I J Pre Clin Dent Res 2014;1(1):26-30
January-March

International Journal of Preventive & Clinical Dental Research

Periodontal Disease and Cardiovascular Diseases: An Intriguing Connection

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Abstract

Advances in science and technology over the last century have greatly expanded our knowledge of the pathogenesis of periodontal diseases. Periodontal disease is an infectious disease, but environmental, physical, social, and host stresses may affect and modify disease expression. Certain systemic conditions clearly may affect the initiation and progression of gingivitis and periodontitis. The relationship between oral infections and cardiovascular disease is well known, particularly with respect to orally derived bacteremias as a source of organisms that infect damaged heart valves causing bacterial endocarditis. There are several genetic and environmental factors which influence the progression of inflammatory periodontitis in response to plaque biofilm, also relevant to associated cardiometabolic disorders in the same subject. This review addresses some common mechanisms in the pathogeneses of periodontitis and cardiometabolic disorders based on regulation of inflammation.

Key Words

Periodontal Disease; Atherosclerosis, Coronary Artery Disease, Ischemic Stroke

INTRODUCTION

The relationship between oral infections and cardiovascular disease is well known, particularly with respect to orally derived bacteremias as a source of organisms that infect damaged heart valves causing bacterial endocarditis. Recently, evidence has emerged relating periodontal infections to coronary artery disease and stroke. Oral infections are related to bacterial endocarditis, coronary artery disease, and stroke.[1,2] Dental and periodontal diseases are common in our population due to lack of proper emphasis on dental hygiene and high incidence of smoking (cigarettes, hukka, bidi) and tobacco chewing. Doctors should be concerned about dental hygiene not only as a cause of caries, tooth loss and periodontal diseases but also because of its association with metabolic syndrome.[1] According to De Stefano *et al.*, patients with periodontitis have a 25% increased risk of coronary heart disease relative to those without it. Periodontal infections are a leading culprit, with studies reporting associations between periodontal disease and CVD.[3]

ORAL INFECTIONS AS A RISK FACTOR FOR ATHEROSCLEROSIS, CORONARY ARTERY DISEASE, AND ISCHEMIC STROKE

Available evidence does allow an interpretation of periodontitis as being a risk factor for atherosclerosis and coronary heart disease. There is now a convincing body of evidence that mechanism of atherosclerosis has a major inflammatory component and it is much more than the simple accumulation of lipids on the vascular walls. Studies have shown that certain other mild bacterial infections consists a major risk factor for stroke in young and middle aged patients.[4] Coronary artery disease is characterized by a thickening of the walls of the coronary arteries due to the buildup of fatty proteins. Blood clots can obstruct normal blood flow, restricting the amount of nutrients and oxygen

required for the heart to function properly. This may lead to heart attacks. Another possibility is that the inflammation caused by periodontal disease increases plaque buildup, which may contribute to swelling of the arteries. The association between periodontitis and CVD may be because of common risk factors such as smoking, diabetes mellitus, aging, male gender and socioeconomic factors, but there is also good evidence of periodontitis being an independent risk factor of CVD.[5] The role of infections in atherosclerosis has been discussed for many years. Recently, evidence has accumulated that certain common oral infections play a significant in role in atherosclerosis. Atherosclerosis lesions can occur in large and medium sized elastic and muscular arteries.[6] They can lead to ischemic lesions of the brain, heart, or extremities and can result in thrombosis and infarction of affected vessels, leading to death. Cardiovascular disease, mostly associated with atherosclerosis, remains one of the primary causes of death in the United States, Europe, and much of Asia. The process, supported by a considerable body of evidence, is that atherosclerosis is an inflammatory disease. This concept, also termed the **Ross response-to-injury hypothesis of atherosclerosis** which proposes that the initial lesion results from injury to the endothelium and leads to a chronic inflammatory process in the artery. This results in the migration of monocytes through the endothelium into the underlying tissue and the proliferation of smooth muscle cells. Activation of the monocytes (macrophages) in the blood vessel leads to the release of hydrolytic enzymes, cytokines, chemokines, and growth factors, which induces further damage, leading to focal necrosis. Accumulation of lipids is a key feature of this process, and in later stages, the atheromatous plaque can be covered with a fibrous cap over the focal necrotic area. At some point, the fibrous cap may become eroded and rupture, which leads to thrombus formation and occlusion of the artery, resulting in an infarction.[7] The initial event in the development of an atheroma appears to be endothelial injury that results in the activation of the endothelial cells. This results in the upregulation of surface adhesin molecules and chemokines, both of which result in monocyte recruitment from the bloodstream (Fig. 1). The monocytes then pass through the endothelium into the blood vessel and become macrophages. The macrophages in the atheroma are activated and produce growth factors, which induce smooth muscle proliferation as well as production of cytokines and other mediators that further activate the endothelium. Macrophages also accumulate lipids, especially low-density lipoproteins (LDL) in the oxidized or modified form. Modified LDL can be a major cause of injury of both the endothelium and the underlying smooth muscle. When the LDL particles are trapped in the artery, they can undergo progressive oxidation and be internalized by macrophages, with formation of lipid peroxidases and accumulation of cholesterol esters. This results in the production of foam cells. Modified LDL is chemotactic for other monocytes and can induce the production of factors from macrophages that expand the inflammatory response.[8,9] Antioxidants can increase the resistance of LDL to oxidation, and this may explain why antioxidants, such as vitamin E, can reduce the size of fatty streaks and atherosclerotic lesions and possibly protect against atheroma formation. Diabetes, through hyperglycemia and glycation of LDL and other proteins, as well as the dyslipidemia associated with diabetes, cigarette smoking, through toxic factors in smoke, and hypertension and hyperhomocystinemia are also factors that can lead to endothelial injury and the subsequent cascade of events leading to atherosclerotic lesions.[10]

