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Periodontitis and the Risk of Cardiovascular Disease. "Periodontium, A Bacterial Highway To The Heart"

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Abstract
Periodontitis and cardiovascular disease have an association as there are a couple of common etiological factors between the two. There have been an extensive investigation in the recent years on the relationship between periodontitis and cardiovascular disease. This research mostly focused on the fact that periodontitis is an independent risk factor for cardiovascular disease(CVD). This article reviews the association between periodontitis and CVD. In addition, the potential mechanisms of any association between periodontitis and CVD as well as the effects of periodontal treatment on CVD are discussed. As periodontitis and cardiovascular disease have common risk factors researchers have investigated the relationship between the two in the recent decades. As a result of these research, a relationship between periodontitis and cardiovascular disease has been found. Our aim in this article is to investigate the etiological relationship between periodontal disease and cardiovascular disease and the mechanisms involved in this association.

Keywords: *Periodontal disease(PD),Cardiovascular disease(CVD),Atherosclerotic cardiovascular diseases(ASCVD),Coronary atherosclerotic burden(CAB),Lipopolysaccharide (LPS).*

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I. Introduction

Steven Offenbacher was considered the father of "periodontal medicine", he was a brilliant scientist and was one of the giants in periodontology. Epidemiological studies have established that periodontitis is a risk factor for cardiovascular diseases[1], lung diseases[2], renal diseases[3], and low birth weight in children.[4] Accordingly, it may be assumed that dental plaque bacteria not only influence the oral cavity locally, but may also contribute to the development of some serious systemic diseases. Periodontal disease has been related to coronary heart disease (CHD). A chronic inflammatory periodontal disease that results in breakdown of bone that surrounds teeth, may be associated with increases risk for myocardial infarction (MI). Both the chronic low-level bacteremia that occurs with brushing or chewing and the elevation of inflammatory mediators in response

to bacterial biofilm growing on teeth have been suggested the possible causal pathways for increased risk of MI.[5] A lot of evidence has been generated about the relationship between periodontal disease(PD) and the occurrence of non-infectious systemic diseases like rheumatoid arthritis (RA)[6], and atherosclerotic cardiovascular diseases (ASCVD) such as ischaemic heart disease (IHD)[7], cerebrovascular disease (CBVD)[8], peripheral artery disease (PAD)[9], heart failure (HF)[10] and atrial fibrillation[11]. Coronary atherosclerotic burden (CAB) is a term used to describe the extension of atherosclerosis into coronary vessels. Poor oral health is a major cause of a pro-inflammatory state and may accelerate the atherosclerotic process or precipitate a plaque rupture. Poor oral health may also affect eating behaviour and contribute to poor nutrition, which has been identified as a risk factor for mortality.

Relationship Between Periodontal Disease and Cardiovascular Disease

Although periodontal inflammation has been associated for more than 20 years with a greater incidence of cardiovascular events[12], some issues have been raised about the validity of the evidence suggesting such association. Both periodontal disease(PD) and Atherosclerotic cardiovascular diseases(ASCVD) share an important number of risk factors. Also, both diseases are multifactorial in nature. The presence of multiple shared risk factors has been one of the main limitations of the studies suggesting this association, which have been in the majority, observational. Despite this, through the years, evidence continues to accumulate, with an important part of it suggesting an association[13]. Multiple mechanisms have been suggested as possible links between PD and ASCVD; systemic inflammation, molecular mimicry and direct vascular injury mediated by pathogens are the most important[13].

