



Biochemical Influence of Uric Acid and Some Inflammatory Biomarkers on the Association of Oral Hygiene with Cardiovascular Diseases

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ABSTRACT: Oral hygiene was associated with cardiovascular diseases (CVD), and the link is verified by bacterial colonization of the oral cavity and their products that spread into the circulation, starting endothelial dysfunction, pro-atherogenesis, pro-inflammation, and host immune mechanisms. High levels of serum uric acids are linked with CVD that are intern, associated with worsening gum hygiene. Several studies show that hyperuricemia could modify purine catabolism in case of oral disorders, including periodontal diseases (PD) and dental loss. PD and tooth caries were also linked with diabetes mellitus hypertension, insulin resistance, metabolic syndrome, dyslipidemia, and CVD. Dental caries was defined as an independent risk factor for coronary atherosclerosis too. However, dental restoration was correlated with the burden of arteriosclerosis negatively. Several experimental trials did not affirm the relationship between oral hygiene and CVDs.

Recent research has revealed similar biochemical and inflammatory biomarkers that are involved in CVD and oral diseases like C-reactive protein, interleukins, TNF- α , and others.

This consensus review aims to summarize some of the biochemical and inflammatory evidence connecting poor oral hygiene with the risk of CVD.

KEYWORDS: ASCVD, Biomarkers, Cardiovascular diseases, Dental caries, Inflammation, Oral hygiene, Periodontitis, Periodontal diseases.

INTRODUCTION

The largest etiology of mortality worldwide is cardiovascular disease (CVD) (1, 2). Although the predictable risk factors for CVD are well-known, nonetheless they perhaps represent only 50 to 70% of the entire acute coronary atherosclerotic events (ASCVD). ASCVD is the most common reason for CVD, however, quite a lot of other factors include obesity, lipidemic disorders, genetics, diabetes, hypertension, cigarette smoke, stress, and inflammations (3). Poor oral health (periodontal disease and dental status) is also well recognized that is linked with a high risk for CVD (3-5). Whether this incidence is directly associated with a causal effect on oral health or the result of a shared underlying pathology like inflammation has not been determined (6). It is however obvious that there is an association between oral health and ASCVD with not yet apparent strength of association (6, 7). Dental caries and periodontal diseases are the commonest two causes of oral disorders worrying the worldwide public, with very high frequency (8, 9).

One of the greatest widespread chronic multi-organism infections is periodontal disease distressing 46% of United States' adult people (10). During the latter decades, evidence has been gathered correlating PD with CVD through inflammatory and/or immune-mediated pathways (5, 6).

Dental caries is a lifelong, most abundant, and multifaceted pathology, categorized as one of the principal world problems about oral wellbeing (7, 9, 11). There are abundant researches that correlate teeth pathologies to CVD (11).

Serum uric acid (SUA) is synthesized as the purine metabolic end product as an endogenous body antioxidant that is measured in fluids at a level of around 0.5 mmol/L (12). Once this antioxidant system does not function orally correctly, dental caries may occur. The microbes of dental biofilm can metabolize various sugar isoforms, particularly fructose, producing UA as the end product with subsequent high circulatory SUA levels. Similarly, raised SUA have associated with the severity of PD (13). In contrast, high SUA levels have a protecting outcome to resist bone resorptions, from the latent antioxidative impact of urates (14). High levels of SUA are linked with CVD that are intern, associated with worsening gum hygiene. Several studies show that hyperuricemia could modify purine catabolism in case of oral disorders, including PD and dental loss (5).



Several revisions have exposed that PD and dental loss bring about by oral inflammatory disorders are meaningfully related to CVD, apart from other risk factors (15). Dental loss may have resulted indirectly or directly from PD and tooth caries, and both disorders are linked with the infected tooth biofilm, thus related to raised blood concentrations of inflammatory systemic markers (16). This consensus review aims to summarize some of the biochemical and inflammatory evidence connecting poor oral hygiene with the risk of CVD.

Classification of cardiovascular diseases

Recent data define a wide range of disorders that could affect the entire cardiovascular system. However, CVD is a term that refers mainly to the following 4 entities (17):

1. Coronary artery diseases (CAD): AKA. Coronary Heart Disease (CHD), is caused by reduced myocardium perfusion that results in angina, acute myocardial infarction (AMI), and cardiac failure. It represents 1/3rd to 1/2 of the CVD cases.
2. Cerebrovascular disease: includes stroke and transient ischemic attack.
3. Peripheral artery diseases (PAD).
4. Aortic atherosclerosis: Including thoracic and abdominal aneurysms

Effects of uric acid on CVD

Several pieces of evidence have exposed those high levels of SUA in the blood are associated with CVD. As an inflammatory modulator, uric acid could arouse the vascular endothelium dysfunction and induce smooth muscle cell proliferation, in so doing; it will boost atherosclerosis (18). It was reported that UA was shown in some thrombotic plaques activating platelet aggregation besides its oxidative activity on the vascular endothelium (19). Inflammation is one of the features of atherosclerosis (2, 19-22). The released UA from intracellular stores causes the formation of urate crystals in the damaged cells that may persuade inflammation (23).

