CE5

Overview of Risk Factors for Periodontal Disease and Implications for Diabetes and Cardiovascular Disease

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Abstract

Recent studies have shown that there is a definite relationship between diseases of the oral cavity, especially periodontal infections, and systemic diseases. The effects of periodontal disease on the oral cavity are well known; however, periodontal disease may also produce systemic effects in the body, including an association with cardiovascular disease. Dentists need to understand the pathogenesis and risk factors for cardiovascular disease. The authors discuss the risk factors for periodontal disease, the pathogenesis and risk factors for cardiovascular disease, the relationship between periodontal infection and cardiovascular disease, and the need for future studies to further define the relationship between periodontal disease and cardiovascular disease.

Learning Objectives

After reading this article, the reader should be able to:

- list the risk indicators for periodontal disease.
- discuss the systemic effects of periodontal disease on the body.
- identify the risk factors for cardiovascular disease.
- explain the relationship between infection and cardiovascular disease.

There has always been a definite line between medicine and dentistry. Physicians treated diseases of the body while dentists treated diseases of the oral cavity; there was little overlap between the two. However, this line is slowly eroding. As more is learned about the human body, a definite relationship between diseases of the oral cavity, especially periodontal infections, and systemic diseases is emerging. In addition, it is being shown that some of the risk factors for periodontal diseases are similar to those of certain systemic diseases, and that periodontal disease itself may be a risk factor for some systemic diseases. This article discusses the techniques for risk assessment, the pathogenesis and risk factors for cardiovascular disease and periodontal disease, the association between cardiovascular disease and periodontal disease, and future directions for study.

Types of Studies

Associations have been drawn between certain diseases and everyday habits or actions. How is it determined if any of these associations are clinically important? There is a hierarchy of evidence, which can be determined using case studies, case-control studies, cross-sectional studies, longitudinal studies, and intervention studies. Cross-sectional studies provide stronger evidence for associations than case studies or case-control studies because more people are involved and confounders can be better studied. Key evidence can be obtained from longitudinal studies because a temporal sequence has been established. Even more evi-

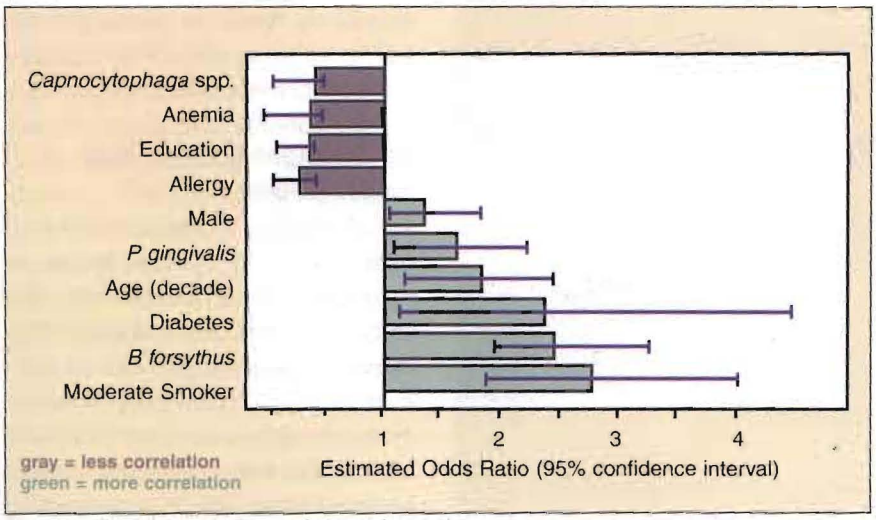

Figure 1—Potential risk indicators for periodontal disease.

dence can be obtained from an intervention study because it answers the question, "So what?" The most clinically important associations or risk factors are those that can be affected by intervention and those in which differences can be obtained as a result of therapy.

Periodontal Disease

A cross-sectional study performed by Löe and colleagues in the mid-1980s[1] showed that not everyone has periodontal disease and that there are different degrees of severity among individuals. This suggests that there are differences in susceptibility or risk.

The Erie County Study looked at the important risk factors for periodontal disease in adults aged 25 to 74 years by measuring clinical attachment loss and alveolar bone loss using x-rays. There were about 500 potential explanatory variables, including subgingival flora, socioeconomic status, demographics, medical history, dental history, medications, and habits such as smoking. Using an immunofluorescent technique with highly specific sera, 12 sites were sampled in each patient to determine the presence or absence of 9 target organisms. *Bacteroides forsythus* and *Porphyromonas gingivalis* were found to be associated with high levels of disease. This study also showed a dose response between smoking and periodontal disease; heavier smoking was associated with more severe disease. A multivariant model was used to study all of the factors.

