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MINIREVIEWS

Relationship between periodontitis and cardiovascular diseases: A literature review

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Abstract

Periodontitis and cardiovascular disease have a complex etiology and genetics and share some common risk factors (*i.e.*, smoking, age, diabetes, *etc.*). In recent years, the relationship between periodontal disease and cardiovascular disease has been investigated extensively. This research mostly focused on the fact that periodontitis is an independent risk factor for cardiovascular disease. Our aim in this article is to investigate the etiological relationship between periodontal disease and cardiovascular disease and the mechanisms involved in this association. According to the current literature, it is concluded that there is a strong relationship between these chronic disorders.

Key words: Periodontitis; Cardiovascular disease; Etiological factors; Serum lipids; Chronic inflammation

Core tip: In recent decades, researchers have investigated the relationship between cardiovascular and periodontal disease because they have same risk factors. As a result of this research, a relationship between periodontitis and cardiovascular disease has been found. Inflammation markers, heat shock protein and serum lipid levels have been found to be higher in patients with periodontal and cardiovascular disease. Therefore, we investigated previous publications and aim to add a new point of view to the literature.

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INTRODUCTION

The relationship between oral and systemic diseases has been discussed frequently in recent years. In many studies, this relationship was focused mainly on periodontal diseases[1,2]. Cardiovascular diseases rank first among the causes of death in developed countries. About 7 million people die from conditions caused by cardiovascular diseases worldwide[3]. Several factors are defined among the causes of cardiovascular diseases; however, a significant portion of these can not be described with traditional risk factors.

It was reported recently that chronic inflammation plays an important role in cardiovascular disease (CVD) etiology. Periodontitis is a chronic inflammatory disease affecting periodontal tissues. During periodontal disease, several chronic inflammation markers rise. Since it was believed that CVD has an etiological origin, the presence of an etiological relationship between periodontal disease and CVD has been considered for years[4]. Thus, a number of studies on the possibility of periodontal disease causing CVD were carried out[5,6] and a relationship between periodontal disease and CVD was established[7,8]. Periodontal pathogens were associated with atherosclerosis[9,10] and coronary heart disease in seroepidemiological

studies[11]. Our aim in this study is to review the research on the relationship between periodontal disease and CVD in the light of the current literature. Therefore, we surveyed a large number of references (126 units) and investigated the Ataturk University database.

Periodontal diseases

Periodontal diseases are chronic diseases that occur as a consequence of interaction between bacteria and host, leading to inflammation and damage in the hard and soft supporting tissues of the tooth[7,12]. According to the World Health Organization reports, periodontal diseases are the most common illnesses in society. In order to diagnose periodontal diseases correctly, clinical measurements such as probing pocket depth and attachment level and radiological analyses are necessary. The primary etiological agent for the disease is dental plaque which consists of approximately $1\text{-}2\times10^{11}$ bacteria/g and is placed over the tooth or around the gingiva. It is reported that oral microbiological flora consists of more than 600 bacterial species[13]. This biofilm that accumulates on the surface of the tooth causes local gingivitis characterized by erythema, edema and bleeding. If dental biofilm can not be removed and if it reaches a sufficient size and complexity, disease that starts as gingivitis transforms into periodontitis, which is a stabilized lesion and causes damaging chronic infections in supporting periodontal tissues.

Chronic periodontitis is the most common periodontal disease associated with systemic diseases. Although approximately 50% of the adult population over the age of 50 have periodontitis, the damaging effect of this inflammatory process displays individual variations[14,15]. Demmer and Papapanou reported that the incidence of chronic periodontitis varies between 8% to 31%[16]. The aggressive form is characterized by rapid damage in periodontal tissues in early ages. Although the incidence of aggressive periodontitis is below 5%, it can vary among societies[17,18]. The most important clinical finding of chronic periodontitis is an increase in periodontal pocket depth. Pocket formation and ulceration of pocket epithelium leads to formation of an ecological environment in which anaerobic and facultative gram negative bacteria can survive, including *Porphyromonas gingivalis* (*P. gingivalis*), *Prevotella intermedia* (*P. intermedia*) and *Aggregatibacter actinomycetemcomitans* (*A. actinomycetemcomitans*).

