Low-Grade Inflammation in Chronic Infectious Diseases

Paradigm of Periodontal Infections

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ABSTRACT: **Increasing evidence implicates periodontitis, a chronic inflammatory disease of the tooth-supporting structures, as a potential risk factor for increased morbidity or mortality for several systemic conditions including cardiovascular disease (atherosclerosis, heart attack, and stroke), pregnancy complications (spontaneous preterm birth [SPB]), and diabetes mellitus. Cross-sectional, case–control, and cohort studies indicate that periodontitis may confer two- and up to sevenfold increase in the risk for cardiovascular disease and premature birth, respectively. Given the recently acquired knowledge that systemic inflammation may contribute in the pathogenesis of atherosclerosis and may predispose to premature birth, research in the field of periodontics has focused on the potential of this chronic low-grade inflammatory condition to contribute to the generation of a systemic inflammatory phenotype. Consistent with this hypothesis clinical studies demonstrate that periodontitis patients have elevated markers of systemic inflammation, such as C-reactive protein (CRP), interleukin 6 (IL-6), haptoglobin, and fibrinogen. These are higher in periodontal patients with acute myocardial infarction (AMI) than in patients with AMI alone, supporting the notion that periodontal disease is an independent contributor to systemic inflammation. In the case of adverse pregnancy outcomes, studies on fetal cord blood from SBP babies indicate a strong *in utero* IgM antibody response specific to several oral periodontal pathogens, which induces an inflammatory response at the fetal–placental unit, leading to prematurity. The importance of periodontal infections to systemic health is further strengthened by pilot intervention trials indicating that periodontal therapy may improve surrogate cardiovascular outcomes, such as endothelial function, and may reduce four- to fivefold the incidence of premature birth. Nevertheless, further research is needed to fully discern the underlying mechanisms**

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by which local chronic infections can have an impact on systemic health, and in this endeavor periodontal disease may serve as an ideal disease model.

KEYWORDS: **periodontitis; acute myocardial infarction (AMI)**

INTRODUCTION

In the last decade, progress in molecular medicine has led us to reconsider the etiology and pathogenesis of numerous conditions. We have now come to understand that inflammation is a principal component in the development of systemic conditions previously thought to be of different etiology, such as atherosclerosis, diabetes, and adverse pregnancy outcomes.[1,2] In view of such findings, local chronic infectious conditions, which may contribute to a systemic "hyperinflammatory phenotype," are seen as potential contributors to the pathogenesis of distal inflammatory conditions. Given the nature of periodontal disease as a chronic infectious disease, its contribution to the development of systemic inflammation and disease has been the topic of extensive study and research.

The term *periodontal disease* has its origin from the Greek words *peri* (around) and *odous* (tooth)[3] and refers to a group of inflammatory conditions with bacterial etiology that target the supporting structures of the tooth. The periodontal structures include the cementum (a calcified structure of the tooth surface under the gum line), the connective tissue attachment between the tooth and the supporting bone, and the supporting osseous structures, all of which function to support the tooth. In periodontal disease, supporting tissues are destroyed and with time teeth become loose, often migrate, and eventually become lost (FIG.1). Together with the oral problems that may arise, the possibility of periodontal disease aggravating and/or causing systemic conditions, such as cardiovascular disease and adverse pregnancy outcomes, has recently attracted considerable attention.

In this report we will review the epidemiological and basic science data supporting the connection of periodontal disease to systemic health. For this we will discuss the pathogenesis of this local chronic inflammatory condition and its role in the development of systemic inflammation in the initiation of distant infection and/or inflammatory conditions and ultimately in the pathogenesis of systemic disease.

