Periodontal Health and Systemic Disorders

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Abstract

Recent studies in periodontal medicine suggest a mild to moderate association between human periodontal disease and certain systemic disorders such as diabetes mellitus, pneumonia, heart disease and preterm birth. The latest evidence, presented at a symposium entitled "Periodontal Health and Systemic Disorders," sponsored by the University of Western Ontario School of Dentistry, showed that indeed such an association is likely. New data suggest that this association is not indicated by traditional clinical signs of periodontal disease but rather by a cluster of host immune and inflammatory mediators. The coming era of periodontal medicine based upon molecular criteria will affect the future of periodontal diagnosis, treatment and professional practice.

MeSH Key Words: *inflammation mediators; periodontal diseases/complications; risk factors*

© J Can Dent Assoc 2002; 68(3):188-92
This article has been peer reviewed.

Studies of the relationship between periodontal disease and certain systemic disorders have shown that a positive association may exist. As part of the celebration of the completion of phase I of the new Dental Clinics and research addition at the School of Dentistry, the University of Western Ontario, and to increase public and professional understanding in this specific field, a state-of-the-science symposium entitled "Periodontal Health and Systemic Disorders" was held on September 27, 2001, in London, Ontario. The focus was on updating our understanding of periodontal disease and its relationship to diabetes mellitus, pneumonia, heart disease and preterm birth. The individual presentations are summarized here.

Diabetes Mellitus and Periodontal Disease — G.W. Taylor

Recent studies have suggested evidence for a bidirectional adverse interrelationship between diabetes mellitus and periodontal diseases. In particular, individuals susceptible to diabetes and those with poor metabolic control may experience one or more complications in multiple organs and tissues. The evidence for a bidirectional relationship between the 2 conditions comes from studies conducted in distinctly different settings worldwide. A comprehensive MEDLINE search of the post-1960 English literature identified a large number of primary reports of the relationships between diabetes and periodontal diseases. Overall, these observational studies, which covered both type 1 and type 2 diabetes, provided consistent evidence of greater prevalence, incidence, severity, extent or progression of at least one manifestation of periodontal disease in diabetic patients. Supportive evidence was found in 44 of the 48 reports reviewed (37 of 41 cross-sectional studies and all 7 of the cohort studies). In addition, no studies refuting the association had superior design features. As with other complications of diabetes, current evidence also supports the suggestion that poorer glycemic control contributes to poorer periodontal health. Of the studies providing information on differences in periodontal health classified by glycemic control status, most have been cross-sectional, with 19 of 34 reporting more frequent or more severe periodontal disease in patients with poorer glycemic control and 15 reporting no differences. Among the 9 follow-up

studies, 8 reported poorer periodontal health in subjects with poorer glycemic control. Furthermore, of the 16 reports published before 1990, only 6 reported more frequent or more severe periodontal disease in subjects with poorer glycemic control, whereas 13 of the 18 papers published since 1990 reported such an association. Finally, this group of studies supports the concept of a "dose–response" relationship, i.e., as glycemic control worsens, the adverse effects of diabetes on periodontal health become greater.[1]

Several reports describing periodontal treatment of diabetic patients have provided direct evidence that periodontal infection has an adverse, yet modifiable, effect on glycemic control. However, not all investigations reported an improvement in glycemic control after periodontal treatment. There were major variations in the design, conduct and results of these studies, as described in recent detailed reviews.[1] Additional evidence to support the suggestion that severe periodontitis increases the risk of poorer glycemic control comes from 2 follow-up observational studies.[1,2]

Overall, the evidence supports the view that the relationship between diabetes and periodontal diseases is bidirectional. Further rigorous, systematic study is warranted to firmly establish that treating periodontal infections can contribute to glycemic management and possibly to a reduction in the complications of diabetes mellitus. However, there is already sufficient evidence to recommend incorporating a thorough oral examination and necessary periodontal care (prevention and treatment) in the management regimens of people with diabetes.