Damage in periodontal tissues occurs in response to various toxic products released from specific subgingival plaque bacteria, as well as bacterial plaque and its byproducts. The most important mediators released by host tissue are interleukin-1B (IL-1B), tumor necrosis factor-α (TNF-α) and IL-6 and these markers and various serum markers triggered by these markers [such as C-reactive protein (CRP)] are reported to be closely associated with CVD.

PERIODONTITIS AND CVD

Complex genetic and environmental factors cause cardiovascular diseases such as atherosclerosis and myocardial infarction[19]. Genetic factors include age, obesity, diabetes and hypertension. Environmental factors include smoking, diet, socio-economic status and exercise. Smoking, hypercholesterolemia and hypertension, classic risk factors, exist in one-third to two-thirds of cases[20]. It is believed that genetic factors play a role in approximately half of the cases with periodontitis[21]. Research suggests that inflammation plays an important role in the pathogenesis of both diseases. Elevation of systemic markers is considered among the risk factors for CVD[22]. In studies done by various groups, the importance of varying inflammatory responses in individuals who are prone to both periodontal disease and the aggressive form is demonstrated[23]. Therefore, periodontal disease is associated with an increase in systemic inflammation[24,25]. The ability of periodontal disease to induce CVD in individuals depends on the amount of gram negative species, detectability of proinflammatory levels, composition of immune or inflammatory infiltration and the high association of peripheral fibrinogen and amount of white blood cells[26]. There are various opinions on periodontal disease inducing cardiovascular disease through the direct or indirect effects of oral bacteria. At first, bacteria such as *Streptococcus sanguinis* (*S. sanguis*) and *P. gingivalis* induce platelet aggregation and lead to thrombus formation[27]. *S. sanguis* caused myocardial infarction when injected in rabbits. Presumably, antibodies against periodontal organisms are localized in the heart and a series of events caused by synthesized T cells induce complement activation and trigger a heart attack[27]. In individuals with severe periodontitis, one or more periodontal pathogen was found within atheromas[28].

The second mechanism is the exaggerated host response of proinflammatory mediators, such as PGE2, TNF-α and IL-1β, reflecting lipopolysaccharide (LPS) or microbial changes[29]. These mediators are related to differences of T cell receptors among the individuals and secretory capacities of monocytes. Usually, peripheral blood monocytes secreted from individuals with a hyperinflammatory monocyte phenotype are 3-10 times more than those with a normal monocyte phenotype[29]. Genes that regulate T cell monocyte response and host-microbe environment can directly trigger and regulate the inflammatory response. A hyperinflammatory monocyte phenotype is seen in individuals with periodontal disease[29,30].

The third mechanism could be the relationship between bacterial and inflammatory products of periodontitis and cardiovascular disease. LPS released by periodontal bacteria can cause bacteremia by passing through serum or bacterial invasion can directly affect endothelium, inducing atherosclerosis[31]. LPS can lead to accumulation of inflammatory cells on major blood vessels and can also stimulate degeneration of vascular muscle, vascular lipid and intravascular coagulation and proliferation of blood thrombocyte function. These changes occur due to activation of biological mediators in smooth muscle, such as PGs, ILs and TNF-α[32,33]. In addition, it was shown that

the presence of LPS increases the sensitivity of endothelial cells against *P. gingivalis* [34]. Ghorbani *et al*[35] reported that an increase was observed in the contractility of coronary arteries accompanied by endothelial dysfunction with LPS originating from *P. gingivalis*. Fibrinogen and WBC count increases noted in patients with periodontitis may be a secondary effect of the above mechanisms or a constitutive feature of those at risk for both cardiovascular disease and periodontitis[36].

BACTERIA

According to general consensus, pathogens considered for periodontal disease are gram negative bacteria, which include *A. actinomycetemcomitans*, *P. gingivalis*, *P. intermedia*, *Tannerella forsythia* (*T. forsythia*) and *Treponema denticola* (*T. denticola*). Periodontal pathogen densities in the subgingival biofilm samples, intima and media thickness of carotid artery[37] were reported as risk factors for CVD incidence[38] and MI[39]. These etiological bacteria obtained from the subgingival samples through various methods were associated with atherosclerosis[38-41].