After adjusting for plaque and the frequency of dental visits, which are clear risk factors for periodontal disease, the following factors were identified as risk indicators for periodontal disease (green bars): infection with *P gingivalis* and *B forsythus*, male gender, age, diabetes, and smoking expressed as estimated odds ratios with the 95% confidence intervals given. Several factors were associated with less disease (gray bars), including higher education, the presence of *Capnocytophaga*, and having anemia or allergies (Figure 1). The protective effects of allergies are likely related to the antihistamine therapies in these patients. Longitudinal and intervention studies on smoking, periodontal pathogens, and diabetes have provided convincing evidence that these are truly risk factors for periodontal disease.[2]

Stress, osteoporosis, and genetics also have been studied as risk indicators for periodontal disease, but not on a longitudinal basis. Stress was measured using two questionnaires. Daily life events (eg, divorce or getting a parking ticket) were graded, as well as daily strains (eg, financial strains or family problems). The amount of distress and associated coping styles also were measured. Financial strain, considered a measure of chronic stress, was related to periodontal disease, and coping styles and strategies were shown to be significant modifiers. People who coped with their financial problems in a problem-focused way had no more disease than if they were not under financial strain.

Stress causes at least two types of reactions: (1) behavioral, because people under stress change their behavior; and (2) production of glucocorticosteroids and cortisone through adrenocorticotrophic hormone and corticotropin-releasing hormone. One effect of these hormonal changes is immunosuppression, which can reduce resistance to infection. Stress was shown to be a risk indicator for periodontal disease.

The relationship between osteoporosis and oral bone loss has been studied. Osteoporosis causes bone to become more porous and there is less trabeculation and cortical plate. With a certain level of bacteria and plaque stimulus, this could lead to more periodontal disease. In a comparison of osteoporosis at different sites in the body (ie, lumbar spine, radial femur, and mandible), there was a correlation between skeletal bone mineral density and periodontal disease in postmenopausal women. The association became clearer when tooth loss was also studied; osteoporosis was clearly related to increased tooth loss. In a study of postmenopausal women, this group had both lower bone mineral density in all areas of bone (ie, skeletal and

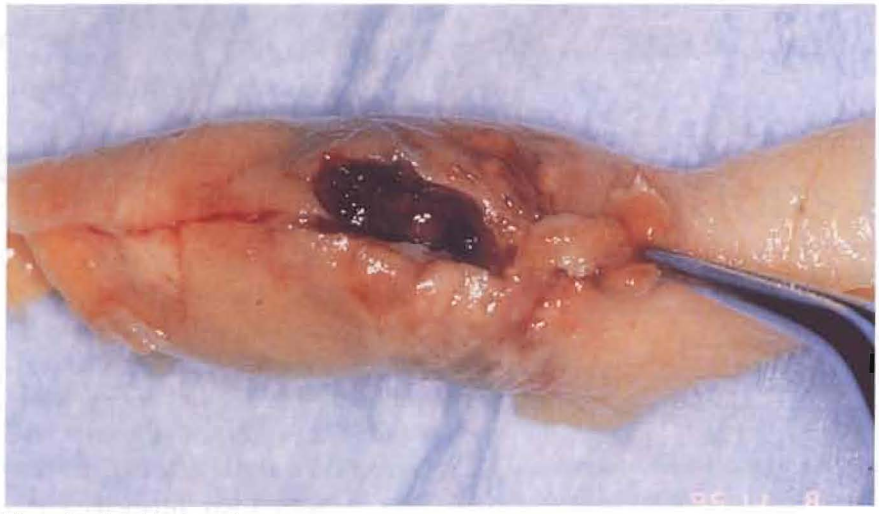

Figure 2—Carotid artery atheroma.

mandibular) and higher levels of periodontal disease.

Postmenopausal osteoporosis is an estrogen-deficient state. Estrogen down-regulates the production of cytokines by osteoblasts. These cytokines activate osteoclasts, including interleukin-1 (IL-1) and interleukin-6 (IL-6). Estrogen reduces the ability of osteoblasts to produce cytokines, so there is less osteoclast activation and bone resorption. The net effect is that estrogen reduces bone resorption. In estrogen-deficient states, greater osteoclast activation occurs, leading to more bone loss. With senile osteoporosis, there is a deficiency in osteoblast function, with less bone deposition. In the future, estrogen derivatives or other bone-sparing agents, such as biophosphonates, may be used for periodontal applications.