Respiratory Disorders and Periodontal Disease — F. Scannapieco

Recent studies suggest that the mouth may play an important role in infections acquired in hospitals and nursing homes, especially infections of the respiratory tract. Dental plaque, a complex biofilm, can serve as a reservoir of infection in hospital inpatients.[3] Several studies have demonstrated that the teeth of patients in the intensive care unit (ICU) become colonized by respiratory pathogens such as *Pseudomonas aeruginosa*, enteric species and *Staphylococcus aureus.* Similar studies have shown that the teeth of nursing home residents can also serve as reservoirs for respiratory infection. One ICU study demonstrated that only patients with oral colonization by a respiratory pathogen went on to experience pneumonia. In some hospitals, a large proportion of the cultivable oral microflora from ICU patients consists of pathogenic species such as *S. aureus, P. aeruginosa* and *Klebsiella pneumoniae.* Superinfection by these bacteria is probably due to exposure of the patients to antibiotics, which suppress the normal flora and allow pathogenic bacteria from the environment (e.g., the hospital) to flourish in the mouth. Several studies have demonstrated that daily mechanical oral hygiene with or without use of an oral antiseptic such as 0.12% chlorhexidine gluconate or 1% povidone–iodine not only reduces the prevalence of colonization by oral pathogens but also reduces the rate of pneumonia by about 50%.

Other studies have suggested an association between poor oral health (e.g., periodontal disease) and chronic obstructive pulmonary disease (COPD). In particular, this association was observed on analysis of existing large databases such as the Veterans Administration Normative Aging Study and the National Health and Nutrition Examination Survey III (NHANES III), after controlling for confounding variables such as smoking, sex, age and socioeconomic status.[4] It is well known that some patients with COPD suffer from periodic acute exacerbations or worsening of lung function. These exacerbations are due in part to infection, typically by bacteria, such as *Streptococcus pneumoniae, Haemophilus influenzae* and *Branhamella catarrhalis*, or rhinovirus. It is presumed that frequent exacerbations accelerate the decline in lung function and lead to disease progression. Perhaps aspiration of saliva into which oral bacterial antigens, lipopolysaccharide and enzymes have been released promotes inflammation and infection of the lower airway. It is also possible that host-derived mediators such as cytokines and prostaglandins, which are elevated in the saliva of subjects with periodontal disease, promote lung inflammation and infection if aspirated into the lower airway. The possibility that bacteria in oral biofilms influence respiratory infection suggests that good oral hygiene may prevent the aspiration of large numbers of oral bacteria into the lower airway and thus prevent initiation or progression of respiratory infection in susceptible individuals. Further studies are required to verify the importance of oral conditions in the pathogenesis of lung diseases such as COPD.

The Cardiovascular Impact of Periodontal Disease — D.F. Kinane

Human periodontal disease and atherosclerosis both have complex causes and genetic and sex-related predispositions. In addition, they may share some risk factors, such as the smoking status. It is now becoming clear that chronic inflammation and infection such as periodontitis may influence the atherosclerotic process.[5] Severe, chronic periodontal disease provides a rich source of subgingival microbial and host–response products and may exert its effect over a long period. Three pathways linking oral infections to systemic effects have been proposed: metastatic spread of infection as a result of transient bacteremia, metastatic injury from the effects of circulating oral microbial toxins and metastatic inflammation caused by an injury induced by oral microorganisms.

Infection theories: Chronic bacterial infections such as those caused by *Chlamydia pneumoniae* and dental infections have been suggested as risk factors for various atherosclerotic diseases. It has been reported that in patients with periodontal inflammation, a *Streptococcus sanguis* protein associated with platelet aggregation and bacteremia associated with *Porphyromonas gingivalis* may contribute to some acute thromboembolic events.[6] Furthermore, *P. gingivalis* can multiply within and activate endothelial cells, thus providing mechanistic support to the above-described association between periodontitis and cardiovascular pathology such as atherosclerosis.

