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Research Article

INVASION OF PERIODONTAL PATHOGENS ON HUMAN CORONARY ARTERY ENDOTHELIAL CELLS

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ABSTRACT

The myth that the atherosclerotic vascular disease (ASVD) has a hereditary or purely nutritive origin is not true. Recently this coronary heart disease is also possibly known to have an infectious etiology. Studies have proved to have a correlation between periodontal disease and coronary heart disease. However, till date, there is minimal information relating to this invasion on periodontal pathogens causing coronary heart disease. Studies are conducted to test the hypothesis that invasion of the coronary artery cells by oral bacteria may start and/or exacerbate the inflammatory response in atherosclerosis. This review thus elaborates the possible molecular mechanisms involved in the interactions between periodontal pathogens and cardiovascular (CV) tissues with a focus on invasion of the cells of the arterial wall. And also determines the role of periodontal pathogens in the cardiovascular disease.

INTRODUCTION

Cardiovascular disease, mostly associated with atherosclerosis which consists of group of disorders of heart and blood vessels, has been the most common cause of death. Atherosclerotic vascular disease (ASVD) is an inflammatory lesion which results from injury to the endothelium resulting in chronic inflammatory process in the artery. Atherosclerosis occurring in large and medium-size elastic and muscular coronary arteries can lead to ischemia of heart and further result in thrombosis and infarction of vessels leading to death.

Periodontal disease is a localized chronic inflammatory disease of gingiva and underlying alveolar bone and connective tissues induced by the bacterial pathogens and its products present in dental plaque. Periodontal diseases is one of the most widespread oral diseases, which includes the inflammatory process initiated by plaque biofilm that results in gingival bleeding, periodontal pocket formation, destruction of connective tissue attachment, and alveolar bone resorption and finally leading to tooth loss. This periodontal disease which is an infectious disease, affecting the dental supporting tissues, is caused predominantly by Gram-negative anaerobic bacteria such as *Porphyromonasgingivalis* and *Prevotellaintermedia*.

Epidemiological studies have proved that periodontitisis a risk factor for cardiovascular disease.[1,2]Thus, dental plaque bacteria influences the oral cavity locally and also causes some serious systemic diseases. Periodontal disease has been related to coronary heart disease (CHD). A chronic inflammatory periodontal disease that results in breakdown of alveolar bone that surrounds the teeth, may be associated with increased risk for myocardial infarction (MI). The pathways that co-relate both the cardiovascular and periodontal diseases are the chronic low-level bacteremia that occurs with brushing or chewing and also the elevation of inflammatory mediators in response to bacterial biofilm growing on teeth.[3–5]

The prevalence of cardiovascular diseases in patients with periodontitis is 25–50% higher than in healthy individuals. Literature suggests that chronic periodontal disease[6–9],lesions of endodontic origin and tooth loss are associated with cardiovascular disease (CVD) and mortality.

The triggering of an inflammatory response by infectious agents is a potential mechanism correlating infection to the acceleration of atherosclerosis.[10]

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Coronary atherosclerotic burden (CAB) is a term which is used to describe the extension of atherosclerosis into the coronary vessels.[11]Poor oral health is the prime cause of a pro-inflammatory state and mayaccelerate the atherosclerotic process or precipitatea plaque rupture.[12] Poor oral health may also affect eating behaviour and contribute to poor nutrition, which has been identified as a risk factor for mortality.

Potential pathogenic mechanisms linking oral infections and AVD are based on three main pathways

1. The role of periodontal pathogens and their products in the development of endothelial dysfunction;
2. The contribution of oral microorganisms to the formation of fatty streaks and atherosclerotic plaques; and
3. The role of oral flora in the modulation and maturation of atheromatous plaques, facilitating their rupture and vascular thrombosis.[12,13]

Poor self-reported oral health (as a possible risk factor for periodontitis) and tooth loss (as a possible consequence of periodontitis) are positively associated with a coronary atherosclerotic burden.[14] Severe tooth loss (likely to be due to periodontal disease)may be a predictor of cerebrovascular disease-silent cerebral infarct.[15]

An association between oral health and cardiovascular disease has been proposed. Common risk factors for these diseases include increasing age, smoking, alcohol abuse, ethnicity, educational and socioeconomic status, being male, diabetes mellitus, and obesity.[16,17]

Pathogenic Mechanisms Proposed As Links between Cardiovascular Disease and Periodontal Disease