An ongoing, population-based, cross-sectional study of 1,300 women is under way at the University of Buffalo research clinics. In this study, there will be the chance to adjust for many risk factors to obtain a clearer picture of the relationships between osteoporosis, oral bone loss, and periodontal disease in postmenopausal women.

Studies of genetics have been extended to assess polymorphisms of investigated cytokines, including IL-1, the IL-1 receptor antagonist, and tumor necrosis factor alpha (TNFα). A certain combination of IL-1A and IL-1B polymorphisms is associated with more severe periodontal disease in patients who do not smoke.[3]

Initial therapy for advanced loss of periodontal support should include the elimination, alteration, or control of risk factors that may contribute to adult periodontitis.

Recently, we have shown that two other genetic polymorphisms are associated with periodontal disease. The first is an antibody Fc receptor polymorphism, termed the FcγR polymorphism, which influences susceptibility to certain infections and autoimmune diseases.[4] The second polymorphism is in the gene-encoding chemotactic factor receptors on phagocytes.[5] It is likely that a mosaic of genetic polymorphisms will affect susceptibility to periodontal disease.

Clinical Application of Risk-Factor Studies

According to the parameters of care developed by the American Academy of Periodontology, the initial therapy for patients with advanced loss of periodontal support should include the elimination, alteration, or control of risk factors that may contribute to adult periodontitis. This is a major step forward now that it is clear that periodontal diseases are infections caused by bacteria and are multifactorial. Modification of these risk factors is important for optimal management of periodontal disease. There will not likely be a "single-bullet cure" for periodontal diseases. Diabetes, infection with human immunodeficiency virus, pregnancy, smoking, substance abuse, and certain medications all have been associated with an increased prevalence of periodontal disease. Management of these risk factors, along with antiinfective and regenerative therapy, is likely to be the most successful approach to periodontitis in the future.

The Association Between Periodontal Disease and Cardiovascular Disease

The effects of periodontal infections on the oral cavity are well known; however, periodontal disease is associated with systemic effects in the body, such as cardiovascular disease. In patients with cardiovascular disease, there is a focal, chronic endothelial injury, followed by the formation of an atheroma, which results from accumulation of lipids and a proliferation of cells. These lipids, mainly low-density lipoprotein (LDL) and very low-density lipoprotein, have a high cholesterol content, and

they become oxidized in atheromas. An interaction among endothelial cells, macrophages, T-lymphocytes, and smooth muscle cells occurs, as does cytokine production. The cytokines, particularly platelet-derived growth factor, stimulate smooth muscle proliferation into the intima, producing a full-fledged fibrofatty atheroma (Figure 2). The atheroma continues to grow and may cause partial or complete occlusion of the coronary artery. On the other hand, the atheroma may develop a fibrous cap with a fatty occlusion. When this fibrous cap ruptures, the interior of the fibrofatty atheroma is exposed and thrombus formation occurs, which occludes the vessel, leading to a distal infarct and myocardial ischemia or a heart attack.

The risk factors for cardiovascular disease include an elevated level of LDL cholesterol (higher than 160 mg/dL), a low high-density lipoprotein cholesterol level (less than 35 mg/dL), smoking (more than 10 cigarettes per day), severe obesity (more than 30% overweight), male gender, elevated homocysteine, diabetes mellitus, and a family history of premature cardiovascular disease. All of these factors contribute to risk for periodontal disease, yet there is still significant unexplained risk for heart disease.

It has been speculated for at least 100 years that there is a relationship between infection and cardiovascular disease. Sir William Osler proposed that cardiovascular disease itself was an infection, but there was no evidence to support this. The first evidence that infection could cause a more severe heart disease was seen with cytomegalovirus (CMV). CMV infection is common in immunosuppressed patients, and arteriosclerosis was found in the hearts of immunosuppressed transplant patients, who often have cardiovascular disease to a greater extent than they did in their own hearts because they were infected with CMV. CMV is also associated with re-stenosis after angioplasty, and any attempt to reduce CMV infection was associated with greater success after angioplasty.

