Position Paper

Periodontal Disease as a Potential Risk Factor for Systemic Diseases*

THIS PAPER ON PERIODONTAL DISEASE as a potential risk factor for systemic diseases was prepared by the Research, Science and Therapy Committee of The American Academy of Periodontology. It is intended to provide information regarding the role of periodontal disease in systemic diseases, including bacteremia, infective endocarditis, cardiovascular disease and atherosclerosis, prosthetic device infection, diabetes mellitus, respiratory diseases, and adverse pregnancy outcomes. *J Periodontol 1998; 69:841–850.*

Periodontitis, one of the most common diseases of humans, is an infectious condition that can result in the inflammatory destruction of periodontal ligament and alveolar bone. Gingivitis is an infectious inflammatory process limited to the gingiva. Periodontal diseases are generally chronic in nature and can persist in the absence of treatment.[1–3] These diseases are the result of exposure of the periodontium to dental plaques, biofilms that accumulate on the teeth to form bacterial masses containing up to 1 to 2 $\times$ 10^{11} bacteria/gram at or below the gingival margin.[4] Dental plaques are complex, with more than 400 bacterial species having been collectively isolated from the plaques of patients with periodontal disease.[5] Periodontal destruction probably results from the action of various toxic products released from specific pathogenic subgingival plaque bacteria, as well as from the host responses elicited against plaque bacteria and their products. The inflammatory response may result in gingival ulceration around the tooth which can allow intact bacterial cells or their products including lipopolysaccharides, peptidoglycan fragments, and hydrolytic enzymes into the systemic circulation. It is also known that the host response to periodontal infections results in the local production of cytokines and biological mediators including interleukins and prostaglandins,[2] as well as systemic responses such as induction of serum antibodies.[6]

In light of the extensive microbial plaques associated with periodontal infections, the chronic nature of these diseases, and the exuberant local and systemic host response to the microbial assault, it is reasonable to hypothesize that these infections may influence overall health and the course of some systemic diseases. However, relatively little attention has been paid to the impact of periodontal infections on human health. This lack of attention to the systemic ramifications of periodontal infection can be traced back to the largely unsubstantiated theory of focal infection which was promulgated during the 19th and early 20th centuries.[7] This theory stated that "foci" of sepsis were responsible for the initiation and progression of a variety of inflammatory diseases, such as arthritis, peptic ulcers, and appendicitis. Thus, microorganisms or their products spread from distant chronically infected sites (such as the mouth) to target organs. Indeed, extreme therapies such as therapeutic edentulation were commonplace as a result of the popularity of the focal infection theory. However, this wholesale removal of oral tissue was often performed in the absence of evidence of infection, and many healthy teeth were indiscriminately removed. This theory was eventually rejected when medical decision making became more dependent on results of controlled, scientific studies.

Despite the legacy of the theory of focal infection, there has been a renewed interest over the last several years in the relationships between systemic and oral health. This may be due in part to the notion that dental medicine must become more integrated with general medicine,[8] and to accumulating evidence that oral diseases may have clinically significant effects on general health. It is also clear that a number of systemic diseases and conditions are risk factors for periodontal disease. These include diabetes mellitus, neutrophil disorders, osteopenia, and stress.[9] The goal of this paper is to review those recent studies that have suggested the potential for periodontal infections to influence several important systemic diseases.

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Bacteremia

The negative impact of oral infection on systemic health generally stems from the entry of oral microorganisms or their products into the bloodstream. Transient bacteremia occurs frequently from incidents such as minor skin abrasion and defecation, and from the oral cavity. Such bacteremia is not only common, but can also be the source of significant microbial entry into the bloodstream.[10] Bacteremias can be provoked by mastication and oral hygiene procedures such as toothpicking, flossing, and toothbrushing. The extent to which bacteremia of oral origin occurs appears to be directly related to the severity of gingival inflammation.[10] Thus, the best means to prevent bacteremia from the oral cavity is the maintenance of periodontal health.

It is also possible that periodontal bacteria or their products can directly invade the periodontal tissues.[11-14] This represents a distinct mechanism by which periodontal disease-associated bacteria may gain access to the systemic circulation. However, there is no evidence to date to indicate that patients with periodontitis experience a greater degree of bacteremia than do patients having only gingivitis.