Several pathophysiological pathways have been proposed as potential links between Periodontal disease and Atherosclerotic vascular disease. These pathways involve both direct and indirect mechanism which relate the periodontal pathogens with the coronary heart disease.[18]

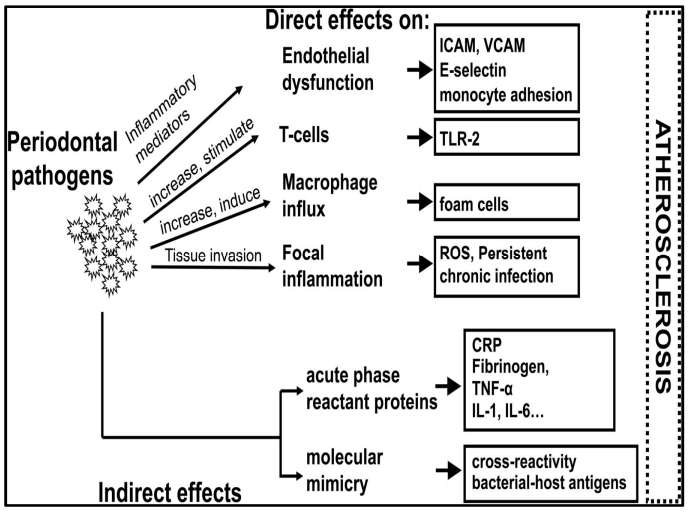

Fig I Process of atherogenesis and role of direct and indirect periodontal factors. Periodontal pathogens may directly and indirectly affect blood cells and blood vessels resulting in foam cell formation, the hallmark of atherosclerosis.

ICAM, intercellular cell adhesion molecule; VCAM, vascular cell adhesion molecule, TLR-2, Toll-like receptor-2; ROS, reactive oxygen species; CRP,C-reactive protein; TNF-α, tumor necrosis factor- α; IL-1,interleukin-1; IL-6,interleukin-6

Indirect Mechanisms: Systemic Inflammation

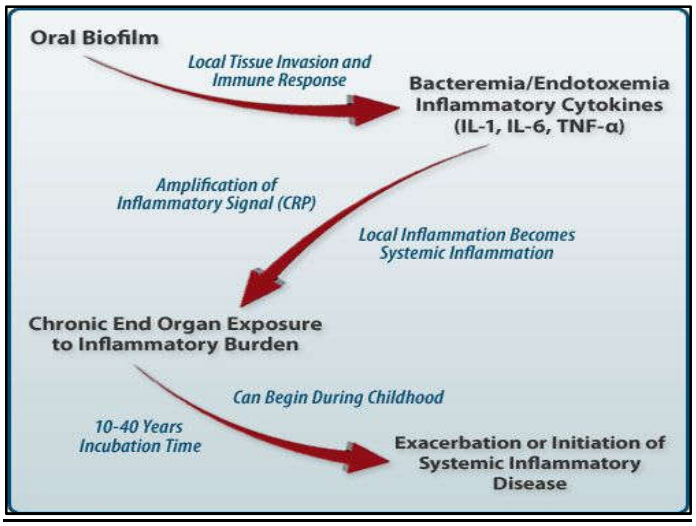

Fig II Pathway of systemic inflammation linking periodontal disease with the cardiovascular disease

Atherosclerosis may begin during childhood, with initial infiltration of the endothelium with fatty substances, and progresses over many decades. Chronic, quiescent atheromatousplaque can transit to a more dangerous state in which its vulnerability to rupture is increased. Plaques that contain a soft atheromatous core are unstable, and their rupture will expose highly thrombogenic contents to blood, with activation of thrombosis and ensuing Atherosclerotic coronary syndrome, Myocardialinfartion, or stroke.

Major determinants of increased plaque vulnerability are size and consistency of the atheromatous core and both thinning and inflammation of the fibrous cap covering the core. Such inflammation manifests as infiltrates of monocytes or macrophages, T-cells, and neutrophils within the cap tissues, as well as by increased circulating markers of inflammation in the blood.

The link between coronary heart disease and inflammatory mediators in blood are associated with each other by the levels of systemic inflammatory markers which increases the cardiovascular risk in the subjects.

