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Periodontal disease and systemic conditions: a bidirectional relationship

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Abstract

For decades, physicians and dentists have paid close attention to their own respective fields, specializing in medicine pertaining to the body and the oral cavity, respectively. However, recent findings have strongly suggested that oral health may be indicative of systemic health. Currently, this gap between allopathic medicine and dental medicine is quickly closing, due to significant findings supporting the association between periodontal disease and systemic conditions such as cardiovascular disease, type 2 diabetes mellitus, adverse pregnancy outcomes, and osteoporosis. Significant effort has brought numerous advances in revealing the etiological and pathological links between this chronic inflammatory dental disease and these other conditions. Therefore, there is reason to hope that the strong evidence from these studies may guide researchers towards greatly improved treatment of periodontal infection that would also ameliorate these systemic illnesses. Hence, researchers must continue not only to uncover more information about the correlations between periodontal and systemic diseases but also to focus on positive associations that may result from treating periodontal disease as a means of ameliorating systemic diseases.

Keywords

Periodontal diseases; Systemic diseases; Cardiovascular diseases; Diabetes; Adverse pregnancy outcomes; Osteoporosis

Etiology and pathogenesis of periodontal disease

Periodontal disease refers to the inflammatory processes that occur in the tissues surrounding the teeth in response to bacterial accumulations, or dental plaque, on the teeth. The bacterial accumulations cause an inflammatory response from the body. The chronic and progressive bacterial infection of the gums leads to alveolar bone destruction and loss of tissue attachment to the teeth. Periodontal disease has many states or stages, ranging from easily treatable gingivitis to irreversible severe periodontitis. Periodontal disease is increased by several risk factors: cigarette smoking; systemic diseases; medications such as steroids, anti-epilepsy drugs and cancer therapy drugs; ill-fitting bridges; crooked teeth and loose fillings; pregnancy; and oral contraceptive use. In addition to these variables, any medical condition that triggers host

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antibacterial defense mechanisms, such as human immunodeficiency virus (HIV) infection, diabetes, and neutrophil disorders, will likely promote periodontal disease.[1]

The most prevalent form of periodontal disease is a mild form called gingivitis. Gingivitis affects 75% of adults in the United States[2] and is characterized by inflammation of the gums, redness, swelling, and frequent bleeding.[3] More advanced forms of periodontitis are also prevalent, affecting approximately 30% (moderate disease) and 10% (advanced disease) of the adult population in the United States.[4] The symptoms are similar to those of gingivitis, but are more severe due to higher accumulations of bacteria and stronger inflammatory responses.

In diagnosing the extent of periodontal disease, the probing depth is a good indicator of the advance of the disease. In a healthy periodontium, there is no loss of epithelial attachment or pocket formation, and the periodontal pocket is less than 2 mm deep.[5] Periodontal pockets can extend between 4 and 12 mm. Clinically, patients with periodontal pockets of 4 mm or more are diagnosed with periodontitis. Patients with periodontal pockets of 6 mm or more are diagnosed with advanced or severe periodontitis.[6,7] Due the minimal symptoms of gingival bleeding and attachment loss, many individuals neglect to treat their disease. Left untreated, gingivitis may progress to irreversible periodontitis, resulting in tooth loss.

Once diagnosed, most periodontal diseases can be treated successfully. The therapeutic goals in periodontal disease are: first, to alter or eliminate the origin of the microbes as well as contributing risk factors, thereby preventing the progression of the disease and preserving the healthy state of the periodontium. Second, the recurrence of periodontitis must be prevented. Finally, in severe cases, regeneration of the periodontal attachments must be attempted.[8] The first nonsurgical step involves special cleaning called scaling and root planing. Supplemental treatment may include an antiseptic mouth rinse and medication, either to aid the healing process or to further control the bacterial infection. Often, antibiotics may be administered, which may offer an effective alternative to scaling and root planing. Tetracycline or a combination of amoxicillin and metronidazole may be used in order to kill a broad range of bacteria.[9,10] However, if overused, these agents may not kill the bacteria. Another drawback to antibiotic therapy lies in the difficulty of identifying and targetting a specific pathogen, due to the numerous species residing in the plaque. Surgical treatment along with antibiotic therapy may therefore be beneficial to periodontal disease patients. If the periodontal pockets are not reduced, or if further loss of alveolar bone is observed, then surgical intervention is clearly needed to try to prevent tooth loss.

Surgical treatment of periodontal disease by a periodontist consists of removing inflamed tissues to reduce the damage to the alveolar bone around the area of infection. Furthermore, surgery allows dentists to access areas where scaling and root planing cannot remove tartar and plaque. The elimination of bacterial accumulations helps regenerate bone and tissue, to help reduce pockets. Additional procedures, such as bone grafts, target bone regeneration and growth. If the periodontal disease has caused excessive loss of gum tissue, then soft-tissue grafts may be performed to reduce further gum recession and bone loss.

The oral cavity is an open system exposed to the environment. Furthermore, the possibilities of foreign material entering the system from the oral cavity are heightened due to the constant intake of food and liquids through the mouth. The presence of the large numbers of bacteria can induce tissue destruction indirectly by activating host defense cells, which in turn, produce and release mediators that stimulate the effectors of connective tissue breakdown. Components of microbial plaque have the capacity to induce an initial infiltrate of inflammatory cells, including lymphocytes, macrophages, and polymorphonuclear leukocytes (PMNs). Microbial components, especially lipopolysaccharide (LPS), activate macrophages to synthesize and secrete a variety of proinflammatory molecules, including the cytokines interleukin-1 (IL-1)

and tumor necrosis factor-alpha (TNF-alpha); prostaglandins, especially prostaglandin E_2 (PGE_2); and hydrolytic enzymes. Similarly, bacterial substances activate T lymphocytes to produce IL-1 and lymphotoxin (LT), a molecule with similar properties to TNF-alpha. These cytokines manifest potent proinflammatory and catabolic activities, and play key roles in periodontal tissue breakdown through collagenolytic enzymes such as metalloproteinases (MMPs).[11] These latent collagenolytic enzymes are activated by reactive oxygen species in the inflammatory environment, giving rise to elevated levels of interstitial collagenase in inflamed gingival tissue.[12] The attachment loss deepens the sulcus, creating a periodontal pocket. This provides a microbial niche, such that periodontal pockets with depths of 4 to 12 mm can harbor on the order of 10^7 to 10^9 bacterial cells.[13] This event marks the transition from gingivitis to periodontitis.

Several amplification and suppression mechanisms are also involved in the process. The progression and extent of tissue degradation is determined in large part by the relative concentrations and halflives of IL-1, TNF-alpha, and related cytokines, of competing molecules such as the IL-1 receptor antagonist, and of suppressive molecules such as transforming growth factor (TGF)-beta and PGE_2.[14]

Another effective host defense mechanism is the highly vascularized nature of the gingival tissue, presenting an oxidative barrier to the penetration of anaerobic bacteria from dental plaque.[15] Conditions such as smoking and stress are risk factors for periodontal disease, because they cause vasoconstriction of the peripheral arterioles, thereby reducing blood flow to the gingival tissue.This provides the anaerobes ample time to survive in the tissues and to activate latent collagenases. The selection for anaerobes rather than for more harmful facultative species may actually be beneficial to the host, because facultative species, if dominant, have even worse effects, causing tissue invasion and necrosis.[1]

In the past three decades, marked advances have occurred in our understanding of the infectious agents of periodontal disease. Approximately 500 different bacterial entities and various human viruses are associated with dental microbial plaque.[16] The most frequently identified periodontal pathogens include three microaerophilic species (Actinobacillus actinomycetemcomitans, Campylobacter rectus, and *Eikenella corrodens*) and seven anaerobic species (*Porphyromonas gingivalis, Bacteroides forsythus, Treponema denticola, Prevotella intermedia, Fusobacterium nucleatum, Eubacterium*, and spirochetes). Socransky et al.[17] divided the pathogens into two main clusters of microorganisms and deemed them the “red” and “orange” complexes. Furthermore, they defined “green”, “yellow”, and “purple” complexes as the bacterial colonies that formed on the tooth surface prior to the colonization of the “orange” and “red” complexes. The “red” complex consisted of three tightly related species: *T. forsythensis*, *P. gingivalis* and *T. denticola*. This complex is strongly related to pocket depth and bleeding on probing. Another complex (“orange” complex”) included F. nucleatum/periodonticum subspecies, P. intermedia, P. nigrescens, Peptostreptococcus micros, C. rectus, C. gracilis, C. showae, Eubacterium nodatum, and *Streptococcus constellatus*, and seemed to precede colonization by species of the “red” complex. The “yellow” complex comprised six *Streptococcus* species: *Streptococcus sp.*, *S. sanguis*, *S. oralis*, *S. intermedius*, *S. gordonii*, and *S. mitis*, while *Capnocytophaga ochracea*, *Capnocytophaga gingivalis*, *Capnocytophaga sputigena*, *E. corrodens*, and *A. actinomycetemcomitans* serotype a made up the “green” complex. The fifth and final complex, the “purple” complex, consisted of Veillonella parvula, Actinomyces odontolyticus, A. actinomycetemcomitans serotype b, *Selenomonas noxia*, and *Actinomyces naeslundii* genospecies 2 (*Actinomyces viscosus*), but these did not constitute any cluster or ordination group.[17] Within the past 7 years, various herpes viruses, such as human cytomegalovirus (HCMV) and Epstein-Barr virus (EBV-1), have also emerged as pathogens in destructive periodontal disease.[18]

