Periodontal Disease and Overall Health: A Clinician's Guide

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CHAPTER 1

Overview

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

—Former U.S. Surgeon General C. Everett Koop

INTRODUCTION

We welcome you to the Second Edition of *Periodontal Disease and Overall Health: A Clinician's Guide*. Research into the relationship between periodontal disease and general health continues to emerge at a rapid pace. Thus, an update to our 2010 edition seems appropriate and necessary.

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

Periodontal Disease as an Integral Link to Systemic Disease

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

THREE HISTORICAL ERAS OF PERIODONTAL DISEASE

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

Etiopathologic Era

The etiopathologic era included landmark investigations into the microbial etiology and pathogenesis of periodontal disease. The role of bacteria as a cause of periodontal disease was demonstrated by a series of seminal studies conducted from the 1960s to the

1980s. Classic studies by Löe and colleagues[2,3] clearly demonstrated that microbial plaque buildup on the teeth was associated with the onset of gingivitis and that the removal of microbial plaque resulted in the resolution of gingivitis. These studies provided unarguable evidence that microbial dental plaque buildup, rather than other suspected agents such as calculus, was responsible for gingivitis.

In the 1970s and 1980s, Socransky and coworkers[4] conducted studies showing that specific organisms were associated with periodontal disease (for review see Socransky and Haffajee, 2005). 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. More recent studies using 16S rRNA sequencing techniques, which reveal most if not all of the organisms at a site (i.e., the microbiome), have revealed a set of new potential pathogens.[5] These new studies support the shift from a gram-positive community in health to a gram-negative–dominated community in periodontal disease. Several new genera and species—some not able to be cultivated and others newly described—emerge as potential periodontal pathogens.

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

Other investigators began to explain the pathogenesis of periodontal disease, describing how the host in fact was responsible for tissue destruction. We came to understand that the initial response to the bacteria on the tooth and subgingivally is a series of immunopathologic actions. Antibodies to these bacteria are formed, which in combination with neutrophils, provide important protection.[7,8] It was seen that when neutrophils are suppressed, more severe periodontal disease occurs. Soon thereafter, the role of the macrophage was understood. This important cell invades the gingival tissue and, on triggering by bacterial products such as endotoxin, produces proinflammatory cytokines and matrix metalloproteinases that destroy the connective tissues of the periodontium. Inflammatory mediators such as prostaglandin E_2 and interleukin 1 induce alveolar bone resorption. As the role of the host becomes more understood, inflammation and the inflammatory response can explain much of the tissue destruction caused by periodontal disease.[9,10]

Risk Factor Era

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

Periodontal Disease-Systemic Disease Era

The understanding of periodontal disease is currently focused on the relation of peri-

odontal disease as a risk for certain systemic diseases. Robust studies have shown that periodontal disease is independently associated with certain systemic diseases such as cardiovascular disease,[14–16] diabetes and complications of diabetes,[17–20] adverse pregnancy outcomes,[21,22] and respiratory infections.[23]

Evidence supporting the association of periodontal disease with systemic disease was reviewed by a panel of experts from the United States and throughout Europe.[24] The authors concluded that scientific evidence shows a strong association between periodontal disease and several systemic disorders. Periodontal disease likely contributes to the bacterial burden that causes a destructive systemic inflammatory response, thus contributing to these diseases. Treatment of periodontal disease reduces this burden. It is clear that periodontal disease, especially severe periodontitis, may also initiate general health issues.[25]

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

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

THE ROLE OF DENTISTRY IN RISK FACTOR MODIFICATION

Common Risk Factors

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

GOALS FOR THIS TEXTBOOK

Much research is focused on understanding how periodontal disease increases the risk for systemic diseases. It is not yet clear what impact the biofilm in the oral cavity might have on distant sites and organs; likewise the

role of the inflammatory response is not fully understood. Some chapters review the biologic plausibility of periodontal disease as a risk for systemic conditions. Mechanisms through which periodontal disease can confer this risk are also presented.

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

Textbook Organization

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

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

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

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

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

Our Hope for This Textbook

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

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

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CHAPTER 2

Periodontal Diseases: Classification, Epidemiology, Pathogenesis, and Management

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INTRODUCTION

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

TYPES OF PERIODONTAL DISEASE

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

The classification of periodontal diseases *now* includes eight general types[3]:

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

The overall classification system is presented in Table 1.[3] In addition, this classification is different from that of case types pre-

viously developed by the AAP.[4,5] The current case types for periodontal diseases are:

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

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

Table 1. Periodontal Diseases

I.	Gingival diseases
	Dental plaque-induced gingival diseases
	Non-plaque-induced gingival lesions
II.	Chronic periodontitis
	Localized
	Generalized
III.	Aggressive periodontitis
	Localized
	Generalized
IV.	Periodontitis as a manifestation of systemic diseases
V.	Necrotizing periodontal diseases
	Necrotizing ulcerative gingivitis (NUG)
	Necrotizing ulcerative periodontitis (NUP)
VI.	Abscesses of the periodontium
	Gingival abscess
	Periodontal abscess
	Pericoronal abscess
VII.	Periodontitis associated with endodontic lesions
VIII.	Developmental or acquired deformities and conditions

Adapted from: *Ann Periodontol* 1999;4:1–6.

Gingival Diseases

Gingival disease is further characterized into plaque-induced and non-plaque-induced categories.[3]

Plaque-Induced Gingival Diseases

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

Dental Plaque Only: Gingivitis is initiated by local accumulation of bacteria (i.e., dental plaque organized in a biofilm) adjacent to the tooth.[6] The bacterial antigens and their metabolic products (e.g., endotoxin) stimulate epithelial and connective tissue cells to produce inflammatory mediators that result in a localized inflammatory response recruiting polymorphonuclear leukocytes (PMNs or neutrophils) to the site. An antibody response to bacterial antigens is also mounted. Inflammatory cells and their products, such as cytokines and enzymes, are present at the site of inflammation. Thus, a host immunoinflammatory response is established in the gingival tissues, and the clinical signs of gingivitis develop, including redness, swelling, and bleeding. The plaque-host interaction can be altered by the effects of local factors, systemic factors, or both.

Systemic Factors: Systemic hormonal change associated with puberty, menstrual cycle, and pregnancy, as well as chronic diseases such as diabetes, can alter the host response to dental plaque.[1,7] Hormonal changes and certain diseases can upregulate systemic cellular and immunologic function, resulting in local severe gingival inflammation even in the presence of minimal plaque. Significant gingivitis is commonly seen in pregnant women who have not had adequate oral hygiene before becoming pregnant. Blood dyscrasias such as leukemia may also alter immune function by decreasing normal immunologic function. Patients usually present with gingival enlargement and bleeding, which is associated with edematous and erythematous gingival tissues.

Medications: Medications such as anticonvulsant drugs (e.g., dilantin), immunosuppressive

drugs (e.g., cyclosporin A), and calcium channel blockers (e.g., diltiazem) can cause severe gingival enlargement and pseudo-periodontal pocketing (i.e., increased probing depths with no associated attachment or bone loss).[8] Medication-associated gingival conditions are often reversed after discontinuation of the offending medications.

Malnutrition: The host immune system can be diminished when malnutrition develops, resulting in excessive gingival inflammation. Severe ascorbic acid (vitamin C) deficiencies (scurvy) can produce bright red, swollen, and bleeding gingival tissues.[1] In vitamin C deficiency, gingivitis is associated with a suppressed synthesis of both connective tissue collagens (e.g., types I and III) and basement membrane collagen (type IV), because vitamin C is one of the elements required for collagen synthesis. Improved dietary intake and/or vitamin C supplements can reverse this condition.

Non-Plaque-Induced Gingival Lesions

Non–plaque-induced gingival lesions usually are rare and are mainly due to systemic conditions. In addition, bacteria, viruses, and fungi that are not normally part of the dental biofilm can cause these types of gingival lesions. Sexually transmitted diseases such as gonorrhea (*Neisseria gonorrhoeae*) and syphilis (*Treponema pallidum*) can cause lesions in the tissues of the periodontium.[9] In addition, primary streptococcal gingivitis is an acute inflammation of the oral mucosa associated with pain, fever, edematous and erythematous gingival tissues, with bleeding or abscess formation. These lesions can be managed with routine periodontal scaling and root planing and targeted antibiotic therapy. Herpes simplex virus type I is a common virus that can cause gingival lesions.[10] In children and young adults, herpes infections can be primary and usually without symptoms, but in some cases pain and fever are reported. In these cases, the gingival tissues appear red and swollen, followed by the formation of small blisters, which eventually break down to form shallow, painful ulcers. These lesions are usually self-limiting and heal within 1 to 2 weeks. After a primary infection, the herpes virus becomes latent and is preserved in the ganglion of the trigeminal nerve. The virus may be reactivated later in life by reduced immune function or stress, resulting in recurrent herpes labialis, gingivitis, and stomatitis.

Gingival lesions of fungal origin usually occur in people with diabetes or other immunocompromised states. A shift in the normal oral flora related to the long-term use of systemically administered antibiotics can also lead to lesions of fungal origin.[11] The most common fungal infection is candidiasis, caused by *Candida albicans,* often seen in patients wearing removable prosthetic devices such as dentures, and in patients with dry mouth due to multiple medications or salivary gland dysfunction. Clinical manifestations include white patches on the gingiva, tongue, or oral mucous membranes, which can be removed with a cotton swab or with gauze, leaving behind a bright red, bleeding surface. Treatment with antifungal agents is often necessary to resolve these conditions.

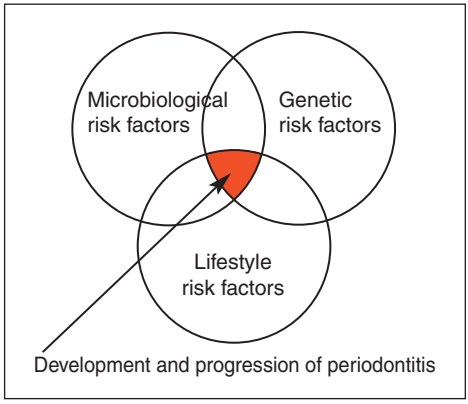
Gingival lesions can also be caused by genetic, systemic mucocutaneous disorders, allergic reactions, trauma, and foreign body reactions. One of the most common genetic conditions associated with gingival lesions is autosomal dominant, hereditary gingival fibromatosis—a benign condition affecting both dental arches.[12] In this condition, the gingival tissues are enlarged and asymptomatic. This may be an isolated finding or associated with other syndromes. Treatment is gingivectomy; recurrence is possible. Systemic conditions, such as pemphigoid, pemphigus vulgaris, erythema multiforme, and lupus erythematosus, can cause desquamative lesions and ulceration.[10,13] Gingival changes due to allergic reactions to certain restorative materi-

als, toothpastes, or mouth rinses are rare, but have been observed.[10] Traumatic lesions are usually produced unintentionally.[10] Aggressive tooth brushing and flossing can cause gingival damage. Traumatic lesions can also be iatrogenically induced by healthcare professionals during oral examinations or dental care. Eating crunchy foods or foods with small particles that can be lodged in the interproximal areas and directly into the gingival tissues can cause these types of lesions as well. Hot foods and drinks can cause minor burns of the gingival tissues. Localized inflammation can also develop when gingival tissue is exposed to foreign materials. The most common example is the amalgam remaining in gingival tissues during restorations or surgical procedures, eventually producing amalgam tattoos.[10]

PERIODONTITIS

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

Figure 1.