Systemic inflammation is measured with several inflammatory markers like C-reactive protein (CRP). Additional inflammatory markers associated with cardiovascular disease include lipoprotein-associated phospholipase A2,matrix metalloproteinases and tissue inhibitors of matrix metalloproteinase, myeloperoxidase, and fibrinogen. Other inflammatory markers (eg, interleukin 6 [IL-6], soluble intercellular adhesion molecule-1, macrophage inhibitory cytokine-1, and soluble CD40 ligand) have been shown to be elevated and cause increased cardiovascular risk, although to a lesser magnitude than CRP.

Similarly, periodontal inflammation is associated with increased systemic inflammatory markers, including CRP, tumornecrosis factor-α, IL-1, IL-6, and IL-8. Systemic inflammation is associated with cellular activation that involves cellular adhesion molecules, toll-like receptors, matrix metalloproteinase, and nuclear factor-κB activation.

The interaction between the endothelium, monocytes, and platelets could be proatherogenic,[19,20]which indirectly leads to atherogenesis or causes adverse cardiovascular effects relating to atheromatousplaque rupture in periodontitis subjects.[21]Studies suggested that CRP is produced locally by the inflamed periodontium, but to what extent locally produced CRP accounts for higher circulatory CRP levels in periodontitis has not been determined.[22]

Indirect Mechanisms: Mimicry

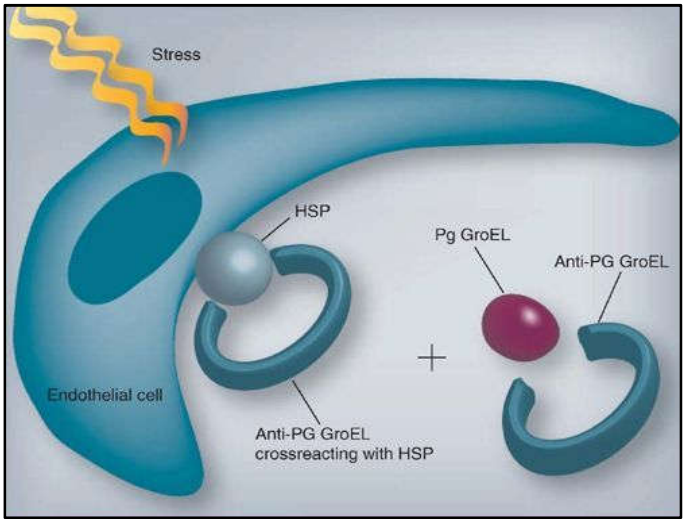

Fig III Molecular mimicry- link between periodontal infection and atherosclerosis.

HSP, Heat shock proteins; PgGroEl, *P-gingivalis* GroEl;Pg, *P-gingivalis*

Molecular mimicry is another pathway by which the periodontal infection is linked with atherosclerosis. Molecular mimicry is thought to occur when sequence similarities between foreign and self-peptides produce cross-activation of autoreactiveT or B cells that can lead to tissue pathology or autoimmunity.

Cross-reactive autoantibodies to periodontal bacterial lipopolysaccharides and heat shock proteins have been identified and invoked as the interlink between Periodontal disease and Atherosclerotic vascular disease. Expression of host protective heat shock proteins (HSPs) such as HSP60 on endothelial cells may be induced by a variety of factors, including cytokines and shear stress, and antibodies to HSP60 have been associated with higher morbidity and mortality from atherosclerotic vascular disease.[23]

In this mechanism, the endothelial damage may be aggravated by an immune response to bacterial HSP, such as the molecular chaperone GroEL, present in P gingivalis and other periodontopathic bacteria. Host antibodies directed against P gingivalis GroEL have cross-reactivity with HSP60 on human endothelial cells.[24] Moreover, cross-reactive T cells have been found in diseased periodontal tissue, peripheral blood, and atherosclerotic lesions.[25]This mechanism help in the linkage of periodontal disease and atherosclerotic vascular disease.

Studies in experimental animals lend further support to the hypothesis that cross-reactivity of the immune response to bacterial HSP has a role in accelerating a therosclerosis. In murine models, atherosclerosis is augmented by immunization with recombinant HSP. ApolipoproteinE–deficient mice infected with P gingivalishave accelerated development and progression of atherosclerosis compared with control mice.[26]

Direct Mechanisms: Bacteremia and Vascular Infection By Periodontal Pathogens

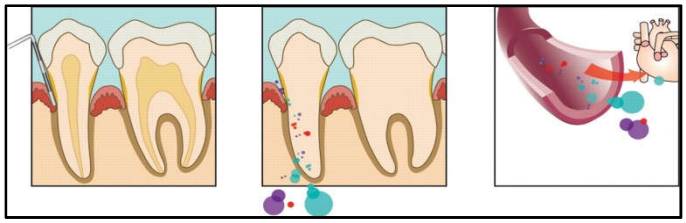

Fig IV Direct mechanism- Periodontal pathogens leading to atherosclerotic vascular disease and bacteremia.