In a study on *P. gingivalis*, it was shown that *P. gingivalis* invaded and adhered to cardiac endothelial cells in fetal bovine, bovine aortic endothelial cells and human umbilical vein endothelial cells[42]. The effects of invasion were 0.1%, 0.2% and 0.3% for bovine aortic endothelial cells, human umbilical vein endothelial cells and fetal bovine cardiac endothelial cells, respectively. It was reported that atherosclerotic lesions develop in the aorta by injecting *P. gingivalis* in mice[43]. In a study on *gingipain R.*, a proteolytic enzyme released by *P. gingivalis*, it was shown that *gingipain R.* can activate Factor X, prothrombin and protein C and enhance thrombotic tendency, platelet aggregation, transformation of fibrinogen to fibrin and formation of an intravascular clot. It was also shown that there is an association between *gingivalis* and *Prevotella nigrescens* and increase in intima-media thickness[41]. In studies, the relationship between *P. gingivalis* and *A. actinomycetemcomitans* was demonstrated[28,44,45]. Spahr *et al*[38] and Andriankaja *et al*[39] reported a relationship between *Aggregatibacter actinomycetemcomitans* and periodontal pathogen density. Kati Hyvärinen *et al*[46] showed that the relationship between a 10-fold increase in *A. actinomycetemcomitans* in saliva and stable coronary arterial disease and acute coronary disease was consistent with the study done by Spahr *et al*[38]. In this study[13], IgA levels against *A. actinomycetemcomitans* were found to be higher in individuals with acute coronary disease compared to those with no cardiovascular disease. When *A. actinomycetemcomitans* was incubated with whole blood cells, the surface materials of *A. actinomycetemcomitans* increase the release of various proinflammatory cytokines, such as IL-6 and TNF-α[35], and this can demonstrate that, besides survival of bacteria in various human tissues, broken bacterial fragments can lead to proinflammatory effects. Mäntylä *et al*[13] reported that *A. Actinomycetemcomitans* is not a specific agent for only periodontitis, but *P. gingivalis*, *T. forsythia* and *T. denticola* (red complex) are also not specific for CVD. In a study on *streptococcus mutans*, it was demonstrated that this bacteria can pass into human endothelial cells and can survive there[47]. A relationship between *P. intermedia* and *T. forsythia* with non-fatal MI was shown[39]. In their 2007 study, Nonnenmacher *et al*[40] reported that the amount of subgingival *P. intermedia* is higher in individuals with CVD compared to a control group.

SYSTEMIC MEDIATORS OF INFLAMMATION

Periodontal inflammation is reported to be associated with increase in systemic inflammation markers[2,48-50]. CRP is a plasma protein synthesized by the liver in response to inflammation. Its basic function is thought to be activating the complement system. Plasma levels of CRP in humans shows a rapid increase as a result of acute inflammation and this increase reaches up to 1000-fold. The reason for this rapid increase is enhancement of these proteins by hepatocytes that are stimulated by various cytokines, especially IL-6[51].

The effect of CRP on cells occurs through various mechanisms such as binding of many ligands together[52]. These cells contribute to the formation of atheroma by releasing nitric oxide (which is increased in periodontal disease)[53]. IL-6 is generally released from macrophages, monocytes, T cells and fibroblasts and they are basic activators of acute phase response. IL-6 increases synthesis and release of acute phase proteins, such as CRP, β-fibrinogen, amyloid A, C3 complement component and ceruloplasmin[54]. In a study on IL-6, healthy individuals were followed for 6 years and during this period, IL-6 levels were higher in patients who had an MI compared to those who did not have an MI[55]. This indicates that the level of IL-6 is a predictable risk factor for future MIs in healthy individuals. It was reported in several studies that periodontitis leads to an increase in serum IL-6 levels[2,56]. Higashi *et al*[57] found that the IL-6 level was higher in individuals who had coronary artery disease accompanied by periodontitis compared to those who only had coronary heart disease. TNF-α, however, is a cytokine that plays a modulator-like role in both the immune system and in bone resorption and formation through extracellular matrix catabolism and proliferation and differentiation of osteoclast progenitors[58]. TNF-α is released by lymphocytes, macrophages, T cells and other cells. It is reported that TNF-α and IL-6 can result in significant systemic effects and play a role in pathogenesis of CVD[59,60]. Several studies report that TNF-α induces and advances coronary artery disease[61,62]. TNF-α levels were found to be higher in patients with periodontitis[63]. A correlation between an increase in TNF-α and periodontitis and peripheral arterial disease was also reported[64].