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

Notably, the junctional epithelium proliferates and also produces cytokines and other immune mediators and tissue-destructive proteinases. These participate in the degradation of the basement membrane and allow for the apical migration of the junctional epithelium along the root surface, contributing to the deepening of the gingival crevice and producing periodontal pockets and associated attachment loss—the hallmark of periodontitis. Osteoclasts are then stimulated to resorb the underlying alveolar bone. Some of the clinical signs include bleeding on probing, deep pockets, attachment loss and recession, radiographic evidence of alveolar bone loss, and tooth mobility. Often, this destructive process is silent and painless and continues for years without being identified. Eventually, teeth can become loose and may be lost on their own or deemed hopeless and require extraction. There are many forms of periodontitis.

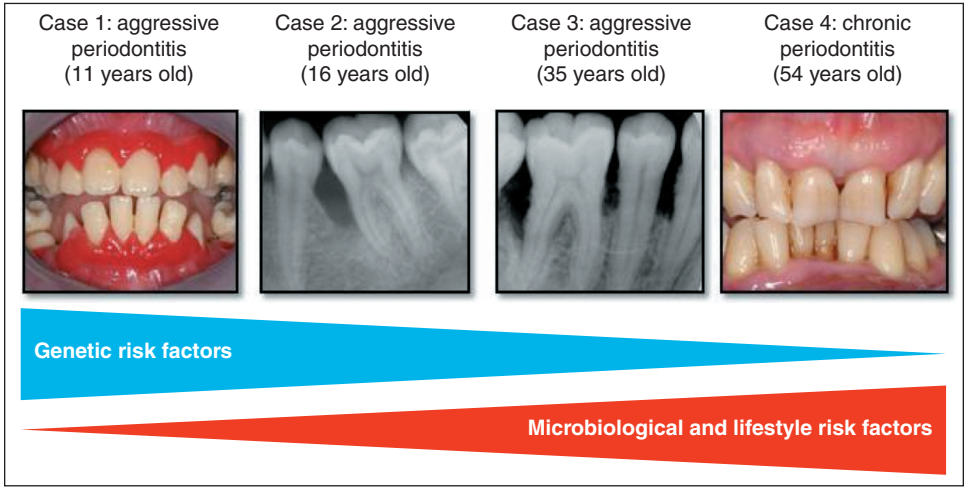
Chronic Periodontitis

Chronic periodontitis is the most common form of periodontitis and is characterized by pockets with associated attachment and bone loss and/or recession of the gingival tissues. It is common in adults, but can occur at any age. Progression of attachment loss usually occurs slowly, but periods of rapid progression or periods of remission can occur. Several studies have addressed the "episodic" nature of periodontitis.[16] The rate of disease progression may be influenced by local or systemic conditions; the latter can alter the immune response to the biofilm. Local factors such as large accumulations of dental plaque and calculus due to poor oral hygiene and lack of preventive measures (lifestyle factors) or, less commonly, to subgingivally placed fillings or crowns, can promote gingival inflammation and clinical attachment loss. Other lifestyle risk factors such as smoking, lack of proper micronutrients and vitamins, and stress, reduce in general the host resistance to the dental biofilm.[17] Genetic factors play a less important role in chronic periodontitis than in aggressive periodontitis (Figure 2). Systemic factors such as diabetes and HIV infection can decrease host defenses to bacterial infection. Lifestyle risk factors such as smoking and stress can also decrease host immune function, resulting in increased susceptibility to disease. Chronic periodontitis can occur as a localized form, in which less than 30% of sites are involved, or as a more generalized form, in which more than 30% of existing sites demonstrate increased pocket depth, attachment, and bone loss.[4] As previously mentioned, the severity of disease can be described as slight, moderate, or severe, based on the level of destruction.

Aggressive Periodontitis

Aggressive periodontitis was previously categorized as early-onset periodontitis, as in juvenile periodontitis. Common features are rapid attachment loss and bone destruction in the absence of large accumulations of plaque and calculus.[18] These forms of periodontitis usually affect young persons (juveniles, adolescents, post-adolescents), often during puberty from 10 years to 30 years of age, with a strong genetic predisposition (see Figure 2). The microbiologic risk factor most often associated with aggressive periodontitis is *Aggregati-*

Figure 2. Genetic and Microbiologic Risk Factors Associated with Periodontitis



Genetics contribute more in relatively younger patients with aggressive periodontitis than in adults with chronic periodontitis. Conversely, in relatively older patients, the microbiologic risk factors and lifestyle factors contribute the most to onset and/or progression, whereas genetics plays a smaller role.

bacter actinomycetemcomitans (previously *Actinobacillus actinomycetemcomitans*). Individuals present with hyperactive inflammatory cells producing high levels of cytokines and enzymes causing rapid, aggressive destruction of periodontal tissues. Aggressive periodontitis can be further characterized as localized or generalized. The localized form usually affects first molars and incisors. The generalized form usually involves at least three teeth other than first molars and incisors.

Periodontitis as a Manifestation of Systemic Diseases

Systemic conditions such as diabetes are associated with this form of periodontitis.[19] Diabetes, and any other chronic condition that lowers the host resistance to bacterial infections, increases the susceptibility and progression of periodontitis. Several hematologic and genetic disorders have also been associated with the development of periodontitis, such as acquired, familial, and cyclic neutropenias; constitutive neutropenia (Kostman syndrome [case 1 in Figure 2]); leukemias; Down syndrome; certain types of Ehlers-Danlos syndrome, such as types IV and VIII; Papillon-Lefevre syndrome; Cohen syndrome; and hypophosphatasia. The mechanisms by which all these disorders affect the health of the periodontium are not fully understood and continue to be investigated by many basic and clinical researchers. However, the strong genetic component is clear for most of these syndromes. Genetic mutations affect host defense mechanisms in various ways and cause hypo- or hyperinflammatory responses, resulting in fast progressive and aggressive periodontal destruction.

Necrotizing Periodontal Diseases

Necrotizing lesions are most commonly observed in persons with a poor state of health and systemic condition and strongly associated with smoking, stress, and poor nutrition. Certain systemic conditions, such as HIV infection, but also immunosuppression can increase the risk. Necrotizing periodontal diseases are further divided into two forms: necrotizing ulcerative gingivitis (NUG) and necrotizing ulcerative periodontitis (NUP). These two diseases have the same etiology and clinical signs, except that NUP involves clinical attachment and alveolar bone loss.[20]

Abscesses of the Periodontium

Periodontal abscess is a localized purulent infection of the periodontal tissues.[21] Iatrogenic abscess formation can be precipitated after inadequate scaling and root planing, leading to a tightening of the coronal epithelial cuff with continued subgingival calculus driving inflammation. Abscesses can also occur in healthy periodontal tissues owing to the presence of foreign objects lodged in the gingival crevice such as a toothbrush bristle or a popcorn kernel being tightly packed into the interproximal spaces or between the tooth and the tissues.

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

EPIDEMIOLOGY AND RISK FACTORS

Epidemiology of Gingivitis

Gingivitis can occur in early childhood, becomes more prevalent during teenage

years, and decreases in older persons.[22] In 1986–1987, the National Institute of Dental Research (NIDR) conducted a national survey of oral health in US school children[23] and reported that approximately 60% of children 14–17 years of age were found to have gingivitis. A 2005 AAP position paper reported that over 50% of adults had gingivitis on an average of three to four teeth, whereas 63% of 13- to 17-year-old teenagers had gingival bleeding according to the National Health and Nutrition Examination Survey (NHANES III) conducted from 1988 to 1994.[24,25] Both surveys assessed gingival bleeding by a gingival sweep method.

Epidemiology of Periodontitis

Basic clinical measurements for periodontitis are gingival bleeding on probing (BOP), clinical attachment loss (CAL), and pocket depths accompanied by radiographic bone loss. These types of clinical measurements may be somewhat subjective. As our knowledge of the pathogenesis of periodontitis improves, new diagnostic markers for periodontitis may emerge to better screen for, diagnose, and manage periodontitis. Inflammatory cytokines, enzymes, and bone breakdown products released into the gingival crevicular fluid reflect the host response to the bacterial challenge. These biochemical markers may be good candidates for new diagnostic or prognostic markers of disease. A number of cytokines have been associated with active disease, including prostaglandin E_2 (PGE_2), tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and others.[26,27] Enzymes such as matrix metalloproteinases (MMPs) and breakdown products, such as the collagen telopeptide (ICTP), have been studied as well.

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

The national data suggest that the milder forms of periodontitis are close to universal.[25] The more severe forms are less prevalent. According to a review of the literature by Brown and Löe[28] focused on a number of epidemiologic studies resulting from a 1981 national probability survey, the prevalence of chronic periodontitis was about 36% for the adult US population as assessed by pocket depth measurements. The prevalence of periodontitis increased with age; 29% in those age 19 to 44 years of age had chronic periodontitis, which increased to 50% for people 45 years or older. In general, moderate periodontitis occurred in 28% of all people, and 8% had advanced disease. However, the prevalence of moderate and severe periodontitis increased to 44% in the population greater than 45 years of age. Based on the presence of periodontal pockets ≥ 4 mm, it was determined that 30% of the population had periodontitis on an average of three to four teeth. Severe pockets of ≥ 6 mm were found in less than 5% of the population.[24] The prevalence of aggressive periodontitis was low with less than 1% in this 1991 survey.[29]

Following this report, the NHANES III reported the prevalence of periodontitis for adults ages 30 to 90 years old.[30] Attachment loss and probing depths were assessed at two sites per tooth. Attachment loss of ≥ 3 mm was found in 53% of the population. The prevalence of attachment loss increased with age, from approximately 35% for the 30-year-old participants to 89% for the 80-year-

old participants. Probing depths of ≥ 3 mm were found in approximately 64% of the population. The prevalence of periodontitis increases with age and was found to be more prevalent in males than females, and in African and Mexican Americans than Caucasians. Most recently, it was reported that periodontal disease may have significantly decreased between NHANES III and NHANES 1999–2004.[31] However, on further evaluation, it was recognized that partial-mouth periodontal examination protocols used in NHANES underestimated the prevalence of periodontitis by approximately 50% when compared with a full-mouth "gold standard" periodontal examination in a convenience sample of 454 adults ≥ 35 years of age.[32] These findings prompted a full mouth assessment of pocket depth and clinical attachment loss in NHANES 2009–2010 revealing periodontitis in over 47% of the population aged 30 years and older, with 8.7% mild, 30% moderate, and 8.5% severe.[33]

Risk Factors

As previously explained, periodontitis is a complex disease, with three main causal factors simultaneously playing a role—microbiologic, genetic, and lifestyle (see Figure 1). Within these clusters, various risk factors have been identified.[34-39] Estimating and/or determining risk is helpful in developing recommendations for prevention and in determining strategies for the overall management of periodontitis. It has been recognized that the severity and progression of periodontal disease varies from individual to individual. Within the microbiologic cluster of risk factors, the known periodontal pathogens and other still unknown bacteria are essential for the initiation of the disease. However, it is the host response to the bacterial challenge that determines the severity and progression of the disease. The original concept of host susceptibility by Page and Schroeder in 1976[40] has recently led to a new paradigm shift in our understanding of the etiology of periodontal disease: namely, that periodontal destruction is not caused by dental plaque in a biofilm per se, but rather by the host's inflammatory response.[41] Both hyper- and hyporesponsiveness of the immune system toward the microbial challenge in periodontitis has been described.[42] Host susceptibility is essentially the aggregate of unfavorable genetic and lifestyle factors, which in turn determines disease expression and/or progression of an existing disease.[15,43] The complexity of these interrelated factors explains the variation in phenotypes between individuals and among populations.