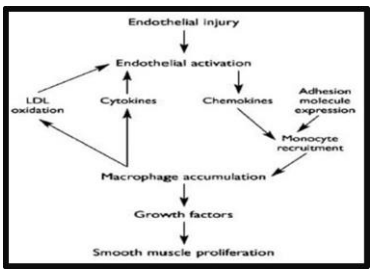

Fig. 1: Mechanism of atherosclerosis resulting from endothelial injury

A fatty streak can become a fibrous plaque, which becomes complex with a lipid core, calcification, and deposition of extracellular matrix protein. Activated T cells may stimulate metalloproteinase production by macrophages, which remodel the fibrotic plaque. Eventually, a uniformly dense fibrous cap can cover the atheroma resulting from deposition and remodeling of the extracellular matrix in the plaque. Through remodeling of the extracellular matrix, the fibrous cap may become thin and rupture, leading to activation of the clotting system with thrombosis. It is thought that thrombosis and subsequent occlusion of the artery may be responsible for as many as one-half of the

cases of acute myocardial infarction.[11] Fig. 2 depicts the intersecting protease cascade that connects the blood clotting system with extracellular matrix deposition and degradation. The extracellular matrix is produced by smooth muscle cells and endothelium and remodeled through degradation with endopeptidases, the matrix metalloproteinases. From Fig. 2 it can be seen that plasminogen is converted to plasmin in the presence of tissue plasmin activator (TPA).

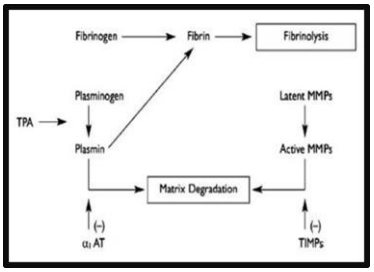

Fig. 2: Intersecting protease cascade that connects the blood clotting system with

Plasmin then activates the latent matrix metalloproteinases, which results in matrix degradation. Tissue inhibitors of matrix metalloproteinases (TIMPs) can inhibit matrix degradation whereas alpha-1-antitrypsin can inhibit plasmin mediated degradation of the extracellular matrix. Plasmin can also result in the production of fibrin from fibrinogen, which then undergoes fibrinolysis. It is likely that inflammatory mediators, such as cytokines and proteases produced by macrophages, and other cells in the atheromatous plaque, as well as bacterial proteases,

contribute to extracellular matrix remodeling of fibrofatty atheromatous plaques through activation at various stages in the protease cascade depicted in Fig. 2.

DIRECT EFFECTS OF INFECTIOUS AGENTS IN ATHEROMA FORMATION

There are three lines of evidence suggesting that periodontal bacteria may have direct effects on atheroma formation. The first comes from studies finding *Porpbyromonus gingivulis* in carotid and coronary heromas. The second comes from the findings of Deshpande and colleagues showing in vitro that *P gingivulis* invade and may proliferate in the endothelial cells. The third line of evidence comes from studies by Herzberg and Meyer showing that *P gingivulis* is able to induce aggregation of platelets, which is thought to be associated with thrombus formation. Other possible mechanisms include protease production by *P gingivulis* and other periodontal pathogens, which may contribute to remodeling of the extracellular matrix in atheromatous plaques. Evidence for any of these mechanisms is, at this point, in vitro or preliminary. However, it is not unreasonable to expect that organisms that infect atheromatous plaques may contribute to their formation or to the thrombotic events associated with myocardial infarction.[14]