Elevation of the CRP level is suggested as a risk factor for atherosclerotic complications. It can also be a sign for coronary heart disease and be useful in detecting acute myocardial infarction and cerebrovascular accidents[65-67].

In studies carried on healthy individuals, it was stated that plasma CRP concentration is a risk indicator for a future MI and stroke. In two prospective cohort studies in which CRP level was evaluated, CRP levels were measured in healthy individuals who were followed for a long period and an evaluation was done on whether or not future vascular incidents increased. CRP levels were higher in individuals who had experienced MI and stroke compared to those who had not[68,69]. CRP levels were found to be higher in individuals with chronic periodontitis compared to those with no chronic periodontitis[70]. In another study, CRP levels were higher in individuals with advanced periodontitis compared to those with moderate degree periodontitis and CRP levels in both groups were higher than the control group[2]. In a study, the relationship between CRP and CVD was evaluated and for this goal, individuals with no periodontal disease or CVD were compared to those who have one or both of these diseases. CRP level was about 8 times higher in individuals who have both of these diseases compared to the control group[71]. In some clinical studies, serum levels of CRP and other inflammatory markers following periodontal treatment decreased[72,73]. Aggressive periodontitis is related to change in serum components consistent with the acute phase response and an increase in circulating IL-6 and CRP levels[74]. However, critical levels of CRP show differences among societies. In a study, serum CRP levels were found to be higher in western societies compared to Japanese society. Critical levels of CRP are considered as > 1 mg/L for CVD in Japan[75], while this value is > 2 mg/L for western societies.

SERUM LIPID LEVEL

Hyperlipidemia is characterized by an increase in total serum cholesterol and triglyceride levels due to changes in lipid metabolism[76]. Triglycerides are formed by esterizing one fatty acid with 3 hydroxyl groups and they constitute majority of body fat. Cholesterol, however, is a steroid found mainly in animal tissues and plays an important role in the pathogenesis of atheroma in arteries. Low density lipoprotein (LDL) consists of both fat and protein and provides transportation of cholesterol from the liver to other tissues. High density lipoprotein (HDL) also consists of protein and fat and plays a role in excretion of cholesterol from the liver to gall bladder[77]. It is believed that hyperlipidemia is a risk factor for CVD[78]. LDL, generally taken with animal fats, leads to atherogenesis through lipid oxidation and accumulation of lipid products on arterial walls. Increase in serum lipid levels is an independent risk factor for cardiovascular disease and atherosclerosis. In order to prevent atherosclerotic CVD, daily fat intake is restricted and pharmacological measurements are performed to control a low serum level of LDL. Patients with low LDL are at an advantage in terms of cardiovascular disease. People who have 20% of normal LDL levels during childhood were shown to have a decrease of 88% of developing CVD[79]. Lipid lowering statins are given to individuals aged from 50-70 years in cardiology and the risk of giving statins decreases by 25% in these individuals. This explains that LDL is an atherogenic lipoprotein. The relationship between serum lipid level and periodontal status was also reported in a study[80]. It was shown that periodontitis increases plasma cholesterol level by 8%. HDL is an antiatherogenic lipoprotein because it has no direct effect on circulating LPS and protects LDL against oxidation. The impact of periodontitis is associated with an increase in atherosclerosis by lowering the antiatherogenic effect of HDL. In a study, HDL level in individuals with periodontitis was low and returned to normal range with periodontal treatment[81]. LDL level was higher in individuals who had deep periodontal pockets[82]. Montebugnoli *et al*[83] found that oxidized LDL levels showed a decrease within 3 mo following periodontal treatment. Oxidative modification of LDL is a critical phase for initiation of atherosclerosis and its advancement and it was demonstrated that high levels of circulating oxidized LDL increased the risk of CVD[84,85]. Lowering LDL following periodontal treatment shows the relationship between periodontitis and oxidized LDL. Machado *et al*[86] demonstrated a positive relationship between triglyceride, total cholesterol and LDL with tooth loss and a negative relationship between HDL and tooth loss. In two randomized controlled studies, it was shown that LDL and total cholesterol decreased following periodontal treatment[87,88]. In a study done in Japan[89], serum lipoprotein levels were measured before and after periodontal treatment and HDL levels were found to be lower in individuals with cardiovascular disease. Although the correlation between periodontitis and lipid levels is not fully known, it is believed that periodontal bacteria and products of these bacteria join the circulation and activate the immune response, changing serum lipid and proinflammatory cytokine levels[90,91].