Effects of uric acid on oral health

Cells of vascular endothelium have abundant dynamic bioactivities, like antithrombosis effect, regulation of vessels tone via modulators and nitrous oxide (NO), and cellular interactions with platelets, WBCs, and monocytes. The inflammatory (and host immune) responses, in turn, increase the risk of ASCVD even in subjects lacking vascular risk-factors, via a decrease in NO concentrations in which systemic inflammatory response perhaps, is a source of endothelium dysfunction, causing CVD (24). Many studies estimating the bacterial link of PD with vascular inflammation revealed the same microbes in gum samples and samples taken from cardiac valves and aorta (23, 24).

Oral health (definition)

Though oral health disorders are seldom life-threatening, they endure a main public health issue due to their burden caused by high incidence and as it can contribute to financial, societal, and emotional consequences. Oral health (OH) is defined as the condition of the mouth and related structures (25). It includes a spectrum of disorders that comprise caries and loss of teeth, oral cancer, periodontal disease, noma, oro-dental injuries, and congenital abnormalities (cleft lip or palate) (3, 25, 26).

The role of inflammation in oral health

Normally, the oral cavity environment colonizes plentiful microbes that live on the teeth' exteriors. The dental plaque is surrounded by certain biofilm that naturally familiarizes the local microbiota and oral environmental fluctuations (27). Gingival inflammation progressed when the dental biofilm is transmitted to the adjacent gingival tissues, starting innate host immune mechanism and inflammation. Thereafter, gingival inflammation could develop into periodontitis when infective agents travel apically along the exterior of the root and then attack the periodontal and bony tissues. Furthermore, chronic PD may persuade permanent damage to fibers of the connective tissue close to the alveolar bones, causing dental resorption, with subsequent dental loss (28). Dysbiosis is an inconsistency of the oral flora that may cause bacteremia with systemic involvement (27). Consequently, by generating bacteremia, periodontitis can induce intense systemic and local inflammation and immune responses (6, 29). The classical risk factors of periodontitis are practically similar to that of ASCVD, thus perplexing the link between periodontitis with atherosclerosis (30, 31). More than a few preceding studies established a strong relationship between periodontal diseases and ASCVD, possibly due to endothelial dysfunction (5, 32).



Biochemical and inflammatory contribution to oral hygiene and CVD

Role of bacteria

Experimental research has transported hints for PD as the hidden moderator of arterial atherosclerosis, via direct microbial spread or by indirect immune-mediated responses (33). The intensity of periodontitis will affect the severity of bacteremia (32). The oral cavity and tooth pocket reciprocally offer reservoirs of anaerobic and gram-negative bacteria, which can attack the vascular wall tissue (34). Numerous circulatory inflammatory biomarkers have been correlated with systemic bacteremia, described by various researchers right after tooth extraction or even simple brushing (35). The DNA of odontogenic bacteria has been recognized in aortic thrombus too (36) and coronary thrombi from cases of AMI (37), suggesting a systemic direct effect of oral microflora. Likewise, oral bacteria such as *P. gingivalis* and *A. actinomycetemcomitans*, have been described as a source of coronary endothelial dysfunction by the "lipopolysaccharide-mediated" mechanism (38).

Recent research has revealed similar markers of systemic inflammation are involved in CVD and periodontal diseases. Periodontitis is the typical situation of immune intermediaries, like IL-1, IL-6, and TNF- α , (39-41). Antibodies directed against *P. gingivalis* interrelate biologically with "heat shock proteins" that are released from vessels' endothelium, causing their injuries (42). In the interim, oral microflora and their detrimental molecules may get their pathways into the circulation causing insulin resistance and systemic inflammatory responses that are elaborated in entire steps of atherogenesis, defining the periodonto-systemic association (43).

Numerous injurious products of dental flora like adhesins, proteases, and lectins can adjust the tooth biofilm; worsen host immune mechanism as well, through cytokines; and permits the production of sclerotic plaque by triggering cellular proliferation of "vascular smooth muscle" and platelets accumulation (44).

Dental interventions associated with CVD prognosis

Elders who underwent dental interventions revealed a reduced risk of CVD, and systemic inflammation. As well, they revealed a better lipidemic state, arterial blood pressure, and vascular endothelium, besides fewer ASCVD and/or arrhythmia attacks (45). Scaling of the teeth thrice annually is related to decreased risk of a trial tachyarrhythmia, through its protecting influence on periodontal diseases (46). In contrast, other scholars reported contradictory results and shown that oral interventions do not constantly improve CVD outcomes (47). Hence, and due to disparities in primary health care models, culture, heritable factors, and health knowledge, it is uncertain whether the evidence published from other republics is generalizable to other populations (15).