Evidence from intervention studies

In 1989, two Scandinavian reports revived a century-old hypothesis relating chronic infections with vascular disease that originally was proposed by French and German scientists.[14]Mattila and colleagues[15] found higher combined levels of caries, periodontitis, periapical lesions and pericoronitis (all serving as surrogate markers of oral infections) more frequently in patients with recent myocardial infarction than in healthy control patients from the same population. Syrjanen and colleagues[16] observed relatively poor oral health among patients who had experienced a recent stroke compared with control patients who had not experienced stroke. These authors drew careful conclusions, primarily because of the substantial overlap noted between risk factors for both periodontal disease and CVD—being older, being male, cigarette smoking, diabetes and low socioeconomic status. If periodontal disease and CVD simply share common risk factors, a correlation between the two would be expected even if a causal link did not exist. This epidemiologic phenomenon is referred to as "confounding." These studies enrolled patients when they came to a hospital with a heart attack or stroke, which meant that measures of oral health were taken after the cardiovascular event had occurred, raising the possibility that the cardiovascular event might have influenced oral health negatively. The geographical homogeneity and small number of participants enrolled in these studies precluded any reliable generalizations beyond the specific study population. Subsequently, studies addressing many of these limitations have made substantial contributions to our understanding of periodontal disease and CVD associations.

Cross- sectional data of The Scottish Health Surveys from 1995 to 2003 pertaining 11,869 men and women (mean age of 50 years) were linked to a database of hospital admissions and deaths with follow- up until December 2007 (Information Services Division, Edinburgh) (de Oliveira et al., 2010). Participants who brushed less than once a day exhibited the highest incidence of ACVD events (Hazard Ratios(HR) = 1.7, 95% Confidence Intervals(CI) [1.3; 2.3]) compared with those who brushed twice a day, indicating that self- performed oral hygiene routines may reduce the incidence of ACVD.[17]

A retrospective nationwide, population- based study in Taiwan, including 511,630 participants with periodontitis and 208,713 controls, used the Longitudinal Health Insurance Database 2000 to estimate the incidence rate of ACVD events from 2000 to 2015 (Lee et al., 2015). The hazard ratio for acute myocardial infarction was reduced more in the group of periodontitis patients who received dental prophylaxis (HR = 0.90, 95% CI [0.86; 0.95]) than intensive treatment (including gingival curettage, scaling and root planing, and/or periodontal flap operation and/or tooth extraction) (HR = 1.09, 95% CI [1.03; 1.15]). Consistent reductions in the incidence rate of ischaemic stroke were observed in both the dental prophylaxis (HR = 0.78, 95% CI [0.75; 0.91]) and intensive treatment groups (HR = 0.95, 95% CI [0.91; 0.99]).[18]

Consistent observational evidence suggests that several oral health interventions including self- performed oral hygiene habits (toothbrushing) (two studies (de Oliveira, Watt, and Hamer, 2010; Park et al., 2019)), dental prophylaxis (one study Lee, Hu, Chou, and Chu, 2015)[18], increased self- reported dental visits (one study (Sen et al., 2018)) and periodontal treatment (three studies (Holmlund, Lampa, and Lind, 2017; Lee et al., 2015; Park et al., 2019))produced a reduction in the incidence of Atherosclerotic Cardiovascular Disease(ACVD) events.

A cohort of 8,999 patients with periodontitis who received a complete (non- surgical and if needed surgical) periodontal treatment protocol was followed between 1979 and 2012 (Holmlund et al., 2017). During

the study follow- up, poor responders to the periodontal treatment had an increased incidence of ACVD events (incidence rate –IR = 1.28, 95% CI [1.07; 1.53]) compared with good responders, suggesting that successful periodontal treatment could reduce the incidence of ACVD events.[19]

In the Atherosclerosis Risk in Communities (ARIC) study including 6,736 participants followed during 15 years, self reported regular dental care users had a lower risk for ischaemic stroke (HR = 0.77, 95% CI [0.63; 0.94]) compared with episodic care users (Sen et al., 2018).[20]