PATHOGENESIS OF PERIODONTAL DISEASE IN A NUTSHELL

Bacterial Etiology

Although periodontal disease is considered an infectious disease, there is no single bacterial species or group of microorganisms whose mere presence leads

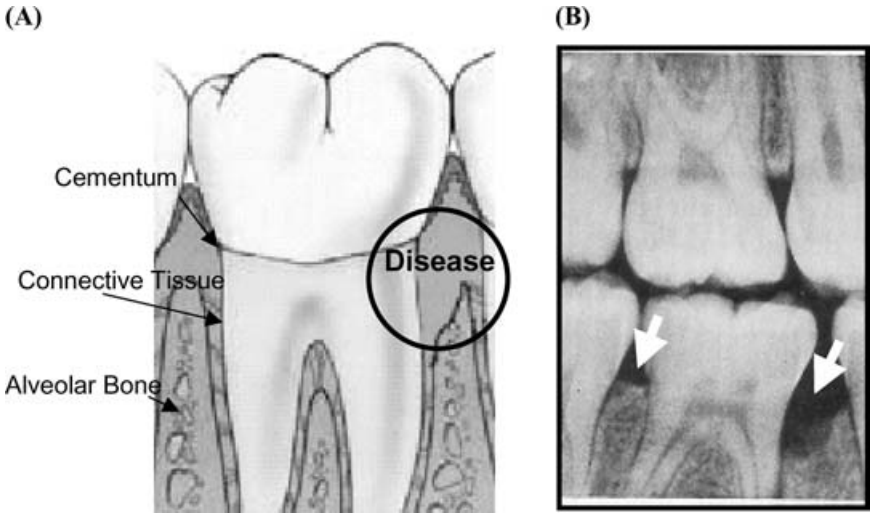

FIGURE 1. Periodontal tissues and disease destruction. (**A**) Cartoon depicts a tooth with the periodontal tissues (cementum, connective tissue, and alveolar bone) being healthy on the left side and compromised due to periodontal disease on the right side of the tooth. Tissues are labeled and *arrows* point to the corresponding areas. (**B**) Radiograph of molar teeth. Local destruction supporting alveolar bone due to periodontal disease is demonstrated by the right arrow, while bone levels are shown to be optimal by the left arrow.

to the disease, but rather a shift in the microbial ecology of the dental plaque biofilm that may account for disease progression. Dental plaque in health and in disease is a well-organized and complex multicellular ecosystem that contains over 600 different aerobic and anaerobic bacteria.[4] The composition shifts from a predominantly Gram-positive aerobic flora in health to a Gram-negative and anaerobic flora in disease. The group of bacteria that has been mostly associated with disease is referred to as the "red cluster" group and includes *Porphyromonas gingivalis, Tannerella forsythia (*formerly known as *Bacteroides forsythus),* and *Treponema denticola.*[5] Nevertheless, most of the oral organisms that are associated with disease are also present in low numbers in health, indicating that in biofilm-induced disease states, several commensal organisms appear to emerge as opportunistic pathogens to cause disease in genetically susceptible individuals.

Inflammatory Etiology

Periodontal disease is initiated by infectious agents, but disease pathogenesis and progression are immune-mediated. Histologically, periodontitis is a chronic inflammatory cell lesion, characterized by lymphocytic

(T and B cell) and monocytic infiltrate, connective tissue destruction, and bone resorption. On a molecular basis, periodontitis is mediated by increases in tissue levels of inflammatory mediators, such as interleukin-(IL-1) 1β, tumor necrosis factor-α (TNF-α), IL-6, prostaglandin E2 (PGE2), and matrix metalloproteinases (MMPs), that mediate collagen and extracellular matrix degradation and bone resorption,[6] indicating that the tissue destruction in this disease is not primarily due to infectious agents, but rather the result of a persistent but not effective inflammatory response.

The mechanisms underlying this chronic inflammation are not fully understood but are speculated to involve the deregulation of immunoregulatory pathways that are meant to "contain" inflammation after infection is cleared.[7] In periodontal disease it appears that the host overreacts to infectious stimuli by secreting increased amounts of proinflammatory cytokines, such as IL-1β, TNF-α, and IL-6, and tissue destructive mediators, such as oxygen intermediates and matrix MMPs. Hints that individual differences in cytokine secretions may contribute to periodontal susceptibility have come from data demonstrating that peripheral blood mononuclear cells from periodontitis patients secrete increased levels of proinflammatory cytokines in response to stimuli.[8] This "hyperinflammatory phenotype" has been attributed to a particular genetic background. The main focus of the studies of genetic susceptibility in periodontal disease has been the polymorphisms found in the IL-1 gene cluster, which may lead to increased cytokine production and therefore increased inflammatory destruction. A susceptible periodontitis-associated genotype (PAG) has been documented that comprises the combination of two rare alleles at separate single nucleotide polymorphisms (SNPs) in the IL-1 gene cluster (one in position −899 in the IL-1α promoter and the second at position +3954 of the IL-1β). This genotype has been correlated with the severity of chronic periodontitis, although PAG was only shown to be a significant factor in nonsmoking patients.[9] Smoking is a major risk factor for periodontal disease, estimated to be responsible for more than 50% of cases of periodontitis in the Western world[9] and appears to be a confounding periodontitis risk factor similar to the susceptible IL-1 genotype.

