandins ( $\text{PGE}_2$  and  $\text{PGD}_2$ ) may promote expression of the 15-LO gene, leading 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 pro-

inflammatory activity of neutrophils and leading to apoptosis. As a result, they stop secreting the chemo-attractant  $\text{LTB}_4$  and several cellular pathways are activated, producing, at a local level, other dual-acting anti-inflammatory and proresolution lipid mediators, including resolvins and protectins.

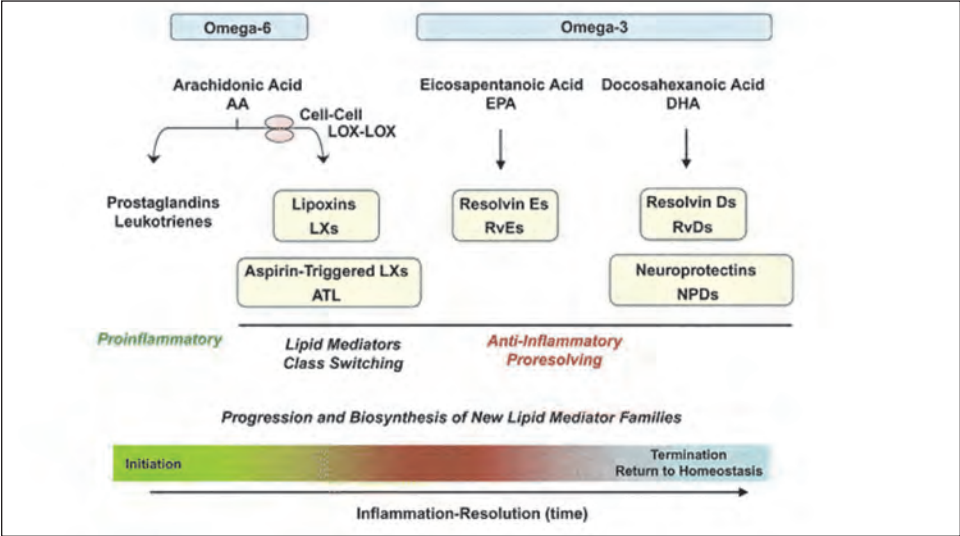
### ***Mechanisms of Inflammation Resolution***

Resolvins and protectins provide potent signals that orchestrate and accelerate mechanisms that promote resolution of inflammation and homeostasis. Specifically, as depicted in Figure 3, pro-resolution mediators stop neutrophil infiltration and drive neutrophils to apoptosis, while at the same time attracting monocytes to the lesion.<sup>41</sup> Lipoxin-stimulated monocytes/macrophages obtain a nonphlogistic phenotype, which results in phagocytosis of apoptotic neutrophils and enhanced mucosal clearance of bacteria without concomitant secretion of pro-inflammatory mediators that could contribute to tissue damage.<sup>42</sup> Moreover, pro-resolution 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 pro-inflammatory 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

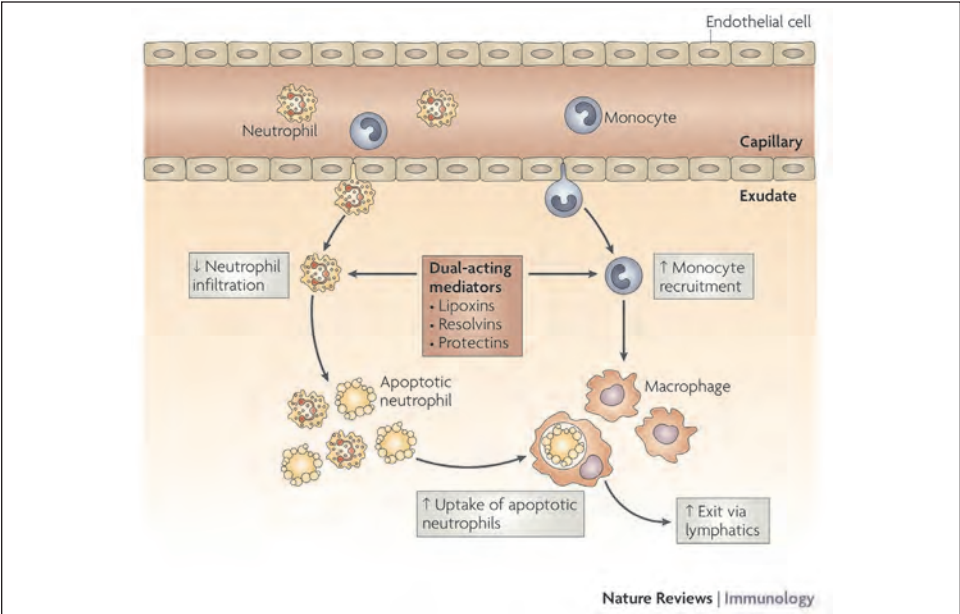


**Figure 2.** Progression and Biosynthesis of Lipid Mediators During Inflammation Resolution



Chemical mediators involved in the initiation of acute inflammation, such as prostaglandins (PGs) and leukotrienes (LTs), induce “class switching” toward pro-resolving lipid mediators. The pro-resolving mediators include  $\omega$ -6 PUFAs, AA-derived LXs, ATLs,  $\omega$ -3 PUFA EPA-derived RvEs, docosahexanoic acid (DHA)-derived RvDs, and protectins (PDs) (or neuroprotectins in neural tissues).  
Reprinted by permission from Wiley-Blackwell: *Br J Pharmacol* 2008;153(Suppl)S200–S215.

**Figure 3.** Dual Anti-Inflammatory and Pro-Resolution Actions of Specific Lipoxins, Resolvins and Protectins



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maintained, tissue destruction continues and inflammation persists. If pro-resolution 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, there is a growing and promising literature from *in vitro* work and animal models that supports the beneficial actions of resolution agonists both on periodontal and other systemic diseases.<sup>5</sup>

### The Role of Pro-Resolution Mediators

Examples of the actions of therapeutic pro-resolution mediators in periodontal disease include over-expression of lipoxin A<sub>4</sub> in transgenic rabbits protecting against periodontitis and atherosclerosis.<sup>43</sup> In another study, topical treatment with resolvins ( $\omega$ -3 fatty acid derived resolution agonists, *vide infra*) prevented more than 95% of alveolar bone destruction in rabbits. Moreover, histological 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-1 $\beta$  levels. Finally, in established periodontal disease, resolvins prevented further tissue destruction, and both gingival and osseous tissues that were lost during disease were regenerated.<sup>44</sup>

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 peritonitis.<sup>42</sup> Moreover, in cystic fibrosis, lipoxins decreased neutrophil inflammation, pulmonary bacterial burden, and disease severity.<sup>45</sup> Resolvins in a colitis model in mice decreased neutrophil recruitment and pro-inflammatory gene expression, improved survival, and reduced weight loss.<sup>46</sup> In addition, resolvins protected against neovascularization in retinopathy.<sup>47</sup> Finally, in an asthma model, protectins protected against lung damage, airway inflammation, and airway hyper-responsiveness.<sup>48</sup> Table 2 lists the impact of lipoxins, resolvins, and protectins on various inflammatory disease models.

It is conceivable that the use of pro-resolution 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 pro-resolution 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 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.

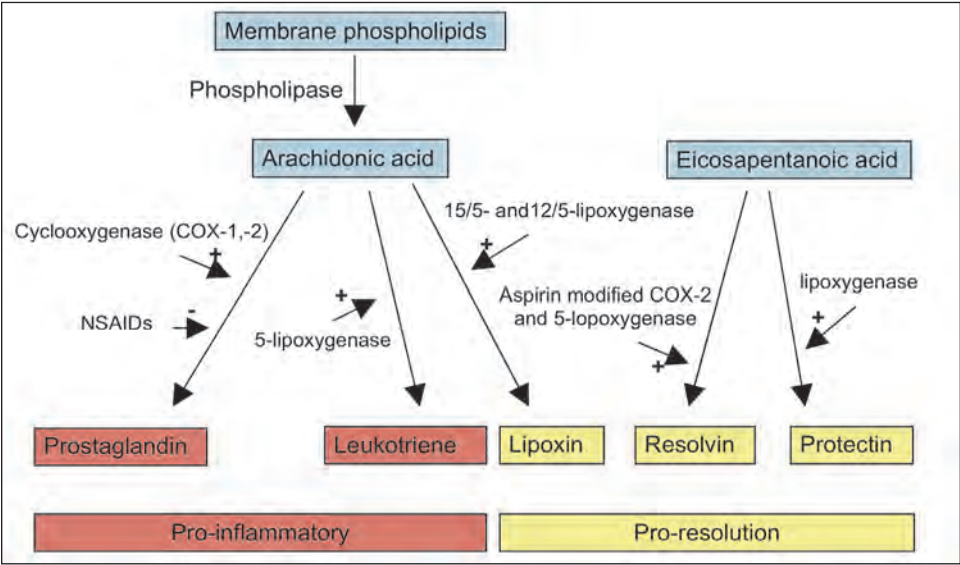
### Origins of Pro-Resolution Mediators

In order to manipulate resolution of inflammation more effectively, it is imperative to understand the biological origin of the pro-resolution mediators. Lipoxins (e.g., lipoxin A<sub>4</sub>) 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 poly-unsaturated fatty acids ( $\omega$ -3 PUFAs), such as eicosapentaenoic acid (EPA) and docosahexanoic acid

**Table 2.** Impact of Lipoxins, Resolvins, and Protectins on Various Inflammatory Disease Models

Disease Model	Species	Action(s)
<b>Lipoxin A4/ATL</b>		
Periodontitis	Rabbit	<ul style="list-style-type: none"> <li>–Reduces neutrophil infiltration</li> <li>–Prevents connective tissue and bone loss</li> </ul>
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	<ul style="list-style-type: none"> <li>–Attenuates pro-inflammatory gene expression</li> <li>–Reduces severity of colitis</li> <li>–Inhibits weight loss, inflammation, pulmonary dysfunction</li> </ul>
Asthma	Mouse	Inhibits airway hyper-responsiveness and pulmonary inflammation
Cystic fibrosis	Mouse	Decreases neutrophilic inflammation, pulmonary bacterial burden, and disease severity
Ischemia-reperfusion injury	Mouse	<ul style="list-style-type: none"> <li>–Attenuates hind-limb ischemia-reperfusion lung injury</li> <li>–Causes detachment of adherent leukocytes in mesenteric ischemia-reperfusion injury</li> </ul>
Corneal disorders	Mouse	<ul style="list-style-type: none"> <li>–Accelerates cornea re-epithelialization</li> <li>–Limits sequelae of thermal injury (such as neovascularization and opacity)</li> <li>–Promotes host defense</li> </ul>
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	<ul style="list-style-type: none"> <li>–Reduces leukocyte rolling and adherence</li> <li>–Decreases neutrophil recruitment</li> </ul>
Hyperalgesia	Rat	<ul style="list-style-type: none"> <li>–Prolongs paw withdraw latency and reduces hyperalgesic index</li> <li>–Reduces paw oedema</li> </ul>
Pleuritis	Rat	Shortens the duration of pleural exudation
<b>Resolvin E1</b>		
Periodontitis	Rabbit	<ul style="list-style-type: none"> <li>–Reduces neutrophil infiltration</li> <li>–Prevents connective tissue and bone loss</li> <li>–Promotes healing of diseased tissues</li> </ul>
Peritonitis	Mouse	<ul style="list-style-type: none"> <li>–Regenerates lost soft tissue and bone</li> <li>–Stops neutrophil recruitment</li> <li>–Regulates chemokine and/or cytokine production</li> <li>–Promotes lymphatic removal of phagocytes</li> </ul>
Dorsal air pouch	Mouse	Stops neutrophil recruitment
Retinopathy	Mouse	Protects against neovascularization
Colitis	Mouse	<ul style="list-style-type: none"> <li>–Decreases neutrophil recruitment and pro-inflammatory gene expression</li> <li>–Improves survival</li> <li>–Reduces weight loss</li> </ul>
<b>Resolvin D1</b>		
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
Retinopathy	Mouse	Regulates macrophage
	Mouse	Protects against neovascularization
<b>Protectin D1</b>		
Peritonitis	Mouse	<ul style="list-style-type: none"> <li>–Inhibits neutrophil recruitment</li> <li>–Regulates chemokine and/or cytokine production</li> <li>–Promotes lymphatic removal of phagocytes</li> <li>–Regulates T-cell migration</li> </ul>
Asthma	Mouse	Protects from lung damage, airway inflammation, and airway hyper-responsiveness
Asthma	Human	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
Retinopathy	Mouse	Regulates macrophages function
Ischemic stroke	Mouse	Protects against neovascularization
	Rat	<ul style="list-style-type: none"> <li>–Stops leukocyte infiltration</li> <li>–Inhibits nuclear factor-kB and cyclo-oxygenase-2 induction</li> </ul>
Alzheimer's disease	Human	Diminishes protecting D1 production in human Alzheimer's disease

**Figure 4.** Schematic Illustration of Lipid-Mediated Pro-Inflammatory and Pro-Resolution Pathways



(DHA). EPA and DHA can be metabolized by aspirin-modified COX-2 pathways to form resolvins, while 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 pro-resolution 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 and certain LO inhibitors, have been shown to impair resolution of inflammation and lead to systemic inflammatory complications.

### Summary of Part III

Theoretically, combining pro-resolution mediators and anti-inflammatory agents such as aspirin and statins—agents that decrease the extent of inflammation without interfering with the endogenous pro-resolution 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 that new treatment strategies will 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 it is only recently that 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 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 micro-organisms would localize from the source focus to the distant, systemic focus and 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 as far back as from the ancient Egyptians (2100 BC) mention tooth pain associated with women's reproductive system diseases.<sup>1</sup> 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."<sup>2</sup> 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.<sup>3</sup> Aristotle, perhaps the first dental anatomist—especially from the standpoint of comparative anatomy—stated that "those persons who have the most teeth are the longest lived."<sup>4</sup> In his book, *On Hygiene*, the Roman physician Galen (166–201 AD) emphasized the inter-relationship between the oral cavity and other illnesses.<sup>5</sup>

From the end of the Roman Empire until the middle ages, all sciences fell into abeyance, and 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.<sup>4</sup> 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.”<sup>6</sup>

In 1548, Ryff wrote a monograph that dealt exclusively with dental afflictions. In his pamphlet titled *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.”<sup>5</sup>

In 1768, Berdmore in *A Treatise on the Disorders and Deformities of the Teeth and Gums* described the relationship 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.”<sup>7</sup> 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.”<sup>7</sup>

All of these statements over the course of history were made without sufficient supporting evidence, yet they were current beliefs at the time. These 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 to be anything more than guess work based on simple observation. However, it is of great interest to see that historically there existed a suspicion or hunch that an inter-relationship existed between oral disease and systemic conditions.

## ORAL SEPSIS AS A CAUSE FOR DISEASE

The importance of oral hygiene in relation to bacteriology was first detailed by Dutch scientist Antonie von 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 the 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.

An American dentist working at Koch’s Institute for Infectious Diseases, Miller was convinced that the bacteria residing in the mouth could explain most illnesses. In 1880, to support his theory, Miller published a book with the title *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.<sup>8</sup> 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/sections:

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

The diseases he felt could be traced to bacteria colonizing the mouth included osteitis, 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 fistulae that opened on the neck, shoulder, arm, or 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 he 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.<sup>5,8</sup>

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 an article titled “Oral Sepsis as a Cause of Disease,” which was published in the *British Medical Journal*.<sup>9</sup> 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.<sup>5,9</sup>

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.<sup>5,10</sup> In 1902, Colyer described the resolution of irregular heart beat, gastric effects and “general debility” after the treatment of any oral sepsis present. He also suggested a good maxim with which a dentist should work was “better no teeth than septic ones.”<sup>5,11</sup>

In an article published by Wilcox in 1903, antral disease was put forward as an important sequelae of oral sepsis.<sup>12</sup> It was believed that prolonged antral suppuration could lead to extreme mental depression, often ending in suicidal tendency.<sup>5,12</sup> Other relationships that were put forward were those between oral sepsis and migraine headaches, laryngeal pain and spasm (which could induce cough, loss of voice, and wasting), blindness, and deafness, all of which Wilcox hypothesized could be cured with treatment of the oral sepsis.<sup>5</sup> 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* with the title “Mouth Infection: the Cause of Systemic Disease.”<sup>13</sup> In this article he stated that “there is a general disposition on the part of the medical and dental professions to underestimate 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.” He also stated that “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.”<sup>15</sup> His address was published in *The Lancet*, which was the leading British medical journal at the time, as well as in the *Dental Register*.<sup>14,15</sup> 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.” It appears that Hunter’s condemnation of conservative dentistry was 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 often of substandard quality. Some well-respected dentists at the time, 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 as Hunter’s observations were primarily based on the disastrous effects of a very low-standard dentistry.<sup>5</sup>

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 with 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.<sup>5,16</sup> Billings advocated 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.<sup>17,18</sup> One of the first studies measuring the clinical benefit of removing focal infection in 1917 confirmed his suggestions. The study was conducted as a retrospective postal survey, and 23% reported a cure for their arthritis following removal of infective foci. An additional 46% reported experiencing some improvement in symptoms.<sup>5,19</sup>

One of Billings' research associates was Rosenow. He was a graduate of the Rush Medical College where he had been a student of Billings. He utilized 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. He 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.<sup>5</sup>

Physicians like 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."<sup>20</sup> In an article in 1938, he 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."<sup>21</sup> 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."<sup>3,5</sup>

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.<sup>5,22</sup> All teeth that were endodontically or periodontally involved were extracted to avoid a possible focus of infection. This approach came to be known as the "hundred percent." The leading spokesperson for this radical approach was the physiologist Fisher. He regarded a tooth with a root filling as a dead organ that needed to be extracted.<sup>5</sup>

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.<sup>22,23</sup> Others noted that Rosenow inoculated animals with such high counts of bacteria that it was inevitable that every organ or joint would be affected.<sup>24, 25</sup> 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.<sup>25</sup>

Cecil, a great proponent of the focal infection theory, together with the rest of the medical community, started to re-evaluate 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 three 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.”<sup>21</sup>

In 1940, Reiman and Havens wrote a critical review of the theory of focal infection in the *Journal of the American Medical Association*.<sup>26</sup> 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<sup>27</sup> 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, sin, 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.<sup>26</sup> An editorial in the *Journal of the American Medical Association* in 1952<sup>28</sup> 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, 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.<sup>5</sup> According to Gibbons,<sup>22</sup> the role of economics in the spreading 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.”<sup>22</sup>

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, there were dental scientists who continued to question whether oral infection (and inflammation) might in some way contribute to a person’s overall health, but 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.<sup>29</sup> It was not until the last decade of the twentieth century that dentistry and medicine started again to consider 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.<sup>30</sup> According to Barnett<sup>30</sup> this response was a result of several factors: (a) greater analytical and statistical knowledge, and a better understanding of the constraints of epidemiological 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<sup>31</sup> in Finland conducted a case-control study on 100 patients who had suffered an acute myocardial infarction. They compared these patients to 102 control subjects selected from the community. A full dental examination was performed on all of the subjects studied. Additionally, a dental index was computed. This index computed the sum of scores from the number of missing teeth, carious lesions, peri-apical lesions, probing depths, and the presence or absence of pericoronitis. It was found that dental health was significantly worse in patients with a history of acute

myocardial infarction than in control subjects. This association remained valid even after adjustment for age, social class, smoking, serum lipid concentrations, and the presence of diabetes. It was mainly this study that renewed the interest of physicians and dentists in the relationship 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.<sup>32</sup> and Offenbacher et al.<sup>33</sup>—was the beginning of a new era of understanding the impact of oral health and disease on overall health and disease.<sup>25,30</sup> 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.<sup>34</sup>

### **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 that it might pose threats to those with chronic disease, e.g., diabetes, respiratory diseases, and osteoporosis.<sup>35-38</sup> Periodontal diseases are infections that are caused by micro-organisms 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 (such

as *Porphyromonas gingivalis*) from the biofilm within the periodontal pocket. Several different pathways for the passage of periodontal pathogens and their products into the circulation have been suggested and are currently the subject of intensive research.

The focal infection theory, as proposed and defended the first time around, was mainly based on anecdotal evidence and the occasional case report. In order for the hypothesis not to fall into disrepute the second time around, different levels of evidence must be examined in order to establish a relationship between the periodontal condition and 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 relationship 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 don't, but are otherwise similar. These studies may lead to cross-sectional analyses. Observational studies are used to examine associations between exposures and disease. These are relatively inexpensive and frequently used for epidemiological studies. However, the fact that they are retrospective and not randomized limits their validity.

Cross-sectional analysis studies the relationship between different variables at a point in time. These type 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 the ones without. The same applies for intervention trials that provide the strongest form of evidence. Unfortunately, not only are these difficult to conduct, they are expensive and involve many ethical considerations.

### What Is Risk?

Risk is the statistical likelihood that certain factors are associated with the development of disease. It 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 if certain factors are modified, compared to the same likelihood if they are not. It is easy to understand that if 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 one indicates an equal chance as to whether or not an association will occur. An odds ratio of two indicates a two-fold chance of an association being present. Care should be exercised inferring causation from odds ratios. Association does not, in itself, infer causation. In the interpretation of odds ratios, it is important that the confidence interval of the odds ratio not traverse one. If it does, the odds ratio—regardless of magnitude—cannot be relied upon.

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.<sup>39</sup> In this review, it was pointed out that in addition to pre-existing 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 are risk factors common to many chronic, noncommunicable diseases, such as heart disease, stroke, and diabetes, all of which are associated with periodontitis.<sup>39</sup>

### **Periodontitis/Oral Health as a Risk for Specific Diseases: Evidence for an Association**

#### **Cardiovascular**

There are at least three possible mechanisms by which oral infections may contribute to cardiovascular disease:<sup>40</sup>

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

Bahekar<sup>35</sup> and colleagues recently conducted a systematic review of the literature in order to evaluate if such an association exists. This review revealed five prospective cohort studies involving 86,092 patients for at least six years. The authors considered that three out 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 relationship 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.<sup>41</sup> Additionally, a large number of patients with periodontal disease also exhibit cardiovascular disease; this could be an indication that periodontal disease and atherosclerosis share similar or common etiologic pathways.<sup>42</sup> The literature also suggests that a number of pathogens, antigens, endotoxins, and cytokines of periodontitis might be significant contributing factors.<sup>43,44</sup> According to Williams et al.,<sup>45</sup> controlling for such confounding factors when carrying out epidemiological 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 *Porphyromonas gingivalis* and *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 to support a role for C-reactive protein as a predictive, pathogenic factor for vascular risk, it is recognized that more research is needed.<sup>35</sup>

There is a need for large-scale prospective intervention studies to assess whether or not periodontitis can be considered an effective modifiable risk factor in the prevention of cardiovascular disease.

#### **Adverse Pregnancy Outcomes**

Several studies on laboratory animals that took place in the 1970s and 1980s revealed that bacterial endotoxin (a cell wall component isolated from *E. coli*) is capable of producing spontaneous abortion, low fetal weight, and malformations.<sup>46</sup> Collins and colleagues successfully demonstrated that oral anaerobes such as *P. gingivalis* had similar effects.<sup>47,48</sup>

In 1996, Offenbacher and colleagues constructed a case-control study with the title "Periodontal Infection as a Possible Risk



Factor for Preterm Low Birth Weight.”<sup>33</sup> In this investigation, they sought to determine whether or not the prevalence of maternal 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 postpartum 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 this kind.

In the last seven years, there has been an explosion of data 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 due to 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.

There is a need for large-scale prospective intervention studies in which adverse pregnancy outcomes and the severity of periodontal disease can be clearly defined.

### ***Diabetes: A Two-Way Relationship***

It is clear from epidemiologic studies that diabetes mellitus increases the risk for periodontal disease.<sup>49,50</sup> 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.<sup>45</sup> 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 that there is an increased risk of periodontitis in patients with diabetes, but Taylor and

coworkers 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 once a diabetic has periodontitis, it leads to worsening diabetes or glycemic control.<sup>51</sup> This was followed by a paper by Grossi and Genco in which periodontal disease and diabetes mellitus was presented as a two-way relationship.<sup>52</sup> 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.<sup>53</sup> Recently, 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.<sup>45</sup> Researchers tried to evaluate the effects of periodontal therapy on systemic inflammatory markers and on glycemic control.<sup>54</sup> 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.

There is emerging evidence to suggest that periodontitis predicts the development of overt nephropathy and endstage renal disease in patients with Type 2 diabetes.<sup>37,55</sup> A prospective study by Shults<sup>37</sup> and colleagues was conducted exclusively in individuals with diabetes. It also included a proportionally large number of individuals with kidney disease. Whether or not 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<sup>45</sup> and colleagues, these groups can provide more immediate answers than studies with a more heterogeneous diabetic population.

### ***Respiratory Infections***

Scannapieco<sup>56</sup> 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 micro-organisms 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 investigated evidence for a possible etiological association between oral health and pneumonia or other respiratory diseases.<sup>57</sup> They concluded that there is fair evidence of an association of pneumonia with oral health, and poor evidence of an association of chronic obstructive pulmonary disease with oral health. Additionally, there is good evidence that implementation of high-quality and frequent oral healthcare decreases the occurrence and progression of respiratory diseases among elderly hospitalized or institutionalized individuals.<sup>57</sup>

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 there is an association between osteoporosis and reduced alveolar crestal height in postmenopausal women.<sup>58</sup> In another study, osteoporosis and periodontal infection were found to be independent risk factors for oral bone loss.<sup>59</sup> Other studies, especially longitudinal studies, are necessary to determine the temporal nature of this relationship and to further evaluate it.

Some studies investigated the effect of hormone replacement therapy or vitamin D intake on tooth loss.<sup>60</sup> 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 others may have affected the results.<sup>40</sup>

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

## **CONCLUSIONS**

There is a long-standing and well-accepted principle 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 there are a number of well-

constructed, controlled intervention studies providing “hard” evidence, treatment recommendations need to be guarded.

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# CHAPTER 5

## Diabetes Mellitus: A Medical Overview

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### INTRODUCTION

Diabetes mellitus (DM) is a quintessential metabolic disease in which the characteristic phenotype is loss of control of glucose homeostasis, but the pathophysiology also affects fat and protein metabolism. Resulting hyperglycemia is associated with both short- and long-term complications, making early diagnosis and treatment of this condition essential. The key hormonal disturbance causing DM can be either a defect in insulin secretion, 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/pathophysiology, clinical presentations, complications, and diagnosis of the disease, as well as a brief overview of treatment options.

Key educational objectives are to understand that

- 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 counter-regulatory 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, or ameliorating disabling or life-threatening complications.

### CLASSIFICATION OF DIABETES MELLITUS

DM is classified into several subtypes, based upon etiology, which can help explain clinical manifestations and provide a rationale for various treatments (Table 1). The majority of patients with DM have Type 2 disease (85%–90%) marked by defective insulin action as well as relative deficiency in insulin secretion. Another 5%–10% of patients have Type 1 disease (absolute defect in insulin secretion). The remaining sub-types are rare (Table 1). This chapter will focus on the major subgroups: Type 1 DM, Type 2 DM, and gestational DM (GDM); the latter affects fetal and maternal health and is a risk factor for later development of Type 2 DM.

### EPIDEMIOLOGY

According to 2007 estimates, 23.6 million people (or 7.8% of the population) in the United States have DM.<sup>1</sup> About 6 million of these individuals do not know they have this disease and present to healthcare providers after a point of no return in preventing complications. Prevalence increases with advancing age, affecting almost 24% of individuals over the age of 60. An epidemic of Type 2 DM is underway in both the developed and developing world, but the brunt is being felt sharply in developing countries.<sup>2–4</sup> Globally, the number of people with diabetes is expected to rise from the current estimate of 150 million to 220 million in 2010 and 300 million in 2025, making the cost of treating DM and its complications a pressing economic as well as clinical concern.<sup>5</sup>

Patients with DM are at a two- to four-fold higher risk for developing heart disease and stroke compared to people without DM.



**Table 1.** Etiologic Classification of Diabetes Mellitus

I. Type 1 diabetes ( $\beta$ -cell destruction, usually leading to absolute insulin deficiency)
A. Immune mediated
B. Idiopathic
II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)
III. Other specific types
A. Genetic defects of $\beta$ -cell function
1. Chromosome 20, HNF-4 $\alpha$ (MODY1)
2. Chromosome 7, glucokinase (MODY2)
3. Chromosome 12, HNF-1 $\alpha$ (MODY3)
4. Chromosome 13, insulin promoter factor-1 (IPF-1; MODY4)
5. Chromosome 17, HNF-1 $\beta$ (MODY5)
6. Chromosome 2, NeuroD1 (MODY6)
7. Mitochondrial DNA
8. Others
B. Genetic defects in insulin action
1. Lipodystrophic syndromes
2. Type A insulin resistance
3. Leprechaunism
4. Rabson-Mendenhall syndrome
5. Others
C. Diseases of the exocrine pancreas
1. Pancreatitis
2. Trauma/pancreatectomy
3. Neoplasia
4. Cystic fibrosis
5. Hemochromatosis
6. Fibrocalculous pancreatopathy
D. Endocrinopathies
1. Cushing's syndrome
2. Acromegaly
3. Glucagonoma
4. Pheochromocytoma
5. Others
E. Drug- or chemical-induced
1. Glucocorticoids
2. Atypical Antipsychotics
3. Pentamidine
4. Diazoxide
5. $\alpha$ -Interferon
6. Others
F. Infections
1. Congenital rubella
G. Uncommon forms of immune-mediated diabetes
1. "Stiff-man" syndrome
2. Anti-insulin receptor antibodies
3. Others
H. Other genetic syndromes sometimes associated with diabetes
1. Down's syndrome
2. Turner's syndrome
3. Wolfram's syndrome
4. Laurence-Moon-Biedl syndrome
5. Prader-Willi syndrome
6. Others
IV. Gestational diabetes mellitus (GDM)

**Note:** 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. Adapted from the American Diabetes Association. *Diabetes Care* 2009;31(Suppl 1).<sup>37</sup>

In addition, DM is the leading cause of new cases of blindness and kidney failure among adults ages 20 to 74.<sup>1</sup> Gingivitis and periodontitis are also more common in people with DM. Almost one-third of people with DM have severe periodontal disease with loss of attachment of gums to teeth measuring five millimeters or more.<sup>1</sup>

In addition to enormous morbidity associated with DM, this disease was the seventh leading cause of death listed on US death certificates in 2006. Overall, the risk for death among people with DM is about twice that of people without DM of similar age.<sup>1</sup>

### **PATHOPHYSIOLOGY**

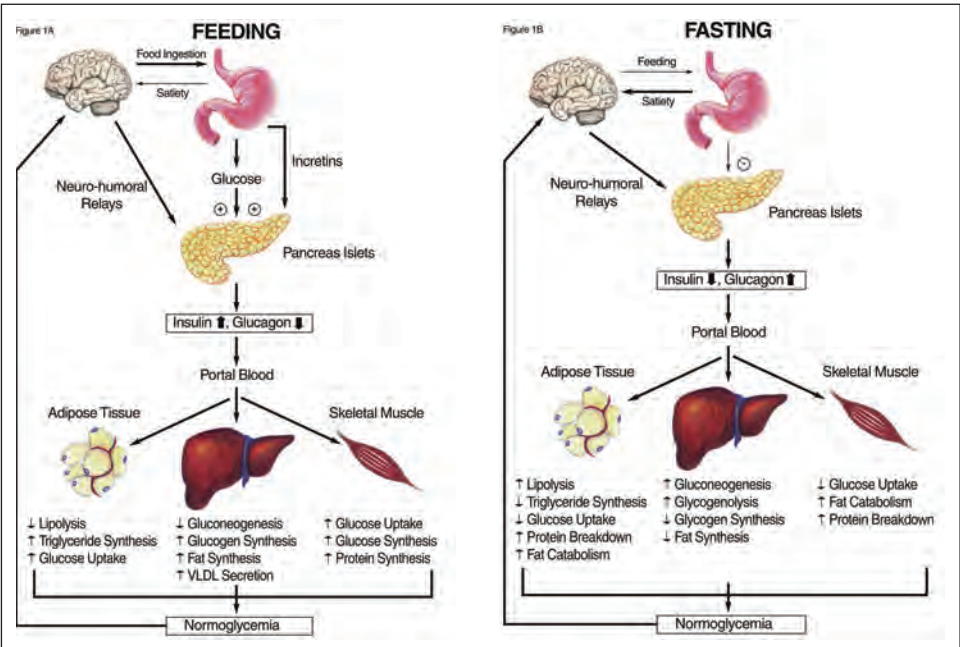
The pathophysiology of DM revolves around impairment of insulin secretion, insulin resistance, or both, resulting in reduced utilization of glucose, hyperglycemia, and impairment of fatty acid metabolism. Symptoms and complications of DM are due to hyperglycemia as well as lack of adequate insulin action.

### **Glucose Metabolism**

Carbohydrates, broken down mainly into glucose, are an important source of energy in humans. Consideration of glucose and insulin metabolic pathways is crucial to understanding the pathophysiology of DM (Figure 1).

Glucose is derived from three sources: intestinal absorption following digestion of dietary carbohydrates; glycogenolysis, the 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.<sup>5</sup> Only the liver and kidneys are capable of releasing glucose into circulation by glycogenolysis and gluconeogenesis. All tissues can utilize glucose as a substrate for energy production, but only the brain is wholly dependent upon glucose as its main energy source. Thus,

**Figure 1.** Action of Insulin & Glucagon Under Feeding & Fasting Conditions



Feeding, satiety, and the neurohumoral 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 will 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 VLDL secretion and increased glycogen storage. Although the majority of 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 neurohumoral 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 of these actions are tightly regulated and coordinated to account for all physiological processes, ranging from short-term energy expenditure (such as 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.

mechanisms to maintain a steady-state supply of glucose to the central nervous system are integral to metabolic control.

Both insulin-dependent and non-insulin-independent pathways can determine whole body clearance of glucose.<sup>6</sup> Glucose is transported into the cells by specific transporters,<sup>7</sup> activated by phosphorylation to glucose-6-phosphate by the tissue-specific enzymes hexokinase or glucokinase, allowing it to

enter metabolic pathways such as the glycolysis, glycogen synthesis, hexosamine biosynthesis (alternative pathway to glycolysis), or pentose phosphate pathways.<sup>6</sup> These pathways are subject to regulation by insulin, as well as glucagon. 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 (GLUT)-4, to the cell surface, whereas in the brain, GLUT-1 is constitutively active and not dependent upon insulin action. Insulin regulates glucose uptake, inhibits glycogen breakdown and gluconeogenesis, whereas glucagon has the opposite effects.<sup>8</sup> Hence, absolute deficiency of insulin (as in Type 1 DM), or relative (as in Type 2 DM), is associated with decreased clearance of blood glucose from the body and leads to hyperglycemia (Figure 1).

### Role of Insulin in the Body

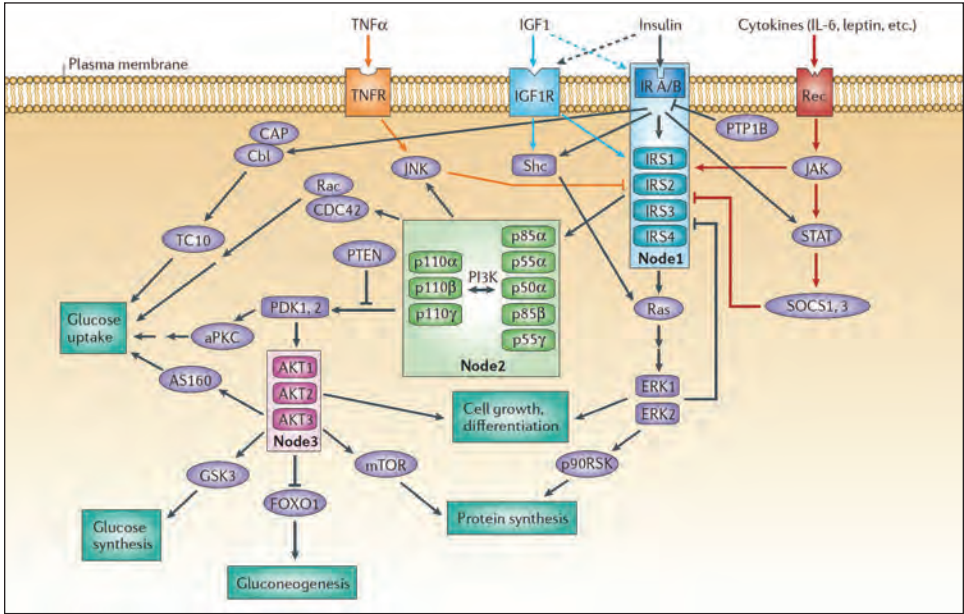
Insulin is secreted by  $\beta$ -cells of Islets of Langerhans, an endocrine organ, present in the pancreas. The pancreatic islet comprises a group of cells, termed  $\alpha$ -,  $\beta$ -, and  $\delta$ -cells, surrounded by exocrine pancreas. These islets synthesize and release a number of hormones, the classic ones being insulin and amylin from the  $\beta$ -cell, glucagon from the  $\alpha$ -cell, somatostatin from the  $\delta$ -cell, as well as a number of other bioactive polypeptides. Insulin is synthesized as a pro-hormone, transported to granules where it is processed by a pro-protein convertase, resulting in mature insulin, C-peptide (by product of pro-insulin processing), and amylin.<sup>9,10</sup> These are stored in these mature granules until released upon stimulation of the  $\beta$ -cell. Insulin production usually exceeds the need, so the unreleased granules are stored or destroyed in the lysosomal compartment of the  $\beta$ -cell. Glucose is the primary stimulant of insulin secretion, and oxidative metabolism of glucose is required for glucose to stimulate granule exocytosis.<sup>11-15</sup> 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 and regulating catabolism of stored fuel. Its main target tissues are liver,

skeletal muscle, and adipose tissue and its action on these tissues (or lack thereof) is responsible for the systemic effects of insulin.<sup>16</sup> If insulin is the "Yin," a group of hormones such as glucagon, cortisol, and growth hormone comprise the "Yang" to counteract and keep the metabolism in balance for energy needs. Under feeding conditions, with entry of nutrients, insulin increases and glucagon decreases, resulting in storage of the incoming nutrients. Under fasting conditions, insulin decreases, glucagon increases, resulting in increased lipolysis from fat to allow fatty acids to be transported to the liver and other tissues, and increased gluconeogenesis from the liver (and kidney) to maintain blood glucose, and some glycogenolysis. Under prolonged starvation, fatty acids are metabolized to ketone bodies to supply the central nervous system with fuel, in addition to the glucose.

Insulin exerts its action by binding to a cell-surface receptor, the insulin receptor (IR), which has an extracellular and intracellular domain.<sup>17</sup> Intracellular domain possesses tyrosine-specific protein kinase activity, which activated by insulin binding, phosphorylates several intra-cellular proteins, specifically insulin receptor substrates (IRS) -1, -2, -3, and -4 (Figure 2). These phosphorylated IRSs lead to activation of multiple downstream signaling pathways and ultimately to activation of metabolic pathways, including increased uptake of glucose by muscle and fat, activation of glycogen synthesis, and suppression of gluconeogenesis by liver and lipolysis by fat.<sup>17</sup> In addition to carbohydrate metabolism, insulin has several other actions. Its principle effect on adipose tissue is to suppress lipolysis, increase uptake of fatty acids, and synthesize triglycerides, thus keeping circulating free fatty acid levels in check.<sup>18,19</sup> Elevated free fatty acids inhibit glucose utilization by peripheral tissues<sup>20</sup> and also increase hepatic gluconeogenesis. Disordered metabolism of fatty acids has been proposed

**Figure 2.** Insulin Signaling Pathways



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- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6), and leptin interfere with insulin signaling through crosstalk (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.<sup>17</sup>

as having a major effect on pathophysiology in diabetes.<sup>21</sup> 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  $\beta$ -islet cell dysfunction/destruction, but also involves action of insulin in the periphery. Although attention is usually focused on insulin, it is important to acknowledge the role counter-regulatory hormones (the "Yang") play to fully understand the pathophysiology of DM.

### **Type 1 DM**

In the majority of patients, Type 1 DM is an autoimmune disorder with selective destruction of the  $\beta$ -cells in the pancreatic islets, resulting in absolute insulin deficiency.<sup>22-24</sup> Autoantibodies are detected as epiphenomenon in 85%–90% of individuals in the beginning stages of the disease, but the immune damage is cell-mediated, involving CD4+ T cell dysfunction. Autoantibodies are directed against insulin, glutamic acid decarboxylase (GAD65), and tyrosine phosphatases. In a few patients, autoantibodies may have dissipated by the time of diagnosis, or an alternate pathway for destruction of pancreatic  $\beta$  cells is present. Although there are no good markers to predict impending development of Type 1 DM, the presence of these autoantibodies have been used to identify high-risk individuals.

### **Genetics of Type 1**

Type 1 DM develops in the background of 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 have begun to elucidate many of these genes.<sup>25,26</sup> Although the prevalence of Type 1 DM in Western populations is approximately 0.3%,<sup>27</sup> it increases to 6% if the father is affected and 3% if the mother is affected.<sup>28</sup> Although the risk of DM

is greater for the relatives of patients with Type 1 DM, > 85% of people who develop Type 1 DM do not have a first-degree relative with the disease.<sup>29</sup> The risk for an identical twin is estimated to be 30%–50%, suggesting a strong environmental effect.<sup>30-33</sup> These environmental factors have not been identified. There is a robust association between Type 1 DM and the major histocompatibility complex on chromosome 6, especially, with polymorphisms in Class II immune response genes (HLA-DR and HLA-DQ).<sup>34,35</sup> Specific alleles of both HLA-DR and HLA-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, thereby sensitizing them to auto-antigens. 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), and pernicious anemia (vitamin B12 deficiency).<sup>36</sup>

### **Type 2 DM**

Type 2 DM, also known as non-insulin dependent DM or adult-onset DM, is associated with impairments in both insulin action (insulin resistance) and insulin secretion.<sup>37</sup> Insulin resistance requires elevated levels of insulin for glucose and lipid homeostasis; a person can maintain normoglycemia as long as his or her pancreas can increase the production of insulin. However, in predisposed individuals, over time the  $\beta$ -cells are unable to increase insulin production to the levels required to compensate for insulin resistance, a condition occasionally called " $\beta$ -cell exhaustion," resulting in increasing hyperglycemia and finally, diabetes.

### **Insulin Resistance**

It is likely that several processes, such as elevations in free fatty acid levels, increases in inflammation of tissues, and rising counter-

regulatory hormones lead to the development of insulin resistance.

Obesity can predispose a person to develop insulin resistance, and thereby Type 2 DM, by causing insulin resistance via several mechanisms, though many of these mechanisms remain to be elucidated.<sup>38</sup> One of the mechanisms attributed to increased insulin resistance in obesity was decreased insulin receptor tyrosine kinase activity in the skeletal muscle<sup>39</sup> and possibly other tissues.<sup>40,41</sup> Weight loss improves the activity of insulin receptor tyrosine kinase.<sup>42</sup> 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.<sup>43,44</sup> Another hypothesis posits that substances secreted by adipose tissue cause tissues to become insulin resistant. These substances include fatty acids, as well as pro- and anti-inflammatory adipocytokines such as leptin, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), adiponectin, etc.<sup>45</sup> Some products, such as free fatty acids, may create a vicious cycle whereby 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. At least some of the defects related to obesity seem to be acquired and partially reversible.<sup>46</sup> Adipose tissue may also secrete factors that are beneficial for insulin sensitivity, such as adiponectin, and the fall in their levels may be contributory.

Glucose toxicity results from chronic exposure of the pancreatic islet cells to supraphysiological concentrations of glucose in the blood leading to cellular dysfunction.  $\beta$ -cell toxicity, which is to some extent reversible, may become irreversible over time.<sup>47</sup> In addition, in animals, hyperglycemia is also associated with insulin resistance by decreasing glucose transport

into the cells.<sup>48,49</sup> Thus, high glucose concentrations can cause secretory defects as well as increase insulin resistance, but with timely treatment, this could 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.<sup>50-52</sup> The protein component of these deposits was found to be the  $\beta$ -cell secretory product amylin.<sup>53,54</sup> However, the mechanism for the initiation of amyloid formation and deposition in the islets is not yet clear. It may have both genetic and environmental etiology.<sup>55</sup> A number of types of insulin secretory abnormalities have been described in Type 2 DM, including the timing and intensity of response to glucose challenge and other secretagogues.<sup>56-64</sup>

### ***Genetics of Type 2***

Type 2 DM has a stronger genetic predisposition than Type 1 DM,<sup>26,65</sup> with superimposed environmental influences.<sup>66-69</sup> Several aspects of development of Type 2 DM are under genetic control, including intra-abdominal obesity, insulin resistance, and insulin secretory defects.<sup>70-78</sup> Studies on monozygotic twins show an extremely high concordance rate of close to 90%, which is much higher than that of Type 1 DM, suggesting higher heritability.<sup>79</sup> Although environmental issues are also important, unlike Type 1 DM, more information about some of the environmental influences is available. These include increased centripetal obesity, development of hypertension and dyslipidemia, and a sedentary lifestyle.

### **CLINICAL PRESENTATION**

In general, Type 1 DM patients present in a more acute and dramatic fashion than do Type 2 DM patients, which is usually more insidious in presentation. In both cases, the commonest 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.

### **Type 1 DM**

Type 1 DM, although 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, this could progress to ketoacidosis with tachypnea, tachycardia, hypotension—a condition called diabetic ketoacidosis (DKA)—and may lead to an altered mental state and coma. Frequently, an intercurrent illness or 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 autoimmune diseases, or have had damage (typically caused by 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-onset disease, although increasing numbers of children and young adults are being diagnosed with this disease. The disease can evolve over several years and the natural history may differ between patients. Many patients with Type 2 DM are older than 40, overweight or obese, with an increased waist circumference (a surrogate marker for visceral fat accumulation).<sup>80</sup> The presence of metabolic syndrome markers (e.g., increased waist-to-hip ratio, hypertension, low levels of high-density lipoprotein [HDL] cholesterol, impaired fasting glucose) is strongly predictive of development of Type 2 DM.<sup>81</sup> Although insulin resistance is the primary cause for 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 noticeable symptoms. However, this mild hyperglycemia and associated lipid and blood pressure abnormalities are not entirely benign as they increase the risk of macro- and microvascular complications; up to 20% of newly diagnosed Type 2 DM patients manifest signs of diabetic complications. With worsening hyperglycemia, symptoms of polyuria, weight loss, etc., may result in the condition coming to light. It is not uncommon for an intercurrent illness, such as stroke, myocardial infarction or infection, to also uncover diabetes. Rarely, acute severe hyperglycemia (over 1–2 days) can lead to a 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 but may appear in conjunction with other illnesses, such as acute myocardial infarction. Type 2 DM could be considered to evolve in two stages; Stage 1 is development of impaired glucose tolerance or impaired fasting glucose (also called as prediabetes) and Stage 2 is the development of overt diabetes (Table 2).

### **Gestational Diabetes**

GDM is a form of DM that has its initial onset during the later stage of the second trimester of pregnancy and resolves at the end of pregnancy. As many as 4% of pregnancies in the United States are complicated by the development of GDM. During pregnancy, GDM increases both fetal growth (macrosomia) as well as obstetric complications. Although screening guidelines differ among various groups of physicians, most agree that screening between 24 and 28 weeks of pregnancy in women who are obese, have a first-degree relative with diabetes, are older than 25, and come from a higher-risk



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

Test Criteria	Pre-Diabetes Mellitus	Overt Diabetes Mellitus
Fasting plasma glucose <sup>a</sup>	≥ 100 mg/dL	≥ 126 mg/dL
Plasma glucose post 75 g oral glucose tolerance test <sup>b</sup>	140–199 mg/dL	2 hours: ≥ 200 mg/dL
Random plasma glucose <sup>c</sup> with symptoms of hyperglycemia <sup>d</sup>	—	≥ 200 mg/dL

<sup>a</sup> Fasting defined as no caloric intake for 8 hours.

<sup>b</sup> Oral glucose tolerance test involves measurement of plasma glucose at specified time after consuming a glucose load of 75 or 100 g dissolved in water.

<sup>c</sup> Random plasma glucose defined as any time of the day without any temporal association to caloric intake.

<sup>d</sup> Symptoms of hyperglycemia include polyuria, polyphagia, polydipsia, and unexplained weight loss.

ethnic group (Hispanic, African American, or Native American) should be undertaken. Many of the risk factors and the pathophysiological processes for GDM are similar to those of Type 2 DM.<sup>82</sup> With increase in insulin resistance during the pregnancy, women who are susceptible to develop Type 2 DM due to a concomitant secretory defect may 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 will have a recurrence in future pregnancies, as well as a 30%–60% risk of developing established diabetes long term.<sup>83</sup> 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.<sup>84</sup> DKA is most common in

patients with Type 1 DM, although it can occur in patients with Type 2 DM as well; HHS is more common in patients with Type 2 DM. Although these conditions are discussed as separate entities, they are part of the same spectrum of diseases characterized by inadequate insulin. DKA results when there is *absolute* insulin deficiency, while HHS develops with *relative* insulin deficiency. However, they do differ in the degree of dehydration, ketosis, and metabolic acidosis. For both disorders, precipitating factors could be the same, including missed insulin doses, dehydration, infection, certain medications, or other major illnesses.<sup>85,86</sup> However, restricted water intake resulting from ill health or immobilization, compounded by altered thirst response, may contribute to dehydration and HHS in elderly patients with Type 2 DM.

### Diabetic Ketoacidosis

DKA is characterized by varying degrees of hyperglycemia, ketonemia, and metabolic acidosis.<sup>87</sup> When combined, these elements give rise to the clinical syndrome of DKA, which is associated with dehydration, electrolyte abnormalities, and altered sensorium.

Due to severe insulin deficiency, there is unchecked gluconeogenesis, glycogenolysis, and decreased glucose utilization resulting in hyperglycemia.<sup>88</sup> Gluconeogenesis is also fueled by increased availability of amino acids that are a result of increased catabolism, again due to decreased insulin. Elevated blood glucose results in increased plasma osmolality (hyperosmolar state) levels causing a shift of water from the intracellular space and intracellular dehydration. Increased plasma osmolality promotes osmotic diuresis, resulting in net loss of body water, 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

will contribute to acidosis. 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 free fatty acid production; these fatty acids are metabolized by the liver into ketone bodies (acetone, acetoacetate, and  $\beta$ -hydroxy butyrate, a source of energy for the heart and brain used during starvation).<sup>89</sup> Initially, the ketonemia may be mild as the body tries to metabolize these fatty acids.<sup>90,91</sup> As the acidosis from tissue hypoxia, with further reduced insulin action occurs, excessive numbers of ketone bodies are produced. Acidosis promotes movement of potassium from intracellular to extracellular space, from where it can 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, and increased 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, create a fertile ground for a prothrombotic state.<sup>92</sup>

### ***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. The levels of insulin required to inhibit lipolysis are much

lower than required to increase tissue uptake of glucose or inhibit gluconeogenesis. Since patients with Type 2 DM have this residual insulin, they are less likely to develop DKA but are prone to develop severe hyperglycemia and dehydration.<sup>93</sup> Other factors such as diuretic use, febrile illness, diarrhea, nausea, and vomiting can contribute to excessive volume losses. Mortality from HHS is higher in the presence of older age, comorbid conditions, and the severity of dehydration. While DKA begins rapidly within a few hours of precipitating events, HHS can be insidious in onset and may not be apparent until it is very severe.

Laboratory abnormalities include a significant hyperglycemia (typically  $> 500$  mg/dL), but no significant alteration in blood pH, increased blood osmolality, and either normo- or hypernatremia. Hypokalemia may be less severe and the goals of therapy in these patients are to restore circulatory volume and tissue perfusion, gradually reduce serum glucose (as rapid reduction may result in cerebral edema), and correction of electrolyte abnormalities. Precipitating causes such as infection should be identified and treated. Intravenous fluids and insulin infusion are 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. The following complications are responsible for considerable morbidity and mortality. These conditions 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 ten years after diagnosis.



**Table 3.** Chronic Complications of Diabetes Mellitus

Chronic Complication	Salient Features
<p>Eye disease:</p> <ul style="list-style-type: none"> <li>• Retinopathy</li> <li>• Macular edema</li> <li>• Cataracts &amp; glaucoma</li> </ul>	<p>Annual screening should begin at the time of diagnosis in patients with Type 2 DM and 5 years after the onset of Type 1 DM</p> <p>Retinopathy progresses in two stages: Nonproliferative and proliferative. Laser photocoagulation of retina is the major modality of treatment to prevent further loss</p> <p>These conditions are more common in patients with DM, occurring at a younger age and progressing faster than usual</p>
<p>Kidney disease:</p> <ul style="list-style-type: none"> <li>• Nephropathy</li> <li>• Renal Failure</li> </ul>	<p>Annual screening of urine for microalbumin</p> <p>Microalbuminuria (30–300 mg/24 hours), potentially reversible</p> <p>Overt proteinuria (&gt; 300 mg/24 hours) irreversible</p> <p>Major cause of renal failure and dialysis requirement</p>
<p>Generalized symmetric neuropathy:</p> <ul style="list-style-type: none"> <li>• Acute sensory</li> <li>• Chronic sensorimotor</li> <li>• Autonomic</li> </ul> <p>Focal or multifocal neuropathy:</p> <ul style="list-style-type: none"> <li>• Cranial, truncal</li> <li>• Diabetic amyotrophy</li> </ul>	<p>Annual screening for neuropathy by examination of feet using monofilament testing</p> <p>Podiatry referral for custom footwear should be considered in all patients with neuropathy</p> <p>Pharmacotherapy management of pain remains a challenge</p>
<p>Coronary artery, peripheral arterial, and cerebrovascular disease</p>	<p>Cardiovascular disease leading cause of premature death in Type 2 DM</p> <p>Well-developed treatment guidelines and medications for lipid and blood pressure management</p> <p>Smoking cessation is vital</p>
Infections	Strict glycemic control reduces the chance for infections
Skin changes	<p>Most are self-limiting</p> <p>Skin infections can be prevented with good glycemic control</p> <p>Moisturizing can prevent dryness of the skin</p> <p>Necrobiosis lipoidica seen occasionally in Type 1 DM patients</p>
Gum and periodontal disease, tooth loss	Poor oral health associated with increased cardiovascular morbidity/mortality
Hearing loss	Increased sensorineural hearing loss
Osteoporosis	No evidence-based guidelines for management, risk of bone loss increased by DM
Musculoskeletal complications	<p>Stiff joints and arthralgias much more common than previously suspected</p> <p>Diabetic cheiro-arthropathy, flexor tenosynovitis, Dupuytren's contracture, and Charcot's joints (secondary to neurological deficits) require some intervention</p>

### Microvascular Complications

Large, randomized clinical trials of individuals with Type 1 or Type 2 DM, such as the Diabetes Control and Complications Trial

(DCCT)<sup>94</sup> and the UK Prospective Diabetes Study (UKPDS),<sup>95</sup> have conclusively demonstrated that reducing chronic hyperglycemia prevents or delays these complications (Table 3).

It must be noted that not all individuals with poor glycemic control develop these complications, suggesting that other factors, such as genetics or environment, may modulate their development.

### **Ophthalmic Complications**

Diabetic retinopathy is the leading cause of blindness in individuals between the ages of 20 and 74. Nonproliferative retinopathy 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. It is present in almost all individuals who have had DM for more than 20 years. Neovascularization in response to retinal hypoxia is characteristic of proliferative retinopathy. These newly formed blood vessels lack sufficient integrity, rupture easily, resulting in intra-vitreous hemorrhage, and subsequently lead to fibrosis and retinal detachment.

Intensive glucose control from the time of DM diagnosis is necessary for the prevention of onset and progression of retinopathy. An annual exam for early detection and laser photocoagulation (panretinal or focal) can delay or prevent blindness.

### **Renal Complications**

DM is the most common cause of renal failure in United States. The earliest pathological changes alter microcirculation, causing structural changes in the glomerular matrix, thereby increasing glomerular filtration rate (GFR). This increases excretion of small amounts of albumin in the urine (microalbuminuria 30–300 mg/day). Approximately 50% of these individuals will progress to overt proteinuria (300 mg to 1 g/day) or nephrotic syndrome (urine protein > 1 g/day). Urinary protein excretion is considerably exacerbated by uncontrolled hypertension, and the combination of diabetes and hyper-

tension is the most frequent predisposing factor for endstage renal disease.

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.

### **Neurological Complications**

Approximately half of patients with Type 1 or Type 2 DM will develop neuropathy. It is usually a symmetrical sensory polyneuropathy but may also be a focal mononeuropathy and/or an autonomic neuropathy, with loss of both myelinated and unmyelinated nerve fibers. Up to 50% of individuals with neuropathy may not be symptomatic.<sup>96</sup>

Generalized symmetrical polyneuropathy is the most common manifestation and can involve sensorimotor somatic nerves; however, distal nerves of hands and feet are most commonly affected in a “glove-and-stocking” distribution. Symptoms include pain, tingling, and numbness, and physical exam reveals loss of fine touch, vibration, and position sense. This may later progress to wasting of small muscles of the hands and feet, resulting in Charcot’s joints and sensory ataxia. Mononeuropathy is associated with pain and weakness in one nerve distribution that is self-limiting. Diabetic amyotrophy, seen mainly in elderly Type 2 patients, is associated with pain in the lower limbs followed by muscle weakness in major muscles of the buttocks and thighs. It is a self-limiting condition, resolves in 12 to 24 months, and treatment is supportive. Autonomic neuropathy, though not well diagnosed, can affect all the major organ systems. Multiple cardiovascular abnormalities are noted, including resting tachycardia, diminished heart rate variability, reduced heart

rate and blood pressure response to exercise, and development of postural hypotension. The typical pain response to cardiac ischemia is lost, leading to “silent myocardial ischemia/infarction.” Altered small- and large-bowel motility (constipation or diarrhea) and gastroparesis (anorexia, nausea, vomiting, and bloating) are frequent manifestations of gastrointestinal system involvement. Genitourinary systems are also involved and present with bladder hypotonia (incomplete emptying, dribbling, and overflow incontinence), erectile dysfunction, and female sexual dysfunction. Abnormal sweat production may result in xerosis, cracking of skin, and decreased sweating in response to hypoglycemia. In addition, entrapment syndromes (e.g., carpal tunnel syndrome) are also common among diabetics.