A study was done between December 2017 to June 2018 by Boyapati et al. in India, 70 individuals diagnosed with coronary artery diseases, 32 patients with chronic periodontitis constituted the test group, 31 without chronic periodontitis constituted the control group. Cardiac-biomarkers analyzed were Troponin T, Troponin I, Myoglobin; low density lipoprotein (LDL), high-density lipoprotein, very LDL (VLDL), total cholesterol (TC), and highly sensitive C-reactive protein (Hs-CRP). Periodontal characteristics were drawn from the plaque index (PI) and gingival index, probing depth (PD), clinical attachment loss, and periodontal inflammatory surface area (PISA). Statistical analysis was done in order to separate any association between cardiac biomarkers and clinical parameters of periodontitis, detailed statistical analysis through independent *t*-test and Pearson test of correlation was done and the results were statistically significant with respect to not only PI, PD, and PISA between both the groups ($P < 0.05$), but also between various cardiac parameters of test and control groups ($P < 0.001$). Positive relations were seen in the test group, between cardiac biomarkers such as TC, VLDL, Hs-CRP, and Troponin T with periodontal parameters such as PD and PISA. Therefore, the study reveals, a strong association between periodontitis and diseases of cardiovascular nature, highlighting the need for awareness and timely medical interventions to prevent periodontitis from scaling up and interfering with the risk of cardiovascular problems.[21]

Potential pathogenic mechanisms linking Periodontitis and Cardiovascular diseases

Research suggests that inflammation plays an important role in the pathogenesis of both diseases. Elevation of systemic markers is considered one of the most important risk factors for CVD. 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. Therefore, periodontal disease is associated with an increase in systemic inflammation. 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. 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 Porphyromonasgingivalis (P. gingivalis) induce platelet aggregation and lead to thrombus formation(Figure 1).[22] 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. In individuals with severe periodontitis, one or more periodontal pathogen was found within atheromas.[22]

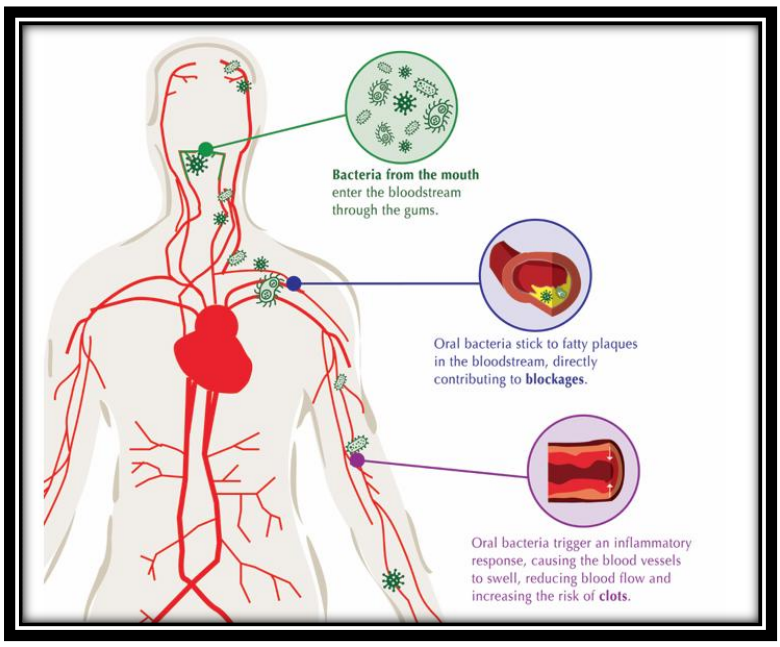

Figure 1: Cardiovascular disease through the direct or indirect effects of oral bacteria.

