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Periodontal Diseases and Possible Future Cardiovascular Events, Are they Related? An Overview

Shahryar Karami,[1] Nazanin Ghobadi,[1] Amirhossein Pakravan,[2] Mojdeh Dabirian,[3,*] and Farhad Sobouti[4]

[1]Department of Dentistry, Faculty of Dentistry, Mazandaran University of Medical Sciences, Sari, Iran
[2]Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Mazandaran University of Medical Sciences, Sari, Iran
[3]Cardiologist, Clinical Research Development Unit of Bou-Ali Sina Hospital, Mazandaran university of Medical Sciences, Sari, Iran
[4]Orthodontic Department, Dental Faculty, Mazandaran University of Medical Sciences, Sari, Iran

[*]*Corresponding author*: Mojdeh Dabirian, MD. Assistant Professor of Cardiology, Department of Cardiology, Fatemeh Zahra Cardiac center Hospital, Artesh Boulevard, Mazandaran Province, Sari, Iran. Tel/Fax: +98-1133344506, E-mail: dr.dabirian@gmail.com

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Abstract

Context: The association between periodontal disease (PD) and cardiovascular disease (CVD) has been evaluated in many epidemiological studies; however, the results are controversial. Herein, we aimed to review if the childhood periodontal diseases are associated with future cardiovascular events or not.
Evidence Acquisition: The current literature regarding childhood periodontal disease and future cardiovascular events in children aged less than 18 years was searched on PubMed, Scopus, ISI, and Google Scholar from January 2005 to March 2017. All studies investigating the association between periodontal disease and CVD were searched by using the following search terms: "coronary artery disease", "coronary disease", "heart disease", "ischemic heart disease", "myocardial infarction", Children, "periodontal disease", and "periodontitis".
Results: The most common form of periodontal disease is gingival bleeding and calculus. Periodontitis is associated with an elevated level of CRP, fibrinogen, and cytokines, which involved in the pathogenesis of atherosclerosis-induced disease.
Conclusions: Timely diagnosis and treatment of periodontal diseases is essential to maintain good oral health and help to decrease pathological changes like atherosclerosis, acute MI and stroke.

Keywords: Atherosclerosis, Coronary Artery Disease, Periodontitis, Risk Factor

1. Context

Coronary artery disease (CAD), as a main cause of coronary heart disease (CHD) and death, with a rapidly increase in developing countries and Eastern Europe, is an inflammatory disease resulting from interactions of immune mechanisms with metabolic risk factors (1). For more than 100 years, a close association has been proposed between oral health and early development of coronary artery disease (2). The most common risk factors for CAD include smoking, alcohol abuse, lack of physical activity, diabetes mellitus, and obesity (3). Nowadays, a possible association between periodontitis and atherosclerosis have been proposed (4, 5).

Recently, it is shown that the intestinal flora called microbiome is responsible for the digestion of food and also plays an active role in inflammation as well as metabolism. These processes are strongly associated with numerous conditions ranging from hypertension and diabetes to heart and renal diseases (6).

It is believed that infectious agents such as periodontopathic pathogens and inflammatory markers in the blood are correlated with elevated risk of cardiovascular disease (CVD) (7). The most common markers of CVD are high-sensitive C-reactive protein (hs-CRP), tumor necrosis factor (TNF-α), fibrinogen, serum amyloid A, interleukin-6 (IL-6), and cellular adhesion molecules (8). Different theories have emerged for the potential mechanisms of association between periodontal disease and CVDs including bacterial invasion, cytokine, and autoimmunization theory (9).

Periodontitis, as an infectious disease, affects the tissues around the teeth and shows a wide range of clinical, microbiological, and immunologic manifestations (10). A strong association was found between periodontitis and cardiovascular diseases, such as myocardial infarction and cerebrovascular attack in the last 2 decades (11). Many co-

hort studies, with long time follow-up periods, have shown an association between tooth loss and future CVD mortality (12, 13). In this study, we aimed to review the previous studies that have investigated the association between 2 conditions.

2. Evidence Acquisition

We searched PubMed, ISI, and Embase from January 2005 to March 2017 for eligible studies investigating the association between periodontal disease and CVD using the following search terms: "coronary artery disease", "coronary disease", "heart disease", "ischemic heart disease", "myocardial infarction", Children, "periodontal disease", and "periodontitis". All studies investigating the association between periodontal disease and CVD in children less than 18 years were included. We also added some articles out of the publication date, which identified through reference checking. The qualitative results of the reviewed articles were discussed here.