Tight glycemic control from the time of onset of DM is necessary to prevent diabetic neuropathy. Treatment is difficult once neuropathy affects various organ systems. For symptomatic treatment of painful neuropathy, several therapies have been tried with limited efficacy and include tricyclic antidepressants, anticonvulsants, selective serotonin and norepinephrine reuptake inhibitors, and topical therapies. 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 related more to coexisting conditions such as dyslipidemia and hypertension.

Cardiovascular disease risk is increased in individuals with Type 2 DM by two-fold and four-fold in women. It is unclear if patients with Type 1 DM are also at high risk of cardiovascular complications. The presence of Type 2 DM is now counted by the American Heart Association and the American Diabetes Association as a major cardio-

vascular risk factor, the equivalent of having had a cardiovascular event in the absence of diabetes. Additionally, some patients with DM may suffer silent myocardial ischemia or infarction, which often does not manifest itself by chest pain or other symptoms that are typical of coronary artery disease. The presence of insulin resistance is associated with an increased risk of cardiovascular complications in individuals both with and without DM. Individuals with insulin resistance and Type 2 DM have elevated levels of plasminogen activator and fibrinogen, which enhance the coagulation process and impair fibrinolysis, thus favoring the development of thrombosis. Cardiovascular risk is increased when either retinopathy, nephropathy, hypertension, or dyslipidemia coexist with DM.

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 cardiovascular disease and nephropathy. Management includes aggressive control of blood pressure and may require multiple medications.

As a preventive measure, aspirin should be prescribed for all Type 2 DM patients, unless contraindicated.

### **Miscellaneous Complications**

Elaborated below are several other complications of DM.

### **Infections**

DM is associated with greater frequency and severity of common infections; in addition, some infections are seen exclusively in patients with DM. Hyperglycemia

results in impaired white blood cell function and enhances the colonization and growth of various bacterial and fungal species. Bacterial infections such as styes, boils, and carbuncles are most common. Frequently seen fungal infections include intertrigo caused by *Candida albicans*, and ringworm infections.

### ***Dermatologic Manifestations***

Dermatologic problems are common in diabetes, with approximately 30% of patients experiencing some cutaneous involvement during the course of illness. Several skin conditions are more common among patients with DM, including bacterial infections, fungal infections, and itching, but these 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; they may even precede DM diagnosis by several years.<sup>97</sup>

Some conditions occur exclusively in patients with DM. Diabetic dermopathy is an asymptomatic, benign condition that arises due to small vessel changes and presents as oval or circular pigmented and scaly patches on the legs. Necrobiosis lipoidica diabetorum is another disease caused by changes in blood vessels. 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 dermopathy, can be itchy and painful, and can ulcerate. There are no proven treatments, but occlusive steroid dressings have been used to prevent ulceration and breakdown of the skin. Bullous diabetorum is a condition in which blisters can occur on the backs of hands and feet, and are self-limiting. A 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.

Fungal skin infections, as well as vitiligo, etc., occur more frequently in patients with diabetes.<sup>97</sup>

### ***Complications Related to Bones***

Osteoporosis is the most underappreciated complication of DM.<sup>98</sup> The association of osteoporosis and fracture risk with Type 1 DM is relatively noncontroversial.<sup>99</sup> For subjects with Type 2 DM, general bone density seems to be preserved. However, there is an increased risk of fracture that has been attributed to several causes, including falls following hypoglycemia, poor balance due to diabetic neuropathy, foot ulcers and amputations, poor vision due to cataracts and retinopathy, and orthostatic hypotension.

### ***Periodontal Disease***

Oral health is now increasingly recognized as an important part of diabetes management; there is a mutually reciprocal relationship between glycemic control and oral health. Periodontal infection worsens metabolic control of DM while improving oral hygiene enhances glycemic control.<sup>100,101</sup> People with poorly controlled DM are more likely to develop periodontal disease, dry mouth, dental abscess and fungal infections, and slow wound healing.<sup>102</sup>

### ***The Diabetic Foot***

The key causes of diabetic foot problems are neuropathy, vasculopathy, or both, usually on a background of poor glycemic control. Other factors that exacerbate this are hypertension and smoking. Approximately 15% of diabetic patients may experience foot ulceration in their lifetime. In addition, foot deformities from muscle weakness and visual defects add to the predisposing factors for foot injury. Preventive care is essential and should include not only professional care (Table 4), but also care by the individual on a day-to-day basis. Daily inspection of the feet and wearing clean, soft

**Table 4.** Comprehensive Principles for Preventing DM Complications

<p>Lifestyle changes:</p> <ul style="list-style-type: none"><li>• Diet: Sugar-free diet for Type 2 DM; no restrictions for Type 1 DM<ul style="list-style-type: none"><li>◦ Fat 20%–35% of total calorie intake; saturated fat &lt; 7% of calories, &lt; 200 mg/dL dietary cholesterol</li></ul></li><li>• Exercise: At least 150 minutes/week of aerobic physical activity</li><li>• Optimum weight (BMI &lt; 25)</li><li>• Smoking cessation</li></ul>
<p>Modifiable risk factors:</p> <ul style="list-style-type: none"><li>• Glycemic control:<ul style="list-style-type: none"><li>◦ Glycosylated hemoglobin—measured at least twice a year (HbA1c &lt; 7%)</li><li>◦ Self-monitoring of blood glucose (SMBG)—no recommended optimal frequency, but probably should be measured 3–4 times a day in patients who are insulin-treated (pre-prandial plasma glucose 90–130 mg/dL, 2-hour postprandial plasma glucose of &lt; 180 mg/dL)</li></ul></li><li>• Lipid management (LDL &lt; 100mg/dL, optimal goal &lt; 70mg/dL; HDL &gt; 45mg/dL in men and &gt; 55 mg/dL in women; triglycerides &lt; 150mg/dL)</li><li>• Blood pressure control (&lt; 130/80 mmHg; &lt; 125/75 mmHg preferred in those with nephropathy)</li><li>• Aspirin prophylaxis (primary prevention in diabetics over the age of 40)</li></ul>
<p>Preventive care:</p> <ul style="list-style-type: none"><li>• Annual screening<ul style="list-style-type: none"><li>◦ Screening for microalbuminuria</li><li>◦ Annual eye exam</li><li>◦ Podiatric exam</li></ul></li><li>• Annual influenza vaccination</li><li>• Pneumococcal vaccination</li></ul>

socks and properly fitting shoes are among many precautions one could take to prevent foot ulceration. Once the ulcer is formed, antibiotics, relief of pressure to the ulcerated area, control of blood glucose, and efforts to improve blood flow form the mainstay of treatment.

At present, there is no unifying mechanism to account for the pathogenesis of diabetic complications. It seems likely that several different mechanisms are involved.

**DIAGNOSIS OF  
DIABETES MELLITUS**

Criteria for diagnosis of DM are based on plasma glucose levels and symptomatology. The threshold values for plasma glucose were not chosen arbitrarily, but due to their ability to predict retinopathy.<sup>103,104</sup> The diagnosis of diabetes is met if fasting plasma glucose level is > 126 mg/dL, 2-hour post-oral glucose tolerance test is 200 mg/dL, or random blood glucose is > 200mg/dL with clinical symptoms in an otherwise stable

subject. Although these cutoff values are useful for clinical management, it should be pointed out that there is a continuous progression in the level of glucose from normal to impaired glucose to diabetes. Subjects with impaired glucose levels have been shown to have increased cardiovascular risk, thus these biochemical definitions are likely to undergo revision in the future.

**MANAGEMENT OF  
DIABETES MELLITUS**

The goals of managing DM should be to achieve near-normal glucose homeostasis, prevent progression of the disease, and avoid long-term complications. 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 needs to include teaching good dietary habits and nutrition, weight loss and

exercise, self-monitoring of blood glucose (SMBG), awareness of acute and chronic complications and how to prevent them, treatment options, and insulin administration (if applicable). Patients also need to be taught to recognize and treat hypoglycemia and modify lifestyle choices, such as smoking cessation.

### **Lifestyle Modification**

Medical nutrition therapy (MNT) and exercise are central components to the management of DM. Patient education regarding these aspects should be continuous and reinforced at every healthcare visit. Although the role of diet in managing Type 1 DM is not as critical as it is for Type 2 DM, attention to calorie intake and a heart-healthy diet is still important.

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), managing existing Type 1 and Type 2 DM (secondary prevention), and preventing complications of DM (tertiary prevention). Goals of MNT should be individualized, and diets should be balanced with respect to fat, protein, and carbohydrate content, and should include fruits, vegetables, and fiber. For Type 2 DM patients, avoidance of dietary sugar is mandatory, whereas for Type 1, this needs to be tempered as well as matched with insulin delivery. Monitoring carbohydrate intake, through carbohydrate counting or food exchanges, is essential for achieving glycemic control. Mixed meals (those with protein/carbohydrate/fat combination) decrease postprandial excursion of blood glucoses; low-glycemic index foods (associated with lower postprandial rise in blood glucoses) may improve glycemic control. Patients who are on insulin should learn to estimate carbohydrates in their diet and match insulin dose to carbohydrates.

In overweight and obese individuals, even modest weight loss of 5%–10% is

associated with improvement in insulin resistance, and will prevent development of DM in individuals with prediabetes or improve treatment requirements in those who already have DM. Increase in physical activity is also an essential component, especially to maintain the weight loss achieved by dietary modification. Weight loss medications may be considered as these can help achieve weight loss of 5%–10% as recommended, but the effects may be short-lived, especially if lifestyle changes are not implemented. Exercise is essential to maintain weight loss, improve physical fitness, and reduce plasma glucose concentrations. Bariatric surgery is growing as a choice and has some scientific support for efficacy.<sup>105</sup> Older diabetics starting a new exercise program may need to have medical clearance due to a high prevalence of asymptomatic cardiovascular disease.

Certain dietary restrictions may be necessary once complications set in (e.g., limiting protein intake to 0.8 g/kg of body weight per day may be essential in patients with overt diabetic nephropathy with proteinuria).

### **Monitoring the Level of Glycemic Control**

Long-term assessment (every three months) of glycemic control is made by measuring levels of glycosylated hemoglobin (HbA1c) in a clinical setting. Blood glucose leads to a nonenzymatic glycosylation of hemoglobin. There is a relationship between HbA1c and average blood glucose levels that allows for the overall level of glycemic control to be assessed clinically. Since the mean erythrocyte (and its hemoglobin) life span is 120 days, HbA1c levels are taken to represent the mean glycemic control over the past three months. In general, target HbA1c should be < 7% (mean blood glucose of ~150 mg/dL), but it may be individualized with both lower and higher goals being acceptable in some patients. SMBG with the help of glucometers (long the standard of care for Type 1 DM



patients) is important when insulin is used as daily treatment to help with insulin dosing and to prevent hypoglycemia. Continuous glucose monitoring systems are a new method that can be used to monitor glycemic control. These systems measure glucose in interstitial fluid that is in equilibrium with blood glucose.

### Pharmacologic Treatment

Insulin is the required treatment for Type 1 DM (oral agents are not indicated for Type 1 DM), whereas patients with Type 2 DM can be managed with diet alone or may require oral hypoglycemic agents and/or insulin. For the latter, multiple-agent use is common and includes pharmacotherapy for cardiovascular risk factor management. Oral agents, summarized in Table 5, can work to stimulate  $\beta$ -cells to secrete insulin (sulfonylureas, miglitinides); sensitize response to insulin (thiazolidinediones, biguanides); inhibit intestinal glucose absorption (alpha-glucosidase inhibitors); or improve incretin function that results in increased insulin and decreased glucagon secretion (gliptins or incretin-mimetics). These agents and their major effects can have other benefits as discussed below. For insulin therapy, there are now many types of insulins that allow differing onset, peak, and duration-of-action times as well as delivery systems. All of the insulins used currently are synthetic with animal-derived insulins being rarely used.

### Oral Antidiabetic Agents

**Sulfonylureas:** These time-honored drugs have been available since the 1950s, and although some older-generation agents (e.g., glyburide) continue to be used, the more common first-line agents are glipizide and glimepiride. Unlike glyburide, which is excreted primarily via the kidneys, glipizide and glimepiride are metabolized in the liver and are safer for patients with deteriorating renal function. The sulfonylureas, dosed

once or twice a day, result in increased insulin secretion from  $\beta$ -cells by binding to the sulfonylurea receptor. The major side effect of these agents is hypoglycemia, especially when used in combination with other agents, or if there is extant renal or liver disease. These agents (along with metformin, see below) are the most frequently prescribed agents for Type 2 DM and are now generic.

**Miglitinides:** These agents (repaglinide, nateglinide) also stimulate the sulfonylurea receptor, but have very different pharmacokinetics; they bind, stimulate, and have a very short action time, allowing these agents to be used as “real-time” agents. These drugs are particularly useful in the elderly or in subjects for 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, adipose tissues). This group includes the biguanide metformin (the action of which is to inhibit hepatic gluconeogenesis, along with improving skeletal muscle uptake of glucose) as well as the 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 because it promotes weight loss or weight maintenance (an issue for most Type 2 DM patients). However, the major side effect of GI upset (pain and/or diarrhea) can limit its use. Additionally, a potential side effect is lactic acidosis, an effect that can occur in the context of significant major organ (kidney, liver or heart) failure. These adverse effects, however, are almost negligible when metformin is used per prescribing guidelines. Because metformin is excreted via the kidneys, it is not used in subjects with renal impairment. Its use is suspended when intravenous-contrast agents need to be used for radiologic purposes as contrast nephropathy can result.

**Table 5.** Oral Hypoglycemic Agents

Agent	Characteristics	Adverse Effects
	<b>Insulin Secretagogues</b>	
Sulfonylureas: —Glipizide —Glyburide —Glimepiride	<ul style="list-style-type: none"> <li>Bind and activate the sulfonylurea receptor on <math>\beta</math>-cells</li> <li>Duration of action and daily doses vary by agent</li> <li>May be excreted by liver (glimepiride, glipizide) or kidneys (glyburide)</li> </ul>	<ul style="list-style-type: none"> <li>Hypoglycemia</li> <li>Weight gain</li> </ul>
Meglitinides: —Repaglinide —Nateglinide	<ul style="list-style-type: none"> <li>Bind and activate the sulfonylurea receptor on <math>\beta</math>-cells</li> <li>Short duration of action, quick onset of action, can be taken 15 min before meals to target postprandial hyperglycemia</li> <li>Contraindicated in those with gastroparesis and chronic renal insufficiency</li> </ul>	<ul style="list-style-type: none"> <li>Generally none, but possible hypoglycemia</li> </ul>
	<b>Insulin Sensitizers</b>	
Biguanide: —Metformin	<ul style="list-style-type: none"> <li>Exact mechanism not characterized, likely is a low-grade mitochondrial poison and leads to activation of AMP kinase</li> <li>Decreases hepatic gluconeogenesis and increases peripheral glucose uptake</li> <li>Contraindicated in renal insufficiency (GFR &lt; 40 mL/min), age over 80, heart failure, hepatic failure, alcohol abuse, acute illness</li> <li>Promotes modest weight loss and has a low risk for hypoglycemia</li> </ul>	<ul style="list-style-type: none"> <li>GI distress with diarrhea, nausea, crampy abdominal pains, and dysgeusia</li> <li>Rarely, lactic acidosis can develop in patients with renal insufficiency</li> <li>Can cause contrast nephropathy</li> </ul>
Thiazolidinediones: —Pioglitazone —Rosiglitazone	<ul style="list-style-type: none"> <li>Activate nuclear transcription factor peroxisome proliferator-activated receptor-gamma (PPAR-<math>\gamma</math>)</li> <li>Improve peripheral glucose uptake in skeletal muscle and fat and reduce free fatty acid levels thus reducing insulin resistance</li> <li>Take up to 6–12 weeks to attain optimal therapeutic effect</li> <li>Contraindicated in those with heart failure</li> <li>No significant risk of hypoglycemia</li> </ul>	<ul style="list-style-type: none"> <li>Weight gain</li> <li>Fluid retention, may precipitate congestive heart failure in susceptible individuals</li> <li>Possible increase in risk of bone loss</li> </ul>
	<b>Agents that Decrease Glucose Absorption</b>	
Alpha-glucosidase inhibitors: —Acarbose —Miglitol	<ul style="list-style-type: none"> <li>Inhibit alpha-glucosidase in the gut and thus prevent breakdown of some complex carbohydrates into simple sugars, which then cannot be absorbed</li> <li>Prevent post-prandial glucose excursions</li> </ul>	<ul style="list-style-type: none"> <li>Bloating, diarrhea, and flatulence due to action of colonic bacteria on undigested carbohydrates</li> <li>Possible angioedema in rare cases</li> </ul>
	<b>Agents that Augment Incretin Pathways</b>	
Dipeptidyl peptidase IV inhibitor: —Sitagliptin	<ul style="list-style-type: none"> <li>Inhibit degradation of native GLP-1 and GIP, enhancing incretin effect</li> <li>Clinical experience with this agent is limited</li> </ul>	<ul style="list-style-type: none"> <li>Well tolerated and safe in renal failure</li> <li>Possible angioedema</li> </ul>
GLP-receptor agonist: —Exenatide	<ul style="list-style-type: none"> <li>Injectable only</li> <li>Acts by mimicking incretins</li> <li>Can act centrally as well as peripherally</li> <li>Causes satiety and leads to weight loss</li> </ul>	<ul style="list-style-type: none"> <li>Rash, skin reactions</li> <li>Nausea</li> <li>Pancreatitis has been reported</li> </ul>

Thiazolidinediones act in adipose and muscle tissues to sensitize the action of insulin. Like metformin, these agents have 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 (due to fluid retention as well as adipose tissue increase), and they have been associated with potential bone loss, limiting widespread use. However, in subjects with considerable insulin resistance, they are particularly useful in limiting the need for insulin therapy.

**Alpha-Glucosidase Inhibitors:** These act by decreasing glucose absorption from the intestine. Major side effects include intestinal upset (e.g., diarrhea and flatulence); high cost also limits their use.

**Incretins and Incretin-Mimetics:** Incretins are hormones that upon dietary challenge, amplify glucose-stimulated insulin secretion, decrease glucagon action, and may improve islet cell health (the latter has been demonstrated only in animal models).<sup>106</sup> 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. In response to nutrients, these stimulate insulin secretion in a glucose-dependent fashion, thereby inhibiting glucagon secretion, slowing gastric emptying, reducing appetite, and improving satiety. They act by binding to their cognate receptors and are inactivated in the blood stream by dipeptidyl peptidase IV (DPP-IV). One FDA-approved inhibitor to DPP-IV activity is the drug sitagliptin; others (e.g., vildagliptin, alogliptin) are likely to be approved in the near future. Because the mechanism of action is related, one injectable agent, exenatide, is discussed here because it also uses the incretin pathway. This drug was identified as the active ingredient that causes hypoglycemia in the saliva of the Gila monster. Exenatide binds and

activates the GLP-1 receptor in the hypothalamus to suppress feeding and increase satiety, in addition to action in the periphery. Sitagliptin is generally well tolerated but has not been on the market long enough to conclude it is generally safe. Exenatide is also generally well tolerated; nausea, vomiting, and diarrhea are common but may be transitory with continued use. Rarely, pancreatitis has been reported with exenatide.

**Combination Therapy:** It is common (often necessary) to use combination therapy in the management of Type 2 DM. Using 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, insulin sensitizer, and DPP-IV inhibitor are used. Metformin and thiazolidinediones can be used together as they target different tissues to improve insulin sensitivity and act via different pathways. With all combination therapies, the risk of hypoglycemia is increased and may require appropriate dose titration. In general, once insulin therapy is initiated, most oral agents, except for insulin sensitizers, are discontinued.

### ***Insulin Therapy***

For Type 1 DM patients, insulin is the mainstay and in the majority of 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; it can also be used as the sole therapy for Type 2 DM patients. Many patients with Type 2 DM will need insulin as the disease progresses and the oral hypoglycemic agents fail to achieve good control of blood sugars. Although early insulins were extracted from bovine or ovine pancreata, all of the currently

used insulins are recombinant and range from generic regular and isophane (NPH), to the more expensive analogs (Table 6). Each of these insulins has a relatively predictable onset, peak, and duration of action. The choice of insulin and method of administration is based on patient characteristics, costs, and health insurance. The type and regimen used is individualized to control blood sugar and minimize hypoglycemia. No currently available insulin regimen can mimic the way the endogenous pancreas releases insulin. A favored regimen is a basal insulin, supplemented with bolus insulin, to cover meals. The newer long-acting insulins, such as once-daily administered glargine and detemir, allow for a basal profile, though NPH given twice a day can also accomplish this task. Mealtime insulins are given with each meal and typically use the newer analogs (aspart, lispro or glulisine), which are fast-acting and have a short duration of action (< 3 hrs), but regular insulin can also be used. Insulins are self-administered with a

calibrated syringe and ultra-fine needles, although devices, such as a pen or continuous pump are available. Continuous subcutaneous insulin infusion (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 needle stick (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 three days. This system is probably the closest of all available technologies to mimicking the secretion of insulin by the pancreas. The rate of infusion can be set automatically for several segments throughout the day, and the pump can be programmed for multiple basal rates during the 24-hour cycle, based on exercise and activity level. The pump is an open-loop system, requiring the pump-wearer to decide how much basal or bolus dose to be given. In addition to eliminating

**Table 6.** Different Types of Insulin and Their Profiles

Type of Insulin	Characteristics	Action in Hours
Rapid-acting insulin: —Lispro —Aspart —Glulisine	<ul style="list-style-type: none"> <li>• Analog insulins</li> <li>• Altered amino acid sequence promotes insulin monomers that are rapidly absorbed</li> <li>• Injected shortly before meals</li> <li>• Shorter duration of action results in fewer hypoglycemic episodes</li> </ul>	Onset of action: < 1 hr Peak action: 1–2 hrs Duration of action: 2–3 hrs
Short-acting insulin: —Regular	<ul style="list-style-type: none"> <li>• Soluble human insulin, generic</li> <li>• Injected 30–60 minutes before meals for optimal action, failing to do so results in postprandial hyperglycemia</li> <li>• Less convenient than rapid-acting analogs</li> </ul>	Onset of action: 0.50–1 hr Peak action: 2–4 hrs Duration of action: 4–6 hrs
Intermediate-acting insulin: —NPH (isophane suspension)	<ul style="list-style-type: none"> <li>• Formed by adding protamine to human insulin, generic</li> <li>• Acts as both basal and bolus insulin due to a peak at 4–6 hrs</li> <li>• Hypoglycemia a problem due to these peaks</li> </ul>	Onset of action: 2– 3 hrs Peak action: 4–6 hrs Duration of action: 6–8 hrs
Long-acting insulin: —Glargine —Detemir	<ul style="list-style-type: none"> <li>• Insulin analogs</li> <li>• Lesser incidence of hypoglycemia than NPH insulin</li> <li>• Glargine: Provides consistent level in plasma over long duration</li> <li>• Detemir: Binds to albumin via fatty acid chain, hence slower absorption and consistent levels, shorter duration than glargine</li> </ul>	Onset of action: 1– 4 hrs Peak action: none Duration of action: up to 22 hrs

multiple daily injections, it can deliver small amounts of insulin with great accuracy, thereby reducing the risk of hypoglycemia. However, like all regimens, its success is user-dependent and requires some self-discipline.

### **Other Therapies**

**Pramlintide:** Amylin is a hormone that is usually cosecreted with insulin in response to glucose by pancreatic beta cells. Its effects are mostly on the gut and include suppression of glucagon secretion, slowing 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 a deficiency of amylin as well as insulin. Pramlintide, a synthetic amylin analogue, is currently approved for use along with insulin in patients with Type 1 and Type 2 DM. It is given before meals, usually in conjunction with prandial insulin, but in a separate subcutaneous injection. Side effects include nausea and vomiting, especially at higher doses. A frequent dosing schedule (3 times daily) also makes it inconvenient for many patients. Because of its effect on promoting weight loss, pramlintide seems to be most attractive for patients who are overweight. Insulin dose may need to be reduced due to increased risk of hypoglycemia.

**Exenatide:** See **Incretins**, above.

**Transplantation:** Transplanting the whole pancreas (common) or isolated islet cells (experimental) is a treatment option for patients with Type 1 DM. Solid-organ pancreas transplantation is usually carried out in conjunction with renal transplant (thus most patients are those who have renal failure), as the treatment necessitates taking antirejection medications that have potential side effects. Both forms of transplantation eliminate or reduce the need for intensive insulin therapy, which has been associated with severe hypoglycemia, to attain near normal glycemic

control.<sup>107</sup> Whole pancreas transplantation, either performed alone or in combination with kidney transplantation, is limited by organ availability, graft failure, surgical complications, and morbidity associated with immunosuppressive therapy.<sup>108</sup> Improvements in surgical techniques and immunosuppressive therapy regimens have helped reduce morbidity and mortality, making this a viable therapeutic alternative for treating DM.<sup>109</sup>

The greatest promise of islet cell transplantation is the possibility of immunosuppression-free transplantation, allowing patients to avoid the high side effects associated with antirejection medications. Currently, this procedure is experimental. Major potential adverse effects from islet cell transplantation include failure from rejection, as well as side effects associated with anti-rejection drugs (e.g., increased risk of long-term immune suppression, steroid-induced bone and skin changes, certain malignancies, atherosclerotic disease).

### **Pregnancy and DM**

Maternal hyperglycemia at the time of conception from either Type 1 or Type 2 DM greatly increases the risk of spontaneous miscarriage and elevates risk of morbidity and mortality to both mother and fetus.<sup>110,111</sup> In addition, DM in pregnancy is an independent risk factor for pregnancy-induced hypertension and pre-eclampsia.<sup>82</sup> Uncontrolled blood glucose in the last trimester is associated with fetal macrosomia (due to high blood glucoses reaching the fetus and stimulating fetal insulin production, which increases fetal growth), polyhydramnios (increased amniotic fluid due to high blood glucoses), and sudden fetal death. Intensive control of DM from the prepregnancy period throughout the pregnancy, along with aggressive fetal surveillance and perinatal care can improve outcomes.<sup>82</sup> Control of blood glucose during this period is now regarded as a standard of care. Insulin is the preferred

treatment for managing DM during pregnancy, not only in Type 1 DM, but also in those with Type 2 DM or GDM in which diet therapy alone does not result in good control. Insulin requirements drop precipitously in the immediate postpartum period, so necessary adjustments should be made. Although there is evidence from clinical trials that oral hypoglycemic agents may be used under some circumstances in pregnant women with Type 2 DM, these are not FDA-approved at this time.

### Hypoglycemia

This is the most common daily complication that can occur in patients with Type 1 or Type 2 diabetes. Hypoglycemia results when blood glucose levels fall below 65 mg/dL, though the onset of symptoms can vary. Almost all hypoglycemia events in a diabetic subject are a result of medication; relative nondeliberate insulin overdose is the most frequently cited reason. For example, taking the morning breakfast-time insulin but not eating enough carbohydrates can result in a falling blood glucose within 1 or 2 hours. For Type 2 DM patients, the medications most commonly associated with hypoglycemia are sulfonylurea agents. In a well-controlled patient, an event such as skipping a meal or over-exercising are common reasons. Another iatrogenic cause sometimes occurs when patients who are on insulin are asked to fast (usually for laboratory tests), but nonetheless take their usual insulin doses.

Other risk factors for hypoglycemia include exercise (causing increased utilization of glucose), alcoholism (which interferes with gluconeogenesis), and renal failure (decreased insulin clearance). All subjects are educated to recognize these symptoms, confirm with a glucometer, if available, and to treat promptly with an appropriate snack.

When blood glucose levels reach a threshold of approximately 70–80 mg/dL,

counter-regulatory hormones such as glucagon, epinephrine, growth hormone, and cortisol increase. These hormones stimulate glycogenolysis and gluconeogenesis (Figure 1). In individuals with DM, these thresholds may not be the same as for healthy individuals. Blood glucose levels at which counter-regulatory mechanisms get initiated change 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. Hypoglycemia is “sensed” centrally, resulting in activation of the sympathetic nervous system, as well as release of catecholamines from the adrenal glands. Autonomic symptoms and signs include palpitations, tremors, anxiety, sweating, intense craving for food, and a rise in blood pressure and pulse rate. With continued glucose, neuroglycopenic symptoms can result in behavioral changes, confusion, fatigue or weakness, visual changes, seizure, loss of consciousness, and rarely—if hypoglycemia is severe and prolonged—permanent neurological damage or death. Once neuroglycopenia (otherwise known as severe hypoglycemia) develops, patients are no longer able to take care of themselves and need assistance. It is important to minimize the frequency of hypoglycemic reactions because glucose can drop significantly close to levels that can compromise mental function without the person being aware. While intensive control of DM is recommended to prevent microvascular complications, it is important to recognize the limitations of such intensive therapy. Goals of treatment should be individualized based on age, comorbidities, and financial restrictions. Most episodes are mild to moderate (with or without symptoms) and can be effectively treated by oral glucose supplementation and parenteral treatment if necessary in patients who are unwilling or unable to take oral carbohydrates (Table 7).



### CONCLUSION

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 diabetes, 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 cardiovascular disease (heart attacks, stroke and peripheral vascular disease), and loss of limbs. Many other organs or systems are also 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

**Table 7.** Identification and Treatment of Hypoglycemia

Symptoms of Hypoglycemia	Signs of Hypoglycemia
<ul style="list-style-type: none"> <li>• Shakiness</li> <li>• Anxiety</li> <li>• Palpitations</li> <li>• Increased sweating</li> </ul>	<ul style="list-style-type: none"> <li>• Tremors</li> <li>• Tachycardia</li> <li>• Sweating</li> <li>• Confusion, inappropriate behavior</li> </ul>
<p>General Principles:</p> <ul style="list-style-type: none"> <li>• Treatment should be initiated as soon as possible</li> <li>• All patients should be given instructions as to how to treat hypoglycemia</li> <li>• When in a healthcare institution, staff should not wait for lab results or wait for response from a physician</li> <li>• If blood glucose is extremely low on the glucometer, e.g., &lt; 40 mg/dL, blood should be drawn and sent to the lab for accurate blood glucose level as the precision of glucometers is low at extremely low blood glucose levels</li> </ul>	
<p>Treating the Conscious Hypoglycemic Patient:</p> <ul style="list-style-type: none"> <li>• Treat with ~15 gm of simple carbohydrates orally                             <ul style="list-style-type: none"> <li>◦ ½ can of regular soda</li> <li>◦ 4 oz of regular fruit juice, or</li> <li>◦ 3–4 glucose tablets</li> </ul> </li> <li>• Repeat finger stick glucose in 15 minutes</li> <li>• If blood glucose is &lt; 60 mg/dL, repeat 15 gm of simple carbohydrates and check blood glucose in 15 minutes; continue this protocol until blood glucose is &gt; 60 and then follow with a mixed snack</li> <li>• Ascertain cause and if hypoglycemia not likely to recur, ask patient to discuss the hypoglycemia with his or her physician</li> </ul>	
<p>Treating the Unconscious Hypoglycemic Patient or Otherwise Unable to Consume Oral Carbohydrate:</p> <ul style="list-style-type: none"> <li>• With IV access:                             <ul style="list-style-type: none"> <li>◦ 25 to 50 gm of 50% dextrose can be given immediately</li> </ul> </li> <li>• Without IV access:                             <ul style="list-style-type: none"> <li>◦ Glucose gel can be applied to the mouth or the rectum in the semi-obtunded patient</li> <li>◦ Treat with 1 mg of glucagon intramuscularly or subcutaneously; patient should regain consciousness in 15 to 20 minutes.</li> <li>◦ Repeat the blood glucose in 15 minutes</li> </ul> </li> </ul>	

greater cardiovascular morbidity and mortality. An increasingly sophisticated group of therapies are available to manage this disorder to improve the health of the patient.

### Supplemental Readings

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# CHAPTER 6

## Association Between Periodontal Diseases and Diabetes Mellitus

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### INTRODUCTION

Both diabetes and periodontal diseases are common chronic disorders in many parts of the world. This chapter will provide a description of the evidence supporting a bi-directional relationship between diabetes and periodontal disease. This bi-directional relationship is one in which we recognize that diabetes adversely affects periodontal health, and periodontal infection (or periodontal disease) adversely affects diabetes by contributing to poorer glycemic control, increasing the risk for certain diabetes complications, and possibly increasing the risk for the development of diabetes. It is important for not only dental health professionals, but for all healthcare professionals, to understand the role and importance of oral health in managing diabetes patients. With a relatively small but concerted effort, a potentially large gain might be obtained in improving the quality of life for individuals with diabetes, while reducing the immense burden of diabetes on the patients, their families and employers, and on society as a whole.

The following educational objectives provide an overview of the topics in this chapter:

#### 1. Effect of Diabetes on Periodontal Health

- Describe in general terms the types and strength of empirical evidence, e.g., studies conducted on humans, that support the concept that diabetes has an adverse effect on periodontal health.
- Describe the mechanisms by which diabetes is thought to contribute to poorer periodontal health, e.g., tissue, cellular, and molecular dynamics or interactions.

#### 2. Effect of Periodontal Infection on Glycemic Control in Diabetes

- Describe the mechanisms by which periodontal infection is thought to contribute to poorer glycemic control in people with diabetes.
- Describe the current state of empirical evidence derived from observational studies regarding periodontal infection having an adverse effect on glycemic control.
- Describe the current state of empirical evidence from treatment studies that show periodontal therapy has a beneficial effect on improving glycemic control.

#### 3. Periodontal Infection and Development of Complications of Diabetes and Possibly Diabetes Itself

- Describe the role blood glucose control plays in preventing the occurrence and/or progression of diabetes complications and the definitive evidence from clinical trials supporting this concept.
- Describe the current state of the evidence regarding the effect of severe periodontal disease on the risk of diabetes complications and the development of Type 2 diabetes.

### ADVERSE EFFECTS OF DIABETES ON PERIODONTAL HEALTH

#### Evidence from Epidemiologic and Other Clinical Studies

The evidence that diabetes adversely affects periodontal health comes from studies conducted in different parts of the world.

Figure 1 shows the countries from which published reports investigating the role of diabetes on periodontal health originate. Only studies that include people both with and without diabetes are displayed. The colors represent the relative number of reports coming from each of the countries shown globally.

The variety in the body of evidence comes 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 conclusions about causality that can be inferred from the results. Causality factors relevant in human health issues can be defined as follows: a factor is a cause of a disease or health-related condition if its operation increases the frequency of the disease or condition.<sup>1</sup>

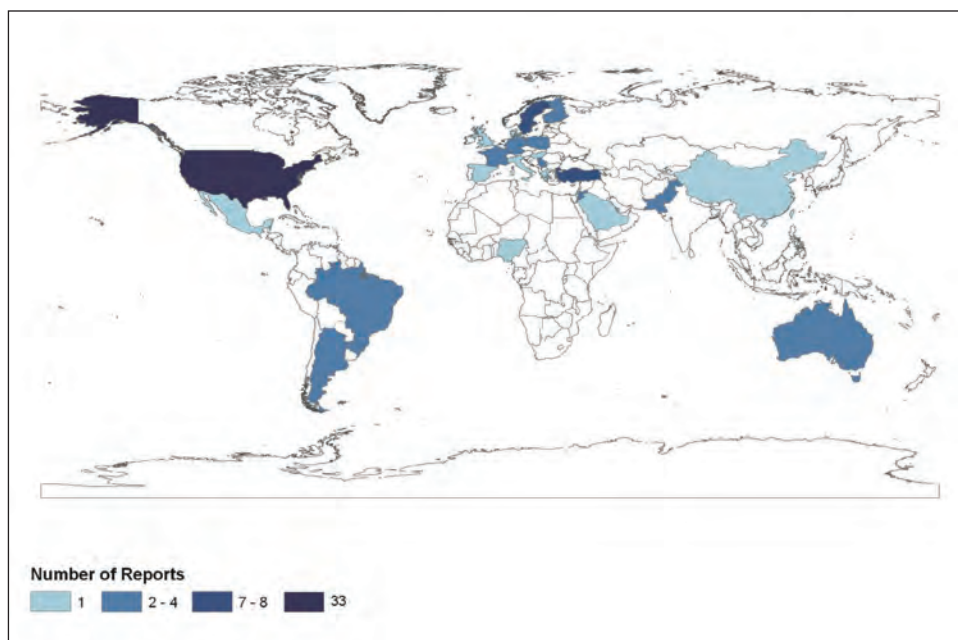
In studying inter-relationships between diabetes and periodontal disease, our principal interests are determining whether diabetes

causes (or contributes to) poorer periodontal health, whether periodontal infection contributes to poorer glycemic control or complications of diabetes, and finally, whether periodontal infection contributes to the development or pathogenesis of Type 2 diabetes. Because the inter-relationship between diabetes and periodontal disease is being evaluated in both directions, it is called a bi-directional (two-way) relationship. Depending on the type of question asked, the causal factor can be related to either diabetes or periodontal disease.

### Research Study Designs and Evidence to Support Causal Relationships

Research study designs differ in the strength with which they support causal relationships. The following section about study designs and causal relationships draws from a clear and comprehensive treatment of these topics by Elwood.<sup>1</sup> The simplest, most

**Figure 1.** Effect of Diabetes on Periodontal Health



The 89 studies, which include a nondiabetes control group (Table 1), were conducted in 30 countries from six continents.

direct test of causation in health is an experimental study in which there are two groups of people who are as similar as possible in all of their relevant characteristics, but the suspected (i.e., putative) causal factor is applied to only one group. Relevant characteristics are those factors, other than the one being studied, that could affect the frequency or severity of occurrence of the disease or condition. In studies of human health, this type of experiment is called a randomized controlled trial (RCT). The RCT has been used most extensively in comparing methods of treatment, in which groups receiving different treatments are selected by chance assignment (i.e., random allocation) and, when possible, neither the participants nor the investigators are aware of which treatment is given (double-blinding or masking). By “blinding” both the investigators and the study participants, the observations of the outcomes can be made the same way for all study participants, without knowledge of the treatment affecting the assessment by the investigators or perception of the effects by the study participants. The double-blind RCT is the most definitive way to test a causal relationship in human health. In appropriate circumstances, RCTs are considered the “gold standard” or best possible method for causal evidence.

However, for practical and ethical reasons, RCTs are not always appropriate. RCTs can be used only to assess methods of treatment that are likely to be beneficial. In studies of human health, many important relationships are those in which we are concerned about harmful, rather than beneficial, effects or exposures. This is the case in conducting studies to establish whether diabetes has an adverse effect on periodontal health. On the other hand, RCTs involving periodontal treatment are appropriate in providing evidence to demonstrate that treating periodontal infection contributes to improved glycemic control or perhaps reduces the risk

of development of diabetes or its complications. However, in studying the role of periodontal disease in the pathogenesis of diabetes or its complications, the RCT might be impractical because of the length of time required to observe complications or to diagnose diabetes, or the large number of participants required to demonstrate such a causal relationship.

### **Analytical Observational Study Designs: Cohort, Case-Control, and Cross-Sectional Studies**

Because of the ethical, methodological, and practical limitations of experimental studies (i.e., RCTs) for answering questions about causation for many types of health-related issues, other study designs are also used. The three main types of analytical, nonexperimental study designs used to support or explore causal relationships in human health are the cohort, case-control, and cross-sectional study designs. These three study designs are considered “observational” studies that differ in the way study participants are chosen and the relationship in time between the occurrence of exposure to the putative causal factor and the occurrence of the disease or condition, referred to as the “outcome.”

#### ***Cohort Studies***

These studies compare groups of people exposed to a putative causal factor with those who are not exposed. The exposures are identified at a point in time when none of the people in either group have the outcome of interest. The groups are observed over a period of time to compare differences between the groups in the occurrence of the outcome. If a greater number of people in the group exposed to the putative causal factor develop the outcome, and other relevant characteristics have been considered, then it can be inferred that the putative causal factor is likely to be a cause or risk factor for the outcome.

### ***Case-Control Studies***

These studies compare a group of people who have already experienced the outcome (cases) with a group of similar people without the outcome (controls). Investigators then look backward in time, or retrospectively, to assess the frequency with which the cases and controls were exposed to the putative causal factor in the time period prior to the diagnosis of the outcome. If the cases had a higher frequency of exposure to the putative causal factor, then one can make an inference about causality after accounting for other relevant characteristics.

### ***Cross-Sectional Studies***

This study design selects participants who comprise a population or are considered a sample of people representative of a population. All data on the putative causal factor (or exposure) and the outcome are collected at the same point in time, i.e., a cross-section in time. One is able to assess whether there is an association between the putative causal factor and the outcome by comparing differences in the frequency of the outcome in those who have the putative causal factor with people who do not. Although a greater frequency of the outcome may be observed in the people exposed to the putative causal factor, the ability to make causal inferences about the relationship is limited because the time sequence of events cannot be established. That is to say it cannot be determined if the exposure to the putative causal factor occurred before the disease or condition or vice versa. The cross-sectional study design does allow testing hypotheses regarding how strongly associated a putative causal factor may be with an outcome.

To address the question of whether diabetes adversely affects periodontal health, it is not ethical to use an RCT in humans, because doing so would require researchers to cause some individuals to develop diabetes. (However, a section later in this chapter will

describe experimental evidence in rodent models). Therefore, the evidence about whether or not diabetes adversely affects periodontal health must come from observational studies.

### **Adverse Effects of Diabetes on Periodontal Health: Evidence from Observational Studies**

As might be expected, reports in the literature provide answers to different kinds of questions and vary in their ability to help us understand how diabetes can be considered a cause of poorer periodontal health and establish how strong that relationship is. The majority of the reports are cross-sectional studies that provide information about the association between diabetes and the prevalence of periodontal diseases. Studies of prevalence allow us to compare the differences in percentages or proportions of individuals with periodontal disease between those with and without diabetes. The vast majority of studies reporting on the prevalence of periodontal disease conclude that the prevalence is greater in people who have diabetes.

Some of the studies provide information about the extent or severity of periodontal disease in people with diabetes. The studies reporting on the extent of periodontal disease assess the number of teeth or sites affected, while studies of severity assess the amount of periodontal destruction by considering the extent of pocket depth or attachment loss. People with diabetes are more likely to have deeper periodontal pockets and greater attachment loss than people who do not have diabetes.

The strongest type of evidence supporting the role of diabetes contributing to poorer periodontal health comes from studies of incidence and progression of periodontal disease. These types of studies must follow people over time and hence can allow for conclusions to contribute to establishing

a causal relationship between diabetes and poorer periodontal health. Incidence is a measure of the rate of new cases of periodontal disease over time. Progression of periodontal disease is a measure of the worsening of periodontal status over time.

Cross-sectional studies provide information on the prevalence, extent, and severity of periodontal disease in people with diabetes at a single point in time. Studies following individuals with diabetes over time (i.e., prospective, cohort, or longitudinal studies) allow quantification of the degree to which diabetes increases the risk for periodontal disease incidence, severity, or progression.

Table 1 summarizes the conclusions of studies reported in the literature that address the question of whether or not diabetes adversely affects periodontal health. To interpret the contents of Table 1, first look at the column headings and then the row headings. The column headings indicate the type of diabetes included in the study and the row headings indicate the type of study. Notice that there are both cohort and cross-sectional studies that have addressed the question of whether diabetes has an adverse effect on periodontal health. It is important to keep in mind that RCTs would not be appropriate for addressing the question summarized in Table 1, i.e., if diabetes adversely affects periodontal health, because it would be unethical to use an intervention in humans

that caused diabetes in an experimental group. Therefore, the highest level of evidence useful in addressing this question would come from the results of cohort studies.

In each category (group of studies) within Table 1, the numerator is the number of studies confirming that diabetes adversely affects one or more of several measures of periodontal health (e.g., gingivitis, probing pocket depth, attachment loss, radiographic bone loss). The denominator represents the total number of studies of that particular kind (e.g., cross-sectional studies with participants having Type 2 diabetes). For example, all four of the reports from cohort studies that included people with Type 2 diabetes concluded that periodontal health was worse in people who had diabetes than in those without diabetes. Similarly, all three of the reports investigating gestational diabetes mellitus (GDM) concluded that women with GDM were more likely to have poorer periodontal health than pregnant women without GDM. In the bottom row there are roughly equal numbers of studies reporting on Type 1 diabetes (26) and Type 2 diabetes (27), exclusively; only three reports address GDM. From the information presented in Table 1 we can see the vast majority of reports, namely 79 of 89 studies as shown in the extreme bottom right corner, provide evidence that diabetes adversely affects periodontal health.

**Table 1.** Effects of Diabetes on Periodontal Health: Conclusions of the 89 Studies that Include a Nondiabetes Control Group (Figure 1)

Study Design	Diabetes Mellitus Type					Total Number of Studies (# with Effect/# All Studies)
	Type 1	Type 2	Type 1 or 2	Gestational (GDM)	Type Not Reported	
Cohort	3/3	4/4	0/0	0/0	0/0	7/7
Cross-sectional, Descriptive	22/23	20/23	15/18	3/3	11/15	72/83
Total:	25/26	24/27	15/18	3/3	11/15	79/89

*Note:* The numerator represents the number of studies reporting diabetes having an adverse effect on periodontal health; the denominator represents the total number of studies in each group: # Studies with Effect/Total # Studies.

Another set of studies in the literature addresses the question of whether the degree of glycemic control of diabetes is associated with poorer periodontal health. The degree to which diabetes is controlled or managed is usually assessed by measuring the amount of hemoglobin A1c (HbA1c) in the blood, called glycosylated (or glycated) hemoglobin. HbA1c is a measure of how much glucose has been present in the blood and has bound to the hemoglobin in the red blood cells over the lifetime of those cells. Blood from a simple finger stick can be analyzed, and the result indicates the level of control of glycemia for the previous 60 to 90 days, measured as a percent of HbA1c. The current therapeutic target for HbA1c is to achieve a level less than 7%. People without diabetes usually have a level of 4.5%–6%.

Table 2 summarizes the conclusions of studies that provided information comparing the effects of better or poorer glycemic control on periodontal health in people with diabetes. Similarly to Table 1, the evidence comes from both cohort and cross-sectional studies, as indicated in the row titles of the table; the column headings indicate the type of diabetes of the participants in the studies. The majority of the studies in Table 2 concluded that people with poorer glycemic control had worse periodontal health than those with better glycemic control (42 of the 61 studies). The stronger evidence comes from

the set of cohort studies that followed people over time, allowing for more definitive conclusions regarding causality. Eight of the 10 cohort studies supported the conclusion that poorer glycemic control leads to poorer periodontal health over time.

Although the majority of studies reporting on the adverse effects of diabetes are cross-sectional and involve convenience samples of patients, principally from hospitals and clinics, a smaller subset of longitudinal and population-based studies provide additional support for the association between diabetes and periodontal disease. The 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 probing pocket depth, loss of periodontal attachment, or radiographic evidence of alveolar bone loss). The studies used different parameters to assess periodontal disease occurrence (e.g., prevalence, incidence, extent, severity, or progression). This inevitable variation in methodology and study populations limits the possibility that the same biases or confounding factors apply in all the studies and provides support for concluding that diabetes is a risk factor for periodontal disease incidence, progression, and severity. In addition, there is substantial evidence to support a “dose-response” relation-

**Table 2.** Effects of Degree of Glycemic Control on Periodontal Health: Conclusions of the Studies

Study Design	Diabetes Mellitus Type				Total Number of Studies (# with Effect/# All Studies)
	Type 1	Type 2	Type 1 or 2	Type Not Reported	
Cohort	4/4	3/3	1/3	0/0	8/10
Cross-sectional, Descriptive	11/18	15/17	7/11	1/5	34/61
Total:	15/22	18/20	8/14	1/5	42/61

*Note:* The numerator represents the number of studies reporting increasing degree of glycemic control having decreasing adverse effect on periodontal health; the denominator represents the total number of studies in each group: # Studies with Effect/Total # Studies.



ship, i.e., as glycemic control worsens, the adverse effects of diabetes 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 articles by Mealey and Ocampo,<sup>2</sup> Lamster et al.,<sup>3</sup> and Taylor and Borgnakke.<sup>4, 5</sup>

### **ADVERSE EFFECTS OF DIABETES ON PERIODONTAL HEALTH: EVIDENCE FROM *IN VITRO* AND ANIMAL STUDIES**

This next section provides insight into mechanisms of diabetes-enhanced periodontal disease from animal and *in vitro* studies. Studies in people with diabetes clearly indicate that diabetes causes an increase in the inflammatory response. This has significant impact on periodontal diseases, which largely result from inflammatory changes triggered by bacterial invasion into connective tissue.<sup>6</sup> Diabetic rats have increased inflammation of the periodontal epithelium and connective tissues, along with increased degradation of connective tissue and increased bone loss.<sup>7, 8</sup> Similarly, diabetic mice have been shown to have increased inflammation, oxidative stress, and bone loss.<sup>9</sup> Furthermore, diabetes may increase the systemic response to periodontal bacteria or their products.<sup>10</sup>

#### **Heightened Inflammatory Response: Cellular and Molecular Events**

Insight into mechanisms of diabetes-enhanced periodontitis come from *in vitro* and animal studies that established cause-and-effect relationships between specific cellular and molecular events that cannot be performed easily in human studies.<sup>11</sup> Cell culture studies have demonstrated that lipopolysaccharide (LPS)-stimulated monocytes isolated from individuals with diabetes exhibit greater production of tumor necrosis factor-alpha

(TNF- $\alpha$ ) than in individuals who do not have diabetes.<sup>12</sup> Neutrophils from individuals with diabetes have increased production of superoxides, which enhance oxidative stress.<sup>13</sup> In an animal model, injection of *Porphyromonas gingivalis*, an established periodontal pathogen, into connective tissue was shown to stimulate more prolonged formation of an inflammatory infiltrate with higher levels of inflammatory cytokines.<sup>14</sup> This was linked to higher levels of TNF- $\alpha$  since a specific TNF inhibitor reversed the increased inflammation in the diabetic mice stimulated by *P. gingivalis*.<sup>15</sup> In another animal model, Type 2 diabetes was shown to significantly increase periodontal inflammation induced by the onset of periodontal disease compared to matched healthy rats.<sup>16</sup> Diabetic rats had significantly more prolonged gingival inflammation as well as greater osteoclast numbers and increased bone loss.

#### **Uncoupling of Bone Resorption and Bone Formation**

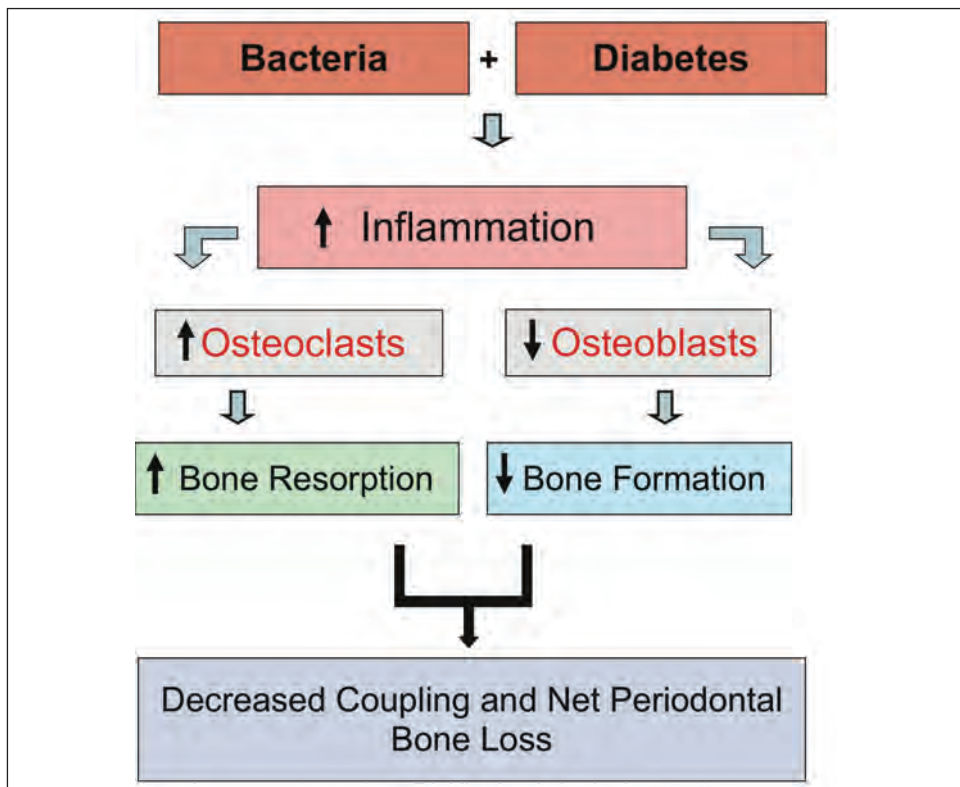
A second mechanism is proposed to contribute to greater bone loss in the diabetic animals, namely an uncoupling of bone resorption and bone formation.<sup>16</sup> Once bone is resorbed, it is repaired by new bone formation by a process referred to as coupling.<sup>17</sup> Thus, the amount of bone lost is equal to the amount of bone resorption minus the amount of reparative new bone formation. The diabetic animals had significantly less coupling so that there was less reparative bone formation following an episode of resorption, which contributes to the net bone loss. A potential mechanism was indicated by decreased numbers of bone-lining and periodontal ligament cells, which could be explained by higher levels of cell death (apoptosis).<sup>16</sup> This interpretation is supported by studies in which a cause-and-effect relationship between diabetes-enhanced apoptosis and the ability to form bone after an episode of resorption,<sup>18</sup> since inhibition of

apoptosis with a caspase inhibitor significantly improves the amount of reparative bone formation in diabetic animals following bone resorption induced by *P. gingivalis*. Inflammation could also affect bone-lining cells by reducing proliferation or interfering with differentiation to osteoblasts.<sup>6</sup> A schematic of this process is shown in Figure 2. TNF dysregulation was also suggested as a mechanism since a TNF inhibitor significantly reduced cell death and improved bone formation.<sup>19</sup> Interestingly, TNF inhibition significantly improved these parameters in diabetic animals, but not in normal animals, suggesting that the level of TNF- $\alpha$  in the diabetic group is especially problematic.

### Advanced Glycation End-product Formation

Enhanced inflammation through advanced glycation end-products (AGEs) has been implicated in *P. gingivalis*-induced bone loss in a murine periodontal model.<sup>20</sup> AGEs are long-lived molecules formed by the irreversible binding of glucose to protein and lipids in the plasma and tissues during persisting hyperglycemia. In these studies, a soluble receptor for advanced glycation end-products (sRAGE) was used to prevent the binding of AGEs to cell surface AGE receptors in mice. Treatment with sRAGE decreased the levels of TNF- $\alpha$  and interleukin-6 (IL-6, an inflammatory mediator)

**Figure 2.** Impact of Diabetes on Periodontal Bone Loss



Diabetes enhances the inflammatory response to oral bacteria. Increased inflammation could affect alveolar bone by increasing resorption as well as inhibiting bone formation, resulting in uncoupling and greater net bone loss. One of the mechanisms of diminished bone formation is through reduced numbers of osteoblasts caused by the impact of inflammation on apoptosis, proliferation, or differentiation of bone-lining cells.

in gingival tissue and suppressed alveolar bone loss. These findings link AGEs with an exaggerated inflammatory response and increased bone loss in diabetes-enhanced periodontal disease.

### **Other Mechanisms**

Several other studies have provided insight into mechanisms by which diabetes increases periodontal bone loss in animal models. In one example, treatment with N-acetylcysteine significantly inhibited alveolar bone loss in a murine model.<sup>21</sup> Since N-acetylcysteine reduces inflammation and oxidative stress, these studies suggest that elevated levels of inflammation and oxidation in diabetic animals promote greater periodontal tissue loss. Mahamed and colleagues have demonstrated that increased production of receptor-activator of nuclear factor kappaB (NF- $\kappa$ B) ligand (RANKL) occurs in the periodontium of diabetic mice.<sup>22</sup> A cause-and-effect relationship was shown between diabetes-increased RANKL and accelerated bone loss by successful reduction in bone loss via treatment with a RANKL-inhibitor, osteoprotegerin.

Increased bone loss in diabetic rats has also been linked to increased matrix metalloproteinase (MMP) activity.<sup>23</sup> MMPs are a group of enzymes that can break down proteins, such as collagen, that are normally found in the spaces between cells in tissues (i.e., extracellular matrix proteins). When MMP activity was inhibited, there was significantly reduced bone loss in diabetic rats.<sup>23</sup> Paradoxically, an enhanced inflammatory response may also be associated with a less effective reaction that results in deficits in bacterial killing.<sup>24</sup> Decreased bacterial killing may potentially enhance the growth of pathogens and increase the possibility that opportunistic bacteria will cause periodontal tissue loss. An altered host response to bacteria can lead to greater or prolonged expression of cytokines that stimulate bone re-

sorption and may limit bone repair. Similar alterations are noted in other diabetic complications, such as retinopathy, nephropathy, and impaired fracture healing.