Another mechanism is the exaggerated host response of proinflammatory mediators, such as Prostaglandin E_2 (PGE2), Tumor necrosis factor alpha (TNFα) andInterleukin-1β (IL-1β), reflecting lipopolysaccharide (LPS) or microbial changes(Figure 2).[23] 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.[23] 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.[23,24]There is also a 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(Figure 2).[25] 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.[26,27] In addition, it was shown that the presence of LPS increases the sensitivity of endothelial cells against P. gingivalis.[28]Ghorbani et al[29] reported that an increase was observed in the contractility of coronary arteries accompanied by endothelial dysfunction with LPS originating from P. gingivalis. Increased fibrinogen and WBC countnoted 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.[30]

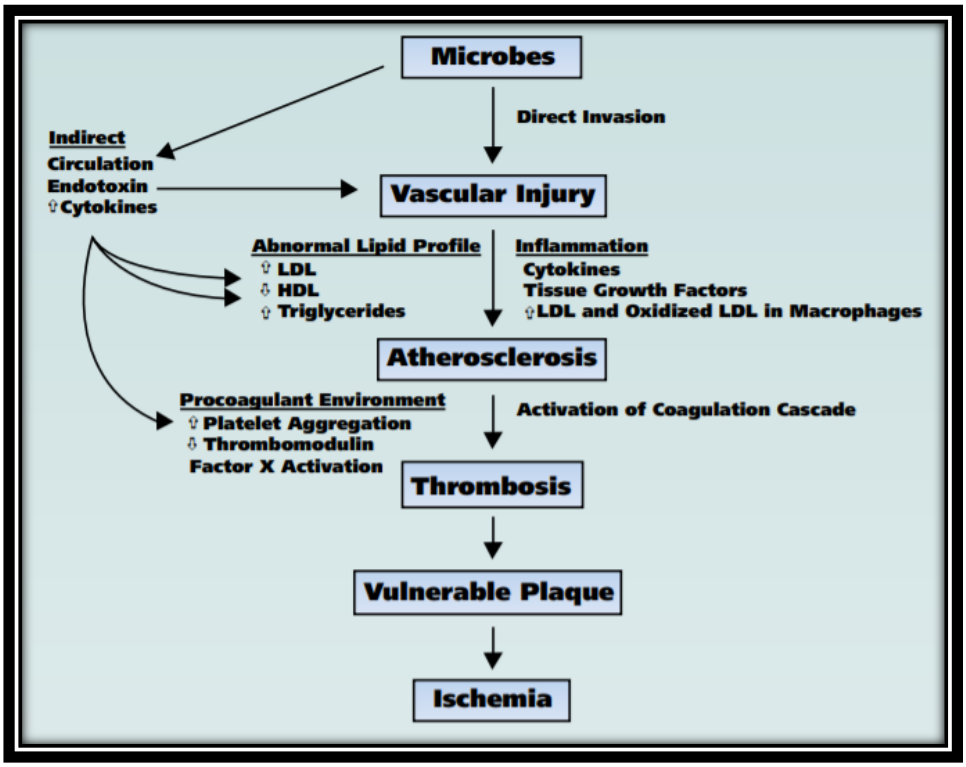

Figure 2: Potential mechanism of infectious agents in atherosclerosis.
[LDL: Low-density lipoprotein; HDL: High-density lipoprotein]

Effects of periodontal treatment on cardiovascular diseases

A 2018 study cited research concluding nonsurgical periodontal treatment reduced serum levels of C-reactive protein (CRP).[31] The article also stated: "This agrees with the results obtained in the meta-analysis performed in the present review, where a decrease in CRP values was noted to be statistically significant when patients were submitted to nonsurgical periodontal treatment in contrast to receiving no treatment at all."high- sensitivity C- reactive protein (hsCRP) has been shown to be the strongest biomarker for predicting cardiovascular events.[32] A meta-analysis of 10 cross-sectional studies showed that CRP in periodontitis patients is elevated in comparison to controls without periodontitis.[31] In addition, the presence of P. gingivalis in periodontitis patients is associated with increased CRP levels, suggesting that the elimination of the periodontopathic bacteria might reduce the serum CRP levels.[33] Available data from pilot studies suggests that periodontal intervention can improve surrogate serum biomarkers and vascular responses associated with CVD.

