10.5005/jp-journals-10029-1051

REVIEW ARTICLE

Interrelationship between Periodontitis and Cardiovascular Diseases

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ABSTRACT

Cardiovascular disease (CVD) contributes to a large number of morbidities and mortalities globally. The main cause is due to development of atherosclerosis. Many risk factors have been identified and are treated to improve the disease outcome. Besides traditional risk factors (such as hyperlipidemia, diabetes mellitus and smoking), systemic inflammatory process was found to increase risk of cardiovascular events, as inflammation promotes atherosclerosis. Periodontal disease is a chronic disease of tooth-supporting structure, reported to have a high prevalence worldwide. The earliest step of the disease is bacterial biofilm formation on tooth surface which subsequently triggers host inflammation, both locally and systemically. With chronic inflammatory response, periodontitis can enhance atherosclerosis, and is considered a potential contributive factor for development of CVD. The purpose of this review is to provide information on periodontitis, CVD, an association between these two conditions and current knowledge on the effect of periodontal treatment on improving cardiovascular outcome.

Keywords: Periodontitis, Inflammation, Atherosclerosis, Cardiovascular disease.

How to cite this article: Yooprasert P, Siribamrungwong M. Interrelationship between Periodontitis and Cardiovascular Diseases. J Experiment Dent Sci 2013;2(2):110-117.

Source of support: Nil

Conflict of interest: None declared

INTRODUCTION

Cardiovascular disease (CVD) is a major public health concern as it contributes to a majority of morbidity and mortality worldwide. Various studies in the past 5 decades were conducted for better understanding of the pathogenesis of the diseases in order to improve the treatment outcome. In 1989, correlation between dental diseases and acute myocardial infarction was reported.[1]

Furthermore, periodontal disease (PD) was reported to increase the risk for development of many other systemic diseases, for example, hypertension, diabetes mellitus, osteoporosis, rheumatoid arthritis and chronic kidney diseases.[2-6]

Periodontal Diseases

The PD is a noncommunicable infectious and inflammatory disease of the gum and teeth-supporting tissues, including soft tissue structures and alveolar bone. From a survey done by the World Health Organization (WHO), the periodontal health status was assessed with the community periodontal index (CPI); it reported a high prevalence of PD worldwide. In middle-aged population, the prevalence of mild PD (CPI: 1-2) was around 30 to 50%, 20 to 25% for the moderate form (CPI: 3), and approximately 10 to 15% for severe PD (CPI: 4).[7] Moreover, in elder population and in developing countries with limited access to health education and dental care, the prevalence was higher and patients generally have more serious PD.

Pathophysiology

The disease generally progresses slowly. With inadequate oral hygiene, there is a formation of bacterial plaque (biofilm) on teeth. Various bacteria, *Porphyromonas gingivalis, Treponema denticola, Prevotella intermedia, Tannerella forsythia* and *Aggregatibacter actinomycetemcomitans*, were identified as potential causative organisms with *P. gingivalis* being the most studied and is implicated as a major causative organism. Over time, this bacterial plaque can spread and continue to grow below the gum line, producing local inflammatory response which leads to progressive surrounding tissue destruction. This enables the bacteria to enter the blood circulation and activate the systemic inflammatory response.

Multiple factors can accelerate the inflammatory process of periodontitis. The most important local risk factor is poor oral hygiene. For nonoral risk factors, smoking, diabetes mellitus, obesity, physical inactivity and depression are reported to potentiate risk of periodontitis and its severity.

DIAGNOSIS

Most patients are asymptomatic, similarly if symptoms are presented, they are usually nonspecific. Clinically, PD is categorized into gingivitis and periodontitis. Gingivitis involves only the gum and is manifested by redness, swelling with bleeding that may occur with tooth brushing. It is superficial and relatively harmless, unless in some cases which can advance to periodontitis if left untreated. For periodontitis, which is more severe, gums retract and separate from the teeth creating periodontal pockets (spaces between teeth and gums). It results in loosening and increase tooth mobility, abscess formation, alveolar bone loss and

eventually spontaneous tooth loss. Patients generally have no systemic signs of infection such as fever or leukocytosis.

