Periodontal disease is a common, mixed oral infection affecting the supporting structures around the teeth (Figure 1). Seventy-five percent of the adult population has at least mild periodontal disease (gingivitis), and 20% to 30% exhibit the severe destructive form (periodontitis). Periodontal disease begins with a pathogenic shift in the bacterial flora around teeth (Figure 2). More than 500 bacterial species inhabit the human oral cavity; however, only a characteristic subset causes gingivitis and periodontitis. Gram-negative bacteria, such as Prevotella intermedia, Fusobacterium
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**ORAL AND SYSTEMIC INFLAMMATION AND CVD**

CVD is the world’s leading cause of death. Atherosclerosis, which is a major component of CVD, affects 1 in 4 persons and contributes to 38% of deaths annually in the United States. Traditional CVD risk factors—such as smoking, poor diet, lack of exercise, hypercholesterolemia, hypertension, diabetes, and some genetic markers—do not appear to fully account for the development of atherosclerosis, because many patients with atherosclerosis lack these exposures or genotypes entirely. Therefore, current attention has focused on potential links between CVD and periodontal disease.

Researchers have been conducting studies to identify mechanisms that may explain the association between periodontal disease and CVD. Four possible pathways have been hypothesized: (1) bacterial effects on platelets, (2) endocrine-like effects of inflammatory mediators, (3) autoimmune responses, and (4) endothelial invasion of bacteria.

Two types of oral bacteria, P. gingivalis and Streptococcus sanguis, express virulence factors called collagen-like platelet-aggregation–associated proteins that induce platelet aggregation in vitro and in vivo. These outer-membrane–associated proteins appear to contain the same amino acid sequence as the platelet-interactive domains of types 1 and 2 collagen. Thrombi secondary to oral pathogens may exacerbate the progression of ath-

**nucleatum, Porphyromonas gingivalis, Tannerealla forsythenis, Treponema denticola, and Actinobacillus actinomyctematocimilans**, infect the subgingival space and organize as a biofilm. This bacterial biofilm is in direct contact with host tissues along an ulcerated epithelial interface called a gingival or periodontal pocket. The break in the epithelial integrity directly exposes the host to bacteria and their products (e.g., lipopolysaccharide [LPS] endotoxin). If the bacteria can be effectively cleared via the polymorphonuclear leukocyte axis, the disease is limited to gingivitis. However, if this axis is ineffective, the bacteria and their products penetrate host periodontal tissues, which may initiate periodontitis. This event stimulates the monocyte-macrophage axis and upregulates the expression of local inflammatory mediators, such as prostaglandin E2, interleukin-1 (IL-1), and tumor necrosis factor-alpha (TNF-α). These mediators, in turn, trigger catabolic events leading to the clinical signs of periodontal disease (gingival erythema, edema, bleeding, periodontal pocket formation, clinical attachment loss, and alveolar bone resorption).

Mounting evidence indicates that local periodontal infection triggers systemic inflammatory responses via transient bacteremias in affected patients (Figure 3). Accordingly, bacteremias can occur in periodontally diseased patients after mastication or manipulation of oral tissues, and bacterial load appears to increase with periodontal disease severity. In addition, periodontal pathogens shed vesicles of endotoxin at the biofilm–host interface and thus cause chronic, low-grade endotoxemias. Circulating LPS associates with a host-binding protein (LPS-binding protein) and promotes adipose tissue production of interleukin-6 (IL-6), which subsequently stimulates the hepatic acute-phase response. Two recent analyses from the Third National Health and Nutrition Evaluation Survey (NHANES III) confirm that clinical periodontal disease is significantly associated with increased serum levels of the acute-phase markers C-reactive protein (CRP) and fibrinogen. Independent studies demonstrate that patients with elevated serum CRP and fibrinogen exhibit an increased risk for cardiovascular disease (CVD) events, such as myocardial infarction (MI) or stroke. In pregnant women, these CVD events may trigger early uterine contractions and preterm delivery. Lastly, these bacteremias and the subsequent systemic inflammatory responses may complicate glycemic control in diabetic patients.
erosclerosis and promote ischemic events.