Distant injury: Distant injury may derive from the effects of circulating oral microbial toxins or products associated with bacteremia. Although the molecular mechanisms are still unclear, one possibility is that bacteria-derived lipopolysaccharides trigger hyperreactive leukocyte responses to initiate the association, whereby both processes collaborate to promote cardiovascular pathology.

Distant inflammation: It has been suggested that periodontal infection can induce changes in immune functions that result in metabolic dysregulation of serum lipid metabolism through proinflammatory cytokines. Thus, these locally produced proinflammatory cytokines (for example, interleukin 1ß [IL-1ß] and tumour necrosis factor alpha) may exert systemic effects by predisposing the patient to a systemic disorder such as atherosclerosis. This hypothesis is further supported by recent findings that total cholesterol, low-density lipoprotein and triglycerides are significantly higher in subjects with periodontitis than in controls: by 8% ($p < 0.03$), 13% ($p < 0.003$) and 39% ($p < 0.001$), respectively.[7] However, for prediabetic patients, it is not clear whether periodontitis causes an increase in hyperlipidemia or whether periodontitis and cardiovascular disease share hyperlipidemia as a common risk factor.

Whatever mechanisms are involved, it is evident that periodontitis may affect the host's susceptibility to systemic disease through subgingival biofilms acting as reservoirs of gram-negative bacteria and creating transient bacteremia, through release of microbial toxins and through a reservoir of inflammatory mediators. In parallel, all these factors are capable of predisposing the host to vascular changes or disorders. Further studies are required to find ways of intercepting these pathological changes, which may involve developing new generations of antimicrobial, anti-inflammatory, anti-infective or antithrombotic therapeutic agents.

Preterm Delivery of Low-Birth-Weight Infants and Periodontal Disease — M. Curtis

The growing consensus that infection remote from the fetal–placental unit may influence preterm delivery of low-birth-weight infants has led to an increased awareness of the potential role of chronic bacterial infections in the body. Periodontal diseases are associated with chronic gram-negative infections, which result in local and systemic elevations of proinflammatory prostaglandins and cytokines. Furthermore, there is ample evidence that periodontal bacteria frequently enter the circulation. Hence, maternal periodontal infection may influence preterm delivery through mechanisms involving inflammatory mediators or a direct bacterial assault on the amnion. We examined the association between maternal periodontal disease and preterm delivery of low-birth-weight infants (PLBW) in a case-control study of over 700 mothers attending the Royal London Hospital in east London, United Kingdom.[8] Attention was paid to potential confounding variables, and the study confirmed well-known risk factors for PLBW, including hypertension, tobacco use, previous PLBW and untreated genitourinary (GU) tract infection. For example, mothers with an untreated GU infection were significantly more likely to have a PLBW infant than those without such an infection (odds ratio [OR] 2.21 [95% confidence interval, CI, 1.00–4.62]) and those whose infections had been treated (OR 1.35 [95% CI 0.94–1.94]). However, we found no difference between the study cases and control mothers for any of the periodontal indices (pocket depth, bleeding index or Community Periodontal Index of Treatment Needs [CPITN]). Furthermore, after controlling for confounding factors, we detected no greater risk of PLBW in association with periodontal disease. Explanations for the difference between these data and previous reports are several: first, there may in fact be no association; second, the differences may reflect differences in the study populations; and finally, periodontal diseases may be associated with PLBW but only in the presence of other specific environmental or genetic risk factors not controlled for in this study. Hence, on the basis of the data available, an association between clinical measures of maternal periodontal disease and PLBW may not be consistently demonstrable in all populations.

