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ORAL INFLAMMATION

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Oral Inflammation and Cardiovascular Diseases

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Cardiovascular Disease and Atherosclerosis

Atherosclerosis, the thickening and hardening of arteries produced by a build-up of plaque, is the underlying cause of cardiovascular disease (CVD). It is essentially an inflammatory disease, whereby an initial lesion, in response to injury to the endothelium of elastic and muscular arterial tissue, leads to a complex chronic inflammatory process.[1] There is accumulating evidence of a role for infectious agents in atherogenesis; by causing endothelial injury, they may, in part, trigger the inflammatory response.[2] The levels of inflammatory mediators in the systemic circulation, such as C-reactive protein (CRP) and fibrinogen, are indicators of a general inflammatory response and atherosclerosis.[1] This link between inflammation and atherosclerosis suggests that chronic infections, such as oral infections from periodontal disease, may predispose to cardiovascular disease.[3] Significant similarities in the pathogenesis of atherosclerosis and periodontitis have suggested a common underlying biological mechanism for the two conditions. Based on this paradigm, several studies have investigated the relationship between periodontitis and cardiovascular disease.[4]

Indirect Evidence: Epidemiological Studies

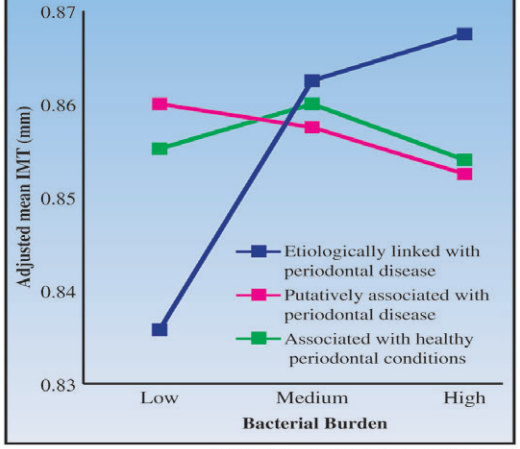
Most of the evidence supporting a relationship between periodontal disease and CVD comes from epidemiological studies. In the late 1980s, pioneer work showed that patients who had a history of myocardial infarction (MI) generally had worse oral health than control subjects.[5] Subsequently, cross-sectional data from the Third National Health and Nutrition Survey (NHANES III) indicated that patients with severe clinical attachment loss were at greater risk for MI than subjects with a healthy periodontium (odds ratio: 3.8).[6] Since then, systematic literature reviews have indicated that most studies report a modest association between periodontal disease and CVD, between a 1.3 and 2-fold increase in the risk of CVD in people with periodontitis.[7] Conversely, treatment of periodontitis was shown to decrease serum concentration of CRP, interleukin (IL)-6 and tumor necrosis factor (TNF)-a, indicating that infection of the periodontium can influence systemic conditions. What remains unclear from these studies, however, is whether periodontitis can predispose to atherosclerosis.[8]

Direct Evidence: Experimental Studies

Direct evidence for the role of oral infection in predisposing to atherosclerosis comes from several lines. The presence of predominant oral pathogens such as *Porphyromonas gingivalis*, *Tannerella forsythensis*, and *Prevotella intermedia* was detected in atherosclerotic plaque, suggesting a possible invasion of atheromas by oral pathogens.[9] In addition, *P. gingivalis* can invade endothelial cells[10] and can also induce platelet aggregation, a key process in atheroma and thrombus formation.[11] Whether these pathogens actively contribute to the development of atheroma, however, remains to be established.

Most of the experimental evidence supporting a relationship between CVD and periodontal disease comes from animal model studies. Using apolipoprotein E-deficient mice, research has shown that clinically induced bacteremia or oral infection with *P. gingivalis* increase atheroma size compared to non-

Figure 1. Mean carotid intima-media thickness (IMT), adjusted for CVD risk factors, as a function of periodontal bacterial burden



Adapted from Desvarieux *et al.*, 2005[3]

infected mice.[12] Similarly, pigs exposed orally to *P. gingivalis* had elevated CRP and increased atheroma size compared to control animals, suggesting a role for this particular periodontal pathogen in the development of atherosclerosis.[12]