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

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

The specific genetic risk factors for periodontitis are largely unknown. The initial candidate gene studies that examined the association of genetic polymorphisms with periodontitis focused on genes that are involved in the innate and adaptive immunity and thus have the potential to determine disease susceptibility and severity, e.g., genes of the interleukin [IL] and Toll-like receptor families, MMPs, or various metabolic pathways.[15] Recently, 23 genes, which were repeatedly proposed to be associated with increased disease risk in white populations, were replicated in a comprehensive associa-

tion study using a large population of northern European patients with aggressive periodontitis.[45] The potential relevance of the observed association was subsequently tested in chronic periodontitis subjects. It was concluded that all analyzed putative susceptibility genes, except for *IL-10*, do not carry common risk variants and that previous positive reports were probably caused by false-positive results (type 1 errors). For complex diseases, large case-control populations are the indispensable prerequisite for any association study to overcome the inherent heterogeneity within populations. It is currently believed that in complex diseases, common markers or causative genetic variants usually do not exceed an odds ratio (OR) of 1.3, with many having even much smaller ORs.[46-49] To identify such a variant in the population (OR 1.3 and with a variant allele frequency of 20%, for example), a minimum of 1,000 well-defined cases is necessary to reach the required statistical power of 0.8, and at least the same amount of healthy controls.[50] None of the early candidate gene studies reached this sample size and were underpowered. Hence, most associations of the past seem arbitrary and suffer from a lack of successful replication, the gold standard of any association study.

In addition to power and sample size issues, another important limitation of candidate gene studies in the field of periodontitis is that initial studies did not capture the complete genetic information of a particular region of interest. In almost all studies, only one or a few variants rather than the complete set of all haplotypes of a gene were genotyped.[50] However, information about the complete haplotypes must be assessed to ensure that all potentially relevant polymorphisms are analyzed. Further limitations of most previous studies on genetics in periodontitis often include inadequate phenotype classification for disease and control subjects, as well as that of failing to take into account lifestyle effects such as smoking, age, and the presence of other diseases.[50]

Within the cluster of specific genetic risk factors, the IL-1 composite genotype ad modum, Kornman and colleagues[51] deserve special attention because of the large number of studies that have been carried out on the relation between this composite genotype and the two main forms of periodontitis in a variety of ethnic populations. The *IL-1* genes, comprising *IL-1A*, *IL-1B,* and *IL-1RN*, are located in close proximity to each other on the long arm of chromosome 2. *IL-1A* –889 (rs1800587, in linkage with +4845), *IL-1B* –511 (in linkage with –31), *IL-1B* +3954 (rs1143634, also mentioned in the literature as +3953) and *IL-1RN* VNTR (in linkage with +2018 [rs419598]) have been studied extensively in relation to chronic periodontitis.[15] Kornman and colleagues[51] were the first to report that the combined presence of the minor allele of the *IL-1A* gene at position –889 and the minor allele of the *IL-1B* gene at position +3954 was associated with severity of chronic periodontitis, in particular in nonsmoking whites; these authors proposed this combination to be the "IL-1 composite genotype." Carriage rates of the IL-1 composite genotype vary across populations; for example, a low minor allele frequency ([MAF] < 5%) was seen in Asian populations compared with white populations. The IL-1 composite genotype and the other IL-1 candidate single-nucleotide polymorphisms (SNPs) are not associated with European patients with aggressive periodontitis.[45,52] A recent systematic review on *IL-1* gene polymorphisms in chronic periodontitis patients and controls in whites suggested evidence for the minor alleles in *IL-1A*, in *IL-1B* and the composite genotype to be risk factors.[53] However, the latter results also demonstrated significant heterogeneity among the included studies, indicating that some of the included studies may suffer from a type 1 error. In that respect, a recent

letter is useful for the evaluation of systematic reviews on genetic risk factors.[54]

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

- *GLT6D1*: In 2010, in the first genome-wide association study on periodontitis, *GLT6D1* was found to be associated with AgP.[55] *GLT6D1* encodes a protein belonging to a family of proteins that is characterized by a glycosyltransferase domain-1. It was shown that the rare allele of SNP rs1537415 resulted in impaired binding of the transcription factor GATA-3.
- *ANRIL:* This gene was identified as the first genetic risk factor of coronary artery disease.[56–59] In 2009, *ANRIL* was identified to be a shared genetic risk factor of coronary artery disease and aggressive periodontitis.[60] This association was further replicated in several independent aggressive and chronic periodontitis case-control samples of Northern European descent,[61] a combined group of aggressive periodontitis patients in a German and Northern Irish population,[62] and in a Turkish aggressive periodontitis case-control population.[45] Functional characterization of the molecular function of *ANRIL* showed, apart from others, a long-distance regulatory effect on the activity of the CAMTA1/VAMP3 region.[63] This region was previously shown to be associated with increased periodontal pathogen colonization.
- *COX-2:* Associations of *COX-2* with periodontitis were first identified in Taiwanese and Chinese case-control populations and subsequently validated in a Northwest-European population.[64–66] *COX-2* converts arachidonic acid into prostaglandin H_2, which is the precursor of PGE_2). PGE_2, which mediates proinflammatory and anti-inflammatory reactions in many tissues, is also partly responsible for the resorption of the alveolar bone during the pathogenesis of periodontitis.
- *DEFB1*: Genetic markers within *DEFB1* coding for beta defensin B1 were also validated for periodontitis.[67] In a fine mapping approach, SNP rs1047031 was best associated with both aggressive and chronic periodontitis, and the rare allele was predicted to impair a microRNA binding site at the 3'-untranslated region *(*UTR) of *DEFB1*. The antimicrobial peptide that is encoded by *DEFB1* was suggested to be responsible for maintaining a healthy status in the mucosal epithelia prior to infection with pathogenic bacteria.[68]

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

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

Table 2. Risk Assessment for Periodontitis

1. Estimate the relative contribution of genetic factors by the age of the patient and by family history
2. Smoking, including frequency, current use, and history
3. Hormonal variations such as those seen in:
   a. Pregnancy, in which increased levels of estradiol and progesterone may change the environment and permit the virulent organisms to become more destructive
   b. Menopause, in which the reduction in estrogen levels leads to osteopenia and eventually osteoporosis
4. Systemic diseases such as:
   a. Diabetes (duration and level of control are important)
   b. Osteoporosis
   c. Immune system disorders such as HIV
   d. Hematologic disorders such as neutropenias
   e. Connective tissue disorders such as Marfan's and Ehlers-Danlos syndromes
   f. Metabolic syndrome and obesity
5. Stress as reported by the patient
6. Nutritional deficiencies that may require a dietary analysis
7. Medications such as
   a. Calcium channel blockers
   b. Immunomodulatory agents
   c. Anticonvulsants
   d. Those known to cause dry mouth or xerostomia
8. Faulty dentistry such as overhangs and subgingival margins
9. Poor oral hygiene resulting in excessive plaque and calculus
10. History of periodontal disease

Sources: *J Dent Res* 2012;91:914–20; *Periodontol* 1994;65:260–7; *J Periodontol* 1995;66:23–9; *J Periodontol* 1999;70:711–23; *J Periodontol* 2000;71:1057–66; *J Periodontol* 2000;71:1215–23; *J Periodontol* 2000;71:1492–8. (Refs. 33–39).

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

ETIOLOGY AND PATHOGENESIS OF PERIODONTAL DISEASE

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

Table 3. Risk Reduction Strategies

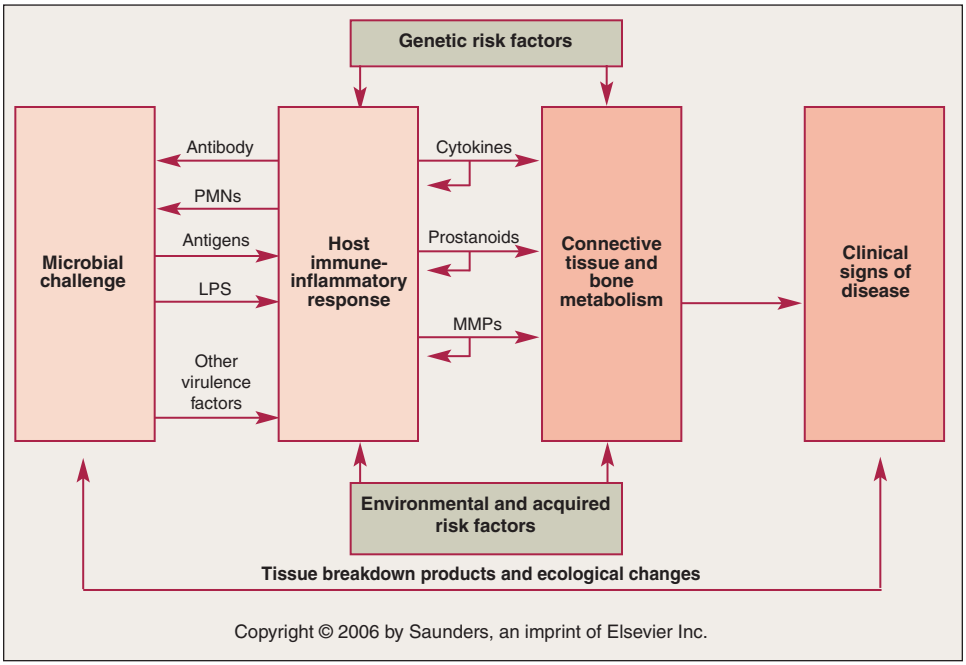
1. More frequent visits for those with a high estimated genetic predisposition; use of pharmacotherapeutics for the management of periodontitis
2. Smoking cessation, using one or more of the six approved regimens; these regimens rarely are successful as sole therapies (multiple forms of therapy often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

Source: *Dent Clin N Am* 2005;49:611–36.