Together with the increased cytokine production, the persisting and at times disproportionate inflammatory response observed in periodontal disease may also be attributed to a dysfunction of mechanisms of immune resolution in this patient group. With the recent characterization of the "proresolution" lipid mediators, such as the arachidonic cascade-derived lipoxins and the omega-3-fatty acid-derived resolvins, which restrain the immune activity of phagocytes, the pathogenesis of periodontal disease, which is dominated by "uncontrolled" neutrophil-mediated destruction, may be studied under a new light. Furthermore, the observation that animal models overexpressing lipoxins are resistant to periodontal disease points to potential therapeutic potential of these compounds/pathways.[10]

LOCALIZED DISEASE WITH SYSTEMIC "SIDE EFFECTS": BACTEREMIA AND SYSTEMIC INFLAMMATION

Despite the localized nature of periodontal disease a plethora of systemic markers of this condition have been reported and speculated to contribute to systemic diseases.[11] In health, the epithelial barrier in the oral cavity together with the protective innate immune molecules inhibit oral bacteria from entering into the tissues and the bloodstream and therefore in health only small numbers of mostly facultative bacteria enter the circulation.[12] With the advent of periodontal disease it is speculated that the inflamed and ulcerated subgingival pocket epithelium forms an easy port of entry for dental plaque bacteria, many of which are Gram-negative and obligate anaerobic. Bacteremia in periodontitis has been reported after oral examination[12] and periodontal pathogens have been shown to colonize distant sites.[13] Additionally, bacterial components, such as major outer membrane proteins and endotoxins (i.e., lipopolysaccharide [LPS]), may be disseminated. Gram-negative organisms release LPS (lipopolysaccharide, endotoxin) that can trigger significant systemic inflammation. In response to the bacteremia and bacterial antigens that are systemically dispersed, white blood cells as well as tissue cells at locations where the antigens are relocated, such as endothelial cells and hepatocytes, may produce proinflammatory immune mediators. Furthermore, the locally produced proinflammatory mediators, such as IL-1β, TNF-α, IL-6, and PGE2 may "spill" into the circulation and exert systemic or distant effects. The systemic cellular and molecular markers of inflammation in periodontitis include among others an increase of the number of peripheral leukocytes and an increase in the levels of cytokines and acute-phase proteins.[14]

Peripheral Blood Leukocytes

The total number of white blood cells in the peripheral blood is a diagnostic measure of infection or inflammatory disease. In periodontitis, leukocyte counts have been shown to be slightly elevated in patients compared to healthy subjects, although not always significantly.[11] This increase in the number of leukocytes is attributed to the increase mainly of polymorphonuclear leukocytes (PMNs), which are key participants in the periodontal lesion. It has also been shown that this increase in leukocytes is aggravated by increasing severity and extent of disease, and periodontal therapy (local inflammatory control) may lead to a decrease in the number of leukocytes.[15,16]

Proinflammatory Cytokines

In health, cytokine levels in the systemic circulation are minimal and at times undetectable without the use of hypersensitive methodology. In periodontal

disease, of the proinflammatory cytokines studied, levels of IL-6 have been consistently shown to increase in the periphery[11]. Furthermore, IL-6 in plasma showed a positive relation to the extent of disease. IL-6 is also a principal procoagulant cytokine and may also activate hepatocytes to produce acute-phase reactants, such as fibrinogen, plasminogen activator inhibitor 1, and CRP.