Results from a meta-analysis indicate that the periodontal treatment could lower the levels of CRP after therapy.[31] Furthermore, a multi-centered randomized control study (the Periodontitis and Vascular Events; PAVE) showed that periodontal treatment can reduce the CRP levels from high to moderate levels in non-obese periodontitis patients.[34] IL-6 is also a marker for identifying patients with unstable coronary artery disease independent of other risk indicators.[35] The patients with plasma levels of IL-6 higher than 5 pg/ml have increased mortality. The plasma IL-6 levels are also different among ethnic groups. The mean levels of IL-6 in Chinese (1.1 pg/ml) are lower than those in African American (1.7 pg/ml), Hispanic (1.7 pg/ml) and non-Hispanic white (1.5 pg/ml). After adjustment for age, gender, ethnicity, smoking, diabetes, hypertension, dyslipidemia and BMI, 1-SD increments in the IL-6 levels are associated with the increased odds for peripheral arterial disease.[36] These results suggest that IL-6 might also be used as a surrogate marker to examine the effect of periodontitis on cardiovascular diseases. Although the data from intervention studies have suggested that the values of serum markers of inflammation may significantly decrease after periodontal treatment, they were increased immediately after periodontal therapy.[37] Whether such increases in values suggest serious adverse events remains unknown. Full-mouth disinfection was introduced as a method to suppress periodontopathic bacteria by completing the scaling and root planning (SRP) in a short period of time (within 24 h). Full-mouth disinfection is based on the hypothesis that conventional quadrant-wise SRP might cause re-infection of the treated sites from the un-treated quadrants. There are clinical benefits of single-visit full mouth mechanical debridement (FMD) over quadrant-wise mechanical debridement (QMD). Furthermore, the effects of the treatments on the levels of serum IL-6 and CRP were examined.[38] A transient increase of serum IL-6 is observed in both treatment groups, and it is higher in the FMD group than in the QMD group. The mean CRP levels are increased in the FMD group and decreased in the QMD group at 1 month after treatment, although the difference between the two groups is not statistically significant. These results suggest a potential effect of periodontal treatment on systemic inflammation.

II. Discussion

Both periodontitis and CVD are chronic in nature, and those chronic inflammatory conditions may develop over a number of years before the diseases are diagnosed. The contributory effects of periodontitis on cardiovascular disease take place over an extended period of time. Therefore, it may be difficult to reduce future cardiovascular events or symptoms by simply treating periodontal disease at the time when one or both diseases are diagnosed since the damage might have already occurred over the decades and become largely irreversible. Nevertheless, clinicians and patients should recognize the consistent association between periodontal diseases and CVD along with the potential preventive benefits of appropriate periodontal intervention. Further investigations are warranted to determine the benefits of periodontal therapy on the development and progression of CVD.Although there are some studies claiming that no relationship exists between periodontitis and cardiovascular disease[39,40,41], 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.[42,43] 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.Thepossible mechanisms in which oral infections are associated with periodontitis are 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.[44,45] The relationship between tooth brushing and cardiovascular disease was also reported.[46,47,48] In many studies, it was shown that periodontitis is a risk for bacteremia.[49,50] Periodontitis can initiate and worsen atherosclerosis since it enhances systemic inflammatory 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 considered to initiate cardiovascular disease.

III. Conclusion

The potential mechanisms of the association between periodontitis and CVD are not fully understood. However, periodontopathic bacteria and inflammation, are suggested to be the relevant mechanisms which link periodontitis to CVD. Dental plaque bacteria are one of the risk factors for atherosclerosis development. In patients with early inflammatory symptoms in the periodontium, a dental examination should be supplemented with a laboratory examination of cardiovascular markers. Timely therapy of both diseases diminishes the risk of developing initial as well as serious changes at a later time. The effects of periodontal treatment on CVD might be different among the different treatment modalities. Further studies should therefore be conducted to elucidate the effects of periodontal therapy on the prevention of CVD.

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