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Mechanisms Linking Periodontal Disease and Cardiovascular Disease: A Review and Update

Kamalkishor Mankar[1], Pranjali Bawankar[2],

[1]Associate Professor, [2]Lecturer,
VSPM Dental College & Research Centre, Department of Periodontology,
Digdoh Hills, Hingna Road, Nagpur-440019

Corresponding Author: Pranjali Bawankar

ABSTRACT

Aim: To present review of current literature regarding association between periodontal and cardiovascular diseases and the mechanisms involved in the association.

Materials and Methods: Thorough search was carried out on PUBMED, MEDLINE databases and Google on the association between periodontal disease and cardiovascular diseases and the mechanisms involved selected literature included review articles, observational studies, case control studies, randomized control trials and meta-analysis. Priority was placed on papers published within last 10 years. Brief description of periodontal disease and atherosclerosis underlying pathophysiology has also been included.

Results and Conclusion: Preponderance of data appears to support the concept that a potential link does exist between periodontal disease and CVD independent of confounding factors. Interventional trials have shown that periodontal therapy is associated with reduction in surrogate markers of atherosclerotic cardiovascular disease. Prospective interventional studies are required to determine the exact link between PD and CVD as well as to evaluate whether periodontal treatment may reduce the risk of developing CVD.

Clinical Significance Pre assessment of developing cardiovascular disease using biomarkers can help in diagnosis of developing or worsening periodontal diseases at earlier stages and can aid in providing screening services and advice to seek immediate dental care.

Keywords: Coronary Artery Disease, Chronic Periodontitis, Interrelationship, Periodontal disease, Systemic conditions.

INTRODUCTION

Concept of periodontal medicine which explores relationship between periodontal disease and systemic diseases has been introduced in 1996, by Offenbacher.[1] Periodontitis is a chronic inflammatory disease caused by bacterial infection of tooth supporting tissues,[2] and is the most common oral condition affecting human population.[3] According to a survey in united states about 50% of adults above 30 years have some periodontitis, and nearly 10% have severe disease.[4] Annually CVD accounts for 40% of all deaths worldwide, with atherosclerosis as underlying etiology in majority of cases.[5,6] Atherosclerosis is a disease process in which fatty deposits, inflammation, cells and scar tissue buildup within the walls of arteries. Inflammation plays a central role in the pathogenesis of atherosclerosis, from its initial stage to development of clinical signs and symptoms.[7] Several factors are defined as risk factors for cardiovascular diseases; however incidence of atherosclerosis cannot be explained by traditional factors alone.[8] American Heart Association (AHA) working group concluded that periodontal disease is associated with atherosclerotic vascular disease (ASVD) independent of known confounders.[9] This relationship was demonstrated with level A evidence. The focal infection theory proposed by William

Hunter in 1909 was revisited in 1951 by the American Dental Association and a confirmation of the link of periodontal diseases and systemic diseases was established. [10'11] European society of cardiology concluded that "oral health has an influence on systemic health in general and on cardiovascular disease (CVD) in particular. Therefore we should promote oral health in general and periodontal health in particular as part of a healthy life style and hence as an important component in the prevention of CVD.[12] Several systematic reviews have shown a significant association between periodontal disease and atherosclerotic cardiovascular disease, independent of known confounders. [13,14,15] Patients with periodontal disease share many of the same risk factors as patients with CVD including age, gender (predominantly male), lower socioeconomic status, stress, and smoking.[16] Several direct and indirect mechanisms have been proposed as pathophysiological links between chronic periodontitis and atherosclerotic cardiovascular disease.[9] In order to ensure optimal treatment it is important for cardiologists to be aware of all of the potential risk factors for CVD. This review provides an overview of research on the relationship between periodontal disease and CVD in the light of current literature.

Pathophysiology of periodontitis

If biofilms on the teeth are not disrupted on regular basis, it leads to emergence of gram negative bacteria. Low redox potential, supply of nutrients in crevicular fluid and limited amount of oxygen in periodontal pocket provides favorable environment for survival and multiplication of gram negative bacteria. Periodontal disease is caused by bacteria in dental plaque, pathogens frequently associated with periodontal disease include Aggregatibacter actinomycetemcomitans, Capnocytophaga, Campylobacter rectus, Fusobacterium nucleatum, Porphyromonas-gingivalis, Prevotella intermedia, Tannerella forsythia and Treponema denticola.[17] These bacteria disrupt host mechanisms involved in bacterial clearance by activating many host immunoinflammatory processes. Host inflammatory processes are dependent on environmental, genetic and acquired risk factors. Although periodontitis is initiated by microbes, host modifying factors play an important role in determining severity and extent of disease.