Adults harbor more than a billion bacteria in their mouths. The greatest amount of bacteria which shows relevance to the atherosclerotic disease is found in the periodontal pocket. The total surface area of the pockets in periodontitis subjects is found to be between 8 and 20 cm_2.The bacterial biofilm are formed in the pocket in such a way that they can easily enter the systemic circulation.

Bacteremia that originates from the mouth is a common event that can occur during chewing and tooth brushing. It potentially occurs multiple times per day in individuals with some degree of gingivitis and periodontitis.[27]The literature provides a list of more than 275 bacterial species identified in blood cultures after routine daily events or dental procedures.[28] The nature of the bacterial species that enter the circulation reflects the resident flora at that location, from those that colonize the supragingival region down to the deep subgingival sulcus.

Viridans group streptococci represents a significant proportion of the microflora around teeth, particularly in dental biofilm that grows above the gingival crest. Incontrast, other microbes such as anaerobic microorganisms and gram-negative species are found to be in maximum amount in the deeper periodontal pockets. In a study carried out in 2008 by Bahrani-Mougeot FK *et al*.,the association between the incidence of bacteremia after tooth brushing and oral hygiene index and gingival, plaque, calculus, and gingival bleeding indexwas assessed and it was found that as the severity of indices increases, the incidence of bacteremia also tend to rise. Thus it can be concluded that, gingival sulcus is the main source and portal to the bloodstream for oral bacterial species detected in the blood.[29]

From there, periodontal pathogens circulate in the bloodstream either within phagocytic cells or extracellularly and finally get deposited inanvascular cells as atheromatous plaque. The periodontal pathogens like *P-gingivalis* adhere to the human vascular endothelial cells.[30] These bacteria also tend to invade the vascular cells thus causing aninfection of aortic endothelial cells which further induces a procoagulant response contributing to a vasculopathic role.[31]

Role of Periodontal Bacteria in Cardiovascular Disease

There are several mechanisms by which dental plaque bacteriamay initiate or worsen atherosclerotic processes[32]

1. Activation of Innate Immunity
2. Bacteremia related to Dental Treatment
3. Direct involvement of Mediators activated by dental plaque antigens in Atheroma processes

Activation of Innate Immunity

The oral cavity is permanently exposed to the activity of bacteria colonizing it. The epithelium forms not only a physiological barrier but also interacts with an innate immune response resulting in the production of antimicrobial peptides. Important components of innate immunity at sites of contact with microorganismsare alkaline antimicrobial peptides that contain less than 100 amino acids and are phylogenetically very stable. The most important are defensins and cathelicidins. These antibacterial peptides kill various microorganisms and some of them are chemotactic.

The most important components of innate immunity for defense in the oral cavity are defensins, calprotectin, histatin and, only in humans, cathelicidin-LL37/hCAP18.[33]Defensins and histatin present in the phagocyte granules are produced by mucosal epithelium and by salivary glands. Cathelicidin is produced by phagocytes, the epithelium and salivary glands. It binds LPS, neutralizes endotoxine activity and acts chemotactically on neutrophils, monocytes, T lymphocytes, and mast cells and exhibits bactericidal activity. Its presence in large quantities in the junctional epitheliumas a result of themigration of neutrophils is of great importance for the defense of the oral cavity.[34]

The Gram-positive and Gram-negative microorganism present in the dental plaque, contain different components which directly causes damage to the periodontal tissue.

The cell walls of Gram-negative bacteria are formed of peptidoglycans, polysaccharides, proteins, lipids, lipopolysaccharides, and lipoproteins.[35] The walls of Gram positive bacteria consist of peptidoglycans, teichoic acid, and polysaccharides. Lipopolysaccharide (LPS) which are found in the outer membrane of Gram-negative bacteria, influences the immune reaction by binding to Toll-like receptor-4 (LPS of Escherichia coli and Aggregatibacteractinomycetemcomitans) or to Toll-like receptor-2 (LPS of Porphyromonasgingivalis). LPS also stimulates expression of costimulatory molecules CD80/CD86, via binding to Toll-like receptor-4; furthermore, it stimulates molecules of the major histocompatibility complex MHC-II which are important for activation of T-cells.