### **Lipid Dysregulation and Impaired Wound Healing**

Three reviews provide discussion of investigations providing additional perspective on metabolic dysregulation in diabetes and the effects of hyperlipidemia on monocyte/macrophage function in wound signaling.<sup>25-27</sup> The monocyte/macrophage is considered the major mediator of the inflammatory phase in wound healing, having primary roles in wound signal transduction and in the initiation of the transition of healing from the inflammatory to the granulation phase. One hypothesized effect of hyperlipidemia occurs through fatty acid interaction with the monocyte cell membrane, causing impaired function of membrane-bound receptors and enzyme systems. This leads to impaired amplification and transduction of the wound signal. Another postulated pathway leading to impaired monocyte function in diabetes and wound signaling is via the nonenzymatic glycosylation of lipids and triglycerides in addition to proteins. These AGEs are thought to affect normal differentiation and maturation of specific monocyte phenotypes throughout the different stages of wound healing. The net result of both of these pathways is exacerbated host-mediated inflammatory responses and tissue destruction. In impairing monocyte function, diabetes-associated lipid dysregulation, leading to high levels of low-density lipoproteins and triglycerides, may be a major factor in the incidence and severity of periodontal disease.

### **Molecular Dysregulation in Diabetes that Enhances Inflammation**

A number of metabolic pathways are affected by diabetes. In many cases they

have been linked to hyperglycemia, although the potential contribution of hypoinsulinemia should also be considered. One of the changes that occurs is increased shunting through the polyol pathway that leads to enhanced aldose reductase activity and greater production of the sugars sorbitol and fructose. As a result, there is increased formation of AGEs and enhanced formation of reactive oxygen species (ROS) and nitric oxide (NO). AGEs, ROS, and NO are pro-inflammatory. That this pathway is important in diabetes has been shown by the use of aldose reductase inhibitors. When aldose reductase is inhibited, there is reduced protein kinase C (PKC) activation, less nuclear translocation of NF- $\kappa$ B, and reduced expression of markers of inflammation.<sup>28,29</sup> Inhibiting aldose reductase also decreases the production of ROS.<sup>28,29</sup> In addition, bacterial killing by neutrophils, which is reduced in individuals with diabetes, is improved by use of an aldose reductase inhibitor.<sup>30</sup> This may have implications for periodontal disease as diabetes reduces the capacity of neutrophils to kill periodontal pathogens such as *P. gingivalis*.<sup>24</sup> As indicated above, oxidative stress is significantly increased by diabetes and is associated with both enhanced formation of ROS and decreased antioxidant capacity.<sup>6,7</sup> One of the mechanisms by which this occurs is through overloading the electron transport chains in mitochondria, which leads to escape of electrons that react with oxygen-producing superoxides. ROS cause cell damage and also stimulate the production of inflammatory cytokines. The importance of oxidative stress in diabetic conditions has been demonstrated by improvements of diabetic complications by treatment of diabetic animals with antioxidants.<sup>31</sup>

Diabetic complications have been linked to elevated activation of PKC. Diabetes increases glycolysis, which in turn causes increased levels of dihydroxyacetone phosphate that may be converted to diacylglyc-

erol. PKC is activated by diacylglycerol and by an increased ratio of nicotinamide adenine dinucleotide (reduced form) to nicotinamide adenine dinucleotide (NADH/NAD<sup>+</sup> ratio) associated with diabetes.<sup>32</sup> Increased PKC activity then stimulates formation of ROS and inflammation. PKC- $\alpha$ /PKC- $\beta$  inhibitors reverse this increase. Hyperglycemia is also linked to increased formation of advanced glycation end-products, which are pro-inflammatory.<sup>20,39</sup> AGEs also possess pro-apoptotic activity.<sup>33-37</sup> Inhibition of one of the receptors for AGEs, RAGE, reduces inflammation that is enhanced by diabetes.<sup>20,38</sup> The use of a RAGE inhibitor in a periodontal model was discussed in a previous section.

#### ADVERSE EFFECTS OF PERIODONTAL INFECTION ON GLYCEMIC CONTROL

This next section assesses the evidence for an effect going in the opposite direction, namely *periodontal infection adversely affecting glycemic control in people with diabetes*.

In addition to the substantial evidence demonstrating diabetes as a risk factor for poorer periodontal health, there is a growing body of evidence supporting the long-held clinical observation that periodontal infection adversely affects glycemic control. There is also increasing evidence that periodontal infection contributes to greater risk for diabetes complications. Diabetes complications are the conditions or diseases that people with diabetes often develop due to their diabetic status, such as increased risk of coronary heart disease (CHD), stroke, myocardial infarction, and other cardiovascular events; nephropathy (diseases of the kidney, ultimately leading to end-stage renal disease [ESRD], requiring renal dialysis for the patient to survive); neuropathy (diseases of the peripheral and autonomic nerves); retinopathy (diseases of the retina, possibly leading to blindness); extremely decreased

wound healing; and amputations due to one or more of the complications mentioned.

Evidence supporting the biologic plausibility of periodontal infection contributing to poorer glycemic control, complications of diabetes, and perhaps the development of Type 2 diabetes, comes from integrating several converging perspectives. This biologic plausibility is grounded in periodontitis being a chronic inflammatory response to a predominantly Gram-negative bacterial infection and the emerging evidence linking chronic infection and inflammation, insulin resistance, and the development of diabetes and its complications.<sup>39</sup>

### **Periodontal Infection: Contribution to a Chronic Systemic Inflammatory Burden**

Periodontal infection, if untreated, can lead to extensive destruction of local soft connective tissue and alveolar bone, and is a major cause of tooth loss.<sup>40</sup> Periodontal infection elicits a local chronic inflammatory response and is considered a contributing source for the total chronic, systemic, inflammatory burden.<sup>41</sup> The highly vascular, inflamed, and ulcerated periodontal pocket epithelium provides a ready portal of entry for periodontal pathogens from the dental plaque biofilm, many of which are Gram-negative and obligate anaerobes. Bacteremia, a situation in which bacteria have penetrated into the blood stream and therefore are circulated throughout the body, is recognized to occur in periodontitis. Periodontal pathogens have been identified in atheromatous plaques and shown to invade aortic and coronary endothelial cells.<sup>42</sup> Bacterial components (e.g., LPS) are also disseminated into the systemic circulation. The bacteremia and subsequent systemic dispersal of periodontal pathogens and bacterial components may relocate antigenic stimuli at sites such as endothelial cells and hepatocytes, eliciting their production of pro-inflammatory immune mediators. Additionally, the pro-inflammatory

mediators, such as IL-1 $\beta$ , TNF- $\alpha$ , IL-6, prostaglandins E<sub>2</sub> (PGE<sub>2</sub>), and thromboxane B<sub>2</sub>, produced locally at the periodontal lesion, may also enter the systemic circulation and produce distant systemic pro-inflammatory effects at target tissues and organs.<sup>41,42</sup> Hence, the inflamed periodontal tissue behaves as a potential endocrine-like source for increased chronic systemic inflammatory challenge.

TNF- $\alpha$ , IL-6, and IL-1 $\beta$ , all mediators important in periodontal inflammation, have been shown to have important effects on glucose and lipid metabolism as well as insulin action, following an acute infectious challenge or trauma.<sup>43-47</sup> Additionally, chronic, low-grade inflammation, in which these same mediators are involved, has been shown to be associated with the development of insulin resistance, diabetes, and its complications.<sup>39,48</sup>

The mechanisms by which periodontal infection could contribute to insulin resistance, poorer glycemic control and complications of diabetes, and possibly the development of Type 2 diabetes, are perhaps best understood by considering the emerging evidence regarding the systemic effects of obesity. Adipose tissue is now recognized as important in chronically activating the innate immune system and contributing to a chronic, low-grade systemic inflammatory burden. The adverse effects of obesity-related activation of systemic inflammation also include development of insulin resistance, glucose intolerance, and increased risk for the development of Type 2 diabetes.<sup>49</sup>

Adipose tissue secretes several bioactive proteins, known as adipokines, that have local autocrine/paracrine effects as well as systemic hormonal effects. Several of the adipokines are pro-inflammatory mediators that can contribute to a state of chronic, low-grade systemic inflammation.<sup>50</sup> As previously mentioned, a subset of the adipokines produced by the adipose tissue are also among the set of inflammatory mediators

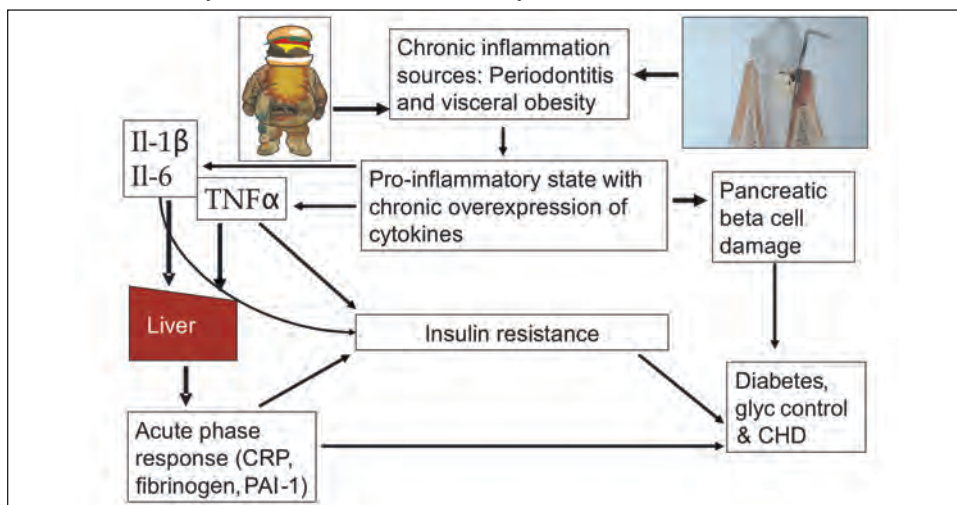


produced locally in periodontal tissue as part of the host response to periodontal infection. These include  $\text{TNF-}\alpha$ ,  $\text{IL-1}\beta$ , and  $\text{IL-6}$ . These mediators have direct effects in activating the innate immune system and its systemic component, the acute-phase response; inhibiting the action of insulin; and contributing to insulin resistance; all leading to glucose dysregulation and hyperglycemia. Figure 3 illustrates a conceptual model integrating the

clinical picture of periodontitis and obesity with the hypothesized role of inflammation in the pathogenesis of diabetes, poor glycemic control, and CHD.

There is a growing body of compelling evidence from cohort and cross-sectional epidemiologic studies and experimental studies in humans and animal models linking obesity, chronic inflammation, insulin resistance, and the development of Type 2

**Figure 3.** Conceptual Model Integrating the Clinical Pictures of Periodontitis and Obesity with the Hypothesized Role of Inflammation in the Pathogenesis of Diabetes, Poor Glycemic Control, and Coronary Heart Disease



Adapted from Donahue RP, Wu T. *Ann Periodontol* 2001;6:119-124.<sup>107</sup> This conceptual model integrates the clinical pictures of periodontitis and obesity with the hypothesized role of inflammation in the pathogenesis of diabetes, poor glycemic control, and coronary heart disease (CHD). The model depicts CHD because of the evidence supporting inflammation as a major factor in the pathogenesis of CHD, and the recognition of diabetes as a risk factor for this condition. In this model, sources of chronic inflammation, such as periodontitis and visceral obesity, produce a generalized pro-inflammatory state that includes chronic overexpression of cytokines and other inflammatory mediators. As shown here, a prevailing linking hypothesis is that the host response to periodontal infection can be an important site of chronic, low-grade inflammation, and a source for the systemic burden of pro-inflammatory cytokines. However, it should be noted that the metabolic disorders associated with diabetes affect many pathways, some of which are linked to inflammation, while others may aggravate pathologic processes in a cytokine-independent manner.

$\text{IL-6}$ ,  $\text{TNF-}\alpha$ , and  $\text{IL-1}\beta$  are among the important pro-inflammatory mediators that are produced in periodontitis. These mediators have been reported to be important in pathways for the pathogenesis of insulin resistance, CHD, and more recently, diabetes itself. In one hypothesized pathway,  $\text{IL-6}$  and  $\text{TNF-}\alpha$  stimulate the acute-phase response in the liver, resulting in the production of acute-phase reactants such as C-reactive protein (CRP), fibrinogen, and plasminogen activator inhibitor-1 (PAI-1). These acute-phase reactants have been reported to contribute to insulin resistance, as well as to be risk indicators and risk factors for the prevalence and incidence of both CHD and diabetes in epidemiologic studies.  $\text{IL-6}$ ,  $\text{TNF-}\alpha$ , and  $\text{IL-1}\beta$  have also been shown to disrupt insulin signaling, leading to reduced uptake of glucose by the cells. Further, insulin resistance, as a component of the metabolic syndrome, is recognized as a risk factor in the pathogenesis of diabetes and its complications, as well as CHD. Not included in this diagram are all of the adipokines and other factors that are thought to significantly contribute to insulin resistance.



diabetes. The epidemiologic studies have shown markers of inflammation are associated with Type 2 diabetes and features of the metabolic syndrome in cross-sectional studies of individuals without diabetes or with impaired glucose tolerance or impaired fasting glucose; markers of inflammation predict Type 2 diabetes; inflammation is involved in the pathogenesis of atherosclerosis, a common feature of Type 2 diabetes; anti-inflammatory agents (e.g., aspirin, statins, glitazones) decrease the acute-phase response and may reduce the risk of developing Type 2 diabetes and improve glycemic control in established diabetes; and GDN, a risk factor for Type 2 diabetes, is associated with an inflammatory response. The experimental studies have involved pharmacologic, nutritional, and genetic interventions providing further understanding of the cellular and molecular mechanisms through which chronic stressors (e.g., overnutrition, microbial products, hyperglycemia, hyperlipidemia, oxidative stress, and psychological stress), innate immunity, chronic systemic inflammation, obesity, insulin resistance, and metabolic dysregulation are integrated.<sup>49-55</sup> Connecting this evidence to the potential systemic effects of periodontal infection on chronic inflammation is the emerging body of evidence linking epidemiologic and intervention studies of periodontal infection to markers of systemic inflammation and changes in levels of the inflammatory markers after periodontal treatment.<sup>41,42,56-58</sup>

**Periodontal Infection Adversely Affecting Glycemic Control: Empirical Evidence from Nonsurgical Periodontal Treatment Studies**

More direct, empirical evidence regarding the effects of periodontal infection on glycemic control of diabetes comes from treatment studies using nonsurgical periodontal therapy and observational studies. The

treatment studies are a heterogeneous set of 31 reports that include 10 RCTs and 21 non-randomized clinical treatment studies as displayed in Table 3. The RCTs used control groups that were either nontreated controls,<sup>59,60</sup> positive controls (i.e., the control group received a relatively less intense form of periodontal treatment),<sup>61-66</sup> or controls advised to continue their usual dental care.<sup>67</sup> Of the 10 RCTs reviewed, six reported a beneficial effect of periodontal therapy.<sup>60-63,65,66</sup>

Among the set of 21 periodontal treatment studies that were not RCTs, 12 reported a beneficial effect on glycemic control<sup>68-80</sup> while nine did not.<sup>81-89</sup> It is remarkable that only two of these 21 studies included control or comparison groups.<sup>68,81</sup> These studies had marked variation in the use of adjunctive antibiotics, with four of the five studies that

**Table 3.** Effects of Nonsurgical Periodontal Therapy on Glycemic Control: Conclusions of the 31 Studies

Study Design	Number of Studies with Significant Improvement in Glycemic Control/ All Studies
<b>Randomized Clinical Trials (RCTs):</b>	
Nontreated control group	1/3
Positive (i.e., less intensely treated) control group	5/6
Usual source of care control group	0/1
<b>Total RCTs</b>	<b>6/10</b>
<b>Nonrandomized Clinical Trials (Non-RCTs):</b>	
Nontreated control group	1/2
No control group	11/19
<b>Total Non-RCTs</b>	<b>12/21</b>
<b>Total All Nonsurgical Treatment Studies (RCTs + Non-RCTs)</b>	<b>18/31</b>

\*These 10 RTC studies are further described in Table 4.  
*Note:* The numerator represents the number of studies reporting nonsurgical therapy being associated with increasing degrees of glycemic control; the denominator represents the total number of studies in each group: # Studies with Effect/Total # Studies.

used systemic antibiotics reporting a beneficial effect on glycemic control<sup>71,74,76,79</sup> and one finding a numerical decrease in the HbA1c level that did not reach statistical significance.<sup>81</sup>

For the body of literature consisting of both RCTs and other types of studies, 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, sample size and power to detect differences in periodontal and metabolic response, and specific hypotheses tested.<sup>90</sup> The details of the variation in this body of literature have been extensively described in several reviews.<sup>43,91,92</sup>

Table 4 provides additional information about the RCTs summarized in Table 3. For each study, information on the number of participants and the type of diabetes included

is given, along with indication of whether antibiotics were used in conjunction with the treatment. The types of antibiotics used and information on their dispensing mode (local, systemic, rinse) can be seen in the table's footnote marked with one asterisk (\*). Finally, in the far right column is the outcome achieved, indicating whether the study treatment resulted in improved glycemic control as measured by a decrease in the level of HbA1c.

One remarkable observation is the relatively small numbers of participants in some of the studies. This is mostly due to the immense resources required for conducting clinical trials, especially those that have a long follow-up period. Also, it is difficult to identify individuals meeting inclusion criteria and those free of exclusion criteria, and to recruit, enroll, and keep participants returning for all study visits that typically are of long duration due to their many components (e.g., interview, clinical examination, blood draw, radiographic exposure, and initial

**Table 4.** Effects of Nonsurgical Periodontal Therapy on Glycemic Control (HbA1c): Descriptions and Conclusions of the 10 Randomized Clinical Trials (RCTs) Summarized in Table 3

Clinical Study Design by Type of Control Group	Sample Size	Diabetes Type	Adjunctive Antibiotics Used*	Statistically Significant Beneficial Effect on HbA1c
<b>RCT with Nontreated Control Group:</b>				
Aldridge et al. study 1 (1995) <sup>59</sup>	31	1	No	No
Aldridge et al. study 2 (1995) <sup>59</sup>	22	1	No	No
Kiran et al. study 1 (2005) <sup>60</sup>	44	2	No	Yes
<b>RCT with Positive (i.e., Less Intensely Treated) Control Group:</b>				
Grossi et al. (1997) <sup>61</sup>	113	2	Yes <sup>a</sup>	Yes
Al-Mubarak et al. (2002) <sup>64</sup>	78	1,2	No	No
Rodrigues et al. (2003) <sup>62</sup>	30	2	Yes <sup>b</sup>	Yes**
Skaleric et al. (2004) <sup>63</sup>	20	1	Yes <sup>c</sup>	Yes
Yun et al. (2007) <sup>66</sup>	46	2	Yes <sup>a</sup>	Yes
O'Connell et al. (2008) <sup>65</sup>	30	2	Yes <sup>a</sup>	Yes
<b>RCT with Usual Source of Care-Control Group:</b>				
Jones et al. (2007) <sup>67</sup>	165	2	Yes <sup>a</sup>	No

\*Adjunctive antibiotic types: a) systemic doxycycline, b) amoxicillin and augmentin, c) minocycline, locally delivered.

\*\*The group *not* receiving antibiotic showed greater improvement.

therapy and maintenance visits). In addition, clinical studies typically last several months or years.

An important source of variation in the RCTs is the use of adjunctive antibiotics with the nonsurgical periodontal therapy. Among the six RCTs that included adjunctive antibiotics, five used the antibiotics systemically<sup>61,62,65-67</sup> and one was locally delivered.<sup>63</sup> Five of the six RCTs using antibiotics showed beneficial effects on glycemic control.<sup>61-63,65,66</sup> However, it is important to note the significant improvement for one study was in the positive control group that did not receive the systemic antibiotic.<sup>62</sup> Also, one of the six RCTs reporting a beneficial effect did not use any antibiotics.<sup>60</sup> Hence, to date there is suggestive, but not clear-cut evidence to support the use of antibiotics in combination with nonsurgical periodontal treatment in order to observe an improvement in glycemic control.

#### **Periodontal Infection Adversely Affecting Glycemic Control: Empirical Evidence from Observational Studies**

Additional evidence to support the effect of periodontitis on increased risk for poorer glycemic control comes from a small number of observational studies. A longitudinal epidemiologic study of the Pima Indians in Arizona found at baseline that subjects who had Type 2 diabetes, that was in good to moderate control, but also had severe periodontitis, were approximately six times more likely to have poor glycemic control at a two-year follow-up than those who did not have severe periodontitis at baseline.<sup>93</sup> In another observational study of 25 adults ages 58 to 77 with Type 2 diabetes, Collin et al. also reported an association between advanced periodontal disease and impaired metabolic control.<sup>94</sup>

Finally, two cross-sectional studies report findings consistent with poorer periodontal health associated with poorer

glycemic control. One of these studies, which included 127 pregnant women with diabetes, reported that 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 to recommended medical treatment for the diabetes.<sup>95</sup> The other study, analyzing the association between number of bleeding sites and degree of glycemic control (HbA1c), reported a statistically significant association, i.e., the HbA1c values increased (poorer control with higher HbA1c) as the number of bleeding sites increased. However, the authors determined this result would have no clinical significance<sup>96</sup> because the measure of association between the number of bleeding sites and glycemic control was very small.

#### **Periodontal Infection as a Potential Risk Factor for Diabetes Complications: Empirical Evidence from Observational Studies**

It is well recognized that poor glycemic control is a major determinant for the development of the chronic complications of diabetes. Results from the landmark Diabetes Control and Complications Trial (involving Type 1 diabetes) and the UK Prospective Diabetes Study (UKPDS, involving Type 2 diabetes) demonstrated that attaining and maintaining good glycemic control could reduce the risk for and slow the progression of microvascular complications in patients with Type 1 and Type 2 diabetes.<sup>97-99</sup> Additionally, the UKPDS observed a 16% reduction ( $p = 0.052$ ) 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 glycemia; every percentage point decrease in HbA1c (e.g., 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.<sup>100</sup>

There is emerging evidence from observational studies regarding the association between periodontal disease and the risk for diabetes complications. Thorstensson and colleagues<sup>101</sup> studied 39 case-control pairs of individuals with Type 1 and Type 2 diabetes for six 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. They found that cases were significantly more likely to have prevalent proteinuria and cardiovascular complications, including stroke, transient ischemic attacks, angina, myocardial infarction, and intermittent claudication than controls at their follow-up medical assessments.

Two reports from the ongoing longitudinal study of diabetes and its complications in the Gila River Indian Community in Arizona, conducted by the National Institute of Diabetes and Digestive and Kidney Diseases, address nephropathy and cardiovascular disease. Saremi and colleagues<sup>102</sup> 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 cardio-renal mortality (i.e., ischemic heart disease and diabetic 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 cardio-renal mortality, including age, sex, diabetes duration, HbA1c, body mass index, hypertension, blood glucose, cholesterol, electrocardiographic abnormalities, macroalbuminuria, and smoking.

In the second report, Shultis and colleagues<sup>103</sup> investigated the effect of periodontitis on risk for development of overt nephropathy (macroalbuminuria) and ESRD in a group of 529 Gila River Indian Com-

munity adults with Type 2 diabetes. Their proportional hazards model analyses, adjusted for age, sex, diabetes duration, body mass index, and smoking, indicated 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, than those with none/mild periodontitis. The incidence of ESRD was also 2.3, 3.5, and 4.9 times greater for individuals with moderate or severe periodontitis or for those who were edentulous, respectively, than those with none/mild periodontitis.

### **Periodontal Infection as a Potential Risk Factor for Development of Diabetes:**

#### **Empirical Evidence from Observational Studies**

In addition to evidence supporting periodontal disease as a potential risk factor for developing diabetes complications, there is also evidence emerging that periodontal disease may be a risk factor for the development of Type 2 diabetes and possibly GDM. Demmer and colleagues<sup>104</sup> investigated the association between periodontal disease and the development (i.e., incidence) of new 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, for the period between 1971 to 1992. The study used a cohort study design because information on the presence or absence of periodontal disease (i.e., the hypothesized causal factor) 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

50–100% greater risk for developing Type 2 diabetes, after controlling for other established risk factors for diabetes. The greater risk for diabetes was also consistent with previous research using NHANES I and NHEFS, in which risk factors for diabetes that did not include periodontal disease, for example, measures of adiposity (body mass index and subscapular skinfold thickness), having hypertension, and increased age, were also statistically significant.<sup>105</sup>

Finally, Dasanayake and colleagues<sup>106</sup> investigated whether or not pregnant women who develop GDM, compared to pregnant women who do not develop GDM, had poorer clinical periodontal health and/or demonstrated higher levels of other biological markers of periodontal disease approximately two months before their GDM diagnosis. The other biological markers included bacteriological (in dental plaque and cervicovaginal samples), immunological, and periodontitis-related inflammatory mediator analytes. This study found that women who had higher levels of *Tannerella forsythia* (*T. forsythia*), a recognized periodontal pathogen, in the vaginal flora were statistically significantly more likely to develop GDM than those women with lower levels. The Dasanayake et al. study concluded that *T. forsythia* in the vaginal flora is a potential risk factor for GDM.

## SUMMARY AND CONCLUSIONS

The evidence reviewed in this chapter supports the conclusion that a bi-directional association exists between diabetes mellitus and periodontal health: Diabetes is associated with increased development and progression of periodontitis, and periodontal infection is associated with poorer glycemic control in people with diabetes.

There is also evidence emerging that gestational diabetes may adversely affect periodontal health.

Additionally, evidence is emerging to suggest that periodontal disease is associated

with increased risk for diabetes complications, the development of Type 2 diabetes, and perhaps the development of GDM.

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 glycemic control, and possibly in delaying the onset or progression of diabetes and its complications.

Therefore, dental health professionals might fulfill an important role in maintaining or improving the health, and ultimately the quality of life, of individuals with diabetes and GDM, as well as aiding in lessening the immense burden of diabetes and periodontal diseases on our society in general.

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# CHAPTER 7

## Atherosclerosis: A Pervasive Disease Affecting Global Populations

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Stanley S. Wang

### INTRODUCTION

Atherosclerotic disease results from the pathological formation of plaques in arterial walls. Plaque development, or atherosclerosis, 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 will review the clinical manifestations of atherosclerosis and explore 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 ATHEROSCLEROTIC DISEASE

Atherosclerosis may occur in any arterial bed with the most clinically relevant ones being the coronary, cerebrovascular, and peripheral arterial circulation. Atherosclerotic plaques may be stable or unstable, based on whether or not the plaque has ruptured. More recently, studies have shed additional light on “vulnerable” atherosclerotic plaques, which are stable plaques with a propensity to 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 2009 statistical update.<sup>1</sup> Manifestations of

coronary atherosclerosis range from stable angina, resulting from 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. 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 in 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 (often called “ministrokes”) and strokes.

Atherosclerotic disease also occurs in the aorta, manifesting as aortic atherosclerosis and aneurysms, as well as in the peripheral arteries. In addition, atherosclerosis is thought to contribute to valvular heart diseases such as aortic stenosis.<sup>2,3</sup>

### MECHANISMS OF ATHEROMA FORMATION

Atherosclerotic disease is thought to progress from microscopic endothelial events that eventually lead to plaque development, growth, and rupture. Multiple complex mechanisms appear to contribute to the formation of atheromatous plaques. The initiating

process involves endothelial injury, which may occur due to mechanical, biochemical, or immunological 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 chemo-attractants interleukin (IL)-1 and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ).<sup>4</sup> Selectins and antigens on the leukocyte surface induce movement of the monocytes.<sup>5</sup> Endothelial cellular 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.<sup>6</sup> After they move into a subendothelial position, monocytes transform into macrophages and begin to secrete many inflammatory cytokines, proteases, and metalloproteinases.

Subsequently, the macrophages accumulate and oxidize low-density-lipoprotein cholesterol (LDLC), becoming the foam cells that are the precursors of atherosclerotic plaque.<sup>7</sup> C-reactive protein (CRP) appears to stimulate the process of LDLC uptake by macrophages,<sup>5</sup> which may explain why statin treatment of patients with elevated CRP levels appears to be clinically beneficial.<sup>8</sup> Ongoing LDLC deposition and inflammation leads to plaque growth, and hemodynamic mechanisms appear to play an important role as well.<sup>9</sup>

Plaque rupture may occur at any point in the process, producing significant clinical events. It has been estimated that in about two-thirds of patients with acute coronary syndromes, the inciting event is rupture of a coronary plaque that had been less than 50%–70% occlusive.<sup>10</sup> Ruptured plaques have distinctive histopathological features, including having a fibrous cap that is deficient in collagen and smooth muscle content, a rich lipid core, and an inflammatory infiltrate of macrophages and other inflammatory cells.<sup>11</sup>

### **Role of Inflammation in Atherosclerotic Disease**

Although the precise mechanisms of atherosclerosis are not completely understood, at the molecular level atherosclerosis appears to arise from an inflammatory reaction to cardiovascular risk factors.<sup>12,13</sup> Chronic inflammation underlies the processes of plaque formation and progression, while acute inflammatory processes are likely involved in plaque rupture.

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”<sup>14</sup> are pro-inflammatory, including IL-1, IL-12, IL-18, interferon gamma, and TNF- $\alpha$ . Others are anti-inflammatory, including IL-4, IL-10, IL-13, and transforming growth factor-beta.

In many cellular mediators of atherosclerosis, including macrophages and endothelial cells, pro-inflammatory cytokines stimulate the nuclear factor-kappa-beta ( $\kappa\beta$ ) pathway, leading to the increased production of cellular adhesion molecules, chemokines, growth factors, and other enzymes such as cyclo-oxygenases and nitric oxide synthase.<sup>15</sup> Enhanced activity of the nuclear factor- $\kappa\beta$  pathway appears to correlate with an increased risk of developing atherosclerotic plaques.

### **RISK FACTORS FOR CARDIOVASCULAR AND CEREBROVASCULAR DISEASES**

Traditional risk factors for atherosclerotic disease seem to have an association with inflammation in common. These risk factors include dyslipidemia, hypertension, diabetes mellitus, tobacco use, and adiposity.

#### **Dyslipidemia**

Dyslipidemia appears to contribute directly to atherosclerotic disease, with the risk



of cardiac events rising in direct proportion to plasma cholesterol levels,<sup>16</sup> especially cholesterol particles containing apolipoprotein  $\beta$  (including LDLC).<sup>17</sup> 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 LDLC uptake in the intima precedes LDLC oxidation and subsequent endothelial activation and monocyte recruitment.<sup>18</sup> Oxidized LDLC appears to increase endothelial expression of cellular adhesion molecules, attracting monocytes and promoting their differentiation into macrophages. LDLC also stimulates the release of pro-inflammatory cytokines from macrophages. Apolipoprotein B particles containing the lipoprotein(a) moiety appear to be particularly atherogenic.<sup>19,20</sup> In addition, the ratio of apolipoprotein B to apolipoprotein A holds promise in the prognostication of cardiovascular disease across multiple populations.<sup>21</sup>

### Hypertension

Systemic hypertension contributes by enhancing monocyte preactivation, increasing production of IL-1 and TNF- $\alpha$ ,<sup>22</sup> and raising circulating levels of cellular adhesion molecules.<sup>23</sup> Studies have shown a clear relationship between elevated high-sensitivity CRP levels in normotensive patients and risk of developing incident hypertension, underscoring its inflammatory nature.<sup>24</sup>

### Diabetes Mellitus

Diabetes mellitus appears to be associated with inflammation, which may explain its close relationship to atherosclerosis. Studies have shown that adipose tissue and macrophages recruited into adipose tissue release cytokines, including IL-1, IL-6, and TNF- $\alpha$ . 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 adrenocorticotrophic hormone.<sup>25</sup> 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.<sup>26</sup> Evidence is accruing to suggest that the formation and accumulation of advanced glycation endproducts (AGEs) may be a pathophysiologic link between diabetes and cardiovascular disease, mediated in part by the receptor for AGEs (RAGE).<sup>27</sup> 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.<sup>28</sup> 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.<sup>29</sup> 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.<sup>30</sup>

### Tobacco Use

Cigarette smoking contributes to coronary heart disease through at least four pathophysiological pathways,<sup>31</sup> including induction of a hypercoagulable state through increased plasma levels of factor VII and thromboxane A<sub>2</sub>, 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 past 40 years, but remains a public health problem with approximately 20% of the population continuing to smoke.<sup>32</sup>

Of note, cocaine use also causes hemodynamic effects as well as significant inflammation. Studies in mice suggest that cocaine increases the expression of cellular adhesion molecules and promotes greater neutrophil adhesion to the coronary endothelium.<sup>33</sup> In human cells, cocaine exposure appears to increase the expression of gene coding for numerous inflammatory markers, including IL-1, IL-6, and TNF- $\alpha$ .<sup>34</sup>

### **Obesity**

Obesity with visceral adiposity is another emerging atherosclerotic risk factor. Adipose tissue acts as a metabolically active and dynamic endocrine organ with pro-inflammatory actions. Adipocytes secrete many inflammatory cytokines, including IL-6 and TNF- $\alpha$ .<sup>35</sup> Although cytokine levels vary in proportion to overall adiposity, visceral adipose tissue appears to contribute to inflammation to a greater degree than subcutaneous fat.<sup>36</sup> There is an inverse relationship between visceral adiposity and plasma levels of the anti-inflammatory adipocyte-derived protein, adiponectin.<sup>37</sup> Lower adiponectin levels correlate with reduced insulin sensitivity and a higher risk of having diabetes mellitus,<sup>38</sup> as well as endothelial dysfunction, increased inflammation, and clinically significant atherosclerotic events such as myocardial infarction.<sup>39</sup>

### **EPIDEMIOLOGY OF HEART DISEASE AND STROKE**

Although the overall death rate from cardiovascular diseases has declined by 29.2% from 1996 to 2006, cardiovascular diseases remain the number one cause of mortality in the United States, accounting for 34.3% of the 2,425,900 deaths (or 1 of every 2.9 deaths) in the United States in 2006.<sup>1</sup> Based on 2004 International Classification of Disease-10 data from the Centers for Disease Control and Prevention, cerebrovascular diseases (including stroke)

account for an additional 5.7% of deaths.<sup>40</sup>

The American Heart Association estimates that 785,000 Americans will suffer a new heart attack in 2010 and another 470,000 will experience a recurrent heart attack.<sup>1</sup> Furthermore, an additional 195,000 will have a silent first heart attack. Although less lethal, strokes are expected to be highly prevalent in 2009, with an anticipated 610,000 new and 185,000 recurrent cases.

Despite these numbers, overall cholesterol screening and treatment remain sub-optimal. Data from the 2005–2006 National Health and Nutrition Examination Survey suggested that 30% or more adults failed to undergo cholesterol screening in the prior five years, and 16% of adults had total cholesterol levels of 240 mg/dL or greater. Similarly, achieving adequate blood pressure control has proven to be challenging. In 2003 and 2004, only 44% of blood pressure recordings in approximately 176 million individuals demonstrated readings lower than 140/90 mmHg.<sup>41</sup> Almost two-thirds of the population in the United States is overweight or obese, and more than one-fourth of the population meet diagnostic criteria for metabolic syndrome, a multiplex cardiovascular risk factor that arises from the interplay between adiposity and inflammation.<sup>42</sup>

### **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.<sup>43</sup> More than one billion individuals meet the medical criteria for being overweight or obese, but the rates of atherosclerotic disease and risk factors vary between countries.<sup>44,45</sup> 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 LDLC, raise the risk of atherosclerotic disease by a similar amount across people of different nationalities and ethnicities.<sup>46</sup> The central implication is that variations in cardiovascular risk between populations likely reflect differences in total exposure to risk factors rather than biological differences in sensitivity to these risk factors.<sup>47</sup> When comparing developed and developing worlds, data indicate that low-income countries have the highest burden of high blood pressure and related sequelae,<sup>48</sup> including stroke mortality and morbidity.<sup>49</sup>

## CONCLUSION

It is clear that more study is needed on 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.<sup>50</sup>

## Supplemental Readings

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# CHAPTER 8

## Association Between Periodontal Disease and Atheromatous Diseases

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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.<sup>1</sup> CVD accounts for 29% of deaths worldwide and ranks as the second leading cause of death after infectious and parasitic diseases.<sup>2</sup>

In atherosclerosis, large- to medium-sized muscular arteries and large elastic arteries become occluded with fibro-lipid 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 past decade in developed countries.

### The 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.<sup>3</sup> 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. Lastly, 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 relationship 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.<sup>4</sup> Additionally, a large proportion of patients with periodontal disease also exhibit atherosclerosis or CVD.<sup>5</sup> 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. In one systematic review, Scannapieco and colleagues asked the focused question, “Does periodontal disease influence the initiation/progression of atherosclerosis and therefore CVD, stroke, and peripheral vascular disease?”<sup>6</sup> The investigators identified 31 human studies. Although the authors did not perform a meta-analysis due to differences in reported outcomes, they noted relative (not absolute) consistency and concluded, “Periodontal disease may be modestly associated with atherosclerosis, myocardial infarction, and cardiovascular events.” A recent 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.<sup>7</sup>

### Meta-Analyses

In the interval between this initial review and the recent consensus report, at least three other meta-analyses on the atherosclerosis-periodontal disease association have been conducted and published. 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).<sup>8</sup> Similarly, Khader et al. 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.<sup>9,10</sup> 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

Accordingly, 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). Matilla et al. first reported that poor oral health (including periodontal disease) was a predictor for MI among a Finnish population of 100 cases and 102 control subjects.<sup>11</sup> 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 infection were 30% more likely to present with MI compared to subjects without 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.<sup>12</sup> More recently, Arbes et al. evaluated available cross-sectional data from the Third National Health and Nutrition Survey (NHANES III).<sup>13</sup> 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 to periodontally healthy controls. In addition, the probability for a coronary event rose with increasing periodontitis severity. While 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 the periodontitis exposure precedes the CVD (Table 2). Beck and colleagues evaluated 1,147 males ages 21–80 who were participants in the Normative Aging Study and who were free of CAD at baseline.<sup>14</sup> Periodontal status for this population

**Table 1.** Summary of Evidence from Case-Control Studies Investigating an Association Between Periodontal and Atheromatous Diseases in Human Populations

Reference	Study Design	Population	Periodontal Outcome or Exposure	Cardiovascular Outcome	Findings and Conclusions
Matilla et al. 1989 <sup>11</sup>	Case-control	100 cases and 102 controls	Dental Severity Index (sum of scores for caries, periodontal disease, periapical pathosis, and pericoronitis)	Evidence of MI from EKG and elevated enzyme levels (creatinine phosphokinase isoenzymes)	Dental health significantly worse in patients with MI versus controls after adjusting for smoking, serum lipids, and diabetes
Matilla et al. 1993 <sup>12</sup>	Case-control	100 cases	Dental Severity Index	Clinical diagnosis or radiographically confirmed MI	Significant association between dental infections and severe coronary atheromatosis in males (but not females)
Arbes et al. 1999 <sup>13</sup>	Case-control	5,564 subjects (NHANES III)	Percent attachment loss of all teeth (> 3 mm) and categorized according to four levels	Self-reported MI	Positive association between periodontal disease and CHD (OR = 3.8 for severe attachment loss) and after adjusting for age, gender, race, etc.
Söder et al. 2005 <sup>28</sup>	Case-control	82 cases and 31 controls	Clinical periodontitis defined as having ≥ 1 site with a pocket depth ≥ 5 mm	Carotid IMT values	Significant association between periodontal disease and carotid atherosclerosis (OR = 4.64)
Andriankaja et al. 2006 <sup>26</sup>	Population-based case-control	537 cases and 800 controls	Various including continuous CAL, PD, and missing teeth; also various case definitions	Incident MI	Significant association between periodontal disease and incident MI regardless of measurement or definition of periodontal disease used, after adjusting for multiple potential confounders
Andriankaja et al. 2007 <sup>27</sup>	Population-based case-control	574 cases and 887 controls	Mean CAL	Incident MI	Significant association between periodontal disease and incident MI in both genders, and in nonsmokers as well as smokers, after adjusting for multiple potential confounders
Lu et al. 2008 <sup>32</sup>	Case-control	3,585 subjects (NHANES III)	Percent attachment loss of all teeth (>3 mm) and categorized according to four levels	PAD defined ABI < 0.9	Significant association between periodontal disease and PAD (OR = 2.25 for severe attachment loss) after adjusting for age, gender, race, poverty, and traditional risk factors for PAD
Chen et al. 2008 <sup>33</sup>	Case-control	25 PAD cases 32 controls	Clinical periodontitis defined as having at least one probing site with PD ≥ 4 mm or CAL ≥ 4 mm in each quadrant	PAD diagnosed via clinical symptoms, ABI, and angiographic finding	Significant association between periodontitis and PAD (OR = 5.45) after adjusting for age, gender, diabetes, and smoking

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

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

Reference	Population	Periodontal Outcome or Exposure	Cardiovascular Outcome	Findings and Conclusions
Beck et al. 1996 <sup>14</sup>	1,147 males (Normative Aging Study)	Percent radiographic alveolar bone loss	Incidence of total and fatal CAD and stroke	Periodontal disease is associated with moderate risk for CAD (OR = 1.5–1.9) and stroke after adjusting for age and CVD risk factors (OR = 2.9)
DeStefano et al. 1993 <sup>15</sup>	9,760 subjects (NHANES I)	Subjects classified with no periodontal disease, with gingivitis, periodontitis ( $\geq 4$ probing depth), or edentulous	Hospital admission or death due to CAD	Periodontitis is associated with small increased risk for CAD (RR = 1.7) among males
Wu et al. 2000 <sup>16</sup>	9,962 subjects (NHANES I and follow-up)	Subjects classified with no periodontal disease, with gingivitis, periodontitis ( $\geq 4$ teeth with overt pocketing), or edentulous	Incident cases of stroke	Compared to periodontal health, relative risk for stroke with periodontitis was 2.1 and significant
Hujoel et al. 2000 <sup>17</sup>	8,032 dentate adults (NHANES I)	Periodontal pocketing and attachment loss	Death or hospitalization due to CAD or revascularization obtained from medical records	Periodontitis was not associated with a significant risk for CAD
Howell et al. 2001 <sup>18</sup>	22,037 male subjects (Physician's Health Study I)	Self-reported presence or absence of periodontal disease at baseline	Incident fatal and nonfatal MI or stroke	No significant association between self-reported periodontal disease and CVD events
Elter et al. 2004 <sup>19</sup>	8,363 subjects (ARIC Study)	Severe periodontitis defined as clinical attachment loss $\geq 3$ mm at $\geq 10\%$ of sites or tooth loss ( $< 17$ remaining teeth)	Prevalent CAD	Significant associations for attachment loss (OR = 1.5) with prevalent CAD
Beck et al. 2001 <sup>20</sup>	6,017 subjects (ARIC Study)	Severe periodontitis defined as clinical attachment loss $\geq 3$ mm at $\geq 30\%$ of sites	Carotid artery IMT $\geq 1$ mm	Periodontitis may influence atheroma formation (OR = 1.3)
Beck et al. 2005 <sup>21</sup>	15,792 subjects (ARIC Study)	Serum antibodies to periodontal pathogens	IMT $\geq 1$ mm	Presence of antibody to <i>C. rectus</i> was associated with carotid atherosclerosis (OR = 2.3)
Hung et al. 2004 <sup>22</sup>	41,407 males from the HPFS and 58,974 females from the NHS	Self-reported tooth loss at baseline	Incident fatal and nonfatal MI or stroke	For males with tooth loss, the relative risk for coronary heart disease was 1.36; for females with bone loss, the relative risk was 1.64
Joshipura et al. 2004 <sup>23</sup>	468 males from the HPFS	Self-reported "periodontal disease with bone loss" at baseline	Serum CRP, fibrinogen, factor VII, tPA, LDL cholesterol, von Willebrand factor, and soluble TNF receptors 1 and 2	Self-reported periodontal disease was associated with significantly higher levels of CRP, tPA, and LDL cholesterol after controlling for age, cigarette smoking, alcohol intake, physical activity, and aspirin intake

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

Reference	Population	Periodontal Outcome or Exposure	Cardiovascular Outcome	Findings and Conclusions
Engelbreton et al. 2005 <sup>24</sup>	203 subjects from INVEST	Radiographic alveolar bone loss	Carotid plaque thickness via ultrasonography	Severe periodontal bone loss was independently associated with carotid atherosclerosis (OR = 3.64)
Desvarieux et al. 2005 <sup>25</sup>	1,056 subjects from INVEST	Subgingival bacterial burden	Carotid artery IMT ≥ 1 mm	Severe periodontal bone loss was independently associated with carotid atherosclerosis (OR = 3.64)
Pussinen et al. 2004 <sup>29</sup>	6,950 Finnish subjects in the Mobile Clinic Health Survey	Serum antibodies to <i>P. gingivalis</i> or <i>A. actinomycetemcomitans</i>	Incident fatal or nonfatal stroke	Seropositive subjects had an OR of 2.6 for stroke
Pussinen et al. 2005 <sup>30</sup>	1,023 males in the Kuopio Ischemic Heart Disease Study	Serum antibodies to <i>A. actinomycetemcomitans</i>	Incident MI or CAD death	Subjects with the highest tertile of <i>A. actinomycetemcomitans</i> antibodies were two times more likely to suffer MI or CAD death (RR = 2.0) compared with those with lowest tertile of antibody levels
Abnet et al. 2005 <sup>31</sup>	29,584 rural Chinese subjects	Tooth loss	Incidence of fatal MI or stroke	Tooth loss was associated with an increased odds for death from MI (RR = 1.29) and stroke (RR = 1.12)

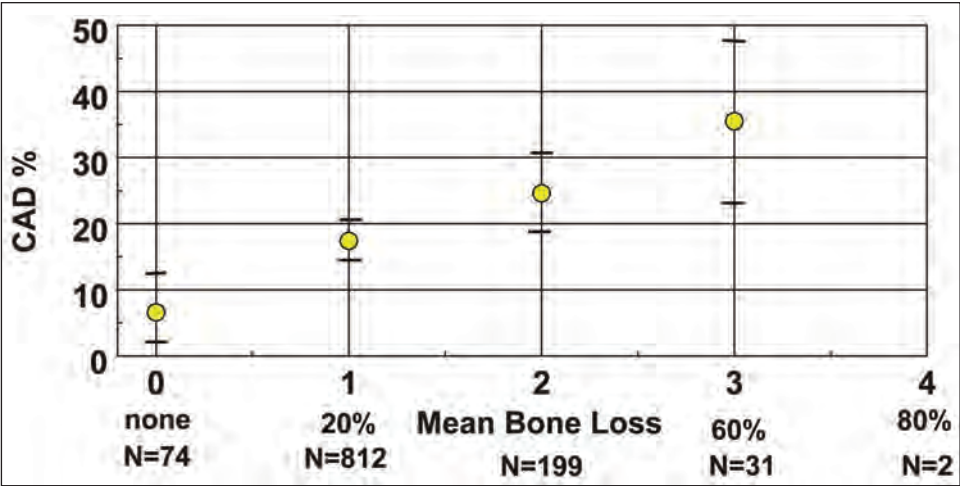
ARIC: Atherosclerosis Risk in Communities; CAD: coronary artery disease; CRP: C-reactive protein; CVD: cardiovascular disease; HPFS: Health Professional Follow-up Study; IMT: intima-media wall thickness; INVEST: Oral Infections and Vascular Disease Epidemiology Study; LDL: low density lipoprotein; MI: myocardial infarction; NHANES: National Health and Nutrition Examination Survey; NHS: Nurses Health Study; OR: odds ratio; RR: relative risk; tPA: tissue plasminogen activator

was assessed via percent alveolar bone loss using dental radiographs. Over an 18-year follow-up period, 207 men developed CAD, 59 died from CAD, and 40 experienced strokes. Odds ratios (OR) 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 relationship such that increasing severities of periodontitis were accompanied by increasing occurrences of CVD (Figure 1).<sup>14</sup>

Another cohort study conducted by DeStefano et al. assessed this risk relation-

ship among 9,760 adults followed for 14 years in NHANES I.<sup>15</sup> 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, individuals with pre-existing clinical signs of periodontitis were 25% more likely to develop CAD relative 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 to their periodontally healthy counterparts. Similarly, Wu et al. evaluated the potential contribution of periodontitis to stroke risk within this same NHANES I population (n = 9,962 adults).<sup>16</sup> The investigators

**Figure 1.** Linear Relationship Between Cumulative Coronary Artery Disease (%) Versus Bone Loss Among Male Participants in the Normative Aging Study



Source: *J Periodontol* 1996;67:1123–1137.<sup>14</sup> Reproduced with permission.

reported that the presence of clinical periodontitis significantly increased the risk for fatal and nonfatal strokes two-fold. Increased relative risks (RR) for total and nonhemorrhagic strokes were observed for both genders, Caucasians, and African Americans with periodontitis.

In contrast, two prominent cohort studies failed to detect any significant association between periodontitis and atheromatous diseases in primary or secondary analyses. Hujoel et al. re-examined 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.<sup>17</sup> In addition, Howell et al. found no association between self-reported periodontal disease and CVD events for 22,037 participants in the Physicians’ Health Study I.<sup>18</sup> 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). Opponents have criticized these studies for their over-adjustment of confounders or misclassification of exposures with the long follow-up or with self-reporting methods.

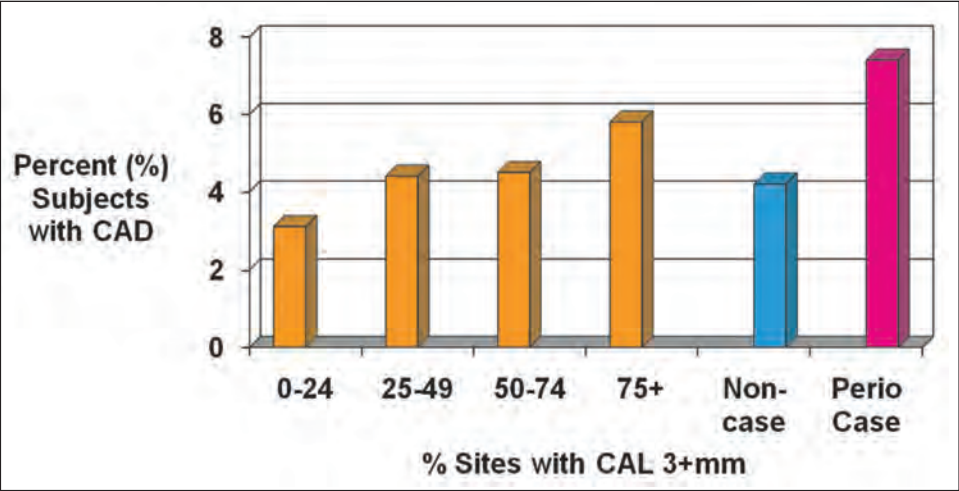
**Population Studies**

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.

Beck and colleagues collected periodontal clinical data on 6,017 persons ages 52–75, who participated in the ARIC study.<sup>19–21</sup> These 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 ( $\geq 10\%$  of sites with attachment loss  $> 3$  mm) and high tooth loss ( $< 17$  remaining teeth) exhibited elevated odds of

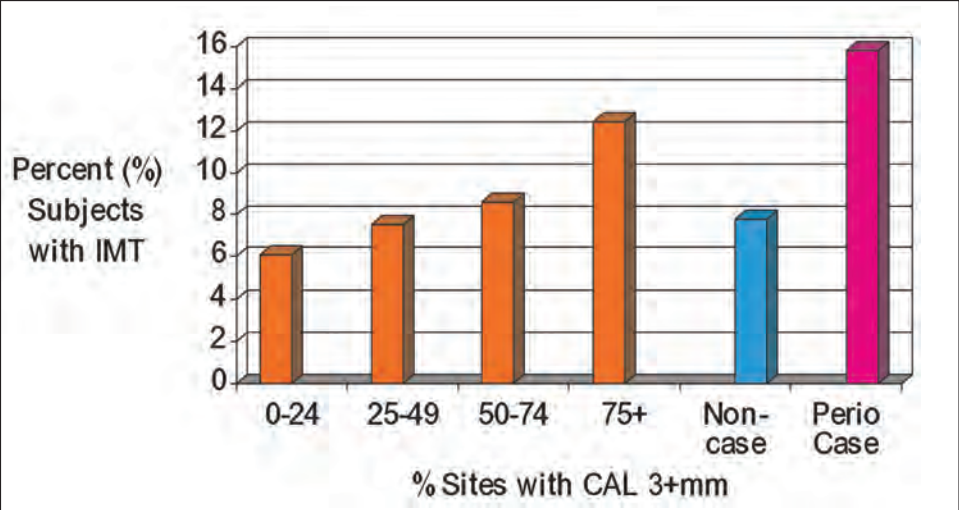
prevalent CAD compared to individuals with low attachment loss and low tooth loss (OR = 1.5, 95% CI: 1.1–2.0 and OR=1.8, CI: 1.4–2.4, respectively; Figure 2).<sup>19</sup> A second logistic regression analysis indicated a significant association between severe periodontitis and thickened carotid arteries after adjusting for covariates such as age, gender, diabetes, lipids, hypertension, and smoking (Figure 3).<sup>20</sup> Accordingly, the odds ratio for

**Figure 2.** Percent of Subjects with Coronary Artery Disease (CAD) Versus Severity of Clinical Attachment Loss (CAL)



**Note:** Prevalent CAD was significantly higher among periodontitis cases versus noncases. **Source:** *J Periodontol* 2004;75:782–790.<sup>19</sup> Reproduced with permission.

**Figure 3.** Percent of Subjects with Carotid Atherosclerosis or Intima-Media Wall Thickness (IMT) Versus Severity of Clinical Attachment Loss (CAL)



**Note:** IMT was significantly higher among periodontitis cases versus noncases. **Source:** *Arterioscler Thromb Vasc Biol* 2001;21:1816–1822.<sup>20</sup> Reproduced with permission.



severe periodontitis (i.e., 30% or more of sites with  $\geq 3$  mm clinical attachment loss) and subclinical carotid atherosclerosis was 1.31 (95% CI: 1.03–1.66). In a third report, these investigators quantified serum IgG antibody levels specific for 17 periodontal organisms using a whole bacterial checkerboard immunoblotting technique.<sup>21</sup> Analyzing mean carotid IMT ( $\geq 1$  mm) as the outcome and serum antibody levels as exposures for this same population, the investigators noted the presence of antibody to *Campylobacter rectus* increased the risk for subclinical atherosclerosis two-fold (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 prevalence 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.

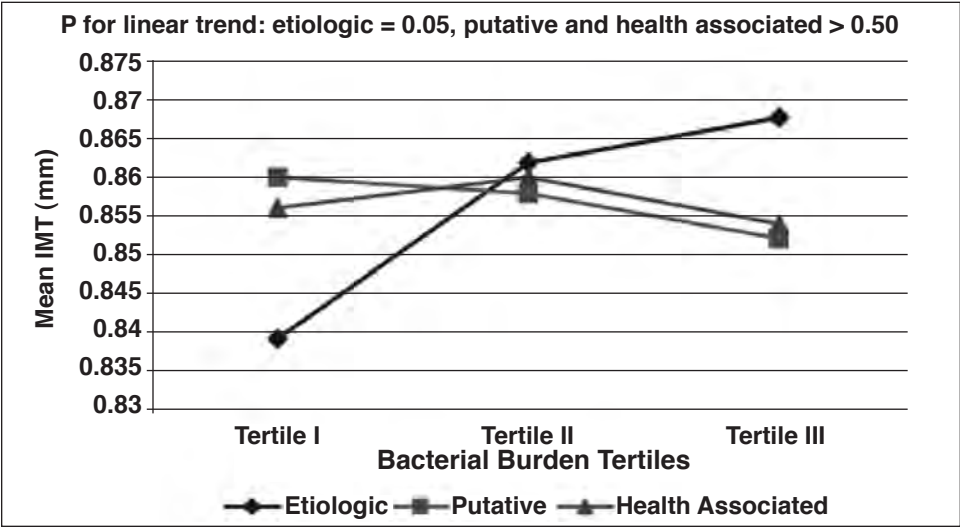
Hung and Joshipura and colleagues assessed self-reported periodontal disease outcomes and incident CVD in two extant databases, HPFS (n = 41,407 males followed for 12 years) and NHS (n = 58,974 females followed for 6 years).<sup>22</sup> After controlling for important cardiovascular risk factors, males with a low number of reported teeth ( $\leq 10$  at baseline) had a significantly higher risk of CAD (RR = 1.36, 95% CI: 1.11–1.67) compared to 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 to 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).<sup>23</sup> 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 noncases), 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. Engebretson 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 ( $\geq 50\%$  measured radiographically) than among those with less bone loss ( $< 50\%$ ).<sup>24</sup> Indeed, the group noted a clear dose-response relationship 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.<sup>25</sup>

**Figure 4.** Mean Carotid Intima-Media Wall Thickness (IMT) Across Tertiles of Bacteria Burden (Etiologic, Putative, and Health-Associated) for Participants in the INVEST Trial



Adjusted for age, BMI, smoking, systolic blood pressure, race/ethnicity, gender, diabetes, education, LDL cholesterol, and HDL cholesterol. **Source:** *Circulation* 2005;111:576–582.<sup>25</sup> Reproduced with permission.

