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Interrelationship Between Cardiovascular and Periodontal Diseases

Mohammed Abrar Khan

Department Periodontology Subharti Dental College and Hospital Swami Vivekanand Subharti University Meerut, U.P, India

Mayur Kaushik

Department Periodontology Subharti Dental College and Hospital Swami Vivekanand Subharti University Meerut, U.P, India

Sameer Ahmed

Department Periodontology Subharti Dental College and Hospital Swami Vivekanand Subharti University Meerut, U.P, India

Abstract---In the recent times studies relating the association of Oral and Systemic diseases has gained immense importance because the high occurrence of oral diseases is an extremely common source of infection. Periodontitis is ranked as the sixth most prevalent disease affecting humans affecting 740 million people worldwide. Periodontitis and cardiovascular disease have a complex etiology and genetics and share some common risk factors (i.e., smoking, age, diabetes, etc. The aim of this review is to look at the link between these two diseases. PD is a potential risk factor that may initiate the development, maturation, and instability of atheroma in the arteries. Two mechanisms were proposed to explain such association, either periodontal pathogens directly invade bloodstream or indirectly by increasing systemic level of inflammatory mediators. Interestingly, According to the current literature, it is concluded that there is a strong relationship between these chronic disorders. Improvement in the condition of one disease positively impact the condition of the other one emphasizing the association between these two diseases.

Keywords---atherosclerosis, cardiovascular disease, inflammation mediators, myocardial infarction, periodontitis.

Introduction

Periodontitis is a chronic inflammatory multifactorial disease that is associated with dysbiotic plaque biofilms and is characterized by progressive destruction of the tooth-supporting apparatus. Periodontitis has a complex aetiology, with microorganisms playing a key role 1. Bacteria are necessary, but not sufficient, for periodontitis to develop. The host reaction to the challenge posed by the microorganisms in the biofilm is ultimately what determines whether disease develops or not. Genetic ancestry is a key element in the host response, and it is estimated that 50% of people with periodontitis have genetic characteristics that predispose them to disease development². Other than genetic factors and microorganisms, behavioural habits such as smoking, stress, and systemic disorders have been found to be a predisposing factor for periodontitis (1).

Cardiovascular diseases (CVD), including acute myocardial infarction and angina pectoris are major health concerns in developing nations, and are amongst the most frequent medical conditions amongst the general population. The hypothesis was first proposed in mid 90's where periodontitis was considered to be an unrecognized risk factor for development of atherosclerosis and thromboembolic events. Chronic periodontitis is linked with the increased risk of coronary heart disease (CHD) among younger men, independent of established cardiovascular risk factors. The possible link could be due to both direct and indirect effects of periodontal infection; another pathway could be linked to genetic and other host characteristics that promote vulnerability to both atherosclerosis and chronic periodontitis (3). Periodontitis has been linked to higher systemic levels of C-reactive protein, interleukin (IL)-6, and neutrophils. These elevated inflammatory factors may increase inflammatory activity in atherosclerotic lesions, potentially increasing the risk for cardiac or cerebrovascular events. These inflammatory systemic indicators are also thought to be predictors of current and future cardiovascular events and illness. Furthermore, oral bacteria have been detected in carotid atheromas, and some oral bacteria have been linked to platelet aggregation, a critical event in thrombosis. There have also been studies suggesting a link between chronic oral infections and myocardial infarction (4).

Potential Mechanism of association between periodontitis and CVD

- **Direct Mechanisms:** This hypothesis assumes that bacteria or their products have direct access to the vessel wall via the bloodstream and influence plaque development and evolution. Several investigations have found evidence of living oral bacteria or their genetic material in atheromatous plaque samples from various vascular beds, supporting this concept.
- **Indirect Mechanisms:** The possible impacts of PD on a number of conventional CVD risk variables, such as LDL serum cholesterol, blood pressure, glucose metabolism, and platelet aggregation, are indirect routes by which PD can affect CVD. Several observational studies have found substantial connections between PD and serum total cholesterol and glucose metabolism. The mechanisms causing these changes are unknown, however they could be linked to PD effect on endothelial function or the

inflammatory process. Another way in which PD can influence CVD is by its effect on platelet aggregation 5 Fig. 1