Infective Endocarditis

Infective endocarditis (IE) is characterized by bacterial infection of damaged heart valves or mural endocardium.[15,16] Bacteria gain access to the bloodstream and adhere to damaged or otherwise receptive endocardial surfaces. IE is commonly, but imprecisely, divided into acute and subacute forms which have different clinical manifestations and, frequently, differing bacterial etiologies. Acute bacterial endocarditis follows a rapid clinical course (weeks) and death is usually the outcome, unless interrupted by antibiotic therapy. Subacute bacterial endocarditis (SBE) takes a more chronic course, in which the patient is often unaware of a problem until the onset of a low grade fever, anemia, and debility. These symptoms may continue for months without treatment. While SBE is curable in its early stages and, in most cases preventable, it is ultimately fatal in the absence of antimicrobial intervention.

It is well accepted that dental and other surgical procedures predispose susceptible patients to IE.[17] The most common etiologic agents of SBE are oral streptococci.[18] For example, many studies have found *Streptococcus sanguis*, a numerically prominent species of supra- and subgingival dental plaque, to be a prevalent blood isolate from patients suffering from SBE.[16,19] These bacteria may have an affinity for sterile thrombotic vegetations deposited on cardiac valves. Furthermore, strains of *S. sanguis* specifically adhere to and aggregate platelets by a calcium-independent mechanism.[20] Once bound, the bacterial cells induce calcium-dependent platelet activation. These bacteria may also cause in vivo thrombus formation[21] which may participate in the formation of endocardial vegetations.[22]

While the majority of endocarditis cases are caused by Gram-positive species, Gram-negative bacteria can also cause endocarditis.[23] Gram-negative bacteria found in the oral cavity have been isolated from patients with SBE, including a wide variety of putative periodontal pathogens including *Haemophilus aphrophilus, Actinobacillus actinomycetemcomitans, Eikenella corrodens, Capnocytophaga* sp., and *Fusobacterium nucleatum.*[23,24] It is possible that the interactions by which these organisms participate in SBE are similar to that noted between *S. sanguis, P. gingivalis,* and platelets.[25] Thus, individuals having the classic risk factors for SBE (history of rheumatic fever, aortic stenosis, and murmurs including valve prolapse with regurgitation) and periodontal disease may be at greater risk for SBE than those with healthy periodontal tissues, since bacteremia is more likely to occur in the former.[10]

Prevention of SBE centers on limiting the entry into and dissemination of bacteria through the bloodstream. Current recommendations focus on antibiotic prophylaxis for procedures that are likely to provoke bacteremia.[26,27] Thus, most patients with risk factors for SBE who require dental procedures that will induce bleeding should be covered by antibiotic prophylaxis. However, it is clear that not all oral bacteria are susceptible to amoxicillin, the current prophylactic antibiotic of choice. Indeed, a considerable proportion of oral bacteria have been reported to be resistant to the ß-lactam class of antibiotics.[28-31]

It is particularly important to minimize gingival inflammation in patients at risk for SBE in order to limit the incidence and severity of bacteremias from the periodontium. This can be best accomplished by prevention of the initiation of periodontal disease by proper home care, frequent dental recall, and modification of risk factors. In addition, it has been suggested that irrigation with antimicrobial agents immediately before dental procedures, such as povidone-iodine or chlorhexidine, may be of value in reducing the microbial burden and degree of subsequent bacteremia in dental patients with high risk for SBE and gingival inflammation.[32,33] While it is also possible that the force required to inject irrigants subgingivally may promote a greater degree of bacteremia than that which would occur in the absence of irrigation, the evidence supporting this contention is equivocal.[34] Ultimately, maintenance of periodontal health is desirable to minimize the incidence and degree of bacteremia in IE-susceptible patients.

