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Review Article

Periodontal associations in cardiovascular diseases: The latest evidence and understanding

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ABSTRACT

Periodontal and cardiovascular diseases (CVD) are inflammatory diseases. Recent epidemiological studies have associated the effect of periodontitis on CVD progression. Findings of oral pathogens in carotid atheromas provided a plausible relationship between these two diseases. One possible mechanism is the infiltration of oral/periodontal pathogens through inflamed and ulcerated gingival epithelium. This results in translocation of oral pathogens throughout the systemic circulation affecting vascular tissues, and initiating a cascade of inflammatory reactions detrimental to the cardiovascular system. In addition, leakage of pro-inflammatory cytokines/chemokines from the ulcerated periodontium into the bloodstream may cause the production of hepatic acute-phase proteins. Moreover, as chronic bacteremia occurs, the adaptive immune system is activated. Antibodies produced in response to periodontal pathogens trigger a cross-reaction between endothelial cells and modified low-density lipoprotein to enhance the movement of lipids into cells within the vessel wall. Some antibodies and inflammatory cytokines promote the Th1 response, thereby further activating macrophages within the atheroma. These plausible mechanisms are contributing factors in initiating and propagating atherogenesis. This review discusses the current understanding of CVD pathology/periodontitis, potential underlying mechanisms regarding this association, and general guidelines for treating patients with CVD risks.

1. Introduction

Cardiovascular disease (CVD) encompasses diseases affecting the heart and/or blood vessels. Atherosclerosis, or arteriosclerotic vascular disease, is a condition whereby progressive plaque (atheroma) buildup occurs in the midsize to large arteries due to endothelial damage and activation of the host's immune system's inflammatory response.[1] Atherosclerotic lesions can lead to thromboembolism in the brain, heart, and other distal sites, resulting in stroke and infarction. According to the World Health Organization (WHO), cardiovascular diseases are projected to continue to be the single leading cause of death in men and women around the world.[2]

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Periodontal disease refers to bacteria-induced, chronic inflammatory diseases that destroy the structures supporting the dentition.[3,4] The two most common forms of periodontal disease are gingivitis and periodontitis. The former is localized to the soft tissues surrounding the teeth and can readily be reversed with treatment. However, periodontitis results in irreversible damage to the attachment apparatus of teeth.[4,5] With its latest associations to CVD, and many other systemic conditions (such as diabetes), periodontitis has a large impact on the patient's quality of life and poses a high financial burden not only to the patient but also to the society as well.[3]

As both CVD and periodontitis are multifactorial inflammatory conditions with many shared confounding factors (smoking, obesity, type 2 diabetes), the key link between the two conditions is the propagating impacts of inflammation on the progression of the diseases.[3,5,6] It is broadly perceived that the inflamed and ulcerated subgingival epithelium in periodontitis allows for the entry of oral bacteria and/or bacterial components into the blood stream which leads to the increased risk and progression of CVD.[5] Lockhart et al., an American Heart Association (AHA) group, established that although there is currently no evidence of a causal relationship, there exists an association between periodontal disease and atherosclerotic vascular disease independent of known confounders.[7]

2. Overview of atherosclerotic cardiovascular disease (ACVD) pathology

Atherosclerosis is initiated by damage to vessel endothelium. Following injury, there is an increase in platelet aggregation and leukocyte migration as a result of an upregulation of adhesion molecule expression (ICAM-1, VCAM-1, E-selectin, P-selectin) as well as chemoattractants (IL-8, thrombin) by endothelial proinflammatory signals.[5,6] These proinflammatory signals also initiate smooth muscle cell proliferation and endothelial cell apoptosis. Migrated leukocytes further release proinflammatory cytokines (IL-1, IL-6, TNFα) and release reactive oxygen species (ROS) and proteinases that destroy the endothelium extracellular matrix.[5,6] Low-density lipoproteins (LDL) accumulate under the intima layer of the endothelium and are subsequently phagocytized by macrophages to become foam cells. Foam cell formation further increases the release of pro-inflammatory cytokines IL-1, IL-6, and TNFα.[1,6] Meanwhile, smooth muscle cells in between the intima and media layer of the vessels secrete metalloproteinases[8] (MMPs) that promote myogenesis. The growth of smooth muscle cells causes fibrosis and formation of a fibrous plaque. Over time, cholesterol deposits upon the plaque and forms lipid streaks that can occlude the vessel. Rupture of the plaque releases thrombotic factors that initiate coagulation when in contact with platelets and can cause a thromboembolism.