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

To better treat and manage periodontal diseases, we need a more detailed understanding of periodontal pathogenesis (Figure 3).[70–72] The bacteria and their metabolic products (e.g., endotoxin) stimulate the junctional epithelium to proliferate and to produce tissue-destructive proteinases. This infection also increases the permeability of the junctional epithelium, which allows microbes and their products to gain access to the subepithelial connective tissue. Epithelial and connective tissue cells are thus stimulated to produce inflammatory mediators that result in an inflammatory response in the tissues. Microbial products also chemotactically attract a constant flux of proinflammatory cells migrating from the circulation to the gingival crevice. Neutrophils, or PMNs, are predominant in the early stages of gingival inflammation. Thus, an immune response is generated in the periodontal tissues, and proinflammatory cytokines such as IL-1β, TNF-α, and MMPs are produced by inflammatory cells recruited to the lesion site. The functions of PMNs include phagocytosis and destruction of bacteria. Initially, the clinical signs of gingivitis are evident. This response is essentially protective in nature to control the bacterial infection. In persons who are not susceptible to periodontitis, the primary defense mechanisms control the infection, and chronic inflammation (i.e., chronic gingivitis) may persist. However, in persons susceptible to periodontitis, the latter inflammatory process persists and eventually extends apically and laterally to involve deeper connective tissues and alveolar

Figure 3. Schematic Illustration of the Pathogenesis of Periodontitis

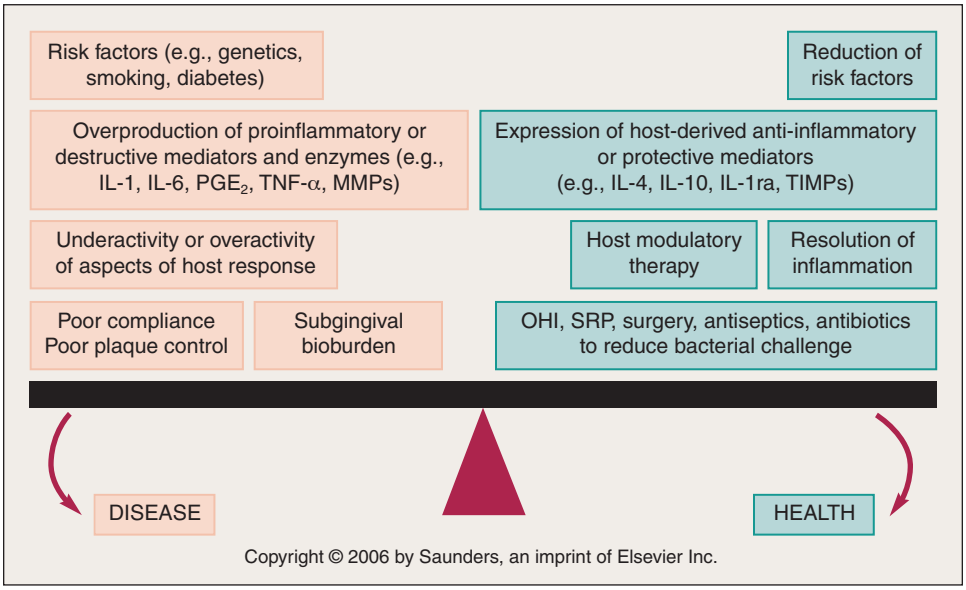


Source: *Carranza's Clinical Periodontology*, 10th ed. WB Saunders Company; 2006:275–82. With permission.

bone, recruiting monocytes and lymphocytes to the site of infection at later stages. These monocytes and macrophages are activated by the bacterial endotoxins such as LPS, leading to the production of high levels of prostaglandins (e.g., PGE_2), interleukins (e.g., IL-1α, IL-1β, IL-6), TNF-α, and MMPs by the host cells. The MMPs break down collagen fibers, disrupting the normal anatomy of the gingival tissues, resulting in destruction of the periodontal apparatus. If left untreated, the inflammation continues to extend apically, and osteoclasts are stimulated to resorb alveolar bone triggered by the high levels of prostaglandins, interleukins, and TNF-α in the tissues. The elevated levels of proinflammatory mediators and MMPs are counterbalanced by a protective response in the host with elevations in anti-inflammatory mediators such as the cytokines IL-4 and IL-10, as well as other mediators such as IL-1ra (receptor antagonist) and tissue inhibitors of matrix metalloproteinases (TIMPs) (Figure 4).[71,72] Under normal healthy conditions, the anti-inflammatory mediators are balanced with inflammatory mediators, thereby controlling tissue destruction. If an imbalance occurs, with excessive levels of the proinflammatory mediators, upregulated MMP expression, and insufficient levels of protective anti-inflammatory mediators, the loss of periodontal connective tissue and bone will occur.

Thus, plaque bacteria initiate the disease, followed by an inflammatory response mounted by the host producing excessive levels of proinflammatory mediators (prostaglandins, interleukins) and enzymes (MMPs) and resulting in the destruction of periodontal tissue. If this inflammation continues and extends farther apically, more bone is resorbed, and more periodontal tissue is broken down. This leads to deeper and deeper pockets and associated attachment and bone loss revealed as the clinical and radiographic signs of periodontitis. In people with periodontitis, these inflammatory mediators (e.g.,

Figure 4. The Periodontal Balance



Source: *Carranza's Clinical Periodontology*, 10th ed. WB Saunders Company; 2006:275–82. With permission.

prostanoids and cytokines) and local oral bacteria eventually enter into the circulation, stimulating the liver to produce acute-phase proteins (notably C-reactive protein [CRP]), but also fibrinogen, haptoglobin, etc.), which are biomarkers of a systemic inflammatory response. Emerging evidence supports the fact that this chronic systemic inflammatory response driven by the chronic infection and inflammation associated with periodontitis eventually increases a person's risk for developing a number of systemic diseases, including cardiovascular diseases, adverse pregnancy outcomes, and diabetic complications. In a recent workshop jointly held by the European Federation of Periodontology and the American Academy of Periodontology, potential mechanisms linking periodontitis to systemic conditions were discussed. Metastatic infections, innate inflammatory responses, and adaptive immunity were proposed as three basic mechanisms for this association.[73] Although the causative relation between periodontitis and systemic diseases cannot be established, current studies have identified shared common risk factors and plausible mechanistic pathways. Despite our gap in research, it is clear that periodontitis can be considered a contributing factor to many systemic conditions and diseases. The details are presented in other chapters of this book.

MANAGEMENT OF PERIODONTAL DISEASES

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

In the past, treatments that focused on reduction of the microbial load were basically the sole consideration for all periodontal therapy. Currently, because of increased knowledge of the host response, host modu-

lation therapies have been used as adjunctive approaches to both nonsurgical and surgical treatments to aid in reducing probing depths, increasing clinical attachment levels, and regenerating the lost attachment apparatus. In the future, more effective therapeutic approaches are likely to include multiple synergistic host modulation therapies combined with treatments that target the microbial etiology.

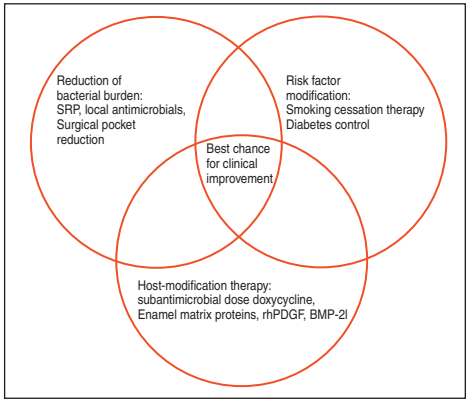
In addition to reducing the bacterial challenge and modulating the host response, reduction of risk is also a key treatment strategy when managing periodontitis. For example, it is known that smoking can contribute to periodontal disease and can make the management of the disease more difficult.[74,75] Therefore, smoking cessation would benefit all patients with periodontitis. Smoking cessation can be undertaken in the dental office (if the staff is appropriately trained) or in a medical setting. A variety of medications aid in smoking cessation, counseling is important, and alternative medicine such as acupuncture may be used. When poorly controlled, systemic diseases such as diabetes increase a patient's risk for periodontitis.[76] When treating people with diabetes, knowing the patient's level of diabetic control is important in assessing risk. Collaboration with medical colleagues to improve control of diabetes is essential to ensure successful periodontal treatment. Periodontitis is also prevalent in patients with cardiovascular disease. Periodontal therapy may have a positive impact on the overall health status of these individuals.

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

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

It is the responsibility of the dentist to provide appropriate treatments on an individual basis. A combination of treatment approaches for each patient provides optimal periodontal treatment and results in a better prognosis (Figure 5).[77]

Figure 5. Complementary Treatment Strategies in Periodontitis



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

The Antimicrobial Approach

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

Mechanical Therapy

Preventive and maintenance strategies for the patient include adequate home care. Brushing and flossing make up the most basic approach to microbial reduction and control for the patient. Good oral hygiene can effectively reduce bacterial loads to prevent gingivitis and aid in the treatment and management of periodontitis. This simple approach

relies on an individual's knowledge of the correct techniques and compliance with home care instructions. The Bass technique of brushing for 2 minutes twice daily, along with flossing once daily, is the current recommendation. The use of end tuft and proxybrushes as well as powered toothbrushes can improve home care in certain patients.

Routine scaling of teeth every 6 months by the dental care provider is also a key component in treating and preventing gingivitis. Scaling and root planing is the traditional nonsurgical treatment of periodontitis, with many clinical studies demonstrating that it effectively reduces the microbial load and leads to reductions in bleeding on probing, reduces probing depths, and allows for gains in clinical attachment.[78] However, this procedure can be very time-consuming and is operator-dependent.[79] Surgical procedures can be used to visualize remaining subgingival calculus, and through resective or regenerative procedures will also lead to decreased probing depths that are more manageable for long-term maintenance of patients with periodontitis. Although nonsurgical and surgical procedures aimed at reducing the bacterial load, reducing probing depths, and restoring the attachment apparatus continue to be the most widely used methods of treating periodontitis, these strategies alone may be insufficient at reducing the bacterial load adequately. It has been recognized that significant numbers of microorganisms may be left behind, requiring additional therapeutic approaches. Many putative pathogens remain within the oral cavity at distant sites, allowing for repopulation in the future. Therefore, the need for the development of chemotherapeutic agents as adjuncts to mechanical debridement was deemed necessary.

Antiseptics and Toothpastes

Antiseptic Mouthrinses

Unfortunately, many patients are not compliant with brushing and flossing. They lose motivation and do not spend a sufficient amount of time brushing or flossing on a daily basis.[80] For this reason, oral antiseptic rinses have been developed. Antiseptic mouthrinses have been found to improve on plaque reduction as well as reductions in gingival inflammation seen with brushing and flossing alone. Therefore, antiseptic rinses have been accepted as adjuncts to the mechanical approach of brushing and flossing. Two clinically proven American Dental Association (ADA)-accepted antiseptic mouthrinses are Peridex® (chlorhexidine gluconate) and the four essential oils in Listerine®. An association between oral conditions such as periodontal disease and several respiratory conditions such as pneumonia and chronic obstructive pulmonary disease has been noted. The plaque surrounding the teeth is an excellent harbor for respiratory pathogens. Studies have shown that using a chlorhexidine oral rinse can reduce the risk of pneumonia in institutionalized patients with poor oral hygiene.[81]

Locally Applied Antiseptics

Periochip® contains the active ingredient of chlorhexidine gluconate (2.5 mg) that is released into the pocket over a period of 7 to 10 days. It has been found to suppress the bacteria in the pocket for up to 11 weeks after application.[82] Periochip is the only ADA-approved locally applied antiseptic used as an adjunct to scaling and root planing procedures to aid in the reduction of pocket depths.

Dentifrices

Major improvements in the oral health of populations in developed countries have been seen over the last 50 years. Most of this has resulted from reduction in the caries rate of about 50%. The principle reason for this is thought to be the addition of fluoride to dentifrices. Modern commercial dentifrices, in addition to providing the anticaries effects

of fluoride, also contribute to reduction of plaque, gingivitis, calculus formation, and tooth stain. They reduce halitosis and result in a clean, fresh mouth feel. Two dentifrices available in the United States that are approved by the ADA for their effects on the reduction of gingivitis include a stannous fluoride/sodium hexametaphosphate dentifrice and a sodium fluoride/triclosan/copolymer dentifrice.