According to a second pathway hypothesis, proinflammatory mediators produced locally in diseased periodontal tissues could spill over into the vascular compartment for systemic, endocrine-like effects. This pathway hypothesis is supported by the finding of increased hepatic production of CRP and fibrinogen among patients with periodontal disease.\(^5,10\) CRP and fibrinogen, in turn, may induce cellular events in atherogenesis, such as intercellular adhesion molecule-1 expression and clot formation.\(^11,18\) It has also been suggested that autoimmune responses secondary to periodontal infection may occur in cardiovascular tissues. Antibodies cross-reacting with periodontal bacteria and human heat-shock proteins have been identified and may explain inflammatory events in CVD.\(^19-21\)

CVD may also be directly affected by the bacteria from periodontal disease. Deshpande and colleagues have demonstrated that oral pathogens, such as \(P\) ginvialis, can invade aortic and heart endothelial cells via fimbriae.\(^22\) At least 3 investigative groups have independently identified oral pathogens in atheromatous tissues. Using immunologic staining, Chiu detected \(P\) ginvialis in 42% of human atherosclerotic lesions.\(^23\) Haraszthy and colleagues analyzed human carotid atheromas using polymerase chain reaction (PCR) techniques and demonstrated that 30% of the specimens were positive for \(T\) forsythen-sis, 26% for \(P\) ginvialis, 18% for \(A\) actinomycetemcomitans, and 14% for \(P\) intermedia.\(^24\) In a third study, \(A\) actinomy-cetemcomitans was found in samples of aortic aneurysms.\(^25\) Collectively, these findings indicate that specific periodontal pathogens may play a direct role in the development of CVD.

Experimental data from animal models also support the association between periodontal disease and CVD via periodontal bacterial–host inflammatory mechanisms. Informative studies of inbred heterozygous and homozygous apo-E-deficient mice exhibited increased aortic atherosclerosis when mice were challenged orally or intravenously with invasive strains of \(P\) ginvialis.\(^26-29\)

While \(P\) ginvialis challenges increased aortic atherosclerosis in apo-E-deficient mice in a hypercholesterolemic background only, normocholesterolemic pigs recently were shown to develop both coronary and aortic lesions with \(P\) ginvialis challenges.\(^30\) This finding suggests that \(P\) ginvialis bacteremias may exert an atherogenic stimulus independent of hypercholesterolemia in pigs.

Of note, a wide range of \(P\) ginvialis doses were used in the mice studies ranging from approximately \(4 \times 10^9\) colony-forming units (CFU)/kg intravenously weekly,\(^26,29\) to \(8 \times 10^7\) CFU/kg orally weekly,\(^27\) to \(4 \times 10^4\) CFU/kg orally weekly,\(^28\) while the pigs received \(5 \times 10^9\) CFU/kg intravenously 3 times weekly. The clinically relevant dose is unknown at present and probably varies greatly.\(^11-13\)

Of note, \(P\) ginvialis challenges consistently increased the amount of atherosclerosis despite the different routes of administration and dosing regimens used for both species. However, these animal models make it possible to determine the significance of the different routes of \(P\) ginvialis administration or access to the vasculature. Also, \(P\) ginvialis 16-ribosomal deoxyribonucleic acid (DNA) was detected by PCR in some but not all of these mutant mice and the pigs. Taken together, these data suggest that both the host response and the virulence of the specific \(P\) ginvialis strains are 2 of the most important variables in these models.\(^26,34-36\)

Recent findings from a large population study, the Oral Infections and Vascular Disease Epidemiology Study, support a relationship between periodontal bacteria and subclinical atherosclerosis.\(^37\) Within a population of approximately 1,000 individuals without histories of MI or stroke, the presence of subgingival bacteria was evaluated using DNA techniques and atherosclerosis was evaluated using B-mode ultrasound. Mean carotid artery intimal medial thickness (IMT) was significantly related to overall periodontal bacterial burden and to the presence of specific bacteria causally related to periodontal disease (\(P\) ginvialis, \(T\) forsythen-sis, and \(A\) actinomycetem-comitans). These findings provide strong evidence that specific periodontal pathogens are associated with subclinical vascular disease.