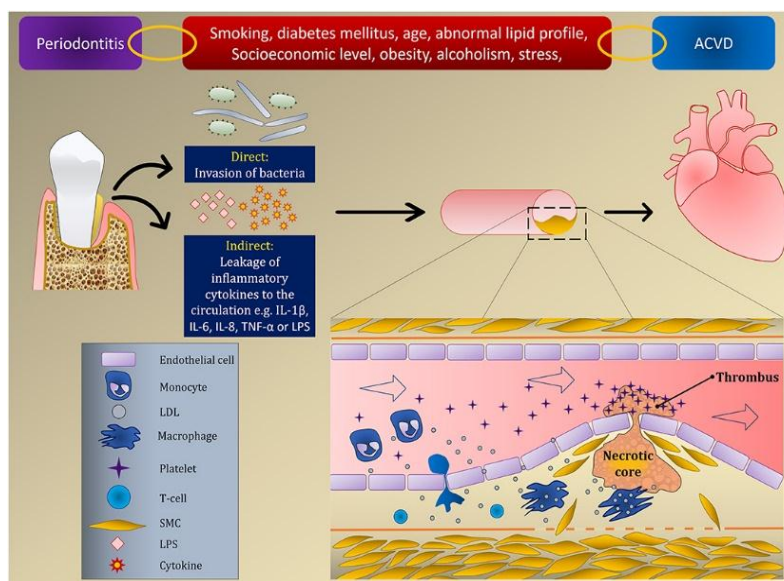


Figure 1. Mechanisms by which periodontitis may relate to cardiovascular disease

Assosiation of Atherosclerosis with periodontal disease

Atherosclerosis is a progressive disease characterized by the accumulation of lipids and fibrous elements in the large arteries. Atherosclerotic plaques may develop early in life and progress to severe ("high risk") plaques Fig 2. When an atheromatous plaque disrupts an acute ischemic event can occur (6). The link between periodontal disease and atherosclerosis issues could be explained in a variety of ways.

- It may merely reflect confounding by common risk factors that cause both periodontal disease and atherosclerosis, such as smoking, obesity, and diabetes.
- The link could be due to an individual's proclivity for developing an exuberant inflammatory response to intrinsic (age, sex, genes) or extrinsic (diet, smoking, etc) stimuli, which subsequently predisposes to periodontal disease and atherosclerosis.
- The pathogenic bacteria in periodontal tissues, particularly Gram-negative bacteria, invade blood circulation, resulting in bacteremia; the lipopolysaccharide of oral bacteria may combine with lipid-binding protein and CD14 receptor, which is used for mononuclear/macrophage activation resulting in release of various cytokines that can damage endothelial cells.
- The next step is to trigger a systemic inflammatory response. Periodontal inflammation can raise blood levels of cytokines including IL-1, IL-6, and tumour necrosis factor (TNF- α), which can then cause the generation of intrahepatic inflammatory mediators like CRP. By stimulating humoral and cell-mediated inflammatory pathways, the presence of an inflammatory

focus in the oral cavity may aggravate the atherosclerotic process. This could result in systemic inflammation, endothelial cell injury, and arterial plaque formation. CRP may also interact with LDL and participate in atheromatous plaque development and complement activation before integrating into a portion of the plaque or thrombus (7).

- It also causes a systemic immune response. Because the structures of heat shock proteins (HSP) from bacteria and humans are so similar, cross-reactions between HSP60 from *P. gingivalis* and humans are common. The overexpression of HSP60 in *P. gingivalis* can harm endothelial cells and enhance cellular immunologic responses in plaques, resulting in plaque inflammation.
- At last, it also influences the lipid metabolism. Periodontal pathogenic bacteria can enhance the oxidation and aggregation of low-density lipoprotein cholesterol (LDL-C), which can then be absorbed by macrophages via the scavenger receptor after oxidative alteration. During this process, phagocytes become foam cells, which then produce the first fatty streak (8).