3. Results

3.1. Pathophysiology

3.1.1. Immunopathogenesis and Histopathology

Periodontal infections are known to directly cause the pathogenesis of atherosclerosis (ATH) and thromboembolic events by providing repeated systemic challenges with liposaccharides and inflammatory cytokines (14). Furthermore, *Streptococcus sanguis* and *Porphyromona gingivalis* induce platelet aggregation and activation through the expression of collagen-like platelet aggregation-associated proteins. The aggregated proteins may also contribute to atheroma formation and thromboembolism (14).

The oral bacteria that may cause development of periodontal disease can penetrate gingival tissue and move into the blood stream and cause increase C-reactive protein, which eventually increases the risk of heart disease and stroke (15).

The chronically infected periodontium acts as a potential reservoir of endotoxin, cytokines, and lipid mediators for other parts of the body and increases the risk of CVD (16). The cytokines released at periodontal tissue include TNF-α, IL-6, IL-12 and IL-1, as well as matrix metalloproteinases (17).

Activation of monocytes in the blood vessels leads to the release of hydrolytic enzymes, cytokines, chemokines, and growth factors, which induce further damage leading to focal necrosis. Macrophages also accumulate lipids, especially LDL. Injury to endothelium and underlying smooth muscles can be a major cause of change (18).

In children, CVD complicates the dental care by making them more susceptible to infective endocarditis, increase the risk associated with general anesthesia, and for those children who are taking warfarin, the risk of prolonged bleeding increases. About 1 of 100 babies is born with a cardiac defect (19).

Patients with high alveolar bone loss at the baseline are at risk of developing heart disease. There is also an approximate 2 fold increased risk of fatal CVD and 3 fold increased risk of a stroke (20). There is a positive independent association between carotid intima media thickness and the cumulative periodontal bacterial burden. Carotid plaque increases substantially and peaks among individuals missing 10 - 19 teeth compared with those missing 0 - 9 teeth. When someone loses a periodontitis infected tooth, although the evidence of periodontitis is removed, the systemic damage may partly persist (15).

A recent study by Haraszthy et al. identified periodontal pathogens in human carotid atheromas (21). The nutritional assessment is an important part of clinical evaluation in children with dental caries. Long term calcium and vitamin D malabsorbtion can reduce bone mineral density and increase dental caries. Vitamin deficiency, especially A and C, can increase periodental disease (22).

Regarding the association between Uric Acid level and severity of CAD, hyperuresemia may be correlated to dental caries that increase heart disease (23).

Geerts, et al. found a statistically significant association between periodontitis and coronary artery disease. As it turns out, 66% of the control group had moderate to severe periodontitis, which is higher than estimates of the prevalence of periodontitis in the adult population (24).

Recently, it is shown that infections caused by periodontal pathogens such as Aggregatibacter actinomycetemcomitans and Porphyromonas gingivalis are associated with an increased risk of stroke, MI, and ACS (25-27). Periodontitis has been known to increase the risk of CAD by 25% and overall death by 46% (28, 29). The systematic review of Humphrey et al. showed that periodontal disease increased cardiovascular risk by approximately 24% - 35% (30).

A case-control study by Cueto et al. used soft tissue measures to define periodontal disease and the percentage of sites with loss of attachment > 3 mm to grade the severity of disease. The cases included patients admitted with acute MI and controls who were selected from trauma patients. Their results confirmed a significant association between periodontitis and acute MI (31).

Hujoel et al. published a study by data from the First National Health and Nutrition Examination Survey Epi-

demiologic follow-up study and found that periodontitis insignificantly associated with an increased risk for CHD (32). A prospective study by Howell et al. evaluated the association between self-reported periodontal disease and incidence of CVD over 12 years of follow-up. They suggested that self-reported periodontal disease is not an independent predictor of subsequent CVD in middle-aged to elderly men (15).

A prospective study with 25 - 30 years of follow-up by Mendez et al. examined the association between peripheral vascular disease (PVD) and periodontal disease. Periodontal disease was significantly associated with PVD after adjusting for other established risk factors (33).

Results of a systematic review revealed that periodontal disease increase the risk of CHD 1.14 times compared to controls. They concluded that both the prevalence and incidence of CHD are significantly increased in periodontal diseases (34). Few studies have also shown the association between extent and severity of periodontitis with extent and severity of CVD. Kodovazenitis et al. showed a consistent association between periodontitis and acute MI (35). Holmlund and Lind showed that the number of missing teeth was inversely correlated with the number of carotid arteries with atherosclerotic plaques (36).