There is a large amount of literature on the latter dentifrices and other dentifrices containing chlorhexidine and other agents in the control of gingivitis. A review of the role of triclosan/copolymer toothpaste in the management of periodontal disease was carried out by Blinkhorn and colleagues.[83] They found approximately 200 articles dating from 1998 to 2008 relating to triclosan/copolymer dentifrice and concluded that twice daily use of this dentifrice will result in clinically significant improvements in plaque control and gingivitis with slowed progression of periodontal disease. Further long-term studies extending over several years with these dentifrices are needed to establish whether the short-term effects will be sustained over the long term and indeed result in preventing the initiation of periodontitis and slowing the progression of already existing periodontitis.

Furthermore, the Cochrane Oral Health Group has recently published a review of 30 clinical trials that included 14,835 participants and examined the effect of triclosan/copolymer as compared to an ordinary fluoride toothpaste on various endpoints and concluded that there was "moderate-quality evidence" supporting the fact that toothpaste containing triclosan/copolymer reduced plaque and gingivitis, including gingival inflammation and gingival bleeding, as compared to a regular fluoride toothpaste.[84]

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

Antibiotics

Locally Applied Antimicrobials

Atridox: An FDA-approved locally delivered tetracycline system, Atridox® is a 10% formulation of doxycycline in a bioabsorbable, "flowable" poly(DL-lactide) and *N*-methyl-2-pyrrolidone mixture delivery system that allows for controlled release over 7 days. This system is applied subgingivally to the base of the pocket through a cannula. Atridox is a resorbable, site-specific, locally applied antibiotic proven to promote clinical attachment gains and reduce pocket depths, bleeding on probing, and levels of pathogenic bacteria for up to 6 months after placement.[70] Periodontal disease has been linked to systemic diseases such as diabetes. Research has shown that periodontal treatment with topically delivered doxycycline (10 mg) in periodontal pockets produces favorable clinical results in diabetic patients.[85]

Arestin: An FDA-approved minocycline microsphere system, Arestin® is bioadhesive and bioresorbable, allowing for sustained release of 1 mg of minocycline. Arestin can be used as an adjunct to scaling and root planing procedures for reduction of pocket depth in patients with adult periodontitis. Arestin is delivered to sites of 5 mm or greater. Periodontitis has been associated

with increased systemic inflammation, which is directly linked to diabetes and cardiovascular diseases. Recent research has shown that periodontal therapy with local Arestin administration resulted in decreased HbA1c levels in diabetic subjects[86] and significant reductions in systemic inflammatory biomarkers, which are risk factors for cardiovascular disease.[87,88]

Systemic Antimicrobials

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

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

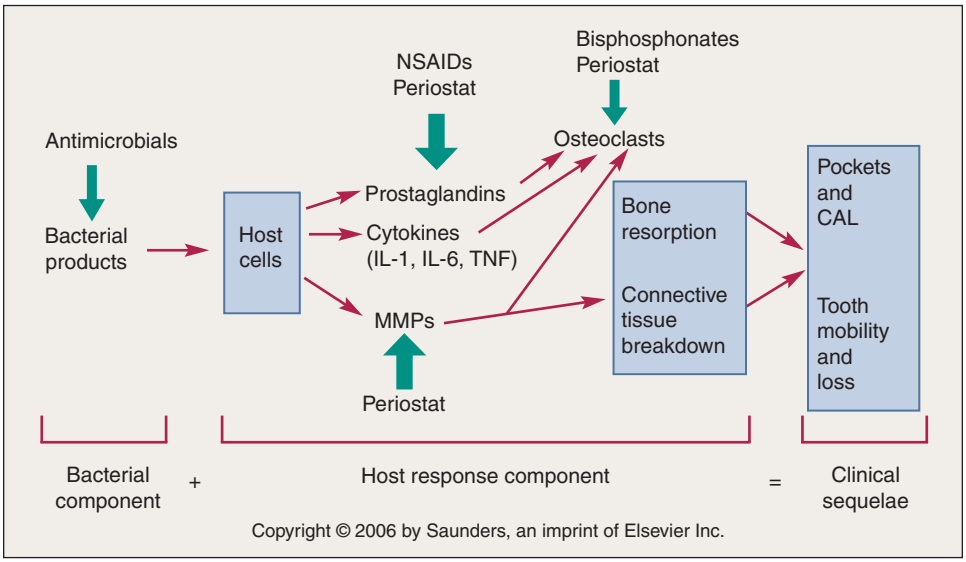
Researchers have shown that periodontal treatment can improve on systemic diseases known to be associated with periodontitis, such as diabetes. Periodontal therapy, including the use of antibiotics and extraction of hopeless teeth, reduced the number of insulin injections required daily in young patients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

Host Modulation Therapy

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

Host modulation was first introduced to dentistry by Williams[96] and Golub and colleagues.[97] Williams stated: "There are compelling data from studies in animals and human trials indicating that pharmacologic agents that modulate the host responses believed to be involved in the pathogenesis of periodontal destruction may be efficacious in slowing the progression of periodontitis."[96] Golub and colleagues discussed "host mod-

Figure 6. Potential Adjunctive Therapeutic Approaches



Source: *Carranza's Clinical Periodontology*, 10th ed. WB Saunders Company; 2006:275–82. With permission.

ulation with tetracyclines and their chemically modified analogues."[97] A variety of drug classes have been evaluated as host modulation agents, including the non-steroidal anti-inflammatory drugs (NSAIDs), bisphosphonates, tetracyclines (Figure 6), enamel matrix proteins, growth factors, and bone morphogenetic proteins.

Systemically Administered Agents

Subantimicrobial-Dose Doxycycline

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

1. Can effectively reduce the levels of localized and systemic inflammatory mediators (hsCRP) in osteopenic patients in addition to improving on the clinical measurements of periodontitis[98,99]
2. Has been shown to reduce systemic inflammatory biomarkers (hsCRP) in patients with cardiovascular disease[100]
3. Decreases HbA1c in patients who are taking normally prescribed hypoglycemic agents[101]

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

Locally Administered Agents

Enamel Matrix Proteins, Growth Factors, and Bone Morphogenetic Proteins

A number of local host modulation agents have been investigated for potential use as adjuncts to surgical procedures to improve periodontal health. These have included

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

CONCLUSION

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

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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 Löe et al.[1] in 1965. Using a novel—now classic—experimental design, it was demonstrated that when students with healthy gingiva abstained from oral hygiene practices for 10 to 21 days, marginal inflammation of the gingiva (gingivitis) developed as a result of plaque accumulation. When oral hygiene was reinstated, gingival health returned. Today, in vitro and in vivo experiments, along with histologic assessments of inflamed and healthy gingiva, have provided a clearer understanding of the nature of the interactions between bacteria and host cells. However, current understanding of the etiology and pathogenesis of the periodontal diseases is far from complete.

Periodontal bacteria possess a plethora of virulence factors that, upon interaction with host cells, induce production of inflammatory mediators at the gingival level. These mediators are thought to be important for the initiation and progression of an inflammatory response, which though intended to eliminate the bacterial challenge, inevitably results in tissue damage when the bacterial challenge persists. It is also important to note that inflammation is not confined solely to periodontal tissues. Bacteria and inflammatory mediators may enter blood circulation to induce systemic inflammation. Evidence is increasing that cardiovascular disease (CVD),[2] adverse pregnancy outcomes,[3] diabetes mellitus,[4] and possibly cancer[5,6] are associated with oral organisms entering the circulation and elevated systemic inflammation. The coexpression of inflammatory periodontitis with other inflammatory diseases suggests a common pathway in pathogenesis.

Depending on the effectiveness of the innate immune response, bacterial infection may persist and lead to perpetuation of inflammation, which may become chronic with the development of acquired immunity. However, if the infection is cleared, then resolution of inflammation occurs with the return of tissue homeostasis without permanent damage. Recent discoveries have altered our understanding of inflammation resolution and return of tissue homeostasis. We now understand that resolution of inflammation is an active process, not the passive decay of proinflammatory signals as once thought. The ability to manipulate these processes may provide a new treatment paradigm for both local and systemic inflammatory diseases.[7]

Chapter Goals

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

of inflammatory diseases; and (5) introduce new strategies directed at mechanisms of inflammation resolution that may be used in treating inflammatory diseases.

PART I: INFLAMMATION AT THE GINGIVAL LEVEL

Periodontal disease is an inflammatory disorder of the supporting tissues of the teeth in a susceptible host. Bacteria in the oral cavity colonize the teeth, the gingival sulcus, and eventually the periodontal pocket, forming an organized biofilm. Depending on the stage of maturation, the biofilm may consist of several hundred bacterial species, many of which have yet to be identified.[8] Some of these species are associated with health, whereas others are associated with pathology.[9] However, the identity of the organisms that actually initiate disease remains unknown.

Bacterial Components

The formation of organized biofilms enhances the ability of bacteria to survive. Bacteria have also evolved a variety of virulence factors to further enhance their survival, such as toxins, proteases, and glycosidases. Virulence factors are presumably intended to hide the bacteria from host detection as well as to provide essential molecules for nourishment. Conversely, the host has evolved mechanisms for detection of bacteria through the recognition of structural components of the bacterial surface, such as lipopolysaccharide (LPS), peptidoglycan (PGN), and other cell surface components such as fimbriae, which perform essential physiologic functions for the bacteria. Variations of these bacterial components may be seen among various species, or even among different strains of the same species. Despite their structural heterogeneity, most of these molecules have conserved motifs known as *pathogen-associated molecular patterns* (PAMPs), which are recognized by host cell receptors called *pattern recognition receptors* (PRRs). These highly conserved innate immune receptors evolved for detection of invading bacteria. Binding of PAMPs by PRRs activates specific signaling pathways in host cells that are important for the initiation of an inflammatory response. Although this response is intended to eliminate the microbial challenge, the inflammatory mediators that are secreted may lead to further tissue damage if bacterial clearance is not achieved. Today, the most studied bacterial factors are LPS, PGN, lipoteichoic acids (LTAs), fimbriae, proteases, heat-shock proteins (HSPs), formyl-methionyl peptides, and toxins. Host PRRs include the Toll-like receptors (TLRs) and other G-protein–coupled receptors (GPCRs). Table 1 presents a summary of the results by actions of various bacterial factors after interaction with specific host cells.[10]

Bacteria and Gastrointestinal Equilibrium

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

Current understanding of the steps leading to periodontal disease includes periodontal bacteria attaching to epithelial cells using their fimbriae and PRR recognition of PAMPs, inducing epithelial cell secretion of

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

	Responses of Host Cells				
Bacterial Factor	**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_2 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.[10]

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

Bacteria in Connective Tissue

Bacteria and/or their virulence factors found in the periodontal pocket epithelium and the connective tissue directly stimulate host cells residing in this area, such as leukocytes, fibroblasts, mast cells, endothelial cells, dendritic cells, and lymphocytes. Neutrophils, macrophages, fibroblasts, and mast cells release more proinflammatory cytokines (TNF-α, IL-1β, IL-6, IL-12), chemoattractants (IL-8, MIP-1-α, MIP-2, MCP-1, MCP-5), and prostaglandin E_2 (PGE_2) in the connective tissue. In addition, degranulation of mast cells results in the secretion of histamine and leukotrienes, further amplifying the inflammatory cascade.[12,13]