Cardiovascular Disease (CVD) and Atherosclerosis

Atherosclerosis is a progressive degenerative condition involving large to medium-sized arteries. Atheromatous plaques within these arteries composed of lysed cells,

Table 1. Adjusted Odds Ratios for Cardiovascular Disease (CVD), Fatal CVD and Stroke for Patients With Periodontal Disease

Number of Cases/Controls	Total CVD	Fatal CVD Stroke	Reference
5,203/891	1.5		45
8/891		2.2	45
40/911		2.8	45
66/60		2.6	46
1,786/3,542	1.29		40
2,031/3,367		1.46	40
757/44,119	1.67		44

cholesterol-ester crystals, foam cells, and plasma proteins such as fibrin and fibrinogen are the source of thrombi that can occlude the artery or be released to cause infarction at distant sites. Atherosclerosis and resulting coronary thrombosis, ischemic heart disease, and stroke are together the major causes of death in the United States.[35,36]

It is interesting to note that the classical risk factors of CVD (hypertension, hypercholesterolenemia, cigarette smoking) can only account for one-half to two-thirds of the variation in the incidence of CVD cases. Thus, it is likely that other, as yet unrecognized, factors may also contribute to the pathogenesis of CVD. Several studies have pointed to a possible relationship between chronic oral infections and the pathogenesis of atherosclerosis and disease associated with thromboembolic events such as myocardial infarction and stroke.[37–46] Indeed, a positive association between the presence of periodontal infection and CVD/stroke has been noted (Table 1), with patients with periodontal disease having a 1.5 to 2.0 fold greater risk of incurring fatal CVD than patients without periodontal disease. Importantly, dental infections appear to increase the risk of coronary artery disease to a degree similar to the classical risk factors for CVD including age, smoking, diabetes, hypertension, and elevated serum triglycerides.

A case control study compared subjects who experienced recent acute CVD with healthy controls matched for age, gender, and social class in which all subjects received clinical and radiographic evaluation for dental infections (caries, periodontal disease, periapical disease, and pericornitis).[38] The results suggested that patients with recent CVD had significantly more dental infections than the healthy controls. The low association reported between dental disease and CVD in women probably stemmed from the fact that few women were included in this study.

The findings of a more recent study support the possible role of dental infections such as periodontal disease as risk factors for CVD.[40] Furthermore, this study suggests that men with periodontal disease have a stronger propensity for CVD than men without periodontal disease, with those under 50 with periodontal disease having a greater risk than those over 50. While the data were adjusted for many factors known to affect periodontal disease and cardiovascular disease (e.g., age, gender, etc.), smoking history data were incomplete.

Combined data from the Normative Aging Study and the Dental Longitudinal Study of the Department of Veterans Affairs were analyzed to evaluate the association of periodontal disease and CVD and stroke. Radiographic measures of periodontal disease were obtained for 1,147 men from 1968–1971.[45] It was found that 207 of the men who entered the study developed CVD over the next 15 years. Incidence odds ratios for bone loss and total CVD, fatal CVD, and stroke were 1.5, 2.2, and 2.8, respectively, after adjusting for some of the traditionally accepted CVD risk factors. This study was limited to men; hence no assessment of the association of periodontal disease with thromboembolic events in women was possible.

A more recent study[46] has also pointed to a possible association between dental infections and stroke. In this study, 66 patients having acute cerebrovascular ischemia were compared to 60 control subjects. It was noted that patients with cerebrovascular ischemia were more likely to have a dental infection than the control subjects (odds ratio, 2.6).

Data from the Health Professionals Follow-Up Study were also analyzed to determine associations between oral health status and coronary vascular disease.[44] Of 44,119 male health professionals followed for 6 years, 757 cases of CVD (both fatal and non-fatal myocardial infarction) were recorded. A positive association was noted between CVD and tooth loss due to periodontal disease, with a relative risk of 1.67 after adjusting for standard CVD risk factors.

The biological basis for the hypothetical association of CVD and periodontal infections is presently unclear. Infection in general appears to be a risk factor for atherogenesis. For example, the risk for CVD may increase following chlamydial[47] or viral[48] infection. Bacterial products such as lipopolysaccharides likely elicit recruitment of inflammatory cells into major blood vessels, proliferation of vascular smooth muscle, vascular fatty degeneration, and intravascular coagulation.[45,47] These changes are the result of the action of various biologic mediators, such as prostaglandins, interleukins, and tumor necrosis factor α (TNFα) on vascular endothelium and smooth muscle. It has been proposed that some individuals with a genetically predetermined hyperinflammatory monocyte phenotype have a higher risk for both atherosclerosis and periodontal disease.[41,45] It may well be that the inflammatory response characteristic of periodontal disease, marked by high levels of inflammatory mediators, exacerbates the process of atherogenesis.