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 forsythensis*; Figure 4). Similarly, white blood cell values (but not serum CRP) increased across these burden tertiles. These data from INVEST provide evidence of a direct relationship 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 patients ages 35–69.<sup>26</sup> Five-hundred thirty-seven cases were survivors of incident MI, and 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,<sup>27</sup> 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 from the possible confounding effects of smoking, since it was found in both cigarette smokers (OR = 1.49, 95% CI: 1.26–1.77) as well as nonsmokers (OR = 1.40, 95% CI: 1.06–1.86), after adjusting for age, gender, body mass index, physical activity, hyper-

tension, cholesterol, diabetes, and total pack-years of cigarette smoking. This is an important finding because there is an active debate among authors suggesting smoking is a causal confounding factor between periodontal disease and CVD. The positive association of periodontal disease and MI in non-smokers provides greater evidence that periodontal disease could 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 to periodontally healthy controls.<sup>28</sup> Multiple logistic regression analysis 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 et al. 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).<sup>29</sup> 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 cases with MI or CAD death were more often seropositive for *A. actinomycetemcomitans* than those controls who remained healthy (15.5% versus 10.2%).<sup>30</sup> 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.<sup>31</sup> Tooth loss was evaluated as an exposure outcome for periodontal disease, and mortality from heart disease or stroke were modeled as dependent 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 stroke (RR = 1.12, 95% CI: 1.02–1.23). These elevated risks were present in males and females irrespective of smoking status. Collectively, these findings indicate consistent associations for periodontal disease and pathogenic exposures with CVD.

### Observational Studies

Two recent observational studies have focused on the relationship 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 1999–2002.<sup>32</sup> 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%, 6–33% and more than 33% of sites with clinical attachment loss  $\geq 3$  mm). While 4.8% of subjects were recognized as PAD cases, 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 PAD, and were significantly associated with clinical attachment loss or periodontitis. A second case control study included 25 patients diagnosed with PAD (aorto-iliac and/or femoro-popliteal occlusive disease), and 32 generally healthy control subjects.<sup>33</sup> Polymerase chain reaction was used to identify *P. gingivalis*, *T. denticola*, *A. actinomycetemcomitans*, *Prevotella intermedia*, Cytomegalo-

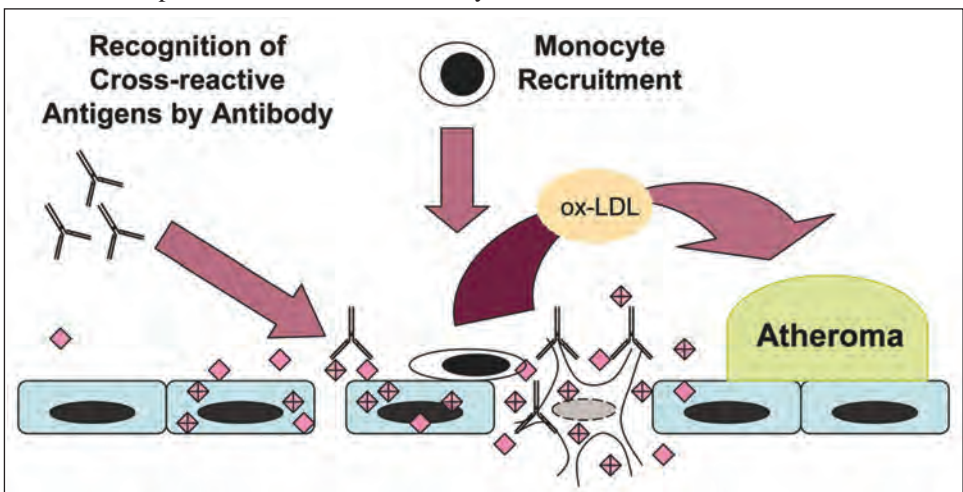
virus (CMV), *Chlamydia pneumoniae*, and *H. pylori* in tissue specimens obtained at the time of bypass grafting. After adjusting for age, gender, diabetes, and smoking, periodontitis increased five-fold the risk of having PAD (OR = 5.45, 95% CI:1.57–18.89). In addition, periodontopathic bacteria were 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. These early observational data suggest a higher likelihood of PAD among subjects with periodontal disease, and that DNA sequences specific to periodontal pathogens may be present in PAD lesions.

### BIOLOGICAL PLAUSIBILITY AND EVIDENCE FROM ANIMAL MODELS

Since periodontal infections result in low-grade bacteremias and endotoxemias in affected patients,<sup>34,35</sup> systemic effects on vascular physiology via these exposures appear biologically plausible. Four specific path-

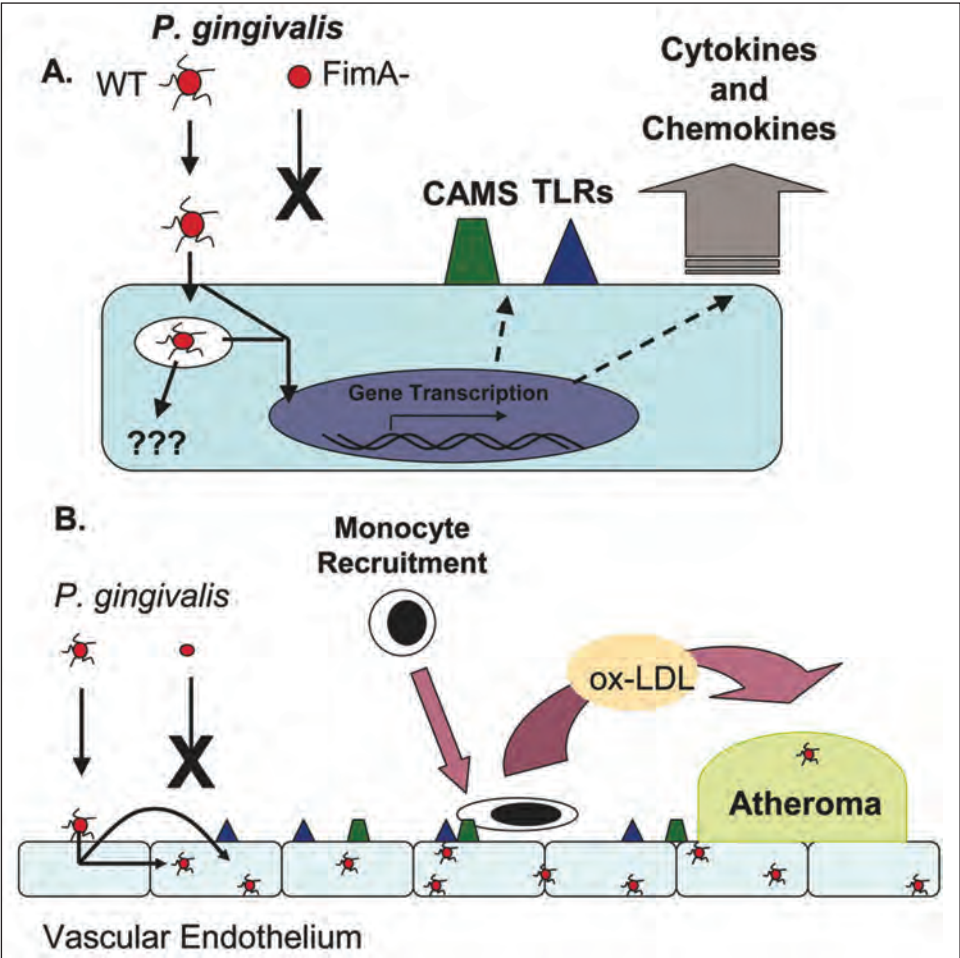
ways have been proposed to explain the plausibility of a link between CVD and periodontal infection. These pathways (acting independently or collectively) include: 1) direct bacterial effects on platelets; 2) autoimmune responses; 3) invasion and/or uptake of bacteria in endothelial cells and macrophages; and 4) endocrine-like effects of pro-inflammatory mediators.<sup>36</sup> In support of the first pathway, two oral bacteria, *P. gingivalis* and *Streptococcus sanguis*, express virulence factors called “collagen-like platelet aggregation-associated proteins” that induce platelet aggregation *in vitro* and *in vivo*.<sup>37,38</sup> Secondly, autoimmune mechanisms may play a role since antibodies that cross-react with periodontal bacteria and human heat shock proteins have been identified (Figure 5).<sup>39,40</sup> Deshpande and colleagues have thirdly demonstrated that *P. gingivalis* can invade aortic and heart endothelial cells via fimbriae (Figure 6).<sup>41</sup> Several investigative groups have independently identified specific oral pathogens in atheromatous tissues.<sup>42,43</sup> In addition, macrophages incu-

**Figure 5.** 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;85:106–121.<sup>36</sup> Reproduced with permission.

**Figure 6.** Invasion of the Vascular Endothelium by Pathogenic Bacteria Results in the 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;85:106–121.<sup>36</sup> Reproduced with permission.

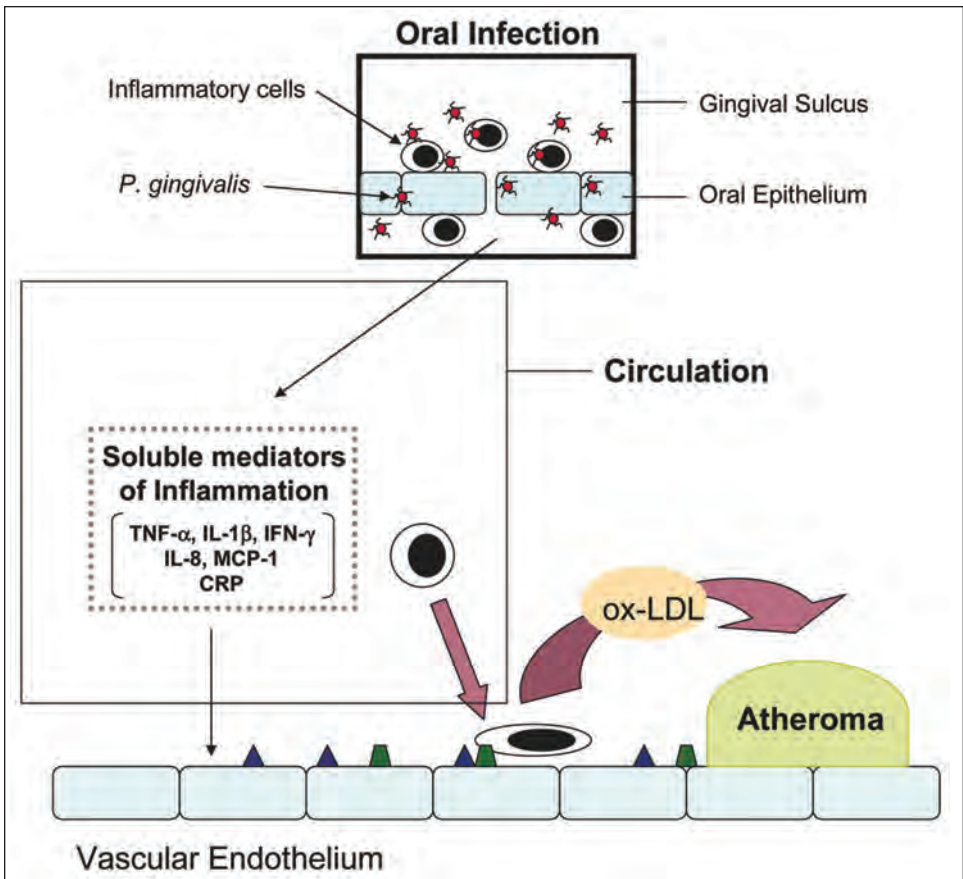
bated *in vitro* with *P. gingivalis* and LDL uptake the bacteria intracellularly and transform into foam cells.<sup>44</sup> In the last potential pathway, systemic pro-inflammatory mediators are up-regulated for endocrine-like effects in vascular tissues, and studies consistently demonstrate elevations in CRP and fibrinogen among periodontally diseased subjects (Figure 7).<sup>16,45</sup>

### 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*.<sup>46–49</sup> In one of these experiments,



**Figure 7.** Persistent Periodontal Infection May Promote Atherosclerosis via Chronic Up-Regulation of Inflammatory Cascades



**Note:** These include tumor necrosis factor-alpha ( $\text{TNF-}\alpha$ ), interleukin-1 ( $\text{IL-1}$ ), interferon ( $\text{IFN}$ ),  $\text{IL-8}$ , 1 monocyte chemo-attractant protein-1 ( $\text{MCP-1}$ ), and C-reactive protein ( $\text{CRP}$ ). **Source:** *J Dent Res* 2006;85:106–121.<sup>36</sup> Reproduced with permission.

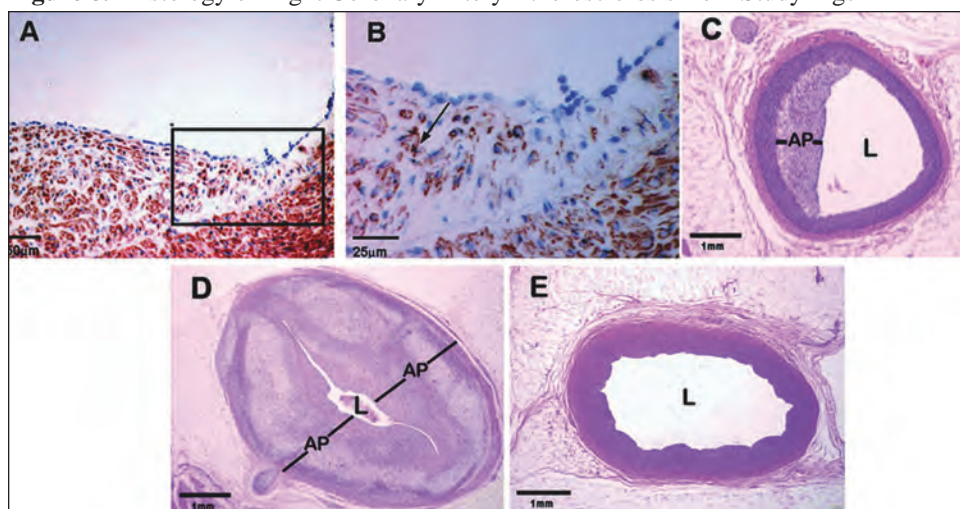
Lalla and colleagues randomized 50 male homozygous apoE-null mice to either topical inoculation with *P. gingivalis* (strain 381 both orally and anally because of the coprophagic nature of the animals) over three weeks, or antibiotics plus vehicle (sterile phosphate-buffered saline) on the same schedule.<sup>48</sup> 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 importantly, morphometric analyses revealed a statistically significant 40% increase in mean atherosclerotic lesion area for *P. gingivalis*-infected animals compared with controls.

#### Porcine Model

Similarly, Brodala and colleagues have demonstrated accelerated atherogenesis in a



**Figure 8.** 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;25:1446–1451.<sup>50</sup> Reproduced with permission.

pig bacteremia model.<sup>50</sup> Accordingly, the investigators allocated pigs ( $n = 36$ ) to either low- or high-fat diets. They sensitized some animals with heat-killed *P. gingivalis* ( $10^9$  organisms), and then challenged them with live *P. gingivalis* ( $10^6$ – $10^7$  organisms) injected intravenously three times weekly over a five-month period. Other animals that were sensitized with *P. gingivalis* (no live challenge) or that were treated with saline served as controls. Results indicated that *P. gingivalis*-challenged pigs developed significantly more coronary and aortic atherosclerosis than controls in the low-fat (normocholesterolemic) group, and nearly as significant in the high-fat (hypercholesterolemic) group (Figure 8). *P. gingivalis* was detected by polymerase chain reaction in arteries from most (94%) of the challenged pigs, but not controls. This finding suggests that *P. gingivalis* bacteremia may exert an atherogenic stimulus independent of high cholesterol levels in pigs.

### Animal Studies Summary

It is worth noting that a wide range of *P. gingivalis* doses was used in these murine and porcine studies. While the clinically relevant dose for human subjects is unknown at present, it probably varies greatly.<sup>51–53</sup> Importantly, *P. gingivalis* challenges enhanced atherosclerosis despite different routes of administration and dosing regimens in both species. While *P. gingivalis*' 16 ribosomal DNA could be detected in atheromas 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 TRIALS

Human evidence demonstrating beneficial effects of periodontal therapy on atheromatous disease outcomes is limited and indirect at present. In an initial intervention

trial, D'Aiuto and colleagues demonstrated that periodontitis patients treated with scaling and root planing exhibited significant serum reductions in the CVD biomarkers, CRP, and interleukin-6.<sup>54</sup> 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 relative to patients with a poor clinical periodontal response.

### **The PAVE Study**

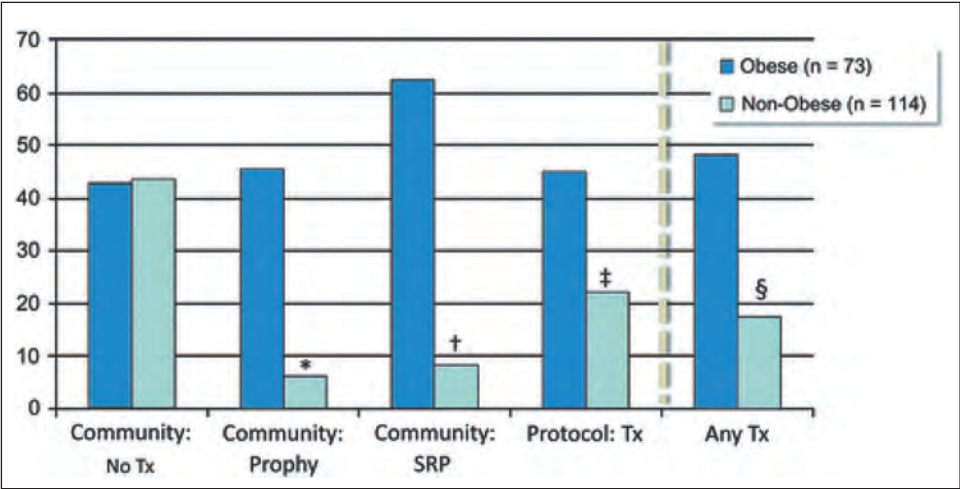
In 2009, Offenbacher and collaborators published results from the Periodontitis and Vascular Events (PAVE) pilot study, which was conducted to investigate the feasibility of a randomized secondary-prevention trial.<sup>55</sup> Accordingly, five clinical centers recruited participants who had documented CAD ( $\geq 50\%$  blockage of one coronary artery or previous coronary event including MI, coronary artery bypass graft surgery, or coronary transluminal angioplasty three to 36 months prior to enrollment) and who met study criteria for periodontal disease ( $\geq 3$  teeth with probing depths  $\geq 4$  mm,  $\geq 2$  teeth with interproximal clinical attachment loss  $\geq 2$  mm, and  $\geq 10\%$  of sites with bleeding on probing). Three-hundred and 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). Serum samples obtained at baseline (prior to randomization) and at six months were analyzed for levels of high-sensitivity (hs) CRP. While the intensive treatment protocol significantly improved periodontal probing parameters over six months, the treatment did not significantly improve mean serum hsCRP levels in the overall population. Interestingly, in secondary analyses it was noted that 48% of the community care control group received

some form of preventive or periodontal therapy over the six-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 9). Among non-obese individuals in the community who received no treatment, 43.5% had elevated hsCRP ( $> 3$  mg/L) at six 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 2.38-fold lower odds for high hsCRP (OR = 0.42, 95% CI: 0.18–0.99). The effects were even stronger among the non-obese subjects, with a 3.85-fold lower odds for having high hsCRP at six months with any treatment (OR = 0.26, 95% CI: 0.09–0.72). 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 9 also suggests that even a dental prophylaxis, which includes supragingival removal of plaque and oral hygiene instruction, has an effect on systemic inflammation. From Figure 9 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 ( $p = 0.009$ ). It is reasonable, then, to recommend good oral hygiene practices in cardiovascular patients, including tooth brushing using 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

**Figure 9.** Percent of Subjects with Elevated Serum High Sensitivity C-Reactive Protein (hsCRP) > 3 mg/L at Six Months by Treatment Group and Stratified by Obesity for the Periodontitis and Vascular Events (PAVE) Pilot Study



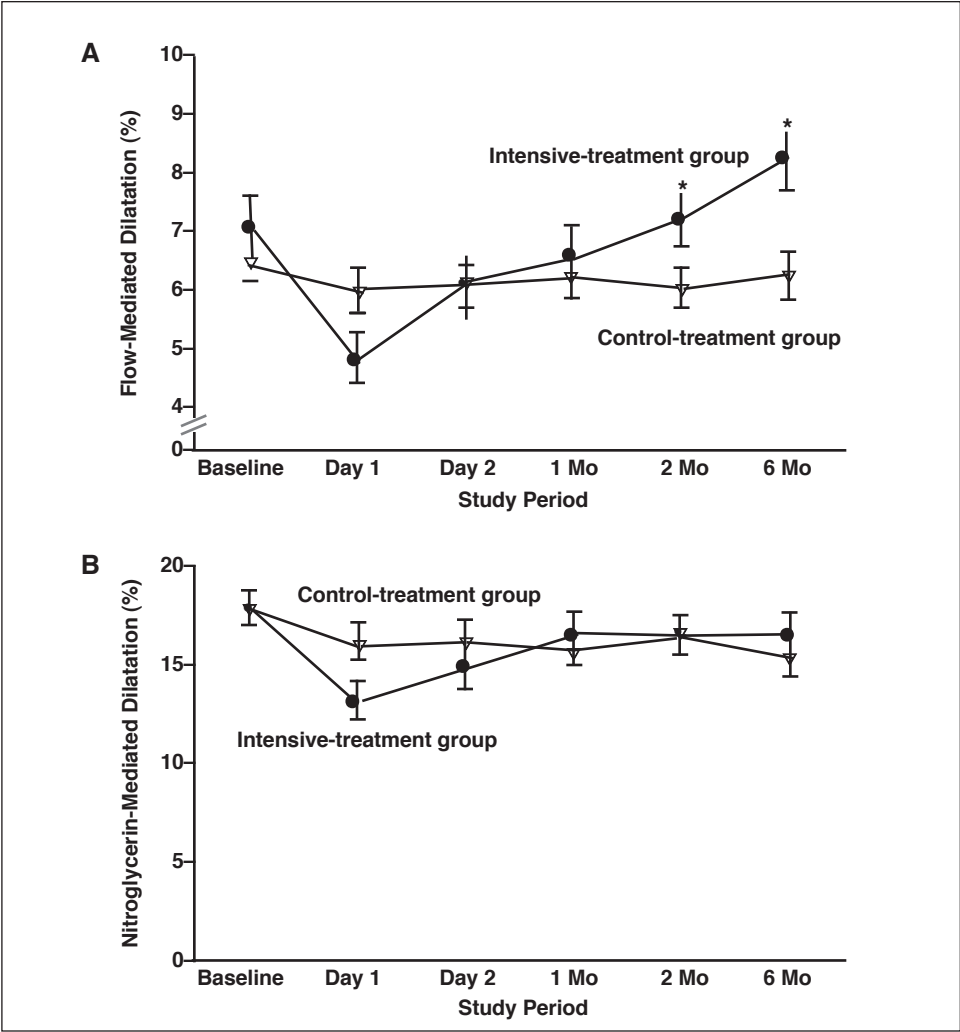
\*p = 0.009; †p = 0.03; ‡p = 0.04; §p = 0.006; Tx = treatment; Prophy = prophylaxis; SRP = scaling and root planing. Vertical dashed line designates that “Any Tx” is a composite of the three treatment groups. **Source:** *J Periodontol* 2009;80:190–2001.<sup>55</sup> Reproduced with permission.

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 two-week interval) and observed significant improvements in endothelial function (flow-mediated dilation of the brachial artery) and serum biomarkers such as interleukin-6.<sup>56</sup> Similarly, Seinost and colleagues tested endothelial function in 30 patients with severe periodontitis versus 31 periodontally healthy control subjects.<sup>57</sup> Prior to 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 re-treatment) 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.<sup>58</sup> 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 10), 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 the plasma levels of soluble E-selectin compared to control subjects.

While the effects of periodontal therapy on endstage events in patients with atheromatous diseases have yet to be determined, the available evidence suggests that periodontal interventions may be associated with three- to six-month improvements in serum

**Figure 10.** Flow-Mediated Dilatation and Nitroglycerin-Mediated Dilatation Over Six Months for Periodontitis Subjects Treated with Intensive Therapy Versus Community Controls



**Note:** Monitored over a six-month period for periodontitis subjects treated with intensive therapy vs. community controls. **Source:** *N Engl J Med* 2007;356:911–920.<sup>58</sup> Reproduced with permission.

inflammatory biomarkers and endothelial function that are predictive of atheromatous diseases.

**CONCLUSION**

Human observational studies and experimental animal models continue to implicate periodontal infection as a systemic exposure

that may perpetuate inflammatory events in vessels, and that may contribute to the progression of atheromatous diseases. 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 are 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

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# CHAPTER 9

## Periodontal Disease and Pregnancy Complications

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### INTRODUCTION

Since the first publication that linked periodontal disease with pregnancy complications in 1996, there have been numerous studies exploring the association.<sup>1</sup> These 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 infection can serve as a distant site of infection, affecting prematurity and fetal growth. 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 experience preterm delivery, there is direct biological evidence that periodontal organisms are associated with amniotic fluid inflammation, intrauterine fetal exposure, and fetal inflammation. Despite the evidence supporting an association and the biological data suggesting 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 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 biological 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 bona fide 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 researchers begin to better understand the linkages between periodontal infection and systemic health and to examine intervention studies, the concept has emerged that the treatments used to control oral manifestations of periodontal disease may not be sufficient to halt 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 biological 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.

This chapter will discuss the evidence linking periodontal diseases to pregnancy and neonatal development abnormalities, including prematurity, fetal growth deviations, and obstetric complications. The condition of preeclampsia is quite different in clinical presentation and pathogenesis, and is discussed separately. Animal model data as well as population studies in humans will be highlighted. The data linking periodontal disease to fetal demise and stillbirth are quite limited and are included under both human and animal discussions. Recently published meta-analyses and reviews will be cited as background information to focus on recent trials

and the interpretation of findings that impact clinical practice and healthcare policy.

Key educational objectives include acquiring the ability to:

1. understand the types of obstetric complications that have been associated with periodontal disease;
2. learn the evidence linking periodontal disease to obstetric complications, as it relates to other risk factors for adverse pregnancy outcomes;
3. gain insight into the current models of pathogenesis that establish biological plausibility and the evidence from human and animal models that support these mechanisms; and
4. appreciate how this information impacts our thinking regarding the clinical management of the pregnant mother and the potential implications for maternal-child health.

### **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.<sup>1</sup> 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 biofilm pathogens. Increases in serum progesterone serve to amplify gingival crevicular fluid flow rate, altering conditions within the subgingival flora, and leading to elevated levels of *Porphyromonas* species. There is an overgrowth of the Socransky Red and Orange complexes. This 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 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 the neovascularization within the gingival tissues increases during pregnancy, as the gingival changes almost mirror that 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, which serves to protect the fetus from host versus graft immunorejection. Thus, alteration in the maternal immune response likely contributes 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 preterm birth, fetal growth restriction, preeclampsia, fetal loss (spontaneous abortions and fetal demise), and stillbirths. 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, it appears that oral infection is 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 pathological signals or 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 who have obstetric complications have a genetic trait that creates an abnormal hyperinflammatory response that can result in pregnancy complications and 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 for oral infections, or any infection, to increase the risk for 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 oral infection’s relevance to managing maternal-child health outcomes, since the effects of oral infection would be exaggerated in an individual 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 at the placental tissue are important cytokine producers and may be critical 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

the overactivation may be linked to placental defects and pregnancy complications.

### **PRETERM BIRTH AND FETAL GROWTH RESTRICTION**

In the United States, preterm birth (PTB), defined as birth of an infant born before 37 weeks completed gestation or before 259 days of gestational age,<sup>2</sup> 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.<sup>3,4</sup> Furthermore, in 2004, low birth weight (LBW; < 2,500 gm) 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, so LBW becomes a worldwide reporting standard. The increased rate of prematurity is due to three factors: an inability to identify all causal risk factors; the inability to adequately control known risk factors; and an 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.<sup>5–7</sup> With prematurity remaining the leading cause of perinatal morbidity and mortality worldwide, and with widespread recognition that inflammation is responsible for a substantial fraction of PTBs,<sup>8–10</sup> 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.<sup>11,12</sup> Furthermore, periodontal disease and the systemic bacteremias caused by periodontal pathogens are significant contributors to a systemic maternal inflammatory response during pregnancy, involving cytokinemia and the release of acute-phase

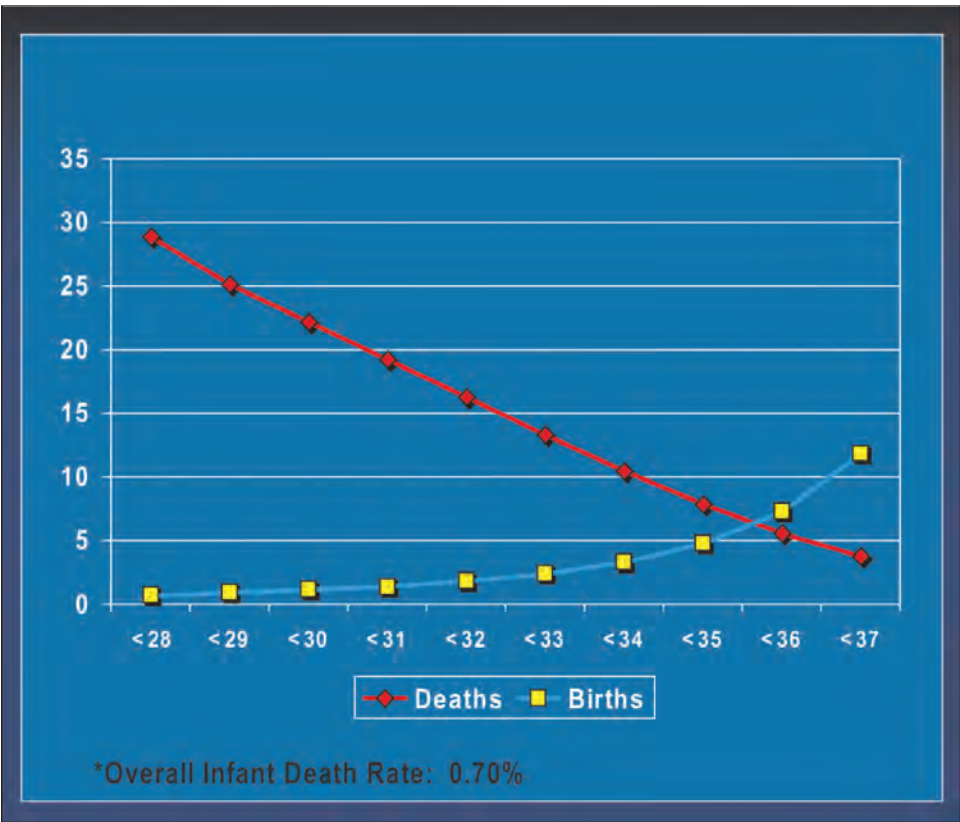
proteins by the liver, such as C-reactive protein. Inflammation, in turn, can serve as an independent biochemical threat to the fetal-placental unit by inducing labor, rupture of membranes, and early parturition. These inflammatory processes can extend to the developing fetus to also threaten the health of the neonate, an effect that may persist into childhood and even into adulthood by early intrauterine exposures that permanently affect neurological and metabolic systems. Most of these concepts have been demonstrated in animal models and reflected in human data.<sup>13-15</sup>

Normal-term deliveries occur at 40 weeks. *Very* PTB are babies that are born at less than 32 weeks 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 one half of the preterm deliveries occur near term between 35–37 weeks gestation, and the rate of morbidity and mortality in this group is relatively low compared to earlier gestations. Figure 1 shows that the rate of mortality increases 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.<sup>16</sup> Even late premature infants, those born between 34

**Figure 1.** Cumulative Percent Infant Death Rate and Births by Gestational Age



Vital statistics from years 1999–2000 (single births only), N = 349,688.

and 36 weeks,<sup>17</sup> have a greater risk of feeding difficulties, thermal instability, respiratory distress syndrome, jaundice, and delayed brain development.<sup>15</sup> Prematurity is responsible for almost 50% of all neurological complications in newborns, leading 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 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 uni-directional nutrient and vitamin exchange from the mother to the fetus. For example, if the mother is starving, the maternal liver will shrink to one-third its normal size during pregnancy and the fetus will continue 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 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, one-third due

to preterm labor, and one third from everything else, including preeclampsia, as well as 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 10th 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 respiratory distress to cognitive and learning disabilities. For example, fetal neurologic tissues are especially susceptible to damage via cytokines, such as interferon gamma (IFN- $\gamma$ ), which induce apoptosis and impair development of synapse connections among embryologic neurons.<sup>18</sup>

Although there have been advances in technology to help save those 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:

- Increased risk for motor and neurological disabilities
- Chromosomal abnormalities
- Hypoglycemia
- Increased risk for hypoxia
- Decreased oxygen levels

Selected neonatal complications following PTB include:

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

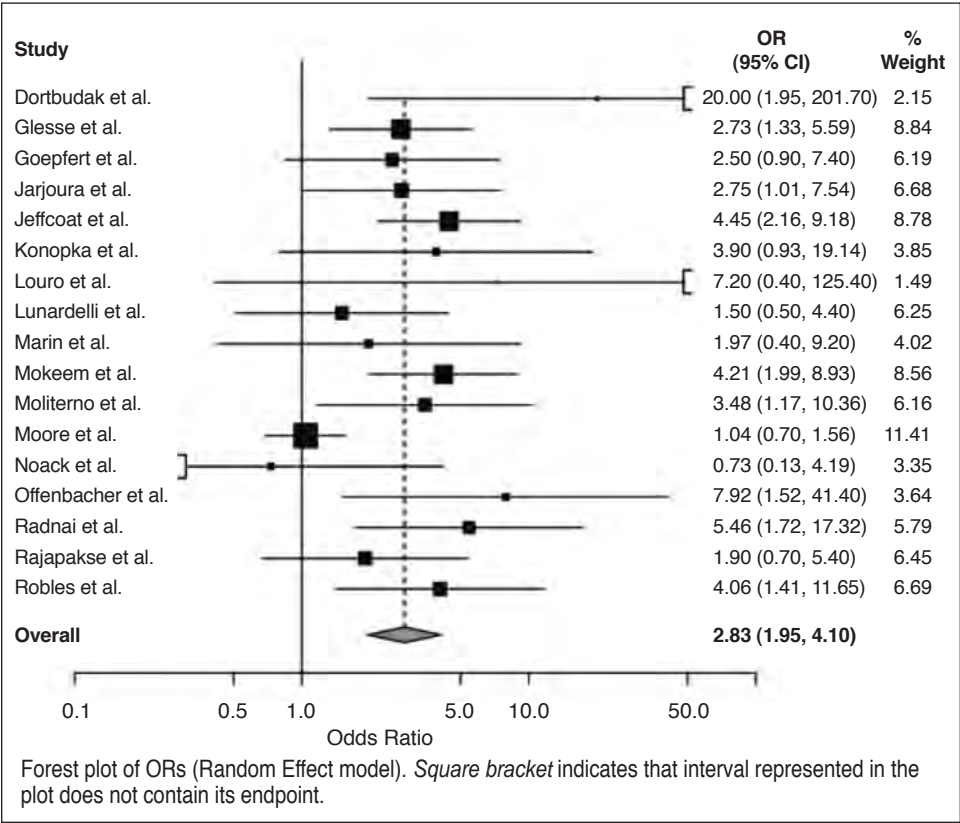


# **ASSOCIATION OF PTB AND FETAL GROWTH RESTRICTION WITH PERIODONTAL DISEASE**

The human data supporting an association between maternal periodontal disease and preterm delivery has recently been reviewed in a meta-analysis by Vergnes and Sixou.<sup>19</sup> The authors conducted a meta-analysis of 17 peer-reviewed studies and found an overall odds ratio of 2.83 (95% CI: 1.95–4.10,  $p < 0.0001$ ) was significant ( $n = 17$  studies: 7,150 patients), concluding that periodontal disease may be an independent risk factor for preterm and LBW deliveries. In Figure 2, the Forest plot shows the results of these clinical investigations that have been conducted around the world.

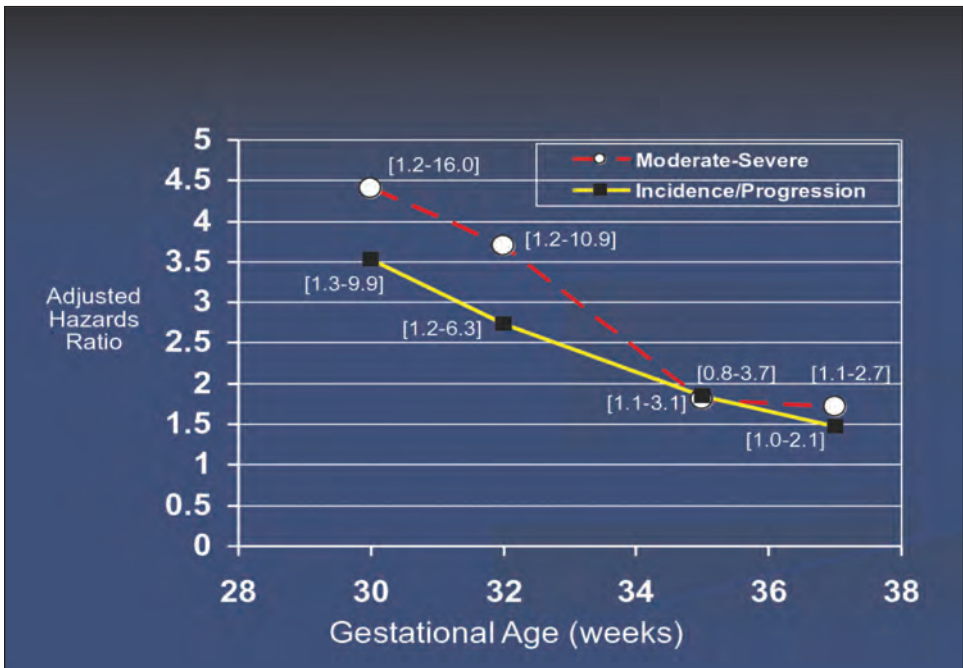
Thus, the consensus of the available data support the concept that maternal periodontal disease is associated with prematurity. The specifics of maternal infection have been studied in a few publications and some trends appear. First, antenatal maternal disease status or periodontal progression during 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. This is illustrated in Figure 3. As the exposure occurs closer to term, the risk diminishes, but remains statistically significantly greater than 1.0. For example, the hazards ratio of delivery at 32 weeks gestational age for moderate-severe periodontal disease is about

**Figure 2.** Meta-Analysis of Preterm LBW and Maternal Periodontal Status



Source: *Am J Obstet Gynecol* 2007;196:135.e1–7.<sup>19</sup> Reproduced with permission.

**Figure 3.** Hazards Ratio for Preterm Delivery at Various Gestational Ages Based on Maternal Periodontal Status



**Source:** Offenbacher S, Beck J. Has periodontal treatment failed to reduce adverse pregnancy outcomes? The answer may be premature. *J Periodontol* 2007;78:195–197. Reproduced with permission.

3.7, but less than 2.0 by 35 weeks (Figure 3). A similar relationship can be seen with bacterial vaginosis, which is 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.

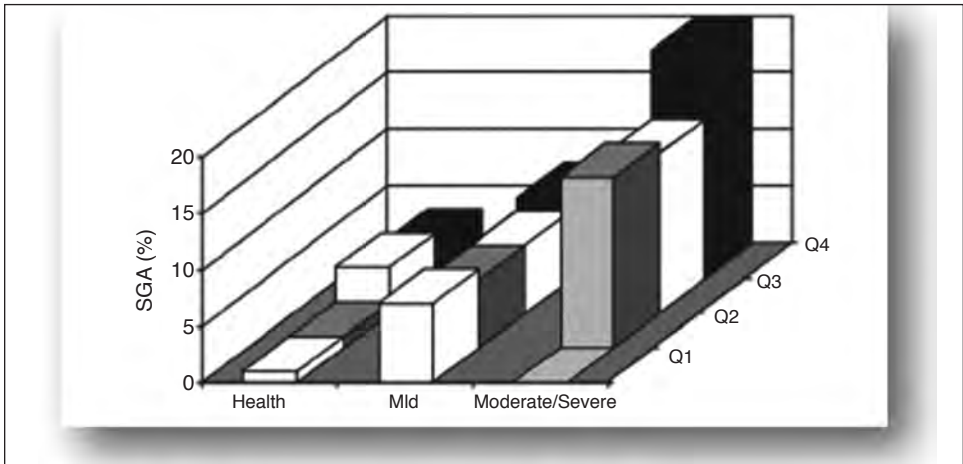
Other, less common, adverse pregnancy outcomes (e.g., diabetes, SGA birth weight, miscarriage) may also be associated with maternal periodontal infection. Infants who are SGA have significantly higher neonatal mortality rates compared to appropriate- and large-for-gestational-age infants.<sup>2</sup> In 2006, Boggess and coworkers reported in a study with 1,017 women, analyzing periodontal disease status and pregnancy complications, that from the 67 women who delivered an SGA infant, the SGA rate was higher among women with moderate or severe periodontal

disease compared to those with health or mild disease (13.8% versus 3.2% versus 6.5%,  $p < 0.001$ ).<sup>20</sup> Moderate or severe periodontal disease was associated with an SGA infant, at a risk ratio of 2.3 (1.1 to 4.7), adjusted for age, smoking, drugs, marital and insurance status, and preeclampsia, concluding that moderate or severe periodontal disease early in pregnancy is associated with delivery of SGA infants (Figure 4).

### PREECLAMPSIA: RISK FACTORS AND COMPLICATIONS

Preeclampsia, a pregnancy complication recognized by new-onset gestational hypertension and proteinuria, is considered one of the most significant health problems in human pregnancy, and it complicates 8% to 10% of all pregnancies.<sup>21</sup> The disorder affects both mothers and their infants with

**Figure 4.** Rate of Delivery of an SGA Infant by Maternal Periodontal Disease Category and C-Reactive Protein Quartile



Categories: Health versus mild and moderate/severe. C-reactive protein quartiles: Q1, less than 25th percentile; Q2, 25th to 49th percentile or greater; Q3, 50th to 74th percentile or greater; Q4, 75th percentile or greater. **Source:** *Am J Obstet Gynecol* 2006;194:1316–1322.<sup>20</sup> Reproduced with permission.

considerable fetal mortality and morbidity due to the effects of the disease on the fetus, as well as prematurity. The induced delivery of women, to prevent the progression of preeclampsia, is responsible for 15% of all PTBs.<sup>20</sup> In the last two decades, appreciation that preeclampsia is a multi-systemic 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.<sup>21</sup> 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.<sup>22</sup>

Women with preeclampsia are three to four times more likely to deliver an SGA infant than normal women. Conservatively estimated, 20,000 PTBs at less than 34 weeks

occur annually in the United States due to 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.<sup>23</sup> There are epidemiologic data supporting the premise that chronic infection could link preeclampsia with later atherosclerosis, especially given the increased susceptibility to chronic infection due to reduced cell-mediated immunity in pregnancy, which is the outcome of trophoblastic activity in the placenta protecting the fetus from maternal immune attack by reducing cell-mediated immunity.<sup>24</sup> 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 with the development of preeclampsia.<sup>25</sup>

Maternal clinical periodontal disease at delivery has been associated with an increased risk for the development 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 the presence of periodontal disease progression, was also associated with an increased risk for preeclampsia.<sup>26</sup>

### ASSOCIATION OF PREECLAMPSIA WITH PERIODONTAL DISEASE

Boggess and colleagues were the first investigators to report an association between maternal clinical periodontal infection and the development of preeclampsia.<sup>27</sup> In a longitudinal study of more than 1,000 women, the presence of periodontal infection at delivery, or disease worsening during the course of pregnancy, was associated with a two-fold increased risk for preeclampsia compared to 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 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.<sup>26</sup> In another case-control study, Barak and coworkers also found that women with preeclampsia had more severe periodontal disease in comparison to healthy controls, with significant elevation in gingival crevicular fluid levels of PGE-2, interleukin (IL)-1 $\beta$ , and tumor necrosis factor alpha (TNF- $\alpha$ ).<sup>28</sup> In another study, women with preeclampsia were also found to have worse periodontal infection than normal healthy women. In addition, two “red complex” micro-organisms, *Porphyromonas gingivalis* and *Tannerella forsythensis*, were more prevalent in the oral plaque among preeclamptic women than among controls.<sup>29</sup>

All of these studies raise the question as to whether periodontal treatment may be a potential preventive intervention therapy for preeclampsia through periodontal infection control.

### HUMAN STUDIES ON THE ASSOCIATION OF PERIODONTAL DISEASE AND ADVERSE PREGNANCY EVENTS

Several studies suggest a significant association between maternal periodontal disease and pregnancy complications, including premature delivery and preeclampsia.<sup>27,28,30</sup>

Since the first reported case-control study in humans published in 1996,<sup>1</sup> showing that mothers with premature LBW babies had 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 five 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.<sup>11,31,32</sup> 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, and it has been suggested that the difference in periodontal disease prevalence may, in part, explain the observed increased risk in preterm delivery and fetal growth restriction among African-Americans.<sup>33</sup> Studies exploring the connection between maternal infection with specific periodontopathogenic organisms and periodontal disease progression in relation to fetal immune response to oral pathogens have, in general, supported

the notion that periodontitis is independently associated with PTB and LBW.

In 2001, Madianos<sup>33</sup> and colleagues analyzed clinical data from the first 812 deliveries from a cohort study of pregnant mothers titled Oral Conditions and Pregnancy. This study 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 immunoglobulin (Ig)M to *Campylobacter 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 colleagues collected samples, including dental plaque and amniotic fluid, from 48 women attending for elective caesarean section.<sup>12</sup> Data analysis indicated that *Streptococcus* species and *Fusobacterium nucleatum* in the amniotic fluid may have an oral origin. Han and colleagues also demonstrated that in certain cases of chorioamnionitis-associated preterm birth, the same clonal type of organism was found in both the maternal plaque and the amniotic fluid.<sup>34</sup> Later, this same group reported a term stillbirth caused by oral *Fusobacterium nucleatum* in a woman with pregnancy-associated gingivitis and an upper respiratory tract infection at term. The linkage was confirmed by examination of different microbial floras from the mother identifying the same clone in the placenta, fetus, and subgingival plaque; but not in supragingival plaque, vagina, or rectum. The authors also suggested that the translocation of the oral bacteria to placenta was facilitated by the weakened maternal immune system.<sup>35</sup>

In 2007, Lin and coworkers explored the underlying microbial and antibody responses associated with oral infection with complexes

most often linked with periodontitis, Socransky Orange and Red.<sup>36</sup> They found that high levels of periodontal pathogens and low maternal IgG antibody response to periodontal bacteria during pregnancy are associated with an increased risk for preterm delivery, with higher levels of periodontal pathogens, measured antepartum, in the preterm compared to the full-term deliveries. Overall, the data from meta-analyses that combine information from several studies continue to demonstrate a significant association between periodontal disease severity and abnormal pregnancy outcomes.

### ANIMAL STUDIES

Early studies in animal models using oral organisms as a challenge in the 1980s demonstrated there is a dose-response related to obstetric outcomes. At low microbial challenges, there is a mild systemic inflammatory response which is associated with transient increases in circulating cytokines, such as TNF- $\alpha$ , and increases in the 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, as compared to C-reactive protein 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 to 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. 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 there is clear linkage between placental exposure of the organisms and fetal outcomes. For example, a pregnant mouse would typically have seven or eight fetal pups, each with their own placenta and membranes. A maternal challenge of  $10^7$  colony forming units/mL of *P. gingivalis* during pregnancy, as an example, would cause three of the eight fetuses to have impaired growth, and these would be runts. Analysis of placentas from all eight fetuses shows that when *P. gingivalis* is found within the placenta the fetus is runted, whereas *P. gingivalis*-negative placentas would have normal-sized fetuses. Increasing the concentration to  $3 \times 10^7$ , one sees three normal fetuses, four runts, and two that have been resorbed. That means that the fetus is nonviable and is analogous to fetal demise in humans or fetal loss. 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*.<sup>37</sup> 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 to cause growth restriction.<sup>37-39</sup> The importance of placental dissemination was convincingly demonstrated when it was shown that 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 T helper (TH)-1 and TH-2 immune response.<sup>39</sup> Evidence from pregnant murine infection models indicates that maternal challenges with *P. gingivalis* that resulted in growth restriction were also associated with increases in maternal TNF- $\alpha$  and a suppression of IL-10 within the serum.<sup>38</sup> This was accompanied by an increase in placental mRNA expression of IFN- $\gamma$  and IL-2, as well as a decrease in IL-10, IL-4, and tumor growth factor- $\beta$ . Thus, *P. gingivalis* challenge was associated with an overall increase in the placental TH-1/TH-2 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- $\alpha$ , mRNA, and attendant growth restriction. This was accompanied by deviations in neurodevelopment, with altered myelination and white matter damage in the hippocampus.<sup>38</sup>

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.<sup>40</sup> This zone is the point of maternal-fetal vascular anastomoses that regulate nutrient and oxygen exchange, and is rich in spongiotrophoblasts which secrete growth factors such as insulin-like growth factor (IGF) that stimulate fetal growth and development. In humans, impairment of placental IGF-2 expression is associated with intrauterine growth restriction (IUGR). Bobetsis et al. examined whether the alterations in placental structure seen in the pregnant mouse infection model were related to IGF-2 suppression in murine IUGR.<sup>40</sup> Not only did the investigators 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,” because it does not involve a sequence change, but does result in a change in gene expression that 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 down-regulation of this gene that plays a critical role in fetal growth and development programming.<sup>41</sup> With these findings, the investigators proposed a new mechanism

linking an environmental infectious and inflammatory insult to now include epigenetic modifications.

Epigenetic modifications carry important consequences for development as they can be permanently retained in the genome. These potentially permanent alterations may in part explain the poor prognosis of the infant born SGA, since 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 neurological impairments and adult-onset conditions, such as diabetes and cardiovascular disease.<sup>42,43</sup> This concept raises the possibility that intrauterine exposure to oral organisms of maternal origin may have more permanent effects that extend beyond the perinatal 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 López et al. suggested that periodontal treatment may reduce the rate of preterm deliveries five-fold.<sup>44</sup> However, many additional clinical trials are still in progress. The data are encouraging, but not conclusive. A recent meta-analysis conducted by Polyzos and colleagues summarized the available data from seven randomized trials and reported that overall treatment reduced prematurity.<sup>45</sup> The overall reported odds ratio was 0.48 ( $0.23 - < 1.0$ ,  $p = 0.049$ ).<sup>45</sup> 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 two-fold. 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, multi-centered study conducted by Michalowicz and colleagues that was included in this treatment meta-analysis failed to show any obstetric benefits,<sup>46</sup> suggesting that additional treatment studies need to be conducted to better understand the potential risks and benefits of periodontal care. 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, biological gradient, biological 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 or they fail to modify the components of the vaginal infection. Importantly, maternal periodontal health is in itself an extremely important outcome irrespective 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 biological processes that underlie the association between maternal periodontal disease and pregnancy complications, as well as the effects of treatments, will provide greater insight into pathogenesis. In other words, there needs to be a better understanding of the cellular and molecular events that underlie the association between periodontal progression and fetal exposure, and how treatments, whether successful or not, modify these biological components. For example, Lin and coworkers reported that although periodontal treatments reduced the risk of PTB among treated mothers, there was a significant persistence of high levels of oral *P. gingivalis* infection.<sup>36</sup> This suggested that the treatment provided did not adequately control infection in all mothers, and was therefore insufficient to improve obstetric outcomes.

Understanding the mechanism of pathogenesis is the cornerstone of knowledge that enables us to identify who is at risk, so we understand who needs to be treated, and how we should treat to show maximum benefit and minimized risks. These are critical questions that await further study.

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### Supplemental Readings

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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 could be exogenous pathogens that 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 the release of biologically active inflammatory mediators and hydrolytic enzymes into the oral fluids that 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 that have significant morbidity and mortality. Furthermore, some respiratory illnesses (such as asthma) may have an effect on orofacial morphology or even on dentition. This chapter discusses several important respiratory diseases that may be influenced by oral microflora or oral inflammation. Much of the material presented has been previously reviewed and discussed.<sup>1-5</sup>

### 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 increased medical costs. Bacterial pneumonia is comprised of several subtypes: community-acquired pneumonia, aspiration pneumonia, hospital-acquired (nosocomial) pneumonia, ventilator-associated pneumonia, and nursing home-associated pneumonia. In all cases, correlations have been made with oral health status.

### 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 that 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.<sup>6</sup>

The major etiologic agents of CAP are viruses; for example, respiratory syncytial virus or rhinovirus. Early in life, bacterial causes of CAP include group B streptococci or gram-negative enteric bacteria, as well as *Streptococcus pneumoniae*, while *S. pneumoniae* and *H. influenzae* are often the cause of CAP in adults.

### CAP Epidemiology

About 4 million CAP cases occur in the United States each year.<sup>7</sup> Most of these patients are treated outside of the hospital. For example, a recent large, population-based cohort study of 46,237 seniors 65 years of age or older were observed over a three-year period.<sup>8</sup> The overall rate of community-acquired pneumonia ranged from 18.2 cases

per 1,000 person-years among those who were 65 to 69 years old, to 52.3 cases per 1,000 person-years among those who were 85 or 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.

### **CAP Risk Factors**

Risk factors for CAP include age, male sex, chronic obstructive pulmonary disease (COPD), asthma, diabetes mellitus, congestive heart failure, and smoking.<sup>8</sup> In a study of 1,336 patients with CAP and 1,326 controls for risk factors, multivariate analysis found cigarette smoking, usual contact with children, sudden changes of temperature at work, inhalation therapy (particularly those containing steroids), oxygen therapy, asthma, and chronic bronchitis to all be independent risk factors for CAP.<sup>9</sup> Interestingly, this study also showed 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 could limit colonization by respiratory pathogens.

### **CAP Symptoms, Diagnosis, and Resistant Strains**

Common clinical symptoms of CAP include cough, fever, chills, fatigue, dyspnea, rigors, and pleuritic chest pain.<sup>7</sup> 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.

The 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.<sup>7</sup> However, chest radiography performed early in the course of the disease could be found to be negative.

A worrisome recent development is the emergence of community-acquired methicillin resistant *Staphylococcus aureus* (MRSA) infections, including CAP.<sup>10</sup> While still a rare infection, a 2008 analysis of the medical literature published in the previous two years found 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.<sup>10</sup>

### **CAP Treatments and Outcomes**

Antibiotics are the cornerstone of CAP treatment. Typical antibiotic regimens include the use of oral azithromycin (Zithromax®), clarithromycin (Biaxin®), erythromycin (various brand names) or doxycycline (various brand names) in otherwise healthy patients, or oral moxifloxacin (Avelox®), gemifloxacin (Factiv®), or levofloxacin (Levaquin®) in patients having other comorbidities.

While the focus for CAP is typically on short-term outcomes, it is becoming more apparent that there are sometimes long-term negative consequences of CAP, particularly in the elderly.<sup>11</sup> For example, a large study of the Medicare database used a matched case-control design to evaluate the one-year mortality rate of 158,960 older CAP patients to 794,333 control subjects hospitalized for reasons other than CAP.<sup>12</sup> The single-year mortality rate for CAP patients exceeded that of control subjects (40.9% versus 29.1%, respectively); the differences could not be explained by the types of underlying disease. These findings suggest that the consequences of CAP in the elderly are important to long-term survival, and thus should be prevented.<sup>11</sup>

### **Aspiration Pneumonia**

Aspiration pneumonia is an infectious process caused by the inhalation of oropharyngeal secretions colonized by pathogenic bacteria.<sup>13</sup> This is differentiated from aspiration pneumonitis, which is typically caused by



chemical injury following 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 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.

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, will 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 (explained in further detail below). However, there is little information available regarding the effect of periodontal therapy in the prevention of aspiration pneumonia in vulnerable populations.