Within the past 10 years, many studies have been published indicating a positive or negative relationship between periodontal disease and various systemic disorders and diseases. Depending on the outcome of the studies, a positive correlation reflects a strong case for the relationship as opposed to a negative or no correlation. Significant associations between periodontal disease and cardiovascular disease, diabetes mellitus, preterm low birth weight, and osteoporosis have been discovered, bridging the once-wide gap between medicine and dentistry. Researchers have hypothesized the etiologic role of periodontitis in the pathogenesis of these systemic illnesses. Therefore, patients diagnosed with periodontal disease may be at higher risk due to a compromised immune system. Infectious and opportunistic microbes responsible for periodontal infection may thus bring a burden onto the rest of the body. Furthermore, these microbes can release products that elicit an inflammatory response. Periodontal lesions are recognized as continually renewing reservoirs for the systemic spread of bacterial antigens, Gram-negative bacteria, cytokines, and other proinflammatory mediators.[19,20]

Periodontal disease and cardiovascular disease (CVD)

Cardiovascular disease (CVD) is a common cause of death, accounting for 29% of deaths worldwide.[16] Estimates from the year 2002 show that more than 70 million Americans were diagnosed with one of the forms of CVD, which include high blood pressure, coronary heart disease (myocardial infarction and angina pectoris), peripheral arterial disease, and stroke, with atherosclerosis as the principal cause of all CVDs. Atherosclerosis is thus responsible for 50% of all mortality in the United States, Europe, and Japan.[21] After adjustment of other risk factors, studies indicate that severe periodontal disease is associated with a 25% to 90% increase in risk for CVD.[22] One study showed that 91% of patients with CVD demonstrated moderate to severe periodontitis, while 66% of cardiologically healthy patients had periodontitis. The same study showed a statistically significant correlation between coronary artery disease and periodontitis.[13]

Periodontal disease may be associated with CVD due to mutual risk factors for atherogenesis and periodontal disease. In order to consider periodontal disease as a risk factor for atherosclerosis and other CVDs, the presence of pathogens associated with periodontal infection should be localized in serum or atheromatous plaques.[23] Investigating this by sampling carotid atheromatous plaques, Cairo et al.[24] detected *T. forsynthensis* DNA in 79%, *F. nucleatum* in 63%, *P. intermedia* in 53%, *P. gingivalis* in 37%, and *A. actinomycetemcomitans* in 5% of the samples from carotid atheroma patients. In addition to carotid, coronary, and aortic atherosclerotic plaques, these various oral bacteria were also detected in occluded arteries from patients with Buerger Disease.[25] One would expect that these pathogens would induce the release of proinflammatory cytokines. Etiologically, gentle mastication releases bacterial endotoxins from the oral cavity into the bloodstream, inducing cytokine production (TNF, IL-1, and PGE_2).[13] Further, animal studies should be able to demonstrate atherosclerosis induced by periodontal pathogens.[26] Animal models provide a more thorough understanding of the pathogenesis of CVD; specifically, with the use of gene-targeted animals such as the apolipoprotein E-knockout (apoE −/−) mouse.[27–29]

Etiologically, the chronic presence of periodontal microbes can lead to atherogenesis via two pathways: (1) direct invasion of the arterial wall[23] and (2) the release, in response to infection, of systemic inflammatory mediators with atherogenic effects.[30] These pathogens, especially *P. gingivalis*, have demonstrated the ability to interact with the endothelial surface and to induce smooth-cell proliferation, causing damage and impairing the vasomotor functionality of the endothelial cells.[2,26,31,32] Serum C-reactive protein (CRP) plays a role in endothelial dysfunction, and elevated levels of CRP provide insight into the linking of periodontal disease and CVD.[2,33–36] In patients with periodontal disease who have elevated plasma levels of both

fibrinogen[37] and TNF-alpha, there is an association with increased carotid intima-media thickness (IMT).[38] IMT and left ventricular mass (LVM) are alternative, yet valuable tools in measuring carotid atherosclerosis.[5,19,22,39] However, our understanding of the mechanism linking these inflammatory markers with atherosclerosis progression is unclear.

Recent studies have shown that CRP may directly interfere with endothelial nitric oxide (NO) availability, by both decreasing the expression of NO synthase and simultaneously increasing the production of reactive oxygen, which inactivates NO.[40] Elevated CRP serum levels are the signal feature of the transition from stable coronary artery disease to the formation of a platelet-rich thrombus following plaque rupture or erosion.[4] These findings shed light on the fact that endothelial activity, associated with elevated CRP serum levels, is characterized by the impaired systemic bioavailability of NO in coronary artery disease patients. Further investigation of this hypothesis (i.e., the rote of CRP on NO) has led to the discovery that CRP serum levels are important in predicting the availability of NO in the systemic circulation in coronary artery disease patients.[41]

Another mechanism through which the bioavailability of NO is decreased is oxidative inactivation by reactive oxygen species. Triggered by bacterial components such as LPS from *P. gingivalis*, macrophages and other cells release cytokines, leading to the systemic activation of phagocytic cells. Thus, PGE_2, IL-1 beta, and TNF-alpha all reach high and potent systemic levels. These macrophages can then transform into foam cells, inducing the production of proinflammatory cytokines, leading to endothelial dysfunction.[26] In a recent study, Pussinen et al.[42] found that the main serum mediators of macrophage activation in response to periodontal disease were low-density lipoprotein (LDL) cholesterol, LPS, β_2-glycoprotein I (β_2-GPI), and modified phospholipids. These results led to the conclusion that periodontitis was directly associated with the ability of isolated LDL to activate macrophages through its main mediators. Moreover, the binding of LDL and the formation of foam cells have been shown to be mediated by CRP.[42,43] Recent data suggest that the subtle but broad effects of periodontitis on the metabolism and biochemical properties of lipoproteins may be reversed by periodontal treatment.[44] Pussinen et al.[45] determined that periodontitis diminished the anti-atherogenic potency of high-density lipoprotein (HDL), further increasing the risk of CVD. These findings may prove valuable clinically, because impaired endothelium-dependent vasodilation induced by increased CRP serum levels may be used as a precursor in diagnosing CVD in the future. This information is considered important enough that the American Heart Association deemed the use of CRP and LDL cholesterol to be essential predictors of CVD.[46]

Another predictor of CVD, in particular coronary heart disease (CHD), may be serum levels of antibodies directed against periodontal pathogens. Pussinen et al.[47] reported the association of CHD with serum antibodies, suggesting that periodontal disease may play a role in the pathogenesis of CHD. In a linear regression model, they concluded that the combined antibody response to *P. gingivalis* and *A. actinomyecetemcomitans* were directly associated with prevalent CHD.[47] Two years later, these researchers supported their findings in another study, in which measured serum antibody levels to major periodontal pathogens were associated with the development of CHD. The study was the first of its kind and was quite insightful in expanding beyond *P. gingivalis*, suggesting that infection with *A. actinomyecetemcomitans* may also be associated with an increased risk of CHD.[48]

An alternative approach for studying the link between periodontal disease and CVD may be through the evaluation of peripheral arterial disease (PAD). PAD of the legs is a state of insufficient tissue perfusion to meet metabolic demand. PAD shares similar pathological features to both stroke and CHD, in that atherosclerotic plaques are present. Recognizing the relationship between periodontal disease and PAD is valuable in trying to understand the

clinical effect of periodontal diseases and how the treatment of these diseases may reduce the risk of developing CVD.[34]

New findings have suggested that tooth loss, rather than periodontal disease, may be the important link between CVD and oral health. Elter et al.[6] concluded, in their study, that edentulous individuals had 1.8-fold elevated chances of developing CHD. However, the investigation of this claim has many limitations, which explains the weaker association between periodontal disease and CHD in older subjects.[49] Based on these admitted limitations, the conclusion of Elter et al.[6] may need further support or supplemental research to directly support the association between periodontal disease and CHD.