Nonetheless, there remain plausible biological hypotheses to support a causal link between maternal periodontal disease and PLBW, hypotheses that are partially supported by experimental data. A fuller understanding of the potential mechanisms may assist in designing further epidemiological analysis of this question. In this regard, data from an ongoing microbiological study of the amniotic fluid of mothers undergoing cesarean section in London do support a link between periodontal disease and pregnancy outcome. In that study, there has been a significant association between detection of microbial DNA in amniotic fluid and previous pregnancy complications, including spontaneous abortion, intrauterine death, neonatal death, premature delivery and premature rupture of the membranes ($p \leq 0.05$). Furthermore, *Fusobacterium nucleatum*, an organism considered to have a predominantly oral habitat, was

detected in 12% of the infected amniotic fluid samples, which suggests that periodontal bacteria can gain access to the amnion.

In conclusion, our current epidemiological results do not support a specific drive to improve the periodontal health of pregnant women as a means of improving pregnancy outcomes in east London. However further research in this area is justified, particularly with respect to the effect of population differences on this potential association and the use of markers of periodontal infection other than the extent of historical destructive disease.

Systemic Disorders and Periodontal Disease — J.D. Beck

There is a substantial microbial and inflammatory burden associated with human periodontal disease, and considerable evidence is accumulating that this systemic burden may contribute to specific systemic diseases and conditions. The current presentation focused on 2 potential systemic outcomes of periodontal disease: coronary artery disease and preterm birth. The evidence presented at this symposium represented the latest findings from a wide range of studies, including large population surveys (such as NHANES III), multicentre longitudinal studies (such as 2 studies based at the University of North Carolina, the dental Atherosclerosis Risk in Community [ARIC] study and the Oral Conditions at Pregnancy [OCAP] study), other clinical studies and animal models. After adjustment for all confounding factors, 3 main conclusions have emerged: there was no significant association between clinically evident loss of periodontal attachment and coronary artery disease, but there was an association between levels of immunoglobulin G (IgG) antibodies to periodontal pathogens and coronary artery disease (OR = 1.4 for antibody to 1 pathogen, 2.4 for antibodies to 2 pathogens and 3.3 for antibodies to 3 pathogens); there was a significant association between attachment loss and subclinical signs of atherosclerosis as measured by the intima–media wall thickness of the carotid artery determined by B-mode ultrasonography;[9] and the greatest risk (OR up to 10.3) of a preterm baby occurs when the maternal IgG response is negative to periodontal pathogens and the fetal immunoglobulin M response is positive.[10] These data indicate that it is the inflammatory and host responses, not the clinical signs of periodontitis, that are associated with cardiac events and subclinical coronary artery disease (atheroma formation) and with preterm births.[9,10] The preliminary results of a separate intervention study in Chile also suggest that periodontal scaling and root-planing therapy during pregnancy significantly lower the incidence of preterm births.

Although there is not yet enough evidence to conclude that periodontitis causes these complex systemic conditions, information was presented to indicate that part of the mechanism explaining the associations between periodontitis and both heart disease and premature birth involves the character of the infection and the quality of the host response. Future research will need to focus on periodontitis as an exposure rather than as an outcome by investigating the effects of the components of periodontitis (clinical signs, infection and host response) in both mechanistic and population-based studies, which would also include intervention studies. If periodontal disease is eventually shown to be a risk factor for these systemic problems, there will likely be major diagnostic and treatment implications for future dental practice.

Conclusions

The "foci of infection" theory was thought to be an archaic concept in dentistry. However, conflicting data now exist.[11,12] Although clinical signs of periodontal disease such as pocket depth and attachment loss do not correlate positively with the severity of systemic diseases and conditions such as coronary artery disease and preterm birth, these traditional measures are not the critical parameters for discerning true association. On the basis of the data outlined above, host responses to periodontal pathogens, such as IgG titres and the proinflammatory mediators IL-1ß and prostaglandin E_2, do correlate significantly with clinical coronary artery disease and preterm births. New studies are under way, and the results generated will help us to better understand the mechanisms, interactions and potential for treatment. As we gain further insight into these complex mechanisms, we can anticipate that the use of molecular determinants for assessing the risks of systemic inflammation and infection will become an integral part of the clinical practice of dentistry. ◆

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The views expressed are those of the authors and do not necessarily reflect the opinions or official policies of the Canadian Dental Association.

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