Review Article

Critical Appraisal of Bidirectional Relationship between Periodontitis and Hyperlipidemia

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Abstract

Periodontal disease and hyperlipidemia are both multifactorial disease with a high prevalence Worldwide. Cross-sectional and longitudinal prospective clinical studies show some evidence for a bidirectional relationship. Periodontitis and hyperlipidemia share some common risk factors and there exist a mechanistic link between both. Studies have found a positive response to periodontal therapy among hyperlipidemic patients, and statin use by hyperlipidemic patients has shown to influence the periodontal health. However, in spite of the rising prevalence of both diseases, many people remain unaware of their association with each other. Hence, this article summarizes the cyclic relationship between periodontal disease and hyperlipidemia.

Keywords: *Hyperlipidemia, lipopolysaccharide, periodontitis, statin*

Introduction

Periodontitis is a chronic inflammatory disease primarily caused by pathogenic microbiota of dental plaque and affects the supporting structures of the tooth. Although 700 different bacterial species are identified in the oral cavity,[1] red complex bacteria comprising of *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia* are recognized as the most important pathogens associated with advanced periodontal disease.[2] There is ample evidence for *P. gingivalis* as the keystone species in the development of chronic periodontitis[3] Besides microorganisms several contributing factors (cardiovascular disease [CVD], diabetes, smoking, stress, and hyperlipidemia) also play an important role in the development of periodontal disease.

Hyperlipidemia is a state of abnormal lipid profile, which is characterized by elevated blood concentrations of triglycerides (TGs), elevated levels of total cholesterol and low-density lipoprotein (LDL), and decreased levels of high-density lipoprotein cholesterol (HDL).[4] The incidence of dyslipidemia is defined as having at least one of the following criteria: fasting plasma HDL cholesterol <40 mg/dL, LDL cholesterol ≥140 mg/dL, fasting TG ≥150 mg/dL, or self-reported physician-diagnosed dyslipidemia.[5] Modern lifestyle including the food habits and lack of regular exercise has increased the prevalence of hyperlipidemia, which is one of the major concerns of the modern society. It has been observed that infections may hasten the development of atherosclerosis.[6] Hyperlipidemia is considered as an evident risk factor for cardiovascular disease.[7]

Recent literatures have demonstrated an association between periodontal disease and hyperlipidemia. A statistically significant association between borderline to high level of serum total cholesterol and periodontitis have been reported.[8] Periodontitis and hyperlipidemia are chronic inflammatory diseases with complex etiologies. They share some common risk factors such as lipopolysaccharide (LPS)-related responses, hyper-responsive monocytes, genetic and gender predispositions, smoking, and stress and they also share common underlying pathologic mechanisms.[9]

Periodontal microorganisms present in the subgingival plaque particularly *P. gingivalis* produce endotoxins.

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These endotoxins and other products produced by the microorganisms can appear in the bloodstream and can impact distinct site and promote local and systemic inflammatory reactions in the host[10] by inducing changes in the plasmatic concentration of cytokines and hormones.[11] These microorganisms can also stimulate foam cell production which is the characteristic features of atherosclerosis.[12] Moreover, periodontal pathogens have been identified and isolated from atheromatous plaques[13] emphasizing the role of periodontal bacteria in atherosclerosis.

Studies have found that periodontal treatment has a beneficial effect on hyperlipidemia[14] and statins a group of medications used to lower lipid level has a protective effect against periodontal attachment loss.[15]

With the rising prevalence of both these diseases, many studies have stated a relationship between hypercholesterolemia and chronic periodontitis [Figure 1].[16] This article evaluates the association between hyperlipidemia and periodontal disease.

After a thorough literature search in the PubMed, Embase, Scopus, EBSCO, and Google Scholar, we present this article to provide a brief overview of the bidirectional relationship between periodontitis and hyperlipidemia.

Evidence Based Overview Linking Periodontal Infection And Hyperlipidemia

Infection and hyperlipidemia

Periodontal disease and hyperlipidemia are both chronic inflammatory diseases with an increased number of inflammatory mediators. Chronic local and acute systemic inflammation can alter the lipid metabolism and increase plasma concentration of unregulated cytokines and hormones. Inflammatory chemical mediators released in response to bacterial invasion can spill over into the circulation and can influence the initiation or propagation of atherosclerotic plaque.[17] Fentoğlu *et al*. concluded that increased concentration of tumor necrosis factor alpha (TNF α), interleukin-1β (IL-1β), and IL-6 in gingival crevicular fluid (GCF) and serum could be linking factors between periodontitis and hyperlipidemia.[18] Periodontal disease is significantly associated with a reduction in HDL and elevation of LDL and TG which supports the rationale that periodontal disease is associated with lipid metabolic control.[19]

