

Periodontal infections and cardiovascular disease: Is it a mere association?

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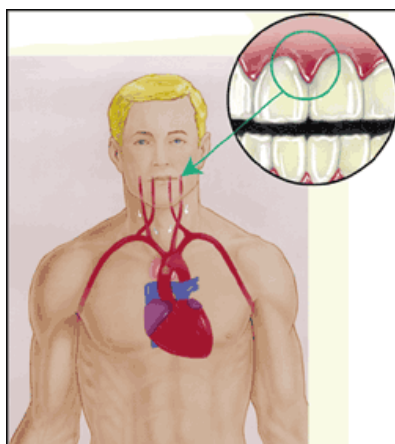
Abstract

The oral cavity is a major site of chronic infection and inflammation, particularly periodontal or chronic gum diseases. In recent years there has been increasing interest in the “periodontal systemic connection” between periodontal health parameters and risks of cardiovascular disease. Given that poor oral health and cardiovascular disease are major worldwide health problems, their association are potentially important. The article summarizes the evidences from epidemiologic studies and studies that focused on potential contributing mechanisms to provide an insight of this association

Cardiovascular disease including atherosclerosis and myocardial infarction is a major cause of premature death and occurs because of complex set of genetic and environmental factors. It is interesting to note that classical risk factors for CVD (hypertension, hypercholesterolemia, cigarette smoking) can account for one half to one thirds of the variation in the incidence of CVD cases. Thus, it is likely that others, as yet unrecognized factors may contribute to the pathogenesis of atherosclerosis. Many other putative risk factors for atherosclerosis have been proposed including traits related to obesity, inflammation and infection. Periodontal or chronic gum disease, a candidate risk factor shares many of these related traits. It is likely that exposure to dental microorganisms over a lifetime occurs for more frequently than to any other atherosclerosis-associated microbes. Work to elucidate the relationship between oral infections and systemic disease is now underway on every continent around the globe.

The 2005 Nobel Prize in Physiology and Medicine was awarded to Baray Marshall and Roben Warren who made the remarkable and unexpected discovery of the bacterium *Helicobacter Pylori* and its role in gastritis and peptic ulcer disease. Many diseases in humans such as Crohn’s disease, ulcerative colitis, rheumatoid arthritis and atherosclerosis are due to chronic inflammation. The discovery that one of the most common diseases of mankind, peptic ulcer disease has a microbial cause has stimulated the search for microbes as possible causes of other chronic inflammatory conditions¹.

During the last two decades, there has been an increasing interest in the impact of oral health on atherosclerosis and subsequent cardiovascular disease (CVD). The advent of the inflammation paradigm in coronary pathogenesis stimulated research in chronic infections caused by a variety of micro-organisms—such as *Chlamydia pneumoniae*, *Helicobacter pylori*, and cytomegalovirus—as well as dental pathogens



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Pathophysiology of inflammation in atherosclerosis

Inflammatory processes have become an integral part of the pathophysiology of atherosclerosis and are presumed to be involved from the initiation to the progression and final stages of infarction. Normal endothelium does not allow for the attachment of leukocytes. When initial damage of the endothelium occurs, either by infection or by an atherogenic diet, the endothelial cells express adhesion molecules that allow leukocytes to bind to them. These adhesion molecules are called 'vascular cell adhesion molecules' (VCAM) and 'intercellular adhesion molecules' (ICAM). Selectins and integrins also support leukocyte attachment (Libby *et al.*)².

Once this attachment is established, the atheroma accumulates more lipids and promotes the production of various chemokines and growth factors that stimulate the recruitment of monocytes and macrophages. These chemokines also promote the migration of smooth-muscle cells. These muscle cells respond to the inflammatory stimuli by secreting specific enzymes (metalloproteinases) that are able to degrade elastin and collagen. Further, these metalloproteinases may disintegrate the fibrous capsule holding the cholesterol plaque together, and cause plaque rupture. Plaque rupture greatly increases the risk of myocardial infarction and stroke.

This relationship between chronic inflammation and atherogenesis has been recently expanded to include other pro-inflammatory processes related to a hyperactive immune response (Beck *et al.*)³ or autoimmune reaction to microbial or other metabolic stimuli. For example, systemic lupus erythematosus patients have been found to be at a higher risk for developing cardiovascular disease (Nuttall *et al.*)⁴. These generalized hyper-inflammatory states may be characterized by elevated CRP concentrations (Libby and Ridker, 1999; Mendall *et al.*, 2000)^{5,6}

Wu and colleagues⁷ reported that increased serum levels of CRP and fibrinogen, both well-established biological markers for CHD, were associated with periodontitis. Noack *et al.*⁸ observed statistically significant increases in CRP levels in 109 subjects with moderate to severe periodontitis when compared with 65 periodontally healthy controls. After adjustment for factors known to be associated with elevated CRP, including age, smoking, BMI, triglycerides, and cholesterol, subjects with high levels of periodontal disease had significantly higher mean CRP levels than the controls. The presence of periodontal pathogens—including *Porphyromonas gingivalis*, *Prevotella intermedia*, and *Tannerella*

forsythensis—from subgingival plaque samples was positively associated with elevated CRP levels.