**POOR ORAL HEALTH AND CVD**

Several studies have concentrated on the correlation between poor oral health and CVD. In an early case-control study, Mattila and colleagues reported that poor oral health (including periodontal disease) was a predic-
The investigators found that individuals with evidence of oral infection were 30% more likely to present with MI than subjects without oral infections. This association was significant after adjustment for known risk factors, such as age, total cholesterol levels, hypertension, body mass index (BMI), and smoking. In a follow-up study with the same population, these investigators documented a significant and specific association between dental infections and severe coronary atherosclerosis for men.

More recently, Arbes and colleagues evaluated available cross-sectional data from the NHANES III. For subjects with severe clinical attachment loss and periodontal disease, the odds ratio (OR) for MI was 3.8 compared with periodontally healthy controls.

A longitudinal cohort study conducted by DeStefano and colleagues evaluated the disease association among 9,760 US adults followed for 14 years in NHANES I. Several potentially confounding variables also were examined, including age, gender, race, education, marital status, systolic blood pressure, total cholesterol levels, BMI, diabetic status, physical activity, alcohol consumption, economic level, and smoking.

Individuals with preexisting clinical signs of periodontal disease were 25% more likely to develop coronary heart disease (CHD) than individuals with minimal periodontal disease, after adjusting for other known risk factors or confounders. Indeed, men younger than age 50 with periodontal disease in this study were 72% more likely to develop CHD than their periodontally healthy counterparts.

Using this same database, Wu and colleagues evaluated the potential contribution of periodontal disease to stroke risk and reported that the presence of clinical periodontal disease significantly increased the risk for both fatal and nonfatal strokes 2-fold.

Increased relative risks for total and nonhemorrhagic strokes were observed for both genders, Whites, and African Americans with periodontal disease. Beck and colleagues examined the periodontal status of 1,147 men, aged 21 to 80, who were participants in the Normative Aging Study and were free of CHD at baseline. The ORs adjusted for age and established cardiovascular risk factors were 1.5, 1.9, and 2.8 for periodontal bone loss and total CHD, fatal CHD, and stroke, respectively.

When the researchers graphed the cumulative incidence of CHD or events vs baseline mean alveolar bone loss, they noted a linear relationship between the increasing severity of periodontal disease and the higher rates of CVD.

Recent population studies conducted by Beck and colleagues have focused on the relationship between periodontal disease and subclinical atherosclerosis. The group collected periodontal probing data on 6,017 persons, aged 52 to 75, who were participants in the Atherosclerosis Risk in Communities study. Subclinical atherosclerosis or carotid artery IMT was measured using B-mode ultrasound.

After adjustment for covariates, such as age, gender, diabetic status, lipids, hypertension, and smoking, a logistic regression analysis indicated a significant association between severe periodontal disease and thickened carotid arteries. The OR for severe periodontal disease (eg, 30% or more sites with ≥3 mm clinical attachment loss) and subclinical carotid atherosclerosis was 1.31 (95% confidence interval [CI], 1.03-1.66).

In contrast, at least 3 large observ-

![Figure 2](image-url)
tional studies failed to detect any significant association between the clinical signs of periodontal disease and CVD. Scannapieco and colleagues recently conducted a systematic review addressing the focused question, “Does periodontal disease influence the initiation/progression of atherosclerosis and, therefore, CVD, stroke, and peripheral vascular disease?” Although they could not perform a meta-analysis because of differences in reported outcomes, they noted relative consistency among the studies and concluded, “Periodontal disease may be modestly associated with atherosclerosis, MI, and CV events.” An accompanying consensus report approved by the American Academy of Periodontology recommends, “Patients and health care providers should be informed that periodontal intervention may prevent the onset or progression of atherosclerosis-induced diseases.”

**ORAL INFLAMMATION AND PREGNANCY COMPLICATIONS**

Although there has been an overall decline in infant mortality in the United States over the past 40 years, preterm low birth weight (PLBW) remains a significant cause of perinatal mortality and morbidity, including chronic respiratory diseases and cerebral palsy. Among the known risk factors for PLBW are young maternal age (<18 years); drug, alcohol, and tobacco use; maternal stress; genetics; and genitourinary tract infections. Although up to one half of PLBW deliveries occur in the absence of these factors, there is increasing evidence that periodontal infection may play a significant role in pregnancy complications. 