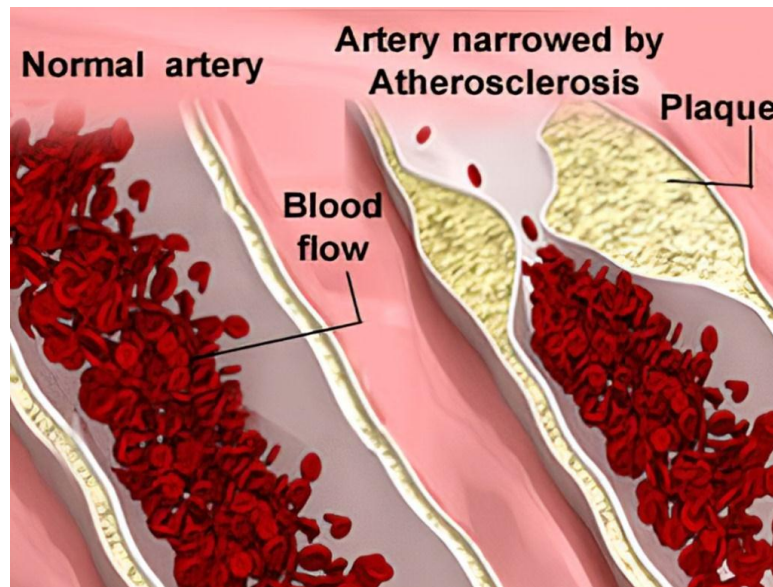


Figure 2. Atherosclerosis

1.4 Coronary heart disease: The accumulation of atheromatous plaques within the walls of the arteries leads to CHD Fig 3. Plaque rupture and endothelial erosion are the two most common causes of coronary thrombosis. Plaque rupture is harmful because it exposes pro-thrombotic material from the plaque's core-phospholipids, tissue factor, and platelet-adhesive matrix molecules to the blood. Ruptures are more common when the fibrous cap is thin and partially destroyed. At these locations, there are a lot of activated immune cells which release a variety of inflammatory chemicals and proteolytic enzymes that weaken the cap and activated cells in the core, turning the stable plaque into a susceptible, unstable structure that can rupture, induce thrombus, and cause acute coronary syndrome (9).

The emergence of gram negative bacteria occurs when bacterial biofilms on the teeth are not physically broken on a regular basis. Inflammation is induced as a result of a prolonged bacterial assault, which sets off a chain of events that leads to the condition progressing from gingivitis to periodontitis. Bacteria and their toxins cause the release of cytokines and other inflammatory mediators in a localised tissue response. Periodontitis causes chronic damage to epithelial tissues and underlying connective tissues, which can cause the periodontal pocket to ulcerate, allowing bacteria to enter the bloodstream. When toxins enter the systemic circulation, all of these mechanisms can disrupt homeostasis. In periodontitis, the proinflammatory cytokines $\text{TNF-}\alpha$, IL-1 α , gamma interferon, and PGE2 attain high tissue concentrations. As a result, the periodontium acts as a replenishing reservoir for these mediators, which are then released into systemic circulation, initiating and prolonging systemic effects. IL-1 promotes coagulation, thrombosis, and fibrinolysis inhibition. Platelet aggregation and adhesion, production of lipid-laden foam cells, and cholesterol deposition in the arteries can all be caused by chemical mediators such as IL-1, $\text{TNF-}\alpha$, and thromboxane (10).