Mediators that are secreted from activated host cells (e.g., IL-1β, TNF-α, PGE_2, and histamine) further assist bacterial virulence factors in the activation of endothelial cells. This leads to secretion of more chemokines (IL-8, MCP-1) and expression of adhesion molecules on the surface of endothelial cells, which are important for leukocyte extravasation (P- and E-selectins as well as intercellular adhesion molecule 1 [ICAM-1] and ICAM-2).[14] Specifically, P- and E-selectins interact with glycoproteins on leukocytes, allowing the cells to adhere reversibly to the vessel wall and causing circulating leukocytes to appear to "roll" along the activated endothelium. Then, IL-8 and other chemokines, bound to proteoglycans on the surface of leukocytes, trigger a conformational change of integrins (LFA-1, CD11b: CD18). As a result, adhesive properties increase dramatically, and leukocytes attach firmly to ICAM-1 expressed on endothelial cells. Tumor necrosis factor-α (TNF-α), PGE_2, and histamine increase vascular permeability, allowing leukocytes to squeeze between the endothelial cells, thereby entering the connective tissue in a process known as *diapedesis*. Finally, chemokines, such as IL-8, which are produced at the site of infection and bind to proteoglycans of the extracellular matrix, and along with bacterial chemoattractants (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, which subsequently differentiate into macrophages. The interaction of these cells with bacterial virulence factors induces further activation, which enhances their phagocytic activity by increasing the production of nitric oxide (NO) and the expression of complement receptors (CR3). If the innate immune response is successful, the bacteria are eliminated, and resolution of inflammation follows. However, persistence of bacteria leads to a chronic response characterized by extracelluar release of neutrophil granule contents, including degradative enzymes and reactive oxygen species that spill into the extracellular milieu, leading to local tissue damage and amplification of acute inflammatory signals.[15]

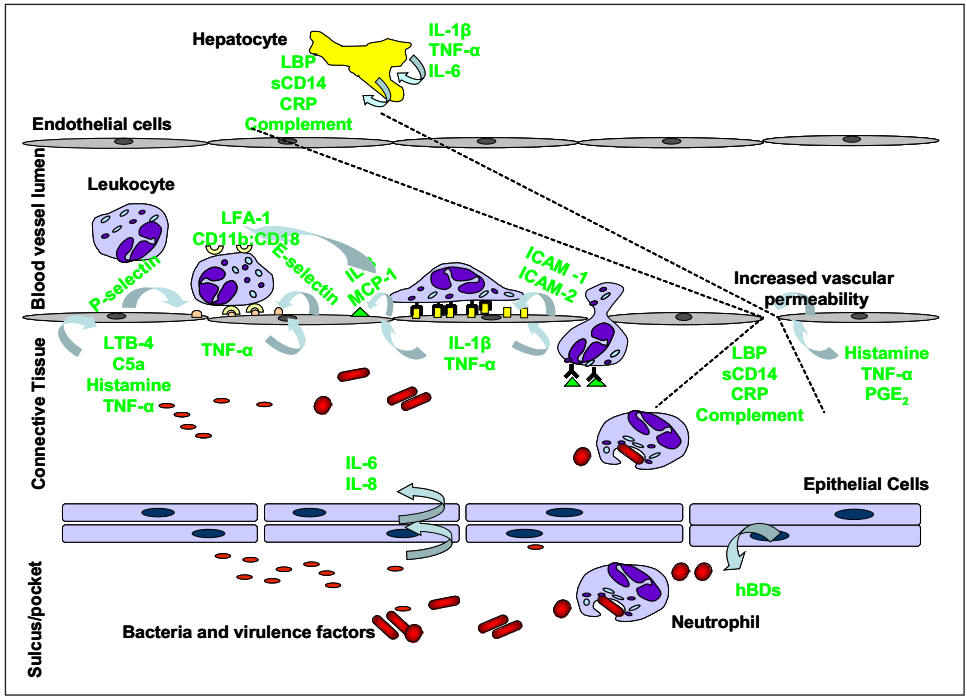
Proinflammatory cytokines (TNF-α, IL-1β, IL-6) from the site of inflammation enter the circulation and reach the liver, where they activate hepatocytes. This leads,

among other events, to the synthesis of plasma proteins known as acute-phase proteins, including LPS-binding protein (LBP) and CD14, which are important for the recognition of bacterial virulence factors. Complement proteins and C-reactive protein (CRP) contribute by opsonizing bacteria, thereby aiding in recognition for phagocytosis. These products enter the circulation and, because of increased vascular permeability, diffuse into the inflamed gingival tissues. Figure 1 illustrates the initiation of inflammation at the gingiva.

The Immune Response

If the infection persists, the acquired immune response is initiated, and the established lesion is created, as described by Page and Schroeder.[16] Briefly, dendritic cells within the epithelium take up bacterial antigens and migrate to the peripheral lymph nodes. The antigens are processed into a form that is recognizable by the immune system; that is, the antigenic peptide binds to a class II major histocompatibility complex (MHC) receptor that consequently "presents" the antigen. As a result, antigen-specific effector

Figure 1. Initiation of Inflammation at the Gingival Level



Neutrophils in the gingival crevicular fluid (GCF) and epithelial cells comprise the first line of defense to prevent bacteria from invading the host. The interaction of the bacterial biofilm with epithelial cells leads to activation and secretion of proinflammatory cytokines (green). Bacteria and their virulence factors (red) may penetrate the epithelial lining and enter the connective tissue. In this compartment, they may interact with host cells, such as macrophages, fibroblasts, and mast cells to stimulate these cells to release more proinflammatory mediators such as TNF-α, IL-1β, IL-8, LTB-4, and histamine. These mediators, along with bacteria/virulence factors, may activate endothelial cells to attract circulating leukocytes in the connective tissues. In this compartment, phagocytic cells take up bacteria and their antigenic molecules. This process, if further enhanced by acute-phase response proteins, such as CRP, which are produced from activated hepatocytes, enter the connective tissue via circulation as a result of increased vascular permeability. If the noxious agents are eliminated, resolution of inflammation follows. However, if the bacterial challenge persists, the more efficient adaptive immune response takes over.
Adapted from *J Clin Periodontol* 2005;32(Suppl 6):57–71.[10]

T cells and antibody-secreting B cells are generated by clonal expansion and differentiation over the course of several days, during which time the induced responses of innate immunity continue to function. Eventually, antigen-specific T cells, and then antibodies, are released into the blood to target the infection site.[17] Macrophages that engulf bacteria at the site of infection express costimulatory molecules (MHC II) and present bacterial antigens on their surface. Antigen-specific T cells see the antigens and activate the macrophages, enabling them to destroy intracellular bacteria more efficiently.

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

Summary of Part I

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

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

PART II: SYSTEMIC INFLAMMATION DUE TO PERIODONTAL INFECTION

Despite the localized nature of periodontal disease, infection of the sulcus/periodontal pocket with periodontopathogens may be responsible for inflammatory responses that develop beyond the periodontium. To date, several biologic pathways have been recognized that present reasonable hypotheses for periodontal disease induction of systemic inflammation.

Inflammatory Pathways

In health, the sulcular epithelium, along with innate immune molecules, acts as a natural barrier system that prevents bacterial penetration. Hence, only a small number of bacteria, mostly facultative anaerobes, manage to enter the gingival tissues and the bloodstream. However, in cases of periodontal disease, the inflamed and ulcerated pocket epithelium is vulnerable to bacterial penetration and forms an easy port of entry for the bacteria. This leads to an increase in the number of periodontopathogens, mainly anaerobic gram-negative, in the gingival tissues and consequently in the circulation. Bacteremia can be further aggravated after mechanical irritation of the inflamed gingiva

during tooth brushing, chewing, oral examination, and scaling and root planing.[20] The microorganisms that gain access to the blood are usually eliminated by the reticuloendothelial system within minutes (transient bacteremia) and usually without any other clinical symptoms except possibly a slight increase in body temperature.[21] 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.[22] Bacteria and bacterial antigens that are systemically dispersed can trigger significant systemic inflammation. Leukocytes as well as endothelial cells and hepatocytes respond to bacteria/virulence factors, producing proinflammatory immune mediators. Moreover, soluble antigens may react with circulating specific antibodies, forming macromolecular complexes that may further amplify inflammatory reactions at sites of deposition.[23]

Proinflammatory Mediators

A different biologic pathway that may explain the systemic inflammation induced by periodontal disease involves proinflammatory mediators, such as IL-1β, IL-6, TNF-α, and PGE_2, which are produced by host cells in the inflamed gingival tissues. These mediators are secreted locally in response to bacterial challenge, but may spill into the circulation and exert distant or systemic effects.

Specifically, cytokines may reach distant sites and further activate endothelial cells, leading in some cases to endothelial dysfunction.[24] Moreover, the circulating mediators, because of the increased vascular permeability at the sites of inflammation, may enter inflamed tissues and exacerbate the inflammatory processes. However, the most important impact of these circulating mediators is systemic. Proinflammatory cytokines may induce leukocytosis, which is characterized by an increase in circulating neutrophils. Moreover, IL-1β, TNF-α, and especially IL-6 may reach the liver and activate hepatocytes to produce acute-phase proteins. The most important acute-phase reactants are CRP, serum amyloid A (SAA) protein, fibrinogen, plasminogen activator inhibitor 1 (PAI-1), complement proteins, LBP, and soluble CD14. These proteins are released in the plasma and possess a wide variety of functions, such as proinflammatory activities and stimulation of tissue repair mechanisms. The production of these proteins is part of an acute-phase response that is characterized by fever, increased vascular permeability, and a general elevation of metabolic processes. An acute-phase response starts within hours or days of most forms of acute tissue damage or inflammation and, despite its name, persists with chronic inflammation. As acute-phase reactants enter the circulation, they may return to the inflamed gingival tissues. However, since they circulate throughout the body, they can affect ectopic sites, causing inflammation or exacerbation of existing inflammatory processes. This concept takes on new meaning in light of the recent implication of CRP in the pathogenesis of CVD.[25]

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

Acute-Phase Proteins

CRP is produced mainly by the liver, but it

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

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

Serum Amyloid A

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

Fibrinogen

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

Plasminogen Activator Inhibitor 1

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

Complement Proteins

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

LPS-Binding Protein and Soluble CD14

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

Systemic Cellular and Molecular Markers of Inflammation

Periodontal infection may induce an inflammatory response that is not limited to the tissues surrounding the teeth, but is also extended systemically. The main cellular and molecular markers of systemic inflammation induced by periodontal disease include the increased number of peripheral leukocytes, the higher concentrations of serum antibodies against periodontopathogens, and the ele-

vated levels of circulating proinflammatory cytokines and acute-phase proteins.

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

Peripheral Blood Leukocytes

In patients with periodontitis, leukocyte counts have been shown to be slightly elevated compared with the counts of healthy subjects, though not always significantly.[29] 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.[30] Polymorphonuclear leukocytes are the main leukocytes that are increased; these cells are possibly recruited at higher levels during episodes of bacteremia and leakage of bacterial virulence factors during periodontal disease.