These important studies shed new light on the association between periodontal disease and atherosclerotic events. Given that endothelial dysfunction appears to be an early event in the development of atherosclerosis, also predicting for plaque instability, these findings strengthen the link between periodontal disease and atherosclerosis. Thus, it is now critical to test the hypothesis that reversal of periodontal disease prevents atherosclerotic events, and to explore different therapeutic approaches to achieve this aim. More studies that elucidate mechanisms for possible anti-atheroscelorosis therapies are needed.[50,51]

Periodontal disease and diabetes mellitus

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia due to the defective secretion or activity of insulin. The condition affects more than 16 million people in the United States.[52] Diabetes mellitus can be divided into three classifications according to signs and symptoms: type 1, type 2, and gestational. Type 1 diabetes mellitus results from the destruction of beta-cells within the islets of Langerhans of the pancreas, which leads to complete insulin deficiency. Type 2 diabetes mellitus ranges from insulin resistance progressively leading to pancreatic beta-cell failure. Lastly, gestational diabetes mellitus is a glucose intolerance that begins during pregnancy. The number of adults diagnosed with type 2 diabetes worldwide is expected to grow from 135 million in 1995 to approximately 300 million in 2025.[53] People with type 2 diabetes constitute 90% of the diabetic population.[54]

A recent hypothesis links chronic subclinical inflammation with insulin resistance, initiating the development of type 2 diabetes. The triggers of inflammation are many and potentially include oral infection, which may lead to a cascade of events, including increased cytokine production, activation of acute-phase protein synthesis, and consequent insulin resistance that produces pathogenic changes resulting in type 2 diabetes.[16] Periodontal pathogens, especially *P. gingivalis*, have the ability to invade deep vascular endothelium associated with the periodontium, and can be found within pathological vascular plaques.[23,26] Studies have investigated the relative prevalence of five periodontal pathogens (A. actinomycetemcomitans, Eikenella corrodens, T. denticola, Candida albicans, and *P. gingivalis*) among individuals with type 1 and 2 diabetes mellitus. However, no statistically significant correlations were revealed.[55] Except for *A. actinomycetemcomitans*, the prevalence of the periodontal pathogens was significantly higher in diseased sites than in healthy sites in both type 1 and type 2 diabetes patients. Furthermore, the results suggested that *E. corrodens*, *T. denticola*, *C. albicans*, and *P. gingivalis* may play important roles in the periodontitis of individuals with either type 1 or type 2 diabetes mellitus.[56] Once periodontal pathogens are established in the diabetic host, periodontal infection may aggravate microvascular complications (retinopathy, nephropathy, and neuropathy), that can progress to macrovascular complications (coronary artery disease, cerebrovascular disease, and peripheral vascular disease).[2,54]

Periodontal disease, more specifically periodontitis, is one of the many complications resulting from type 1 and type 2 diabetes. Numerous studies have found a higher prevalence of periodontal disease among diabetic patients than among healthy controls;[4] thus, an established

relationship exists between periodontal disease and diabetes. Recent studies have presented evidence indicative of a bidirectional adverse interrelationship between both type 1 and type 2 diabetes mellitus and periodontal diseases.[57] The more direct relationship is that periodontal disease may lead to type 2 diabetes; however, the alternative view, that periodontal disease develops resulting from complications from both type 1 and type 2 diabetes mellitus, further strengthens the support for this bidirectional link between periodontal disease and diabetes mellitus.

In patients with periodontal disease, chronic low-level systemic exposure to periodontal microorganisms may exist, leading to significant changes in plasma levels of cytokines and hormones. Due to the dynamic nature of the inflamed periodontium, the tissue may serve as an endocrine-like source of inflammatory mediators.Among the inflammatory biomarkers examined, CRP and IL-6 appear to be promising, due to their plausible biological mechanisms, as exposed in studies of links between periodontal disease and cardiovascular disease.[58,59] Recently, Bluher et al.[60] investigated whether plasma concentrations of inflammatory markers were associated with measures of obesity, insulin sensitivity, and hyperglycemia. In parallel with the impairment of glucose tolerance, there was a significant increase in IL-6 and CRP, and a significant decrease in adiponectin and IL-10 plasma concentrations. Furthermore, Bluher et al.[60] discovered significant correlations between the plasma concentrations of all inflammatory markers examined and percent body fat, insulin sensitivity, and fasting plasma glucose. Fasting plasma glucose was a significant determinant of adiponectin, CRP, and IL-6 plasma concentrations, whereas body fat content was a significant predictor only of CRP plasma concentration.[60] In a similar study, the MONICA/KORA Augsburg Study, the authors concluded that type 2 diabetes was highest among subjects with elevated levels of both IL-18 and CRP or IL-18 and IL-6, respectively.[61] These observations suggest that an enhanced acute-phase response is associated with insulin resistance, and may foreshadow the development of type 2 diabetes.

Other studies have suggested that the presence of periodontal infection may be linked to the control of diabetes. Results from the study by Grossi et al.[62] indicated that the effective control of periodontal infection in diabetic patients could reduce the level of advanced glycation end-products (AGEs) in the serum. AGEs are known to cause hyperglycemia, which is a complication of diabetes; thus, the level of glycemic control seems to be the key factor. Many researchers have noted similar positive correlations of poor glycemic control in patients with high tooth attachment loss.[63–65] Prevention and control of periodontal disease must be considered as an integral part of diabetes control. Major efforts should be directed at preventing periodontitis in patients who are at risk of diabetes, as well as in those patients with poor metabolic control.

The complications of both type 1 and type 2 diabetes are related to the long-term elevation of blood glucose concentrations (hyperglycemia). Hyperglycemia results in the formation of AGEs.[66] These AGEs make endothelial cells and monocytes more susceptible to stimuli that induce the cells to produce inflammatory mediators. Some have speculated that AGE accumulations in the gingival tissue lead to increased vascular permeability, greater breakdown of collagen fibers, and accelerated destruction of both nonmineralized connective tissue and bone.[67] Apart from the accumulation of AGEs, the pathophysiology of diabetes is strikingly similar to that of periodontal disease.[54] It is understood that the connection is counterintuitive, due to the fact that diabetes is a metabolic disorder and periodontal disease is an infectious disease. However, the pathophysiological relationship between diabetes and periodontal disease occurs through the ability of both conditions to induce an inflammatory response, whether through AGE or bacterial accumulation, respectively, leading to the production of inflammatory mediators.

Epidemiological findings linking periodontal disease and diabetes are strengthened by experimental studies demonstrating the hyperglycemic effects of several proinflammatory cytokines, including IL-6 and TNF-alpha, both of which derive in part from adipose tissue.[68] In rodent models of glucose homeostasis, IL-6 impairs the glucose-stimulated release of insulin from isolated pancreatic beta cells.[69] In humans, the exogenous administration of recombinant IL-6 has been found to induce dose-dependent hyperglycemia and elevations in serum levels of glucagons.[70] Excessive TNF-alpha concentrations have been implicated in the development of insulin resistance. TNF-alpha directly impairs glucose uptake and metabolism by altering insulin-induced signal transduction. TNF-alpha infusion into skeletal muscle, carried out by Plomgaard et al.,[70] increased the signaling effects associated with impaired phosphorylation of Akt substrate 160, the most proximal step in the insulin signaling cascade regulating the translocation of glucose transporter-4 (GLUT4) and glucose uptake. Thus, excessive concentrations of TNF-alpha negatively regulate insulin signaling and glucose uptake in humans.[71] Additionally, the elevated levels of soluble TNF receptor 1 and 2 (sTNF-alphaRI and sTNF-alphaRII) shown in obese patients[72] may lead to a hyperinflammatory state, increasing the risk for periodontal disease and also accounting, in part, for insulin resistance. The hyperinflammatory state may be caused by adipocytes, which appear to secrete proinflammatory cytokines, providing the link between the pathogenesis of type 2 diabetes, obesity, and periodontal disease. These findings are further supported by information gathered from a population of 12367 nondiabetic subjects. The highest levels of TNF-alpha and sTNF-alpha receptors were found in those individuals in the highest quartile for body mass index (BMI). These findings provide support for the idea that obesity is a significant predictor of periodontal disease and that insulin resistance appears to mediate this relationship.[72]

Periodontal disease and adverse pregnancy outcomes

The growing evidence that infection remote from the fetal-placental unit may have a role in the preterm delivery of low-birth-weight infants has led to an increased awareness of the potential role of chronic bacterial infections in the body. Preterm low-birth weight (PLBW), as defined by the 29th World Health assembly in 1976, is a birth weight of less than 2500 g with a gestational age of less than 37 weeks. Low birth weight can be a result of this short gestational period and/or retarded intrauterine growth. Some traditional risk factors include genetic features; the use of alcohol; poor prenatal care; poor maternal nutrition; urinary tract infection; and, in particular, smoking and low socioeconomic status. A dose-response relationship between smoking and PLBW was reported, with a positive correlation between the two.[73] As for socioeconomic status, Buduneli et al.[74] took into account this risk factor by evaluating post-partum women of a low socioeconomic level; the study suggested that periodontal disease had a contributory role in PLBW, but cited a negative correlation, due to the lack of a statistically significant link between periodontitis and preterm birth. PLBW remains a significant public health issue, because PLBW infants are at a higher risk for a number of acute and chronic disorders, including respiratory distress syndrome, cerebral palsy, pathologic heart conditions, epilepsy, and severe learning problems.[75]

Initially, the relationship between periodontal disease and PLBW was not so evident in case-control studies.[40,76] Despite these studies, which actually showed a negative correlation for a link between periodontal disease and PLBW, a growing number of studies show a positive association.[77] For example, contradictory results were revealed in Granada, Spain, where statistically significant relationships were observed between low birth weight and maternal periodontal probing depth;[78] the authors of that study concluded that periodontal disease was a significant risk factor for low birth weight, but not for preterm delivery. Due to wavering conclusions in case-control studies and many confounding variables, plausible biological hypotheses are needed to support the link between maternal periodontal disease and PLBW.