3. The effects of periodontitis on ACVD

As previously mentioned, acute- and chronic-systemic inflammation has been shown to have pro-atherogenic effects. Periodontal bacteria can affect all of the discussed processes through a direct interaction (i.e. invading the endothelial cells, smooth muscle cells, leukocytes, and platelets) and/or indirectly through the stimulation of paracrine factor release that ultimately affect cell function (Fig. 1). In the case of periodontitis, once bacteremia occurs, oral pathogens can invade endothelial cells and cause dysfunction. In addition to direct invasion, periodontal bacteria can release products and components into the circulation and induce pro-atherogenic responses in endothelial cells. It has been shown that outer membrane vesicles,[9] gingipains from *Porphyromonas gingivalis*,[10] and free soluble bacterial components from *Aggregatibacter actinomycetemcomitans*[11] irritate endothelial cells and induce inflammation. Leakage of pro-inflammatory cytokines (IL-1, IL-6, TNFα) and other chemokines from the ulcerated periodontium causes the production of acute-phase proteins (i.e. CRP, fibrinogen, amyloid A protein, etc.) by the liver.[5,6] Moreover, as chronic bacteremia occurs, the adaptive immune system is activated in response. Antibodies that are produced in response to pathogen associated molecular patterns (PAMPs) of periodontal pathogens can trigger a cross-reaction between endothelial cells and modified LDL to enhance the movement of lipids into cells within the vessel wall. Some of these antibodies and inflammatory cytokines can promote the Th1 response, thereby further activating macrophages within the atheroma, and propagating atherogenesis.[5,6]

4. Recommendations for clinical practitioners

Recent reviews reveal moderate evidence of the long-term positive effects of periodontal treatment on systemic inflammation levels elucidated through the measurement of C reactive protein (CRP) levels, a marker for systemic inflammation and clinical measures of endothelium function. CRP remains to be the established marker of CVD risk.[3,12,13] In absence of systemic inflammation, high sensitivity CRP level of 1 mg/L indicates a lower risk of CVD, while a level of 3 mg/L indicates an approximate doubling in CVD risk.[14] It is not unusual for patients to have a transient increase in systemic inflammatory mediators and a decrease in endothelial function following non-surgical periodontal treatment within a period of 1 month.[12] However, following this period, these levels will progressively decrease, showing a reduction in basal CRP levels by 6 months.[12] A meta-analysis done in 2012 of four most recent clinical intervention trials reports a 0.23 mg/L reduction ($p < 0.0001$) in CRP levels of patients with periodontitis 2–6 months post-periodontal therapy.[15] Furthermore, patients diagnosed with CVD showed a considerable reduction of CRP from 2.7 ± 1.9 to 1.8 ± 0.9 mg/L ($p < 0.05$) 6 months post-periodontal therapy.[16] With the high number of patients affected by the two diseases, it becomes imperative for practitioners to be informed and aware of the increasing supporting evidence pointing to periodontal disease as a risk factor for ACVD. Therefore, some general clinical guidelines to be considered when treating these patients are as follows[3]:

1. Proper periodontal disease diagnosis and treatment:
   Recognizing the periodontal health status of patients is critical, as the severity of the periodontal disease correlates with the risk level of developing ACVD. The diagnosis and