Serum Antibodies Against Periodontopathogens

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

Serum Proinflammatory Cytokines

In healthy subjects, the levels of circulating proinflammatory cytokines are very low or nondetectable. However, in patients with periodontitis, several proinflammatory cytokines may spill into the bloodstream and increase their concentration in the plasma. Of the proinflammatory mediators studied, only IL-6 levels have been consistently shown to be elevated in the serum. This increase is related to the extent and severity of inflammation in periodontal tissues.[31] However, controversial reports have been published on the impact of periodontal therapy on IL-6 levels, suggesting the need for further research on the topic. Finally, most of the studies looking at the levels of serum IL-1 and TNF-α among healthy and periodontitis patients failed to report any differences, and in most cases cytokine levels were not measurable.[32]

Acute-Phase Proteins

The levels of several acute-phase reactants, such as CRP, fibrinogen, LBP, and soluble CD14 have been studied and have been shown to be elevated in patients with periodontal disease. However, the acute-phase proteins that have received the most attention and are consistent markers of systemic inflammation in periodontal disease are CRP and fibrinogen. A large number of studies, both in animal models and in humans, have revealed a positive association between periodontal disease and circulating CRP levels, whereas a recent meta-analysis limited to human studies has confirmed that plasma CRP is elevated in patients with periodontitis compared with CRP in healthy persons.[33] Moreover, this increase was proportional to the extent and severity of the disease. Several studies report a decrease of plasma CRP after periodontal intervention, but there is modest evidence that periodontal therapy lowers the levels of this protein. Finally, in several studies, the levels of fibrinogen have also been found to be elevated in patients with periodontitis compared with fibrinogen levels in healthy individuals.[34] However, no available evidence exists to support that theory 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.[35] This theory held that foci of sepsis were responsible for the initiation and progression of a variety of inflammatory diseases, such as arthritis, peptic ulcers, and appendicitis. As a result, therapeutic full-mouth extractions became a common dental practice. However, many teeth were extracted without evidence of infection. When it was finally realized that there was no therapeutic benefit, the theory was discredited and the practice abandoned. During the final two decades of the twentieth century—as our knowledge concerning the inflammatory component of systemic diseases was enriched and our understanding of the relation of periodontal disease to systemic inflammation increased—the idea that periodontal infection may affect the progression of systemic disorders such as CVD, adverse pregnancy complications, diabetes mellitus, and other diseases re-emerged.

Hence, to date, a large volume of data has been gathered evaluating the possible association of periodontal disease with systemic diseases. Observational studies have primarily used several clinical parameters such as probing pocket depth, clinical attachment loss, and bleeding on probing to assess the severity of periodontal disease and consequently the risk for systemic exposure. However, the results of these studies are not always consistent, indicating that these parameters separately may not be able to reflect the inflammatory burden at the gingival level. Thus recently, Nesse et al.[36] introduced a new index that incorporates the latter parameters. This index calculates the surface area of the inflamed periodontal tissues (periodontal inflamed surface area, PISA), which may reflect, in a way, the magnitude of systemic inflammatory exposure posed by periodontal disease. This may be important because increasing evidence suggests that elevated levels of the markers of systemic inflammation are associated with an increased risk for systemic diseases.

Cardiovascular Disease

There is now abundant clinical evidence demonstrating that many biomarkers of inflammation are elevated years in advance of first-ever myocardial infarction (MI) or thrombotic stroke, and that these same biomarkers are highly predictive of recurrent MI, recurrent stroke, and death due to CVD.[2] Moreover, studies demonstrate that serum IL-6 levels were significantly elevated in subjects who subsequently experienced an MI compared with IL-6 levels of age-matched controls.[37] Similarly, plasma levels of soluble P-selectin, soluble CD40L, and macrophage-inhibitory cytokine-1 all were significantly increased in healthy subjects who subsequently developed CVD events compared with those of matched controls.[38] Elevated plasma concentrations of TNF-α have also been associated with CVD, and specifically with recurrent nonfatal MI or other CVD events. Moreover, TNF-α levels were persistently higher among post-MI patients at increased risk for recurrent coronary events.

Besides these proinflammatory cytokines, several acute-phase reactants have also been associated with CVD. One of the factors with the strongest evidence as a biomarker for predicting CVD events is CRP (specifically, high-sensitivity CRP, hsCRP). When measured in the blood, hsCRP proved to be a strong, independent predictor of future MI and stroke among apparently healthy asymptomatic men. Also, the relative risk for first MI and ischemic stroke increased significantly with each increasing quartile of baseline concentrations of CRP.[39] As described already, CRP may contribute to the initiation and development of atherothrombotic lesions not only by upreg-

ulating the expression of proinflammatory cytokines, but also by mediating proliferation and activation of smooth muscle cells and by activating the procoagulant system. This last property may be further enhanced by another acute-phase protein, fibrinogen, which is often found to be elevated in patients with CVD.

Adverse Pregnancy Outcomes

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

Diabetes Mellitus

Finally, systemic inflammation has been associated with both type 1 and type 2 diabetes mellitus. Recent studies suggest that in type 1 diabetes, the levels of systemic markers of inflammation, such as CRP, do not differ between healthy persons and persons for which type 1 diabetes has been just diagnosed. However, the levels of circulating CRP are significantly higher in those with long-term diabetes.[40] It is also believed that inflammatory processes may have a more pronounced effect on the development of complications of type 1 diabetes. Thus, elevated levels of plasma CRP and of the proinflammatory soluble adhesion molecule, vascular cell adhesion molecule-1 (VCAM-1) have been found in patients with microvascular disease compared with those without microvascular disease.

In those with type 2 diabetes, inflammatory processes are more strongly associated with the development of the disease. Systemic markers of inflammation are found to be increased in healthy persons who develop type 2 diabetes later in life. Among Pima Indians, a population in whom type 2 diabetes is highly prevalent, subjects with white blood cell counts within the highest tertile were more likely to develop type 2 diabetes over a period of 20 years compared with those in the lowest tertile. Moreover, in two other studies, healthy persons demonstrating serum levels of CRP and IL-6 within the highest quartiles were more likely to develop type 2 diabetes in the next 4 to 7 years compared with those in the lowest quartile.[4] Similar results were found with increased levels of PAI-1, another acute-phase protein. Insulin resistance, which is associated with type 2 diabetes and usually precedes the development of frank diabetes, may also be affected by preexisting systemic inflammation, since several proinflammatory and acute-phase proteins, such as TNF-α, IL-6, MCP-1, PAI-1, and SAA, are associated with the induction of insulin resistance.[41]

Summary of Part II

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

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

Inflammation is thought to play a central role in the progression of periodontal disease and a number of systemic diseases. Experiments in animal models and in man have demonstrated that periodontal destruction is mediated primarily by the inflammatory response, although periodontal pathogens are a necessary etiologic factor.[22,42,43] Genetic polymorphisms and other factors may also be responsible for a hyperinflammatory phenotype, which may further affect the susceptibility of the host to periodontal disease and tissue destruction. Currently, it is believed that in chronic periodontal disease, destruc-

tion does not follow a linear pattern with time, but occurs in random bursts with periods of remission and exacerbation. However, the reasons behind this random progression are not fully understood. Disease progression becomes even more enigmatic considering that it is not always clear why a chronic inflammation of the gingiva remains as gingivitis in some patients and progresses to periodontitis in others. Regardless of the nature of periodontal disease progression, the perpetuation of the inflammatory process in the gingiva may lead to a chronic low-grade systemic inflammatory response, which in turn potentially contributes to the progression of systemic diseases.

Process of Inflammatory Resolution

The landmark events during inflammation include the accumulation of leukocytes in the infected area and phagocytosis of the bacteria and/or their virulence factors. As part of the inflammatory process, activation of neutrophil lysosomal phospholipase releases free arachidonic acid from membrane phospholipids. Once free arachidonic acid is available, two separate pathways can be initiated: (1) the cyclooxygenase (COX) pathway, which leads to the production of prostaglandins (e.g., PGE_2, prostacyclins, and thromboxanes), and (2) the lipoxygenase (LO) pathways, which lead to the production of a series of hydroxyl acids characterized by the 5-LO products, the leukotrienes (e.g., LTB4). There are three cell type-specific LOs: the 5-LO from myeloid cells, the 12-LO from platelets, and the 15-LO of epithelial and endothelial cells. PGE_2 is a potent activator of osteoclast-mediated bone resorption, and with other eicosanoids mediates inflammation and periodontal tissue destruction. LTB4 attracts neutrophils, stimulates the release of granule associated enzymes from neutrophils, and contributes to proinflammatory processes and to further tissue damage.

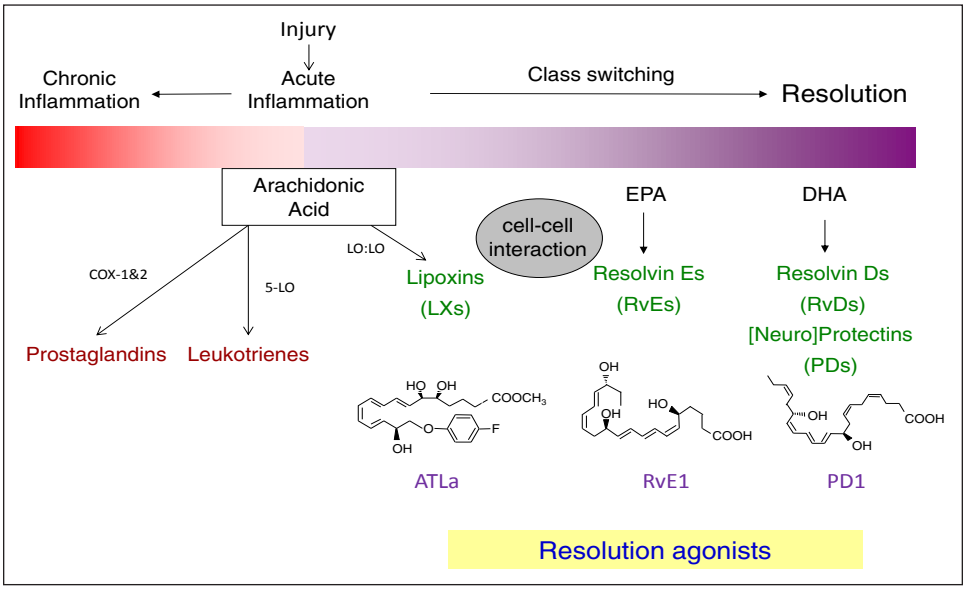
Returning to Homeostasis

After inflammation reaches its peak, resolution of inflammation occurs with the reduction or removal of leukocytes and debris from inflamed sites with a return to homeostasis.[7] Until recently, resolution of inflammation was considered to be a passive process in which the lack of bacterial stimuli decreased the production of inflammatory mediators, which in turn reduced the inflammatory response, thereby returning to normal function. New data suggest that resolution of inflammation is an active biochemical and metabolic process initiated by a newly identified class of receptor agonists that emerge temporally as the inflammatory lesion matures.[7] Although prostaglandins and leukotrienes secreted by neutrophils have proinflammatory properties, as inflammation proceeds, the same prostaglandins (PGE_2 and PGD_2) may promote expression of the 15-LO gene. This leads to a switch in the expression of biosynthetic enzymes by infiltrating neutrophils (Figure 2). Binding of lipoxin A4 to neutrophils leads to a phenotypic change, stopping all proinflammatory activity of neutrophils and leading to apoptosis. As a result, they stop secreting the chemoattractant LTB4, and several cellular pathways are activated, producing, at a local level, other dual-acting anti-inflammatory and proresolution lipid mediators, including resolvins and protectins.