The cause of low birth weight is sometimes unknown. Twenty-five percent to 50% of PLBW deliveries occur without any known etiology.[79] PLBW has been the subject of epidemiologic investigations and a target for public health interventions.[16] Despite the significant advances in the use of drugs to arrest preterm labor and in the understanding of reproductive physiology, the preterm birth rate in the Western world appears to be increasing.[80] However, it is recognized that maternal infections affect the normal development of the fetus. Periodontal disease is associated with chronic gram-negative infections, which result in local and systemic elevations of proinflammatory prostaglandins and cytokines. Furthermore, numerous citations have shown periodontal pathogens entering the systemic circulation. Hence, maternal periodontal disease may be connected with preterm delivery through mechanisms involving inflammatory mediators or a direct bacterial assault on the amnion.

Many risk factors have been proposed to cause preterm rupture of membranes and preterm labor. These risk factors include high/low maternal age, overweight and underweight, parity, primiparous mothers, low socioeconomic status, little or no education, alcohol and drug abuse, hyper-tension, Afro-American ethnicity and genital and urinary tract infections. Smoking is regarded as a well-known risk factor for both periodontitis and preterm birth. However, when Skuldbol et al.[81] studied a random group of Scandinavian women selected based on fairly good health and high socioeconomic status, they concluded that no relationships were revealed between periodontitis and preterm birth. They further concluded that there was no relationship between smoking and preterm birth.[81] Variables leading to the latter conclusion may be due to the fact that periodontal disease is seldom present in women of birth-giving age. It was mentioned that, in Denmark, free access to comprehensive health care was available to the public until the age of 18; thus, although oral infections may play a role, other factors, such as smoking and socioeconomic status are stronger and so may act as confounders.

Another highly studied risk factor for PLBW is infections of the genital and urinary tracts. These include pathogens in the genital tract and also in other organ systems, e.g., viral respiratory infections, diarrhea, and malaria. Also, more localized infections of the genital and urinary systems can affect the duration of gestation.[82–84] The current concept is that associations between chorioamnionitis, infection of the amniotic fluid, and PLBW have been established.[85] Gibbs et al.[83] provided an excellent outline of the possible association between infections and adverse pregnancy outcomes in their review article. In their hypothesis, microorganisms and their LPS enter the uterine cavity during pregnancy by an ascending route from the lower genital tract, or by a blood-borne nongenital route, causing preterm birth.[79] A variety of studies have shown that spontaneous abortion, preterm labor, preterm birth, and preterm rupture of the membranes, as well as chorioamnionitis, are all related to the onset of bacterial vaginosis during pregnancy.[86] Bacterial vaginosis is a clinical condition caused by overgrowth of the vaginal flora with certain aerobic and anaerobic bacteria. Other studies have also provided evidence that distant, low-grade oral infection might trigger inflammation of the human maternal-fetal unit in a manner analogous to that seen with bacterial vaginosis.[84] Bacterial invasion of the choriodecidual space can activate the fetal membranes or trigger the maternal immune system to produce a variety of cytokines and growth factors. The combination of increased fetal adrenal cortisol production, increased prostaglandin production, the release of MMPs, and increased cytokines and chemokines may lead to myometrial contractions, membrane rupture, cervical ripening, and preterm delivery. Furthermore, the inflammatory burden results in distress and fetal growth restriction.[87]

As mentioned earlier, periodontal disease is an infectious disease caused by anaerobic gram-negative bacteria. Madianos et al.[88] extended the work of Socransky et al.,[17] shifting the focus to examine the potential role of maternal infection with specific organisms within both the “orange” and “red” complexes, because these are the complexes most strongly correlated to severe periodontal disease. The highest rate of prematurity (66.7%) was observed among those

mothers without a protective “red” complex IgG response coupled with a fetal immunoglobulin M (IgM) response to “orange” complex microbes.[88] These data support the concept that maternal periodontal infection in the absence of a protective maternal antibody response is associated with the systemic distribution of oral organisms to the fetus, resulting in preterm birth.Additionally, the high prevalence of elevated fetal IgM to *C. rectus* among premature infants raises the possibility that this specific maternal oral pathogen may serve as a primary fetal infectious agent eliciting preterm birth. More recent findings support this claim: when subgingival bacteria were evaluated together, *P. micros* and *C. rectus* were found to play a significant role in increasing the risk for PLBW.[89] Additionally, mouse studies found that maternal *C. rectus* infection induced placental inflammation and decidual hyperplasia, as well as a concomitant increase in fetal brain interferon (IFN)-gamma, leading to brain damage in the hippocampal region of the neonatal brain. The brain damage in mice is analogous to the white-matter damage seen in humans due to the effects of maternal infections.[74]

Recently, *F. nucleatum*, a gram-negative anaerobe ubiquitous to the oral cavity, was isolated from the amniotic fluid, placenta, and chorioamnionic membranes of women delivering prematurely.[90] To test the strength of this finding, pregnant mice were infected with *F. nucleatum*, resulting in premature delivery, stillbirths, and nonsustained live births. The bacterial infection was restricted inside the uterus, without spreading systemically, although invasion of the endothelial cells lining the blood vessels was also observed. The bacteria then crossed the endothelium, proliferated in surrounding tissues, and finally spread to the amniotic fluid. This pattern of infection paralleled that observed in humans.

Upregulation of proinflammatory cytokines resulting from the normal host response to an infectious agent may represent the key mechanism linking periodontal disease to PLBW. Microbiological products such as endotoxin will trigger a host immune response, causing both local inflammation and activation of soluble proinflammatory mediators such as IL-1, TNF-alpha, and MMPs. These inflammatory markers have been shown to cross the placental barrier and to cause fetal toxicity, resulting in preterm delivery and low-birth-weight babies.[91] Therefore, fetal exposure to oral pathogens, as evidenced by an IgM response, is associated with preterm birth, and the risk for preterm birth is greatest among fetuses that demonstrate an inflammatory response.

Although case-control and prospective studies have shown preliminary evidence of the treatment of periodontal disease as a method for preventing PLBW,[92] a consensus has emerged, emphasizing the need for more studies on the effects of periodontal disease treatment in reducing the occurrence of PLBW. A great deal of evidence supports the scenario of periodontal disease as a treatable condition; thus, a positive correlation between periodontal disease and PLBW should create momentum in programs to provide better periodontal care for pregnant women.

Periodontal disease and osteoporosis

Bone loss is a feature shared between periodontal disease and osteoporosis. Osteopenia is a reduction in bone mass due to an imbalance between bone resorption and bone formation, favoring resorption, resulting in demineralization and leading to osteoporosis.[93] Osteoporosis is a skeletal disorder characterized by compromised bone strength, predisposing to an increased risk of fracture, with bone strength determined by both bone density and bone quality.[94] Similarly, periodontal disease is characterized by the absorption of bone, specifically the alveolar bone, as well as by loss of the soft-tissue attachment of the tooth. Due to the commonality of bone loss between periodontal disease and osteoporosis, the outcomes of both are similar. Furthermore, oral osteopenia and systemic osteopenia share risk factors, including age,[95] estrogen deficiency,[3] and smoking.[96]

The underlying mechanism of increased bone resorption may be directed by increased systemic/local osteoclastic activity, or by local cellular or cytokine effects.[16] Excessive osteoclastic resorption is a common feature of chronic inflammatory processes such as periodontal disease. In physiological bone remodeling, the cell-to-cell contact between receptor activator of nuclear factor-κB ligand (RANKL)-expressing osteoblasts and RANK-expressing monocyte/osteoclast precursor cells is crucial. In inflamma-tory processes, activated T lymphocytes express RANKL, and it is therefore possible that cell-to-cell contact between T lymphocytes and monocyte/osteoclast precursor cells is involved in osteoclast formation.[97] The activation of mature osteoclasts is inhibited by osteoprotegerin (OPG) released by stromal cells and osteoblasts. B lymphocytes may also participate in osteoclast formation, either by expressing RANKL or by serving as osteoclast progenitor cells themselves.[98]

In periodontal infection, dense infiltrates of mononuclear leukocytes are found in the gingiva, including T lymphocytes and monocyte/osteoclast progenitor cells.[99,100] This cell-to-cell contact between T cells and monocyte/lymphocyte progenitor cells is important for osteoclast formation in periodontitis. Interestingly, RANKL mRNA is upregulated in the gingiva of patients with advanced periodontitis. On the other hand, OPG mRNA is downregulated.[100] Furthermore, Nagasawa et al.[101] demonstrated that OPG mRNA was upregulated by LPS from *P. gingivalis* and *A. actinomyecetemcomitans*, shedding light on how LPS-stimulated OPG may be involved in the control of osteoclast formation in periodontal disease. The hypothesis linking OPG and periodontal disease is strengthened by studies involving gram-negative bacteria.[102,103] Due to the transient nature of infection by these pathogens, exposure to periodontal infection may trigger RANKL activation and subsequent osteoclast activation and activity, inducing osteoporosis in patients with periodontal infection.