Peptidoglycans activate the cells through binding to the Toll-like receptor-2; they are recognized by the complement as well as by specific receptors[36] and they also participate in the activation of the complement system.

The immune response, directed against an infection, also leads to further destruction of the tissue.[37] It was confirmed in in vitro experiments that cells of the junctional epithelium activated by Porphyromonasgingivalis produce TNF-α and IL-1α and express surface molecules ICAM-1 and VCAM-1. The influence of oral bacteria on the cytokine network is more complicated.

Porphyromonasgingivalis inhibits accumulation of IL-8 in gingival epithelium cells. Porphyromonasgingivalis also produces proteases which cleave and inactivate IL-1β and the cysteine protease-gingipain, which specifically cleaves CD14 (receptor for LPS). This enzyme enables the bacteria to suppress the immune response to LPS.[38] This mechanism is known as "localized chemokine paralysis." Gingipain produced by Porphyromonasgingivalis degrades proteins to generate free arginine or lysine; the primary goal of the degradation is to obtain the peptides and amino acids necessary for survival of the bacteria. However, it also degrades many important molecules on the surface of cells or in its environment and thus it protects *P.gingivalis* against the immune reaction. This gingipainenzyme degrades various inflammatory mediators which includeIL-1β, IL-6,IL-8, CD14, surface adhesion molecules like ICAM-1,molecules on the surface of monocytes and fibroblasts, lipopolysaccharide binding protein (LBP), components of the complement, and also immunoglobulins.

Another sign of an activated innate immune system is an enhanced level of neopterin in the patient's serum. A high concentration of neopterin corresponds to a high degree of activation of the immune reaction in acute coronary syndrome.

Bacteria of dental plaque and their components in the periodontal tissues may penetrate into the circulation system and exhibit pathogenic potential.

Bacteremia Related to Dental Treatment

There is increased incidence of bacteremia by Gram-negative bacteria in infectious endocarditis.

The following bacteria are considered as etiological factors: Aggregatibacteractinomycetemcomitans, Eikenellacorrodens, Streptococcus species, Capnocytophaga, Neisseria, and Lactobacillus.[39]

Dental infection affecting the periodontium can spread into the systemic circulation by dental treatment procedures or teeth brushing and can induce bacteremia. Periodontal probing in patients which severe chronic periodontits has a higher risk of bacteremia as compared to petirnts with chronic gingivitis. The predominant microorganism of dental plaque is *Streptococcus sanguis* which is strongly associated with atherosclerotic vascular disease and endocarditis.[40]

Following tooth extraction, the most frequently found bacteria in the blood cultures were the *Streptococcus species*. High incidence of bacteremia was found in patients without antibiotic prophylaxis after conservative and surgical dental treatment. Bacteremia occurs after periodontal procedures.[41] Dental surgical procedures cause bacterial endocarditis in children. In these cases, *Viridans streptococci* are mainly detected.

In a study carried out in 2004 by Rajasuo *et al*.[42] showed that there was an increased level of dental plaquebacteria in blood circulation followed by tooth extraction. Periodontal probing caused bacteremia in chronic periodontitis patients but chewing did not.

Endotoxins are capable of generating a range of systemic and local host responses.It was also found that after subgingival irrigation, there wasno effects on the incidence of bacteremia.[43]

Direct Involvement of Mediators Activated by Dental Plaque Antigens in Atheroma Processes

The relationship between periodontitis and atherosclerosis is the ability of *Porphyromonasgingivalis* to actively invade aortic and heartendothelial cells.

In an article it was also found that, after the venous system was established by surgical reconstruction, there was presence of

Porphyromonasgingivalis and *Streptococcus sanguis* in atherosclerotic plaques in samples of veins.[44]

A possible link between periodontal disease and abdominal aortic aneurysm was examined from resected specimens from abdominal aortic aneurysm which were positive for periodontal bacterial DNA in 86% of cases.[45]

In a review of 16 studies, the most frequently observed oral bacteria in atheromatousplaque were *Aggregatibacteractinomycetemcomitans* and *Porphyromonasgingivalis*.