Periodontal disease occurs due to a complex interplay of bacterial infection and host response. [18] Bacteria interacts with host through there virulence factors and induce an innate and humoral immune response.[19,20] Immune response to bacterial challenge shows interindividual variations [21] and leads to release of proinflammatory factors, PGE2, IL-1β.[22] Inflammatory processes at periodontium results in increase level of CRP and other mediators such as fibrinogen leading to systemic response. Cytokine and MMP levels also increase in periodontitis. Increase in levels of MMPs along with proliferation of bacteria lead to activation of different cells, such as fibroblasts, keratinocytes, macrophages and endothelial cells. Macrophages secrete large amount of TNF and IL-1 β leading to bone resorption.

Atherosclerosis

Atherosclerosis is a chronic inflammatory disease; inflammatory processes are the vital part of pathophysiology of atherosclerosis and are supposed to be involved from initiation to final stages of infarction. Normally endothelial cells does not allow for the attachment of leukocytes to vessel wall. Dysfunctional lipid homeostasis plays a vital role in initiation and progression of endothelial alterations. When initial damage of epithelium occurs, either by infection or by an atherogenic diet, endothelial cells express adhesion molecules that allow leukocytes to bind vessel wall. Adhesion molecules are called vascular cell adhesion molecule (VCAM), intercellular adhesion molecule (ICAM). Selectins and integrins also support leukocyte attachment.

Endothelial dysfunction is considered as primary step in pathogenesis of atherosclerosis, and may act as risk marker for future cardiovascular events. [23, 24, 25, 26]

After adhesion to arterial wall, monocyte penetrates the vessel wall by diapedesis or migration between endothelial cells. This accumulation of monocytes in vessel intima leads to development of fatty streak, an early atherosclerotic lesion. Fatty streak develops at 11-12 years and fibrous plaque at 15-30 years.[27] LDLs (low density lipoproteins) play a key role in development of atherosclerotic lesions.[28,29,30] LDLs accumulated under intima layer are subsequently phagocytosed by macrophages and transform them into foam cells. Accumulation of foam cells in subendothelial space is the hallmark of fatty streak. Foam cells along with altered endothelium release various growth factors and cytokines, which stimulates migration of smooth muscle cells from tunica media into tunica intima. [23] Smooth muscle cells synthesize majority of extracellular matrix of complex plaque, forming the typical atherosclerotic plaque. Accumulation of fibrous tissue in vessel is characteristic of advanced atherosclerotic lesion, complex plaque. Inflammation influences integrity of fibrous cap not only by blocking creation of new collagen fibers but also by stimulating destruction of existing collagen.

Smooth muscle cells secrete specific enzymes (metalloproteinase's) on inflammatory stimulation. Metalloproteinase's may disintegrate fibrous capsule leading to rupture of plaque. migrated leukocytes release proinflammatory cytokines (IL-1,IL-6,TNFα).foam cells formation further increases release of proinflammatory cytokines IL-1,IL-6,TNFα.Activated T cells may stimulate MMP production by macrophages, MMP causes destruction of fibrous capsule leading to activation of clotting system with thrombosis and subsequent arterial occlusion, that may be responsible for many cases of MI. Rupture of plaque releases thrombotic factors that initiate coagulation, when in contact with platelets and cause thromboembolism.

Following are the potential mechanisms linking periodontitis to cardiovascular disease:

a) Direct bacterial effects on platelets and host cells.
b) Systemically or locally induced inflammatory mediators.
c) Autoimmune responses.

a. Bacteremias and endotoxemias

Inflamed periodontal tissue give access to periodontal bacteria and its products, into bloodstream through inflamed periodontal tissues, especially after dentaltreatment,[31,32,33] gentle mastication or tooth brushing.[32,34]Bacteria may access the circulation during daily routine, oral hygiene procedures and during periodontal therapy. Virulent Gram-negative organisms in the blood stream causes recurrent and transient bacteremia, as well as low-grade systemic inflammation.[32,33,35] Systemic inflammation caused by periodontal pathogens or virulence factors affects all stages of atherosclerotic process. Locally secreted pro-inflammatory cytokines such as TNF-α, IL-1 and IL-6 enter circulation, trigger the release of acute-phase reactants (e.g. C-reactive protein) and promote cell activation. Bacteremia is transient, bacteria are undetectable in the blood within 15 to 30 minutes, it can lasts longer in patients with periodontitis. [32]