Another mechanism proposed to explain the association between periodontal disease and cardiovascular disease suggests that oral bacteria such as *S. sanguis* and *P. gingivalis* induce aggregation of platelets through the

binding of a specific surface protein which share sequence homology with a platelet-activation region of collagen.[25] Experimental evidence demonstrating that rabbits infused with a strain of *S. sanguis* known to induce platelet aggregation showed perturbations in blood pressure, electrocardiograms, heart rate, and cardiac contractility.[21] Affected rabbits exhibited ischemic damage to their heart muscle at necropsy. No such effects were produced by a strain of *S. sanguis* that does not induce platelet aggregation. These findings suggest that platelet-aggregating bacteria, such as *S. sanguis* or the periodontal pathogen *P. gingivalis*, that enter the bloodstream may increase the risk for thrombogenic events including myocardial infarction and stroke.

The studies reviewed above suggest that periodontal and other oral infections may modulate CVD and stroke. Our present knowledge, however, is incomplete. Further studies are necessary to verify and quantitate the role of oral infections in the process of atherogenesis.

Prosthetic Device Infection

Patients with artificial joints are an ever-increasing segment of the population. These prosthetic devices are vulnerable to bacterial colonization and infection.[49] Such infection can lead to prosthetic failure as well as serious infection and even death. It is recommended by the American Heart Association that a patient with prosthetic heart valves be treated as a patient having risk factors for subacute bacterial endocarditis and receive antibiotic prophylaxis.[26] Unlike SBE, most prosthetic joint infections are caused by non-oral bacteria such as staphylococci. This has led to ambiguity with respect to antibiotic prophylaxis for dental patients with artificial joints.[50] Given the absence of definitive clinical studies, the decision as to which antibiotic prophylaxis regimen to employ for patients with artificial joints should be made using sound clinical judgment in consultation with the patient's physician.

Diabetes Mellitus

Diabetes mellitus (hereafter referred to as diabetes) is the most common endocrine disease. It is characterized by metabolic abnormalities and long-term complications involving the eyes, kidneys, nerves, vasculature, and periodontium.[51,52] There are two major forms of diabetes; type 1, or insulin-dependent (IDDM) and type 2, or non-insulin-dependent (NIDDM). The fundamental derangement in IDDM is the hypoproduction of insulin, due to destruction of the beta cells of the pancreas. In NIDDM, the derangement involves resistance of target tissues to insulin action. Gestational diabetes occurs in women during pregnancy, but is usually transient, with glucose metabolism returning to normal after parturition.

The association between diabetes and periodontal disease is well documented.[53-55] Epidemiologic studies found periodontal attachment loss to be more prevalent in subjects with either IDDM or NIDDM than in non-diabetic subjects. It has been assumed that this association is due to the fact that diabetic patients have a compromised ability to respond to infectious challenges which predisposes the patient to bacterial infections such as periodontal disease. However, the converse possibility, that periodontal disease either predisposes or exacerbates the diabetic condition, has received only little attention. For example, one study has noted that 7 of 9 diabetic patients treated for periodontitis subsequently required reduced needs for insulin.[56] Another study showed a reduction in the need for insulin following periodontal treatment of 9 diabetic subjects.[57] These studies, while preliminary, provide intriguing clues to suggest that periodontal disease may influence the course of diabetes.

Certain metabolic end-products such as glycated hemoglobin (glycosylated hemoglobin) are thought to contribute to the degenerative retinal and arterial changes commonly found in diabetic subjects. The concentration of glycated hemoglobin in serum is a direct function of the time hemoglobin is exposed to elevated glucose levels. A recent epidemiologic study has tested the hypothesis that severe periodontitis in persons with NIDDM increases the concentration of glycated hemoglobin in serum.[58] The data analyzed were collected during a longitudinal study of diabetes and periodontal disease of the Gila River Indian Community,[54] the majority of whom are from the Pima tribe, a population having a prevalence of NIDDM of about 50%, the highest reported prevalence of NIDDM in the world.[59] Poor glycemic control was defined for purposes of this study as the occurrence of glycated hemoglobin of 9% or more at follow-up. The results of this study suggested that severe periodontitis at baseline was associated with increased risk of having poor glycemic control at follow-up 2 or more years later.