INDIRECT OR HOST-MEDIATED EFFECTS TRIGGERED BY INFECTION

One possible mechanism that has garnered considerable support is that periodontitis induces an inflammatory response that is manifested, in part, by the production of acute-phase proteins, such as C-reactive protein and fibrinogen, by the liver. C-reactive protein and fibrinogen are independent risk factors for coronary artery disease. A recent study by Wu and colleagues using the NHANES III database, found that C-reactive protein and plasma fibrinogen were related to poor periodontal health, which provides support for this hypothesis. Another indirect effect of periodontal infection that may explain the association between periodontal disease and heart disease is that periodontal organisms contain proteins which cross-react with the heart. In fact, the heat-shock protein-60, which is produced by *Bucteroidesforytbus* and *P gingivulis*, has about 60% homology with the mammalian heat-shock protein. It is known that antibodies to the heat-shock protein are found in patients with periodontal disease. It is conceivable then that these antibodies to heat-shock proteins of periodontal bacteria are cross-reactive with the heat-shock protein that is exposed in an injured endothelium or atheromatous plaque. This could set in motion autoimmune phenomena and contribute to atheroma formation.[1]

COMMON GENETIC PREDISPOSITION FOR PERIODONTAL DISEASE AND ATHEROSCLEROSIS

There may be common genetic mechanisms which provide the link between periodontal disease and cardiovascular disease. Beck and colleagues have provided a model proposing that there is a genetically determined hyperinflammatory macrophage phenotype in periodontal disease, which contributes to the susceptibility for atherosclerosis.[15]

COMMON RISK FACTORS AFFECTING BOTH PERIODONTAL DISEASE AND HEART DISEASE

DeStefano and colleagues found that periodontal disease and poor oral hygiene are stronger

indicators of risk of total mortality and of coronary heart disease. They suggest that oral hygiene may be an indicator or a surrogate for lifestyle affecting personal hygiene and health care and might explain the relationship between periodontal disease and heart disease. Multiple studies showing the relationship between periodontal disease and heart disease, after adjusting for many factors associated with lifestyle, such as smoking and overweight, suggest that the relationship is not simply explained by lifestyle. Also, the finding that the graded exposure of periodontal disease leads to an increased cumulative index of coronary heart disease argues against lifestyle as a simple explanation for this association. The association between periodontal disease and cardiovascular disease or stroke could be due to residual confounders or incomplete control of confounders. As with most studies that adjust for possible confounders, the adjustments may not be complete, so associations of this magnitude may be due to residual confounders. Perhaps new studies with more detailed adjustments for confounders will clarify this issue. In fact, there are two studies in progress, supported by the National Institutes of Health (NIH), which may help resolve this issue. Further research will be needed to determine which, and to what extent, factors act singly or in concert to contribute to the formation of atheromatous plaques. It is important to know the mechanisms, however, since they add evidence to support the association between periodontal infection and atherosclerosis. In addition, knowing the mechanisms may well lead to simple, cost-effective interventions that would moderate, in part, the contribution of infection to atherosclerosis.[1]

MANAGEMENT OF PERIODONTAL DISEASE IN PATIENTS AT HIGH RISK FOR ATHEROSCLEROSIS [16-19]

Since there is mounting evidence relating periodontal infections to atherosclerosis, it is reasonable that patients with periodontal disease who are at risk for atherosclerotic disease should be managed in the following manner:

1. Patients at high risk for atherosclerotic disease should be subjected to a complete periodontal examination.
2. Patients that have periodontal disease should have a thorough medical history evaluating systemic conditions, medications, and risk factors for atherosclerosis and related conditions such as heart disease and stroke.
3. Treatment of patients with periodontal disease and pre-existing atherosclerotic disease, such as stroke, nonfatal myocardial infarction, and atherosclerosis in general, should be coordinated among health professionals to ensure that patients are adequately managed taking into account medical as well as dental considerations and complications.
4. Aggressive prevention of periodontal disease should be undertaken in patients at high risk for atherosclerotic disease. If periodontal disease exists in these high-risk patients, comprehensive treatment should be instituted to eradicate, as much as possible, the periodontal infection and prevent its recurrence.
5. Patients should be made completely aware of the possible relationship between heart disease, stroke, and periodontal disease, without unduly alarming them, so that they may participate in the modification of risk factors for both artherosclerosis and periodontal disease.

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