Host cells (macrophages, endothelial cells, and gingival epithelial cells) are susceptible to invasion by certain periodontopathogenic bacteria (Porphyromonasgingivalis, Aggregatibacter actinomycetemcomitans, and Fusobacterium nucleatum) through invasion or adhesion. [36] Platelets play a critical role in hemostasis and thrombosis. Staphylococcus aureus and Streptococcus sanguis can induced platelet aggregation in vitro.[37,38,39] Platelet aggregation and increase in protease activity can be induced by P. gingivalis.[40, 41, 42] When P. gingivalis was added to human

platelet rich plasma (PRP) sharp and rapid increase of small-sized platelet aggregates was observed followed by the formation of medium and large-sized aggregates within 2-3 min.[43]P. gingivalis through its fimbriae can invade aortic and heart endothelial cells.[44]When macrophages are incubated with P.gingivalis and low density lipoprotein bacteria get internalized in macrophages and increases foam cell formation.[45]ICAM-1 and VCAM-1 in human umbilical vein endothelial cells (HUVECs) is upregulated by LPS fraction of P.gingivalis, and facilitate mononuclear cell adhesion to HUVECs.[46]

b. Inflammatory cytokines & acute phase protein

A number of inflammatory cytokines and various molecules (IL-1, TNF-α, IL-2, ICAM, VCAM, Heat shock proteins [HSPs] and fibrinogen) which are involved in atherothrombogenesis are found to be elevated due to periodontal disease.[47, 48, 49]

C – Reactive Protein (CRP)

Rise in concentration of CRP an acute phase reactant to inflammation can be induced by local and systemic tissue damage, infection and inflammation.CRP is produced mainly by liver in reponse to IL-6, extrahepatic production also occurs in the endothelium of atherosclerotic plaque, smooth muscle cells, infiltrated macrophages and inflammed gingival tissues.[50,51,52] High sensitivity CRP is regarded as one of the consistent markers of systemic inflammation and poor cardiovascular prognosis.[53,54] CRP is associated with atherogenesis through production of cytokines (IL-1,IL-6,TNF-α and interferon-α),CRP also mediate binding of LDL and formation of foam cells.[55,56,57,58]Various studies have shown a positive association between increased levels of CRP and periodontitis. [59,60,61,62] CRP is found to be elevated in patient with periodontitis in comparison to control without periodontitis, moreover meta analysis also indicated that periodontal treatment could lower the levels of CRP after therapy.[63]Results of multi centered randomized study showed that periodontal treatment can lower CRP levels from high to moderate levels in non-obese periodntitis patients.[64]Results from studies indicate that plasma CRP concentration can be used as a risk indicator for future MI and stroke.[65,66]Concentration of CRP shows dose dependency, higher in patients with advanced periodontitis as compared to moderate periodontitis, and higher crp level in both groups compared to control group.[67]A positive correlation has also been found between CRP levels and markers of endothelial dysfunction.[68,69]

Tumor Necrosis Factor-α (TNF-α)

TNF-α is released by lymphocytes, macrophages, T cells and other cells. TNF-α performs a modulator like role not only in the immune system but also in bone formation and resorption.[70]In the pathogenesis of cardiovascular diseases TNF-α and IL-6 play certain role and it also has significant systemic effects. [71,72] According to several studies TNF-α not only induces but also advances coronary artery diseases. [73,74] It has been found that patients with periodontitis have higher level of TNF-α, and correlation has also been reported between increase in TNF-α and periodontitis and peripheral arterial disease. [75,76] Some studies showed that periodontal therapy has an effect on serum TNF-α concentration,[77,78,79] while other studies failed to find any effect of periodontal therapy on serum TNF-α concentration.[80]

Interleukin – 6 (IL-6)

IL-6 a proinflammatory cytokine is released from macrophages, monocytes, T cells and fibroblast, which act in an autocrine manner.IL-6 trigger systemic inflammation and production of acute phase proteins such as CRP, βfibrinogen, amyloidA, C3 complement component and ceruloplasmin.[50,51,81] IL-6 release leukocytes and platelets into systemic circulation, alters hepatic or endothelial

synthesis and release of plasma proteins, thereby seems to be promoting vascular thrombosis.[82] IL-6 levels were found to be higher in patients who had myocardial infarction compared to those who did not have myocardial infarction in a 6 years long follow-up study on healthy individuals.[83] This indicates that IL-6 levels can be used as a predictable risk marker for future myocardial infarction in healthy individuals. Several studies reported that patients with periodontitis have higher levels of IL-6.[67,84] When levels of IL-6 were compared between patients with coronary heart disease along with periodontitis and coronary heart disease alone, it was found that patients having both coronary heart disease and periodontitis have higher IL-6 levels than those having coronary heart disease alone.[85] Regarding effect of periodontal therapy on levels of IL-6 evidence is not conclusive, several studies showed decrease in IL-6 levels following periodontal treatment while others showed no significant effect of periodontal treatment on IL-6 levels.[86,87,88,89]

c. Endothelial dysfunction:

Endothelial dysfunction is a pathological state of endothelium which is characterized by imbalance between vasodilatory and vasoconstricting substances produced by endothelium. Arteries synthesize and release various vasoactive substances, such as nitric oxide which act as vasodilator protecting against initiation and progression of atherosclerosis. In the initiation and progression of endothelial alterational dysfunctional lipid homeostasis plays a crucial role.[90,28,30,29] Oxidized-LDLs (Ox-LDLs) are considered as the major causative factor in the atherosclerotic plaque development, and are the major lipids found in atherosclerotic lesions.[91] Ox-LDLs also plays a role in the development of endothelial dysfunction, as it act as a potent inflammatory agent, thereby stimulating expression of adhesion molecules on endothelial cells.[92,93,94] Macrophages take up Ox-LDLs to form foam cells which are found in fatty streak.[30,95] Endothelial dysfunction can be evaluated by observing values of different factors, such as acute phase proteins (CRP), TNF-α and IL-6 which are found to be elevated in periodontitis patients.[96,63,80] Flow mediated dilation is found to be reduced in patients with severe periodontal disease.[97] P.gingivalis has the ability to adhere, invade and proliferate in coronary endothelial cells causing endothelial cell damage, thereby affecting physiological dilatory function of vessels.[44,98,99,100] Increase in the carotid intima media wall thickness has also been reported in patients with periodontal disease.[101,102]

d. Molecular mimicry

When local immune response is induced by periodontal bacteria, it cross reacts with self antigens expressed on the vascular epithelium leading to vascular inflammation and atherosclerosis. Immune response to bacterial heat shock genes and heat shock proteins might be the mechanism by which infection may initiate and facilitate the progression of atherosclerosis. All cells when exposed to various forms of stress (temperature, oxidative injury and infection) express HSPs.[103,104]Heat shock proteins have high molecular resemblance with each other,[105]therefore immune system may not be able to differentiate between self HSP and bacterial HSP (GroEL).Antibodies generated by host immune system for bacterial HSP could result in an autoimmune response to identical human HSP (hHSP) in the host.[103] Endothelial dysfunction leading to development of atherosclerosis may result from cross reactivity of antibodies to bacterial HSP with hHSP60 on endothelial cells.[106,107] Increase in morbidity and mortality due to atherosclerosis in patients with high anti-HSP 60/65 antibody titers has been demonstrated.[108]Antibody to Hhsp60 cross- reacts with periodontopathic bacterial GroEL as GroEL antigens share high degree of homology with hHSP60 proteins.[109] It has been reported that patients with

atherosclerosis have highest levels of antibody to human Hhsp60 and P.gingivalis HSP60 (GroEL), followed by periodontitis patients and healthy subjects.[110] P.gingivalis has an Hsp60 and an Hsp90 homologue which were found to cross react with corresponding human Hsp.[111,112] It has been demonstrated that periodontal destruction is less in patients with higher levels of anti-Hsp antibodies,[113] whereas inability to produce anti-Hsp antibodies might result in tissue destruction induced by pathogens. In the serum and atheromas of patients with periodontal disease and atherosclerosis a T-cell response specific to Hsp60 of P.gingivalis has been observed.[114,115,] Presence of Anti-hsp65/60 antibodies in the saliva of patients with chronic periodontitis has been reported.[116]

CONCLUSION

Preponderance of data appears to support the concept that a potential link does exist between periodontal disease and CVD independent of confounding factors. Some or all of these biological mechanisms most likely work simultaneously and could be the direct or indirect consequence of the pathogenic microbiota in periodontal lesions. In order to determine the exact biological mechanism and confirm a direct or causal relationship more interventional and longitudinal studies are required. Periodontal therapy is associated with reduction in surrogate markers of atherosclerotic cardiovascular disease. Prospective interventional studies are required to determine the exact link between PD and CVD as well as to evaluate whether periodontal treatment may reduce the risk of developing CVD. Based on the accumulated evidence since two and half decade we can state that oral health has an influence on systemic health in general and CVD in particular and should promote oral health in general and periodontal health in particular as a part of healthy life style.

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