Joshi *et al.*⁹ have recently published cross-sectional data from the prospective male health professionals follow-up study, where self-reported periodontal disease was analyzed in a sample of 468 men with respect to a variety of biomarkers of CVD. Their results showed, in part, that periodontal disease was associated with higher levels of CRP and LDL, thereby supporting the hypothesis that periodontal disease might also be causally linked with CVD.

Taylor-Robinson and colleagues¹⁰ isolated several infectious agents by DNA identification methods from all major arteries affected by atherosclerosis. Among these were periodontal pathogens *A. actinomycetemcomitans* and *P. intermedia*, in addition to *C. pneumoniae*. Nearly 40% of specimens were positive for *C. pneumoniae* DNA, and 35.4% were positive for a mixture of *Chlamydia* and orodental pathogen DNA. These findings suggest a possible invasion of the major arteries by oro-dental pathogens together with *Chlamydia*. Interestingly, Mäntylä *et al.*¹¹ have recently shown that traces of *Chlamydia* can also be detected in periodontal pocket samples. The examination of atherosclerotic plaque which had been obtained from diseased part of arteries during bypass operation in 50 patients made identification of perio-pathogenic bacteria possible besides *C. pneumoniae* and *H. pylori* (Harzasthy *et al.*)¹².

Further evidence of association between Periodontal infection and CVD:

Several epidemiological studies investigating the relation between infections – including dental infections – and various clinical manifestations of atherosclerotic vessel disease have been published in the last decade suggesting periodontal disease as a risk factor for CHD. The topic has proved difficult to study and this is especially true for dental infections, as they share several common etiologic factors with CHD. These include smoking, low socio – economic class and unfavourable health care practice of the individual.

A study conducted by Buhlin *et al.*¹³, suggests that periodontitis, once considered purely a local disease can cause systemic inflammation lipid changes known to increase risk of CHD. The study of Pearson *et al.* 2003¹⁴ concluded that patients who demonstrate evidence of bone loss around several teeth can predictably be identified as being risk for future AMI.

A case control study by Mattila et al¹⁵ observed that the patients with periodontal infections had significant elevation of plasma fibrinogen and white blood cell count, leading to the hypothesis that periodontal disease might increase risk of CHD in part by inducing a systemic proinflammatory, prothrombotic state.

Pussinen et al¹⁶, report that antibodies to select periodontal pathogens are associated with coronary heart disease. Importantly, only antibodies to *Porphyromonas gingivalis* were associated with CHD. Similarly, DeStefano et al¹⁷, found 25% increased risk of CHD in individuals with mild to moderate periodontitis compared to individuals with gingivitis.

A study conducted by D'Aiuto F et al¹⁸, showed that control of periodontitis achieved with non surgical periodontal therapy, significantly decreases serum mediators and markers of acute phase response. The significance of serum response was associated with the half of the population that responded better to non – surgical periodontal therapy. The result of this pilot study indicates that severe generalized periodontitis cause systemic inflammation. This is consistent with the causative role of periodontitis in atherosclerosis. A meta- analysis of prospective follow up studies by Jukkha et al 2004¹⁹, has shown that periodontal disease may increase the risk of cardiovascular disease by approximately 2%. Similarly in a recent study conducted by Sabine O et al²⁰, periodontitis was revealed to be a significant risk factor for CAD after adjusting for other confounding factors, with the level of association increasing with the individual extent of periodontal lesions.

Choi and colleagues²¹ isolated *P. gingivalis* heat-shock protein-specific T-cells in atherosclerotic plaque from subjects with severe atherosclerosis. Bacterial heat-shock proteins are believed to be involved in regulating autoimmune mechanisms, and they also appear to be associated with the pathogenesis of periodontitis²².

These important studies shed new light on the role of the periodontal disease in causation of atherosclerotic events and CHD. However, they are unable to prove the causal relation between periodontitis and CHD but, definitely they provide valuable new information about this controversial topic.

Conclusion

The accumulation of epidemiologic, in vitro and animal evidence presented to date suggests a potential role of periodontal infection as a risk factor

for CVD. These findings from the cross – sectional and longitudinal epidemiologic studies are supported by in vitro and animal studies describing plausible mechanisms linking periodontal infection to development of atherosclerotic diseases, to the triggering of clinical coronary events or to both.

The cumulative evidence presented in this report supports, but does not prove a mere association between periodontal infection and atherosclerotic cardiovascular disease or its sequelae. We are aware of the fact that research into the relationship between the periodontal infection and CVD is still in its early stage compared with research on more established risk factors for CVD.

More prospective and interventional studies in various populations are needed to confirm the association and to elucidate its nature. However, the current evidence supporting an association raises an important question: “If periodontal infection is suppressed by anti-infective intervention, will this result in a decreased risk of heart disease?” Answers to this question would be clinically meaningful and may more directly implicate periodontal disease as risk factor cardiovascular disease, and possibly as one of its causes.

Because periodontal infection is common in population, it can be account for a significant portion of the proposed infection associated risk factor of CVD. If periodontal disease is found to be a causative risk factor for CHD, the patients who receive treatment for periodontal disease have significantly reduced the risk for CHD. If causative relationship is not proven, the patient will receive benefit of treatment of periodontal infection. Periodontal infection obviously merits prevention and treatment as a health problem in itself.

Therefore the new knowledge being gained in the discipline of periodontal medicine will serve as an impetus to further coalesce medicine and dentistry. Dentists will need to assume a large responsibility for the overall health of the patients and periodontal care may become a medical necessity.

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