### **Nosocomial Pneumonia**

Hospital-acquired pneumonia (HAP) was originally defined as pneumonia occurring with onset > 48 hours after admission to the hospital. This classification scheme was straightforward and easy to apply. However, over the past decade there has been a shift in delivery of medical care from the hospital to the outpatient setting for delivery of services such as antibiotic therapy, cancer chemotherapy, wound management, outpatient dialysis centers, and short-term rehabilitation. As a result, the classification scheme for HAP pneumonia has changed. This shift in care from the hospital to the outpatient, home setting, or nursing home leads to cases of pneumonia that occur outside the hospital setting, but clearly within other healthcare delivery settings. Thus, such pneumonia has been referred

to as “healthcare-associated pneumonia.”<sup>14</sup> Nursing-home associated pneumonia (NHAP) is the most important common infection affecting nursing home residents because of its high morbidity and mortality.<sup>15</sup> Pneumonia is also a common reason for transfer of residents from the nursing home to the hospital.<sup>16</sup> HAP 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.<sup>17</sup>

VAP is the second most common hospital-acquired infection.<sup>18,19</sup> It is a leading cause of death in critically-ill patients in the ICU, with estimated prevalence rates of 10%–65% and mortality rates of 25%–60% depending on the study, patient populations, and medical/surgical conditions involved.<sup>17,20–25</sup> VAP and other forms of HAP are independent risk factors for mortality in hospitalized patients, irrespective of the severity and type of underlying illness.<sup>26</sup> An episode of HAP adds approximately 5–6 days to the length of hospital stay and thousands of dollars in medical care costs.<sup>20–25</sup> The risk of developing VAP in the medical and surgical ICU varies from 5–21 per 1,000 ventilator days.<sup>27</sup> The onset of pneumonia easily can 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 case.<sup>28</sup> Pneumonia is also prevalent in nursing homes, comprising 13%–48% of all infections.<sup>29</sup> The mortality rate of nosocomial pneumonia can be as high as 25%.<sup>28</sup>

### **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 are then aspirated into the respiratory tract.

### ***Mechanisms Causing Pulmonary Infection***

Bacteria causing CAP are species such as *S. pneumoniae*, *Haemophilus influenzae*, and *M. pneumonia* that normally colonize the oropharynx. 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 in institutionalized subjects and in people living in areas served by unsanitary water supplies.<sup>1</sup> Respiratory pathogens, such as *S. aureus*, *P. aeruginosa*, and *Escherichia coli*, are found to be present in substantial numbers on the teeth in both institutionalized elders<sup>30</sup> and intensive care patients.<sup>31</sup>

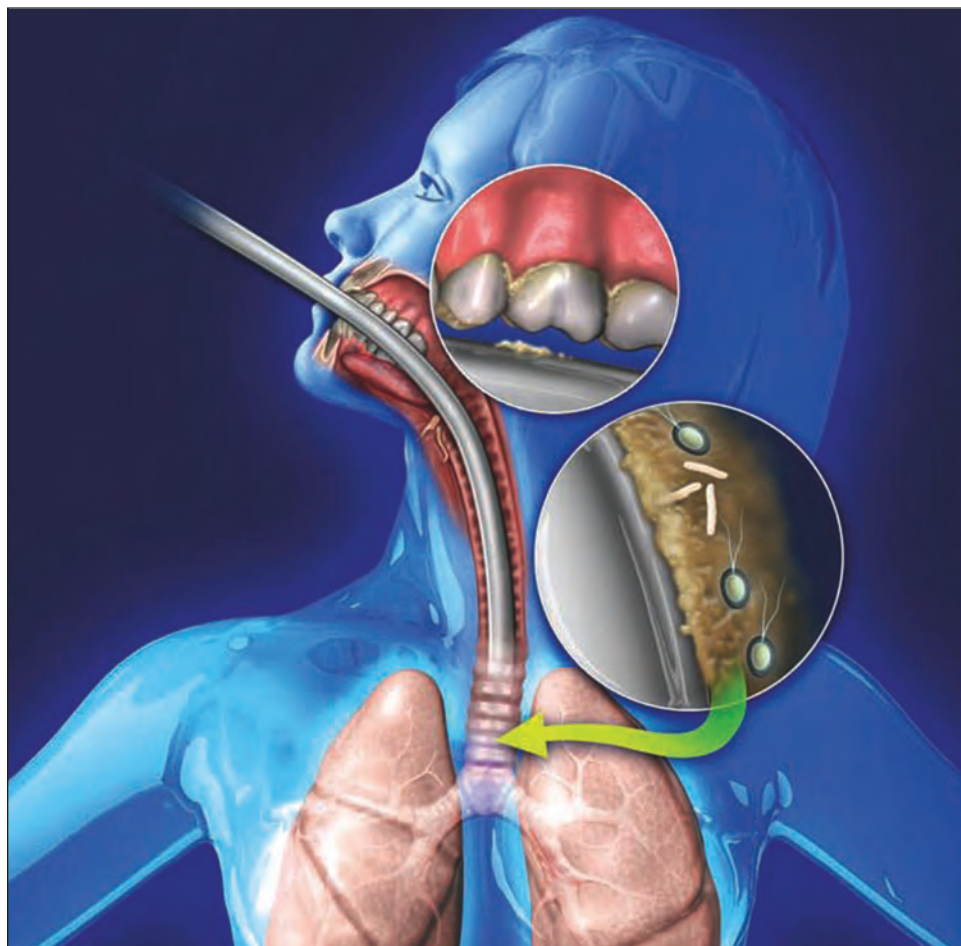
One cubic millimeter of dental plaque contains about 100 million bacteria and may serve as a persistent reservoir for potential pathogens, both oral and respiratory bacteria. It is likely that oral and respiratory bacteria in the dental plaque are shed into the saliva and are then aspirated into the lower respiratory tract and the lungs to cause infection.<sup>1,31</sup> 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 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.<sup>1,31</sup> Other possible mechanisms to explain pulmonary infection are inhalation of airborne pathogens or translocation of bacteria from local infections via bacteremia.

### ***Patients at Increased Risk***

In a healthy subject, the respiratory tract is able to defend itself against aspirated bacteria. 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 ICUs with no ability to clear oral secretions by swallowing or by coughing, are at particularly high risk for VAP, especially if the ventilation lasts for more than 48 hours.<sup>32</sup> Oral bacterial load increases during intubation and higher dental plaque scores predict risk of pneumonia.<sup>33</sup> Anaerobic bacteria are frequently found to colonize the lower respiratory tract in mechanically ventilated patients.<sup>32</sup> Colonization of bacteria in the digestive tract has been suggested to be a source for nosocomial pneumonia, but recently oral and dental bacterial colonization has been proposed to be the major source of bacteria implicated in the etiology of VAP.<sup>34</sup> It is likely that bacteria that first colonize the dental plaque are shed before subsequently attaching to the tubing that passes through the oral cavity into the lung (Figure 1).

In the institutionalized elderly, the 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, for aspiration pneumonia.<sup>35</sup> For example, the major oral and dental risk factors for aspiration pneumonia in veteran residents of nursing

**Figure 1.** Bacteria Associated with Dental Plaque

Bacteria associated with dental plaque are shed from the biofilm to attach to the tubing, which facilitates entry of the bacteria into the lower airway. **Source:** *Inside Dentistry* 2007;3(Special Issue 1):12–16. Reproduced with permission.

homes were number of decayed teeth, periodontitis, oral *S. aureus* colonization, and requirement of help with feeding.<sup>36</sup> In another study of 613 elderly nursing-home patients, inadequate oral care and swallowing difficulties were also associated with pneumonia.<sup>37</sup>

Recent systematic reviews of the literature substantiated the link between poor oral health and pneumonia,<sup>38–40</sup> but more studies on the possible role of periodontitis are needed. Dentate status may be a risk factor for pneumonia and respiratory tract infections; patients with

natural teeth develop aspiration pneumonia more often than edentulous subjects.<sup>41,42</sup> The presence of 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.<sup>35,36</sup> 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 enteric bacteria colonize periodontal pockets.<sup>43,44</sup> Periodontitis,

along with abundant dental plaque, may together facilitate colonization of dental plaque by respiratory pathogens and therefore promote pneumonia.

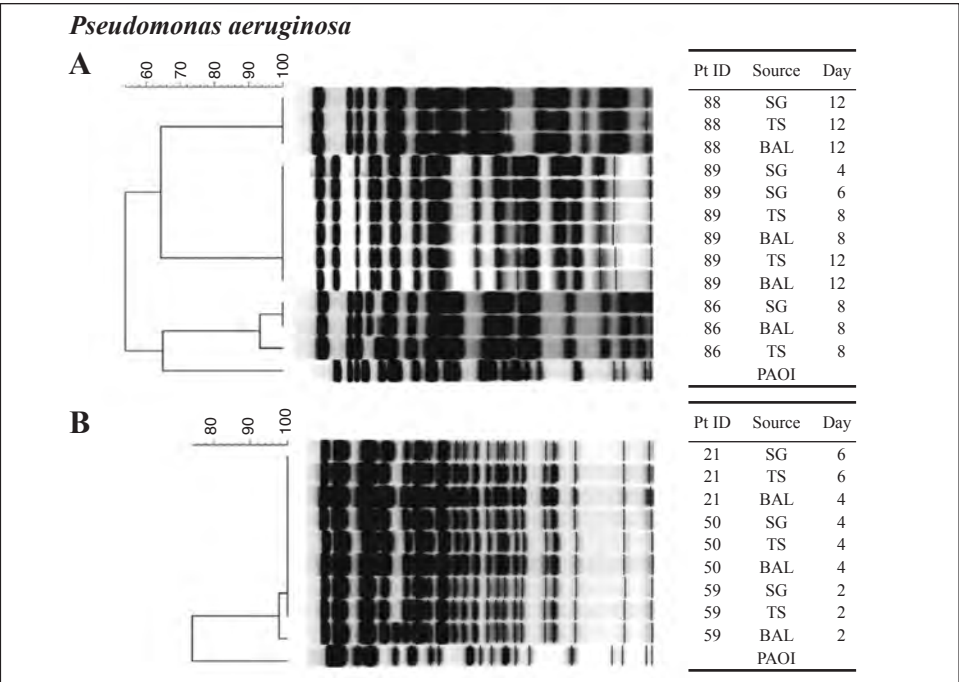
**Bacterial Strains Genetically Identified**

Several recently 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 pulse-field gel electrophoresis to isolates of the same species from the dental plaque of critically ill residents of long-term care facilities transferred to an ICU.<sup>45</sup> 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 relationship between strains of respiratory pathogens first isolated from the oral cavity and later isolated from bronchoalveolar lavage fluid from patients admitted to a trauma critical care unit undergoing mechanical ventilation with suspected VAP.<sup>46</sup>

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 *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

**Figure 2.** Pulse-Field Gel Electrophoresis Patterns with Dendrogram for *P. 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:** *Clin Infect Dis* 2008;47:1562–1570. Reproduced with permission.

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 who are admitted to the hospital from both nursing homes and the community. Thus, dental plaque is an important reservoir for VAP infection.

### ***Oral Interventions to Reduce Pulmonary Infections***

Oral interventions to reduce pulmonary infections have been examined in both mechanically ventilated ICU patients and non-ventilated elderly patients.<sup>38-40</sup> These studies included chemical intervention using topical antimicrobial agents and traditional oral mechanical hygiene performed by a professional. The use of oral topical chlorhexidine (CHX) reduces pneumonia in mechanically ventilated patients, and may even decrease the need of systemic intravenous antibiotics or shorten the duration of mechanical ventilation in the ICU.<sup>47-50</sup> Also, oral application of CHX in the early post-intubation period lowers the numbers of cultivable oral bacteria and may delay the development of VAP.<sup>51</sup> Studies validating the effectiveness of oral CHX on reducing pneumonia are not unanimous. For 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.<sup>52</sup> Another study reported that a significant reduction in pneumonia using CHX rinse in ICU patients was achieved only after 24 hours of intubation.<sup>53</sup> However, 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. The use of antimicrobial gels, including polymyxin B sulfate, neomycin sulfate, and vancomycin

hydrochloride<sup>54</sup> or gentamicin/colistin/vancomycin<sup>55</sup> also reduce VAP. Recently, the first study showing that mechanical oral care in combination with povidone iodine significantly decreases pneumonia in ventilated ICU patients was published.<sup>56</sup> This suggests that tooth brushing combined with a topical antimicrobial agent is a promising method for oral cleansing of mechanically ventilated patients.

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 among residents in long-term care facilities.<sup>57-59</sup> 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.<sup>60</sup> 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.<sup>61</sup> Similar once-a-week professional oral cleaning significantly reduced influenza infections in an elderly population.<sup>62</sup> Dental plaque is known to form clearly visible masses on 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 may have an effect on reducing the risk of pneumonia. More studies are needed to find the easiest oral decontamination methods to reduce pulmonary infections in elderly nursing home patients.

Oral cleansing reduces pneumonia in both edentulous and dentate subjects, suggesting that oral colonization of bacteria contributes to nosocomial pneumonia to a greater extent than periodontitis. However, intervention studies of the treatment of periodontitis



on the incidence of pneumonia have not been performed due to the complexities required in investigating ICU or bed-bound nursing home patients. In edentulous people, dentures may easily serve as a similar reservoir as natural teeth for oral and respiratory bacteria if not cleaned properly and daily.

### **Suggestions for Oral Care of Hospitalized and Nursing Home Residents to Prevent Pneumonia**

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. Traditional nursing teaching recommends that toothbrushing be performed twice a day together with swabbing of the mouth with glycerine and lemon swabs for comfort. In light of the recent findings described above, routine nursing practice needs to include more rigorous oral care procedures.

A recent 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 healthcare personnel.<sup>63</sup> The findings showed that while 512 (92%) of 556 respondents perceived oral care to be a high priority, 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 the use of antiseptic rinses such as CHX, appear to be used infrequently in critical care settings.<sup>64</sup>

While no official guidelines promulgated by professional societies or regulatory agencies have been published to date, a number of prudent actions may be considered when caring for the vulnerable patient:

1. Remove all dental appliances upon admission to the critical care unit.
2. Conduct oral examination initially and daily by a registered nurse.

3. Brush teeth two or three times per day; also floss if possible.
4. Rinse all oral surfaces with antimicrobial rinses.
5. Perform frequent deep suction of oral and pharyngeal secretions as needed, as well as prior to repositioning the tube or deflating the cuff.
6. Remove hard deposits (e.g., tartar/calculus) from the teeth, if possible.
7. Request that teeth be professionally cleaned before admission to the hospital for elective procedures.

Several suggestions can also be made to advise healthcare providers on the proper oral hygiene techniques to reduce risk of oral colonization by respiratory pathogens in ventilated patients:

1. Place the patient's head to the side or place in semi-fowlers (semi-reclined) body position.
2. Provide deep suction, as needed, in intubated patients to remove oropharyngeal secretions that can migrate down the tube and settle on top of the cuff.
3. Brush teeth using a wet soft toothbrush for approximately one to two minutes.
4. Brush tongue and vestibular surfaces.
5. Apply mouth moisturizer inside mouth and lip balm if needed to reduce risk of oral ulceration.

### **CHRONIC OBSTRUCTIVE PULMONARY DISEASE**

Patients with COPD have chronic airflow obstruction due to narrowing of the airways, with excess production of sputum resulting from chronic bronchitis and/or emphysema.<sup>65</sup> 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 three months of the year over two consecutive years.<sup>66</sup> Emphysema results from the 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 and Costs of COPD**

Chronic bronchitis is quite prevalent, with 20%–30% of all adults over the age of 45 years having some history of this condition,<sup>67</sup> typically as a sequela of smoking. The incidence of emphysema is less well known since the main tool for noninvasive diagnosis (CT scanning) cannot be practically applied in population studies. While it is rare to find lungs completely free of emphysema postmortem, the majority of 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.<sup>68</sup> These genetic defects account for only a small percentage of individuals with COPD.

Worldwide, the prevalence of physiologically defined COPD in adults ages 40 or older is approximately 9%–10%.<sup>69</sup> In 2001, approximately 12.1 million adults older than 25 were diagnosed with COPD in the United States, and another 24 million showed impaired lung function.<sup>70</sup> It is likely that COPD in the community remains underreported due to difficulties in diagnosing this disorder. COPD is the fourth leading cause of morbidity and mortality in the United States, and is projected to become the fifth most common cause for morbidity and the third most frequent cause of mortality worldwide by the year 2020. It has been estimated that the mean excess costs of COPD, after adjustment for sociodemographic factors and smoking status,

is \$4,932 per patient.<sup>71</sup> Inpatient costs are greater than outpatient and emergency costs (\$8.3 versus \$7.8 billion) and hospital and medication costs account for most resources spent.<sup>72</sup>

### **Pathogenesis of COPD**

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.<sup>73</sup> Smoking is related to macrophage-predominant inflammation and airspace enlargement. High concentrations of reactive oxygen species 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, an MMP-inhibitor in development, AZ11557272, prevented smoke-induced increases in lung inflammatory cells, lavage desmosine (a marker of elastin breakdown), and serum tumor necrosis factor-alpha (TNF- $\alpha$ ) in a guinea pig model of cigarette smoke-induced COPD.<sup>74</sup>

COPD is a complex disease that is influenced by a variety of environmental and genetic factors. Several environmental factors, for example cigarette smoking and air pollution, have been strongly associated with the initiation and progression of the disease. It is clear that not all smokers develop COPD. Thus other factors, likely genetic, may help explain why some people develop COPD while others do not.<sup>75,76</sup> It is well known that COPD is related to alpha-1 antitrypsin deficiency,<sup>77,78</sup> 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.

It appears that, to date, attempts to associate COPD experience with specific genetic polymorphisms, for example targeting cytokine or global promoter genes, have proven inconclusive.<sup>76</sup>

A major complication of COPD is the occurrence of periodic “exacerbations” or periods of aggravation of disease symptoms. Exacerbations have recently been associated with bacterial infection,<sup>79,80</sup> typically by nontypable *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis*. Viral infection has also been implicated in initiating this process.<sup>81</sup> Acute exacerbations of COPD are thus often treated using empiric antibiotic therapy. The cost of therapy for this group of 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.

### **Treatment and Management of COPD**

A mainstay of therapy is the use of 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.<sup>82</sup> However, antibiotics may not be generally indicated for patients with mild-to-moderate exacerbations.

### **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 (NHANES) I data.<sup>83</sup> This database contains information on the general health status of 23,808 people. 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 a confirmed chronic respiratory disease had a significantly greater oral hygiene index than subjects without respiratory disease. Further, 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 that periodontal disease, measured as alveolar bone loss that occurred between baseline and later measurements from periapical radiographs, was an independent risk factor for COPD in adult males enrolled in the VA Normative Aging study.<sup>84</sup>

These results were supported by a subsequent study that measured associations between poor oral health and chronic lung disease, and 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 US subjects from 1988 to 1994, were analyzed.<sup>85</sup> This cross-sectional, retrospective study of the NHANES III database included a study population of 13,792 subjects  $\geq 20$  years of age 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/forced vital capacity. Oral health status was deduced

from the Decayed Missing Filled System index (summary of cumulative caries experience), gingival bleeding, gingival recession, gingival pocket depth, and periodontal attachment level.

Subjects with COPD had, on average, more clinical attachment loss (CAL;  $1.48 \pm 1.35$  – mean  $\pm$  SD) than those without COPD (mean CAL:  $1.17 \pm 1.09$ ). 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 a history of COPD. The risk for COPD appeared to be significantly elevated when mean attachment loss (MAL) was found to be severe ( $MAL \geq 2.0$  mm) compared to 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  $\geq 3.0$  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 between any of the measures of oral health and acute respiratory diseases, such as influenza or pneumonia.

### ***Chronic Lung Disease in Hospitalized Patients***

Dental plaque may serve as a reservoir of respiratory pathogen colonization in hospitalized patients with chronic lung diseases.<sup>86</sup> Using a checkerboard DNA-DNA hybridization technique to determine prevalence 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, while only 12 of 31 (38.7%) non-hospitalized subjects were colonized. These results indicate that dental plaque may serve

as a reservoir of infection in hospitalized patients with chronic lung diseases.

Another recent analysis examined the relationship between airway obstruction and periodontal disease in a cohort of 860 community-dwelling elders enrolled in the Health, Aging, and Body Composition Study.<sup>87</sup> Results showed that after stratification by smoking status and adjustment for age, race, gender, center, and pack-years, those with normal pulmonary function had significantly better gingival index ( $p = 0.036$ ) and loss of attachment ( $p = 0.0003$ ) scores than those with airway obstruction. Thus, a significant association between periodontal disease and airway obstruction was noted, especially in former smokers.

Finally, 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 in 50 patients with other very severe respiratory diseases.<sup>88</sup> It was found that prevalence of periodontitis was 44% in the COPD group versus 7.3% in the non-COPD group, and this difference was significant after adjustment for age, gender, and pack-years smoked.

## **CONCLUSION**

Recent research points to possible associations between oral health, especially dental plaque and periodontal disease, and respiratory diseases such as community-acquired and nosocomial pneumonia and COPD. Further research into these associations may allow development and routine implementation of simple and effective strategies to prevent respiratory disease in vulnerable populations.

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### **Supplemental Readings**

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# CHAPTER 11

## Periodontal Disease and Osteoporosis

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### 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 reduced 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 physiological challenges is compromised. Due to the above-mentioned factors, microdamage accumulation and increased fracture susceptibility can occur. Within this context, numerous pro-inflammatory cytokines have been identified as important determinants of bone loss.<sup>1-7</sup> A significantly increased production of pro-inflammatory cytokines occurs in conditions such as periodontitis, a disease initiated by bacterial plaque biofilms. Understanding the impact of osteoporosis on host susceptibility to periodontal breakdown is a developing area.<sup>8-11</sup> This chapter will review and evaluate 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 overall bone structural integrity and homeostasis.

### OSTEOPOROSIS AND BONE REMODELING

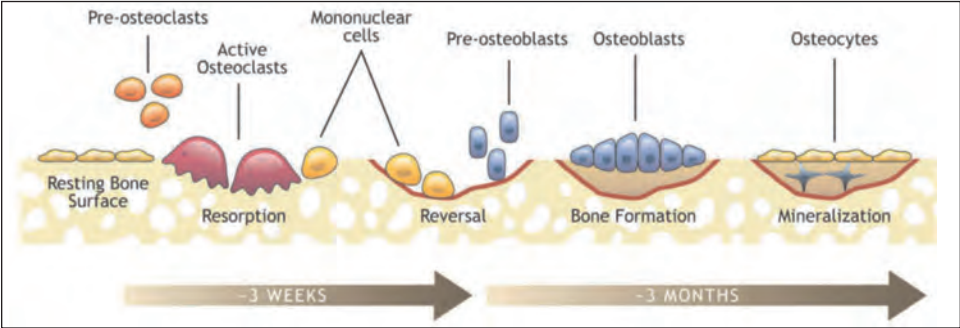
Bone is a highly dynamic tissue that has the capacity to adapt based on physiological

needs. Hence, bone adjusts its biologic properties according to metabolic and mechanical requirements.<sup>12-14</sup> 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.<sup>15</sup> From the perspective of bone remodeling, it has been proposed that osteoclasts recognize and target skeletal sites of compromised mechanical integrity, thereby initiating the bone remodeling process for the purpose of generating new bone that is mechanically competent.<sup>16</sup>

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 present 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. The number of new and active BMUs is regulated by a variety of hormones and cytokines, which dictates the spatiotemporal synchronization and coupling of anabolic and catabolic remodeling events.

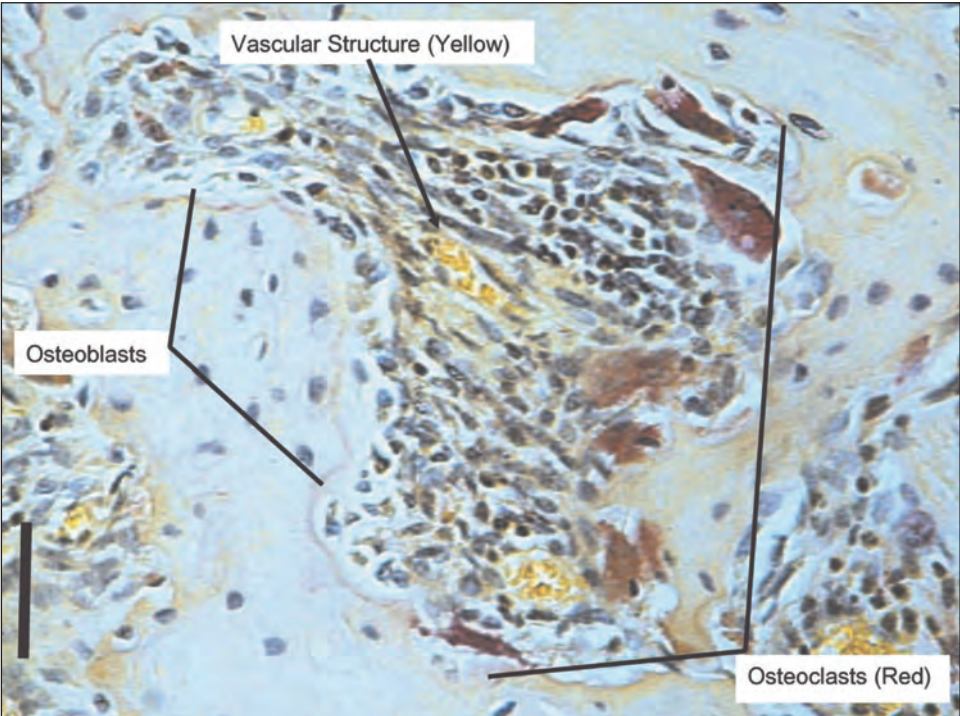
One of the best-studied remodeling coupling mechanisms is the receptor activator for nuclear factor  $\kappa$ B ligand (RANKL)-mediated activation of osteoclasts (Figure 3). RANKL is a cytokine produced by osteoblasts and other cells (e.g., lymphocytes); it resides on the surface of osteoblast-like cells.

**Figure 1.** Bone Remodeling

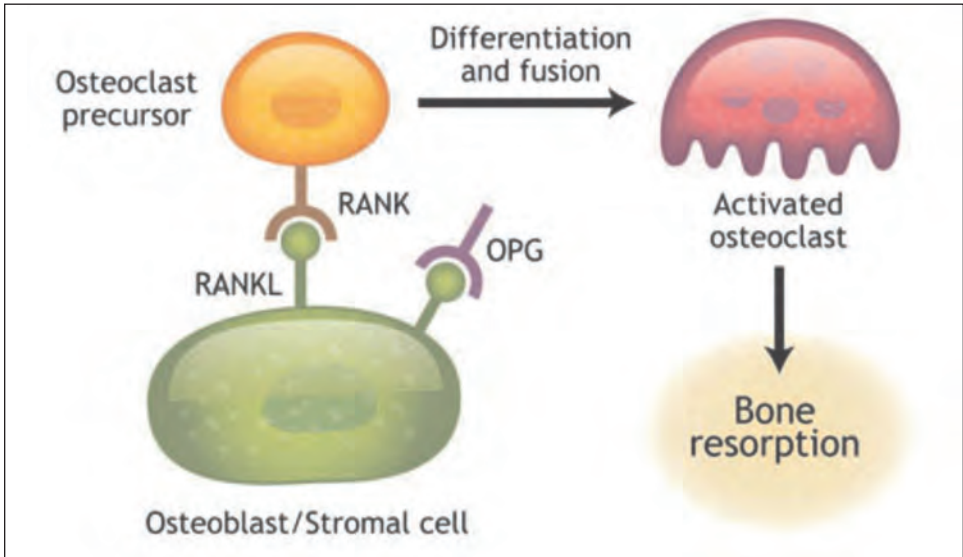


The bone remodeling cycle involves a complex series of sequential steps that are highly regulated. The “activation” phase of remodeling is dependent on the effects of local and systemic factors of mesenchymal cells of the osteoblast lineage. These cells interact with hematopoietic precursors to form 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:** McCauley LK, Nohutcu RM. Mediators of periodontal osseous destruction and remodeling: principles and implications for diagnosis and therapy. *J Periodontol* 2002;73:1377–1391. Reproduced with permission.

**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 acid phosphatase) highlights the resorption front. Notice 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, and leading 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.

These cells produce RANKL in response to systemic hormones (e.g., 1,25-dihydroxy-vitamin D3) and cytokines (e.g., interleukin [IL]-6). Cell contact between cells expressing RANKL and osteoclast precursors expressing receptor activator of nuclear factor  $\kappa$ B (RANK) induces osteoclast differentiation, fusion, and activation. Modulation of this coupling mechanism occurs through a molecule known as osteoprotegerin (OPG). OPG binds to RANKL before it has an opportunity to bind to RANK. Therefore, OPG suppresses the capacity to increase bone resorption.

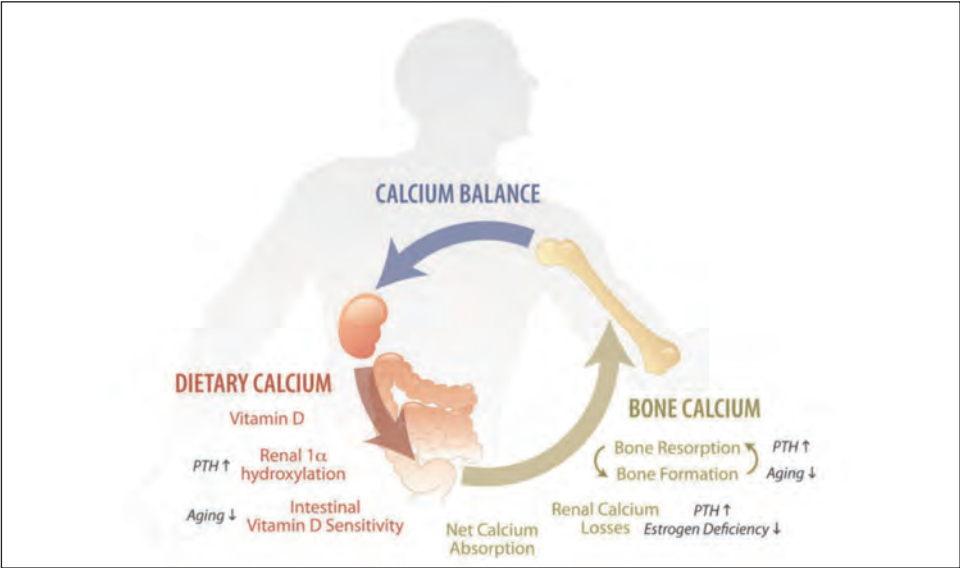
In addition, hormonal factors have a major impact on the rate of bone resorption; lack of estrogen increases bone resorption, as well as decreasing the formation of new bone. Osteocyte apoptosis has been also documented in estrogen deficiency.<sup>17,18</sup> In addition to estrogen, calcium metabolism plays a significant role in bone turnover; 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 numbers of 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 being resorbed by osteoclasts.<sup>19</sup> Such disruption in normal remodeling events compromises the ability to adapt to external and internal demands. Without an efficient coupling mechanism, each remodeling event results in a net loss of bone, which ultimately compromises bone strength due to altered architecture (Figure 5).

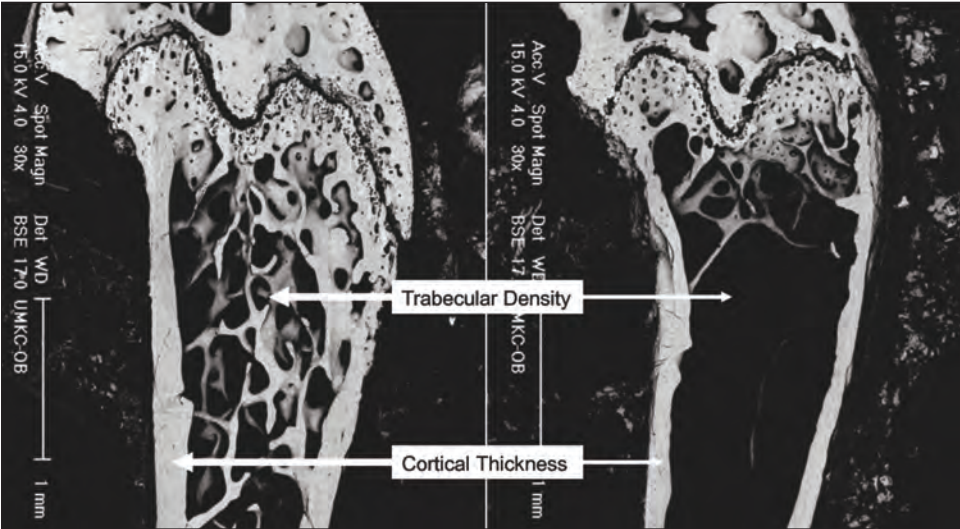


**Figure 4.** Calcium and Bone Metabolism



Calcium homeostasis is of major importance for many physiological 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 the bones, and excretion via the gastrointestinal tract and urine maintain homeostasis. Vitamin D is involved in the absorption of calcium, while PTH stimulates calcium release from the bone, reduces its excretion from the kidney, and assists in the conversion of vitamin D into its biologically active form (1,25-dihydroxycholecalciferol). Decreased intake of calcium and vitamin D and estrogen deficiency may also contribute to calcium deficiency.

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



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

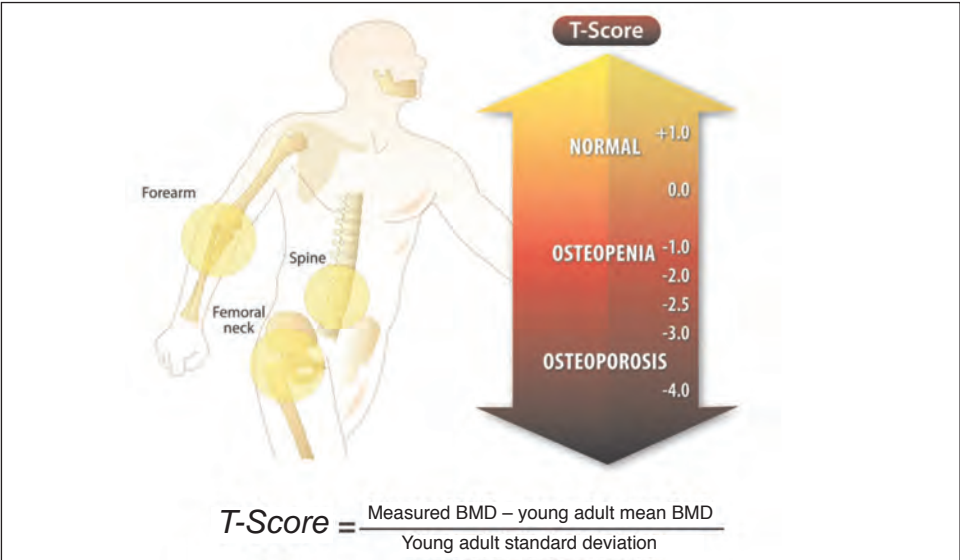
The affected skeletal integrity in osteoporosis is characterized by cortical and trabecular thinning, as well as through the loss of trabecular connectivity. In addition, the number of osteons per unit volume of bone decreases, offering less resistance to bone-crack initiation. The diminished bone quality in osteoporosis is also reflected by a decrease in cell density. The decreased osteocytic density in interstitial bone degrades the ability to detect damage. If bone formation is lessened in the BMU due to decreased numbers of osteoblasts, then impaired synthesis of osteocytes may contribute to the deficit in this cell type, which is considered the orchestrator of bone remodeling. Reduced periosteal bone formation in adulthood contributes to skeletal fragility because endocortical resorption is not compensated for, creating 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 summary, 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 skeletal integrity. However, fractures tend to occur late in the disease process. Today, it is generally accepted that bone mineral density (BMD) measurement is the most valuable parameter to identify patients who are more susceptible to, or at greater risk for, fractures. The widespread availability and popularity of bone densitometry has led to a widely accepted definition proposed by the World Health Organization (WHO) in 1994, based on BMD measurements in standard deviation units called “T-scores” (Figure 6).<sup>20</sup>

**Figure 6.** Bone Mineral Density (BMD)



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



Essentially, the T-score indicates the difference between an individual's BMD and normal BMD. As illustrated in Figure 6, 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 if the individual has a T-score  $\leq -2.5$
- Established osteoporosis refers to those individuals with 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. The ability to recognize and classify etiologic differences among conditions that may appear clinically similar will impact the ability to successfully treat these patients. Primary osteoporosis is simply the form seen in older individuals and women past 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, whether Type I or Type II, is the amount of calcium remaining in the skeleton and whether it places a person at risk 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 who has 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, or medications (such as corticosteroids). Secondary osteoporosis accounts for  $< 5\%$  of osteoporosis cases. 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, and 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.<sup>1</sup> Chronic inflammation and the immune system remodeling characteristic of aging, as well as of other pathological conditions commonly associated with osteoporosis, may be determinant pathogenetic factors.<sup>6</sup>

The cellular and molecular pathogenetic mechanisms in inflammation-induced osteolysis and sclerosis have been explored by different investigators. There is certainly substantial evidence that bone remodeling is a tightly regulated, finely balanced process influenced by subtle changes in pro-inflammatory and inhibitory cytokines, as well as hormones and cellular components that act primarily, but not exclusively, through the RANK/RANKL/osteoprotegerin 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.<sup>15</sup>

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 the osteoporosis developed during chronic inflammation may result from the inhibition of bone formation,

and is associated with systemic overproduction of pro-inflammatory mediators, such as cytokines, nitric oxide, 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 will be enhanced.

### **ALVEOLAR BMD VS. SKELETAL BMD**

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

Mandibular mineral content is reduced in subjects with osteoporotic fractures.<sup>21</sup> Further, the BMD of buccal (but not trabecular) mandibular bone correlates with osteoporosis (low skeletal BMD).<sup>22,23</sup>

Mandibular density (measured with a DEXA scan) also correlates with skeletal BMD.<sup>24</sup>

Using film densitometry, most investigators have found that the optical density of the mandible is decreased in subjects with osteoporosis compared with controls. Further, mandibular radiographic optical density correlates with vertebral BMD in osteoporotic women,<sup>25</sup> control (nonosteoporotic) women,<sup>26</sup> and in women with a history of vertebral fracture.<sup>27,28</sup> Reduction in cortical and subcortical alveolar bone density has also been reported to correlate with osteoporosis in longitudinal studies.<sup>29-31</sup> As reported by Hildebolt in 1997, the preponderance of the evidence indicates that the jaws of subjects with osteoporosis show reduced bone mass.<sup>32</sup> Table 1 summarizes the available data regarding the relationship between systemic and oral bone loss.

#### **ASSOCIATION BETWEEN OSTEOPENIA 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 loss 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 jawbone 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. In addition to this finding, there are systemic risk factors, such as smoking, diabetes, diet, and hormone levels, that 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.<sup>33</sup>

Several potential mechanisms by which osteoporosis or systemic bone loss may be associated with periodontal attachment loss, reduction of alveolar bone height or density, and tooth loss have been proposed. 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 theory 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., 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 mechanism would be 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.

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

Osteoporosis and osteopenia may influence periodontal disease and tooth loss.<sup>34</sup> Furthermore, it appears that low dietary calcium results in more serious periodontal disease.<sup>35</sup> Although many studies suggest that in elderly men and women, maintenance of normal bone mineral density is associated

**Table 1.** Studies on the Relationship Between Systemic and Oral Bone Loss

Studies	Oral	Systemic	Study Type		Correlation
			Cross-Sectional	Longitudinal	
Earnshaw et al. <sup>a</sup>	Tooth Count	Lumbar BMD	✓		NO
Elders et al. <sup>b</sup>	Bone Height/ Tooth Count	Lumbar BMD	✓		NO
Klemetti et al. <sup>23</sup>	Bone Height/ Tooth Count	Skeletal BMD	✓		YES
Krall et al. <sup>c</sup>	Tooth Loss	Skeletal BMD		✓	YES
Jeffcoat et al. <sup>d</sup>	Mandibular BMD	Femoral Neck BMD	✓		YES
Hildebolt <sup>32</sup>	CAL	Lumbar/ Femoral Neck BMD	✓		YES
Kribbs <sup>25</sup>	CAL	Normal Osteoporosis	✓		NO
Wactawski-Wende et al. <sup>e</sup>	Bone Height	Skeletal BMD	✓		YES
von Wörm et al. <sup>21</sup>	CAL	Forearm BMD	✓		YES
Payne et al. <sup>f</sup>	Bone Height/ Bone Density	Normal Osteopenia Osteoporosis		✓	YES
Yoshihara et al. <sup>g</sup>	CAL	Normal Osteopenia		✓	NO

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

a. Earnshaw SA, Keating N, Hosking DJ, Chilvers CE, Ravn P, McClung M, Wasnich RD. Tooth counts do not predict bone mineral density in early postmenopausal Caucasian women. EPIC study group. *Int J Epidemiol* 1998;27:479–483.

b. Elders PJ, Habets LL, Netelenbos JC, van der Linden LW, van der Stelt PF. The relation between periodontitis and systemic bone mass in women between 46 and 55 years of age. *J Clin Periodontol* 1992;19:492–496.

c. Krall EA, Garcia RI, Dawson-Hughes B. Increased risk of tooth loss is related to bone loss at the whole body, hip, and spine. *Calcif Tissue Int* 1996;59:433–437.

d. Jeffcoat MK, Lewis CE, Reddy MS, Wang CY, Redford M. Post-menopausal bone loss and its relationship to oral bone loss. *Periodontol 2000* 2000;23:94–102.

e. Wactawski-Wende J, Hausmann E, Hovey K, Trevisan M, Grossi S, Genco RJ. The association between osteoporosis and alveolar crestal height in postmenopausal women. *J Periodontol* 2005;76(11 Suppl):2116–2124.

f. Payne JB, Reinhardt RA, Nummikoski PV, Dunning DG, Patil KD. The association of cigarette smoking with alveolar bone loss in postmenopausal females. *J Clin Periodontol* 2000;27:658–664.

g. Yoshihara A, Seida Y, Hanada N, Miyazaki H. A longitudinal study of the relationship between periodontal disease and bone mineral density in community-dwelling older adults. *J Clin Periodontol* 2004;31:680–684.

with improved tooth retention, the evidence is still inconclusive. Hormone replacement therapy and calcium and vitamin D supplements that are used to prevent or treat osteoporosis appear to have beneficial effects on tooth retention as well.<sup>36</sup> Future prospective studies, including randomized clinical trials, are needed to confirm these findings.

THREE CHALLENGES TO PERIODONTAL INTEGRITY

The integrity of the periodontium in osteoporotic patients faces multiple coexisting challenges. Local and systemic factors impact the ability of the host to maintain the homeostasis within these tissues. Hypothetically, three different challenges may be influencing the periodontal integrity in

osteoporotic patients, 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 pro-inflammatory cytokines (e.g., IL-1, tumor necrosis factor- $\alpha$  [TNF- $\alpha$ ], and IL-6) and the osteoclastogenic cytokine RANKL.<sup>14</sup> In primary osteoporosis, the modulatory effect of estrogen in the expression of the bone-resorbing cytokines IL-1, TNF- $\alpha$ , 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.<sup>14,37</sup> In addition, in the presence of a mechanically challenging environment such as that manifested by the oral cavity, the amount of micro-cracks accumulating in the alveolar bone may further signal osteoclasts in an attempt

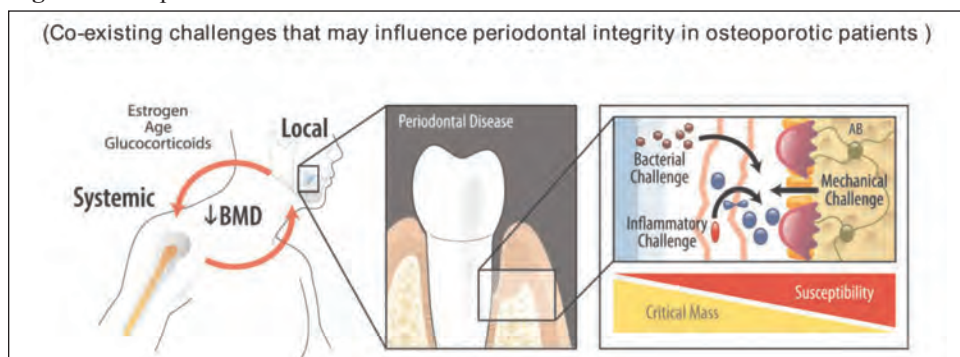
to repair the already compromised osseous architecture.<sup>12,13</sup>

## OSTEOPOROSIS AND ORAL IMPLANTS

The impact of osteoporosis in alveolar bone quality and its potential impact in the implant therapy outcome has been evaluated by several groups.<sup>38-43</sup> Several studies in humans have reported successful implant placement in osteoporotic individuals.<sup>43-46</sup> No correlation between DEXA scores and implant failure has been found, as shown by case-control studies.<sup>45</sup> A retrospective study analyzing sixteen osteoporotic patients 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 six months to eleven years.<sup>47</sup>

Implant success in osteoporotic patients as it relates to the presence of marginal bone loss around implants has also been reported. Von Wöern 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.<sup>48</sup>

**Figure 7.** Proposed Mechanism of Action



Multiple coexisting challenges may influence periodontal integrity in the osteoporotic patient. A microbial, inflammatory, and mechanical front may create an overwhelming situation for the host to maintain the integrity of the attachment apparatus. Systemically, estrogen deficiency may enhance the progression of marginal periodontitis, either by causing increased expression of osteotropic cytokines, or by decreasing the amount of alveolar bone. Locally, the microbial by-products, an increased number of pro-inflammatory cytokines, and a structurally altered alveolar bone due to a significant reduction in bone mass may increase the susceptibility of tissue breakdown, thereby facilitating the progression of periodontal disease.



Bone-to-implant contact (BIC) has consistently been shown to be altered in osteoporotic conditions.<sup>49,50</sup> BIC is significantly decreased in osteoporosis. In an animal study by Cho and collaborators, the greatest decrease in BIC was 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.<sup>50</sup> The results of these studies imply that although osseointegration of implants in osteoporotic bone is possible, the long-term stability of the implants may be compromised by the disease.

The literature supports dental implants as a viable treatment option for patients with osteoporosis. However, it is important to understand that due 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

There are several therapeutic drug options available to treat osteoporosis. They

impact the bone mineral density by targeting different cell populations involved in the bone remodeling process (Figure 8).

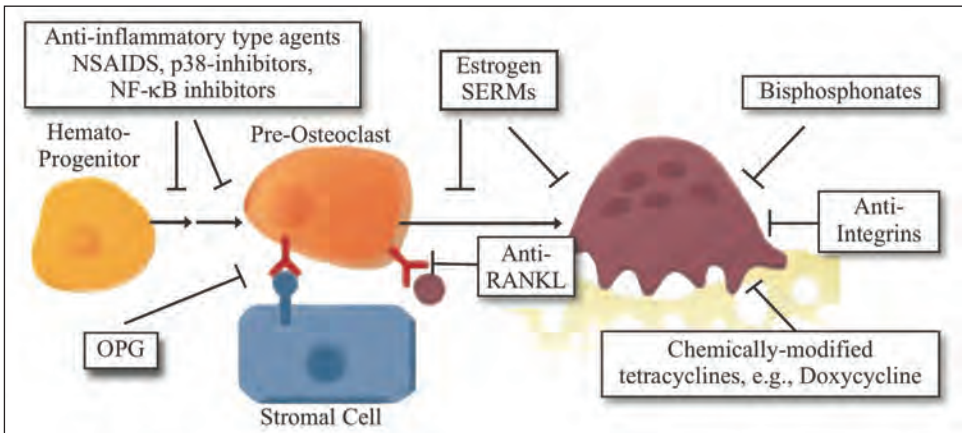
#### Bisphosphonates

In confirmed osteoporosis, bisphosphonate drugs are considered the first-line treatment in women. The most often prescribed bisphosphonates are presently sodium alendronate (Fosamax®) 10 mg a day or 70 mg once a week, risedronate (Actonel®) 5 mg a day or 35 mg once a week, and/or ibandronate (Boniva®) once a 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 (Zometa®) 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% in the study group had died of any cause after 1.9 years, as opposed to 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

**Figure 8.** Pharmacologies to Treat Bone Loss



In general, two groups can be distinguished among all of the known pharmacologic 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. **Source:** *Periodontology* 2000 2007;43:294–315.<sup>73</sup> Reproduced with permission.



to follow for the next 30 minutes. They are associated with esophagitis and are 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 zoledronic acid avoids oral tolerance problems, these agents are implicated at higher rates in a rare but debilitating oral affliction called osteonecrosis of the jaw (ONJ). The American Society of Bone and Mineral Research 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.<sup>51,52</sup>

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 between 1 in 10,000 patients and < 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 who have cancer treated with high doses of intravenous bisphosphonates is clearly higher, in the range of 1–10 per 100 patients (depending on duration of therapy). For this reason, oral bisphosphonate therapy is probably to be preferred, and prescribing advice now recommends any remedial dental work to be carried out prior to commencing treatment.

### Teriparatide

PTH is a potent hormone with catabolic and anabolic effects in bone. Teriparatide (Forteo®, recombinant human PTH) has been shown to be effective in osteoporosis management.<sup>53,54</sup> It stimulates osteoblasts, thus increasing their activity. Currently, it is used mostly for patients with established osteo-

porosis who have particularly low BMD, several risk factors for fracture, or who cannot tolerate oral bisphosphonates. It is given as a daily injection with the use of a pen-type injection device.

The response of the alveolar bone to PTH has been evaluated by several investigators.<sup>55-57</sup> In an animal study by Miller et al., PTH significantly increased crestal bone levels in the mandibles of ovariectomized rats.<sup>56</sup> Furthermore, Barros and collaborators, using a periodontitis animal model, showed decreased bone resorption when treating the animals with PTH.<sup>55</sup>

PTH is not currently used to treat oral bone loss. However, systemic administration may have positive benefits on the oral cavity.

### 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 and leading to the death of pre-osteoclasts.<sup>58</sup> This establishes 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, along with calcium and vitamin D supplements, appears to have beneficial effects on tooth retention.<sup>59</sup>

In a cohort of 488 elderly women, Krall and collaborators found an association between postmenopausal hormone replacement therapy (HRT) and tooth retention. There was also an association between duration of HRT and tooth retention, with the odds of being edentulous reduced by 6% for each year of HRT therapy. This study suggests that postmenopausal HRT reduces the risk of edentulism.<sup>60</sup>

### 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.<sup>61</sup>

Unlike estrogens, which are uniformly agonists, the 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, which in turn determines how strongly the drug/receptor complex recruits coactivators relative to corepressors.

Clinically, the benefits of SERMs therapy on bone are well-established. In postmenopausal women with osteoporosis, SERMs treatment decreases markers of bone turnover by 30–40% after one year, and increases bone density 2–3 % after three years. It also decreased the incidence of vertebral fractures by 30–50%.<sup>62-65</sup>

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

#### Strontium Ranelate

Oral strontium ranelate (Protelos®) belongs to a class of drugs called “dual-action bone agents.” It stimulates calcium-sensing receptors and leads to the differentiation of pre-osteoblasts 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.<sup>66</sup>

Strontium ranelate is prescribed for the treatment of osteoporosis to prevent vertebral and hip fracture. In postmenopausal women with osteoporosis, strontium ranelate 2 g/day increased BMD.<sup>67</sup> This treatment was associated with vertebral fracture reductions of 49% relative to control groups.<sup>68</sup> Strontium ranelate has also shown significant efficacy against peripheral and hip fractures.<sup>69</sup>

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

#### Denosumab

Denosumab is a neutralizing human monoclonal antibody to RANKL, mimicking the biological function of OPG.<sup>70</sup> Using an intermittent regimen either every three or every six months, studies of the clinical efficacy of denosumab demonstrated a strong inhibition of bone resorption as observed by reductions of up to 88% in the levels of serum C-telopeptide, an indicator of bone remodeling, with a rapid onset of action three days after administration and with a sustained, but reversible, antiresorptive effect.<sup>71,72</sup> At one year, denosumab treatment significantly increased bone mineral density, especially in the lumbar spine and, to a lesser extent, in the total hip and distal radius. The clinical benefits of denosumab were similar to or exceeded those induced by alendronate and revealed dose-dependency.<sup>72</sup> Apart from the established increment of dyspepsia during bisphosphonate treatment, no significant differences in adverse events were observed between treatment groups. In summary, the report by McClung and colleagues introduced a promising and presumably safe antiresorptive agent to the drug armamentarium for the treatment of osteopenia and osteoporosis in postmenopausal women.<sup>72</sup> Denosumab has been in evaluation for consideration of clinical use and may be available in 2010.

## CONCLUSION

Although the causality between systemic bone loss and oral bone loss has not been fully elucidated, current evidence demonstrates a plausible association between the two disease entities. Study results imply 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 randomized, controlled clinical trials are needed to clarify the causality and/or association between systemic and oral bone loss.

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# CHAPTER 12

## Association Between Periodontitis and Rheumatoid Arthritis

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### INTRODUCTION

Two of the most common chronic inflammatory diseases affecting humans are periodontitis and rheumatoid arthritis. Both of these 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. Not surprisingly, 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. While the onset of inflammation in periodontitis is related to host responses to bacteria within the subgingival biofilm, the offending stimulus in rheumatoid arthritis remains unknown. Nonetheless, given the very similar pathologic processes, when periodontitis and rheumatoid arthritis co-exist in the same patient, the plausibility of a common underlying pathogenic mechanism (not etiology) is worthy of further consideration.

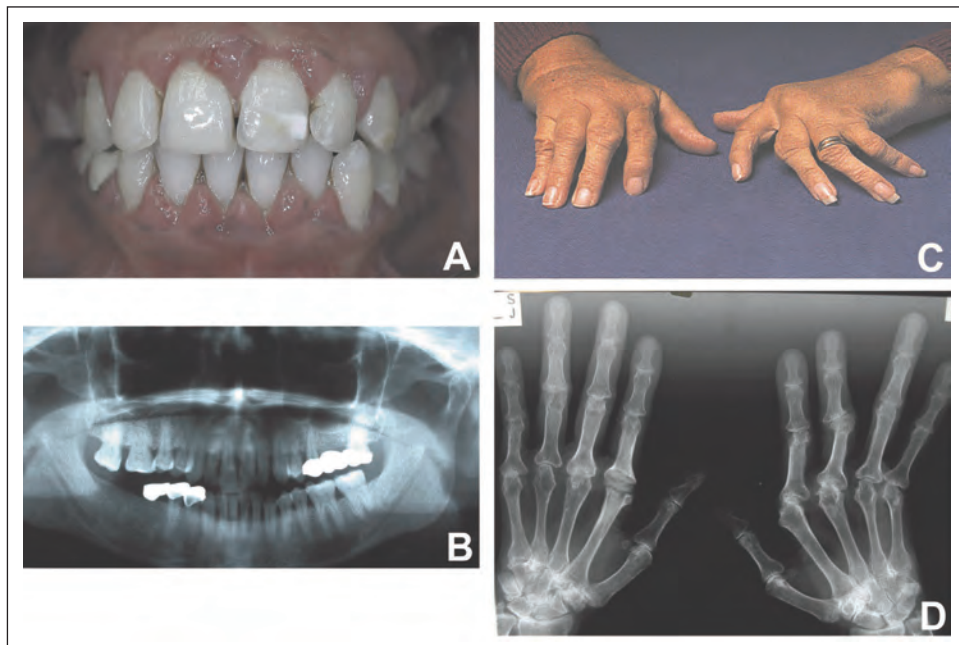
In recent years, the number of reports confirming an association between these two diseases has increased and numerous models for such an association have been proposed. Therefore, the aim of this chapter is to review the similarities between these two chronic inflammatory diseases and consider the evidence to support an association between periodontitis and rheumatoid arthritis.

The educational 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 the 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.<sup>1</sup> Plaque-induced gingivitis, as its name suggests, is confined to the gingival tissues, whereas the various forms of periodontitis affect all of the components of the periodontium (gingiva, alveolar bone periodontal ligament, and cementum). In general, both conditions demonstrate all of 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, inflammatory destruction can be so severe as to put the teeth at risk and tooth loss can be the ultimate outcome of periodontal disease. The diagnosis of gingivitis or periodontitis is largely based on the results of a dental and medical history and clinical examination investigating parameters such as pocket depth, gingival inflammation, clinical attachment loss, furcation involvement, tooth mobility, radiographic evidence of

**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

bone loss, and tooth loss. While a plethora of laboratory diagnostic tests have been proposed, none have proven 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.<sup>2</sup> Etiological, genetic, and environmental factors are thought to account for this variability. The critical factor for periodontitis is the development of a subgingival bacterial biofilm. However, it must be noted that while the bacterial infection is necessary, it is not sufficient for the disease to develop and there are many other factors that must be present in order for overt periodontitis to become clinically evident.

### RHEUMATOID ARTHRITIS

Rheumatoid arthritis is also a chronic inflammatory disease, and like periodontal disease it demonstrates the classic signs of inflammation, including swelling, pain, heat,

and loss of function. Clinically, this condition is characterized by joint swelling, joint tenderness to palpation, morning stiffness, severe motion impairment, progressive degeneration of synovial-lined joints, and radiographic evidence of joint changes (Figure 1).<sup>3</sup> The onset of rheumatoid arthritis can be acute or subacute and can include a palindromic onset, monoarticular presentation (both slow and acute forms), extra-articular synovitis (tenosynovitis, bursitis), polymyalgic-like onset, as well as general symptoms (malaise, fatigue, weight loss, fever). A number of laboratory tests are used to assist in the diagnosis of rheumatoid arthritis, including 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

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

Periodontitis	Rheumatoid Arthritis
<i>Well-Maintained Periodontitis</i> Periodontitis commences, but by following simple treatment it can be contained and with appropriate maintenance, very little progression occurs	<i>Self-Limiting Rheumatoid Arthritis</i> Following commencement of the disease, it does not progress to more severe forms
<i>Downhill Periodontitis</i> Established periodontitis can be largely controlled with a combination of simple and complex treatments. In some cases, some further progression may occur but this is usually only small	<i>Easily Controlled Rheumatoid Arthritis</i> Once the disease becomes established, its progression can largely be controlled through simple treatments including “first line” medications
<i>Extreme Downhill Periodontitis</i> Once established, despite various treatment protocols, the disease progresses over time (not necessarily in a linear manner) and may even result in tooth loss	<i>Progressive Rheumatoid Arthritis</i> Following establishment, the disease continues to progress causing significant joint damage. Advanced treatments including “second line” medications and disease-modifying antirheumatic drugs are of little help in stopping disease progression

Adapted from *J Clin Periodontol* 2003;30:761-772.<sup>22</sup>

well with clinical assessment and radiographic changes. Recently, it has been established that a positive test for citrullinated peptides, with its high sensitivity and specificity, is very close to a diagnostic test for rheumatoid arthritis.<sup>4</sup> Historically, the extent of anatomic changes occurring in joints of rheumatoid arthritis patients has been assessed by radiography. More recently, ultrasonography and magnetic resonance imaging have gained acceptance for studying joint, tendon, and bursal involvement in rheumatoid arthritis. The clinical course of rheumatoid arthritis fluctuates and the prognosis for this disease 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 different types depending on its manifestation and response to treatment. These are termed self-limited, easily controlled, and progressive.<sup>5</sup> It seems that for the majority of people diagnosed with rheumatoid arthritis, progression is in-

evitable. Even following management with second-line medications, only a very small proportion will undergo remission of longer than 3 years. Most patients continue to have progression of the disease even while taking these medications.<sup>6</sup> In general, these patients have a number of poor prognostic indicators, implying that they have significant systemic impairment of the inflammatory and immune responses that would normally be protective against such a disease.