Offenbacher and colleagues conducted the first case-control study to explore the potential relationship between periodontal disease and pregnancy complications among 124 pregnant or postpartum women. These investigators defined cases as mothers having infants weighing <2,500 g, gestationally aged <37 weeks, or with preterm labor or preterm premature rupture of membranes. Overall, mothers with PLBW infants had significantly more advanced periodontal disease, as measured by attachment loss, than the respective mothers with normal birth weight infants. Multivariate logistic regression models, controlling for other known risk factors and covariates, demonstrated that periodontal disease was a statistically significant risk factor for PLBW, with an adjusted OR of 7.9 and 7.5 for all PLBW cases and primiparous PLBW cases, respectively.

Jeffcoat and coworkers confirmed this association in a larger case-control study. Based on data on 1,313 mothers, these researchers found that maternal periodontal disease was associated with preterm birth. With increasing severity of periodontal disease as an exposure, there was an increased risk for preterm birth, with an OR ranging from 4.45 to 7.07 for moderate-to-severe periodontal disease, after adjusting for age, race, smoking, and parity.

Further evidence of this was demonstrated by Madianos and colleagues, who found that mothers with baseline periodontal disease that progressed or worsened during the pregnancy were almost 11 times more likely to have a PLBW infant compared with periodontally healthy, stable mothers. When the investigators evaluated maternal immune responses to periodontal pathogens, they noted a significantly higher rate of prematurity occurring among mothers without a protective immunoglobulin G response coupled with a fetal immunoglobulin M response to periodontal pathogens (combined OR = 10.3). These immunologic data support the concept that maternal periodontal infection in the absence of a protective maternal antibody response is associated with fetal exposure to periodontal pathogens and prematurity.

**ORAL INFLAMMATION IN PATIENTS WITH DIABETES**

Diabetes mellitus—a multifactorial disease process involving genetic, environmental, and behavioral risk factors—affects more than 177 million people worldwide. This long-term condition is marked by defects in glucose metabolism at the pancreatic beta cell or at the target tissue receptor that produce hyperglycemia in patients. End-stage diabetes mellitus is characterized by problems with several organ systems, including
microvascular (retinopathy, nephropathy, neuropathy) and macrovascular disease (atherosclerosis) and periodontal disease.

Numerous epidemiological surveys demonstrate an increased prevalence of periodontal disease among patients with uncontrolled or poorly controlled diabetes mellitus. For example, a cross-sectional analysis of 1,342 dental patients conducted by Emrich and colleagues demonstrated that patients with diabetes are 3 times more likely to present with inflammatory periodontal disease. New data have emerged indicating that the presence of untreated periodontal infection can increase the risk of poor glycemic control. Taylor and coworkers first tested this hypothesis longitudinally within a population prone to type 2 diabetes, the Pima Indians. The investigators found that severe periodontal disease at baseline was significantly associated with poor glycemic control (glycated hemoglobin >9%). Other significant covariates in the regression modeling included patient age, smoking history, baseline severity, and duration of type 2 diabetes.

Several subsequent investigators have evaluated whether periodontal interventions can improve glycemic control in patients with diabetes. These studies, in general, failed to detect improvements in glycated hemoglobin levels using mechanical periodontal therapy.

One clinical trial conducted by Grossi and colleagues is an exception. This trial featured 113 Pima Indians with type 2 diabetes and periodontal disease who received both mechanical and antimicrobial treatment. At baseline, participants were treated with scaling and root planing plus 1 of 5 different antimicrobial regimens (peroral antibiotics and topical mouthrinses). On average, all treatment groups demonstrated periodontal probing and microbiological improvements; however, the patients treated with adjunctive peroral doxycycline exhibited significantly greater reductions in pocket depth and subgingival detection rates for P. gingivalis than patients receiving peroral placebo. Most strikingly, patients with diabetes receiving mechanical therapy plus peroral doxycycline demonstrated significant reductions (10%) in their glycated hemoglobin levels. Two small, uncontrolled cohort studies of patients with type 1 diabetes and periodontal disease demonstrated similar improved glycemic control with combination mechanical-antimicrobial therapy.

The limited evidence from intervention trials suggests that untreated periodontal infections may increase a diabetic patient’s risk for poorer glycemic control and subsequent systemic complications, which may include premature mortality. In a recent longitudinal study of subjects with type 2 diabetes, the age- and gender-adjusted mortality rates for all natural causes (expressed as the number of deaths per 1,000 person-years of follow-up) were 3.7 (95% CI, 0.7-6.6) for no or mild periodontal disease, 19.6 (95% CI, 10.7-28.5) for moderate periodontal disease, and 28.4 (95% CI, 22.3-34.6) for severe periodontal disease. Accordingly, the presence of periodontal disease significantly predicted deaths from ischemic heart disease and nephropathy.

