Periodontal Disease as a Risk Factor for Cardiovascular Disease

SUMMARY
Many studies reported an association between periodontal disease and cardiovascular disease. Accumulation of epidemiologic, in vitro, clinical and animal studies, suggests that periodontal infection may be a contributing risk factor for coronary heart disease. However, several concerns about the nature of this relationship exist in the literature. At present, it seems likely that periodontitis is a moderate risk factor for cardiovascular disease.

Keywords: Periodontitis; Cardiovascular Disease

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Introduction

In 1891 W. Miller published his theory on focal infection, indicating that microorganisms and/or their products are able to access parts of the body adjacent to or distant from the mouth. Recently, for over 12 years, many authors have discussed the possible correlation between oral infections, periodontal disease in particular, and the occurrence of coronary heart disease (CHD), myocardial infarction, and ischemic stroke.

Atherosclerosis is a multifactorial disease which represents the most common cause of CHD. It is the most common cause of myocardial infarction and ischemic stroke.

Periodontitis is one of the most common chronic bacterial infections. It is a common plaque-induced periodontal infection that is a major cause of tooth loss throughout the world. The prevalence of periodontal disease is high, and severe forms of chronic periodontitis affect about 15% of the population worldwide.

Amongst other risk factors for atherosclerosis, bacterial and viral organisms involved in chronic inflammatory processes have also been mentioned.

Periodontitis is associated with Aggregatibacter actinomycetemcomitans, (previously Actinobacillus actinomycetemcomitans), Campylobacter rectus, Eikenella corrodens, Eubacterium timidum, Fusobacterium nucleatum, Peptostreptococcus sp, Porphyromonas gingivalis, Prevotella intermedia, Selenomonas, Treponema denticola and Tannerella forsythensis (previously Bacteroides forsythus).

One of the first researchers who tried to indicate a relationship between oral infections and atherosclerosis were Mattila et al. Having evaluated the oral and dental status of 100 Finnish men and women who had had myocardial infarction, they concluded that their dental health was significantly worse than that of 102 control subjects.

Since then, several studies have been conducted and examined the association between periodontal health status and the risk of cardiovascular disease (CVD). 3 possible metastatic pathways can be considered responsible for the influence of oral infections on CVD:
1. Metastatic spread of infection from the oral cavity, resulting from a transient bacteraemia;
2. Metastatic injury by circulating oral microbial toxins;
3. Metastatic inflammation arising from an immune response to oral microorganisms.

The purpose of this article is to review the knowledge on periodontal disease as a risk factor for the development of CVD.

Epidemiological and Laboratory Evidence

Numerous epidemiological studies have been performed over the last 2 decades trying to show if an association between periodontitis and CVD exists. The findings of these studies vary greatly, ranging from no causative relation between periodontitis and CVD to...
strong causative connections between the 2 conditions. Reasons for the discrepancies in the results of these studies include (1) variations in study populations, including differing age groups, ethnicities, and geographic locations, and (2) differing measures and definitions of periodontitis, with some studies based only on clinical measures (i.e. pocket depth, bleeding with probing, tooth attachment level) and other in which the relation appeared stronger, based on non-clinical measures, such as systemic antibody response or radiographic evidence of alveolar bone loss.

3 hypotheses regarding the association of periodontitis with CVD have emerged from the results of the epidemiologic studies; the first is the theory of bacterial invasion, which assumes direct action of bacteria and their toxins on the endothelium. Second is the cytokine theory; according to this theory, inflammatory mediators released by the cells of the immune system play a key role in the damage of the vascular wall endothelium. Autoimmune theory, is the third theory, emphasizing the significance of heat shock proteins (HSP65) expressed on oral pathogens, such as Porphyromonas gingivalis, Prevotella intermedia, and Actinobacillus actinomycetemcomitans.

A series of earlier case-control, cross-sectional and longitudinal studies have shown a significant association between poor dental health and CVD20,21. Data derived from a meta-analysis of several prospective cohort, case-control, and cross-sectional studies also suggest a positive correlation between periodontal disease and CVD, even after adjusting the known risk factors such as smoking, alcohol consumption, obesity, blood pressure and diabetes.