1. Tumor necrosis factor-alpha and interleukin-beta

A wide array of cytokines is produced in periodontal tissues as a response to Gram-negative LPS exposure. These cytokines particularly TNF-α and IL-1β which are significant in periodontal inflammation can influence lipid metabolism by inducing the production of other cytokines, altering the hypothalamic–pituitary–adrenal axis, increasing plasma concentrations of adrenocorticotropic hormone, cortisol, adrenaline, noradrenaline, and glucagon,[20] or altering hemodynamics[21]/amino acid[22] utilization of various tissues involved in lipid metabolism.[23,24] Thus elevated number of cytokines in chronic inflammatory diseases such as periodontitis can elevate the level of free fatty acids, LDL and TGs and these alterations in serum lipid levels are due to enhanced hepatic lipogenesis,[25,26] increased synthesis of TGs, and reduced clearance of both TGs and LDL (due to reductions in lipoprotein lipase activity)[27,28], increased adipose tissue lipolysis/blood flow. Thus, any condition elevating TNF α and IL-1β can also be associated with hyperlipidemia and atherosclerosis. Significant association was found between periodontitis and low HDL and high LDL cholesterol levels in women.[29]

Cutler *et al*. reported that plasma concentrations of lipids are significantly high in individuals with periodontitis than healthy individuals.[30] An association between periodontal disease and TG/HDL ratio was observed in Korean adults.[31] Lipids can alter the gene expression of macrophage to produce activated macrophage which in turn elevate the level of proinflammatory cytokines such as TNFα and IL1β and essential polypeptide growth factors such as platelet-derived growth factor and TGF1β.[32,33] Furthermore, serum lipids irrespective of mode of induction can increase polymorphonuclear neutrophils (PMN) production and impair wound healing by inhibiting macrophage production of essential polypeptides growth factors.

Role of bacteria

Periodontopathogenic bacteria and their components may have direct access to the circulation through inflamed periodontal tissue, lymphatic vessels or saliva and cause asymptomatic bacteremia[10] or endotoxemia.[34] *P. gingivalis* and *Aggregatibacter actinomycetemcomitans* were detected in endothelial cells derived from homogenized atheromatous tissue cultures through specific antibody detection.

1. Lipopolysaccharide

Lipopolysaccharide stimulates cytokine release

LPS can stimulate the release of inflammatory mediators and pro-inflammatory cytokines[35] such as IL-1β and TNF-α which are related to hyperlipidemia. IL-1β and TNF-α can stimulate the production of other cytokines and can in turn affect lipid metabolism.

Endotoxemia, lipoprotein level and lipid metabolism

Endotoxemia/bacteremia can elevate levels of free fatty acids, LDL, and total serum triglycerides (TRG) by

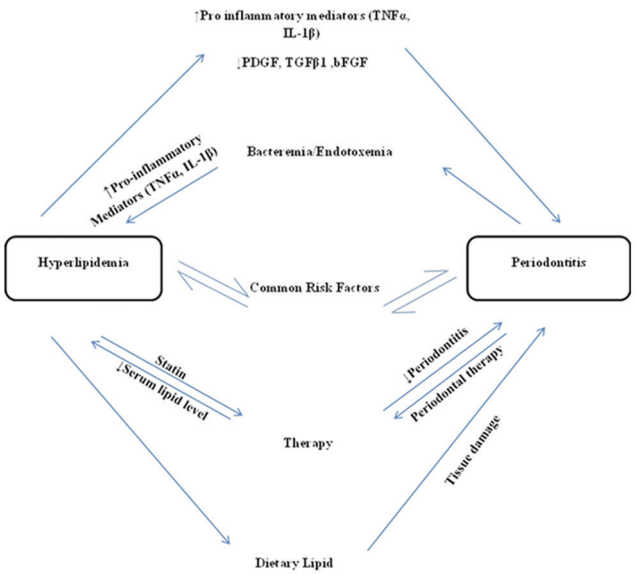

Figure 1: Describe an outline of bidirectional relationship between periodontitis and hyperlipidemia

enhancing hepatic lipogenesis,[25] increasing hydrolysis of fat/blood flow,[36] increasing the production or reducing the elimination of TRG[37] and reducing lipoprotein lipase activity.[27,28]

Lipopolysaccharide interactions

About 80%–97% of LPS is found bound to lipoproteins in the circulation.[38] In healthy individuals, LPS binds to HDL which promotes LPS neutralization. However, in inflammatory conditions instead of HDL, LPS binds to VLDL[39] which can increase hepatic uptake of LPS 3-fold to protect against LPS toxicity.[40]

LPS can also contribute to atherosclerosis by oxidative modification of LDL.