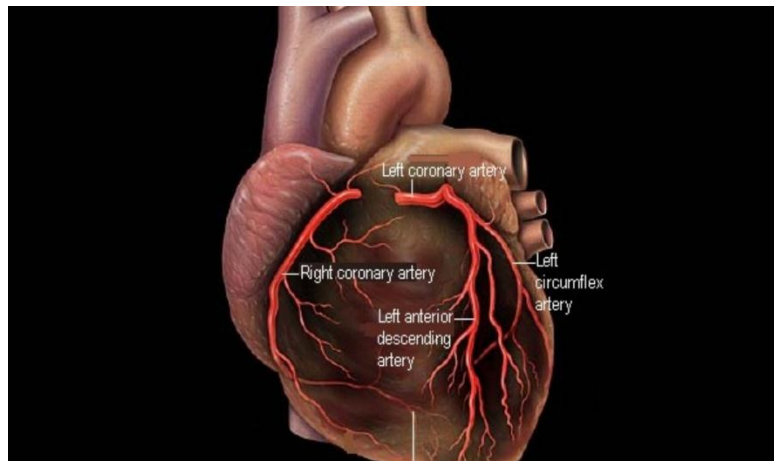


Figure 3. Right and Left coronary arteries

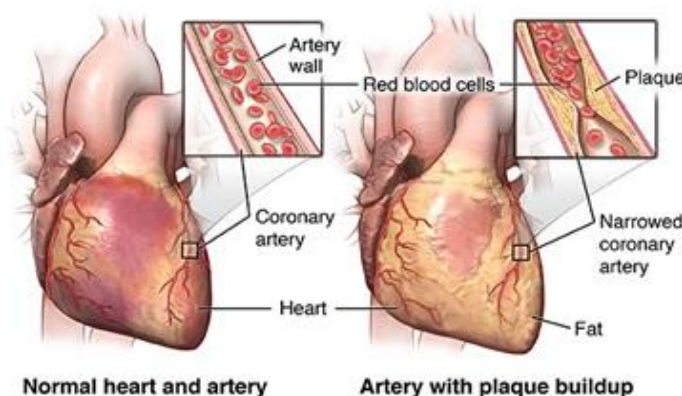


Figure 4. Coronary artery disease

Myocardial infarction

Myocardial infarction occurs when the atheromatous process prevents blood flow through the coronary artery. The main cause of infarction was traditionally assumed to be progressive luminal constriction caused by continuing development of smooth-muscle cells in the plaque. Angiographic studies, on the other hand, have revealed culprit lesions that do not generate significant stenosis, and it is now clear that plaque activation, rather than stenosis, causes ischemia and infarction. Periodontal disease-causing microorganisms can contribute to the production of atheromatous plaques, making them a significant risk factor for CVD (11). Kuramitsu's work in 2001 demonstrated that vesicles formed by the development of lipid cells in the outer membrane of *P. gingivalis* were a significant feature of CVD. They also played a role in the oxidation of LDL and the rupture of atherosclerotic plaques¹². Some bacteria in microbial plaque have a surface protein that is comparable to the platelet-stimulating component of collagen, causing platelet aggregation and causing cardiac and cerebral ischemia diseases through thrombosis development (13).

Stroke and periodontal disease

Stroke is defined as an acute episode of focal dysfunction of the brain, retina, or spinal cord that lasts for more than 24 hours or of any duration as determined by computed tomography/magnetic resonance imaging or autopsy with focal infarction or hemorrhage relevant to the symptoms. Unstable atherosclerotic plaques with a thin fibrous cap, a large lipid core, few smooth muscle cells, and a high concentration of macrophages are prone to rupture. Atherosclerotic plaque rupture produces debris and thrombi, which can migrate distally and cause distal embolization and stroke (14). Theories have been proposed as to the mechanism underlying the link between periodontitis and atherosclerotic plaques: The bacterial invasion theory posits direct action of bacteria and their toxins on the endothelium, whereas the cytokine theory assumes that inflammatory mediators secreted by immune system cells play a vital role in arterial wall endothelium damage. The importance of heat shock proteins (HSP65) expressed on oral pathogens is highlighted by the autoimmunization theory. In periodontitis, bacterial lipopolysaccharides enter into the bloodstream and cause the synthesis of C-reactive protein. High CRP levels are linked to an increased risk of stroke. Acute phase proteins lodge in injured blood arteries and activate phagocytes, which emit nitrous oxide, which contributes to atheromas development. In patients with periodontitis, chronically increased CRP levels worsen inflammatory processes in atherosclerotic plaques. Inflammation causes plaques to become unstable and prone to rupture, increasing the risk of cerebrovascular accidents (15).