Similar to rheumatoid arthritis, periodontitis also manifests in three general forms: rapid progression, moderate progression, and no progression of periodontal disease.<sup>7</sup> More recently, these have been termed aggressive or chronic, and may exist in either stable or active forms of the disease.<sup>1</sup>

**PERIODONTITIS AND RHEUMATOID ARTHRITIS ARE INFLAMMATORY DISEASES**

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 pro-inflammatory mediators perpetuated by

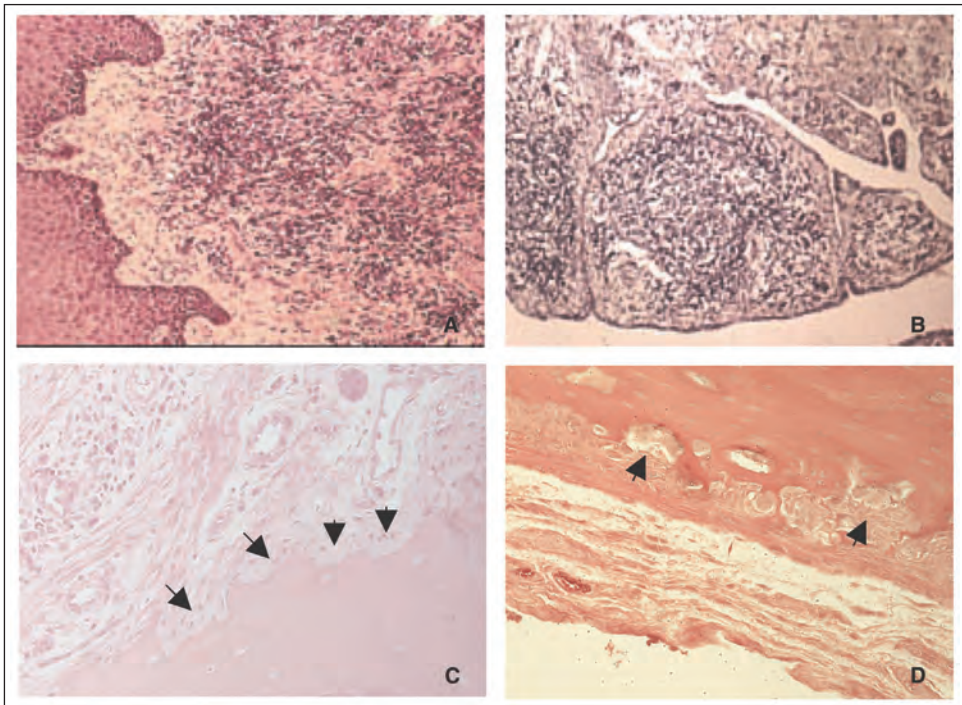
the host's own cells. Both the resident cells (synovial cells and keratinocytes in rheumatoid arthritis, fibroblasts and osteoblasts in periodontitis) and the migrating inflammatory cells are active players responsible for the destruction observed in these two chronic inflammatory diseases (Figure 2).

During the pathogenesis of both periodontitis and rheumatoid arthritis, there is an abundant release of cytokines and other pro-inflammatory mediators (Table 2). While these mediators are present during normal tissue homeostasis, it is during inflammatory processes, such as are 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. Although 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

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



Inflamed gingival (A) and synovial (B) tissues. Note heavy inflammatory cell infiltrates in both specimens. Histological appearance of bone resorption occurring in (C) periodontal tissues and (D) rheumatoid tissues. Note areas of active bone resorption associated with osteoclasts (arrows).

**Table 2.** Cytokines Involved in Periodontitis and Rheumatoid Arthritis

Cytokine	Properties
Chemokines	Produced by: macrophages, endothelium, fibroblasts, platelets, T cell Functions: Leukocyte chemotaxis, activation
IFN- $\alpha$ and IFN- $\beta$	Produced by: macrophages ( $\alpha$ ), fibroblasts ( $\beta$ ) Enhanced by: bacterial endotoxin, TNF- $\alpha$ , IL-1 Functions: All cells: antiviral state, increased class I MHC expression natural killer (NK) cells: activation
IFN- $\gamma$	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: macrophages, 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 costimulators and Class II MHC molecules
IL-12	Produced by: macrophages, dendritic cells Functions: NK and T cells: IFN- $\gamma$ 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- $\gamma$
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- $\alpha$ Functions: Endothelial cell activation: inflammation, coagulation PMN: activation Hypothalamus: fever Liver: acute-phase proteins Muscle, fat: catabolism



of enzymes with a variety of substrates and functions (Table 3). The cells that release MMPs in periodontitis and rheumatoid arthritis are polymorphonucleotides (PMNs), monocytic phagocytes, and fibroblasts. Both IL-1 and TNF- $\alpha$  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-1 $\beta$  and TNF- $\alpha$ , and low levels of cytokines such as IL-10 and transforming growth Factor  $\beta$ , 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 PGE<sub>2</sub>, IL-1, TNF- $\alpha$ , and IL-6.

In both periodontitis and rheumatoid arthritis the immune response is regulated via 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 IN RHEUMATOID ARTHRITIS AND PERIODONTITIS**

The role of genetics in periodontitis and rheumatoid arthritis is of considerable importance. For both chronic periodontitis and rheumatoid arthritis there is considerable variance in the clinical manifestation of the disease. Much of this variance can be accounted for by genetic factors.<sup>8</sup> Many of these

differences in disease manifestation can be related to the overexpression or underexpression of numerous cytokines and other inflammatory mediators. Of these, IL-1, TNF- $\alpha$ , and PGE<sub>2</sub> have been found to be under quite 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 pro-inflammatory mediators such as IL-1 $\beta$ , TNF- $\alpha$ , and PGE<sub>2</sub>, and is typically seen in patients with aggressive periodontitis.<sup>9</sup> The concept of a monocytic hypersecretory state has also been described for rheumatoid arthritis patients.<sup>10</sup>

Many of the genes that regulate the cytokine profiles and responses of monocytes have been mapped to the human leukocyte antigen D related (HLA-DR) region of chromosome 5 in the area of the TNF- $\beta$  genes.<sup>11</sup> Since 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.

### **ROLE OF ENVIRONMENTAL FACTORS ON PERIODONTITIS AND RHEUMATOID ARTHRITIS**

It has been recognized for some time that the clinical manifestation of chronic diseases such as periodontitis and rheumatoid arthritis are significantly influenced by environmental or “modifying” factors. These factors are anything that might modify or alter the host inflammatory response, and include 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,<sup>8,12</sup> other factors, including environmental influences and gene-environment interactions, must explain the rest.



**Table 3.** Human Matrix Metalloproteinases and Their Substrates\*

Protein Name	Collagenous Substrates	Noncollagenous ECM Substrates	Nonstructural ECM Component Substrates
MMP-1	Collagen Types I, II, III, VII, VIII, X, and gelatin	Aggrecan, casein, nidogen, serpins, versican, perlecan, proteoglycan link protein, and tenascin-C	$\alpha_1$ -antichymotrypsin, $\alpha_1$ -antitrypsin/ $\alpha_1$ -proteinase inhibitor, IGFBP-3, IGFBP-5, IL-1 $\beta$ , L-selectin, ovostatin, recombinant TNF- $\alpha$ peptide, and SDF-1
MMP-2	Collagen Types I, IV, V, VII, X, XI, XIV, and gelatin	Aggrecan, elastin, fibronectin, laminin, nidogen, proteoglycan link protein, and versican	Active MMP-9, active MMP-13, FGF R1, IGF-BP3, IGF-BP5, IL-1 $\beta$ , recombinant TNF- $\alpha$ peptide, and TGF- $\beta$
MMP-3	Collagen Types II, IV, IX, X, and gelatin	Aggrecan, casein, decorin, elastin, fibronectin, laminin, nidogen, perlecan, proteoglycan, link protein, and versican	$\alpha_1$ -antichymotrypsin, $\alpha_1$ -proteinase fibrinogen, IGF-BP3, L-selectin, ovostatin, pro-HB-EGF, pro-IL- $\beta$ , pro-MMP-1, pro-MMP8, pro-MMP-9, pro-TNF- $\alpha$ , and SDF-1
MMP-7	Collagen Types I, II, III, IV, V, X, and XI	Aggrecan, casein, elastin, enactin, laminin, and proteoglycan link protein	$\beta_4$ integrin, decorin, defensin, E-cadherin, Fas-L, plasminogen, pro-MMP-2, pro-MMP-7, pro-TNF- $\alpha$ , transferrin, and syndecan
MMP-8	Collagen Types I, II, III, V, VII, VIII, X, and gelatin	Aggrecan, laminin, and nidogen	$\alpha_2$ -antiplasmin and pro-MMP-8
MMP-9	Collagen Types IV, V, VII, X, XIV, and XI	Fibronectin, laminin, nidogen, proteoglycan link protein, and versican	CXCL5, IL-1 $\beta$ , IL2-R, plasminogen, pro-TNF- $\alpha$ , SDF-1, and TGF- $\beta$
MMP-10	Collagen Types III, IV, V, and gelatin	Fibronectin, laminin, and nidogen	Pro-MMP-1, pro-MMP-8, and pro-MMP-10
MMP-11		Laminin	$\alpha_1$ -antitrypsin, $\alpha_1$ -proteinase inhibitor, and IGFBP-1
MMP-12		Elastin	Plasminogen
MMP-13	Collagen Types I, II, III, IV, V, IX, X, XI, and gelatin	Aggrecan, fibronectin, laminin, perlecan, and tenascin	Plasminogen activator 2, pro-MMP-9, pro-MMP-13, and SDF-1
MMP-14	Collagen Types I, II, III, and gelatin	Aggrecan, dermatan sulphate, proteoglycan, fibrin, fibronectin, laminin, nidogen, perlecan, tenascin, and vitronectin	$\alpha_3\beta_3$ integrin, CD44, gC1qR, pro-MMP2, pro-MMP-13, pro-TNF- $\alpha$ , SDF-1, and tissue transglutaminase
MMP-15	Collagen Types I, II, III, and gelatin	Aggrecan, fibronectin, laminin, nidogen, perlecan, tenascin, and vitronectin	Pro-MMP-2, pro-MMP-13, and tissue transglutaminase
MMP-16	Collagen Types I, III, and gelatin	Aggrecan, casein, fibronectin, laminin, perlecan, and vitronectin	Pro-MMP-2 and pro-MMP-13
MMP-17	Gelatin	Fibrin and fibronectin	
MMP-19	Collagen Types I, IV, and gelatin	Aggrecan, casein, fibronectin, laminin, nidogen, and tenascin	
MMP-20		Aggrecan, amelogenin, and cartilage	
MMP-21			$\alpha_1$ -antitrypsin
MMP-23	Gelatin		
MMP-24	Gelatin	Chondroitin sulfate, dermatin sulfate, and fibronectin	Pro-MMP-2 and pro-MMP-13
MMP-25	Collagen Type IV and gelatin	Fibrin and fibronectin	Pro-MMP-2
MMP-26	Collagen Type IV and gelatin	Casein, fibrinogen, and fibronectin	$\beta_1$ -proteinase inhibitor
MMP-28		Casein	

\***Note:** Many of these substrates are found in both the periodontium and synovium. Adapted from Somerville RPT, Oblander SA, Apte SS. Matrix metalloproteinases: old dogs with new tricks. *Genome Biol* 2003;4:216-226.

Of the environmental risk factors identified to date, smoking is probably the single most important environmental factor impacting 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.<sup>13,14</sup>

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.<sup>15,16</sup> The reasons for this are not entirely clear, although suggestions have been made that individuals from lower socioeconomic status may be less compliant with regard to their general healthcare and have less access to the full range of healthcare. However, these explanations do not fully explain this relationship. In this regard, allostatic load has also been proposed to describe dysregulation of physiological adaptive processes, including immune function, that 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 diseases such as periodontitis and rheumatoid arthritis. In this model, low socioeconomic status results in increased exposure to psychosocial stress, which activates primary allostatic mediators, including a wide range of inflammatory mediators. Under these conditions dysregulation of a range of immunomodulatory functions occurs, possibly leading to alterations in the extent and severity of chronic diseases.

**PERIODONTITIS AND RHEUMATOID ARTHRITIS CAN BE CLASSED AS “COMPLEX” OR “ECOGENETIC” DISEASES**

In recent times, periodontitis and rheumatoid arthritis have been considered

“complex” or “ecogenetic” diseases.<sup>17,18</sup> A complex disease is defined as a disorder with a genetic component but does not follow the simple single-gene dominant or single-gene recessive Mendelian law (Table 4). Since

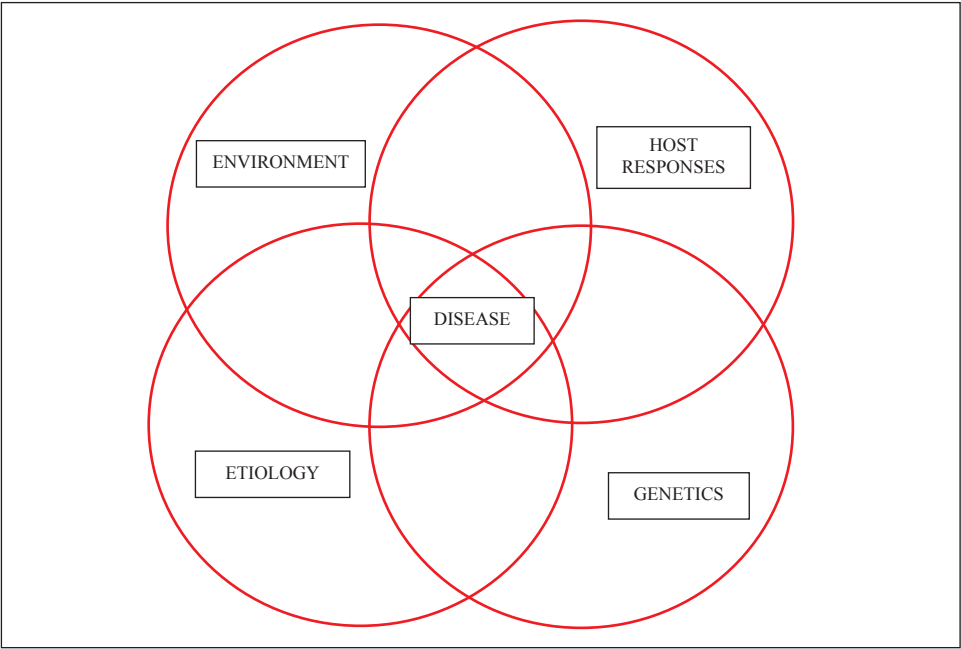
**Table 4.** Features of Complex Diseases or Ecogenetic Diseases

- The diseases interact with ecology, molecular genetics, toxicology, public health medicine, and environmental epidemiology.
- These are common chronic diseases with adult onset that show familial aggregation, but do not follow Mendelian family patterns.
- These diseases appear to be caused by an unknown number of multiple genes, which interact with environmental factors.
- In these diseases, only a small proportion (1%–7%) of affected individuals show a single mutant gene transmitted by Mendelian inheritance with characteristic transmission.
- These genetically exceptional families often have an earlier age of onset and have more severe clinical manifestations.

both inherited genetic variations and environmental factors, such as smoking, hygiene, and pathogenic bacteria interact to determine an individual’s risk for the development of periodontitis and rheumatoid arthritis, these two diseases fit this definition of complex diseases. Hence in these diseases, in response to an initiating event, environmental agents interact with genetic factors to influence disease susceptibility (Figure 3). Such interactions initiate and regulate immuno-inflammatory reactions that ultimately manifest as the clinical signs of rheumatoid arthritis or periodontitis. While understanding the role of dental plaque as being pivotal in the initiating events for periodontal disease is well understood, 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-

**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 between host responses, environmental factors, etiologic factors, and genetics.

recognized environmental risk factors for both diseases is smoking. A relationship 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 the development of both rheumatoid arthritis and periodontitis. From these types of studies it will be possible to define the various environmental risk factors that, in certain genetic contexts, will initiate adverse immune reactions, ultimately leading to clinical symptoms in various subsets of susceptible patients.

In recent years there has been considerable interest in identifying single nucleotide polymorphisms (SNPs) and statistical genetic strategies, such as haplotype mapping, to identify genes that may be of importance in complex diseases such as rheumatoid arthritis and periodontitis. Even though simple one-to-one mapping between

disease gene and disease phenotype does not occur in complex diseases, 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 a better understanding of environmental effects.

**PERIODONTAL DISEASE AND  
RHEUMATOID ARTHRITIS  
HAVE SIGNIFICANT  
INTER-RELATIONSHIPS WITH  
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, which considers the potential interaction between periodontitis and rheumatoid arthritis, it is of interest to note that all of these diseases have also been associated with individuals suffering from rheumatoid arthritis (Table 5). Even after accounting for variable confounders, including various medications, many studies have been able to demonstrate significant relationships between rheumatoid arthritis and systemic conditions.<sup>19</sup> The underlying feature in these relationships seems to be dysregulated chronic inflammation in both periodontitis and rheumatoid arthritis.

**Table 5.** Systemic Conditions Reported to be Associated with Both Periodontitis and Rheumatoid Arthritis

Cardiovascular Disease
Diabetes
Obesity
Obstetric Problems
Pulmonary Conditions
Renal Conditions
Cancer

**WHAT IS THE EVIDENCE FOR A RELATIONSHIP BETWEEN PERIODONTITIS AND RHEUMATOID ARTHRITIS?**

For more than 80 years there have been reports in the literature concerning a possible relationship between rheumatoid arthritis and periodontitis. A number of reviews and commentaries on this topic have been published.<sup>20-24</sup>

One of the earliest reports concerning this relationship was written by Sachs, who commented in 1926 that the relationship between “gelenkrheumatismus and parodontose” was a question of “a constitution with a predisposition to both of these conditions” (quoted from Helminen-Pakkala).<sup>25</sup> Since then, a number of studies considered the relationship between periodontal disease

and rheumatoid arthritis with little agreement being reached as to whether this was indeed possible.

Over the last 30 years, a steady stream of papers that question this relationship have been published. For example, an increase in any dental disease, including periodontal disease, was not seen in a group of South African patients with advanced joint conditions.<sup>26</sup> Similarly, a study of Japanese rheumatoid arthritis patients found no evidence of elevated levels of serum antibodies against several periodontal pathogens.<sup>27</sup> A study that considered clinical and immunological features of periodontitis reported that rheumatoid arthritis patients were not a risk group for advanced periodontal conditions.<sup>28</sup> Furthermore, a case-control study in a group of Scandinavian patients (204 cases and 204 controls) reported a tendency toward better periodontal conditions for the rheumatoid arthritis patients.<sup>29</sup> A study of Norwegian rheumatoid arthritis patients between the ages of 44 and 56 found no correlation between tooth loss and rheumatoid arthritis.<sup>30</sup> In a study using epidemiological data, 523 individuals, initially seen during the first National Health and Nutrition Examination Survey (NHANES I) of 1971–75, exhibited no correlation with self-reported arthritis and the number of missing teeth.<sup>31</sup>

Despite the above investigations, which reported a negative correlation between periodontitis and rheumatoid arthritis, there have been a larger number of studies that have supported such a relationship. While perhaps the least convincing in terms of scientific design, simple pilot studies analyzing data obtained from self-reported illnesses have indicated a higher incidence of rheumatoid arthritis in patients with periodontitis.<sup>32-35</sup>

A number of case-control studies have also been carried out. All of these indicate that rheumatoid arthritis patients have a significantly higher incidence of periodontal disease. For these studies, periodontal

conditions were variously measured as number of teeth missing, gingival bleeding, attachment loss, probing pocket depth, and radiographic bone loss.<sup>32,36-44</sup>

As a result of these findings, studies have been carried out to investigate a number of clinical and laboratory parameters to further ascertain if a relationship between periodontitis and rheumatoid arthritis exists. These have included investigations into cytokine profiles,<sup>45-50</sup> inflammatory mediators,<sup>51</sup> HLA-DR antigens,<sup>52-54</sup> and hormones.<sup>55</sup> All of these studies have supported the notion that periodontitis and rheumatoid arthritis are inter-related, and have led various authors to conclude that inflammation (and its dysregulation) may be the central link between periodontitis and rheumatoid arthritis.<sup>23</sup> At least two studies have concluded that periodontitis may be a risk factor or severity factor for rheumatoid arthritis.<sup>32,56</sup>

As early as 1985, a case report was published describing remission of rheumatoid arthritis following periodontal treatment.<sup>57</sup> This study remained largely forgotten until the publication of two additional studies that indicated periodontal treatment could reduce the severity of rheumatoid arthritis.<sup>56,58</sup> While these studies have involved relatively low numbers of subjects, they highlight the potential for important clinical ramifications for the relationship between periodontitis and rheumatoid arthritis.

Further support for a significant relationship between periodontitis and rheumatoid arthritis has been highlighted in a recent animal study. Moreover, the induction of adjuvant arthritis in rats resulted in an associated periodontal breakdown evidenced by alveolar bone loss and increased matrix metalloproteinase activity in adjacent gingival tissues.<sup>59</sup>

Careful assessment of the data reported from many of these studies allows us to

make some important observations. First, few of these studies support the commonly held tenet that rheumatoid arthritis patients 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.<sup>44,60</sup> Another important observation from recently published studies is that individuals 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 impacting periodontitis (Relative Risk 4.1) rather than periodontitis impacting rheumatoid arthritis (Relative Risk 1.5).<sup>60</sup> Also, it is important that longitudinal studies be carried out from this association to establish the temporal sequence. Finally, from the studies published to date, it is interesting to consider the influence of medications that rheumatoid arthritis patients may be taking, on periodontitis. Many, if not all, of these medications are anti-inflammatory agents and therefore 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.<sup>40,60</sup> It has been proposed that before development of rheumatoid arthritis symptoms, the periodontitis was most likely also developing and not detected.<sup>23</sup> Thus, in the analysis of the association between rheumatoid arthritis and periodontitis, consideration of disease duration (for both periodontal and rheumatoid) will be a critical factor. Therefore, future studies concerning the relationship between periodontitis and rheumatoid arthritis should address and document the disease with regard to severity and duration of both diseases.

## PROPOSED MECHANISMS FOR A RELATIONSHIP BETWEEN PERIODONTITIS AND RHEUMATOID ARTHRITIS

A number of mechanisms for a relationship between periodontitis and rheumatoid arthritis have been proposed. The principal mechanisms may involve changes to blood vessels or infection of host tissues.

### Vascular Alterations

Recent investigations into the relationship between osteoclast activation and vascular damage have suggested 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 receptor activator of nuclear factor Kappa  $\beta$  (RANK)/osteoprotegerin (OPG)/tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) axis, whereby a decrease in OPG leads to reduced vascular protection.<sup>23</sup> In addition, increases in RANK and TRAIL levels within inflamed tissues may result in not only the possible development of vascular damage, but also 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.<sup>61</sup> In this model, reduced caliber of capillaries, along with greater numbers of and elongated capillaries, are noted in both periodontal tissues and rheumatoid synovium.

### Bacterial Infection

Data from a number of animal models demonstrate that arthritis can develop secondarily to several different stimuli and through several 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

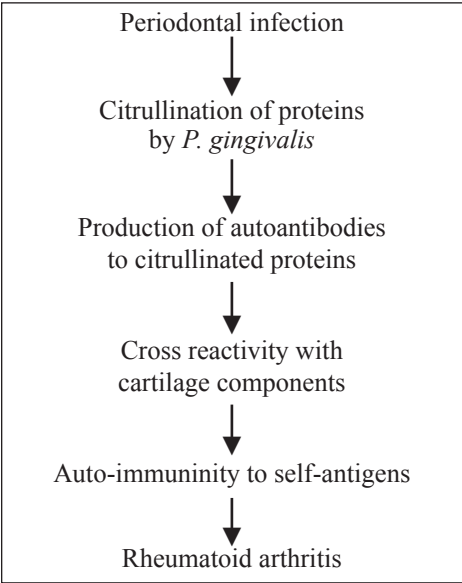
other environmental exposures with capacity to induce excessive pro-inflammatory cytokines in genetically susceptible individuals, may contribute to disease either together with some autoimmune reaction or by themselves.

Many periodontal pathogens exhibit similar characteristics to those 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 lipopolysaccharide. 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*.<sup>27,62-64</sup> Elevated antibodies to *B. forsythus* and *P. intermedia* have also been found in synovial fluid. Further evidence for a role of periodontal pathogens in joint disease have come from a study reporting DNA for *P. gingivalis*, *T. forsythensis* and *P. intermedia* in synovial fluid of rheumatoid patients.<sup>65</sup> No DNA for these bacteria were found in the synovial fluid of nonrheumatoid patients.

A novel hypothesis for the development of rheumatoid arthritis via the humoral response to oral bacteria found in periodontitis has been proposed.<sup>66</sup> 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 the development of rheumatoid arthritis. The production of deimination enzymes by periodontal pathogenic bacteria, such as *P. gingivalis*, can



**Figure 4.** The Humoral Immune Response to Oral Bacteria Provides a Stimulus for Development of Rheumatoid Arthritis



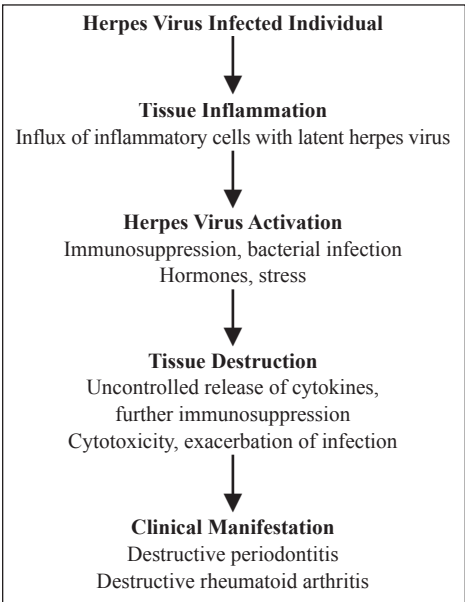
induce autoantibodies, allowing a link between periodontal infection and development of rheumatoid arthritis.

### Viral Infection

Viruses have been implicated in the pathogenesis of both periodontitis and rheumatoid arthritis.<sup>67,68</sup> A number of reports have implicated Epstein-Barr virus in the development of rheumatoid arthritis. Although the mechanisms involved for viruses in the development of rheumatoid arthritis are unclear, it has been proposed that they can act as an adjuvant in the development of autoimmunity, nonspecifically stimulating innate immune responses in genetically susceptible individuals. Epstein-Barr virus may cause periodontal disease via direct infection and replication, or through impairment of host immune responses.<sup>68</sup> Thus, it is possible that a common link between these two diseases could be a viral infection leading to impaired immune function, resulting in uncontrolled

inflammatory reactions at sites such as the periodontium and synovium (Figure 5). At present, this model has not been proven. It does, however, present a perspective that needs to be investigated further.

**Figure 5.** A Possible Mechanism for a Link Between Viral Infection in Periodontitis and Rheumatoid Arthritis



### CLINICAL RELEVANCE OF AN ASSOCIATION BETWEEN PERIODONTITIS AND RHEUMATOID ARTHRITIS

The association between advanced rheumatoid arthritis and advanced periodontal destruction has significant clinical implications with respect to the management of rheumatoid arthritis patients who are at risk of also having periodontitis. Even though most clinical protocols for rheumatoid arthritis patients include an assessment for oral pathology, they do not routinely include a full periodontal assessment. Since 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 the current data, individuals suffering from rheumatoid arthritis seem to be at higher risk of developing periodontal problems. Further, early evidence has suggested that treatment of periodontitis can reduce the clinical symptoms of rheumatoid arthritis. Therefore, early intervention to prevent periodontal destruction occurring in individuals 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 studies, that disease severity and extent may be related for individuals suffering from both rheumatoid arthritis and periodontitis. While causality between the two diseases is very unlikely, the fact that both diseases can impact each other is becoming apparent. Thus, it is proposed that these two diseases can exist as a manifestation of generalized dysregulation of the immune and inflammatory responses. Hence, both periodontitis and rheumatoid arthritis may be considered clinical manifestations of the same disease process presenting in different parts of the body.<sup>69</sup>

### Supplemental Readings

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# CHAPTER 13

## Oral Health, Periodontitis, and Cancer

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### 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 there is a potential for complications or other influences to impact systemic health via bacteremia or dissemination of locally produced inflammatory mediators. 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- $\alpha$ ), interleukins 1 beta and 6 (IL-1 $\beta$  and IL-6), and prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), 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 being focused on oral/systemic interactions, studies have suggested that periodontal disease may be associated with increased cancer risk.<sup>1</sup> 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. While tooth loss may be a poor indicator

of periodontal disease, it has been used as a major surrogate marker for this disease in older individuals.<sup>2</sup> Indeed, there are many reasons for tooth loss and while it can be a result of either dental caries or periodontal diseases, age can also be a major contributing factor for these two conditions. Thus, in early studies, tooth loss in older individuals was assumed to more likely be a result of periodontal disease than caries. In more recent times, such assertions would almost certainly be challenged. Current understanding would indicate that tooth loss in older individuals may be a result of periodontal disease, but this association may not always be particularly strong. This being the case, 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 or not 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 included addressed 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 between 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 between 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,<sup>3</sup> there have been numer-

ous studies investigating the role of oral health and oral cancer (Table 1). While alcohol and smoking are considered two of the most important risk factors for oral cancer, poor oral hygiene and poor dental status have also been reported to carry a significant risk for development of oral cancer.

### Studies of the Relationship Between General Oral Health and Oral Cancer

An early study to investigate the role of dentition, diet, tobacco, and alcohol on risk

**Table 1.** Summary of Findings from Studies Published to Date Concerning Relationships Between Oral Conditions and Oral Cancer

Author(s)	Study Design	Tooth Loss	Poor Oral Hygiene	Gingival Bleeding	Poor Oral Condition	Irregular Dental Check-ups	Periodontal Condition
Graham et al., 1977 <sup>4</sup>	Case-control	Yes	Yes	—	—	—	—
Zheng et al., 1990 <sup>5</sup>	Case-control	Yes	Yes	—	—	—	—
Winn et al., 1991 <sup>6</sup>	Case-control	No	No	No	No	—	—
Marshall et al., 1992 <sup>7</sup>	Case-control	Yes	Not Significant	—	—	—	—
Bundgaard et al., 1995 <sup>8</sup>	Case-control	Yes	—	—	—	Yes	—
Schildt et al., 1998 <sup>9</sup>	Case-control	—	—	—	Yes—for recurrent infections	—	—
Velly, 1998 <sup>10</sup>	Case-control	—	Yes	—	Yes—for denture-related oral sores	—	—
Talamini et al., 2000 <sup>11</sup>	Case-control	—	—	Yes	Yes	—	—
Moreno-López, 2000 <sup>12</sup>	Case control	—	Yes	—	—	No	—
Garrote et al., 2001 <sup>13</sup>	Case-control	Yes	—	—	Yes	—	—
Campisi and Margiotta, 2001	Male population	Yes	Yes	—	—	—	—
Balaram et al., 2002 <sup>14</sup>	Case-control	Yes	—	Yes	Yes	—	—
Lissowska et al., 2003 <sup>15</sup>	Case-control	Yes	Yes	—	Yes	Yes	—
Tezal et al., 2005 <sup>16</sup>	NHANES	—	—	—	—	—	Yes
Rosenquist et al., 2005 <sup>17</sup>	Case-control	Yes	Yes	—	—	—	Yes
Tezal et al., 2007 <sup>18</sup>	Case-control	—	—	—	—	—	Yes
Rezende, 2008 <sup>19</sup>	Case-control	No	—	—	—	—	Yes

for oral cancer was a case study by Graham et al.<sup>4</sup> In this study the cases consisted of 584 males with cancer of the oral cavity at the Roswell Park Memorial Institute, Buffalo, New York. The controls consisted of 1,222 males with no neoplastic diseases at the same institute. Interviews were carried out to obtain information regarding dentition, diet, tobacco, and alcohol consumption.

From this study it was reported that a higher risk of developing cancer was noted 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 7.7 times that of men with none of these features.

In another case-control study carried out in Beijing, Zheng et al.<sup>5</sup> investigated the dentition and oral hygiene status for risk of oral cancer. The cases 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, tobacco use, dentition, and oral hygiene. An oral examination included recording the total number of teeth, jagged teeth, filled teeth, decayed teeth, and 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) if they had replacement teeth, and an OR of 3.7 (CI: 2.2–6.4) if they had 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) if they had replacement teeth and an OR of 8.3 (CI: 3.5–19.6) if they had no tooth

replacement. When oral hygiene was assessed, according to whether the teeth were brushed or not, 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. The findings were interpreted to indicate 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.<sup>6</sup> studied 1,114 oral cancer patients from four population-based registries in the US. 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 the number of teeth, use of dentures, tooth brushing frequency, and 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 relationship 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 relationship between oral/dental conditions and oral cancer.

In another US investigation, Marshall et al.<sup>7</sup> 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, while matched controls were obtained through neighborhood matching. Cases 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 to individuals who had not lost any teeth, an increased risk for oral cancer was noted for those individuals who had lost more than 11 teeth (OR: 3.9; CI: 1.3–11.3). When further analyzed, individuals who smoked cigarettes, drank alcohol, and had lost teeth without having them replaced had an increased risk for 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 on a Danish population has examined if the risk of oral squamous cell carcinoma could be related to occupation, marital status, dental status, and consumption of coffee, tea, alcohol, and tobacco (Bundgaard et al.).<sup>8</sup> In this study, the cases consisted of 161 consecutively admitted patients with histologically verified intra-oral 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. Individuals with fewer than five teeth had an OR of 2.4 (CI: 1.3–4.1) compared to those with 15 or more teeth. Furthermore, those individuals who had irregular dental check-ups had an OR of 2.1 (CI: 1.3–3.3) compared to those who had regular dental check-ups. While significant, these findings were determined to be of less importance 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.<sup>9</sup> investigated the relationship of oral infections and other dental factors for 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 relationship between dental factors and risk of upper digestive tract cancer, Velly et al.<sup>10</sup> studied 717 patients who had newly diagnosed carcinomas of the tongue, gingiva, floor of mouth, and other parts of the oral cavity from three centers in Sao Paulo. Controls (nontumor patients) were selected from the same institutions and data were collected from two controls matched to each case on the basis of gender, five-year age group, trimester of hospital admission, and study site. Information collected by interview included information on socio-economic 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 socio-economic 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). Following 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, broken teeth (OR: 1.8; CI: 1.3–2.7) and infrequent tooth brushing (OR: 1.9; CI: 1.2–2.9) were the only 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 et al.<sup>11</sup> 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 cases of 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. Cases 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. The presence of gingival bleeding was found to be significant (OR: 3.9; CI: 1.2–12.6) when compared to 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 to those who had good oral condition. Interestingly, and 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.<sup>12</sup> 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 intra-oral examination was carried out. While no statistical significance could be found for dental visits, a significant relationship for tooth brushing was found that 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.<sup>13</sup> compared 200 cases of 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, while 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, individuals with greater 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 frequent among cancer cases than controls (OR: 2.6; CI: 1.2–5.2).

In an Indian population derived from three regions (Bangalore, Madras, and Trivandrum), Balaram et al.<sup>14</sup> 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 men (OR: 0.4; CI: 0.19–0.87). Significantly elevated risk for oral cancer for both genders was noted for gingival bleeding (men = OR: 2.8; CI: 1.7–4.7 and women = OR: 3.4; CI: 1.8–6.1), having 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 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.<sup>15</sup> 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.

### **Studies of the Relationship Between Periodontitis and Oral Cancer**

In the first study in which the periodontium was assessed, Tezal et al.<sup>16</sup> 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, individuals who were 20 and older and had at least six natural teeth were included. Subjects requiring antibiotics before a dental examination were excluded. Periodontal measurements included assessment of clinical attachment loss, while other oral assessments included number of missing teeth, caries, restorations, and the presence of partial or full prostheses. Following 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 significant 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 people who never smoked and hence, is probably not an independent risk factor.

Shortly following the Tezal et al.<sup>16</sup> study, Rosenquist et al.<sup>17</sup> 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 cases 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 mucosal assessment was also provided. In an unadjusted analysis, individuals with average (OR: 3.0; CI: 1.7–5.1) or poor (OR: 10.0; CI: 5.1–20.1) oral hygiene, 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), while 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. Upon radiographic assessment, a high level of marginal bone was noted to have 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.<sup>18</sup> carried out a case-control study of pre-existing data for patients seen at the Roswell Park Cancer Center (1999–2005) to assess the role of periodontitis for risk of tongue cancer. The cases consisted of 54 non-Hispanic Caucasian males with primary squamous cell carcinoma of the tongue. Age- and gender-matched non-Hispanic Caucasian men seen in the same hospital department but not diagnosed with any cancer or oral dysplasia served as the 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 following adjustments for the confounders of age, smoking habit, and number of missing teeth indicated that for every millimeter of alveolar bone loss, there was a 5.2-fold increase in the risk of tongue cancer (OR: 5.2; CI: 2.6–10.4). Other variables studied, including caries, restorations, and root canal treatment, failed to show any significant association with tongue cancer.

The most recent published study assessing the association between oral hygiene, periodontal disease, and oropharyngeal and oral cancer was a cross-sectional prospective case-control study.<sup>19</sup> In this study, 50 cases with untreated oral and oropharyngeal squamous cell carcinoma were compared to 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 mouthrinses, dental floss, and other oral hygiene aids. An oral examination was carried out to determine Community Periodontal Index of Treatment Needs (CPITN) scores, missing teeth, caries, restorations, and prostheses, but there was no consideration given to smoking status or



alcohol consumption. Following 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 to 20% of the patients without cancer. No statistically significant differences could be found for caries, missing teeth, restorations, or prostheses.

### **Summary of the Relationship Between Oral Health and Oral Cancer**

It is clear that a number of oral conditions, including tooth loss, poor oral hygiene, poor oral condition, and general periodontal condition are significant risk factors for oral cancer (Table 1). Due to great variability in statistical analyses, it is difficult to determine the real significance of many of these studies. Nonetheless, 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. While the 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 (GI) Cancer**

One of the first reports to suggest an association between oral condition and GI cancer was a case-control study carried out in Germany.<sup>20</sup> The cases included stomach cancer patients ( $n = 257$ ) and healthy, non-cancerous 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. Demirel et al.<sup>21</sup> studied a Turkish population, principally to investigate the relationship between diet and stomach cancer, but used some oral measurements as well. The cancer cases ( $n = 100$ ) had histologically proven adenocarcinoma of the stomach, and age, gender, and residential area-matched subjects with no gastrointestinal 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.<sup>22</sup> As part of this study, information concerning dental hygiene habits was obtained. The cases ( $n = 326$ ) 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 et al.<sup>23</sup> studied a Japanese population to investigate the etiological relation between gastric cancer and lifestyle. The cases of gastric cancer ( $n = 242$ ) and controls ( $n = 484$ ) 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 odds ratio 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.

A number of recent case-control, cohort, and cross-sectional studies have been carried out to ascertain the relationship between oral health and gastric cancer. In a large case-control study of a Chinese population, Abnet et al.<sup>24</sup> investigated the relationship 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 histological confirmation of upper gastrointestinal 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 lost 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, a RR of 1.3 (CI: 1.0–1.6) for the gastric cardiac, and a 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 individuals.

In a similar study, Abnet et al.<sup>25</sup> 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 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  $< 10$  teeth lost was 1.65 (CI: 1.1–2.5). For esophageal squamous cell carcinoma and esophageal/gastric cardiac adenocarcinoma, there were no statistically significant associations with tooth loss.

In another cross-sectional study of a rural Chinese population, Wei et al.<sup>26</sup> investigated the risk factors for oropharyngeal squamous dysplasia. The study population (Linzhou, formerly Linxian, China) was chosen because of a very high prevalence 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 dysplasia (OR: 1.91; CI: 1.2–3.2). These findings were similar to the earlier report by Abnet and colleagues.<sup>25</sup>

A cross-sectional study by Dye et al.<sup>27</sup> investigated the oral health of a non-representative sample of adult participants in an esophageal cancer study. In this 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, clinical attachment levels, and bleeding on probing. As noted earlier,<sup>24</sup> tooth loss was prevalent with 17% of the study population being edentulous. In an unadjusted model, individuals who had 12–31 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: 1.0–6.2.7), and when adjusted for nonsignificant covariates, the 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 an important contributing factor to 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 to suggest 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

There are very few reports in the literature concerning the relationship 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.<sup>28</sup> Data from 11,328 adults between the ages of 25–74 underwent a medical examination, a standardized medical history, and standardized dental examination in 1971–1975. The individuals were followed with a 96.2% success rate until 1992. Death certificates of deceased individuals were obtained and the analysis considered those who had died from malignant neoplasms including lung and bronchus, pancreas, colon, gingiva, oral cavity, and any other cancer. The dental examinations included measuring the extent of gingival inflammation and the size of periodontal 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 while 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 hazard ratio was determined to be 2.14 (CI: 1.30–3.53). With further adjustment for socio-economic status, smoking status, alcohol consumption, and the intake of vitamins A and C, the hazard ratio 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.

The only other published report in which periodontitis and lung cancer was studied also does not support a link. In this study, associations between tooth loss and mortality patterns in a cohort from Glasgow were studied<sup>29</sup> in 223 individuals (median age at baseline was 19) who were followed 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. Following extensive statistical analyses, the authors concluded there was no association 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.

While 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.<sup>30</sup> hypothesized that tooth loss may be associated with pancreatic cancer. This was a cohort study of Finnish men, ages 50–69, who smoked more than five cigarettes per day and had no history of any malignancy apart from nonmelanoma of the skin or carcinoma *in situ*. Baseline information obtained by interview included medical, dental (number of teeth), smoking, and dietary history. Out of the 29,104 participants, 174 developed pancreatic cancer. Cox proportional hazard 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 to individuals missing 10 or fewer teeth (HR: 1.63; CI: 1.09–2.46). However, for people missing 11–31 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.<sup>28</sup> in their study utilizing the NHANES I data to investigate the association between periodontitis and various cancers found no association for pancreatic cancer.

A subsequent study by Michaud et al.<sup>2</sup> 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 US. The study period was 16 years. At baseline, participants reported the number of natural teeth and 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. Individuals who

were assessed to have periodontal disease at baseline had an increased risk of having 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 to 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 individuals with a body mass index of less than 25 kg/m<sup>2</sup> (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 proven, additional studies are required.

In an interesting follow-up to the Michaud et al.<sup>2</sup> publication, Taguchi,<sup>31</sup> 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 have negated their findings. In addition, Taguchi suggested that to better understand the relationship 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.<sup>2</sup> 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 two-fold 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 two-fold 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.

### **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, the majority of studies have reported on the association between tooth loss and cancer risk. Such approaches may be flawed since tooth loss may also result from trauma or, more commonly, caries. However, these studies claim that because teeth lost at an older age are more likely due to periodontal disease compared to those lost at younger ages (which may be due more to dental caries), tooth loss in older individuals can be a good surrogate marker of periodontal disease. On the basis of that, it seems 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 relationship to periodontal disease can be seen in the study by Michaud, et al.<sup>2</sup> In this study, which ran 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, it was noted that tooth loss within the previous four years was a predictor of pancreatic cancer risk. When both periodontal disease and recent tooth loss were assessed jointly, the risk of pancreatic cancer increased significantly compared to 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 socio-economic status. Smoking is a well-recognized risk factor for oral and lung cancer but 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.<sup>28,29</sup> While this may be true for lung cancer, 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.<sup>2,27</sup> 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. A number of studies have adjusted for alcohol intake and found that tooth loss persists as a significant risk factor for this cancer.<sup>15-17</sup> Socio-economic status is also considered an important risk factor for periodontitis and hence there is further potential for socio-economic status to be a confounding issue in

studies considering the effect of tooth loss on cancer. While most studies have included socio-economic status in their questionnaires, adjustment for this component has not always been a prominent feature of the statistical modeling.

Although smoking, alcohol consumption, and socio-economic status may be the three commonly recognized confounders for many studies concerning cancer risk and periodontal disease, it is highly likely that many other, hitherto unidentified confounding factors could be at play and need to be identified before these associations can be confidently accepted.

With these caveats in mind, there are several scientific reports that attempt to evaluate the relationship between periodontal disease, cancer, and mortality. One of the first to report that periodontitis was positively associated with cancer was Hujoel et al.<sup>28</sup> in 2003. This study has been described in more detail in the previous section dealing with lung cancer. Briefly, Hujoel and colleagues followed 11,328 individuals over a 10-year period and compared periodontal status to 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. It was noted that 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 relationship between oral health and increased risk of total death and death from cancer have been made from a cohort study on rural Chinese.<sup>32</sup> This was a follow up to the Abnet et al.<sup>24</sup> 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 individuals with greater than the age-specific median number of teeth lost had 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 from death at other cancer sites showed no significant associations with tooth loss. It was concluded that tooth loss was significantly associated with increased risk for total death from cancer and from upper GI cancer.

In contrast to the above findings, Cabrera et al.,<sup>33</sup> in a study investigating the relationship between tooth loss and chronic disease, 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.<sup>29</sup> 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 relationship between tooth loss and cancer mortality could be explained by other causal or confounding mechanisms.

Tramini et al.<sup>34</sup> investigated tooth loss and associated factors in elderly patients in France who had been institutionalized long term. This was a cross-sectional study of 321 elderly patients in which socio-economic, 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.<sup>35</sup> published the results from a 16-year longitudinal study investigating periodontitis and premature death. In this study 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 greater. 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 individuals 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.<sup>36</sup> examined the relationship 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 non-cancer 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 (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.<sup>37</sup> 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 above 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 and these 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 hazard 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. Following adjustment for known cancer risk factors such as smoking history and diet, compared to individuals with no reported history of periodontal disease, individuals with a self-reported history of periodontal disease demonstrated an increased risk for total cancer (HR: 1.14; CI: 1.07–1.22). For specific cancers, a past 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 hematological 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 hematological cancers were new and have not been reported previously. In contrast to previous studies, the association for esophageal cancer, while 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. Interestingly, 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 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.<sup>38</sup> 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.<sup>39</sup> While this is an interesting theory, 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 increased risk of developing gastric adenocarcinoma.<sup>40,41</sup> Since *H. pylori* can be isolated in the oral cavity, especially in individuals with periodontitis who have the bacterium in their gastrointestinal tract,<sup>42</sup> it has been proposed that the oral cavity may act as a reservoir for *H. pylori*-associated gastric cancer. While it has been suggested that *H. pylori* cannot survive in the oral cavity, there are studies that support the notion that *H. pylori* can be found in dental plaque and periodontal pockets.<sup>43,44</sup> Nonetheless, it is generally accepted that the presence of *H. pylori* in the oral cavity may be independent of infection status of the stomach<sup>45</sup> and no good evidence exists for the presence of periodontal disease, oral *H. pylori*, and gastric cancer.<sup>30</sup>

### POSSIBLE MECHANISMS FOR THE RELATIONSHIP BETWEEN ORAL CONDITIONS AND CANCER

A number of hypotheses have been proposed to explain the observed relationships between periodontal disease and cancer including poor diet, mechanical irritation, chronic infection, systemic inflammation, and immune suppression, as well as increased exposure to carcinogens.<sup>1,32</sup>

#### Diet and Mechanical Irritation

The role of poor oral condition and tooth loss with trauma has been well discussed for both oral and upper gastrointestinal cancer. For decades, an association between poor restorative dentistry and ill-fitting prostheses and oral cancer has been recognized.<sup>46</sup> However, more recently it has been proposed that tooth loss may alter dietary patterns and this may be a contributory factor to the development of upper GI cancer.<sup>32</sup> In addition, it has been suggested that tooth loss may result in inadequate mastication and the resulting poorly chewed food bolus could have an irritating effect on the esophagus, leading to increased risk of cancer through mechanical irritation.<sup>47</sup> To date these hypotheses have not been proven. 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.<sup>32</sup>

#### 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.<sup>48</sup> This is demonstrated with chronic pancreatitis being associated with an increased risk of pancreatic cancer.<sup>49</sup> Indeed, inflammation has been shown, at least in animal studies, to be associated with the progression of liver and colon cancer.<sup>50</sup> Since periodontal disease is an inflammatory disease in which there are 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.<sup>1</sup> Thus, the host

response in periodontal disease may lead to a systemic exposure to pro-inflammatory 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 since 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. While it is possible that elevated systemic levels of inflammatory cytokines may encourage sub-threshold neoplastic states to become neoplastic, local inflammation and local release of inflammatory mediators at a site of potential neoplastic transformation seems more likely. Alternatively, it has been suggested that individuals who suffer from both periodontal disease and cancer may share similar gene polymorphisms in genes encoding inflammatory cytokines; thus periodontitis may merely be 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.<sup>40,41</sup>

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.<sup>18</sup> In addition, chronic inflammation induced by periodontal pathogens results in chronic release of pro-inflammatory cytokines, chemokines, prostaglandins, growth factors, and

enzymes that may have indirect effects on carcinogenesis by deregulating physiological cell turnover and cell growth.

In another hypothesis, it has been proposed that periodontal pathogens may increase the level of certain carcinogens such as nitrosamines.<sup>32</sup> 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.<sup>51</sup> 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.<sup>2</sup>

### 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 an individual at risk of inadequate cellular surveillance for tumor growth. In particular, the stable periodontal lesion consists of a predominantly T helper cell 1 (Th 1) response<sup>52</sup> and is associated with high levels of interferon- $\gamma$  (IFN- $\gamma$ ), an important cytokine in cell-mediated immunity and tumor surveillance.<sup>53</sup> The progressive periodontitis lesion consists predominantly of a Th 2 response with lower levels of IFN- $\gamma$  and a poor innate immune response.<sup>52</sup> 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 between 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 as there may be additional confounding factors that researchers are unaware of and that have not been included in the analyses for adjustment. There is a need for more studies 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

Meyer MS, Joshupura KJ, Giovannucci E, Michaud DS. A review of the relationship between tooth loss, periodontal disease and cancer. *Cancer Causes Control* 2008;19:895–907.

Michaud DS, Joshupura K, Giovannucci E, Fuchs CS. A prospective study of periodontal disease and pancreatic cancer in US male health professionals. *J Nat Cancer Inst* 2007;17:171–175.

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# CHAPTER 14

## Dental and Medical Comanagement of Patients with Diabetes

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### INTRODUCTION

This chapter discusses the comanagement of diabetic patients 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 below. The role of dental and medical professionals in this setting is then reviewed separately and in detail. The 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:

- Appreciate the importance of dental and medical comanagement of the patient with diabetes.
- Understand the responsibilities of the dental team towards 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 practice.
- Identify ways to prevent and treat emergencies related to diabetes in the dental office.
- Understand the ways 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 relationship between diabetes and periodontitis deepens, the comanagement of patients with diabetes is expected to become the standard model of care.

### Diabetes

Diabetes is one of the most common chronic illnesses, affecting approximately 24 million people in the United States and 246 million throughout the world.<sup>1,2</sup> In the decade from 1996 to 2006, the prevalence of diagnosed diabetes nearly doubled in the US,<sup>1</sup> 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 minority populations.<sup>1</sup> Despite being the leading cause of blindness, kidney failure, and amputations not related to accident or injury in the US, nearly one quarter of those with diabetes are unaware that they

have this disease.<sup>1,3</sup> Because the symptoms are neither specific to the disease nor accurately reflective of blood glucose concentration, the diagnosis is frequently not made until severe symptoms or complications appear. Once diagnosed, the clinical sequelae of diabetes 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 individuals by reinforcing the need for good metabolic control.

### Prediabetes

According to the 2010 Standards of Medical Care in Diabetes by the American Diabetes Association,<sup>4</sup> the term prediabetes applies to individuals 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 following a two-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 57 million Americans ages 20 or older, more than twice the number of diabetic cases, and totaling 20% of the adult population. People with prediabetes have a strong risk for developing type 2 diabetes and are already at an increased risk for heart disease, stroke, and microvascular diseases typical of individuals with fully developed diabetes.<sup>5</sup> There is strong evidence indicating 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.<sup>6</sup> 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, and there is no evidence of loss of support around the teeth (referred to as 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 increased risk for many disorders, including cardiovascular and cerebrovascular diseases, diabetes complications, adverse pregnancy outcomes, respiratory disease, and kidney disease. Periodontitis generally takes many years to develop, and more advanced disease is more common with advancing age. Once 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 any evidence of periodontal destruction (e.g., two mm of CAL is generally considered the lower limit of detection, and this must occur on at least one tooth surface) the majority of adults will be identified as affected.<sup>7</sup> It is clear, however, that this very mild form of periodontitis does not affect function or place a tooth at risk for being lost. In contrast, advanced forms of periodontitis affect 5% to 15% of different populations.<sup>8</sup> An interesting trend observed over the last 30 years in developed countries is increased tooth retention. Data

from Sweden indicate there has been a reduction in the percent of the population that is affected by gingivitis and mild-to-moderate periodontitis, and a corresponding increase in the percent of the population that has a healthy periodontium.<sup>9</sup> As examples, the percent of periodontally healthy individuals in 1983, 1993, and 2003 was 23%, 22%, and 44%, respectively. However, the percentage of individuals with severe disease remained essentially unchanged during this time (13%, 13%, and 11%).

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 individuals to be involved in their own care. For diabetes mellitus, that means careful control of carbohydrate consumption, weight control, and following other aspects of a healthy lifestyle. For periodontitis, that means a 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.

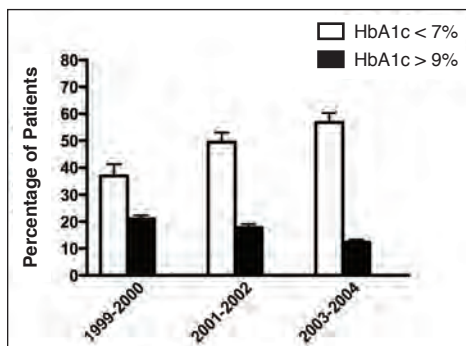
### **Underdiagnosis of Diabetes and Difficulties in Achieving Optimal Metabolic Control in Diagnosed Patients**

A significant percentage of patients with diabetes remain undiagnosed, indicating the need for screening at multiple healthcare locations. Fortunately, some progress has been made over the past few years in this arena. Increased public attention and enhanced public health measures have led to a drop in the percentage of undiagnosed patients with diabetes from 30% in 2005 to 24% in 2007.<sup>3</sup> Further improvement in the detection of diabetes can be achieved by expanding the number of contact points undiagnosed individuals have with a wide range of healthcare providers. Currently in the US, there are only 15,000 certified diabetes educators and 4,000 endocrinologists<sup>10</sup> whose primary

focus is to provide clinical care, numbers that pale in comparison to the escalating disease burden. Therefore, the brunt of the responsibility for diabetes screening and management has fallen on primary care physicians. A shrinkage in the numbers 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,<sup>11,12</sup> pointing to the potential for dental professionals to be involved in the identification of individuals 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)<sup>13</sup> and the United Kingdom Prospective Diabetes Study (UKPDS)<sup>14</sup> have convincingly demonstrated that lowering HbA1c levels was associated with significant reductions in risk for complications. Although progression to diabetes complications is not inevitable with intensive glycemic control, national data from 2004<sup>15</sup> suggest that only 56.8% of the diabetic population in the US achieved glycemic goal, an HbA1c of less than 7% (Figure 1). Consequently in 2007, diabetes costs were over \$174 billion in the US, most of which were related to care for diabetes complications.<sup>1</sup> The percentage of diabetic patients achieving the HbA1c goal of 7% in 2004 appears significantly increased when compared to earlier national data (36.9% in 1999–2000 and 49.4% in 2001–2002), but remains an unsatisfactory outcome.<sup>15</sup> The underlying reasons 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

**Figure 1.** Glycemic Control in US Adults with Diabetes (NHANES Data)



Although, levels of glycemic control in individuals with diagnosed diabetes in the US have improved in recent years, only 56.8% of diabetic patients are at the treatment goal of HbA1c < 7%. Poor control (HbA1c > 9%) was less prevalent in 2003–2004 compared to earlier years, but remains a significant concern. Further improvement in the glycemic control of diabetic patients can be achieved by expanding the number of contact points these individuals have with a wide range of healthcare providers who educate and support them in their efforts to reach glycemic goals and reduce the risk for diabetes-related complications. **Source:** *Diabetes Care* 2008;31: 81–86.<sup>15</sup>

with quality of life. While the adoption of advanced medical regimens and devices has opened up unprecedented possibilities for improved diabetes care, successful outcomes can only come about 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 critical for the management of periodontitis and diabetes, providing 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 medications or enough insulin dosages are given. However, the practical challenge is that intensive diabetes therapy potentiates the risk for frequent and serious hypoglycemic events that in turn

limits the intensity of treatment.<sup>16</sup> Any interruptions such as fasting or stress factors will have significant impact on glycemic levels. All healthcare providers who routinely take care of diabetic patients should have a basic understanding of diabetic 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 by diabetic patients in achieving optimal oral hygiene and in receiving professional dental care highlight the need for support by all healthcare providers.