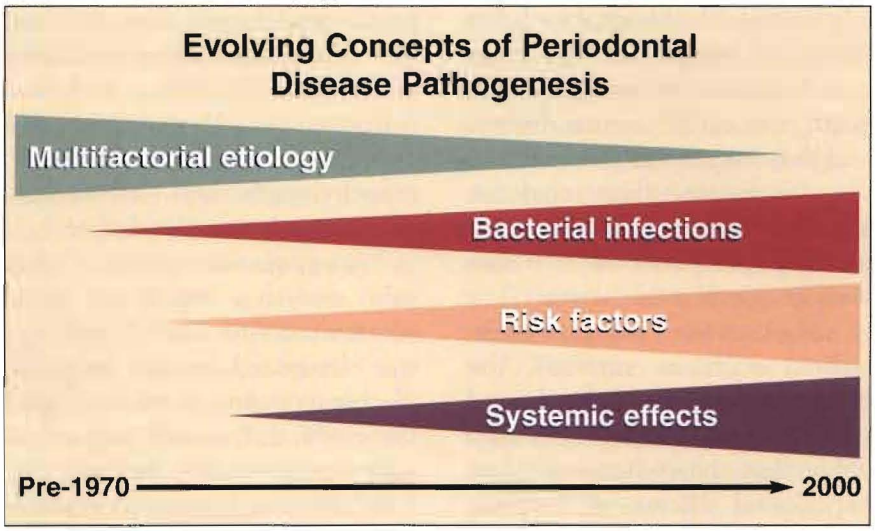

Figure 3—Theories regarding periodontal pathogenesis in the last 30 years.

The higher the dental index, which was the measurement of caries, periodontal disease, endodontic lesions, and pericoronal lesions, the greater the association with heart disease.

The relationship between gastric ulcers and cardiovascular disease was also studied. The causative agent of a gastric ulcer, *Helicobacter pylori*, has been associated with heart disease. *Campylobacter pneumoniae*, a common organism that causes bronchitis and pneumonia in 10% to 18% of the population, was found to be associated with heart disease in seroepidemiologic studies. *C pneumoniae* has been found in atheromas, and atheromas have been induced in rabbits infected with this microorganism.[6]

During the past decade, several interesting studies of the relationship between cardiovascular disease and periodontal infection have been reported.[6] Case-control studies and longitudinal studies based on the case-control studies on this relationship showed that the higher the dental index (which was the measurement of caries, periodontal disease, endodontic lesions, and pericoronal lesions), the greater the association with heart disease.

In a later study, DeStefano showed that there was a relationship between baseline periodontal disease and the subsequent development of heart disease in men younger than age 50 (after age 50, the relationship cannot be determined). The study began in the early 1970s and patients were followed over the next 15 years. At baseline, the author measured caries and periodontal disease or used measurements that were in the database. The end points were mortality from heart disease or

admission to the hospital for heart disease. Looking at the outcomes—death from any cause, death from cardiovascular disease, and hospital admission for cardiovascular disease—their incidence was twice as high in periodontitis patients compared with those without periodontal disease.

The data from a 15-year longitudinal study in veterans, the Normative Aging Study, showed that men younger than age 60 who did not have heart disease, but had periodontal disease at baseline, had a greater risk of developing heart disease in the subsequent 15 years. In this study, the incidence of stroke increased by 2.8 times in those patients who had periodontal disease at baseline. In addition, this study showed a graded response between baseline bone loss and the risk of developing heart disease; people with 60% bone loss had a 30% to 40% increased risk of developing heart disease over the next 15 years.

These results have been confirmed in at least three other studies. In the Harvard Physician Study of 22,000 physicians, about 500 of the participants developed heart disease. These physicians and dentists were asked to count their teeth and provide a self-report of whether or not they had periodontal disease. Overall, self-reported periodontal disease was not found to be associated with heart disease. However, those who reported that they had periodontal disease and had less than 10 teeth were at a greater risk for developing heart disease. A cross-sectional study in elderly veterans found that stroke and heart disease were related to periodontal disease.

We studied Native Americans on the Gila River Indian Reservation because of their low levels of smoking. Information obtained from earlier studies of this population showed that diabetes was a risk factor for periodontal disease. Our longitudinal study was performed over 15 years and contained baseline periodontal disease measurements and subsequent data on cardiovascular disease.

An important aspect of this study was that one of the most common confounders, smoking, was eliminated because only 5% of this population smoked, and those who did smoked only a few cigarettes per day. Among the 1,440 Native Americans studied, a very strong relationship between periodontal disease and cardiovascular disease was observed. As expected, there was also a relationship between diabetes and cardiovascular disease. The risk of developing heart disease was increased by 168% in those who had periodontal disease.