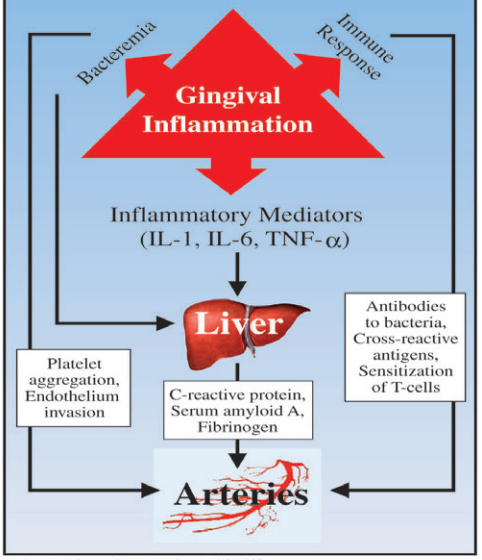
A recent study in humans reported a positive independent association between periodontal bacterial burden and carotid intima-media thickness (IMT).[3] Results were adjusted for known risk factors for CVD (age, ethnicity, gender, education, body mass index, smoking, diabetes, systolic blood pressure, low-density and high-density lipoprotein cholesterol). A positive relationship between carotid IMT and bacterial burden was especially strong in patients predominantly infected by specific bacteria involved in the etiology of gingival disease, including *P. gingivalis, Actinobacillus actinomycetemcomitans, Treponema denticola*, and *Tannerella forsythensis* (Figure 1).[3]

Biological Mechanism and Pathogenesis

Gingival inflammation may influence atherosclerosis in three distinct pathways (Figure 2).[13] Oral infection by periodontal pathogens initiates the formation of dental plaque which leads to inflammation of periodontal tissues. The formation of periodontal pockets increases subgingival space, which is conducive for bacterial growth and deposits. Ensuing local inflammation processes produce micro-ulcerations through the pocket epithelium, promoting risks for distant-site infection and transient bacteremia. Moreover, bacteria release a variety of biologically active molecules, including lipopolysaccharides, endotoxins, chemotactic peptides, proteins, and organic acids, that may then enter the systemic circulation. These products can trigger the host inflammatory response and elevate serum concentration of acute-phase reactants and inflammatory mediators (CRP, serum amyloid A, fibrinogen, haptoglobin, TNF-a, IL-6 and IL-8).[3] Increased levels of circulating inflammatory mediators is thought to contribute to the inflammatory processes leading to atherosclerosis.[2,13]

Immunization against bacterial pathogens may also induce an autoimmune response involved in the development of atherosclerosis. Homology of some bacterial and human proteins (*e.g.*, heat-shock protein HSP60) raises the possibility that antibodies against bacterial versions of the protein may cross-react with the human protein, inducing an autoimmune response. In the case of HSP60, disruption of arterial endothelial cells is thought to stimulate atherosclerosis.[13] Proinflammatory response may also be enhanced by cross-reactive epitopes that stimulate T-cell response reactive with host antigens, enhancing the effects of bacterial pathogens on cardiovascular health.[13]

Figure 2. Pathways by which gingival inflammation may translate into systemic inflammation and atherosclerosis



Adapted from Scannapieco, 2004[13]

Establishing a direct link between periodontal disease and CVD is very difficult due to the multifactorial nature of both diseases with numerous confounding risk factors common to the two.[4,13] Nevertheless, epidemiological observations coupled with the biological plausibility of this association between two inflammatory diseases warrant the need for further investigation and validation of the cardiovascular-periodontal link.

Management and Prevention

Oral inflammation and periodontal disease are generally chronic and can persist asymptomatically for many years in the absence of appropriate treatment. This results in chronic exposure to local and systemic inflammation, which may induce or enhance already existing inflammatory disease, including atherosclerosis. For this reason, appropriate oral preventive care is important not only to preserve oral health, but also systemic health. Management and prevention strategies must sensitize both dental care providers and patients to the importance of good oral health on systemic burden and chronic diseases.

Early control of bacterial plaque accumulation is essential for the prevention of oral inflammation and periodontal disease, with daily mechanical removal of bacterial plaque by tooth brushing supplemented with flossing. Utilization of a dentifrice with antibacterial and anti-inflammation properties will help in achieving this goal. Such a dentifrice, that contains the antibacterial agent triclosan in a copolymer to prolong adherence to the tooth (Colgate® Total® Toothpaste), has been shown to effectively contribute to the control of oral inflammation[14] and to slow the progression of periodontitis.[15] This is due to its 12- hour antibacterial action coupled with its ability to directly inhibit potent inflammatory mediators.[16]

Control of periodontal infection and inflammation will improve the oral health of patients, decrease the systemic chronic inflammation burden caused by oral inflammation, improve general health, and may ultimately contribute to the reduction of cardiovascular disease.

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