Peripheral artery disease

It is a common circulatory problem in which narrowed arteries reduce blood flow to the limbs. Studies have looked into the probable mechanism that could be involved in the link and explain how PD could cause or worsen PAOD. At least three basic mechanisms are suggested by these investigations:

- Periodontal pathogenic microorganisms have been shown to penetrate the bloodstream and infiltrate atherosclerotic plaques at arterial wall injury (16).
- Experiments revealed that inflammatory mediators including serum amyloid A and anti-inflammatory mediators are delivered into the bloodstream from PD-affected oral regions, influencing systemic inflammation (17).
- Autoimmunity to the host protein heat shock protein 60 (HSP60) was demonstrated in patients with PD as a result of the host immune response to the bacterial HSP60 homolog GroEL generated by *Porphyromonas gingivalis* (the principal oral pathogens associated in PD) (18).

Hypertension

The force produced by circulating blood on the walls of the body's arteries, or major blood vessels, is known as blood pressure. When blood pressure is too high, it is known as hypertension. Possible Linking Pathways in the Hypertension-Periodontitis Relationship

Inflammation

The inflammatory response associated with periodontitis has been identified as a significant component that may have negative consequences on blood pressure regulation. The amount of serum high-sensitivity CRP, an acute-phase reactant that has been shown to predict the outcome of CVD, was found to be higher in periodontitis patients than in control subjects. The association of CRP with hypertension in the setting of periodontitis has not been consistent, possibly due to many other factors that can elevate inflammatory markers, or simply hypertension itself is a multifactorial disease. However, it has recently been suggested that hs-CRP may be a valuable marker linking periodontal disease and chronic inflammation which leads to endothelial dysfunction. In experimental rats, periodontitis has been shown to reduce endothelium-dependent vasodilation. The rise in systemic inflammatory indicators (CRP and IL-6), worsening of the lipid profile, increased formation of vascular superoxide radicals, and decreased expression of vascular nitric oxide synthase-3 (NOS-3) all contributed to this negative outcome (19). Periodontitis may therefore be capable to induce vascular inflammation which leads to endothelial dysfunction, an initial step for CVD. Al-Ghurabei has documented that serum levels of hs-CRP and IL-6 were significantly elevated in patients with chronic periodontitis as compared to healthy control group., Vidal et al. on the other hand found that periodontal treatment reduces IL-6, CRP, and fibrinogen levels in patients having hypertension and severe periodontitis. As a result, it's becoming obvious that inflammation may have a role in the development of hypertension and periodontitis (20).

Oral infection

Periodontal bacterial infection may also play a role in the development of hypertension, at least in part. Periodontitis is caused by bacterial species accumulating in the subgingival biofilm, especially Gram-negative anaerobic and microaerophilic bacteria such *P. gingivalis*, *Prevotella intermedia* and others. By

proteolysis, these periodontal bacteria can degrade and penetrate gingival tissues, reach the systemic circulation, causing temporary bacteremia. As a result, periodontal microorganisms may infect the artery wall directly, causing vascular inflammation and atherosclerosis. *P. gingivalis* is the most common bacterium discovered in atheromas. The infection of macrophages with *P. gingivalis* and its outer membrane vesicles causes increased amounts of foam cell production. *P. gingivalis* and its vesicles enhance not only the binding of low-density lipoprotein (LDL) to macrophages, but also the modification of native LDL by macrophages, which is critical in the production of foam cells and the pathophysiology of atherosclerosis (12). Endothelial cells and platelets have been observed to be activated by *P. gingivalis*, which is a characteristic of atherogenesis. Endothelial cell activation has a role in the aetiology of hypertension. As a result, periodontal pathogens released into the circulation from periodontal lesions may convey pathogenic elements to the artery wall, causing foam cell production in macrophages to begin and/or enhance, contributing to the development of CVD (21).