The proposed major pathological pathway for CHD in all these studies is atherosclerosis. Atherosclerosis is believed to be a progressive disease arising from a combination of endothelial dysfunction and inflammation.

Desphande et al27 first published a paper on the invasion of bovine aortic and cardiac endothelium by Porphyromonas gingivalis. Bacterial replication of genetic material, indicating presence of Porphyromonas gingivalis, was observed in these tissues. 2 more studies reported similar results based on the examination of human aorta specimens28,29. All these results of both studies support the theory of bacterial invasion.

As for the theory of inflammatory mediators, it has been shown that certain periodontal pathogenic bacteria, such as Porphyromonas gingivalis and Bacteroides forsythus play an atherogenic role20,30,32. These organisms promote platelet aggregation33, foam cell formation34, and the development of atheromas in experimental animal models35-38. It has been shown that Toll-like receptors (TLRs) present on the surfaces of immune system cells (macrophages/monocytes and granulocytes) play a decisive role in this process. These receptors recognize bacterial endotoxin molecules, initiate intracellular signalling, and mediate the transcription of a factor responsible for the release of proinflammatory cytokines, such as PGE-2, IL-1, IL-12, and TNF-a. These compounds stimulate monocyte/macrophage chemotaxis and adhesion to endothelial cells, which leads to intracellular lipid accumulation and the formation of foam cells39-41. All these findings support the theory of inflammatory mediators.

Danesh and colleagues42 conducted a meta-analysis relative to the role of other infections associated with CHD. Their data supported an association between heart disease and Chlamydia pneumoniae. The authors also concluded that the data demonstrating an association between heart disease and Helicobacter pylori were weak.

Slade and his colleagues provide evidence that periodontal disease is associated with CVD via the increased levels of acute-phase proteins, C-reactive protein (CRP) and plasma fibrinogen. Both CRP and Fibrinogen contribute to atheroma formation, probably via CRP- triggered complement activation and fibrinogen-clotting effects.

Studies supporting the autoimmune theory have shown that anti-hsp65/60 antibodies are present in the saliva of subjects with chronic periodontitis and not in healthy periodontal tissues44. The same antibodies were observed by Mayr et al45, who investigated the potential role of Chlamydia pneumoniae and Escherichia coli infections in atherogenesis. Both of these studies suggest the existence of an autoimmune process where antibacterial antibodies show cross-reactivity with endothelial HSP-60, leading to endothelial cell damage and exposure to inflammatory factors.

Carallo et al46 identified a link between periodontal indices and wall shear stress, suggesting that an alteration of hemodynamic profile might contribute to atherosclerosis in subjects with periodontal disease. However, a direct causal relation between periodontitis and atherosclerotic CVD has not yet been established47-50. Not all epidemiological studies confirm the effect of periodontal condition on cardiovascular morbidity. Joshipura et al51 assessed a total of over 70,000 patients aged 40 to 75 years and found no significant association between tooth loss and CHD. Similarly, Hujoel et al52 and Howell et al53, published 2 longitudinal studies that also failed to show an association between periodontal disease and CHD.

One important question that rises is: if periodontitis is suppressed by appropriate intervention, does this fact result in a decreased risk of CVD? Currently, there is no definitive evidence that the development of CVD can be prevented with periodontal therapy54. However, in patients with CVD and previous diagnosis of periodontitis, it is recommended that dentists and physicians should closely collaborate to optimize CVD risk reduction and periodontal care. Patients with CVD and no previous diagnosis of periodontitis should be examined for
periodontitis, especially if they have signs or symptoms of gingival disease, significant tooth loss, and unexplained elevations of CRP or other inflammatory biomarkers.

**Conclusions**

The evidence suggests a moderate association, but not a causal relationship, between periodontal disease and CVD. According to the current epidemiological findings, it seems likely that periodontitis is a moderate risk factor for CHD. Further research is needed to determine whether periodontal disease can directly influence the development of CVD.

**References**

1. Miller W. The human mouth as a focus of infection. *Dental Cosmos*, 1891; 33:689-713.


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