Mechanisms of Inflammation Resolution

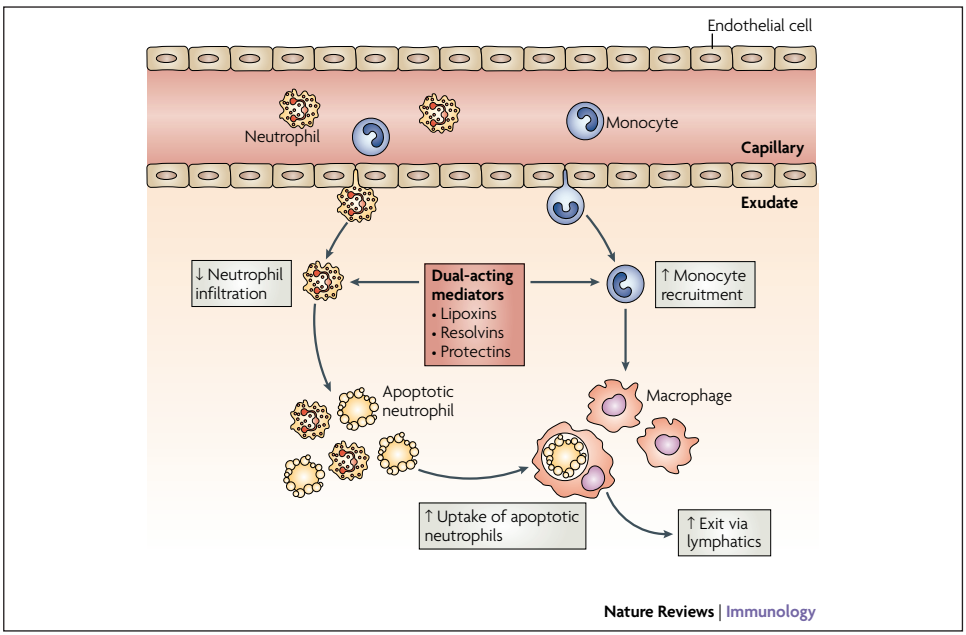
Resolvins and protectins provide potent signals that orchestrate and accelerate mechanisms that promote resolution of inflammation and homeostasis. Specifically, as depicted in Figure 3, proresolution mediators stop neutrophil infiltration and drive neutrophils to apoptosis, while at the same time attracting monocytes to the lesion.[44] Lipoxin-stimulated monocytes/macrophages obtain a nonphlogistic phenotype, which results in phagocytosis of apoptotic neutrophils and

Figure 2. Biosynthesis of Proresolving Lipid Mediators



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

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



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enhanced mucosal clearance of bacteria without concomitant secretion of proinflammatory mediators that could contribute to tissue damage.[45] Moreover, proresolution lipid molecules increase the exit of phagocytes from the inflamed site through the lymphatics. Finally, some of these molecules may also stimulate the uptake and clearance of local cytokines by apoptotic neutrophils. After neutrophils and debris are removed, homeostasis returns and repair mechanisms are initiated; lipoxins are antifibrotic and allow for complete tissue healing without scarring.

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

New Treatment Paradigms

It is reasonable to suggest that the understanding and ability to manipulate resolution of inflammation may provide a new treatment paradigm for inflammatory diseases, local and systemic. Although human data are not yet available, a growing and promising literature from in vitro work and animal models supports the beneficial actions of resolution agonists on both periodontal disease and other systemic diseases.[7]

Role of Proresolution Mediators

Examples of the actions of therapeutic proresolution mediators in periodontal disease include overexpression of lipoxin A_4 in transgenic rabbits, protecting against periodontitis and atherosclerosis.[46] 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, histologic analysis revealed few, if any, neutrophils in the tissue and little tissue damage. At the same time, the numbers of osteoclasts were also found to be reduced. In addition, treatment of periodontitis with resolvins systemically reversed the observed increase in CRP and IL-1β levels. Also, in established periodontal disease, resolvins prevented further tissue destruction, and both gingival and osseous tissues that were lost during disease were regenerated.[47]

Finally, in in vitro bone cultures, resolvins significantly enhanced expression of osteoprotegerin (OPG) without inducing change in receptor activator of NF-κB ligand levels, whereas osteogenic markers alkaline phosphatase, bone sialoprotein, and Runt-related transcription factor 2 remained unchanged.[48] These results indicate that resolvins may modulate osteoclast differentiation and bone remodeling by direct actions on bone, rescuing OPG production and restoring a favorable receptor activator of NF-κB ligand/OPG ratio.

Resolvins, lipoxins, and protectins have also been shown in animal models to have beneficial impact on a variety of other inflammatory diseases. For example, lipoxins stopped neutrophil recruitment and promoted lymphatic removal of phagocytes in periotonitis.[45] Moreover, in cystic fibrosis, lipoxins decreased neutrophil inflammation, pulmonary bacterial burden, and disease severity.[49] Resolvins in a colitis model in mice decreased neutrophil recruitment and proinflammatory gene expression, improved survival, and reduced weight loss.[50] In addition,

resolvins protected against neovascularization in retinopathy.[51] Finally, in an asthma model, protectins protected against lung damage, airway inflammation, and airway hyperresponsiveness.[52] Table 2 lists the impact of lipoxins, resolvins, and protectins on various inflammatory disease models.

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

Origins of Proresolution Mediators

To manipulate resolution of inflammation more effectively, it is imperative to understand the biologic origin of the proresolution mediators. Lipoxins (e.g., lipoxin A4) derive from arachidonic acid after activation of the 12-/5-LO or the 15-/5-LO pathways. Resolvins and protectins are biosynthesized from omega-3 essential polyunsaturated fatty acids (ω-3 PUFAs), such as eicosapentanoic acid (EPA) and docosahexanoic acid (DHA). EPA and DHA can be metabolized by aspirin-modified COX-2 pathways to form resolvins, whereas DHA can be converted to protectins via an LO-mediated pathway (Figure 4).

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

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

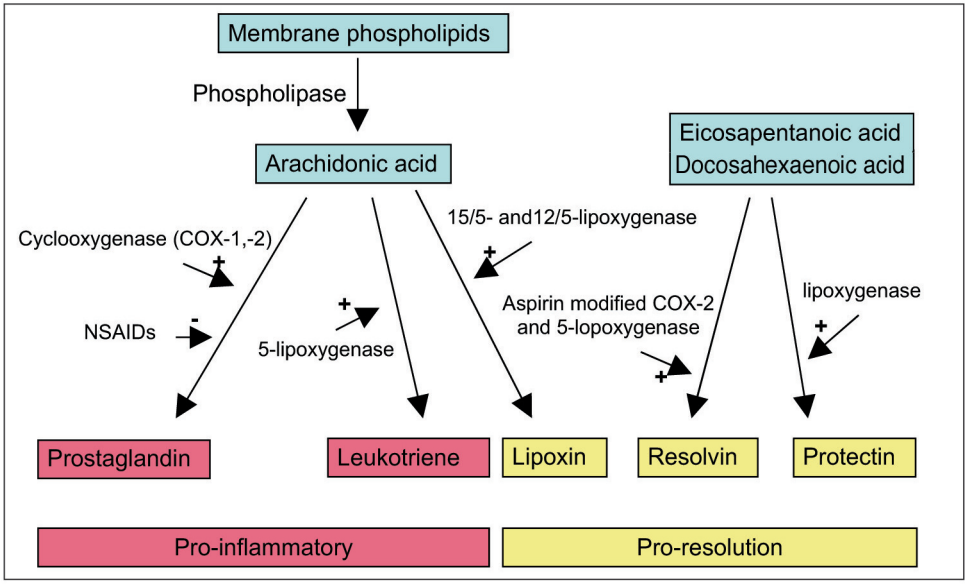

Table 2. Impact of Lipoxins, Resolvins, and Protectins on Various Inflammatory Disease Models

Disease Model	Species	Action(s)
Lipoxin A4/ATL		
Periodontitis	Rabbit	–Reduces neutrophil infiltration –Prevents connective tissue and bone loss
Peritonitis	Mouse	Stops neutrophil recruitment and lymphatic removal of phagocytes
Dorsal air pouch	Mouse	Stops neutrophil recruitment
Dermal inflammation	Mouse	Stops neutrophil recruitment and vascular leakage
Colitis	Mouse	–Attenuates proinflammatory gene expression –Reduces severity of colitis –Inhibits weight loss, inflammation, pulmonary dysfunction
Asthma	Mouse	Inhibits airway hyperresponsiveness and pulmonary inflammation
Cystic fibrosis	Mouse	Decreases neutrophilic inflammation, pulmonary bacterial burden, and disease severity
Ischemia-reperfusion injury	Mouse	–Attenuates hind-limb ischemia-reperfusion lung injury –Causes detachment of adherent leukocytes in mesenteric ischemia-reperfusion injury
Corneal disorders	Mouse	–Accelerates cornea re-epithilialization –Limits sequelae of thermal injury (such as neovascularization and opacity) –Promotes host defense
Angiogenesis	Mouse	Reduces angiogenic phenotype: endothelial-cell proliferation and migration
Bone marrow transplant	Mouse	Protects against bone-marrow-transplant–induced graft-versus-host diseases
Glomerulonephritis	Mouse	–Reduces leukocyte rolling and adherence –Decreases neutrophil recruitment
Hyperalgesia	Rat	–Prolongs paw withdraw latency and reduces hyperalgesic index –Reduces paw edema
Pleuritis	Rat	Shortens the duration of pleural exudation
Resolvin E1		
Periodontitis	Rabbit	–Reduces neutrophil infiltration –Prevents connective tissue and bone loss –Promotes healing of diseased tissues –Regenerates lost soft tissue and bone
Peritonitis	Mouse	–Stops neutrophil recruitment –Regulates chemokine and/or cytokine production –Promotes lymphatic removal of phagocytes
Dorsal air pouch	Mouse	Stops neutrophil recruitment
Retinopathy	Mouse	Protects against neovascularization
Colitis	Mouse	–Decreases neutrophil recruitment and proinflammatory gene expression –Improves survival –Reduces weight loss
Resolvin D1		
Peritonitis	Mouse	Stops neutrophil recruitment
Dorsal skin air pouch	Mouse	Stops neutrophil recruitment
Kidney ischemia-reperfusion injury	Mouse Mouse	–Protects from ischemia-reperfusion kidney damage and loss of function Regulates macrophage
Retinopathy	Mouse	Protects against neovascularization
Protectin D1		
Peritonitis	Mouse	–Inhibits neutrophil recruitment –Regulates chemokine and/or cytokine production –Promotes lymphatic removal of phagocytes –Regulates T-cell migration
Asthma	Mouse	Protects from lung damage, airway inflammation, and airway hyperresponsiveness
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 Regulates macrophages function
Retinopathy	Mouse	Protects against neovascularization
Ischemic stroke	Rat	–Stops leukocyte infiltration –Inhibits nuclear factor-kB and cyclooxygenase-2 induction
Alzheimer's disease	Human	Diminishes protecting D1 production in human Alzheimer's disease

and certain LO inhibitors, have been shown to impair resolution of inflammation and lead to systemic inflammatory complications.

Summary of Part III

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

Supplemental Readings

Serhan CN, Chiang N, Van Dyke TE. Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. *Nat Rev Immunol* 2008;8(5):349–61.

Madianos PN, Bobetsis YA, Kinane DF. Generation of inflammatory stimuli: how bacteria set up inflammatory responses in the gingiva. *J Clin Periodontol* 2005;32(Suppl 6):57–71.

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