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There are several mechanisms that may link coronary artery disease and periodontal disease. The first is the bacterial thrombus hypothesis. Platelet aggregation can be caused by collagen and thrombin, as well as two microorganisms found in the oral cavity, *Streptococcus sanguis* and *P gingivalis*. *S sanguis* causes subacute bacterial endocarditis. Herzberg et al showed that these organisms have a collagenlike molecule, the platelet-aggregation-associated protein (PAAP), on their surface.[7] They also showed that when *S sanguis* is injected intravenously into rabbits, a heart attacklike series of events occurs.[8] With inflammatory mediators, a very strong relationship has been shown between C-reactive protein, soluble intercellular adhesion molecule-1 (sICAM-1), and fibrinogen as risk markers for heart disease. An immunologic concept states that antibodies reactive to periodontal organisms will localize in the heart and trigger complement activation, a series of events leading to sensitized T cells and the pathology that is seen in the heart. There is also the hypothesis of common genetic predisposition—the hypermonocyte trait—as well as the effects of products of infection on lipid metabolism.

It is clear that there are several mechanisms linking periodontal infections to heart disease, and it is likely that most are operative at some time during the development of atheromas in patients with severe periodontal infections. We recently studied 50 carotid atheromas by polymerase chain reaction, and evidence for the following microorganisms was found: CMV, *H pylori*, *Chlamydia pneumonia*, *P gingivalis*, *Prevotella intermedia*, *B forsythus*, and *Actinobacillus actinomycetemcomitans*. Forty-two percent of the atheromas contained at least one of the periodontal microorganisms, and 72% contained bacterial DNA—only 4% of which contained bacterial DNA that was not accounted for by one of these organisms.[9]

The bacteremia thrombus hypothesis may explain why at least some of these microorganisms were found in the atheromas. For example, *P gingivalis* expresses a PAAP surface antigen that resembles collagen, which induces platelet aggregation, and there is a receptor on the platelet surface for this antigen. *P gingivalis* also has fimbriae, which are necessary for platelet aggregation. The forma-

tion of microthrombi occurs during bacteremias and they may localize within the atheromas.

We recently performed a study on the relationship of cardiovascular disease, periodontal disease, and inflammatory cell mediators, including C-reactive protein. Groups of adults who had neither periodontal disease nor cardiovascular disease, one of these diseases, or both of these conditions were assembled. In controls with neither disease, the mean level of C-reactive protein was 1.14 µg/mL, whereas in those with both heart disease and periodontal disease, the level was 8.7 µg/mL—a highly statistically significant difference. Next, we showed that treatment of the periodontal disease caused a 65% reduction in the level of C-reactive protein at 3 months, which remained reduced for 6 months. This suggests that periodontal disease induces C-reactive protein and possibly other inflammatory mediators, which are known to be independent risk factors for heart disease.

How does C-reactive protein participate in heart disease? One possible explanation is that C-reactive protein will form deposits in injured blood vessels. It binds to cells that are partially damaged and fixes complement, which activates phagocytes, including neutrophils, which releases nitric oxide, which contributes to atheroma formation.

How does periodontal infection induce acute-phase proteins? Periodontal disease results in bacteremias and stimulates production of factors such as TNFα and IL-6, which likely stimulate the liver to make C-reactive protein and other acute-phase proteins. Hence, it appears likely that periodontal infection is a significant risk factor for cardiovascular disease linked through bacteremia and inflammatory mediators, and possibly immunologic factors.

Future Studies

For future study of the relationship between periodontal disease and cardiovascular disease, longitudinal studies are clearly needed in which the likely mechanisms linking the diseases are assessed. In addition, longitudinal studies will help establish the temporal sequence of various factors associated with periodontal disease that may contribute to periodontal disease. Longitudinal studies also will help establish attributable risk, the extent to which periodontal infections compared with other risk factors account for the risk of heart disease in the population.

It appears likely that periodontal infection is a significant risk factor for cardiovascular disease linked through bacteremia and inflammatory mediators, and possibly immunologic factors.

To date, no studies have evaluated the relationship between stress and periodontal disease and cardiovascular disease. Studies on women are also needed because most studies, to date, are on men.

Intervention studies are necessary to determine to what extent treatment of periodontal disease will decrease the incidence of cardiovascular events. Will prevention or treatment of periodontal disease reduce the risk of cardiovascular disease? Studies also need to be performed to determine the optimal intervention (ie, anti-inflammatory, anti-infective, or antiadherent). By knowing the mechanisms, treatments and preventive modalities can be designed that not only will interfere with the infection, but perhaps with the mechanisms linking periodontal disease to heart disease as well. The future treatment of periodontal disease will be designed to reduce its effects on systemic diseases, such as cardiovascular disease and diabetes (Figure 3).

Acknowledgment

The authors wish to thank Kathy Barnes for her excellent assistance in writing this manuscript.

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