The diagnosis of PDs is mainly based on physical examination by experienced dentists. Although studies on patient self-reported symptoms showed that the majority of patients could evaluate their periodontal status correctly, but clinical examination is required for better information and treatment planning. Physical findings include evidences of gum inflammation and loss of connective tissue surrounding the teeth. For the assessment, the most greatly used clinical parameter is periodontal pocket probing depth. In addition, other parameters include bleeding on probing, calculus index, clinical attachment level, and number of present teeth; these should be reported to provide a more detail clinical information. Plain radiograph imaging can offer information on alveolar bone loss, reflecting the duration and severity of periodontitis.

TREATMENT

Principle of periodontal therapy focuses on resolution of inflammation and healing of the destructed tissues. Gingivitis can be treated with adequate dental hygiene and supragingival bacterial plaque removal. Patients are encouraged to maintain their oral hygiene to reduce bacterial regrowth. Treatment of chronic periodontitis depends upon the disease severity. Apart from bacterial biofilm removal, antibiotics may be used as an adjunct to control bacterial overgrowth.[8] Topical antibiotic administration such as chlorhexidine mouthwash is recommended for usage in moderate to severe periodontitis. However, patients with other considerable risk factors such as diabetes mellitus, systemic antibiotics may have an advantage over local means.

Another adjunctive treatment includes the administration of host-modulating drugs. Low-dose doxycycline inhibits the matrix metalloproteinase (MMP) enzyme, hence reducing patient's symptoms and progression of the inflammation. The drug is already approved by the US Food and Drug Administration for treatment of periodontitis.[8]

In more advanced periodontitis, patient may necessitate a surgical procedure to gain adequate access for bacterial plaque removal. Tooth extraction is also performed in some cases with a nonviable tooth, either for treatment purpose or prevention against further complication.

Cardiovascular Diseases

CVD is a disorder of the heart or blood vessels. The term usually encompasses coronary heart disease (CHD), congestive heart failure (CHF), cerebrovascular disease (stroke) and peripheral arterial disease (PAD). Atherosclerosis, a formation of atheromatous plaque within the vessel wall, is the major etiology of CVD.

As stated by WHO, CVD is the most common cause of death globally, representing about 30% of mortality. Additionally, it accounts for approximately 10% of global disease burden, measured in a disability-adjusted life year. CVD that has major health impact are CHD and cerebrovascular disease.[9] In the future, with increasing life expectancy, the prevalence of CVD will be higher.

Pathophysiology of Atherosclerosis

Atherosclerosis is an insidious process, beginning with deposition of lipoprotein molecules (mainly low-density lipoprotein: LDL) in the intimal layer of arteries. In the extracellular matrix, these lipoproteins undergo oxidation, releasing bioactive phospholipids that can activate endothelial cells.[10] On their luminal surfaces, activated endothelial cells express adhesion molecules, including intercellular adhesion molecule 1 (ICAM-1), endothelial leukocyte adhesion molecule 1 (ELAM-1), and vascular cell adhesion molecule 1 (VCAM-1). Circulating monocytes and lymphocytes adhere to these surface molecules and in response to chemoattractive stimuli migrate into the intima.[11] This is known as the recruitment process.

Under the influence of macrophage colony stimulating factor (M-CSF) produced in the intimal layer of the arteries, monocytes differentiate to become macrophages. Activation of macrophage is stimulated by binding of surface receptors with oxidized LDL particles, apoptotic cell fragments, stress proteins or bacterial endotoxins. Activated macrophage releases vasoactive agents, reactive oxygen radicals, proteolytic enzymes. It then acts like an antigen-presenting cell (APC), presenting local peptide antigens [e.g. oxidized LDL, heat shock protein 60 (HSP60) and microbial antigen] to T cell, resulting in T-cell activation.[11] Activated macrophage also uptakes modified LDL molecules, leading to accumulation of cholesterol in the cytoplasm and formation of lipid droplets. Thus, the macrophage transforms into a lipid-laden 'foam cell,' characteristic of atherosclerosis.[12]