Acute-Phase Proteins

It has been long established that immune mediators originating from a site of infection or from a site of severe trauma may activate hepatocytes in the liver to produce large quantities of acute-phase proteins. The acute-phase response is characterized by fever, increased vascular permeability, and a general elevation of metabolic processes. The acute-phase reactants include C-reactive protein (CRP), serum amyloid P component, serum amyloid A protein, and alpha-1-acid glycoprotein (AGP) and possess a wide variety of functions, such as multiple proinflammatory properties and stimulation of tissue repair. It has been established in the past decade that acute-phase proteins not only appear in acute and severe disease processes, but also in longstanding, chronic conditions. For example, CRP has often been found at relatively low levels (range 0.3 to 3.0 mg/L) in subjects with chronic stomach ulcers associated with *Helicobacter pylori* and in persons with chronic lung infections. Since periodontitis is a chronic inflammatory and infectious disease, it is not surprising that CRP levels in periodontal patients have been of interest. Significantly elevated levels of CRP in periodontal patients compared to nonperiodontal controls have been shown in several studies (TABLE 1), even after adjustment of confounding factors. Levels of CRP in plasma ranged from 2–10 mg/L, consistent with the presence of a low-grade chronic inflammation. Some intervention studies have demonstrated an effect of periodontal therapy on CRP and systemic

TABLE 1. Plasma CRP levels in periodontitis patients and healthy controls

	Patients		Controls	
Study	*n*	Mean ± SD	*n*	Mean ± SD
Ebersole *et al*., 1997[34]	40	9.12 ± 1.61	35	2.17 ± 0.41
Fredriksson *et al*., 1998[35]	17	2.62 ± 2.9	38	0.87 ± 1.73
Loos *et al.,* 2000[36]	107	2.64 ± 3.48	43	1.21 ± 1.34
Noak *et al*., 2001[37]	50	4.06 ± 5.55	65	1.70 ± 1.91
Glurich *et al*., 2002[38]	26	2.4 ± 1.89	20	1.68 ± 1.42
Craig *et al*., 2003[39]	44	5.78 ± 1.07	25	2.46 ± 1.44
Buhlin *et al*., 2003[40]	50	3.28 ± 4.64	46	1.74 ± 1.68

Adapted from Loos, 2005.[11]

cytokine levels (TABLE 2). For example, Mattila *et al*.[17] reported a reduction of CRP concentrations on 30 patients with chronic periodontitis; the median value at baseline was reduced from 1.05 mg/L to 0.7 mg/L after therapy and the most significant reductions were seen in patients with the highest starting CRP levels.

SYSTEMIC PERIODONTAL "SIDE EFFECTS" MAY PREDISPOSE TO CARDIOVASCULAR DISEASE

Infection is now recognized as a risk factor in the development of cardiovascular disease (CVD). The initial observations that CVD patients have higher titers of *Clamydia pneumoniae*[18] initiated a new way of thinking in the area of CVD pathogenesis. For oral infections, the association with CVD has been speculated to be due to the recovery of periopathogens in surgical specimens from atherosclerotic plaques. Of the atheromas studied 30% were positive by PCR for *Tannerella forsythia* (*Bacteroides forsythus)*, 26% for *Porphyromonas gingivalis,* 18% for *Actinobacillus actinomycetemcomitans*, and 14% for *Prevotella intermedia.*[13] A pathogenic role for such bacteria in atheroma formation is also supported by the ability of oral bacteria such as *Streptococcus sanguis* and *Porphyromonas gingivalis* to induce platelet aggregation *in vitro.*[19]

Separate from the risks of bacteremia, the systemic inflammation induced by periodontal disease may contribute to CVD, given that inflammation plays a key role in the pathogenesis of the disease. In atherosclerotic lesions immune cells dominate, their effector molecules accelerate progression of the lesions, and activation of inflammation can elicit acute coronary syndromes. Furthermore, the markers of systemic inflammation observed in periodontal disease are known risk factors for CVD. First the levels of acute-phase proteins are associated with CVD. More than 20 prospective epidemiological studies demonstrate that slightly elevated (0.3 mg/L up to 3 mg/L) and chronically present levels of CRP (high-sensitivity CRP) are independent predictors of risk for myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death, even in apparently healthy individuals.[20] Secondly, elevated levels of IL-6 have been associated with increased risk of future myocardial infarction in healthy men.[21] Thirdly, other molecular markers elevated in periodontal disease, such as fibrinogen and the procoagulant protein von Willebrand factor,[11] may contribute to the development of thrombi.