There are important changes in the oral cavity associated with diabetes mellitus<sup>17</sup> that may often go unrecognized and therefore untreated. Diabetes is an established risk factor for periodontitis, and is the only disease that has been shown to independently and significantly increase the risk for periodontitis.<sup>18</sup> 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 manifest with symptoms that are obvious to the patient. Further, 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 is dependent upon patient compliance for the most successful treatment outcomes. Patients are required to perform effective oral hygiene, which requires a daily

commitment. Further, maintaining regular appointments with their dentist for oral prophylaxis visits and examinations to determine if the periodontal condition is stable requires a continuous decision to schedule and keep appointments. As is the case for diabetes, patients with periodontitis are challenged on a daily basis to adhere to these regimens.<sup>19</sup> In both cases, the majority of 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 relationship of diabetes mellitus and periodontal disease is bi-directional. 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<sup>20</sup> included a review of how the presence of periodontal disease could 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 pro-inflammatory cytokines and other inflammatory mediators produced in the highly vascular periodontal tissue when periodontitis is present.<sup>21</sup> 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.<sup>22,23</sup>

Older reports have indicated that the presence of periodontitis in patients with diabetes is associated with subsequent development of clinical complications in those patients. A number of recent studies

have defined these associations. Saremi and colleagues<sup>24</sup> 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 individuals with severe periodontitis at baseline (versus a healthy periodontium or mild or moderate periodontitis) were at 3.2 times the risk of dying from cardiac or renal disease. In addition, another report examining the same community found that compared to no disease or mild periodontitis, individuals with moderate or severe periodontitis or who were edentulous were at 2.0 to 2.6 times increased risk for the development of nephropathy.<sup>25</sup> The chance of developing endstage renal disease was even higher for those individuals 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<sup>26</sup> asked an intriguing question: Could the presence of periodontal disease predict the subsequent development of diabetes mellitus? Nearly 9,300 individuals were included in this study, specifically those people who were part of the first US National Health and Nutrition Examination Survey (NHANES I, 1971–1976), had received a dental examination, and were seen at least one other time (1982–1992). Periodontal status was determined by the Periodontal Index, and patients were graded on a zero to five 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 relationship of periodontal disease to subsequent development of diabetes.



Relative to periodontal health (score of zero), the risk of developing diabetes mellitus was not raised for individuals with scores of one or two. 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.

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 Borgnakke,<sup>20</sup> a total of 20 studies were identified that examined the effect of nonsurgical periodontal therapy on metabolic control. Seven of the 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 the use of 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 non-RCTs. It was concluded that the use of antibiotics as part of the approach involving periodontal therapy to improve metabolic management in patients with diabetes has not been proven. Periodontal therapy will improve oral health for patients with diabetes mellitus, and this therapy may also result in improved metabolic control. It is clear that additional clinical research is needed to better understand this finding.

All the above 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 individuals.

## THE ROLE OF DENTAL PROFESSIONALS

The above information strongly suggests a greater 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 is 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 seek to identify patients who may remain undiagnosed and refer such 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 have all 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. Similarly to what has been shown within the medical profession, however, efforts to translate research into primary care have been met with resistance<sup>27</sup> 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<sup>28,29</sup> 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 quite low for both groups of clinicians. A subsequent study of general dentists in New Zealand<sup>30</sup> showed striking similarities in attitudes and orientations compared to those identified in the US study.

These data suggest there is a need to increase dentists' involvement 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. Interestingly, when looking at predictors of active management of the diabetic patient,<sup>31</sup> 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 provide the initial step toward identifying the components of targeted interventions aimed at increasing specialists' and general dentists' level of involvement in the management of the diabetic patient, thereby contributing to the improvement of the dental patient's oral and systemic health.

### **How Can Dental Professionals Be More Involved?**

In order 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 help in the identification of those with pre-diabetes or even those with frank diabetes who remain undiagnosed, it is essential that they have a thorough knowledge of certain aspects of this complex disorder. Dental professionals need to be aware of and appreciate the multiple 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;

and

- appropriate equipment, supplies, and training in order 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 type of dental and/or periodontal therapy and the frequency of follow-up care; and
- 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:

- time since diagnosis;
- 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 associated conditions, i.e., hypertension, hypercholesterolemia, etc.; and
- frequency of prior hypoglycemic episodes and precipitating factors.

One very important next step is that the dentist establish communication with the treating physician. This allows the dentist to confirm answers to the questions above, especially if 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 extensive and/or stressful procedures. Communication should be ongoing, especially if 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; and
- 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 the large majority of cases. Any active infection must be immediately treated as it may also have a significant adverse impact on the diabetic state, especially on 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 prior to any therapy and reviewed at follow-up visits. The oral hygiene regimen should include the use of an over-the-counter toothpaste and/or mouthrinse 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 as it may help the dentist to better assign prognosis and predict outcomes of further treatment, including response to and healing capacity following periodontal surgery, extractions, implant surgery, or regenerative procedures.
- Following 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 sub-antimicrobial 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 glucose levels should be assessed preoperatively and as discussed in detail below.
- Appointments should be kept as atraumatic, short, and stress-free as possible, as 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.
- Post-operative analgesics should be provided to ensure that the patient is pain-free following tooth extraction, periodontal surgery, or any other invasive procedure.

### **Prevention and Proper Management of Diabetes-Related Emergencies in the Dental Office**

Extreme 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.<sup>32</sup> 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 skipped or delayed meals while taking medication, alcohol consumption, excessive physical activity, or a combination of these factors. 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?” or, “Did you adjust your medication and how?”

The classic symptoms of hypoglycemia include hunger, shakiness, nervousness, sweating, or weakness.<sup>32</sup> 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 point, 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 Box 1. 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 or food that contains 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 if glucose level is still below target (90 mg/dL). If the initial glucose is below 50 mg/dL, then consumption of 30 g of simple carbohydrates is indicated. Shortly after the immediate treatment, the patient should follow with a meal or snack. In practice, food such as ½ peanut butter sandwich, 6 saltine crackers, or 3 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 prior to operating a motor vehicle. There always exists the temptation to overtreat hypoglycemia with a large amount of carbohydrates due to the urgency and the discomfort associated with the symptoms. Yielding to this practice will lead to excessive rebound hyperglycemia, thereby generating vicious cycles of glycemic instability. In the event of severe hypoglycemia where the individual is unconscious or too confused to ingest carbohydrates, trained personnel in

### Box 1. 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 ½ 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.

addition to activating the emergency medical service may intramuscularly inject glucagon, which is packaged as a 1 mg ampoule of glucagon with diluents and a syringe. The glucagon injection is expected to restore the patient to consciousness within 10-15 minutes, but the effect may be short-lived. The second line of treatment should include ingestion of juice or soda, followed by a snack of solid food. 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 diabetic

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. Placing diabetic patients early in the appointment schedule can prevent hypoglycemic episodes associated with prolonged fasting or delayed/skipped meals.

Not all diabetic 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 via mechanisms distinct from direct stimulation of insulin production. For others, the stimulation

**Table 1.** Classification of Diabetes Agents According to Their Potential to Lower Glucose Below Physiologic Range

Hypoglycemic Agents	Antihyperglycemic Agents
<b>Sulfonylureas</b> Glyburide (Diabeta®, Micronase®) Glipizide (Glucotrol®, Glucotrol XL®) Glimepiride (Amaryl®)	<b>Biguanide</b> Metformin (Glucophage®)
<b>Short-acting secretagogues</b> Repaglinide (Prandin®) Nateglinide (Starlix®)	<b>Thiazolidinediones</b> Pioglitazone (Actos®) Rosiglitazone (Avandia®)
<b>Insulin</b> <i>Basal/intermediate to long-acting insulin</i> Detemir (Levemir®) Glargine (Lantus®) NPH (Novolin N®, Humulin N®) <i>Short-acting insulin</i> Regular human insulin (Novolin R®, Humulin R®) <i>Ultra-short-acting insulin</i> Aspart (NovoLog®) Lispro (Humalog®) Glulisine (Apidra®) <i>Mixed insulin</i> Aspart 70/30 (NovoLog mix 70/30) Lispro 75/25 (Humalog mix 75/25) Lispro 50/50 (Humalog mix 50/50) Regular human mix 70/30 (Humulin 70/30, Novolin 70/30) Regular human mix 50/50 (Humulin 50/50)	<b>Alpha-glucosidase inhibitors</b> Acarbose (Precose®) Miglitol (Glyset®) <b>Incretins</b> Exenatide (Byetta®) Sitagliptin (Januvia®) <b>Amylin analog</b> Amylin (Symmlin®) <b>Bile acid binder</b> Colesevelam (Welchol®)



of insulin release occurs in a glucose-dependent manner. In other words, the glucose-lowering effect of these drugs moderates as glucose levels normalize. These drugs include biguanide, thiazolidinediones, alpha-glucosidase inhibitors, incretins, and bile acid-binders. The hypoglycemic class of medications lowers glucose levels either by insulin replacement or direct insulin stimulation. Sulfonylureas, short-acting insulin secretagogues, 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. While it is correct that individuals with type 1 diabetes must rely on insulin for survival, many individuals with type 2 diabetes also require insulin at later stages of the disease. It is important to emphasize that antihyperglycemic agents are associated with a profound risk of causing hypoglycemia when combined with drugs from the hypoglycemic class.

Generally, there is no need for adjustment of the medication or insulin regimen prior to or on the day of the dental appointment. If the patient is asked to fast overnight prior to 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. For those who are on NPH or premix insulin in the morning, they should take only

one third to one half of the usual dose. A finger stick glucose check should be performed prior to 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 the treating physician if there is any concern or he/she thinks that a change in the patient's diabetic regimen may be necessary.

It is well known that chronically elevated glucose levels impair wound healing and predispose patients to infections.<sup>33</sup> In contrast, transient hyperglycemia at levels below 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 diabetic medications related to the dental procedure. Reviewing a recent HbA1c test result can help determine if it reflects the underlying glycemic trend. However, for patients with type 1 diabetes, significant ketoacidosis (also known as diabetic ketoacidosis or DKA) can occur at glucose concentrations above 250 mg/dL in which additional insulin administration and hydration are urgently indicated.<sup>34</sup> The telltale signs and symptoms of DKA include excessive thirst, fatigue, rapid breathing, fruity breath, nausea, and vomiting. While most patients with type 1 diabetes have the skills to manage hyperglycemia and mild DKA by aggressive rehydration and insulin administration, a consultation with their medical provider is necessary if the symptoms become severe. When the patient is severely nauseated or unable to keep down fluids with blood glucose above 250 mg/dL, the patient 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 screening for undiagnosed diabetes, the American Diabetes Association has made recommendations for routine screening in adults 45 or older, and has defined the high-risk categories in which screening is advisable more often or in younger individuals (Box 2). The increased risk is associated with certain demographic characteristics (minority, race-ethnicity status, family history of diabetes), clinical characteristics (obesity, physical inactivity, hypertension, dyslipidemia), and prior evidence of abnormal glucose values (gestational diabetes, IFG, IGT).<sup>4</sup>

Historically, the primary method used to diagnose diabetes mellitus has been the fasting plasma glucose test. While valuable for making a diagnosis, this tends to be highly dependent on patient compliance, and is meaningful only for the immediate time period prior to when the test is administered.

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 2010 revisions of the Standards of Medical Care in Diabetes by the American Diabetes Association,<sup>4</sup> the HbA1c assay is also now accepted as a test to diagnose diabetes (with a cut point of  $\geq 6.5\%$ ). In addition, it remains very valuable for monitoring glycemic levels and response to treatment, and 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 it 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 in 2007 show that 68.5% of adults had visited a dentist in the previous year,<sup>12</sup> and data from the Behavioral Risk Factor Surveillance System show an even higher percentage.<sup>11</sup> Insurance utilization patterns indicate that individuals tend to seek routine and preventive oral

#### Box 2. Screening for Diabetes in Asymptomatic Adults

All  $\geq 45$  years of age—if normal, repeat every 3 years. Test at younger ages or more frequently if patient is overweight or obese (body mass index  $\geq 25$  kg/m<sup>2</sup> for most, but not all racial/ethnic groups) and having one or more of the following risk factors:

- Family history of diabetes (parent or sibling)
- High-risk race/ethnicity (African-American, Hispanic/Latino, Alaska Native, American Indian, Asian American, or Pacific Islander)
- Habitual physical inactivity
- Delivery of infant  $> 9$  lbs or history of gestational diabetes
- Polycystic ovarian syndrome
- Blood pressure  $\geq 140/90$  mm Hg
- High-density lipoprotein cholesterol  $< 35$  mg/dL or triglycerides  $> 250$  mg/dL
- Impaired glucose tolerance or impaired fasting glucose
- History of vascular disease or other diabetes-associated conditions

Adapted from the American Diabetes Association "Standards of Medical Care in Diabetes—2010." *Diabetes Care* 2010;33(Suppl1):S11–S61.<sup>4</sup>

healthcare on a more frequent basis than routine and preventive medical care.<sup>35</sup> These facts allow dentists and dental hygienists to be at the front line of screening interventions and risk-reduction strategies.<sup>36</sup> 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.<sup>37</sup> A recent report explored for the first time a predictive model for undiagnosed diabetes<sup>38</sup> that included measures of periodontal disease using national data from the third US NHANES study. Findings revealed that, for example, a 45-year-old person, with self-reported family history of diabetes, self-reported hypertension, high cholesterol levels, and clinical evidence of periodontal disease bears a probability of having diabetes (and being unaware of it) between 27% and 53%, with Mexican-American men exhibiting the highest and white women the lowest.<sup>38</sup> These probabilities increase among individuals 60 years of age to between approximately 48% and 74%. These findings, coupled with emerging supportive data by others,<sup>39</sup> 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 are not definitive, but afford us the opportunity to test and validate such a model in the clinic.

### **Participating in the Management of Patients with Unrecognized or Known Diabetes**

Based on the above, the dentist or dental hygienist should assess the presence of risk factors for diabetes in their patients (Figure 2). A risk calculator is available from the American Diabetes Association and dental professionals can use it to assess (and discuss) levels of risk for diabetes in their patients.<sup>40</sup> If

they identify a patient at risk, then they can either use a screening blood test in the office or refer to a physician for diagnostic testing. Irrespective 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:

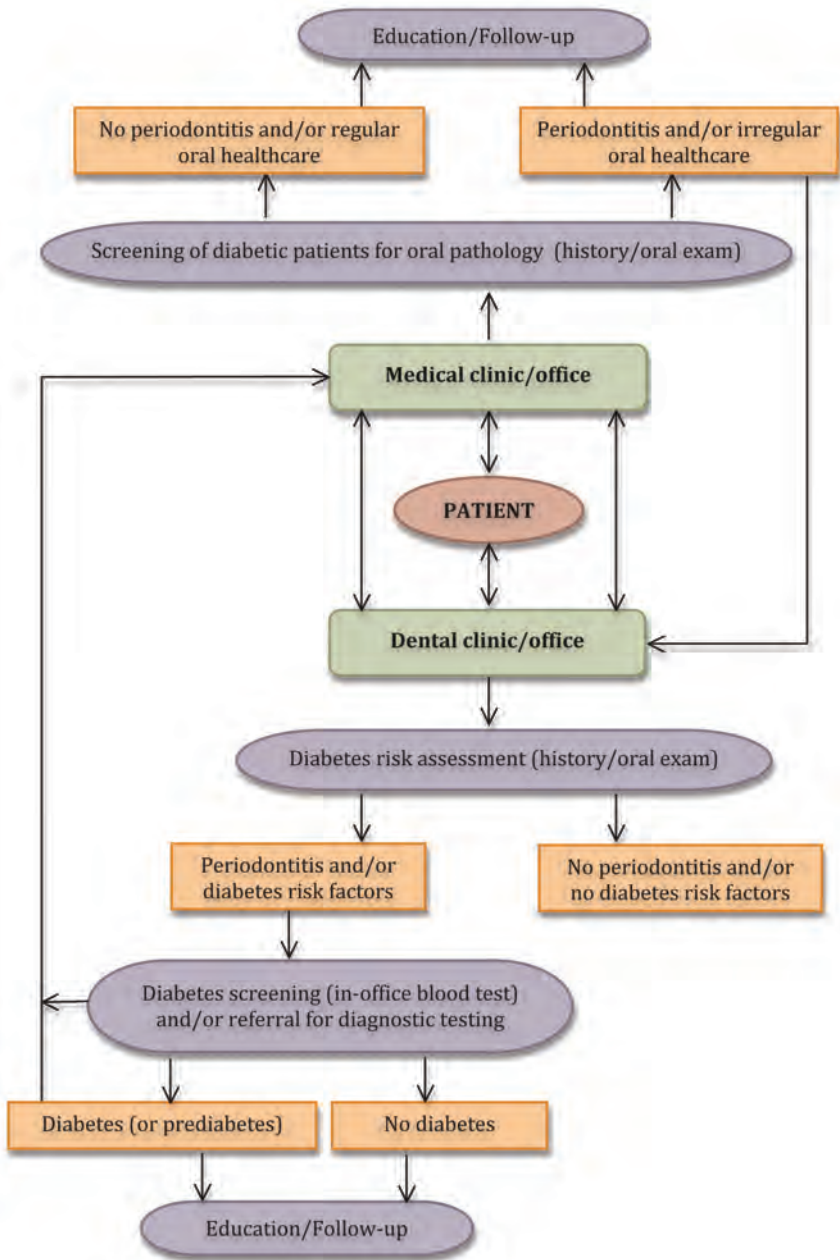
- evaluating and managing risks for oral complications;
- providing guidance in goal setting;
- helping with strategies to achieve goals and overcome barriers; and
- providing continuous education, reinforcement, and support.

Dental practices should establish a system of referrals for routine preventive care as well as for urgent needs. Dentists and hygienists should not just tell the person with a potentially serious problem to consult a health specialist right away, they should contact primary care and specialty providers to discuss criteria for referral and ensure that procedures are in place for seeing a person who is referred for care or on an urgent basis. A list of providers, case managers, phone numbers, and other contact information can be very useful for quick reference. The dental team should also consider giving individuals handouts with referral information, or calling clinics directly. Multidisciplinary team care is key to both successful diabetes recognition and management.

### **Patient Education**

A recent report from the United Kingdom<sup>41</sup> assessed the knowledge diabetic

**Figure 2.** 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.

patients have of their risk for periodontal disease and their attitudes towards oral health. Only a third of the 101 patients who participated in the study were aware of their increased risk for periodontitis as opposed to their knowledge of the risk for other diabetic complications, which ranged from 84% to 99%. History of prior dental care was sporadic, with 43% reporting seeing a dentist within the past year. An earlier study from Sweden<sup>42</sup> 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 were unaware that they even had diabetes. Oral health does not appear to be a priority for patients with diabetes.<sup>11,43-45</sup> Tomar and Lester reported that diabetic individuals were less likely to visit a dentist than a nondiabetic individual in the preceding 12 months and, interestingly, the leading reason for not seeing a dentist was “lack of perceived need.”<sup>11</sup> Competing financial and time commitments may explain the inadequacy of routine dental care in patients with diabetes.<sup>46</sup>

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, dental practitioners and their teams 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 ups, as indicated by the patient’s physician. Patients should be encouraged to achieve the best glycemic control possible, as 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.<sup>4</sup> 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.<sup>20</sup>

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 (Box 3). 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.

### THE 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 few years to address oral-systemic links and discuss issues related to communication among different healthcare professionals and patients.

Recently, 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 that “it is appropriate to develop guidelines to assist medical

**Box 3. 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.<sup>51</sup>

providers in identifying patients who are at risk for periodontal disease or screening patients who may have undiagnosed periodontal disease."<sup>47</sup> Similarly the report following the July 2007 "Oral-Systemic Diseases: From Bench to Chair—Putting Information into Practice" symposium stated that "there is a need for coordination 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."<sup>48</sup>

The concepts emphasized above are especially important for medical professionals who treat patients with diabetes (e.g., internists, diabetologists, nurses, diabetes educators) as 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

relationship to the diabetic state; about the potential sequelae of long-standing, untreated oral infections; and to provide educational brochures and other relevant material. By simply asking patients if they have a dentist and when was the last time they visited him/her, physicians can send a powerful message and play a significant role in promoting oral health and preventing oral complications in 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 2) 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; or
- 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 past year, but presents with detectable signs or symptoms of oral/periodontal infections, he or she should again 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, they should be available to offer advice on medical management modifications that may be necessary, and be open to a meaningful professional interaction in order to assure 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<sup>36</sup> 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.<sup>49</sup> A syndemic orientation has the potential to provide a framework that can guide more efficient and effective initiatives because healthcare providers will not approach diseases like diabetes and periodontitis as discrete problems, and will be prompted to collaborate across and beyond professional boundaries.

The model of "working together" has been discussed in the diabetes literature

extensively. 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."<sup>50</sup> 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 set forth an analysis of the evidence that supports team care as an effective method for 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 US, they cannot do all that is required and often are discouraged that the current medical system does not function well for people with diabetes.<sup>50</sup> 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; and
- 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 healthcare 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 upon to play a role in diabetes primary prevention and in diabetes control.<sup>51</sup> 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.

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# CHAPTER 15

## Dental and Medical Comanagement of Cardiovascular Disease

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### INTRODUCTION

Cardiovascular disease (CVD) accounts for 29% of deaths worldwide, ranks as the leading cause of death, and poses the greatest threat in low-income and middle-income countries.<sup>1</sup> Atherosclerosis, which is a major component of cardiovascular disease, affects one in four persons and contributes to ~40% of deaths annually in the United States.<sup>2</sup>

The estimated cost of treating CVD in 2008 was \$448.5 billion, a 20% increase in recent years (<http://www.americanheart.org/presenter.jhtml?identifier=4475>, accessed 2/20/2010). The pervasiveness of cardiovascular disease 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, the cost of Medicare Part D was estimated to be ~\$70 billion in 2008 (<http://www.cbo.gov/ftpdoc.cfm?index=6076&type=0#table1>, accessed 2/20/2010). Several studies point to the possibility that periodontal care in patients with cardiovascular disease significantly reduced medical care costs.<sup>3</sup> This chapter reviews the known risk factors for CVD that are 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.

### Educational Objectives

After reading this chapter, the reader should be able to:

1. Define the pathogenesis of coronary atherosclerosis and recognize its acute and chronic clinical presentations
2. Comprehend the scientific basis that identifies risk factors for CVD
3. Explain the rationale that justifies intervention by risk factor reduction
4. Describe commonly used medications for patients with CVD and their impact on the delivery of oral and dental care
5. Discuss principles of comanagement of patients with cardiovascular disease and periodontal disease

### ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

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 tissue that is dependent on the blood supply of the diseased artery. Lesions caused by atherosclerosis may also rupture, and the resulting thrombus may be clinically silent or may cause a fatal myocardial infarction (MI, aka “heart attack”). Approximately 40% of deaths in the United States are attributed to the complications of atherosclerosis; about half of these sequelae are represented by coronary atherosclerosis complicated by thrombosis and MI.<sup>4</sup>

### Pathogenesis

Atherosclerosis generally begins in childhood, and manifests as a flat fatty streak usually detected only as an incidental finding

at an autopsy that is performed for other reasons.<sup>5,6</sup> The advanced raised lesion is called an “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 comprised 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 a complicated plaque. Inflammation, oxidative, and mechanical stress through high blood pressure can also induce primary injury of the arterial endothelium by which the pathogenesis of atherosclerosis can be initiated and propagated.

### **Risk Factors for the Development of Coronary Atherosclerosis**

Traditional major risk factors for atherosclerotic cardiovascular disease include:

- Cigarette smoking
- Hypertension ( $> 140/90$  mmHg)
- High levels of low-density lipoprotein cholesterol (LDLC, defined as  $> 100$  mg/dL)
- Low levels of high-density lipoprotein cholesterol (HDLc, defined as  $< 40$

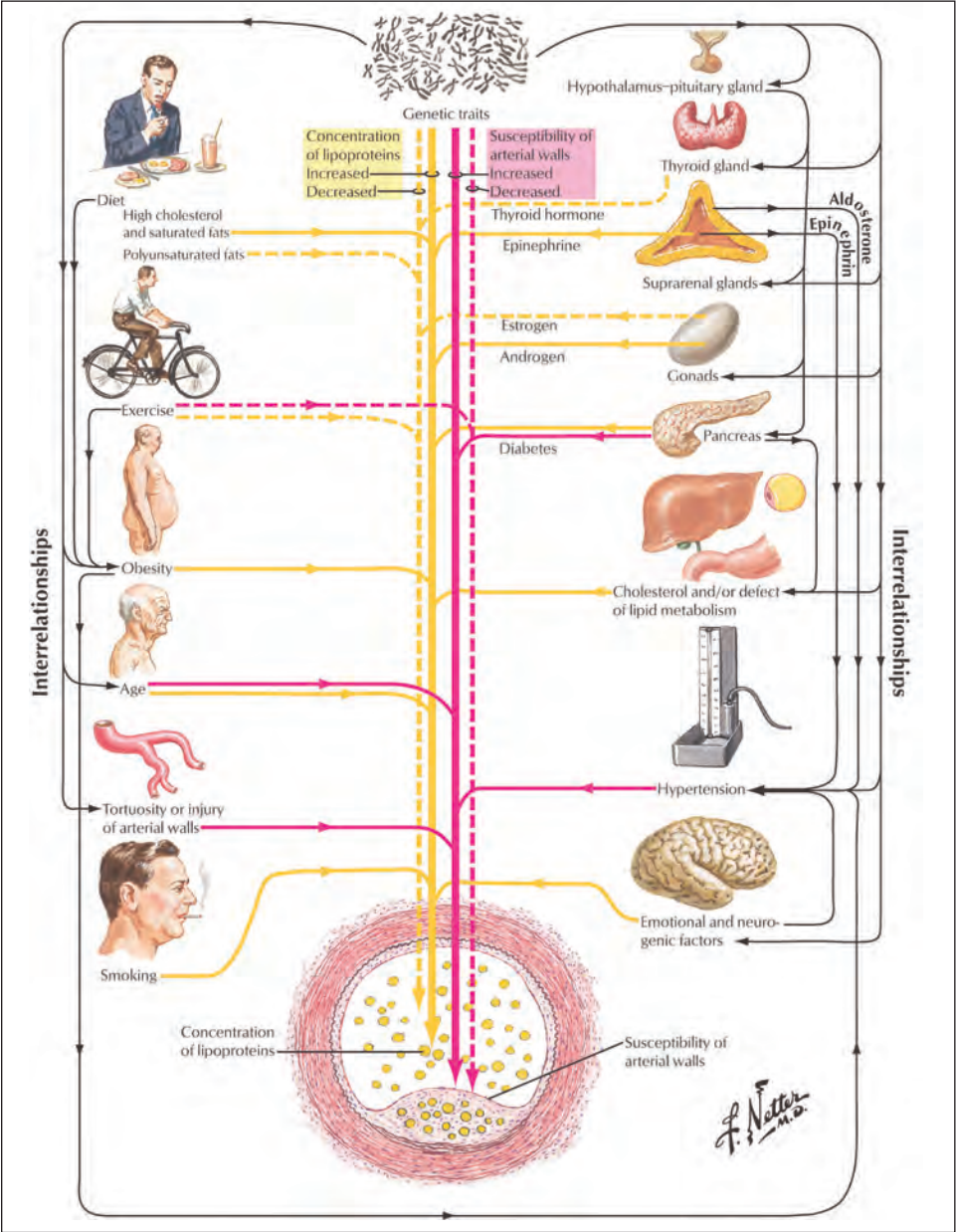
mg/dL for men or  $< 35$  mg/dL for women)

- Insulin resistance
- Diabetes mellitus
- Family history of premature coronary heart disease (occurring in a parent  $\leq$  age 45)
- Age (men  $\geq 45$  years, women  $\geq 55$  years)
- Obesity (body mass index  $> 30$  kg/m<sup>2</sup>)
- Physical inactivity and an atherogenic diet (Figure 1)

It is also recognized that these factors can interact with each other to increase the risk of CVD.<sup>7</sup> For example, the Framingham Heart Study involved more than 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.<sup>8</sup> Data from the Framingham Heart Study and two other large prospective cohort studies, the Chicago Heart Association Detection Project in Industry ( $n = 35,642$ ) and the Multiple Risk Factor Intervention Trial ( $n = 347,978$ ), indicated that the majority of 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.<sup>9</sup> For fatal MI due to coronary artery atherosclerosis, exposure to at least one risk factor ranged from 87% to 100% for all three cohort studies. For nonfatal MI in the Framingham Heart Study, prior exposure to at least one risk factor was found in 92% of men and 87% of women ages 40 to 59 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.<sup>10</sup>



**Figure 1.** Cardiac Risk Factors for Coronary Atherosclerosis Recognition and Management



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.

**The Role of Inflammatory Markers**

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.<sup>11</sup> CRP

is an acute-phase reactant primarily produced 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.<sup>12,13</sup> CRP appears to be directly involved in augmenting the innate inflammatory response via induction of prothrombotic factors (e.g., plasminogen activator inhibitor-1, pro-inflammatory adhesion molecules, and monocyte chemoattractant protein-1) and interference with endothelial nitric oxide synthase.<sup>14</sup> In the Physicians' Health Study, an epidemiologic investigation of more than 22,000 healthy middle-aged men with no clinical evidence of disease, increasing levels of serum high-sensitivity CRP at study entry were associated with up to a three-fold increase in the risk of incident MI and a two-fold increase in risk of ischemic stroke.<sup>15</sup> When compared with other potential serum biomarkers, such as homocysteine, lipoprotein(a), interleukin-6, intracellular adhesion molecule-1, serum amyloid A, and standard lipid measures, CRP proved to be the single strongest predictor of cardiovascular risk in apparently healthy participants in the Women's Health Study ( $n = 28,263$ ).<sup>16,17</sup> 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 LDLC. The poorest event-free survival in women was among those with high LDLC and high CRP levels, and the best event-free survival was among those with low LDLC and low CRP levels. Notably, individuals with low LDLC levels but high CRP levels were at higher risk than those with high LDLC levels but low CRP levels.

Very recent data show that treatment with HMG-CoA reductase inhibitors ("statins")

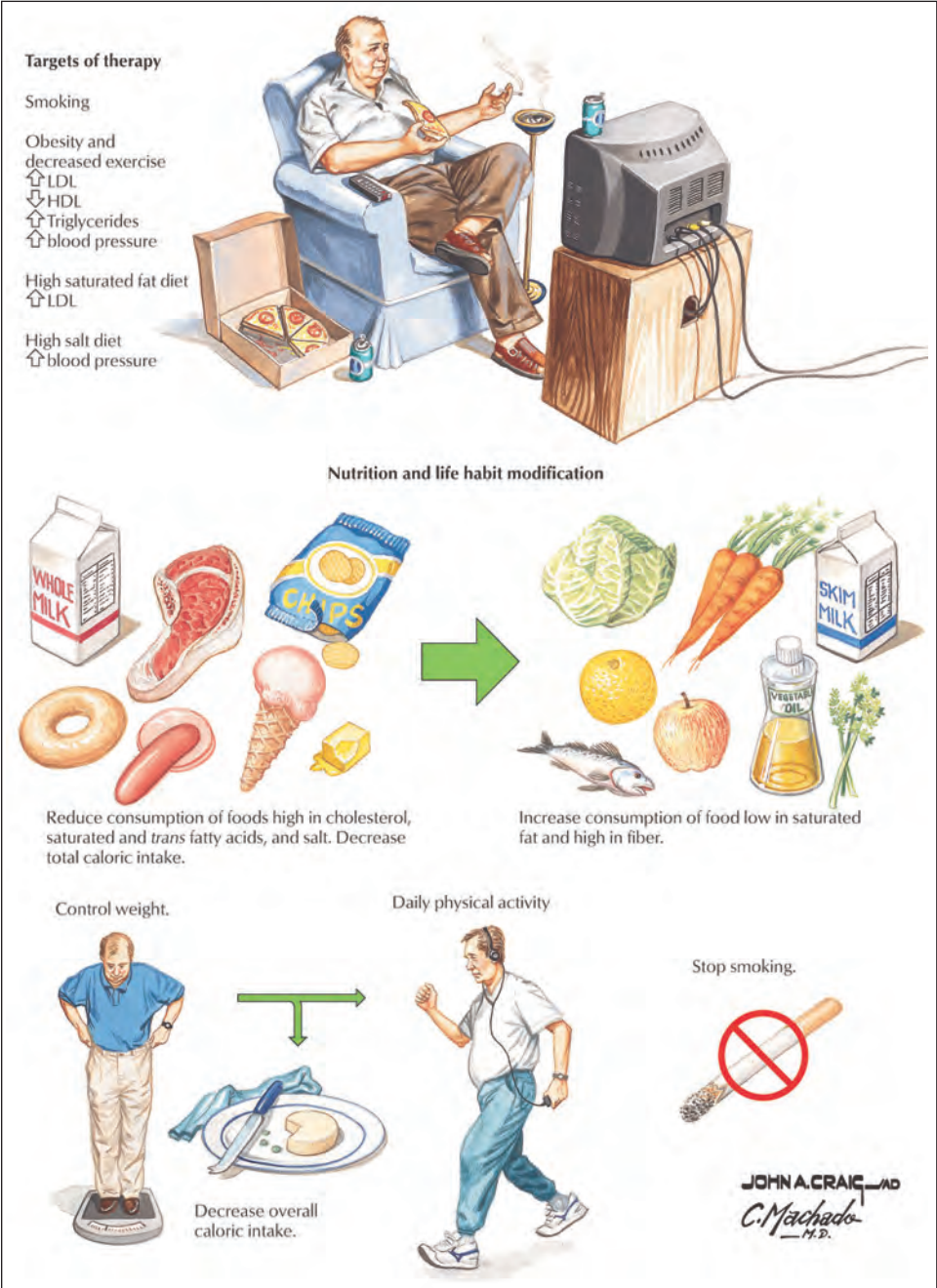
for asymptomatic individuals with elevated CRP levels but normal cholesterol levels reduces risk for future cardiovascular events.<sup>11</sup> These provocative findings have triggered considerable debate that may fundamentally alter our approach to primary prevention of coronary atherosclerosis.

### **Prevention of Coronary Atherosclerosis by Risk Factor Modification**

Since atherosclerosis continues to increase in prevalence in developed countries, it is counterintuitive that death rates from cardiovascular diseases overall have decreased by more than a third in the past 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 (Figure 1) and optimizing strategies for risk factor reduction (Figure 2). These strategies constitute an opportunity for medical and dental professionals to work for a common goal of continued improvement in cardiovascular health, but there are formidable challenges to overcome in order to achieve this goal.<sup>18</sup>

First is to recognize that we are providing encouragement for lifestyle changes that patients may find very difficult, including smoking cessation, weight reduction, dietary changes, regular exercise, and compliance with prescribed medications for elevated cholesterol, blood pressure, and diabetes mellitus. While 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,<sup>19</sup> underscoring the need for sustained efforts at risk factor reduction even in otherwise healthy individuals.

**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 strategy will be continually updated accordingly. From *Netter's Cardiology*. Reproduced with permission.

### **Clinical Presentation of Cardiovascular Disease**

Recognition of the symptoms of coronary atherosclerosis is essential and not always straightforward. Three classical 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 usually called “stable 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 may 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. Patients experiencing an MI usually complain of prolonged and sustained (> 5 minutes) 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, including 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 when 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 have been important factors in improved survival for patients experiencing sudden cardiac death.

### **MEDICAL MANAGEMENT OF CORONARY ATHEROSCLEROSIS**

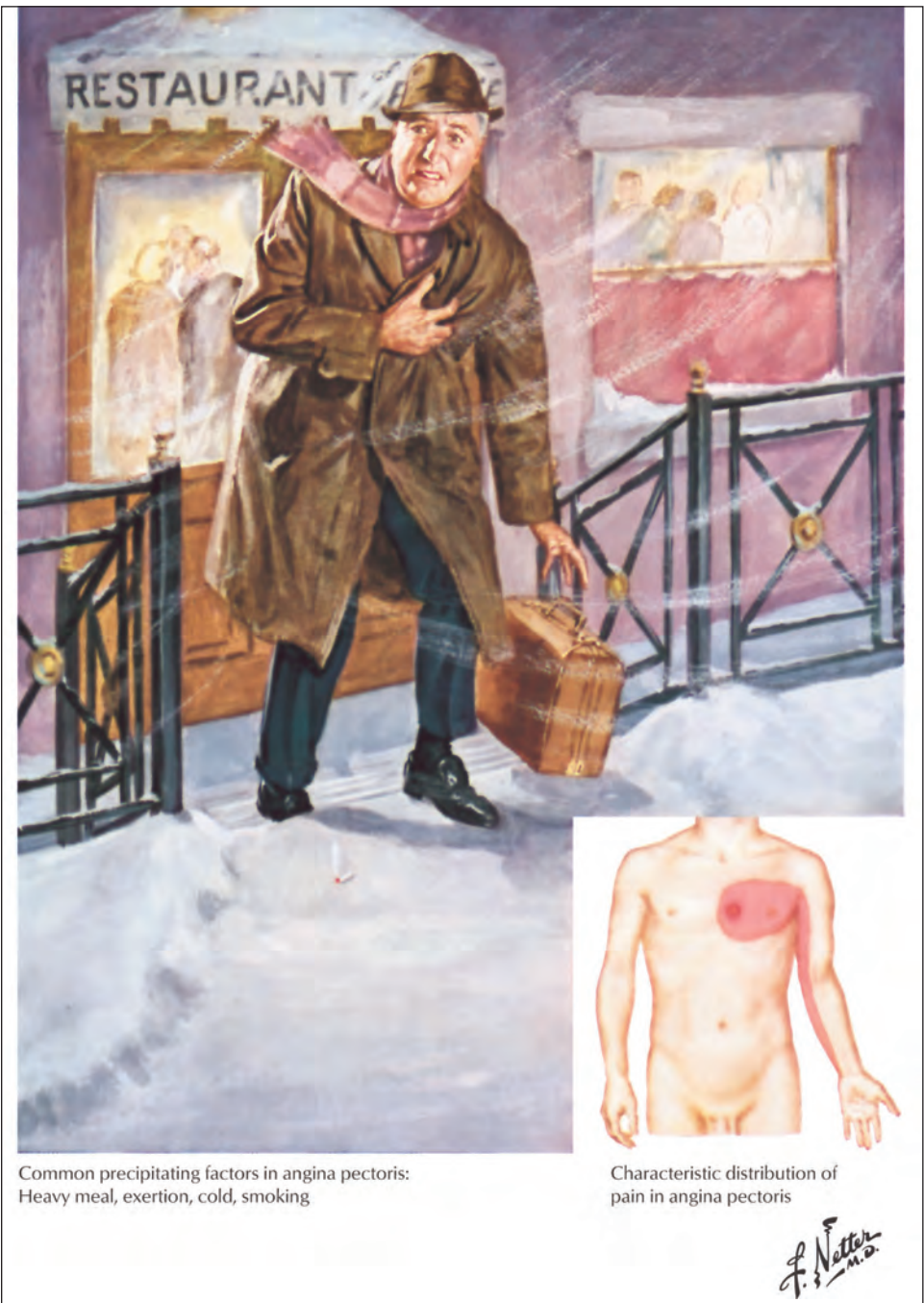
At present, 80 million Americans are thought to exhibit some form of cardiovascular disease.<sup>20</sup> Thus, many patients presenting to oral and dental healthcare providers will have coronary atherosclerosis and will be receiving therapy. It will be important, therefore, to understand the basic classes of drugs that are used in patients with heart disease, especially the ones that might have a direct impact on oral health or may 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 make it the treatment of choice in all patients who can tolerate taking this medication. Another currently available antiplatelet drug is the thienopyridine clopidogrel, and often patients are on both aspirin and clopidogrel. The primary concern for both of these drugs is bleeding, especially with procedures. If the procedure requires temporary interruption of use of either of these two drugs, this should be done in consultation with the patient's regular physician. This is especially important for patients who are on clopidogrel to prevent clotting on drug-eluting stents that have been implanted inside one or more coronary arteries to open athero-



**Figure 3.** Angina Pectoris



Common precipitating factors in angina pectoris:  
Heavy meal, exertion, cold, smoking

Characteristic distribution of  
pain in angina pectoris

Classic angina pectoris is retrosternal, radiates to the left arm or jaw, and feels like a heavy or constricting “vice-like” discomfort. This illustration shows common precipitating factors. From *Netter's Cardiology*. Reproduced with permission.

sclerotic obstructions. Abrupt cessation of clopidogrel during the first year after placement of a drug-eluting stent can be associated with acute thrombosis resulting in an otherwise preventable heart attack.

Several investigational antiplatelet drugs are close to FDA approval. Likely, bleeding will be the major concern for all new antiplatelet drugs. The challenge to all who deliver healthcare will be to maintain a current understanding of the uses and side effects of these novel therapies.

### **Beta Blockade**

As with aspirin, beta blockade is recommended for all patients with cardiovascular disease unless they have 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 in the legs. In general, patients already receiving beta blockers should not experience any complications during oral 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 and these guidelines are constantly being revised as new data become available.<sup>21</sup> Considerable planning and discussion between the cardiologist and dentist would be required in these cases.

### **ACE Inhibitors and ARBs**

Patients with coronary atherosclerosis and depressed heart function are generally encouraged to take angiotensin-converting enzyme (ACE) inhibitors. If they are intolerant to ACE inhibitors due to cough or other issues, they may be prescribed angiotensin II receptor blockers (ARBs). Mortality rates have repeatedly been shown to be lower in post-MI infarction patients who are taking ACE inhibitors. Both ACEs 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- (less than 10 minutes) and long- (several hours) acting 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 Guidelines recommend an LDLC level of < 100 mg/dL for patients with known cardiovascular disease and a total cholesterol of < 200 mg/dL. Secondary causes of hyperlipidemia include diabetes mellitus, liver disease, and renal failure. Regardless of the cause, all patients who have values above these levels should receive dietary counseling, suggestions for weight reduction, and encouragement to increase physical activity. The most commonly used drugs for hyperlipidemia are the 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%.<sup>22</sup> In contrast, the effect of statins and other lipid-lowering therapies on reducing the size of atherosclerotic plaques is much smaller.<sup>23</sup> 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.<sup>11</sup> Thus, the pleotropic effects of these drugs appear to improve outcomes and markers of atherosclerotic cardiovascular disease. 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. The cholesterol absorption inhibitor ezetimibe and bile acid reabsorption inhibitors (e.g., cholestyramine) are often used in combination with other drugs to achieve target goals. Lipid-lowering drugs should not impact 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 their LDLC levels. Patients with familial hypercholesterolemia frequently 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 discussed above, these patients are likely to be on medications that could increase the likelihood of bleeding during dental procedures.

## **CLINICAL RECOMMENDATIONS FOR PATIENTS WITH PERIODONTITIS AND ATHEROSCLEROTIC CARDIOVASCULAR DISEASE**

Current knowledge about the close association between periodontitis and atherosclerotic cardiovascular disease is summarized in

Chapter 8. It is clear that although we do not have ultimate proof, the balance of evidence is sufficiently strong such that recommendations for close cooperation among dental and medical professionals in the management of patients with periodontal disease and cardiovascular disease are reasonable. Recently there was an Editors' Consensus Report published simultaneously in the *American Journal of Cardiology* and the *Journal of Periodontology* that makes clinical recommendations for patients with periodontitis and patients with atherosclerotic cardiovascular disease.<sup>18</sup> The potential benefits of applying current understanding of the association between periodontal disease and cardiovascular disease outweighs any negative effects of premature application of this information. Four major recommendations are made that provide guidance for physicians and dentists who often care for patients either suffering from, or at risk for, periodontal disease and cardiovascular diseases.

These recommendations include:

1. Patients with periodontitis should be informed that they may be at increased risk for atherosclerotic cardiovascular disease. Further, patients with periodontitis who have one or more risk factors for cardiovascular disease should be specifically and clearly referred for medical evaluation if they have not been evaluated in the past 12 months.
2. Patients with periodontitis should have their risk for future cardiovascular events assessed using validated tools such as the Reynolds Risk Score (<http://www.reynoldsriskscore.org>, accessed 2/20/2010) or the National Cholesterol Education Program Risk Calculator (<http://hp2010.nhlbi.nih.net/atpiii/calculator.asp>, accessed 2/20/2010). Those patients at high risk should have a complete physical examination by a physician.

3. Patients with periodontitis who have cardiovascular risk factors including abnormal lipids, smoke cigarettes, have hypertension, or suffer from metabolic syndrome should have their risk factors moderated and be managed by the dentist as well as the physician. It is especially important for the dental profession to be involved in cooperating with the medical team in reducing cigarette smoking and controlling diabetes and weight, and modifying diet in such patients. It is currently well recognized that dentists can play a significant role in assisting patients in smoking cessation programs. We are proposing that dentists extend their efforts to include assistance in weight and diet control, and in reinforcing compliance with blood pressure medications in hypertensive patients.
4. Patients with atherosclerotic cardiovascular disease who do not have a previous diagnosis of periodontal disease should be examined for signs of periodontal disease, including lost teeth, gum recession, or inflamed gingivae. They should be referred by the medical team for a periodontal evaluation. Furthermore, if periodontitis is newly diagnosed or exists in patients with atherosclerotic cardiovascular disease, periodontal therapy should be carried out and a proactive secondary prevention and maintenance program should be instituted. Physicians and dentists should emphasize the importance of timely management of periodontal disease in patients with cardiovascular disease to decrease their inflammatory burden.
5. Patients with both periodontitis and cardiovascular disease should have members of the dental and medical

team work closely together to help reduce risk factors, especially those common to both diseases, such as uncontrolled diabetes, smoking, and obesity.

### **The Use of Sugar**

The dental profession has long been involved in advising patients to reduce their sugar intake to reduce the risk for dental caries. It is reasonable for both dental and medical professionals to make the recommendations of maximum intake of added sugars, especially in cardiovascular patients, both for reduction of risk for cardiovascular disease as well as risk for dental caries.

For example, a recent scientific statement from the American Heart Association addresses dietary sugars and cardiovascular health. It is recommended that patients reduce the intake of sugars added to foods to 100 calories per day for women, and 150 calories per day for men. This is about 5–6 teaspoons of sugar or sugar equivalents per day for the average adult woman, and 9 teaspoons per day for the average adult man. It is realized that reduction of dietary carbohydrates requires a multifaceted approach, and that one, perhaps, easily implemented approach is to reduce energy intake from added sugars to levels suggested above.

Finally, it should be recognized that there is no evidence that suggests that patients with periodontitis and atherosclerotic cardiovascular disease should receive different periodontal treatment from other patients with periodontitis. In fact, recent studies suggest that standard treatments of periodontitis in patients with cardiovascular disease are effective and do not lead to adverse cardiovascular outcomes.<sup>24</sup> As with any patient, the daily management of plaque and gingival inflammation should be encouraged. Oral hygiene instruction should be provided, and the use of an antibacterial toothpaste and mouthrinse and interproximal cleaning should

be recommended with each patient and reinforced at each visit.

## CONCLUSIONS AND FUTURE DIRECTIONS

Dental and medical healthcare providers need to work together closely to provide optimal care for their patients with established cardiovascular disease. A basic understanding of the pathogenesis of cardiovascular disease and commonly used medications will provide a basis for preventing complications during the delivery of dental and oral healthcare in patients with CVD.

The role of the oral and dental health practitioner in the prevention of heart disease has great potential. Such practitioners are uniquely poised to discuss risk factor reduction with their patients that 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 (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 more likely to be adopted by patients who receive consistent advice and encouragement from all of their healthcare providers.

For the present, the role of oral health in atherosclerosis remains an association and not a risk factor. Human trials that directly address the role of periodontitis and atherosclerosis have been limited to the Periodontitis and Vascular Events study. This pilot study was designed to determine how many patients with combined symptomatic atherosclerosis and periodontitis would be needed to document the fact that successful treatment of periodontitis reduces subsequent coronary and carotid events.<sup>24</sup> If periodontitis

is proven to be a risk factor for cardiovascular disease, cardiologists and oral and dental health practitioners will need to work even more closely to provide optimal care for their patients.

## Supplemental Readings

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# CHAPTER 16

## Dental and Medical Comanagement of Pregnancy

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### INTRODUCTION

Pregnancy involves complex physiologic, physical, and psychological changes mediated by female sex hormones that have a profound impact on even 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 that is free of inflammation and infection.

This chapter reviews the physiologic changes that occur during normal gestation, and 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 physiological, 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 frequent 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.

### PHYSIOLOGICAL CHANGES IN PREGNANCY AND THEIR RELATIONSHIP 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 physiological changes in systemic and oral tissues. The most important physiological changes associated with pregnancy that have dental relevance are addressed below.

### Gingival Hyperplasia and Edema

Vasodilatation, increased vascular permeability, and cell proliferation elicited by pregnancy hormones result in the swelling of gingiva and desquamation of cells.<sup>1,2</sup>

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.<sup>1,2</sup> A concomitant shift in oral microbiota promotes the growth of bacteria associated with gingivitis.<sup>3</sup> Immune adaptations that occur during pregnancy may further facilitate infections of oral tissues. For example, gingival fibroblasts exposed to progesterone down-regulate the production of interleukin-6 and a variety of matrix metalloproteinases, making the gingiva more susceptible to inflammatory challenges elicited by bacteria.<sup>4,5</sup>

### **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 gastro-esophageic sphincter, facilitating reflux of stomach content towards the esophagus and mouth. Psychological changes appear early in pregnancy and contribute to the nausea and vomiting syndrome called “morning sickness.” A small fraction (1% to 3%) of these patients progress to hyperemesis gravidarum, which is associated with weight loss, electrolyte imbalance, dehydration, and, eventually, ketonemia. The 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 is dependant on oral-esophageic content delay rather than salivary flow rate. Rarely, patients may lose more than one liter of saliva per day, a disorder known as ptyalism. Additional changes comprise a decreased salivary pH and elevation 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 the section titled “Pregnancy Complications” below.

### **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 intervillous space (mimicking an arteriovenous shunt) decrease arterial resistance. Elevations in blood volume (especially at the expense of maternal plasma) and heart rate compensate 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 in order to alleviate vena cava obstruction.

### **Respiratory Changes**

The most important physiological 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 lessened residual capacity of the lungs. Dyspnea is not an uncommon sign during the third trimester, especially in patients with

twin gestation, large fetuses, and/or polyhydramnios. As stated before, 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. Due to this hematologic adaptation, pregnant women are diagnosed with anemia only if the hematocrit falls below 33%. On the other hand, leukocytosis during pregnancy is established if the white blood cell count is above 15,000 cells/mm<sup>3</sup>. This is important 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” that predisposes to thromboembolism. Several disorders (e.g., antiphospholipid syndrome) aggravate this condition and may require the utilization of aspirin or heparin. These patients should receive close treatment surveillance to determine if dental procedures may be performed without the risk of excessive bleeding.

### **Endocrine Changes**

Most of the physiological adaptations described above 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 in order 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 glucose availability in oral secretions of patients with poorly controlled diabetes provides a suitable environment for the development of dental infections.

## **DENTAL MANAGEMENT OF WOMEN WITH NORMAL PREGNANCY**

Utilization of dental care during pregnancy is lower than expected. Data from surveys indicate that 30% to 50% of women do not receive dental care during pregnancy.<sup>6,7</sup> 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.<sup>8</sup> 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.<sup>9</sup> Moreover, only about one-quarter of patients are referred to a dental examination by health providers during pregnancy.<sup>9</sup> Collectively, these data indicate that both health professionals and patients tend to postpone dental treatments until after delivery.

### **Attitudes of Dentists, Physicians, and Patients Towards Dental Treatment During Pregnancy**

The reluctance of dental practitioners to provide dental care to pregnant women<sup>10</sup> may explain, among other reasons, the low percentage of women who receive dental care during pregnancy. Lydon-Rochelle and colleagues<sup>11</sup> 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 half of pregnant women attend to it.<sup>12</sup>

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 one-half of the third trimester.<sup>13</sup> 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 week 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, due to the large uterus and its content.

Concern about the maternal and fetal effects of pharmacologic agents commonly used in dentistry offers another reason to explain the 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 (Table 1). The recommendation is based more on fear of litigation than on evidence of harm. It is therefore remarkable that there is no evidence linking dental treatments and adverse pregnancy outcomes. On the contrary, there is a growing body of evidence, although controversial, that treatment of periodontal infection may reduce the rate of certain pregnancy complications.<sup>14-16</sup>

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/or 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.<sup>15-17</sup>

### **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, twin gestation, or polyhydramnios) are at risk for supine hypotension due to vena cava compression. Therefore, propping patients to 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 if the potential benefit surpasses the risks.

### **Radiography**

Dental radiographs for acute diagnostic purposes are associated with minimal fetal exposure to ionizing effects. The exam should be performed using a lead apron and thyroid shield; high-speed film and retakes should be avoided. Efforts to avoid the period of embryo organogenesis (up to 12 weeks' gestation) are desirable, but emergency dental treatments that rely on radiographic diagnosis usually incline the risk-benefit balance towards having the exam performed.

### **Pharmacologic Agents**

Drugs used in dental treatment are fairly safe during pregnancy (Table 1). Local anesthetics such as lidocaine and prilocaine are considered safe by the Food and Drug Administration (category B). When possible, co-adjuvant epinephrine should be avoided, since it may impair uterine blood flow through the placenta. Epinephrine is contraindicated in patients with pre-eclampsia and

**Table 1.** Drugs Frequently Used by the Dental Professional During Pregnancy

Drugs	FDA Category	Comments/Suggestions
Analgesics and anesthetics		
Acetaminophen	B	Safe throughout pregnancy
Aspirin	C	Avoid after 34 weeks
Ibuprofen	B	Do not use after 28 weeks
Codeine	C	Use with caution if benefit outweighs risks
Oxycodone	B	Avoid in proximity of labor
Morphine	B	Avoid in proximity of labor
Meperidine	B	Avoid in proximity of labor
Lidocaine	B	Safe throughout pregnancy
Mepivacaine	C	Use with caution if benefit outweighs risks
Prilocaine	B	Safe throughout pregnancy
Antibiotics/Antifungals		
Ampicillin/Amoxicillin	B	Safe throughout pregnancy
Cephalosporins	B	Safe throughout pregnancy
Chlorhexidine	B	Safe throughout pregnancy
Clindamycin	B	Safe throughout pregnancy
Clotrimazole	B	Safe throughout pregnancy
Erythromycin	B	Safe throughout pregnancy. Do not use estolate
Fluconazole	C	Safe when used in single dose
Metronidazole	B	Avoid before 12 weeks
Penicillin	B	Safe throughout pregnancy
Others		
Benzodiazepines	D	Do not use unless benefit outweighs risks
Corticosteroids	B	Prednisone, betamethasone, and dexamethasone, safe throughout pregnancy
Doxylamine	B	Safe throughout pregnancy
Nitrous oxide	—	Avoid before 12 weeks

chronic hypertension. Acetaminophen is appropriate to treat 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 due 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 trimester. Avoiding use of 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 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 the mother and fetus. Penicillin-family agents are frequently used as co-adjuvants in the treatment of periodontal disease, dental abscesses, and cellulitis. Cephalosporins fall in the same category. Except for patients with hypersensitivity, both antimicrobial agents are classified as safe by the Food and Drug Administration (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.

Metronidazole, 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 those women with cardiac conditions associated with a major risk for 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.<sup>18</sup>

- 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 are those involving 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 when injecting anesthetic into non-infected tissue. Appropriate antibiotics for infective endocarditis prophylaxis should be administered 30–60 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 one hour is the choice. Table 2 summarizes the principles guiding dental treatment during pregnancy.<sup>19</sup>

**Table 2. Principles Guiding Dental Treatment During Pregnancy**

- |   |
|---|
| <ol style="list-style-type: none"><li>1. Women should be advised to seek oral healthcare prior to becoming pregnant and throughout gestation.</li><li>2. Oral healthcare is safe and effective during pregnancy.</li><li>3. First trimester diagnosis (including necessary dental x-rays with adequate shielding) is safe.</li><li>4. Acute infection, abscess, and conditions predisposing to bacteremia and sepsis require prompt intervention regardless of the stage of pregnancy.</li><li>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.</li><li>6. Elective treatment for conditions considered not progressive may be deferred until after delivery.</li><li>7. Delay in necessary treatment could result in significant risk to the mother and the fetus.</li></ol> |
|---|

**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 crowns 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.<sup>20</sup> 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,<sup>21</sup> diabetes,<sup>22</sup> rheumatoid arthritis,<sup>23</sup> and adverse pregnancy outcomes.<sup>24</sup>

Maternal dental caries can also increase the risk of early development of caries in children.<sup>25</sup> Dental caries and periodontal disease are both preventable conditions. However, they have a high prevalence in women of childbearing age, especially among low socio-economic 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.”<sup>26</sup>

### Dental Caries and Pregnancy

One-fourth of women of reproductive age in the US have dental caries<sup>27</sup> and the prevalence of dental caries may reach 76% in young women of low socio-economic status in developing countries.<sup>28</sup> There are no definite data indicating whether the incidence of dental caries increases during pregnancy. As 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 is *Streptococcus mutans* which is usually acquired by young children through direct salivary contact from their mothers.<sup>29</sup> Since maternal oral flora is the strongest predictor of infant oral flora,<sup>30</sup> maternal health status is critical to children's oral health. Maternal dental educational and behavioral interventions that reduce caries activity through 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.<sup>31</sup>

### Pregnancy-Associated Gingivitis

Plaque-induced gingivitis is an inflammation of the gingiva resulting from bacterial infection, and is one of the most common oral diseases in pregnant women.<sup>32,33</sup> Pregnant women have more gingivitis than non-pregnant women, with a prevalence ranging from 30% to 75%.<sup>13,34</sup> During pregnancy, the severity of gingivitis has been reported to be elevated, yet unrelated to the amount of dental plaque present.<sup>35,36</sup> Approximately one of two women with pre-existing gingivitis has significant exacerbation during pregnancy.<sup>37</sup> Gingivitis is usually more evident in 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.<sup>36</sup> The characteristics of pregnancy-associated gingivitis are similar to plaque-induced gingivitis, but there is a tendency to more severe inflammation.<sup>35,36</sup>

The factors that have been associated with higher gingival inflammation in pregnancy are increased levels of estrogen and progesterone,<sup>38</sup> changes in oral flora,<sup>3</sup> and a decreased immune response.<sup>39,40</sup> 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.<sup>41</sup> Changes in subgingival flora may occur during pregnancy. An increased ratio of subgingival anaerobic to aerobic bacteria has been found. The proportion of *Prevotella*



*intermedia* increases during pregnancy,<sup>3</sup> but the relation of *P. intermedia* to the clinical signs of gingivitis has rendered controversial results.<sup>42</sup>

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 due to 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 there is a risk of excessive hemorrhage due to its high vascularity.