Foam cells eventually die, leaving a lipid-rich element in the intima. With on-going inflammation, accumulation of lipid occurs, forming a lipid core of atheromatous plaque. Simultaneously, as cytokines and chemokines continue to be released, smooth muscle cells are stimulated and migrate into the intimal layer. They can proliferate and secrete collagen to form a fibrous cap of the atheromatous plaque. The cap acts as a barrier between blood compartment, composing platelet and coagulation factors, and the lipid core, which is abundant in proinflammatory and thrombogenic substances.[13]

Lymphocytes, mainly T cells, migrate through endothelium into the intimal layer with the same mechanism as monocytes. T cells respond to antigen bound to major

histocompatibility complex (MHC) molecules on the surface of APCs and become activated. T-cell activation leads to further inflammation by releasing various cytokines, such as interferon gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and interleukin-1 (IL-1). IFN-γ is considered a major proatherogenic cytokine[11] as it promotes macrophage and endothelial activation with production of adhesion molecules, cytokines, chemokines, free radicals, proteases and coagulation factors. IFN-γ inhibits cell proliferation, cholesterol efflux from macrophage cytoplasm. In addition, it inhibits the ability of smooth muscle cells to secrete collagen required to maintain the integrity of a fibrous cap. Apart from IFN-γ, MMP released from macrophage also attacks on collagen, hence weakens the fibrous cap.[13]

When a fibrous cap ruptures, blood comes into contact with thrombogenic materials in the lipid core, especially tissue factors, and triggers platelet aggregation and thrombin generation. Thrombosis occurs and leads to subsequent arterial occlusion, resulting ischemic signs and symptoms.

Evaluation of Subclinical Atherosclerosis

The established risk factors (traditional risk factors) of atherosclerosis are hyperlipidemia, hypertension, diabetes mellitus, obesity, advanced age and smoking. With approximately 10% of patients have none of the above risk factors; atherosclerosis may develop as a result of chronic systemic inflammation. This inflammation-induced atherosclerosis hypothesis is supported by the increased incidence of atherosclerosis in patients with chronic inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus and chronic infections.[8]

Over the last decade, plenty of studies reported a strong correlation between high level of C-reactive protein (CRP) and development of cardiovascular events. CRP is an acute phase reactant protein produced mainly by the liver in response to IL-6 and TNF-α. In chronic conditions, CRP especially in low level can be detected by the high-sensitivity assay called high-sensitivity CRP (hs-CRP). It facilitates macrophage transformation to foam cell in the presence of oxidized LDL, thereby promoting atherosclerotic plaque formation. The US Centers for Disease Control and Prevention and the American Heart Association have stratified risk for CVD based on hs-CRP level: low risk, <1.0 mg/L; average risk, 1.0 to 3.0 mg/L; high risk, >3.0 mg/L.[14] A recent study stated that rosuvastatin, a LDL lowering agent, significantly reduced the incidence of cardiovascular events in subjects with lower LDL cholesterol level, particularly those who had hs-CRP level more than 2 mg/dl,[15] emphasizing the association between elevated hs-CRP and CVD. Due to its lack of specific correlation with atherosclerosis, there is insufficient evidence to recommend a treatment aimed at reducing hs-CRP as CVD prophylaxis.

Recent studies suggested that endothelial dysfunction precedes obvious atherosclerosis by many years, and is considered as one of the earliest manifestations. Thereby, markers for endothelial dysfunction have been developed to detect individuals with preclinical atherosclerosis that warrant prompt intervention. Novel endothelial biomarkers that are being studied include asymmetric dimethylarginine (ADMA), circulating progenitor cells (CPCs), endothelial progenitor cells (EPCs), circulating endothelial cells (CECs) and endothelial microparticles (MPs). These markers are used to evaluate not only endothelium-dependent vasodilation capacity, but also endothelial cell healing capacity and their role in systemic inflammatory response.[16] However, more information is necessitated before clinical implementation can be recommended.