Finally, impaired endothelial-dependent vascular dilation, an established risk factor for cardiovascular disease, is also associated with periodontal disease. A recent study[22] demonstrated significantly impaired branchial artery flow–mediated dilation in otherwise healthy, nonsmoking subjects with advanced periodontal disease compared with age-matched control subjects. The

TABLE 2. Effect of periodontal therapy on systemic inflammation

Authors	Study Type	No. of patients	Periodontal Therapy	Outcome	Conclusion
Elter *et al.*, 2006[24]	Single masked CT	C = 22 T = 22*	nonsurgical and surgical	C:ΔCRP = 0.1mg/L T:ΔCRP = −1mg/L C:ΔIL-6 = −0.1 pg/L T:ΔIL-6 = −0.6 pg/L	Therapy reduced serum IL-6 and improved endothelial function
Montebugnoli *et al.*, 2005[41]	Single blind CT	C = 18 T = 18*	nonsurgical	C:ΔCRP = −0.01 mg/L T:ΔCRP = −0.9 mg/L	Therapy reduced serum CRP
D'Aiuto *et al.*, 2004[42]	Prospective CT	T = 94	nonsurgical	ΔCRP = −0.5mg/L ΔIL-6 = −0.2 ng/L	Therapy reduced serum CRP and IL-6
Yamazaki *et al.*, 2004[43]	Prospective CT		nonsurgical and surgical; antibiotics for 4 days after surgery	T:ΔCRP = −55.5 ng/mL T:ΔIL-6 = −0.01 pg/mL T:ΔTNF-α = −0.22 pg/mL	Unable to show significant decrease in CRP, IL-6 & TNF- α
Ide *et al.*, 2003[44]	Randomized Controlled CT	C = 15 T = 24	nonsurgical	C:ΔCRP = −0.28 mg/L C:ΔIL-1β = 0.08 pg/L C:ΔIL-6 == −0.03 pg/L C:ΔTNF-α = −0.19 pg/mL T:ΔCRP = −0.14 mg/L T:ΔIL-1β = −0.06 pg/L T:ΔIL-6 = −0.40 pg/L T:ΔTNF-α = −0.01 pg/L	Unable to show significant decrease in CRP, IL-1β, IL-6 & TNF- α
Iwamoto *etal.*, 2003[45]	Prospective CT	T = 15	nonsurgical plus local antibiotic	T: ΔCRP = −733.7 ng/mL T: ΔTNF-α = −0.4 pg/mL	Therapy reduced CRP and TNF-α
Mattila *et al.*, 2002[17]	CT	T = 30	nonsurgical	T: ΔCRP = 0.35 mg/L	Therapy reduced CRP

*Test group served as control after nontreatment period.

T = therapy group; C: Control group; CT = clinical trial; ΔCRP = difference between CRP values at baseline and posttherapy; ΔIL-1β = difference between IL-1β values at baseline and posttherapy; ΔIL-6 = difference between IL-6 values at baseline and posttherapy; ΔTNF-α = difference between TNF-α values at baseline and posttherapy.

stimulation of the vascular endothelium by circulating cytokines and/or pathogens is speculated to be responsible for this "proatherogenic" phenotype. More importantly, the impaired endothelial function of patients with severe periodontitis was improved by periodontal treatment.[23,24] Periodontal treatment has been also shown to lessen other CVD risk factors, such as the levels of lipoprotein-associated phospholipase A_2 (Lp-PLA_2),[24] which hydrolyzes oxidized low-density lipoproteins (LDLs) in products with proinflammatory and proatherogenic activity.[25]

Epidemiological Data

A connection between poor oral health and atherosclerosis-induced heart disease began in the late 1980s with several case and case–control studies.[26] Stimulated by this initial association, a number of cross-sectional studies were conducted and were able to demonstrate a modest association of periodontal disease with CVD after controlling for other cardiovascular risk factors. Also, at least four studies demonstrated a positive association between periodontal disease and stroke, and one study associated periodontal disease with peripheral vascular disease.[26] In addition to the above studies linking periodontal disease with CVD outcomes, a number of studies have associated periodontal disease with CVD risk factors, such as subclinical atherosclerosis, coronary calcification, and high levels of CRP, fibrinogen, von Willebrand factor, IL-6, lipids, and endothelial function.[11,22,27] This variability in CVD outcomes from the various studies as well as the variability of periodontal disease assessments creates limitations when evaluating and comparing the data.