CONCLUSION

A subset of the diverse bacterial flora inhabiting the human mouth causes the common inflammatory conditions of gingivitis and periodontitis. As a person develops these conditions, bacteria and their products can penetrate host tissues and enter the bloodstream resulting in systemic effects. Mounting evidence indicates that oral inflammation may be a significant risk factor for several systemic conditions, such as CVD, PLBW, and complications from diabetes.

Data from human clinical trials are limited; however, recent intervention data indicate that patients with periodontal disease who receive treatment exhibit decreases in CRP, an acute-phase biomarker and predictor of CVD events. Similarly, pregnant women with untreated periodontal disease are more than 4 times more likely to have a preterm birth compared with mothers with periodontal disease who receive treatment during their pregnancy. In addition, patients with diabetes and periodontal disease may...
Emphasizing early management of oral health can be incorporated into the patient’s treatment regimen. According to the Surgeon General’s landmark report on oral health, “the mouth can function as an ‘early warning’ system for some diseases and can provide a useful means to understand organs and systems in other parts of the body.”

During the oral examination, physicians should look for signs of periodontal disease, such as bright red gums, pus around the teeth, lost teeth, bad breath, pain around the teeth, and any bleeding when the teeth are brushed.

Physicians also can play a role in preventing gingivitis and periodontal disease by advising their patients to brush and floss each day, eat right, avoid cigarettes and other forms of tobacco use, and encouraging them to see their dentist on a regular basis. Physicians should remind the patient to conduct a monthly self-exam and to contact the dentist if they notice signs of infection, such as sore, swollen, or bleeding gums or mouth ulcers.

Using dentifrices with fluoride can help prevent these diseases. In addition, there are dentifrices clinically shown to prevent gum disease that have been approved by the US Food and Drug Administration.

Antimicrobial agents also can play a role in the prevention and treatment of periodontal disease. Several antimicrobial agents have been incorporated into mouthrinses and dentifrices to inhibit plaque accumulation. Triclosan, a well-known antibacterial agent, has a wide spectrum of action against plaque-forming supragingival and subgingival bacteria, including many types of gram-positive and gram-negative nonsporulating bacteria.

The combination of triclosan with a copolymer allows the agent to remain on the tooth surface for a prolonged period of time, providing effective inhibition of plaque formation and gingivitis. A dentifrice containing triclosan/copolymer (eg, Colgate® Total® toothpaste) has been shown to effectively contribute to the control of bacterial infection, reduce gingival inflammation, and slow the progression of periodontitis.

Over recent years, we have increasingly begun to focus on inflammation of the oral cavity, not only for disease of the periodontal tissue but also as a risk factor for systemic diseases. For example, because diabetes challenges the host, periodontal infections should be treated aggressively. Oral care for diabetic patients includes frequent oral debridement (ie, 2-3 months) to minimize periodontal infection, scaling and root planing, and topical solutions (eg, mouthrinses, irrigation). For patients who are poorly controlled, prophylactic antibiotics may be indicated.

It is evident that we can no longer view gingivitis simply as a precursor for periodontitis, but that we should treat it as oral inflammation that needs to be controlled and eliminated for overall well-being. Treatment strategies that have a beneficial effect on gingival oral health should have a beneficial effect on both oral health and systemic health.


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REFERENCES

10. World Health Organization. The World Health exhibits improvements in glycemic control secondary to therapy targeted at reducing oral inflammation.

These consistent relationships between oral inflammation and systemic diseases suggest an interdisciplinary model in managing patients who are at risk (Figure 4). Patients, dentists, physicians, and other health care providers should be aware of the emerging interrelationships between oral infection, inflammation, and systemic disease. Clinicians and patients also should appreciate the value of preventive strategies that reduce oral inflammation, improve dental health, and enhance overall patient well-being.

DISCLOSURE

The authors are paid consultants of The Colgate-Palmolive Company and are members of the Advisory Board for this publication.

REFERENCES