Flow-mediated dilatation (FMD) is a recently-introduced noninvasive technique for endothelial function evaluation, which is now regarded as the gold-standard method in vascular epidemiology.[16] Studies reported that FMD decreases in subjects with cardiovascular risk factors (diabetes mellitus, hypertension, obesity or smoking) and atherosclerosis,[17] while incremental FMD is observed after lifestyle modification and administration of some drugs (for example, oral hypoglycemic drugs, statins or angiotensin-converting enzyme inhibitors). It is now widely used in clinical trials to assess improvement in brachial artery blood flow after intervention, suggesting better CVD outcome.

Another parameter often used in evaluation of subclinical atherosclerosis is intima media thickness (IMT). It is an arterial intimal layer thickness measurement, which is normally performed at the carotid artery. The carotid IMT, as supported by many studies, correlates well with degree of atherosclerosis of coronary arteries.

Periodontitis and CVDs

In 1989, Mattila et al found that dental health was significantly worse in patients with acute myocardial infarction than controls in the Finnish population.[1] Since then, a growing number of studies have been conducted to assess the association between PD and CVD. The results varied greatly, thus a statistically significant association between the two conditions cannot be supported.[18-23] Possible reasons for the discrepancy among these studies may be due to:

1. Differences in study design, study population, sample sizes and duration of follow-up.
2. Adjustment for confounding factors which are already known to be independent risk factors for CVD.

3. Differences in the definition of PD (in which some studies include gingivitis whilst some do not) and difference in methods used to assess disease severity.
4. Differences in CVD case identification, with most studies focusing on CHD, some on nonhemorrhagic stroke, while only a few included PADs.

However, recent meta-analysis showed significant association between PD and CVD after adjusting for other risk factors such as sex, age, ethnicity, socioeconomic status, obesity, smoking, hypertension, diabetes mellitus and lipid levels. Estimated relative risk varies from 1.14 to 1.75[24-26] and all suggested a significant correlation between these two conditions.

Association between Periodontitis and Atherosclerotic Diseases

An indirect relationship between PD and CVD is that they share common risk factors.[27] Prevalence of PD is higher with cigarette smoking, diabetes mellitus, hypertension, obesity, hyperlipidemia and advancing age. This is the same as the risk for CVD and they are classified as traditional risk factors of atherosclerosis. However, PD still has positive correlation with CVD with a statistical significance after an adjustment for these factors. Thus, recent studies have been focusing on finding the mechanism of this relationship. Many studies demonstrated the relationship between periodontitis and increment of the inflammatory markers (hs-CRP, IL-1, IL-6 and TNF-α)[28,29] and some reported the association between periodontitis and clinical signs and symptoms of CVD as clinical outcomes.[28,30,31]

The concept about infectious induced atherosclerosis is projected. Recently, not only one single organism but multiple organisms together are potential causative agents for development of atherosclerotic diseases. This is called the 'infectious burden concept' but it is not yet established proven.[32]

Multiple mechanisms have been proposed in order to link periodontitis to atherosclerosis. Studies have found that patients with PD (with or without tooth loss) tend to consume more carbohydrates and less fiber, which may lead to hyperlipidemia.[25,33,34] Moreover, with chronic infection and inflammation, lipid metabolism is disturbed and results in increase triglyceride level. Subsequently, these patients are at increased risk for developing CVD.

To date, there are four major biological mechanisms explaining the relationship between PD and CVD. It is believed that these mechanisms act in unison to increase inflammation and together exacerbate atherosclerosis.[35]

1. *Local tissue inflammation*: With inadequate oral hygiene, biofilm starts to form and accumulates on the teeth overtime. Pathogenic bacteria continue to grow within the biofilm and trigger gingival tissue inflammatory response. The gingival endothelium becomes activated and releases proinflammatory cytokines.[36] These cytokines [prostaglandin E2 (PGE_2), TNF-α, IL-1, IL-6, adhesion molecules and MMPs] promote local tissue inflammation, resulting in progressive endothelial dysfunction, recruitment and activation of inflammatory cells (mainly macrophages and lymphocytes), which lead to surrounding periodontal tissue inflammation and destruction. These cytokines also enter the bloodstream, thereby raising the level of circulating inflammatory substances[29] and trigger systemic inflammation. With continuous growth of bacteria, repetitive activation of inflammation occurs, and the host body inevitably encounters high level of inflammatory cytokines and remains in a chronic inflammatory state.