Estrogen deficiency is another dominant pathogenic factor for osteoporosis in women.[104] Estrogen, either directly or indirectly, modulates cytokines that are important regulators of bone metabolism and also regulators of the host inflammatory response, such as IL-1 alpha, IL-1 beta, TNF-alpha, and macrophage colony-stimulating factor (M-CSF). Thus, estrogen deficiency initiates an increase in the number of osteoclasts, driven by the same cytokines that down-regulate osteoblast generation. This promotes an imbalance in bone metabolism, leading to reduced bone mineral density (BMD).[105] Periodontitis also activates the host proinflammatory response, recruiting cytokines and prostanoids, leading to the activation of osteoclasts, and thus inducing bone resorption. Some cytokines, such as IL-1 beta, TNF-alpha, IL-6, and IL-8, have been found at increased levels in inflamed human gingival tissue, in concentrations capable of inducing bone resorption.[106,107] Hence, many investigations have found a statistically significant positive correlation between periodontal disease and estrogen deficiency.[108] Both of these risk factors, acting cooperatively, may be sufficient to induce osteoporosis. A recent study in Japan investigated this relationship between oral health and BMD; the findings were that periodontitis and tooth loss after menopause (i.e., in estrogen-deficient women) may be useful indicators of metacarpal BMD (m-BMD) loss.[109] In a related study, Wactawski-Wende et al.[110] determined a strong and consistent association between alveolar crestal height (ACH) and osteoporosis through measurements of bone density and ACH in postmenopausal women.

Using osteoporosis treatment as a basis, many studies have tried to use similar approaches in treating periodontal disease, deepening the relationship between the two diseases. Parathyroid hormone (PTH) functions as a mediator of bone modeling and as an essential regulator of calcium homeostasis. PTH produces several distinct effects on the entire bone remodeling process, because it influences both bone formation and bone resorption. Recent studies have indicated that intermittent doses of PTH can be an efficient anabolic treatment, reducing bone loss due to estrogendeficiency-related osteopenia.[111] Furthermore, daily injections of

teriparatide, a portion of human PTH, have been shown to stimulate new bone formation and increase BMD.[112] Of note, NO has anabolic and catabolic effects similar to those of PTH on bone metabolism. The role of NO is controversial, in that low levels of NO maintain homeostasis,[113] whereas high levels of NO, as seen in inflammatory conditions, induce bone resorption.[114] NO is beneficial in periodontal infection, in that it is an important element of the host defense against *P. gingivalis*,a primary periodontal infection pathogen.[115] The administration of the NO donor, isosorbide, to periodontitis-affected rats demonstrated reductions in inflammatory cell infiltration, cementum resorption, and alveolar bone loss.[116]

Although significant advances have been made in determining the relationship between periodontal disease and osteoporosis, further studies are needed to clarify this correlation. In comparison to other systemic diseases, the research done in elucidating the association is limited, and many researchers have highlighted and stressed in their publications this great need for a better understanding of the relationship. The clarification of this relationship may provide useful and beneficial warnings for osteoporosis risk, as well as significant clinical implications for treatment. Another issue encountered with this relationship between periodontal disease and osteoporosis is the fact that periodontal disease is diagnosed largely in males whereas osteoporosis is a disorder predominantly diagnosed in females. Detractors may argue that the relationship is weak because of this fact; however, osteoporosis is found to be a risk factor for periodontal disease within the female population. When tested in the general population, no correlation between sex and the relationship between periodontal disease and osteoporosis was found, reducing this finding to a mere confounding variable.

Conclusion

Periodontal disease as a risk factor for the development of various systemic conditions, such as CVD, diabetes, adverse pregnancy outcomes, and osteoporosis, is a highly researched and debated topic. Although most evidence in regard to the relationship between periodontal disease and those systemic conditions is consistently supportive of this notion, the need for more studies is greatly advocated by physicians and dentists. In general, larger and more randomized populations and better controlled clinical trials will be required to substantiate the correlation of periodontal disease to these systemic conditions.

Each of the specific conditions has its own needs for future research. In the relationship between periodontal disease and CVD, current studies do not provide sufficient information to differentiate between the possibilities of direct infection of the vascular wall versus the stimulation of a proinflammatory state by periodontitis (or both, simultaneously). The distinction is crucial, because some treatment strategies for periodontal disease, such as scaling and root planing, may promote the hematogenous seeding of bacteria.[117] Furthermore, antibiotic and antiinflammatory strategies should be incorporated into studies to evaluate their effectiveness in preventing cardiovascular events through the remediation of periodontal disease.

In addition to more controlled studies of the correlation between metabolic control and periodontal disease, the role of pathogens other than *P. gingivalis* (such as *C. albicans*) should be studied. Also, the current hypothesis that chronic inflammation caused by periodontal infection contributes to the pathogenesis of type 2 diabetes needs further clarification. A logical framework provided by elucidation of the mechanism behind periodontal infection and CVD would aid in this search, and, possibly, a hypothesis unifying both these inflammatory diseases could offer a unique opportunity for improving complications associated with both diseases.

In the relationship between periodontal disease and osteoporosis, detailed knowledge of the molecular mechanisms involved in RANKL-RANK activation and downstream signaling

could generate new pharmacological principles for the inhibition of excessive bone resorption in pathological conditions. Furthermore, additional longitudinal studies may be necessary to explain more fully the usefulness of osteocalcin, parathyroid hormone, and calcitonin as diagnostic indicators of periodontal disease activity. In addition to these research topics, further studies of the mechanism of NO effects on alveolar bone are needed, in association with an understanding of the indications for isosorbide in treating periodontal infection.

Lastly, the mechanisms by which periodontal disease may reduce birth weight have still not been elucidated, but there is evidence that this association has a biologically feasible basis. Nevertheless, the association between maternal periodontal disease and low birth weight should be further explored and clarified to establish whether it is causal or simply associative. Further research in the area of the role of periodontal pathogens, direct or indirect, in contributing to PLBW is required. These developments will be of importance to obstetrics, as periodontal disease may become a modifiable risk factor for several serious systemic conditions, including the pregnancy complications encountered in daily practice.

In this era of evidence-based medicine, further work needs to be done to establish the associations noted above. As greater knowledge becomes available concerning the etiologic factors and pathology of periodontal disease as it relates to the systemic conditions described above, the research must shift towards advances in effective treatment. Most researchers have found statistically significant connections between these systemic conditions and moderate to severe periodontal disease; therefore, better awareness of the effects of oral health on systemic health must be made available to the public. Simple oral healthcare tasks, such as brushing and flossing, and limiting other risk factors, such as smoking, may assist in initially decreasing periodontal pockets and periodontal bacterial flora, consequently decreasing the likelihood of the progression of periodontal disease in causing these detrimental systemic diseases.