The above findings suggest that severe periodontitis may be an important risk factor in the progression of diabetes and that physicians should consider the periodontal status of diabetic patients having difficulty with glycemic control. Thus, diabetics having periodontal disease should be treated to eliminate periodontal inflammation. This recommendation is supported by the findings of a recent study of Pima Indians that investigated the effects of periodontal treatment on the course of diabetes.[60] Subjects were randomly assigned to 1 of 4 groups. All subjects received subgingival ultrasonic debridment of the teeth. Each group also received additional treatment, including systemic doxycycline and subgingival irrigation with water, systemic doxycycline and subgingival irrigation with chlorhexidine, systemic doxycycline and subgingival irrigation with povidone iodine, or subgingival irrigation with water alone (placebo). Glycated hemoglobin concentration was monitored at baseline and throughout the study. Results indicated that while all subjects experi-

enced a reduction in periodontal disease, groups receiving systemic doxycycline and subgingival irrigation with the antimicrobial agents were clearly more improved relative to the placebo treated group. Also, subjects treated with doxycycline all experienced a reduction in glycated hemoglobin. These results suggest that periodontal antimicrobial treatment has the potential to reduce the level of glycated hemoglobin in diabetic subjects.

Respiratory Disease

The pneumonias are a group of diseases caused by a wide variety of infectious agents, including bacteria, mycoplasma, fungi, parasites, and viruses, resulting in infection of the pulmonary parenchyma. Pneumonia can be a life-threatening infection, especially in the elderly and immunocompromised patient[61,62] and it is a significant cause of morbidity and mortality in patients of all ages. Bacterial pneumonia, a prevalent form of the disease, can arise *de novo* or as a superinfection of an underlying viral pneumonia. Bacterial pneumonia will likely assume increasing importance in the near future due to the continuing emergence of antibiotic resistant bacteria. Knowledge of the pathogenesis of, and risk factors for, bacterial pneumonia are therefore critical to the development of strategies for treatment and prevention of these important and often fatal infections.

The pathogenesis of bacterial pneumonia in adults primarily involves aspiration of bacteria that colonize the oropharyngeal region into the lower respiratory tract and failure of host defense mechanisms to eliminate the contaminating bacteria which subsequently multiply and cause infection. Thus, the contents of the oropharyngeal secretions are directly related to the potential for respiratory infection. Common respiratory pathogens such as *Streptococcus pneumoniae, Streptococcus pyogenes, Mycoplasma pneumonia,* and *Haemophilus influenzae* can colonize the oropharynx and be aspirated into the lower airways. In addition, pneumonia can be caused by the aspiration into the lower airways of oral bacteria such as *Actinobacillus actinomycetemcomitans,*[63,64] *Actinomyces israelii,*[65,66] *Capnocytophaga* sps.,[67] *Eikenella corrodens,*[68] *Prevotella intermedia,* and *Streptococcus constellatus.*[69] Studies using careful sampling and strict anaerobic culture conditions have found that up to 10% of community acquired pneumonia and 25% of nosocomial pneumonia could be attributed to anaerobic agents.[70,71]

It is also becoming increasingly apparent that potential respiratory pathogens may become established in the oral flora of patients with periodontal disease. Gram-negative bacilli, such as enteric species and *Psuedomonas aeruginosa* commonly associated with hospital-acquired pneumonia, are cultivable from the subgingival flora of periodontally diseased patients.[72,73] The prevalence of staphylococci, Enterobacteriaceae, and yeasts in plaque samples from subjects with periodontitis has been estimated to be as high as 77%.[74] In most instances, the proportion of these microorganisms in relation to other plaque organisms is usually relatively low (<1%). Importantly, the prevalence of potential respiratory pathogens such as *S. aureus,* Enterobacteriaceae, and *Pseudomonas* increases in periodontal patients following treatment with antibiotics.[75,76]