2. *Bacteremia and systemic inflammatory response*: Normally, transient bacteremia state occurs with tooth-brushing and solid food chewing, which causes minor injury to the gingival endothelium. But with noncontinuous endothelial injury and nonvirulent oral flora, host immune response is able to eliminate these bacteria and the bacteremia is resolved spontaneously. With PD, continuous inflammation leads to gingival endothelial dysfunction and results in bacterial invasion into the underlying soft tissue structures, with some manage to enter the blood circulation. These pathogenic bacteria occupy virulence factors [such as fimbriae and lipopolysaccharide (LPS)] which assist them in surviving from the host immunity and able them to trigger more intense inflammatory response at the same time. Fimbriae promote binding of bacteria to the endothelial cells and activate secretion of proinflammatory substances. LPS or endotoxin binds to receptors on the macrophage cell membrane, triggering macrophage activation.[33]

This oral-hematogenous spread of bacteria is thought to be a main cause of periodontitis-related systemic diseases.[37] It is estimated that the exchange surface between biofilms and blood circulation is about 8 cm^2 in moderate PD, and about 15 to 20 cm^2 in severe cases. With advanced disease, it is easier for bacteria to enter the bloodstream. Once bacteremia occurs, these bacteria can attach onto the vessel wall at any sites. They trigger systemic inflammatory response and stimulate atheroma formation through different pathways, directly by their presentation or by their products (e.g. degraded surface material and LPS), which can activate macrophage by binding on cell surface receptors.

Numerous studies have found an association between PD and increased plasma level of inflammatory cytokines and supported this theory. Also, several studies were able to isolate periodontal bacteria from atheroma specimens obtained from endarterectomy or surgical removal of the

plaques; either by positive bacterial culture or by detecting their DNAs.

3. *Immune-mediated mechanism*: Some specific pathogenic bacterial peptides (antigen) may have only minimal differences in molecular structure from the host's proteins, thus the host immune system may not recognize these differences. This phenomenon is known as 'cross-reactivity'. Because of the molecular mimicry between bacterial antigens and the mammalian proteins, the antibody targeted against the bacterial antigen may bind with the host's protein instead, stimulating an inflammatory response. Antibodies against bacterial HSPs (e.g. HSP60-related GroEL) may react with the host's HSP60 on endothelial cells,[36,38] thereby provoking an infection-induced autoimmune contribution to atherosclerosis.

As seen in other chronic inflammatory diseases, hyper-reactive immune response was reported in patients with periodontitis. Some host immunity may response to stimuli by releasing abnormally large amount of proinflammatory mediators. This phenotype is called 'monocytic hyperinflammatory phenotype.' This group of patients tends to have more aggressive PD and is at a higher risk for developing CVD due to exposure to high level of inflammatory cytokines.[36] This hyper-reactive immune also occurs with polymorphonuclear cell type, resulting in excessive release of oxygen radicals and protease enzymes, increase in inflammatory marker levels, and compromise of the antioxidant defenses.[37]

4. *Platelet activation*: Another virulence factor of some periodontal bacteria is gingipain, a cysteine proteinase. Gingipain is a potent agonist for protease-activated receptor (PAR) on platelet cell membrane. Once they bind with the receptor, they trigger platelet activation and aggregation,[39] thereby, initiating the coagulation cascade.