The highest level of existing evidence comes from longitudinal studies, given that there are no randomized controlled trials to determine the effect of periodontal disease prevention or treatment on cardiovascular events. There are now at least 16 articles published (for review see Beck and Offenbacher[28]). The results have been mixed, with 10 studies reporting positive, adjusted associations between oral status and some type of cardiovascular outcome or CRP and six studies reporting no association or nonsignificant positive trends after adjustment. The OR in the studies with significant positive results ranged from 1.2 to 3.4; however, the majority were under 2.0, indicating low-to-moderate levels of association. In fact, there has been a concern expressed about the inconsistent results among the studies reported, and there has been a great deal of discussion concerning the reasons for these differences. Some points raised have included the moderate level of the associations, lack of control for confounding, residual confounding, no measures of infection, and the wide variety of definitions used for the exposure (periodontal disease) and the outcome (cardiovascular disease).

PERIODONTAL DISEASE MAY LEAD TO ADVERSE PREGNANCY OUTCOMES

Epidemiology

The strongest data for infection-induced preterm labor exist for the association of bacterial vaginosis with premature birth.[29] For periodontal infections, the data generated thus far, from cross-sectional and prospective studies as well as from animal experiments, continue to support the hypothesis that such infections can also serve as an independent risk factor for prematurity and growth restriction. Several studies suggest a significant association between maternal periodontal disease and pregnancy complications, including premature delivery (gestational age [GA] <37 weeks), decreased fetal weight (birth weight [BW] <2,500 g), and pre-eclampsia.

The first reported human case–control study in 1996 suggested that mothers with premature, low-birth-weight babies had more severe periodontal disease than mothers with full-term deliveries and that periodontitis appeared to confer considerable risk independent of other traditional obstetric risk factors.[30] However, this investigation was a relatively small study of 124 cases and this case–control design did not permit the establishment of temporality of exposure (periodontal disease) as it relates to the outcome (preterm birth). Nonetheless, the potential magnitude of the effect of periodontal disease was surprisingly large (adjusted odds ratio [OR] 6.7, $P = 0.003$) and provided impetus for further study, prompting the conduct of cross-sectional studies to confirm this association and prospective studies to appropriately measure attributable risk. A prospective study of 1,313 mothers, conducted at the University of Alabama,[31] reported that antenatal maternal periodontitis is an independent risk factor for preterm birth and low birth weight. These investigators report that severe periodontal disease is associated with an OR = 5.2 (2.05–13.6) for preterm birth (GA<37) and OR = 7.07 (1.7–27.4) for very preterm (VPT, GA<32) deliveries, adjusting for age, race smoking, and parity. However, both studies show a biologic gradient effect in that more severe periodontal disease is associated with stronger risk for earlier-gestational-age deliveries.

Possible Mechanisms

The proposed pathogenesis of infection-induced preterm labor is the ascent of microorganisms from the cervix or vagina, with subsequent colonization of fetal membranes and decidua. Once the organisms colonize the deciduas and fetal membranes and/or invade the amniotic sac, they release LPS or other toxins. The molecular pathways eliciting this microbial effect on pregnancy have been suggested to involve microbial LPS and TLR-mediated (toll-like receptor) pathways, resulting in the release of primary inflammatory mediators,