Several mechanisms can be hypothesized to explain oral colonization and pneumonia caused by respiratory pathogens in susceptible patients. First, medically compromised individuals, such as alcoholics or diabetics, may be prone to oropharyngeal colonization by potential respiratory pathogens.[77,78] This may be due, in part, to their compromised swallowing reflexes that also lead to aspiration. In addition, diabetics also suffer from high levels of periodontal disease.[55] Dental plaques of these subjects may also provide a surface to which respiratory pathogens adhere to provide a reservoir for infection to distal portions of the respiratory tract.[79] This notion is supported by the observation that medical intensive care unit patients, who tend to have poor oral hygiene, often harbor respiratory pathogens in their dental plaque.[80] Hence, potential respiratory pathogens adherent to bacteria in the subgingival plaque of patients with periodontitis may emerge in greater numbers following treatment with antibiotics.[75,76] These bacteria may then be aspirated to cause respiratory disease, especially in patients with compromised defenses.

Subjects with high risk for pneumonia, such as the hospitalized patient, may be more prone to oral colonization by respiratory pathogens following mucosal modification due to prolonged exposure to dental plaque. For instance, *P. aeruginosa* adheres better to oral epithelial cells obtained from patients colonized by respiratory pathogens than to epithelial cells obtained from non-colonized patients.[81] Also, prior protease treatment of epithelial cells from non-colonized patients increases bacterial adherence in vitro. Hence, the protease activity of saliva, which increases with increased plaque formation,[82,83] may have a direct effect on the nature of the surfaces exposed in the oropharynx. These proteolytic enzymes, whose origin is likely dental plaque bacteria, may alter the characteristics of the mucosal surfaces, resulting in increased colonization of the oropharynx by respiratory pathogens.[84,85]

It is also possible that other pulmonary diseases may be adversely influenced by oral conditions. Chronic bronchitis is an inflammatory condition associated with excessive tracheobronchial mucous production sufficient to cause cough with expectoration for at least 3 months of the year for 2 or 3 excessive years. Emphysema is the destruction of the air spaces distal to the terminal bronchiole with destruction of the alveolar septa. Chronic obstructive pulmonary disease (COPD) is characterized by chronic obstruction to airflow due to chronic bronchitis and/or emphysema. It is possible that aspiration of (oral)

bacteria may exacerbate the course of COPD.[86] However, the potential mechanism(s) by which poor oral health might adversely influence COPD is presently unclear.

Adverse Pregnancy Outcomes

While infant mortality rates have declined in past years, low birth weight (<2500 g) in preterm infants remains a significant cause of perinatal morbidity and mortality. Recognized risk factors for preterm low birth weight (PLBW) infants include older (>34 years) or younger (<17 years) maternal age; African-American ancestry; low socio-economic status; inadequate prenatal care; drug; alcohol and/or tobacco abuse; hypertension; genitourinary tract infection; diabetes; and multiple pregnancies.[87] Despite increasing efforts to diminish the effects of these risk factors through preventive interventions during prenatal care, there appears to be a rather small decrease in the number of PLBW infants.[88]

There is reason to believe that other, heretofore unrecognized, risk factors may contribute to the continuing prevalence of PLBW infants. One possible contributing factor to this phenomenon is the effect of infection on PLBW. It is possible that subclinical genitourinary or other infections may adversely effect pregnancy outcomes.[89-91] It is thought that a variety of biologically active molecules such as prostaglandin E_2 (PGE_2) and TNFα, which are normally involved in normal parturition, are raised to artificially high levels by the infection process, which may foster premature labor. Periodontal infection may also influence pregnancy outcomes by providing a source of bacterial components such as lipopolysaccharides, which trigger release of immune modulators such as PGE_2 and TNFα that, in turn, may influence the course of pregnancy. Evidence to support this model has been obtained in rodents where maternal exposure to periodontal infection or bacterial products such as lipopolysaccharides are associated with deleterious effects on the fetus.[92,93] Human studies have attempted to correlate PLBW of infants with the presence of periodontal disease in the mother. In a case control study, mothers of PLBW infants, having otherwise low risk, had significantly more periodontal attachment loss than control mothers having normal weight infants at birth.[87]

Behavioral and Psychosocial Status

The relationship between oral health and the perception of well-being has been examined by a number of investigators.[94-95] Several studies have documented the impact of dental disease on psychosocial, health, and economic aspects of younger and older adults.[96-98] Oral diseases can lead to pain and malaise, such as that associated with dental abscesses and chronic infections, which directly impact a patient's sense of well-being. Also, since the mouth is involved in speech, and much socialization and pleasure is derived from food and drink.[99] poor oral function and hygiene can lead to loss of life satisfaction,[100] and raise concerns with self-presentation and fears of embarrassment. This in turn can affect socialization and self esteem.[101] It has been suggested that oral health promotion among non-depressed older adults can lead to their improved morale.[102] Conversely, individuals who are ill, disengaged, or depressed may not be as conscientious in their oral hygiene and so contribute to poor oral status.