Normally, platelet aggregation results from the binding of plasma factors [such as von Willebrand factor (vWF), fibrinogen and fibronectin] to glycoprotein IIb/IIIa. *In vitro* study showed that *P. gingivalis* can activate platelet aggregation without the requirement of vWF, fibrinogen or fibronectin as a plasma factor, suggesting that *P. gingivalis*-activated platelets may be able to secrete these substances.[40]

Recent study reported that *in vitro* aggregation of platelets in the plasma induced by *P. gingivalis* took place within several minutes, suggesting that the aggregation probably occurs rapidly after the onset of bacteremia.[40]

Effects of Periodontal Therapy on CVDs

Over the last decade, most studies have been focusing on the impact of periodontal treatment on cardiovascular outcome. However, results vary greatly between each study which could be due to different study protocols and different outcomes being assessed. Subjects recruited in each study may suffer from different stages of the disease. Treatment of periodontitis consists of patient self-care and interventions given by dentists, the treatment protocols also vary in each trial. Most of the published studies use laboratory results or biomarkers as their outcomes. Currently, there is no strong evidence to confirm that periodontal treatment can decrease future cardiovascular events.

Hyperlipidemia is widely accepted as a modifiable risk factor for CVD. One meta-analysis[41] reported that reduction in total cholesterol level was associated with a significant lower mortality rate from ischemic heart disease. Another meta-analysis[42] reported that with 1.0 mmol/L reduction in LDL cholesterol, CVD events decrease by approximately 22%. Multiple clinical trials reported reduction in cholesterol and triglyceride level after periodontal treatment.[43,44] However, a recent meta-analysis[49] concluded that nonsurgical treatment of PD results in no statistical significant reduction in any lipid markers (total cholesterol, HDL, LDL and triglyceride).

Various proinflammatory substances have also been studied, including TNF-α, IL-1, IL-6, MMP, adhesion molecules and hemostatic factors (such as fibrinogen or D-dimer). These substances are measured either from local sites (gingival crevicular fluid) or from blood circulation. Studies showed inconsistent results,[35,44-48] with some even reported an increase in level of these substances after receiving treatment. Therefore, it is difficult to conclude that periodontal treatment leads to a reduction in these inflammatory mediators.[49,50]

On the other hand, hs-CRP level, the most studied inflammatory marker, is 1.56 mg/L higher in patients with periodontitis, comparing with the general population.[51] With periodontal treatment, most studies reported a significant reduction in hs-CRP level,[44,46,52] even in patients with other comorbidities such as diabetes mellitus, or chronic kidney disease.[6,53] Systematic reviews and meta-analyses reported that hs-CRP decreased by 0.231 to 0.5 mg/L after receiving nonsurgical periodontal therapy.[49-51,54]

Endothelial function, as measured by FMD, is reported to be lower in patients with periodontitis than in otherwise healthy subjects,[55,56] indicating a higher risk for future CVD. Studies were conducted to evaluate the effect of periodontal treatment on endothelial function. Mostly, they demonstrated a significant improvement in FMD after receiving nonsurgical intervention[56,57] and systematic reviews supported a consistent effect of periodontal therapy on improving endothelial dysfunction.[48,49] Measuring IMT is another mean to detect subclinical atherosclerosis. Cross-sectional study reported that periodontitis was associated

with increased carotid IMT.[58] To date, there is only one published study on periodontal treatment effect on IMT, which showed a significant reduction of IMT after periodontal therapy.[59]

CONCLUSION

Considering data from multiple studies, periodontitis seems to be another independent risk factor for CVD by precipitating or enhancing atherosclerosis. The majority of interventional trials demonstrated positive effect of periodontal treatment on markers of CVD, including inflammatory mediators, hs-CRP, FMD and IMT. Periodontal bacteria are known to invade the systemic circulation. Oral pathogens and inflammatory mediators (IL-1β) (TNF-α) from periodontal lesions intermittently reach the bloodstream inducing chronic low-level bacteremia and systemic inflammatory reactants.[60] However, no large-scale randomized study observed for cardiovascular event has been conducted. Therefore, there is inadequate information to establish a strong recommendation for periodontal treatment as another measure for reducing CVD outcome.

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