HEAT SHOCK PROTEIN

Heat shock proteins have a high molecular resemblance with each other[26] and are rather immunological[92]. Heat shock proteins are crucial for continuity of cellular function. They can also play a role such as a virulence factor against certain bacteria species[93]. Cells excrete Hsp60 as they are exposed to impacts such as trauma and oxidative stress. Cross reaction between bacterial heat shock protein in endothelial cells (GroEL) and human heat shock protein 60 (Hsp60) leads to endothelial dysfunction and atherogenesis[94,95]. *Mycobacterium tuberculosis*, *Chlamydia pneumoniae*, *Helicobacter pylori* and *Escherichia coli* originated immune responses against HSPs are associated with CVD[96,97]. However, GroEL has been identified as a periodontal pathogen[98]. In other studies, the presence of Hsp60 and GroEL-specific T cells and cross reaction were demonstrated in peripheral blood of atherosclerotic patients[99,100]. The relationship between heat shock protein 65 (Hsp65) and CVD with host response is shown[101-104]. In one of these studies[104], a relationship between serum

antibody level against Hsp65 and CVD was detected. The authors claim that bacterial infection stimulates antibody formation against Hsp65. It is shown that chronic periodontal infection increases Hsp65 level in individuals with a high risk of cardiovascular disease[105]. Leishman *et al*[106] found that anti-hHsp antibody level is higher in individuals who have inadequate oral hygiene and in patients with CVD and intense periodontal infection.

DISCUSSION

Although there are some studies claiming that no relationship exists between periodontitis and cardiovascular disease[32,107,108], the majority of studies suggest that there is a relationship between periodontitis and cardiovascular disease. Dental procedures and oral infections are predicted as epidemiological criteria for causes of endocarditis[109,110]. Since most of these studies were done in various geographical regions and various societies, confusing factors such as smoking, alcohol consumption and socioeconomic status were removed in many epidemiological studies.

There are 3 possible mechanisms in which oral infections are associated with periodontitis: direct impact of microorganisms on atheroma formation in endothelium; indirect host mediated response; and genetic tendency for pathogenesis. Bacterial DNA that was defined in atheroma plaques support that periodontal pathogens can play a role in the pathogenesis of cardiovascular diseases[111,112]. The relationship between tooth brushing and cardiovascular disease was also reported[113-115]. In many studies, it was shown that periodontitis is a risk for bacteremia[9,116,117]. Periodontitis can initiate and worsen atherosclerosis since it enhances systemic inflammation markers such as CRP and fibrinogen. It was reported in studies that treatment of periodontitis decreased markers such as CRP, TNF-α, and IL-1β that are thought to initiate cardiovascular disease.

CONCLUSION

These findings obtained from the literature usually support the relationship between periodontitis and CVD. There are still some questions waiting to be answered: (1) Is periodontitis really an independent risk factor for CVD; and (2) If so, what is the mechanism? It is hoped that answers to these questions can be found with future studies. Thus, together with an increase in patient quality of life through periodontal treatment, perhaps the incidence of CVD, which has a high risk of death, would decrease.

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