In contrast to many studies, Syrjala et al. didn't find any association between tooth loss and MI as well as a stroke (37). A cross-sectional study by Frisk et al. reported no such relation between dental infections and CVD; however, they studied females and evaluated endodontic variables and CHD and periodontal variables were not studied (38).

Therefore, periodontitis is associated with elevation of CRP, fibrinogen, and cytokines, which have been causally associated with atherosclerosis-induced disease. It is shown that standard nonsurgical periodontal treatment for periodontal inflammation reduction decrease serum inflammatory markers and CRP (3).

For association between periodontal infection and extend and severity of CAD, several possible explanations were recommended. Hyvärinen and colleagues reported significantly higher salivary levels of Aggregatibacter actinomycetemcomitans in patients with stable CAD compared to patients without pathological findings by coronary angiography (12). High salivary levels of A. actinomycetemcomitans and systemic exposure to the bacterium increase CAD risk. Evidences show a potential causal role for periodontal bacteria that could directly affect atherogenesis or indirectly increase circulating cytokines and inflammatory mediators. Periodontal bacteria may penetrate gingiva or dental site to the blood stream. Many clinical trials have found the presence of DNA from periodontal pathogens in atherosclerotic plaques, in addition to *Porphyromonas gingivalis* and *A. actinomycetemcomitans* from plaque samples (39, 40).

In CHD patients with periodontitis, endothelium damage caused by lipid stripes formation may lead to bacteria penetration into blood stream after oral cavity procedures for patients with acute and chronic periodontitis (39).

It is shown that a potential role exists for periodontal microorganisms, especially T. forsythia, in neutrophil activation within hemorrhagic atherosclerotic carotid plaques (40). Interventional studies revealed positive effects of scaling and root planning on systemic levels CRP, fibrinogen, and white blood cell levels (39). Hence, in these patients, a concise preventive and therapeutic program for periodontal diseases would be essential. Reichert and colleagues found that the use of floss or interdental brushes reduces the risk of new cardiovascular events (41). In the Saffi et al. study, periodontal therapy decreased CRP and other proinflammatory biomarkers in CAD patients (42). Diabetes and smoking are considered to be common risk factors of cardiovascular and periodontal diseases (5, 43). Therefore, the association between periodontal disease and cardiovascular outcomes has been examined in previous studies in nonsmokers and nondiabetic patients (44). However, the interrelationships between these risk factors and periodontal disease may modify the process of developing cardiovascular disease remains unanswered. Also, genetic studies have suggested associations between periodontal disease and CAD. Hence, evaluating the interaction between family history of MI, periodontal disease, and future vascular risks is of more interest (45, 46).

In a large, prospective cohort of middle-aged women, incident and prevalent periodontal disease was associated with statistically significant increased risks of developing future cardiovascular events (47). Over the last 2 decades, different studies have shown periodontal infectious and inflammatory periodontal diseases as a risk factor for initiation or progression of CVD and suggested several pathways involved in the potential mechanism by which periodontal disease may influence the development of CVD (5, 15, 48).

Poor oral health and CVD are major health problems around the world and of significant importance in public health (49). A higher prevalence of periodontal disease is observed in developing countries and the highest rates of periodontal diseases and CVD are found in 5 South-Asian countries (50). It seems that higher prevalence of periodontal disease in developing countries is due to poorer oral hygiene and considerably, more plaque retentive factors in calculus form, often found in younger people (49). An alternative inflammatory pathway includes the direct effects of oral infective agents which cause atheroma formation, indirect effects of chronic inflammation and inheritance to periodontal and vascular diseases (20, 21).

4. Conclusions

Reviewing current evidences indicated that timely diagnosis and treatment of periodontal diseases is essential to maintain good oral health and help decrease pathological changes like atherosclerosis, acute MI, and stroke. A lot of attention has been paid to periodontal diseases and their possible mechanisms involved in cardiovascular diseases. Previous studies have shown the association between acute ischemic syndromes and chronic infections by Gram-negative bacteria including *Helicobacter pylori* and *Chlamydia pneumoniae*. Therefore, the association between periodontal diseases with cardiovascular diseases cannot be neglected. Detecting of periodontal bacterial DNA in a majority of patients with coronary arteries reported in previous studies suggested that this bacteria may play a role in development of atherosclerosis and its progression. Hence, it is said that periodontal microorganisms in coronary and internal thoracic arteries may be associated with atherosclerosis development and progression in addition to cardiac valve lesions.

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