Oxidative stress

Chemically reactive substances such as superoxide anions and hydrogen peroxides are known as reactive oxygen species. ROS are produced naturally in cell membranes, mitochondria, and the endoplasmic reticulum during physiological processes. Excessive generation of ROS, on the other hand, causes oxidative stress, resulting in an increase in the synthesis of free radicals and a reduction in antioxidant levels. There is mounting evidence that periodontitis causes excessive formation of reactive oxygen species (ROS) in periodontal tissue. As a result, oxidative stress may play a role in the development of periodontal tissue damage. As periodontitis progresses, the formation of reactive oxygen species (ROS) rises and ROS reach the systemic circulation. As a result, biomolecule oxidation causes systemic oxidative stress, which can harm multiple organs. As a result, periodontitis-induced increases in circulating oxidative stress may have negative consequences for overall health (22). Locally invading immune cells cause oxidative stress, which contributes to hypertension. The development of hypertension has been linked to oxidative stress. The mediators of vasoconstriction and vascular inflammation are widely acknowledged, and NO bioavailability is strongly linked to hypertension. An imbalance between oxidant and antioxidant activity is caused by reactive oxygen radicals created by periodontal tissue deterioration (19).

Endothelial dysfunction

The endothelium releases NO to maintain the circulatory system's equilibrium. High blood pressure has been linked to an imbalance between antioxidant and ROS production. In hypertensive patients and experimental models, endothelium-dependent relaxation is impaired. This could be owing to a decrease in NO bioavailability, which could be caused by a drop in production or an increase in ROS deactivation in the vascular wall. Peroxynitrite, a cytotoxic prooxidant formed when NO and ROS combine, has the ability to damage endothelium integrity (23). Periodontal disease may contribute to endothelial dysfunction, which eventually increases the risk of hypertension. NO deficiency is strongly

related to the redox imbalance¹⁵⁹. In gingival tissues with periodontitis, inducible nitric oxide synthase (iNOS), which is produced solely under inflammatory conditions to produce huge levels of prooxidative NO, is highly expressed. Furthermore, because inflammation and even oxidative stress can degrade extracellular matrix (ECM), periodontitis could be linked to vascular remodelling. Damage to the ECM has been found to impact cell adhesion, proliferation, and signalling pathways by causing structural and functional changes. As a result, the impairment of major artery elasticity plays an important role in the development and progression of hypertension (24).

Periodontal therapy and cardiovascular risks

Several observational studies have explored the potential association between cardiovascular diseases and infections (5). Since 1980, observational evidence was published that dental health was significantly worse in patients with acute myocardial infarction than in controls.³ The hypothesis that chronic infections, such as periodontitis, could be implicated in the pathogenesis of atherosclerosis was pointed out by prospective results of a large population study.¹¹ Ultimately, the evidence of a strong inflammatory component in the pathogenesis of atherosclerosis has given strength to a plausible mechanism linking periodontitis and cardiovascular diseases (3).

Indeed, numerous clinical trials have reported increased systemic inflammatory profiles (acute-phase reactants, cytokines) in patients with periodontitis compared with controls and decreased inflammatory mediator concentrations following periodontal therapy. Systemic inflammation could, therefore, represent the biologic link between periodontitis and cardiovascular diseases; however, the specific mechanisms linking the two are not clear. In 2013, the European Federation of Periodontology and the American Academy of Periodontology addressed the issue of causality between cardiovascular disease and periodontitis in a joint workshop (25). A summary of the evidence on the impact of periodontal treatment on traditional markers related to cardiovascular health/ risk and surrogate and hard cardiovascular outcomes concluded that the data available at that time were supportive of an association between these disorders, and it further suggested a beneficial effect of periodontal therapy on outcomes relative to cardiovascular diseases. The lack of studies on cardiovascular hard outcomes did not allow drawing robust conclusions on the direct effect of periodontal therapy in reducing the risk of cardiovascular events such as myocardial infarction or stroke (14).

Conclusion

Epidemiologic research have shown that there is a possible association between PD disease and cardiovascular disease. It is the responsibility of oral healthcare providers and medical professionals to prepare for improved preventative programme planning, as scientific evidence suggests that interventional periodontal care is beneficial not only to oral health but also to overall health. Patients with periodontitis should be informed that they have an increased risk of cardiovascular disease, such as myocardial infarction and stroke, and that risk factors should be carefully managed. Furthermore, patients with periodontitis and

cardiovascular disease should be told that they may be at a higher risk of developing cardiovascular issues as a result of their periodontitis, and that they should follow the prescribed dental prevention, treatment, and maintenance regimens.

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