Identification of Periodontal Pathogens in Atheromatous Plaques

Localized infection triggers a chronic inflammatory response leading to the development and progression of atherosclerosis. Several microorganisms including *Chlamydia pneumonia* and *cytomegalovirus* have been implicated in the infectious etiology of atherosclerosis. *Cytomegalovirus* is thought to accelerate the atherosclerosis sometimes observed in heart transplant patients.[46]

Like extra-oral infections due to *C.pneumoniae* and *Cytomegalovirus*, chronic oral infections have been reported to increase the risk for systemic diseases including stroke and myocardial infarction.[47] Patients with periodontal disease are, on average, at twice the risk for coronary vascular disease including myocardial infarction.[48]This increased risk for systemic disease in subjects with periodontal disease may be due to an increased prevalence and severity of bacteremia with oral microorganisms. Such bacteremias often involve species such as *Streptococcus sanguis* and *Porphyromonasgingivalis* that may promote thrombi formation by platelet aggregation and endothelial cell binding.[40,49]

Chronic infections may also indirectly promote atherosclerosis by stimulating cytokine production, hypercoagulability, and monocyte activation. *C. pneumoniae*, in particular, has been identified in aortic, coronary, carotid, iliac, and femoral atherosclerotic lesions by a variety of methods including microbial culture, electron microscopy, immunohistochemistry and the polymerase chain reaction.[50] By contrast, *C. pneumoniae* is found much less frequently in normal blood vessels.[51]

Haraszthy *et al*[52] carried out a study in the year 2000 to test the hypothesis that chronic infections including those associated with periodontitis increase the risk for coronary vascular disease (CVD) and stroke. Also it was found that during bacteremia, periodontal pathogens enter the blood stream and leads to the development and progression of atherosclerosis further causing coronary vascular disease.

In this study, 50 human specimens obtained duringcarotid endarterectomy were examined for the presence of *Chlamydiapneumoniae, human cytomegalovirus*, and bacterial 16S ribosomal RNA using specific oligonucleotide primers in polymerase chain reaction (PCR) assays. The PCR product generated was probed for *Actinobacillusactinomycetemcomitans, Porphyromonasgingivalis, Prevotellaintermedia and Bacteroidesforsythus.*

They concluded that theperiodontal pathogens are present in atherosclerotic plaques where, like other infectious microorganisms such as *C. pneumoniae,* they may play a role in the development and progression of atherosclerosis leading to coronary vascular disease and other clinical sequelae.

SUMMARY AND CONCLUSION

The relation between periodontal disease and Atherosclerotic vascular disease is potentially of great public health importance because of their high prevalence. Although there are different mechanisms which relate the periodontal disease to atherosclerotic vascular disease, they share multiple risk factors like tobaccouse, diabetes mellitus, and age which are prevalent and promote both the diseases.

Antibody levels against the periodontal pathogen *Porphyromonasgingivalis,* as an indication of a systemic response due to periodontal disease, was associated both to acute myocardial infarction and to the oral health parameters, suggestingthe possibility that this bacteria might be a link between oralhealth and cardiovascular disease. The composite effect of multiple infections determine how chronic infections can predispose to cardiovascular disease, as suggested by Armitage.

It can also be concluded that the endothelial damage by formation of lipid stripes in early childhood may lead to the capture of bacteria of dental plaque origin. These bacteria penetrate into blood circulation after treatment of children as well as of patients with aggressive or chronic periodontitis. Preatheroma and atheroma are usually diagnosed in patients aged 20–30 years-similar to the age which aggressive periodontitis (early onset periodontitis) is diagnosed. Fibroatheroma is diagnosed in patients aged 40 years and over, in the similar age group where periodontitis is diagnosed in more than 50%of patients.

Thus, it could be concluded that circulating microorganisms or their products (HSP) may promote pathogenesis and enhance local inflammatory changes in vessel walls that may promote clotting and clot formation. Dental plague bacteria are one of the risk factors for atherosclerosis development.

Recent intervention trials indicate that periodontal treatment which includes elimation of all the periodontal pathogens, seems to attenuate systemic inflammation and endothelial dysfunction (the first step in the process leading to atherosclerosis).Taken together, data show a dose dependent effect: better periodontal treatment outcomes seem to be associated with more significant changes in the systemic parameters. Periodontitis may contribute to the systemic inflammatory burden and process leading to atherosclerosis in otherwise healthy individuals.

Periodontal health and absence of other oral foci of infection are essential and on some occasions prophylacticantibiotic coverage is required. Safe and effective periodontal management of such patients requires close medical and dental coordination, an understanding of the potential hazards during dental treatment, knowledge of drugs used in treatment of cardiovascular diseases, and the potential adverse effects of drugs commonly used in periodontal practice.

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