There is some basis to support the hypothesis that gingivitis may be a potential risk factor for preterm birth. One of the hypotheses to explain 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, the amniotic cavity, similar to transient bacteremia occurring in patients with periodontitis.<sup>43</sup> It has been shown that bacteremia commonly occurs in patients with gingivitis,<sup>44</sup> and bacteria or their products may conceivably reach the placental tissues, providing an inflammatory setting for the onset of labor (Figure 1).<sup>45</sup> 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.<sup>43</sup> *Fusobacterium nucleatum* is one of the most commonly recovered microorganisms from sites with gingivitis,<sup>46</sup> and is frequently isolated from amniotic fluid

cultures obtained from pregnant women with premature labor and intact placental membranes.<sup>47</sup> A study in pregnant mice showed that *F. nucleatum* can cross the placenta and spread to the amniotic fluid, producing premature delivery and stillbirths.<sup>48</sup> The association between pregnancy-associated gingivitis with preterm birth was explored in a randomized controlled trial.<sup>49</sup> 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

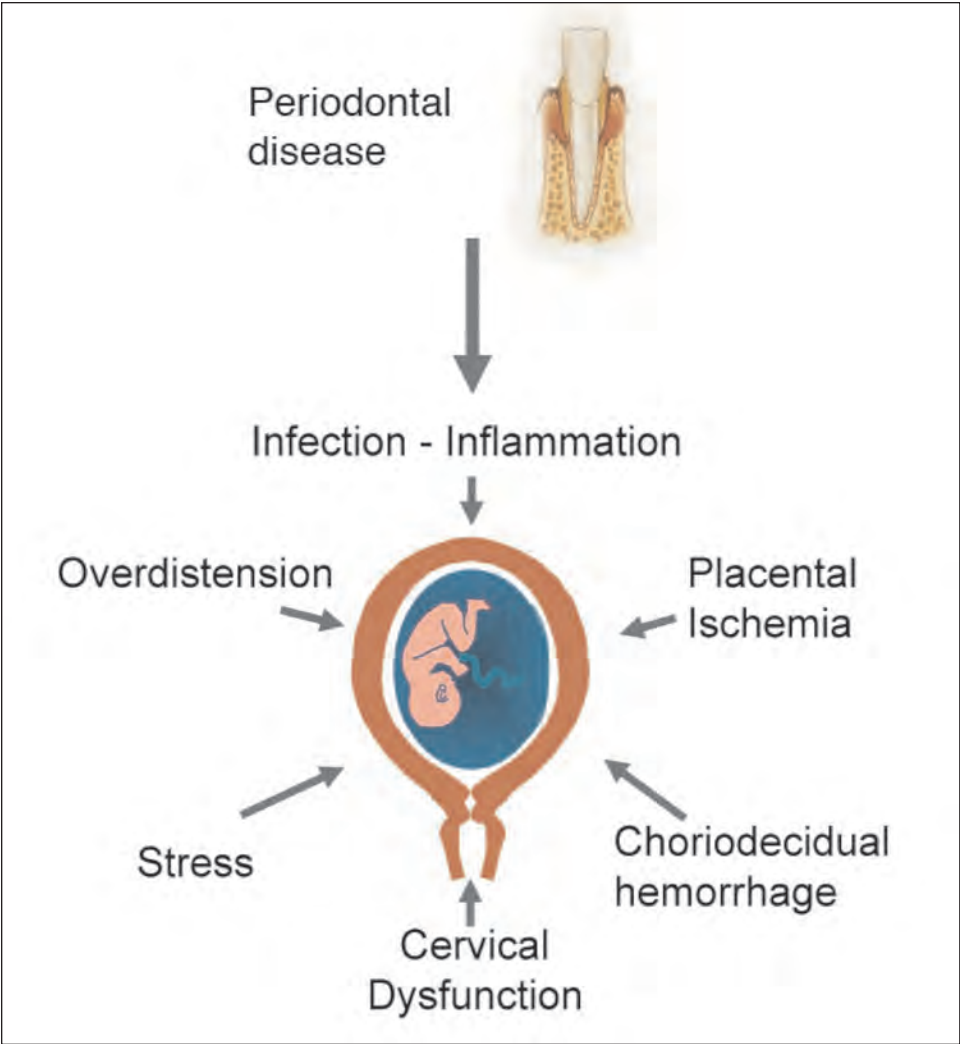
Periodontitis, the destructive form of periodontal disease, affects childbearing-aged women, from 15% in developed countries<sup>50</sup> to 45% in undeveloped countries.<sup>51</sup> In the US, up to 40% of pregnant women have some form of periodontal infection.<sup>52</sup> In some developing countries, such as in Chile, 76% of pregnant women of low socio-economic 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,<sup>24,53</sup> pre-eclampsia,<sup>54</sup> gestational diabetes,<sup>55</sup> delivery of a small-for-gestational-age infant,<sup>56</sup> and fetal loss.<sup>57</sup> 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.

### Pre-Conception 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.”<sup>58</sup> There is no definitive evidence that the association between periodontal infection and

**Figure 1.** Proposed Mechanisms Involved in Preterm Birth Syndrome, Including Periodontal Disease



Inflammatory mediators and/or bacteria of oral origin may reach the placenta and fetus. Alternatively, preterm labor and delivery could result from common variations in the inflammatory response to oral and cervicovaginal micro-organisms.

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 healthcare should be the aim of every person. This is especially important for pregnant women, since there is evidence to support the concept that maternal oral health

influences pregnancy outcome. The obvious and best cost benefits strategy to reduce the effect of periodontal infections on pregnancy outcome is preconception preventive oral healthcare 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 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.

While there are no oral diseases directly attributable to pregnancy, the physiologic and behavioral changes that occur during pregnancy can aggravate preconceptional existing gingivitis<sup>33</sup> or periodontitis.<sup>59</sup> 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 three 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 fraction of these patients. Morning appointments should be avoided. When needed, premedication with antihistaminic agents provide 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.<sup>60</sup>

### **Threatened Abortion**

Approximately 10% of pregnant women experience uterine bleeding during the first five 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.<sup>61</sup> 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.<sup>62</sup> 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, Figure 1), including periodontal disease. Intra-uterine infection is associated with both conditions, especially preterm premature rupture of membranes.<sup>63-66</sup>

Preterm labor is a disorder characterized by regular uterine contractions and cervical changes between 22 and 37 weeks of gestation. Of all patients diagnosed with preterm labor, only 50% will actually deliver before 37 weeks. The clinical identification of this group is difficult at the time of admission to the hospital.<sup>67</sup> 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 utilized in order to delay delivery for at least 48 hours. Antibiotics are not used routinely in patients with preterm labor.<sup>68</sup>

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, prior to 37 weeks of gestation.

Clinical presentation includes fluid leaking from the vagina followed by uterine activity in the majority of patients. Management includes the 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 utilized are ampicillin, erythromycin, clindamycin, and metronidazole.<sup>69,70</sup> 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 above, essential dental procedures may be performed after the patient is admitted to the hospital or clinic, treatment is established, and uterine quiescence obtained. Elective treatment may be postponed until after delivery.

### **Pre-Eclampsia/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 pre-eclampsia. The progression to seizures or coma characterizes the presence of eclampsia. The disorder is multisystemic in nature and affects 3% to 7% of pregnancies. The etiology of pre-eclampsia is heterogeneous, but a common terminal pathway characterized by endothelial dysfunction is the key pathophysiologic landmark of the disease.<sup>71</sup> Patients with pre-eclampsia are at increased risk for maternal and perinatal mortality. Maternal complications include persistent hypertensive crisis, cerebral hemorrhage, liver/hematologic dysfunction, and premature placental separation (abruptio placentae). Fetal/neonatal complications comprise placental insufficiency (chronic fetal hypoxia), fetal growth retardation, and newborn complications derived from medically indicated premature delivery.

The progression of the disease is interrupted only by delivering the fetus and placenta. However, a significant fraction of patients with pre-eclampsia are suitable to expectant management in order to advance in gestational age and decrease the risk of neonatal complications derived from early delivery.<sup>71</sup> Drugs commonly used in women with pre-eclampsia are hypotensors such as labetalol, methyldopa, and hidralazine. Magnesium sulphate is used in the prophylaxis and treatment of seizures, especially around labor and delivery. Patients at risk for pre-eclampsia 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 pre-eclamptic patient is stabilized and goals regarding blood pressure and neurologic status are reached. The dentist should be aware that patients with pre-eclampsia suffer from a fragile neurologic condition. Informing adequately about the procedure and pre-medication 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 frequent 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.<sup>72</sup> 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 there is evidence of maternal disease predisposing to poor fetal growth (hypertension, diabetes, renal disease, etc.). A significant fraction of fetuses reaches 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).<sup>73</sup> There are no specific medications for the treatment of fetal growth restriction. Intramuscular corticosteroids may be necessary if preterm delivery is indicated. In general, the presence of 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. The condition is diagnosed by establishing the absence of cardiac activity by ultrasound. The most frequent causes of fetal death are maternal diseases (pre-eclampsia, pre-gestational diabetes, renal disorders), placental insufficiency (often associated with fetal growth restriction), acute fetal hypoxia (due to placental abruption, 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 etiology.

Of significance for the dental professional is a rare hematologic condition that develops when the deceased fetus remains *in utero* for more than three 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, choriodecidual hemorrhage, uterine overdistension, and stress (Figure 1). A growing number of risk factors associated with these etiologic conditions have been described. The most important risk factors for the development of spontaneous preterm delivery include:<sup>62</sup>

1. Spontaneous preterm birth occurring in a previous gestation
2. Intrauterine infection
3. A short uterine cervical length as determined by ultrasound in the midtrimester
4. Inflammatory biomarkers in cervico-vaginal 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 (Afro-American race, adolescent pregnancy, low socioeconomic status)

### **Dental Care in Pregnant Women at Risk for Preterm Birth**

Several review studies<sup>74,75</sup> have shown that it is safe to provide dental care for pregnant women, although clinical trials supporting such evidence are scarce.<sup>14</sup> The American Academy of Periodontology recommends that pregnant women with periodontal disease should receive periodontal treatment during pregnancy.<sup>58</sup> The notion that periodontal treatment and routine dental treatment do not have

special risk for the pregnant patient is based on indirect observations derived mainly from clinical trials aimed to determine the effect of periodontal treatment on pregnancy outcomes. Six randomized controlled trials of periodontal treatment in pregnant women have been published.<sup>15-17,49,76,77</sup>

**Treatment Before and After  
28 Weeks of Gestation**

López and colleagues<sup>15</sup> performed a randomized trial with 400 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 socio-economic 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 infections were medically treated. Two-hundred women received periodontal treatment that consisted 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 monitored every four to six weeks during the gestational period, and another complete periodontal examination was performed after 28 weeks of gestation. The control group received periodontal treatment after delivery. Carious 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 treatment group and in the group that 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 colleagues<sup>17</sup> did not report safety outcomes for 366 women randomized into a group that 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 that 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<sup>78</sup> showed that oral metronidazole therapy may produce changes in the vaginal flora leading to a heavy growth of *Escherichia coli* and *Klebsiella pneumonia*, 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,<sup>49</sup> 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

**Table 3.** Timing in Which Pregnant Women with Gingivitis Received Periodontal Treatment

Week of Gestation	Received Treatment	
	n	%
Between 7 and 12 weeks	131	23
Between 13 and 20 weeks	376	66
Between 21 and 28 weeks	63	11
Total	470	100



and low-birth-weight infant rates by 68%. 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 to the group that 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 socio-economic status, history of preterm birth, smoking, and genito-urinary infections during pregnancy.

### ***Treatment of Periodontitis***

Offenbacher and colleagues<sup>76</sup> randomized 74 women with mild periodontitis, 40 of who 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, tending 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<sup>77</sup> evaluated the effect of periodontal therapy on pregnancy outcome in a randomized trial with 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 to the treatment group (76.4% versus 53.5%,  $p < 0.001$ ). No adverse effects due to periodontal treatment were reported.

### ***Treatment of Slight-to-Moderate Periodontitis***

Michalowicz and colleagues<sup>16</sup> conducted a multicenter, randomized trial to determine if 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.<sup>14</sup> Participants in the study had generalized, slight-to-moderate periodontitis, and belonged to minority and underserved groups who were at an elevated risk of adverse pregnancy outcomes. The population study consisted of African-American women (45%), Hispanic women (42%), and women who had a history of preterm birth deliveries (9.3%). The authors randomized 413 pregnant women with periodontitis to a group that 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 and eighty-three women needed essential dental treatment and 72.7% of these women completed all recommended treatment. Serious adverse effects were recorded and included spontaneous abortion, stillbirth, hospitalization for more than 24 hours due to 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 one, 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 at 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.<sup>79</sup> Some experts recommend that it is advisable to defer elective dental treatment during the first 12 weeks of gestation because of the potential vulnerability of the fetus.<sup>76,80</sup> However, there is no evidence that routine dental treatment or periodontal treatment may have adverse effects on fetal development or induce malformations.

### ***Treatment During Pregnancy Reduces 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 in order 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 seven days, used in conjunction with root planing, has been shown to be effective to control periodontal infections in patients with chronic periodontitis.<sup>81</sup> The 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 and no secondary effects on the vaginal flora have been reported. López and colleagues<sup>15</sup> 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 was 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<sup>82</sup> and pregnant adolescents are at an increased risk for medical complications.<sup>83</sup> In the US, 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 stillbirths.<sup>84</sup> Poor and low-income adolescents make up 38% of all women ages 15 to 19 in the US, 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 timely 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 (< 2,500 g) and are at greater risk of serious and long-term illness, developmental delays, and dying in the first year of life compared to infants of older mothers.<sup>85</sup> There are no studies about the oral health status in pregnant adolescents, but 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.

In order 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.<sup>86</sup> The study population consisted of pregnant adolescents, ages 14 to 19. All of them were of low socio-economic status; 60% were African-American and 39% Hispanic. These socio-demographic characteristics of young age, minority ethnicity, and low socio-economic

status are well-known risk factors for preterm birth.<sup>82</sup> 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 post-partum to study the prevalence of 12 bacterial species. Preterm low birth weight occurred in 13.5% of women who received periodontal treatment and 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 studied. 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 outcome 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, and 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 coupled with more serious social and legal issues if they are under the age of 18, make their overall management more complex.

### CONCLUSION

In summary, 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 the characteristics of periodontal treatment that should be administered.

### Supplemental Readings

Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet* 2008; 371:75–84.

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# CHAPTER 17

## Dental and Medical Comanagement of Osteoporosis, Kidney Disease, and Cancer

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### INTRODUCTION

Before addressing any therapeutic management, it needs to be determined whether or not there are indeed associations, mechanistic links, or shared risk factors for dental diseases and osteoporosis, kidney disease, and cancer. Fortunately, these are addressed in previous chapters; the goal of this chapter is to consider the management issues that may arise in dealing with the comorbid state. Can we modify treatment? Do we need to prescribe the routine drugs or are there alternatives? How should the dentist or physician manage these patients presenting with both oral and systemic conditions? First we need to consider the diseases and the characteristics that might complicate their dual management. Each section concludes with suggestions for both the physician and 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 as 3% to 6% in men and up to 13% to 18% in women (approximately 8 million women and 2 million men), with a significantly higher prevalence reported for those meeting diagnostic criteria for osteopenia.<sup>1</sup> The risk of developing osteoporosis increases with age, especially in women, due to loss of ovarian function that precipitates rapid bone loss.<sup>2</sup>

Approximately 300,000 hip fractures occur each year requiring hospital admission and, ultimately, surgical correction.<sup>2</sup> Considering the increasing size of the elderly population 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).<sup>3</sup> By World Health Organization guidelines, a diagnosis of osteoporosis is made by DEXA scan demonstration of a BMD which is 2.5 standard deviations below the young adult reference mean based on gender. Classifications for osteoporosis are broken down into primary and secondary etiologies. Secondary causes of osteoporosis are many, and although they are less commonly seen in clinical practice, there are a few, such as diabetes mellitus and chronic obstructive pulmonary disease, that are seen quite often in osteoporosis patients.

#### 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 disorganized trabecular bone formed instead of the

normal pattern of lamellar bone. This disordered bone deposition is weak and prone to deformities as well as fracture. 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.<sup>4</sup> 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 serological and radiographic tests aid in making the diagnosis. Although there are several clinical manifestations of the disease including complaints of upper dentures not fitting anymore, it is the skeletal sequelae that 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 many 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 avoid permanent neurological dysfunction. Although antineoplastic and analgesic therapies are the mainstay of treatment for most metastatic bone lesions, there are alternative strategies that 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 or not they contain an amino group. Mechanism of action differs between the groups. Aminobisphosphonates (zoledronate, alendronate, pamidronate, ibandronate, and risedronate) 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 ATP formation after being metabolized within osteoclasts, also promoting apoptosis. There is, unfortunately, a secondary effect that bisphosphonates exhibit—that is, their ability to inhibit bone mineralization, thereby causing osteomalacia. Once 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 the initiation of therapy.<sup>5</sup> The overall higher potency and lower toxicity of aminobisphosphonates are likely the reasons they are used more often in clinical practice than 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 timeframe for which the compound persists within the bone, which according to some sources can be the lifetime of the patient.<sup>6</sup> This is an important factor to bear in mind when considering interruption of therapy prior to 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 utilized to describe the condition that linked white phosphorus exposure with the disease process of osteonecrosis. Radiation and chemotherapy have also been implicated as possible etiologies 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, and 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 eight 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.<sup>7</sup> The reporting of many cases involving ONJ associated with bisphosphonate use was made prior to 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 relationship 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 utilized (Figures 1-3). Therefore, this chapter will consider the osteoporosis and Paget’s disease patient subsets and those receiving bisphosphonates for skeletal compli-

**Figure 1.** Clinical Photograph of an Upper Jaw Exhibiting Marked Osteonecrosis in a Patient on Bisphosphonate Therapy



Courtesy of Dr. George M. Kushner, University of Louisville Dental School.

**Figure 2.** Orthopantomograph of Osteonecrosis in the Lower Border of the Lower Jaw



Courtesy of Dr. George M. Kushner, University of Louisville Dental School.

**Figure 3.** Computer-Assisted Tomographic View of the Same Subject Seen in Figure 2 Demonstrating Extensive Osteonecrosis of the Lower Border of the Lower Jaw



Courtesy of Dr. George M. Kushner, University of Louisville Dental School.

cations of malignancy as separate entities. 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  $< 1$  in 250,000.<sup>8</sup> The incidence of ONJ in patients receiving bisphosphonate therapy for complications of malignancy ranges between 1% and 10%.<sup>9</sup> A prospective study by Bamias and colleagues of cancer patients receiving bisphosphonate therapy estimated that the risk of developing ONJ increased with length of 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 or not these higher incidence rates are secondary to the higher doses received by patients with malignancy compared to 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 be at high risk for developing 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 will 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. Once 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 prior to initiation of bisphosphonate therapy or oral surgery. This is extremely difficult, however, as 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 negatively impacts the healthcare system financially, and has considerable emotional and physical ramifications for patients. Thus, ongoing preventive measures are necessary in the management of 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 two years. Management of bisphosphonate-associated ONJ will require an interdisciplinary approach, with open communication between medical and dental practitioners and patients alike. Since the incidence and risks of developing this complication are different between patient subsets, this chapter will outline 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.<sup>7</sup>

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 patients initiating treatment with bisphosphonates. Reducing the risk of developing ONJ includes observing strict maintenance of the patient's oral hygiene and regular follow-ups 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.

As previously discussed, the risk of developing ONJ for 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 prior to the initiation of bisphosphonate therapy for these disorders. For patients taking these medications longer than

three 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, it is recommended to temporarily discontinue bisphosphonate therapy; however, there is no evidence to support improved dental outcomes when discontinuing therapy. Also 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, quality communication among 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 prior to 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 prior to 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 will depend on the patient's clinical condition, as 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 employing 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.

### KIDNEY DISEASE

The number of patients with chronic kidney disease (CKD) is growing and is projected to rise in the future. As the incidence 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 might contribute to the development of periodontal disease. There are several documented physiologic changes

in oral tissues that have been associated with CKD. These include xerostomia, decreased salivary pH levels, decreased mineralization, and loss of the lamina dura.<sup>10</sup> Additionally, some of the medications commonly prescribed to 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 in 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 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. Additionally, the kidneys play an important role in bone health by providing the final step in the conversion of vitamin D 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 by-product of protein metabolism, and creatinine, a by-product 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 the

**Table 1.** Classification of Chronic Kidney Disease

Disease Stage	GFR mL/min/1.73 m <sup>2</sup>	Action Required (Additional to Previous Stage)
Patient with risk factors for CKD	≥ 90	Reduce risk factors
1. Kidney damage with normal or increased GFR	≥ 90	Diagnose and treat comorbidities and CVD risk reduction
2. Kidney damage with slight GFR decrease	60–89	Estimate progression
3. Kidney damage with moderate GFR decrease	30–59	Treat complications
4. Kidney damage with severe GFR decrease	≥ 15–29	Consider kidney replacement
5. Kidney failure	< 15 or dialysis	Replace kidney

CKD is defined as either kidney damage (pathological abnormalities in blood, urine, or imaging) or a GFR less than 60 for three months or longer. (Table modified from KDOQI 2002.<sup>11</sup>)

uremic syndrome. The uremic 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, including vasoconstriction, sodium reabsorption, and fluid retention. There are multiple antihypertensive agents targeting this system, including 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. Additionally, there is 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 phosphorous excretion leads 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 filtration rate (GFR).<sup>11</sup> It is estimated that 31 million Americans suffer from CKD and millions of others are at risk (from National Health and Nutrition Examination Survey data 1999-2006). The most common causes of CKD include 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:  $\text{GFR} [\text{mL}/\text{min}/1.73 \text{ m}^2] = 186 \times [\text{S}_{\text{cr}}]^{-1.154} \times [\text{age}]^{-0.203} \times [0.742 \text{ if female}] \times [1.212 \text{ if African-American}]$  [conventional units]). This equation provides a much better estimate of kidney function than creatinine alone.<sup>11</sup> 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 Caucasian female with a creatinine of 1 mg/dL has a decreased estimated GFR of 57 mL/min/1.73 m<sup>2</sup>, while 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 m<sup>2</sup>.

### Renal Replacement Therapy

CKD patients with a GFR of less than 15 mL/min/1.73 m<sup>2</sup> 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 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 it is for the general population (according to the Joint National Committee on Hypertension 7). Major classes of antihypertensive agents include 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 non-dihydropyridines. The dihydropyridines include amlodipine, felodipine, isradipine, nicardipine, nifedipine, and nisoldipine. The non-dihydropyridines include diltiazem and verapamil. Both classes of calcium channel blockers reduce blood pressure by relaxing arteriole smooth muscle and reducing systemic vascular resistance. The non-dihydropyridines also have a significant effect on heart rate through a direct negative chronotropic effect. Calcium channel blockers have been documented to cause gingival hyperplasia in multiple reports (Figure 4). It is a potential adverse effect with all classes of calcium channel blockers, but is thought to occur more often with the dihydropyridine agents.<sup>10</sup> Gingival hyperplasia usually occurs within months after the initiation of therapy and resolves within months of discontinuing therapy.<sup>12</sup> Clinicians may consider discontinuing these medications 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***

Patients who have undergone kidney transplantation require immunosuppressive therapy to prevent rejection. There are both cell-mediated and humoral components to transplant rejection. Transplant medications target both aspects of transplant rejection. Most regimens include calcineurin inhibitors to decrease the T-cell mediated response. The calcineurin inhibitors include cyclosporine and tacrolimus. Cyclosporine has been documented to cause gingival hyperplasia in renal transplant patients in multiple studies.<sup>13</sup> Additionally, this effect is thought to be augmented when cyclosporine is used in combination with a calcium channel blocker.<sup>14</sup> Tacrolimus has shown much lower rates of gingival hyperplasia and may be a safe alternative for a patient experiencing significant cyclosporine-induced hyperplasia.<sup>14,15</sup> Any change in transplant medications should be made by a transplant specialist to ensure efficacy and safety. Another approach to treating gingival hyperplasia might 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.<sup>16</sup>

### **Inflammatory State**

The relationship of kidney disease to periodontal disease is a complex one that requires further study. Periodontal disease contributes to a chronic inflammatory state that has been linked to multiple systemic illnesses. Two recent cross-sectional studies identified periodontal disease as an independent risk factor for chronic kidney disease. However, the temporal relationship between the two is unknown and no conclusions can be made on causality.<sup>17-19</sup>

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 general population. The leading cause of morbidity and mortality of CKD patients is cardiovascular disease.

The increased prevalence of cardiovascular disease among CKD patients is thought to be multifactorial. Many 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 this inflammatory burden in patients with CKD. Periodontal disease is common in CKD patients, often more severe than in the general population, and is frequently overlooked.<sup>20</sup> Death from diabetic nephropathy, and ESRD are significantly greater in diabetic patients with periodontal disease

compared to those with diabetes and little or no periodontal disease.<sup>21,22</sup> Multiple studies have shown the association of inflammatory markers to periodontal disease in dialysis patients.<sup>23,24</sup> Treatment of periodontal disease has been shown to reduce inflammatory markers in non-CKD patients.<sup>25</sup> Furthermore, in a study of CKD patients, treatment of periodontal disease was shown to significantly decrease CRP levels.<sup>24</sup> 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 from 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.<sup>23</sup> Furthermore, the most recent information from the USRDS shows that Medicare spent \$1.9 billion on erythropoietin-stimulating agents in one year alone. Decreasing CRP might result in lower erythropoietin doses and thus have a large and positive financial impact.

### **Treatment of Periodontal Disease in the CKD Patient**

The management of periodontal disease frequently requires significant instrumentation, pharmacotherapy, and sometimes surgery. Some clinicians recommend antibiotic prophylaxis prior to dental procedures in patients with arterial venous grafts because of the risk of infective endocarditis.<sup>26</sup> Multiple antibiotic and analgesic regimens exist. For all antibiotics, it is important to adjust dose based on GFR and avoid nephrotoxic agents in patients who are not yet on dialysis. Non-steroidal anti-inflammatory drugs (NSAIDs) can decrease GFR and are best avoided in patients with CKD. Patients with CKD may be at increased bleeding risk secondary to platelet dysfunction, as well as anticoagu-

lants received on hemodialysis. One might try to implement a procedure on the day following dialysis to decrease the risk.<sup>10</sup> Most renal transplant protocols include a dental workup prior to transplantation to treat any potential problems once immunosuppressive therapy is initiated. Extra caution is necessary in renal transplant patients as they are more susceptible to infection.

### **CANCER AND PERIODONTAL DISEASE**

Almost 11 million people in the US are living with cancer or have a history of cancer, with approximately 1.4 million new cases occurring yearly.<sup>27</sup> “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 from a combination of environmental and intrinsic factors.<sup>27</sup>

Patients with cancer represent a unique segment of the dental population. Many patients with cancer have pre-existing periodontal disease at the time of cancer diagnosis. Additionally, several cancer treatments are 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.<sup>28</sup> Recent studies have shown

a small but significant increase in cancer risk in patients with periodontal disease.<sup>29,30</sup>

**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 regimens, which can affect the entire alimentary tract. Symptoms are numerous, including 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, and a higher prevalence in those undergoing hematopoietic stem cell transplantation (HCT).<sup>31</sup> Multiple factors contribute to the development of mucositis. Tissue damage/cell death, stimulation of a pro-inflammatory 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**

There are numerous chemotherapy regimens available depending on the type of cancer being treated. Some of the more common agents associated with oral toxicity include alkylating agents, anthracyclines, antimetabolites, antitumor antibiotics, taxanes, and topoisomerase inhibitors. There are many more anticancer drugs associated with oral toxicity and a more comprehensive list can be seen in Table 2. While the individual mechanism of action of these medications is not essential to this discussion, 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 pro-inflammatory 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 under-

**Table 2.** Chemotherapeutic Agents Associated with Oral Toxicity and Mucositis

Drug Category	Chemotherapeutic Drug Names (Generic)
Alkylating agents	bisulfan, carboplatin, cisplatin, cyclophosphamide, ifofamide, mechloethamine, melphalan, procarbazine, thiopeta
Anthracyclines	daunorubicin, doxorubicin, iadarubicin, epirubicin, mitoxantrone
Antimetabolites	capecitabine, cytarabine, fluorouracil, fludarabine, gemcitabine, hydroxyurea, methotexate, 6-mercaptopurine, pemetrexed, 6-thioguanine
Antitumor antibiotics	dactinomycin, bleomycin, mitomycin
Taxanes	docteaxel, paclitaxel
Topoisomerase inhibitors	etoposide, topotecan, irinotecan, teniposide

Adapted from *UpToDate*, 2010.



going HCT. Intensive chemotherapy can cause ulcerative mucositis that emerges approximately two weeks after initiation of high-dose chemotherapy.<sup>32</sup> Risk factors for development of mucositis include younger age, quality of dental hygiene, and level of immunosuppression prior to 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 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 include xerostomia, hemorrhage, and neuropathy.

### ***Preventing Oral Mucositis***

There is limited objective data to support the concept of dental therapy prior to the initiation of treatment for cancer. While many feel that aggressive preventive dental care limits the extent of oral complications associated with such medical therapy, one study proposed that such measures had no impact on overall outcome.<sup>33</sup> 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).<sup>34</sup> For patients undergoing standard chemotherapy, evaluation by a dental practitioner is encouraged prior to 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 those 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, it was shown to reduce the incidence of severe mucositis compared with the placebo group.<sup>35</sup> The use of 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. The use of 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 the use of these protocols.

### ***Treating Oral Mucositis***

The treatment of 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 as this will reduce the incidence of secondary infection and promote timely healing. Soft toothbrushes, non-irritating oral rinses, and removal of dentures should all be encouraged as a part of routine care. The use of mucosal coating agents has been employed, although the data to support the efficacy of such agents are weak.

Oral solutions including lidocaine, diphenhydramine, and morphine sulfate have all been employed 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.<sup>34</sup>

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 reduces the risk of infection and fever associated with oral conditions.<sup>36</sup> 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.<sup>36</sup>

In summary, the complication of oral mucositis has a very high prevalence 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. While 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 as 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 based on the cell type

that is involved; these are divided into myelogenous and lymphocytic. Furthermore, leukemias are categorized as acute or chronic. Chronic leukemias occur more commonly in older individuals 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 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 exist several subtypes. Additionally, there are some less-common forms of leukemia that 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.<sup>37,38</sup> The use of 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 leukemic patient with gingival lesions, it is often difficult to distinguish between changes due to the disease process and those brought on by treatment. In order 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.<sup>39</sup>

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 post-extraction hemorrhage, and gingival pain as presenting symptoms that led to various leukemia diagnoses.<sup>37,40</sup>

### **Radiation Therapy in Head and Neck Cancer**

Head and neck cancers include cancer of the oral cavity, the pharynx, the larynx, salivary glands, nasal cavity, paranasal sinuses, and neck lymph nodes. The majority of 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. Collaboration 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 prior to 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 prior to head and neck radiation. The same survey also reported that integrated dental and medical services were available at only 25% of institutions.<sup>41</sup>

Mucositis is a common side effect of radiation therapy and has been reported in up to 80% of patients receiving radiotherapy for head and neck cancer.<sup>42</sup> 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.<sup>42</sup>

As in patients with chemotherapy-induced mucositis, the cornerstone of therapy in patients with radiation-induced mucositis includes adequate pain management and

maintenance of oral hygiene. Recent guidelines specific to radiation-induced mucositis support the use of midline radiation blocks and 3-dimensional radiation therapy to minimize mucosal damage. The guidelines also recommend the use of benzydamine, 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 use of chlorhexidine rinses and antimicrobial lozenges to prevent radiation-induced oral mucositis. They also recommend against the use of sucralfate in the treatment of radiation-induced mucositis.<sup>34</sup>

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 will result in more severe cases of xerostomia. Patients with significant xerostomia are at much higher risk for developing dental caries. For these patients, daily fluoride treatment and meticulous oral hygiene is 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.<sup>43</sup>

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.<sup>44</sup> This complication of radiation therapy 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 preradiation extractions can help limit postradiation dental extractions and the potential development of osteoradionecrosis.

### **Surgery**

Surgical resection is an important treatment modality for head and neck cancers. Unfortunately, these surgeries are frequently disfiguring and debilitating. Furthermore, infection of the oral cavity can lead to significant setbacks in recovery, as well as delay adjunctive chemotherapy or radiation. Thorough preoperative oral and dental evaluation can help 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. There are intra-oral prostheses that can aid in speech and nutrition, while extra-oral prostheses can help to reduce disfiguration. Regardless of the type of prosthesis, a preoperative meeting with the patient and family can help them know what to anticipate postoperatively. Close postoperative monitoring of the surgical site is essential. 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 a recovery of function. There are several commercially available mechanical devices that can aid in oral opening exercises.<sup>45,46</sup>

### **Periodontal Disease and Cancer Risk**

This chapter section has focused on the effect of cancer treatments on oral tissues. A multidisciplinary approach, with involvement of medical and dental professionals, is necessary to optimize oral care in cancer patients. However, it must be noted that poor oral health may be a risk factor for the development of cancer. Multiple studies have demonstrated the inflammatory effects of periodontal disease, and this inflammatory state might have an effect on the development of cancer. There appears to be a relationship 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. Additionally, periodontal disease has been associated with a small, but significant increase in overall cancer risk.<sup>29,30</sup>

### **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 periodontal disease and endodontic lesions may contribute to cancer risk, and if they persist or exacerbate during cancer therapy, they could be a source of life-threatening infection. Pre-treatment 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 may be exacerbated by cancer treatment or if cancer therapy

involves treatments that reduce resistance to infection.

Treatments that may induce xerostomia, such as radiation 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 regularly checked for and treated.

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# CHAPTER 18

## The Role of the Professional in Educating the Public About the Importance of Oral Health

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Casey Hein

### INTRODUCTION

It has been recognized for some time that health outcomes are, in part, a function of health literacy and education of the public.<sup>1</sup> 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 healthcare in the United States;<sup>2,3</sup> almost half of all Americans lack adequate oral health skills, which may account for billions of dollars in added healthcare costs each year.<sup>2,3</sup> It is important to consider whether or not 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."<sup>4</sup> Given the strength of evidence that supports inter-relationships 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 healthcare 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 relationship 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, dental practitioners may be uniquely positioned to identify patients who may be at risk for chronic diseases, such as diabetes and atherosclerotic diseases, which share risk factors common to oral diseases.

As the depth and breadth of evidence to support a relationship between periodontal diseases and several common systemic inflammatory diseases continues to expand, 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, evidence from pilot trials shows that treatment of periodontal disease may improve metabolic control of diabetes.<sup>5-7</sup> However, large-scale, definitive trials are still needed to establish the efficacy of periodontal intervention. Similarly, in the case of pregnancy outcomes, several pilot trials have shown a reduction of adverse pregnancy outcomes associated with periodontal treatment.<sup>8,9</sup> However, a large study failed to show a reduction in adverse pregnancy outcomes associated with treatment of periodontal disease.<sup>10</sup> Several studies have assessed the effect of periodontal therapy on cardiovascular outcomes and have shown improvement in endothelial function.<sup>11-13</sup> However, large, randomized, controlled trials are needed to look at the effects of periodontal therapy on cardiovascular outcomes. Even though there are not yet definitive data on the effects of periodontal treatment on several conditions associated with periodontal disease, association data are strong. Hence, 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.<sup>14-16</sup> As these kinds of evidence-based, authoritative statements are circulated within the medical professions, it is reasonable to assume that more and more physi-

cians 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 connections, and pursue collaborative relationships with dental practitioners in the co-management 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 findings of credible research of oral-systemic relationships into their practices. Simultaneously, medical protocols that include periodontal evaluation, treatment, and monitoring of clinical outcomes related to the care of patients who may be at greater risk for cardiovascular disease (CVD) and diabetes may also begin 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 relationship 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 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 upon 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."<sup>17</sup> This opinion reflects the all-too-real disconnect between oral and overall health and therefore has far-reaching implications. Segregation of the oral cavity from the rest of the body—and consequently the historical schism between dentistry and medicine—has helped contribute to the disparities that currently exist in oral health among Americans.<sup>4</sup> The failure to recognize oral health as integral and essential to general health has also adversely impacted healthcare policy.<sup>18</sup> In 2009, 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 nondental healthcare providers' perceptions of 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 reporting evidence of oral-systemic relationships with increased

frequency. In addition, governmental reports,<sup>4,19</sup> educational institutions,<sup>20,21</sup> and professional associations<sup>22</sup> have called for educational reform that would increase nondental healthcare providers' knowledge of oral health, and collaborative models of care that 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.<sup>23,24</sup> 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 health departments of state agencies have begun to address the importance of oral health in the overall health of their citizenry.<sup>25,26</sup>

Changes in public policy, increased insurance reimbursement, and improved medical/dental education undoubtedly will facilitate interprofessional 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 reprioritize the importance of oral health and its implication to overall health.

The answers to the following four 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 to achieving and sustaining *overall* health?
3. How well are dental practitioners doing regarding educating patients about oral-systemic relationships and what are the hurdles to effectively communicating this information to consumer-patients?
4. What research should be credibly communicated to patients about the relationship 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 about the importance of oral health, thereby increasing 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 there have been numerous sources of information from mainstream media about the relationship between oral and systemic health, including lay publications,<sup>27,28</sup> television,<sup>29</sup> and radio.<sup>30</sup> In 2004, *Time Magazine*<sup>27</sup> 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 of 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."<sup>27</sup> If readers can comprehend such sophisticated information, it is reasonable to assume the public is becoming increasingly aware of the relationship 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.<sup>29</sup> 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 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.

#### **A Snapshot of What the Public Knows**

Piecing together data compiled by various professional and nonprofit organizations and the insurance industry provide 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 vast majority of consumer-

patients are aware that there is 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.<sup>31</sup>

Other data indicate that 85% of Americans believe there is a strong connection between oral health and general health.<sup>32</sup> The large majority (77%) of Americans believe that personal maintenance of their oral health is very important to their own overall health,<sup>33</sup> and 80% of Americans agree that taking care of one's mouth, teeth, and gums is "absolutely needed."<sup>32</sup> 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.<sup>34</sup> 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.<sup>34</sup>

### **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.<sup>34</sup> 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 out of three consumer-patients from a nationally representative sample opted for periodontal examinations instead of routine prophylaxis.<sup>35</sup> The survey question and results of the consumer-patient responses are included in Figure 1.

### **The 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.

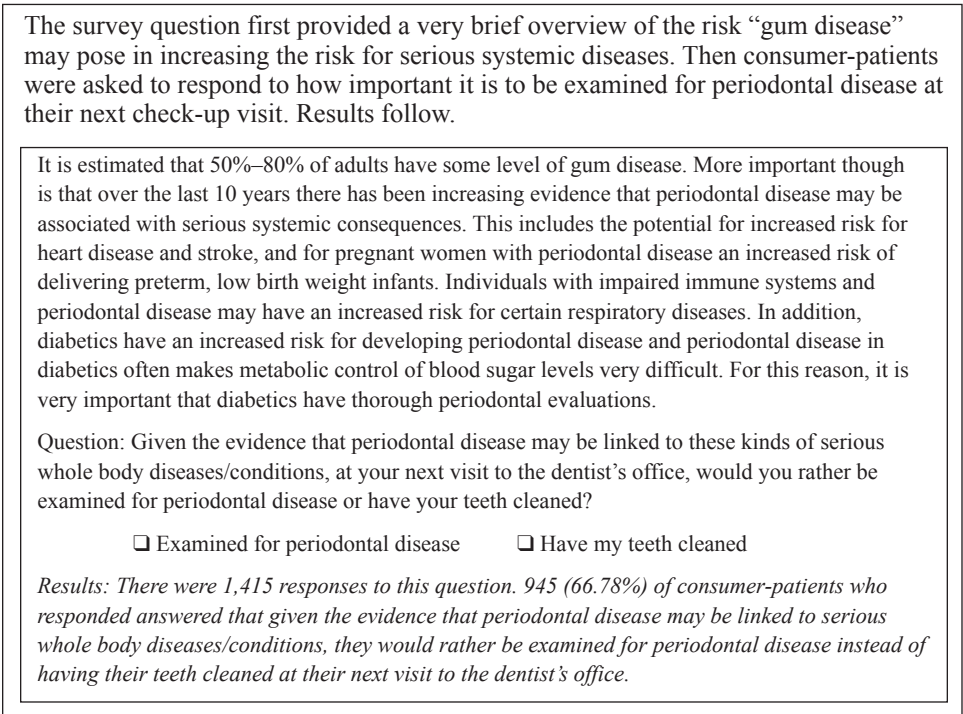
The contribution of medical providers in educating patients about the potential of periodontal disease to elicit systemic inflammation and increased risk for chronic disease states cannot be overlooked. In a February 2008 issue of the *Journal of the American Medical Association*,<sup>36</sup> a patient 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 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



**Figure 1.** Question on Consumer-Patient Survey Conducted in 2005.



Adapted from Hein C et al. Presented at 83<sup>rd</sup> Annual Session of the American Dental Hygienists’ Association; Orlando, Florida; June 2006.<sup>35</sup>

systemic implication of periodontal disease.

4. There are numerous sources of information 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 healthcare practitioners.

**DEVELOPING EFFECTIVE COMMUNICATION WITH PATIENTS ABOUT ORAL-SYSTEMIC HEALTH**

**The American Dental Association (ADA) Weighs in on Oral Health Literacy**

The ADA has defined oral health literacy as “the degree to which individuals have the capacity to obtain, process, and under-

stand basic health information and services needed to make appropriate oral health decisions.”<sup>23</sup> 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.<sup>3</sup>

**Addressing Oral Health Literacy Within the Dental and Dental Hygiene Professions**

In a 2004 National Institutes of Medicine report, it was estimated that 90 million adult Americans have difficulty in obtaining, processing, and understanding basic health information and services needed to make appropriate health decisions.<sup>1</sup> This calls attention to the importance of healthcare providers

**Figure 2.** Patient Education Article About Periodontal Disease Published by the *Journal of the American Medical Association*.

As a public service of *JAMA*, the organization has permitted the article to be photocopied noncommercially by physicians and other healthcare professionals to share with patients.

JAMA PATIENT PAGE

The Journal of the American Medical Association

ORAL HEALTH

## Periodontal Disease

**P**eriodontal disease (unhealthy gums and teeth) often reflects serious health risks. Mild inflammation of the gums (gingivitis) can be prevented by regularly brushing and flossing teeth to remove plaque (buildup of a film on the teeth). This stops the development of tartar (hardened accumulation of plaque at the gum line), which can only be removed by dental cleaning. More serious infection, called periodontitis, can cause not only disease of the gums, but loss of teeth and the bone structures that support the teeth. Periodontitis may be associated with heart disease, stroke, and systemic (whole body) infections. There is also evidence that premature births happen more often to women who have gum disease before or during their pregnancies. The February 6, 2008, issue of *JAMA* includes an article about an association between periodontal disease and smoking marijuana.

**CAUSES**



- Poor dental hygiene—not brushing your teeth or using dental floss regularly—allows the buildup of plaque and tartar, making the gum tissue unhealthy.
- Smoking causes decreased oxygen delivery to the gum tissue and makes it easier for bacteria to invade the gums.
- Some medications may cause gingival hyperplasia (overgrowth of gum tissue) or receding gums.
- Viral or fungal infection
- Poor nutrition, especially vitamin and mineral deficiencies, may cause gum disease or loss of teeth.
- Chronic medical conditions, including diabetes, may lead to greater risk of infections or poor healing in the gums as well as in other body tissues.

**SIGNS AND SYMPTOMS**

- Receding or puffy, swollen gums
- Painful gums
- Bleeding when you brush your teeth
- Tooth loss or loose teeth in adults
- Pus draining from the gums
- Bad breath that is not related to food and does not go away

**PREVENTION AND TREATMENT**

- Brush your teeth at least twice a day.
- Use dental floss daily.
- Periodontitis does not cause symptoms initially, so it is important to have regular dental checkups.
- Maintain good nutrition by eating fruits, vegetables, and whole grains and making sure your diet contains plenty of calcium.
- Do not smoke.
- Control chronic medical problems, especially diabetes (maintaining normal blood sugar levels decreases your risk of infection).
- In severe cases of periodontitis, advanced dental treatments may be offered, including gum surgery, bone grafts, or placement of antibiotics into the gum tissue itself.

**FOR MORE INFORMATION**

- American Dental Association  
[www.ada.org](http://www.ada.org)
- National Institute of Dental and Craniofacial Research  
[www.nidcr.nih.gov](http://www.nidcr.nih.gov)
- American Heart Association  
[www.americanheart.org](http://www.americanheart.org)


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to improve their communications skills and deliver patient education in such a way that it can be readily understood and acted upon by patients.

Given such strong data that suggest patients understand the correlation between oral and systemic health, it seems 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 relationship between oral and overall health.<sup>34</sup>

It has been estimated that 33% of dental patients may not know that periodontal disease needs to be treated and should not be left alone;<sup>2</sup> another 33% believe that a little bleeding from brushing is normal.<sup>2</sup> While 83% of US adults may say their dentist is their primary source of information on oral care practices, a significant portion of these adults also report that they have not discussed their oral health issues with a dental professional.<sup>2</sup> This is especially troubling when considering that more than half of the adults living in the US experience one or more oral health conditions.<sup>2</sup>

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 US ask their patients about smoking,<sup>37,38</sup> and the cessation advice provided in dental offices has been described as "rather ad hoc and somewhat superficial."<sup>39</sup> 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 terms of both quantity and quality of services.<sup>40</sup> Lack of training and incentives were most often

cited to explain the reluctance of dentists and dental hygienists to provide tobacco cessation interventions.<sup>41</sup>

### **Dismantling the Hurdles to Effectively Educate Patients About Oral-Systemic Health**

By virtue of the frequency by which people visit dentists for checkups 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 to 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.<sup>34,35</sup> 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 that patients are starting to view dentists as overall healthcare providers.<sup>34</sup> Accordingly, it is crucial that dentists lead the charge in conveying to patients the importance of maintaining both oral and overall health.<sup>34</sup> Other hurdles associated with effectively communicating important information about oral-systemic health include the barriers listed below.

### ***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 etiological mechanisms that have been implicated in many oral-systemic relationships and are uncomfortable with how these inter-relationships should be explained to patients.

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.<sup>21,42-44</sup> For professionals already in practice, there exists numerous opportunities for continuing education in oral-systemic science, and a routinely conducted literature search of studies related to oral-systemic relationships, that 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-patients' understanding of the significance of oral health, assuming practitioners have adequate communication skills. It is unclear whether or not patients believe their dentists are as concerned with their overall health as they are with their oral health.<sup>34</sup> 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, become proactive in advocating for comprehensive education of patients, and master effective communication skills.

The first step to increasing patients' understanding of oral-systemic relationships is to provide the right kind of training to ensure that all the members of the dental team are able to effectively communicate key messages related to oral-systemic health, and be prepared to appropriately answer patients' questions. The ADA has passed a resolution to seek external funding to support the design and execution of a comprehensive oral health literacy awareness and education strategy targeting the entire dental team.<sup>3</sup> A related resolution encourages the development

of oral health literacy continuing education programs to train dentists and allied dental team members to communicate effectively with patients who have limited literacy skills.<sup>3</sup>

### ***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 or not there is an incentive 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 themselves do.<sup>34</sup> Patients expect dentists to discuss serious health issues they might be confronting and not just discuss the traditional expectations of dental services.<sup>34</sup> A well-recognized practice management expert<sup>45</sup> noted that compared to previous decades, more dental patients are "shopping around" for dental care and changing dental practices. More comprehensive service offerings was cited as an important factor in patients' selection of dentists, and 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."<sup>45</sup> It seems clear that the public wants a different approach to dental care, and those 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 US, a large portion 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 US and is taking steps to address this disparity.
2. It is unclear whether or not the majority of dentists and dental hygienists are proactively educating patients about the relationship between oral and systemic health; however, this is an important factor to consider in determining why oral health literacy is so limited within the US.
3. There are a number of hurdles that 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 relationships, philosophies of practice that may be outdated or preclude providing this level of patient education, and concerns relative to the lack of compensation related to providing patient education. Failure to provide patient education services has both ethical and legal implications.

### KEY AND CREDIBLE INFORMATION TO COMMUNICATE TO PATIENTS ABOUT THE LINK BETWEEN PERIODONTAL DISEASE AND SYSTEMIC DISEASES

Information about the relationship between oral and systemic health originates from numerous 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 from health professionals and industries marketing oral care products. It should be noted that the source that patients often put the greatest weight on is information coming from their dentist or dental hygienist. It is therefore of prime importance that the dental community and dental paraprofessionals stay current with emerging research about oral-systemic connections. Oral health professionals are responsible for filtering second-hand sources of information on oral-systemic health (sources other than well-respected scientific literature) to ensure that what is communicated to patients is scientifically sound.

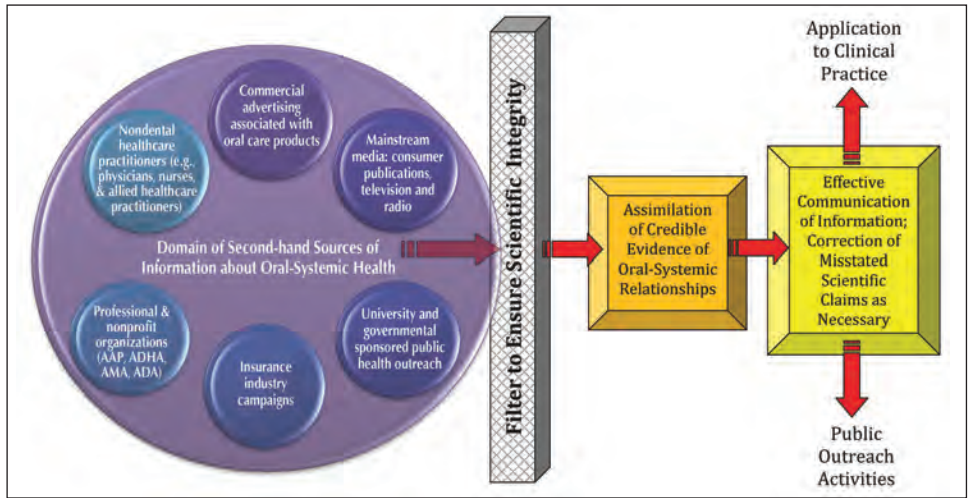
The process of professional development that will prepare individual dentists and dental hygienists to become authoritative experts in the evidence of oral-systemic relationships is illustrated in Figure 3. As practitioners proceed through this process—from surveillance to clinical application and public outreach—confidence in how to communicate this information to patients becomes a natural by-product of the self-learning that occurs throughout the process.

### Key and Credible 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 pathological events in distant organs. This information is



**Figure 3.** The Process of Ensuring Scientific Integrity of Information Related to Oral-Systemic Relationships and Appropriate Integration into Patient Education, Clinical Practice, and Public Outreach Activities to Increase Nondental Healthcare Providers' and Consumer-Patients' Awareness of the Importance of Oral Health.



applicable when describing the etiological mechanisms that have been implicated in most of the oral-systemic relationships under investigation. Each involve describing the inter-relationship between the following:

### ***Periodontal Infection and Systemic Inflammation***

- Today we know that infection from gum disease is not contained simply within the oral cavity.
- Bacteria from gum infection cause inflammation.
- Bacteria and their products enter the blood stream from the gum pockets, leading to systemic inflammation.
- Bacteria and toxins from gum disease can move through blood vessels to distant sites in the body, including the heart, kidneys, lungs, brain, and developing fetuses in infected pregnant women.
- 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 infection and inflammation be treated.

- Gum disease (periodontal disease) is an often overlooked source of infection and inflammation and it is very important that patients be examined. If gum disease is diagnosed, it must be treated to reduce the risk for systemic inflammation that is associated with many of these diseases and conditions.

### ***Diabetes and Periodontal Disease***

- Diabetes increases the risk of infection from any source. Gum disease is an infection and a complication of diabetes that is often unrecognized.
- People with poorly controlled diabetes are much more susceptible to gum disease and may be two to four times more likely to develop gum disease than people without diabetes.



- The presence of gum disease increases the risk of worsening glycemic control over time.
  - Research suggests gum 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. This 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 gum disease.
  - Although more research needs to be conducted, studies that have measured the difference in HbA1c after treatment of gum disease report improvements in blood glucose control over time.
  - Patients with poor blood sugar control may have more rapid recurrence of deep pockets and less favorable long-term response to treatment of gum disease.
  - When gum 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 three 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.
- have a moderately increased risk for coronary heart disease and stroke.
  - It is important to identify those individuals who may be at greater risk for heart disease or stroke and who have gum disease.
  - It is important to understand how gum disease and increased risk for heart disease and stroke may be related.
  - When there is inflammation within heart tissues, arteries become less elastic while 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 gum disease may improve the flow of blood to the coronary arteries; however, more research is needed before it is known for certain how gum treatment affects the heart. In the meantime, the American Academy of Periodontology has determined that treatment of gum disease may prevent the onset or progression of atherosclerosis-induced diseases.

### ***Periodontal Disease and Increased Risk for CVD***

- Accumulated evidence suggests that individuals with gum disease may

### ***Periodontal Disease and Increased Risk for Adverse Pregnancy Outcomes***

- Infection from any source increases the risk of complications during pregnancy. Gum disease may be one of the infections that poses a threat to healthy pregnancy.

- It is estimated that approximately 40% of pregnant women have some form of gum disease.
- Evidence suggests that in some populations, pregnant women who have gum disease may be at two- to five-times greater risk for various pregnancy complications, including pre-term birth, pre-eclampsia, gestational diabetes, and delivery of low birth weight infants.
- Now that oral healthcare providers and obstetricians recognize there might be a 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 gum treatment during pregnancy is safe and improves maternal oral health.
- Cytokines are a type of chemical normally produced by the body to defend itself against inflammation. When produced in gum tissue as a result of infection, cytokines may cause inflammation of the lower respiratory airway following 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 be at greater risk for respiratory problems because of undiagnosed and untreated gum disease.

#### **General Advice to Patients**

#### ***Periodontal Disease and Increased Risk for Respiratory Infection***

- Research suggests that institutionalized elderly people and patients in intensive care units who have poor oral hygiene may be at greater risk for pneumonia and other respiratory infections.
- Oral pharyngeal surfaces, including the teeth, can serve as a reservoir for pathogenic bacteria that are known to cause pneumonia. These bacteria can be aspirated into the lungs where they may cause respiratory infections—many of which can be fatal.
- Respiratory infections related to poor oral hygiene in institutionalized patients in intensive care units and nursing homes can be reduced by effective oral plaque control measures.
- 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 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 mouthrinse 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 on the relationship between oral health and general health, dentists and dental hygienists are responsible for ensuring that what is communicated to patients and 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. If 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 there is much that 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

Table 1. Outreach Activities for Dental Professionals to Influence Nondental Healthcare Providers’ and the Public’s Perception of the Importance of Oral Health Outside the Practice Setting

<ul style="list-style-type: none"><li>• Volunteer to deliver a presentation at the local hospital’s rounds</li><li>• Take physicians and nurses to lunch to discuss building a collaborative relationship and systems of triage</li><li>• Routinely visit physicians’ offices to supply educational materials for patients</li><li>• Dental hygiene organizations may partner with nursing organizations to conduct a health fair in which nurses screen for oral diseases/conditions, and hygienists screen for CVD and diabetes</li><li>• Volunteer to present information at local meetings of civic organizations, hospital programs for the public, churches, etc.</li><li>• Volunteer to write a column about oral-systemic relationships in community newspapers</li><li>• Invite medical colleagues to a study club when information on oral-systemic medicine is being presented</li><li>• Provide volunteer in-service training in oral healthcare for nursing assistants at nursing home facilities</li><li>• Use referral letters to simultaneously educate physicians about oral-systemic relationships</li></ul>
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compromise overall health, especially in individuals who have an amplified inflammatory response to bacterial infections such as periodontal disease. Evidence to support a relationship between periodontal disease and increased risk for heart disease, stroke, worsened glycemic control in individuals 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 government-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 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 inter-relationships 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.

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*Renowned clinicians and scientists worldwide have studied the relationship of periodontal disease to overall health and disease. We are fortunate to have assembled such a respected and scholarly body of contributors who, in eighteen chapters, provide a current and thoughtful perspective on this relationship.*

—Robert J. Genco, Ray C. Williams

**Colgate**