Other Diseases

Occasionally, oral bacteria that enter the systemic circulation can form abscesses in various organs. For example, although rare, brain abscesses caused by oral bacteria are occasionally reported.[66,103-106]

It has also been reported that unusual microorganisms colonizing the oral cavity of patients with inflammatory bowel disease (Crohn's disease, ulcerative colitis) potentially play a role in the pathogenesis of the disease as infectious agents or modifiers of the host response or both.[107] However, at least one clinical study concluded that patients afflicted with inflammatory bowel disease are no more prone to severe periodontal disease than the general population.[108]

Several interesting parallels may be drawn when comparing the pathogenesis of arthritis and periodontal diseases. Both have an inflammatory etiology resulting in the localized resorption of bone. Both diseases can be induced by bacterial products (such as LPS) that bind to and stimulate monocytes and osteoblasts to secrete cytokines and eicosanoids, which can then induce the recruitment and activation of macrophages and osteoclasts[109] and the release of tissue collagenases.[2] Both diseases respond to treatment with non-steroidal-anti-inflammatory medications.[110] However, in spite of the similarities in pathogenic mechanisms, recent reports suggest that the evidence to associate periodontitis and arthritis is equivocal.[111-114] It is therefore somewhat ironic that the focal infection hypothesis was conceived upon the premise that chronic arthritis was caused by "oral sepsis arising largely as a result of the reconstructive efforts of the dental profession."[7]

Future Research Directions

The studies discussed above suggest that periodontal inflammation is a potential contributing factor to a rather wide variety of systemic diseases. In most cases further studies are required to strengthen the associations suggested by preliminary studies. The strongest association noted so far is that between dental plaque and periodontal inflammation with SBE. It also appears that preliminary retrospective and prospective epidemiologic studies support the notion that periodontal disease is a risk indicator for cardiovascular disease.[40,45] The latter association could be further strengthened by interventional studies that at-

tempt to reduce the risk for cardiovascular disease following treatment or prevention of periodontal infections.

A relationship between periodontal disease and diabetes mellitus has been established and it is clear that diabetic control is important in management of periodontal diseases. It also appears that periodontal infections may adversely affect diabetic metabolic control, and treatment of periodontal disease appears to result in better metabolic control of type 2 diabetes. Further longitudinal interventional studies are necessary to better define the utility of periodontal prevention and therapy in the management of both type 1 and type 2 diabetes mellitus.[60]

The association between periodontal disease and respiratory disease remains largely theoretical. Hospitalized patients are an ideal target group to investigate the role of periodontal disease in respiratory infection given their high risk for nosocomial pneumonia. Relevant studies to be performed include prospective longitudinal studies comparing pneumonia rates in hospitalized subjects with and without periodontal disease, and interventional studies to assess the effect of periodontal therapy on the incidence of pneumonia in these subjects.

The relationship between periodontal inflammation and low birth weight newborns merits further study. Given the rather high incidence of low birthweight complications (as high as 10% of all births[115]), it is important to determine if periodontal disease is a true risk factor for low birth weight. It is also important to determine to what extent maintenance of periodontal health through pregnancy would decrease the incidence of this condition.

Presently, the major rationale for the treatment of periodontal disease is to prevent progression of the disease to preserve the dentition. The above discussion points out the potential impact of periodontal disease on systemic health. In the future, an additional rationale for periodontal therapy may be to prevent untoward effects on systemic health. Further intervention studies are needed to clarify the impact of the treatment of periodontal infections to manage or prevent systemic conditions such as subacute bacterial endocarditis; diabetes mellitus; thromboembolic diseases such as coronary artery disease and stroke; respiratory infections; and preterm low birth weight infants.

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