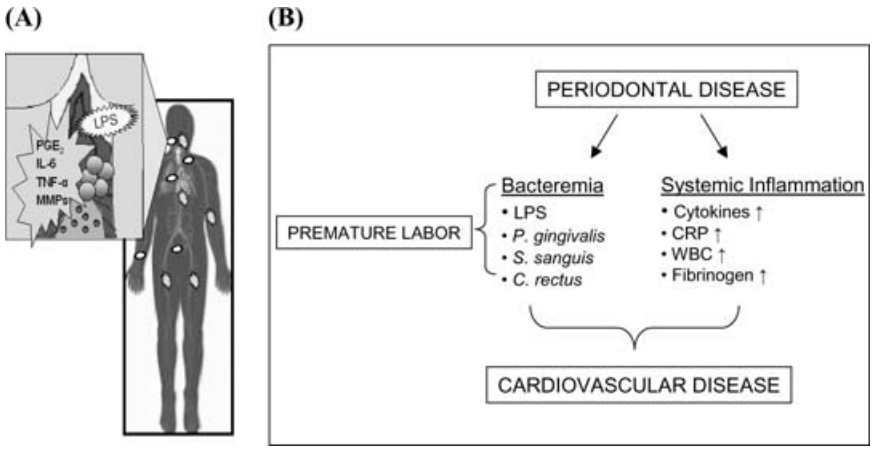

FIGURE 2. Systemic effects of periodontal disease. (**A**) Cartoon illustrates that inflammatory mediators, such as PGE2, IL-6, TNF-α, and MMP as well as infectious components, such as bacteria and LPS, present in the periodontal pocket may enter the circulation and reach distant sites. (**B**) Conceptual diagram illustrating possible mechanisms through which periodontal disease may lead to systemic disease.

such as IL-1, IL-6, TNF-α, and secondarily PGE2 (prostaglandin E2), which is capable of inducing uterine contraction and modulating placental blood flow, and in humans can mediate cervical thinning, dilation, and premature labor.[2] Inflammation of the chorioamniotic membranes can also result in MMP secretion, the breakdown of the collagenous matrix, and mechanical weakening, enhancing the likelihood of premature rupture. However, inflammatory stimuli that predispose to premature rupture of membranes and preterm labor may also have effects on the neonatal environment. Infectious exposure to the mother during pregnancy is currently believed to be a significant factor that triggers the *in utero* fetal stress that ultimately contributes to long-term growth and developmental problems. The fetal response to periodontal infections has been documented by the assessment of fetal IgM levels for 15 periodontal pathogens at birth by means of cord blood.[32] The increased prevalence of IgM seropositivity (2.9-fold increase) for one or more periopathogens in preterm versus full-term neonates demonstrates the relation of periodontal infections to prematurity. Specifically, the prevalence of positive fetal IgM to *C. rectus* and to *P. intermedia* was significantly higher for preterm neonates (20% vs. 6.3%, $P = 0.0002$ and 8.8% vs. 1.1%, $P = 0.0003$, respectively). The highest rate of prematurity was observed among those mothers without a protective IgG response, which may be capable of arresting the systemic microbial dissemination. The rate of prematurity was also higher in cases where a positive fetal IgM was coupled with a fetal inflammatory response shown by detectable CRP, or high 8-isoprostane, PGE2, or TNF-α.[33]

LOW-GRADE INFLAMMATION IN CHRONIC INFECTIOUS DISEASES AND THE PARADIGM OF PERIODONTAL INFECTIONS

We conclude that periodontal disease is a chronic infectious disease in which a persistent local inflammation is responsible for the disease pathogenesis and outcome (i.e., tissue destruction). More importantly in this disease, the systemic dissemination of infectious agents and inflammatory mediators from the oral environment may cause an elevated systemic inflammatory condition, which may contribute to the pathogenesis of distal inflammatory processes, such as the pathogenesis of CVD and the initiation of premature labor (FIG. 2). Nevertheless, the exact mechanisms through which local inflammatory conditions may contribute to systemic inflammation are not fully understood. Furthermore, the possibility of a "common genetic background" predisposing to various inflammatory conditions ("hyperinflammatory phenotype") is also a viable possibility. In this quest to understand immune-mediated disorders and their contribution/effect to systemic health, periodontal disease may serve as a uniquely appropriate model. The large prevalence of the disease, the accessibility of the oral environment for study and the presence of evidence linking this disease to systemic health all point to the fact that the paradigm of periodontal diseases may be viewed as a valuable tool for biomedical research.

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