References

1. Loesche WJ, Grossman NS. Periodontal disease as a specific, albeit chronic, infection: diagnosis and treatment. Clin Microbiol Rev 2001;14:727–52. [PubMed: 11585783]
2. Amar S, Gokce N, Morgan S, Loukideli M, Van Dyke TE, Vita JA. Periodontal disease is associated with brachial artery endothelial dysfunction and systemic inflammation. Arterioscler Thromb Vasc Biol 2003;23:1245–9. [PubMed: 12763762]
3. Genco RJ, Grossi SG. Is estrogen deficiency a risk factor for periodontal disease? Compend Contin Educ Dent Suppl 1998;22:S23–9. [PubMed: 12089758]
4. Fuster V, Badimon L, Badimon JJ, et al. The pathogenesis of coronary artery disease and the acute coronary syndromes. N Engl J Med 1992;326:242–50. [PubMed: 1727977]
5. Angeli F, Verdecchia P, Pellegrino C, Pellegrino RG, Pellegrino G, Prosciutti L, Giannoni C, Cianetti S, Bentivoglio M. Association between periodontal disease and left ventricle mass in essential hypertension. Hypertension 2003;41:488–92. [PubMed: 12623948]
6. Elter JR, Champagne CME, Offenbacher S, Beck JD. Relationship of periodontal disease and tooth loss to prevalence of coronary heart disease. J Periodontol 2004;75:782–90. [PubMed: 15295942]
7. Hujoel PP, Drangsholt MT, Spiekerman C, Derouen TA. Periodontitis-systemic disease associations in the presence of smoking: causal or coincidental? J Periodontol 2000 2002;30:51–60.
8. Ebersole JL, Capelli D, Steffen MJ. Longitudinal dynamics of infection and serum antibody in *A. actinomycetemcomitans* periodontitis. Oral Dis 1995;1:129–38. [PubMed: 8705818]
9. Hayes C, Antezak-Bouckoms A, Burdick E. Quality assessment and meta-analysis of systemic tetracycline use in chronic adult periodontitis. J Clin Periodontol 1992;19:164–8. [PubMed: 1532607]
10. Van Winkelhoff AJ, Tijhof CJ, de Graaff J. Microbiological and clinical results of metronidazole plus amoxicillin therapy in *Actinobacillus actinomycetemcomitans*-associated periodontitis. J Periodontol 1992;63:52–7. [PubMed: 1313103]

11. Sorsa T, Ingman T, Suomalainen K, Haapasalo M, Konttinen YT, Lindy O, Saari H, Uitto VJ. Identification of proteases from periodontopathogenic bacteria as activators of latent human neutrophil and fibroblast-type interstitial collagenases. Infect Immun 1992;60:4491–5. [PubMed: 1398963]
12. Lee W, Aitken S, Sodek J, McCulloch CA. Evidence of a direct relationship between neutrophil collagenase activity and periodontal tissue destruction in vivo: role of active enzyme in human periodontitis. J Periodontal Res 1995;30:23–33. [PubMed: 7722844]
13. Geerts SO, Legrand V, Charpentier J, Albert A, Rompen EH. Further evidence of the association between periodontal conditions and coronary artery disease. J Periodontol 2004;75:1274–80. [PubMed: 15515345]
14. Page RC. The role of inflammatory mediators in the pathogenesis of periodontal disease. J Periodontal Res 1991;26:230–42. [PubMed: 1679130]
15. Loesche WJ, Gusberti F, Mettraux G, Higgins T, Syed S. Relationship between oxygen tension and subgingival bacterial flora in untreated human periodontal pockets. Infect Immun 1983;42:659–67. [PubMed: 6642647]
16. Amar S, Han X. The impact of periodontal infection on systemic diseases. Med Sci Monit 2003;9:RA291–9. [PubMed: 14646984]
17. Socransky SS, Haffajee AD, Cugini MA, Smith C, Kent RL Jr. Microbial complexes in subgingival plaque. J Clin Periodontol 1998;25:134–44. [PubMed: 9495612]
18. Slots J, Kamma JJ, Sugar C. The herpesvirus-*Porphyromonas gingivalis*-periodontitis axis. J Periodont Res 2003;38:312–23.
19. Leivadaros E, van der Velden U, Bizzarro S, ten Heggeler JM, Gerdes VE, Hoek FJ, Nagy TO, Scholma J, Bakker SJ, Gans RO, ten Cate H, Loos BG. A pilot study into measurements of markers of atherosclerosis in periodontitis. J Periodontol 2005;76:121–8. [PubMed: 15830646]
20. Prabhu A, Michalowicz BS, Mathur A. Detection of local and systemic cytokines in adult periodontitis. J Periodontol 1996;67:515–22. [PubMed: 8724710]
21. Lusis AJ. Atherosclerosis. Nature 2000;407:233–41. [PubMed: 11001066]
22. Beck J, Garcia R, Heiss G, Vokonas PS, Offenbacher S. Periodontal disease and cardiovascular disease. J Periodontol 1996;67:1123–37. [PubMed: 8910831]
23. Haraszthy VI, Zambon JJ, Trevisan M, Zeid M, Genco RJ. Identification of periodontal pathogens in atheromatous plaques. J Periodontol 2000;71:1554–60. [PubMed: 11063387]
24. Cairo F, Gaeta C, Dorigo W, Oggioni MR, Pratesi C, Pini Prato GP, Pozzi G. Periodontal pathogens in atheromatous plaques. A controlled clinical and laboratory trial. J Periodontal Res 2004;39:442–6. [PubMed: 15491349]
25. Iwai T, Inoue Y, Umeda M, Huang Y, Kurihara N, Koike M, Ishikawa I. Oral bacteria in the occluded arteries of patients with Buerger disease. J Vasc Surg 2005;42:107–15. [PubMed: 16012459]
26. Chun YH, Chun KR, Olguin D, Wang HL. Biological foundation for periodontitis as a potential risk factor for atherosclerosis. J Periodontal Res 2005;40:87–95. [PubMed: 15613084]
27. Zhang SH, Reddick RL, Piedrahita JA, et al. Spontaneous hypercholesterolemia and arterial lesions in mice lacking apolipoprotein E. Science 1992;258:468–71. [PubMed: 1411543]
28. Plump AS, Smith JD, Hayek T, et al. Severe hypercholesterolemia and atherosclerosis in apolipoprotein E-deficient mice created by homologous recombination in ES cells. Cell 1992;71:343–53. [PubMed: 1423598]
29. Gibson FC 3rd, Hong C, Chou HH, Yumoto H, Chen J, Lien E, Wong J, Genco CA. Innate immune recognition of invasive bacteria accelerates atherosclerosis in apolipoprotein E-deficient mice. Circulation 2004;109:2801–6. [PubMed: 15123526]Epub 2004 May 3
30. Loos BG, Craandijk J, Hoek FJ, Wertheim-van Dillen PM, van der Velden U. Elevation of systemic markers related to cardiovascular diseases in the peripheral blood of periodontitis patients. J Periodontol 2000;71:1528–34. [PubMed: 11063384]
31. Khlgatian M, Nassar H, Chou HH, Gibson FC 3rd, Genco CA. Fimbria-dependent activation of cell adhesion molecule expression in *Porphyromonas gingivalis*-infected endothelial cells. Infect Immun 2002;70:257–67. [PubMed: 11748191]

32. Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. Circulation 2000;101:1899–906. [PubMed: 10779454]
33. Firatli E. The relationship between clinical periodontal status and insulin-dependent diabetes mellitus. Results after 5 years. J Periodontol 1997;68:136–40. [PubMed: 9058330]
34. Hung HC, Willett W, Merchant A, Rosner BA, Acherio A, Joshipura KJ. Oral health and peripheral arterial disease. Circulation 2003;107:1152–7. [PubMed: 12615794]
35. Joshipura KJ, Wand HC, Merchant AT, Rimm EB. Periodontal disease and biomarkers related to cardiovascular disease. J Dent Res 2004;83:151–5. [PubMed: 14742654]
36. Sinisalo J, Paronen J, Mattila KJ, Syrjala M, Alfthan G, Palosuo T, Nieminen MS, Vaarala O. Relation of inflammation to vascular function in patients with coronary heart disease. Atherosclerosis 2000;149:403–11. [PubMed: 10729391]
37. Thompson SG, Kienast J, Pyke SD, Haverkate F, van de Loo JC. Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. N Engl J Med 1995;332:635–41. [PubMed: 7845427]
38. Skoog T, Dichtl W, Boquist S, Skoglund-Andersson C, Karpe F, Tang, et al. Plasma tumour necrosis factor-alpha and early carotid atherosclerosis in healthy middle-aged men. Eur Heart J 2002;23:376–83. [PubMed: 11846495]
39. Desvarieux M, Demmer RT, Rundek T, Boden-Albala B, Jacobs DR Jr, Papapanou PN, Sacco RL. Relationship between periodontal disease, tooth loss, and carotid artery plaque: the Oral Infections and Vascular Disease Epidemiology Study (INVEST). Stroke 2003;34:2120–5. [PubMed: 12893951]
40. Wang CH, Li SH, Weisel RD, et al. C-reactive protein upregulates angiotensin type 1 receptors in vascular smooth muscle. Circulation 2003;107:1783–90. [PubMed: 12665485]
41. Fichtlscherer S, Breuer S, Schachinger V, Dimmeler S, Zeiher AM. C-reactive protein levels determine systemic nitric oxide bioavailability in patients with coronary artery disease. Eur Heart J 2004;25:1412–8. [PubMed: 15321699]
42. Pussinen PJ, Viluna-Rautiainen T, Alfthan G, Palosuo T, Jauhiainen M, Sundvall J, Vesanen M, Mattila K, Asikainen S. Severe periodontitis enhances macrophage activation via increased serum lipopolysaccharide. Arterioscler Thromb Vasc Biol 2004;24:2174–80. [PubMed: 15388525]
43. Zwaka TP, Hombach V, Torzewski J. C-reactive protein-mediated low density lipoprotein uptake by macrophages: implications for atherosclerosis. Circulation 2001;103:1194–7. [PubMed: 11238260]
44. Mattila KJ, Pussinen PJ, Paju S. Dental infections and cardiovascular diseases: a review. J Periodontol 2005;76:2085–8. [PubMed: 16277580]
45. Pussinen PJ, Jauhiainen M, Vilkuna-Rautiainen T, Sundvall J, Vesanen M, Mattila K, Palosuo T, Alfthan G, Asikainen S. Periodontitis decreases the antiatherogenic potency of high density lipoprotein. J Lipid Res 2004;45:139–47. [PubMed: 13130123]
46. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003;107:499–511. [PubMed: 12551878]
47. Pussinen PJ, Jousilahti P, Alfthan G, Palosuo T, Asikainen S, Salomaa V. Antibodies to periodontal pathogens are associated with coronary heart disease. Arterioscler Thromb Vasc Biol 2003;23:1250–4. [PubMed: 12714435]
48. Pussinen PJ, Nyysonen K, Alfthan G, Salonen R, Laukkanen JA, Salonen JT. Serum antibody levels to *Actinobacillus actinomycetemcomitans* predict the risk for coronary heart disease. Arterioscler Thromb Vasc Biol 2005;25:833–8. [PubMed: 15692101]
49. Gilbert GH, Miller MK, Duncan RP, Ringelberg ML, Dolan TA, Foerster U. Tooth-specific and person-level predictors of 24-month tooth loss among older adults. Community Dent Oral Epidemiol 1999;27:372–85. [PubMed: 10503798]
50. Chi H, Messas E, Levine RA, Graves DT, Amar S. Interleukin-1 receptor signaling mediates atherosclerosis associated with bacterial exposure and/or a high-fat diet in a murine apolipoprotein E heterozygote model: pharmacotherapeutic implications. Circulation 2004;110:1678–85. [PubMed: 15353494]

51. Li L, Messas E, Batista EL Jr, et al. *Porphyromonas gingivalis* infection accelerates the progression of atherosclerosis in a heterozygous apolipoprotein E-deficient murine model. Circulation 2002;105:861–7. [PubMed: 11854128]
52. Skyler J, Oddo C. Diabetes trends in the USA. Diabetes Metab Res Rev 2002;18:S21–6. [PubMed: 12324981]
53. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. Diabetes Care 1998;21:1414–31. [PubMed: 9727886]
54. Matthews DC. The relationship between diabetes and periodontal disease. J Can Dent Assoc 2002;68:161–4. [PubMed: 11911811]
55. Tervonen T, Oliver RC, Wolff LF, Bereuter J, Anderson LA, Aeppli DM. Prevalence of periodontal pathogens with varying metabolic control of diabetes mellitus. J Clin Periodontol 1994;21:375–9. [PubMed: 8089237]
56. Yuan K, Chang CJ, Hsu PC, Sun HS, Tseng CC, Wang JR. Detection of putative periodontal pathogens in non-insulin-dependent diabetes mellitus and non-diabetes mellitus by polymerase chain reaction. J Periodontal Res 2001;36:18–24. [PubMed: 11246700]
57. Teng YT, Taylor GW, Scannapieco F, Kinane DF, Curtis M, Beck JD, Kogon S. Periodontal health and systemic disorders. J Can Dent Assoc 2002;68:188–92. [PubMed: 11911816]
58. Pradhan AD, Ridker PM. Do atherosclerosis and type 2 diabetes share a common inflammatory basis? Eur Heart J 2002;23:831–4. [PubMed: 12042000]
59. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? Arterioscler Thromb Vasc Biol 1999;19:972–8. [PubMed: 10195925]
60. Bluher M, Fasshauer M, Tonjes A, Kratzsch J, Schon MR, Paschke R. Association of interleukin-6, C-reactive protein, interleukin-10 and adiponectin plasma concentrations with measures of obesity, insulin sensitivity and glucose metabolism. Exp Clin Endocrinol Diabetes 2005;113:534–7. [PubMed: 16235156]
61. Thorand B, Kolb H, Baumert J, Koenig W, Chambless L, Meisinger C, Illig T, Martin S, Herder C. Elevated levels of interleukin-18 predict the development of type 2 diabetes: results from the MONICA/KORA Augsburg Study, 1984–2002. Diabetes 2005;54:2932–8. [PubMed: 16186395]
62. Grossi SG, Zambon JJ, Ho AW, Koch G, Dunford RG, Machtel EE, et al. Assessment of risk for periodontal disease. I. Risk indicators for attachment loss. J Periodontol 1994;65:260–7. [PubMed: 8164120]
63. Christgau M, Palitzsch KD, Schmalz G, Kreiner U, Frenzel S. Healing response to nonsurgical periodontal therapy in patients with diabetes mellitus: clinical, microbiological, and immunologic results. J Clin Periodontol 1998;25:112–24. [PubMed: 9495610]
64. Stewart JE, Wager KA, Friedlander AH, Zadeh HH. The effect of periodontal treatment on glycemic control in patients with type 2 diabetes mellitus. J Clin Periodontol 2001;28:306–10. [PubMed: 11314885]
65. Offenbacher S, Salvi GE. Induction of prostaglandin release from macrophages by bacterial endotoxin. Clin Infect Dis 1999;28:505–13. [PubMed: 10194068]
66. Lalla RV, D'Ambrosio JA. Dental management considerations for the patient with diabetes mellitus. J Am Dent Assoc 2001;132:1425–32. [PubMed: 11680359]
67. Westfelt E, Rylander H, Blohme G, Jonasson P, Lindhe J. The effect of periodontal therapy in diabetics. Results after 5 years. J Clin Periodontol 1996;23:92–100. [PubMed: 8849844]
68. Strommer L, Wickbom M, Wang F, Herrington MK, Ostenson CG, Arnelo U, Permert J. Early impairment of insulin secretion in rats after surgical trauma. Eur J Endocrinol 2002;147:825–33. [PubMed: 12457459]
69. Tsigos C, Papanicolaou DA, Kyrou I, Defensor R, Mitsiadis CS, Chrousos GP. Dose-dependent effects of recombinant human interleukin-6 on glucose regulation. J Clin Endocrinol Metab 1997;82:4167–70. [PubMed: 9398733]
70. Plomgaard P, Bouzakri K, Krogh-Madsen R, Mittendorfer B, Zierath JR, Pedersen BK. Tumor necrosis factor-alpha induces skeletal muscle insulin resistance in healthy human subjects via inhibition of Akt substrate 160 phosphorylation. Diabetes 2005;54:2939–45. [PubMed: 16186396]