Shared biochemical and inflammatory biomarkers in PD and CVD

There is overwhelming evidence corroborating the concept that there are several biochemical and inflammatory markers shared between CVD and periodontal diseases (3, 6, 8, 9, 11). C-reactive protein as a typical hepatic "acute phase reactant" has been correlated in several studies with both PD and oral health (1, 3, 6, 7, 11). Tumor necrosis factor- α (41) and interleukins (40) are pro-inflammatory cytokines that were found to share in PD and CVD (48-50). The gingival oral index is positively associated with the fibrinogen levels of and differential leukocytes in PD (51). A marker of ischemic myocytes and a biomarker of end-products of oxidative stress "ischemia-modified-albumin" were shown to increase in chronic aggressive periodontitis compared to healthy controls and the levels reduced after a conventional oral intervention was introduced (52). "Matrix metalloproteinase (MMP)", a marker of susceptible plaque, and subclinical coronary arteriosclerosis were also associated with PD (53).

Oral health and it's associating with different CVD

Oral health has been documented to be related to different variants of CVDs, including stroke, coronary artery diseases, peripheral vascular diseases, cardiac arrhythmias, and aortic aneurysms.

Oral health and aortic aneurysm

The aortic abdominal aneurysm has been related to oral hygiene (34). Odontogenic microflora and their products may be involved in the local and systemic pathogenesis of aortic aneurysms, suggesting an infectious pathogenic model of an aneurysm (54). The spread of oral microbiota from the gum to the blood and then to the aortic wall might promote weakening of the aortic wall or even secondary bacterial growth of aneurysm (55). It was stated that severe hemorrhage on dental probing and deeper gum pocket in cases with aortic artery aneurysm compared to non-aneurysmal cases (56).



Oral health and peripheral vascular diseases

Arteriosclerosis may disrupt the periodontal tissue also and harm local vasculature, which may explain the link of PD with peripheral arterial diseases (47). Poor oral hygiene shared inflammatory mechanisms, and raised inflammatory markers were described in patients with peripheral vascular disease (57).

Oral health and cardiomyocyte diseases

Oral health was associated with cardiac hypertrophy as well (53). Remodeling of the cardiac ventricles and hypertrophy after AMI were worsened by *A. actinomycetemcomitans* (58). Oral microbiota increases the levels of matrix MMPs that can damage the periodontal extracellular matrix. MMPs are also released and induced myocardial inflammation, hypertrophy, and perivascular and interstitial fibrotic changes, which trigger systolic/diastolic dysfunction (53).

Oral health and cerebrovascular diseases

Wu et al. have stated that periodontitis is an independent risk factor for cerebrovascular disease, primarily for the stroke of non-hemorrhagic causes (59). PD suggests a systemic problem of bacterial byproducts and endotoxins, which might activate multiple proinflammatory cytokines that intern stimulates the proliferation of inflammatory cells within the arteries. As well it induces liver synthesis of various clotting factors, which might contribute to cerebrovascular atherothrombosis (59, 60).

Periodontitis and cardiac arrhythmias

In a study including 227 cases of atrial fibrillation, the PD was an independent risk factor for arrhythmic events (45). Impart, this can be explained by the inflammatory responses of atrial myocytes causing oxidative stress, hypertrophy, and myocardial injury provoked by synthesized immunoglobulins against *P. gingivalis* and *P. intermedia* bacteria (61). It was identified that treatment of PD may adjust inflammation and thereby may prevent arrhythmia recurrence (45). Others failed to replicate this relationship in patients with hyperthyroidism (46). The evolution of tachyarrhythmia may be predisposed by PD, specifically, *P. gingivalis* and *P. intermedia* were recognized from the saliva of tachyarrhythmic subjects and both bacteria may induce ventricular remodeling too (62).

Oral hygiene associated with risk factors for CVD

Oral hygiene is related to several CVD risk factors, particularly arterial systematic hypertension, smoking, diabetes, and dyslipidemia (39). tobacco is known to interrupt the vascular supply of the gum, immune response, fibroblast activity, and tissue healing, and also trigger vascular endothelial dysfunction (3).

Periodontal disease, inflammation, and dyslipidemia

A bidirectional association of periodontitis with lipidemic disorders was suggested also. Dyslipidemia increases the susceptibility to PD due to the associated inflammatory response, and simultaneously, the inflammatory response associated with PD disrupts lipids body metabolism (44). "Pro-protein convertase subtilisin/Kexin-9 (PCSK9)" controls circulatory concentrations of LDL-cholesterol seriously, and looks to be up-regulated in subjects with PD with antibodies against *P. gingivalis*. A previous Japanese study has also shown that the plasma PCSK9 values were associated with oral hygiene variables (63, 64).

Periodontitis and vascular endothelial dysfunction

Patients with progressive PD have been exposed to increased "flow-mediated dilatation" of the brachial vessels compared to controls (65). Systematic periodontal intervention recovers endothelial function and henceforth, enhanced the brachial artery flow (66). Furthermore, PD can promote the production of reactive species inside arterial walls, and treating PD reduces biomarkers of oxidative stress (67).

CONCLUSION

Oral hygiene and cardiovascular diseases are inflammatory conditions that share some common pathogenesis and assembly of risk factors such as biochemical and inflammatory markers, even with the lack of causality. Henceforth, physicians, dentists, and paramedical personnel should stretch their awareness, given such interrelations connecting oral hygiene and CVD.



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