71. Vendrell J, Broch M, Vilarrasa N, et al. Resistin, adiponectin, ghrelin, leptin, and proinflammatory cytokines: relationships in obesity. Obes Res 2004;12:962–71. [PubMed: 15229336]
72. Genco RJ, Grossi SG, Ho A, Nishimura F, Murayama Y. A proposed model linking inflammation to obesity, diabetes, and periodontal infections. J Periodontol 2005;76:2075–84. [PubMed: 16277579]
73. Berkowitz GS, Papeirnik E. Epidemiology of preterm birth. Epidemiol Rev 1993;15:414–43. [PubMed: 8174665]
74. Buduneli N, Baylas H, Buduneli E, Turkoglu O, Kose T, Dahlen G. Periodontal infections and preterm low birth weight: a case-control study. J Clin Periodontol 2005;32:174–81. [PubMed: 15691348]
75. McCormick MC. The contribution of low birth weight to infant mortality and childhood morbidity. N Engl J Med 1985;312:82–90. [PubMed: 3880598]
76. Davenport ES, Williams CE, Sterne KA, Murad S, Sivapathasundram V, Curtis MA. Maternal periodontal disease and preterm low birthweight: case-control study. J Dent Res 2002;81:313–8. [PubMed: 12097443]
77. Offenbacher S, Lieff S, Boggess K, Murtha A, Madianos P, Champagne C, et al. Maternal periodontitis and prematurity. Part I: obstetric outcome of prematurity and growth restriction. Ann Periodontol 2001;6:164–74. [PubMed: 11887460]
78. Moreu G, Tellez L, Gonzalez-Jaranay M. Relationship between maternal periodontal disease and low-birth-weight pre-term infants. J Clin Periodontol 2005;32:622–7. [PubMed: 15882221]
79. Yeo BK, Lim LP, Paquette DW, Williams RC. Periodontal disease – the emergence of a risk for systemic conditions: pre-term low birth weight. Ann Acad Med 2005;34:111–6.
80. Ventura SJ, Martine JA, Curtin SC, et al. Births: final data for 1997. Natl Vital Stat Rep 1999;47:1–96.
81. Skuldbol T, Johansen KH, Dahlen G, Stoltze K, Holmstrup P. Is pre-term labour associated with periodontitis in a Danish maternity ward? J Clin Periodontol 2006;33:177–83. [PubMed: 16489943]
82. Andrews WW, Goldenberg RL, Hauth JC. Preterm labor: emerging role of genital tract infections. Infect Agents Dis 1995;4:196–211. [PubMed: 8665085]
83. Gibbs RS, Romero R, Hillier SL, Eschenbach DA, Sweet RL. A review of premature birth subclinical infection. Am J Obstet Gynecol 1992;166:1515–26. [PubMed: 1595807]
84. Minkoff H, Grunebaum AN, Schwarz RH, Feldman J, Cummings M, Crombleholme W, et al. Risk factors for premature rupture of membranes: a prospective study of the vagina flora in pregnancy. Am J Obstet Gynecol 1984;150:965–72. [PubMed: 6391179]
85. Offenbacher S, Katz V, Fertik G, et al. Periodontal infection as a possible risk factor for preterm low birth weight. J Periodontol 1996;67:1103–13. [PubMed: 8910829]
86. Slattery MM, Morrison JJ. Preterm delivery. Lancet 2002;360:1489–97. [PubMed: 12433531]
87. Romero R, Mazor M. Infection and preterm labor. Clin Obstet Gynecol 1988;31:553–84. [PubMed: 3066544]
88. Madianos PN, Lieff S, Murtha AP, Boggess KA, Auten RL Jr, Beck JD, Offenbacher S. Maternal periodontitis and prematurity. Part II: maternal infection and fetal exposure. Ann Periodontol 2001;6:175–82. [PubMed: 11887461]
89. Offenbacher S, Riche EL, Barros SP, Bobetsis, Lin D, Beck JD. Effects of maternal *Campylobacter rectus* infection on murine placenta, fetal and neonatal survival, and brain development. J Periodontol 2005;76:2133–43. [PubMed: 16277586]
90. Han YW, Redline RW, Li M, Yin L, Hill GB, McCormick TS. *Fusobacterium nucleatum* induces premature and term stillbirths in pregnant mice: implication of oral bacteria in preterm birth. Infect Immun 2004;72:2272–9. [PubMed: 15039352]
91. Boggess KA, Moss K, Madianos P, Murtha AP, Beck J, Offenbacher S. Fetal immune response to oral pathogens and risk of preterm birth. Am J Obstet Gynecol 2005;193:1121–6. [PubMed: 16157123]
92. Lopez NJ, Silva ID, Ipinza J, Gutierrez J. Periodontal therapy reduces the rate of preterm low birth weight in women with pregnancy-associated gingivitis. J Periodontol 2005;76:2144–53. [PubMed: 16277587]

93. Wactawski-Wende J, Grossi SG, Trevisan M, Genco RJ, Tezal M, Dunford RG, Ho AW, Hausmann E, Hreshchyshyn MM. The role of osteopenia in oral bone loss and periodontal disease. J Periodontol 1996;67(10 Suppl):1076–84. [PubMed: 8910826]

94. Garnero P. Markers of bone turnover for the prediction of fracture risk. Osteoporos Int 2000;11(Suppl 6):S55–65. [PubMed: 11193240]

95. Jeffcoat MK, Chestnut CH 3rd. Systemic osteoporosis and oral bone loss: evidence shows increased risk factors. J Am Dent Assoc 1993;124:49–56. [PubMed: 8227773]

96. Page RC, Sims TJ, Geissler F, Altman LC, Baab DA. Defective neutrophil and monocyte motility in patients with early-onset periodontitis. Infect Immun 1985;47:169–75. [PubMed: 3965394]

97. Lerner UH. Osteoclast formation and resorption. Matrix Biol 2000;19:107–20. [PubMed: 10842094]

98. Manabe H, Kawaguchi H, Chikuda H, Miyaura C, Inada M, Nagai R, et al. Connection between B lymphocyte and ostoclast differentiation pathways. J Immunol 2001;167:2625–31. [PubMed: 11509604]

99. Taubman MA, Kawai T. Involvement of T-lymphocytes in periodontal disease and in direct and indirect induction of bone resoprtion. Crit Rev Oral Biol Med 2001;12:125–35. [PubMed: 11345523]

100. Liu D, Xu JK, Figliomeni L, Huang L, Pavlos NJ, Rogers M, et al. Expression of RANKL and OPG mRnNA in periodontal disease. Possible involvement in bone destruction. Int J Mol Med 2003;11:17–21. [PubMed: 12469211]

101. Nagasawa T, Kobayashi H, Kiji M, Aramaki M, Mahanoda R, Kojima T, et al. LPS-stimulated human gingival fibroblast inhibits the differentiation of monocytes into osteoclasts through the production of osteoprotegerin. Clin Exp Immunol 2002;130:338–44. [PubMed: 12390325]

102. Teng YTA, Nguyen H, Gao X, Kong YY, Gorczynski RM, Singh B, et al. Functional human T-cell immunity and osteoprotegerin ligand control alveolar bone destruction in periodontal infection. J Clin Invest 2000;106:R59–67. [PubMed: 10995794]

103. Jiang Y, Mehta CK, Hsu TY, Alsulaimani FFH. Bacteria induce osteoclastogenesis via an osteoblast-independent pathway. Infect Immun 2002;70:3143–8. [PubMed: 12011008]

104. Jacobs R, Ghyselen J, Koninckx P, van Steeberghe D. Long-term bone mass evaluation of mandible and lumbar spine in a group of women receiving hormone replacement therapy. Eur J Oral Sci 1996;104:10–6. [PubMed: 8653490]

105. Pacifici R. Cytokines, estrogen, and postmenopausal osteoporosis – the second decade. Endocrinology 1998;139:2659–61. [PubMed: 9607769]

106. Gemmell E, Marshall RI, Seymour GJ. Cytokines and prostaglandins in immune homeostasis and tissue destruction in periodontal disease. J Periodontol 2000;1997:14:112–43.

107. Baker PJ. The role of immune responses in bone loss during periodontal disease. Microbes Infect 2000;2:1181–92. [PubMed: 11008108]

108. Tezal M, Wactawaki-Wende J, Grossi SG, Ho AW, Dunford R, Genco RJ. The relationship between bone mineral density and periodontitis in postmenopausal women. J Periodontol 2000;71:1492–8. [PubMed: 11022780]

109. Inagaki K, Kurosu Y, Yoshinari N, Noguchi T, Krall EA, Garcia RI. Efficacy of periodontal disease and tooth loss to screen for low bone mineral density in Japanese women. Calcif Tissue Int 2005;77:9–14. [PubMed: 16007480]Epub 2005 Jul 14

110. Wactawski-Wende J, Hausmann E, Hovey K, Trevisan M, Grossi S, Genco RJ. The association between osteoporosis and alveolar crestal height in postmenopausal women. J Periodontol 2005;76:2116–24. [PubMed: 16277584]

111. Marques MR, da Silva MAD, Manzi FR, Cesar-Neto JB, Nociti FH Jr, Barros SP. Effect of intermittent PTH administration in the periodontitis-associated bone loss in ovariectomized rats. Arch Oral Biol 2005;50:421–9. [PubMed: 15748695]

112. Jeffcoat M. The association between osteoporosis and oral bone loss. J Periodontol 2005;76:2125–32. [PubMed: 16277585]

113. Brandi ML, Hukkanen M, Umeda T, et al. Bidirectional regulation of osteoclast function by nitric oxide synthase isoforms. Proc Natl Acad Sci USA 1995;92:2954–8. [PubMed: 7535933]

114. Lohinai Z, Stachlewitz R, Virag L, Szekely AD, Hasko G, Szabo C. Evidence for reactive nitrogen species formation in gingivomucosal tissue. J Dent Res 2001;80:470–5. [PubMed: 11332535]

115. Gyurko R, Boustany G, Huang PL, et al. Mice lacking inducible nitric oxide synthase demonstrate impaired killing of *Porphyromonas gingivalis*. Infect Immun 2003;18:39–46.

116. Leitao RFC, Rocha FAC, Chaves HV, Lima V, Cunha FQ, Ribeiro RA, Brito GAC. Locally applied isosorbide decreases bone resorption in experimental periodontitis in rats. J Periodontol 2004;75:1227–32. [PubMed: 15515338]

117. American Academy of Periodontology. Systemic antibiotics in peridontics. J Periodontol 1996;67:831–8. [PubMed: 8866324]