1. Oxidized-LDL (Ox-LDL) taken up by macrophage scavenger receptors[41,42] can transform macrophage to foam cells (characteristic feature of atherosclerosis) where further degradation does not take place
2. Ox-LDL is toxic to endothelial cells[43] and is a strong chemotactic agent for human monocytes.[42]

2. Intact periodontopathogens

Pathogens can travel with platelets resulting in platelet aggregation, thrombus formation[44] and can also invade the endothelial cells.[45] Intact periodontopathogens circulating in the bloodstream within the phagocytic cells (intracellularly/extracellularly) can deposit in atherosclerotic plaque.

3. Antibodies

Heat shock proteins

An association between periodontal disease and atherosclerosis can be linked to microbial heat shock protein (HSP) and immune response to these HSP. Stressed human tissues such as in chronic inflammatory conditions express HSP which is regulated by the immune system. Most bacteria express HSP which can cross-react with each other and with human HSP.[46] For example, HSP60 (GroEL) expressed by *P. gingivalis* can cross-react with HSP in endothelial cells, promoting atherosclerosis.

Anti-cardiolipin

Cardiolipin (CL) which is an anionic lipid, bind to serum protein beta-2 glycoprotein 1 (β2GP1) to form a complex. Physiologic function of this protein is to protect damaged endothelial cell surface. Pathogenic anti-CL antibodies which are similar to peptide sequence in β2GP1 are upregulated in systemic lupus erythematosus, antiphospholipid syndrome, and periodontitis.[47] Anti-CL when complex with β2GP1 can disrupt the protective mechanism of β2GP1 protein and induce vascular thrombosis and early atherosclerosis. In subjects with severe periodontal infection, periodontal therapy may significantly reduce serum anti-β2GP1 concentration, indicating the role of anaerobic bacterial infection in the production of anti-β2GP1 in periodontitis.[34]

Common Risk Factors

Periodontitis and hyperlipidemia share some common risk factors such as LPS-related responses, hyper-responsive monocytes, genetic and gender predispositions, stress, and underlying pathologic mechanisms out of which the most important is smoking.[48]

1. Smoking

Smoking can increase fibrinogen levels which further enhance blood viscosity, hemostasis, and ultimately to CVD. Nicotine and other toxic substances present in the cigarette can cause inflammation of vascular endothelial cells either directly or indirectly, which in turn increase von Willebrands factors and tissue plasminogen activator-related hemostatic activity. Smoking can also upregulate vascular adhesion molecules which are related to atherosclerosis plaque formation.[48] Cigarette smoking can stimulate endothelial cells and leads to an activation of key parameters (endothelial nitric oxide synthase 3 and adhesion molecules), known to be involved in the development of endothelial dysfunction and atherogenesis.[49]

Smoking has been considered as a major independent risk factor for periodontitis.[48] A-positive relation was observed between periodontal disease and increasing severity and number of pack-years smoked. Studies have reported that smokers generally have poor oral hygiene. Smoking adversely affects the fibroblast function[50] neutrophils function (impaired chemotaxis and defective phagocytosis),[51] immunoglobulin production[52] and

induction of peripheral vasoconstriction.[53] It can also impair the healing response.

2. Common genetic predisposition

Hyperinflammatory monocyte

Genetically determined hyperinflammatory monocyte phenotypes are seen in periodontitis and hyperlipidemic patients.[54] Hyperactive monocytes associated with periodontitis can create atheromas at distant sites.

Polymorphonuclear neutrophils dysfunction and hyperactivity of white blood cell

Serum lipids, increase PMN/Impair its function[55] and can cause hyperreactivity of white blood cells[56] cells. Hyperreactive white cells were also found to be associated positively with progressive periodontitis in adults.[57] PMN dysfunction provides a biologic explanation for the observed association between periodontal disease and hyperlipidemia.[58]

ANRIL

The long noncoding RNA, ANRIL is the best-replicated risk locus of coronary heart disease (CHD).[59] ANRIL has been consistently associated with CVD by epigenetic modification and gene expression.[60] Since periodontitis and CVD are both inflammatory diseases, the similar link may also exist in periodontal disease suggesting an association between both diseases. Moreover, it was shown that single nucleotide polymorphism in ANRIL is also associated with hsCRP levels in periodontitis patients.[61] However, limited evidence have been provided regarding the frequencies of ANRIL variants in chronic periodontitis patients who often tend to be aged when CVD s occur. Further studies have to be conducted to explore the role of ANRIL and other genetic loci as a contributing genetic risk factor in periodontitis and CVD.

Effect of therapy

1. Effect of periodontal therapy on hyperlipidemia

Studies have suggested that periodontal therapy may be beneficial for individuals with hyperlipidemia.[13] Evidence support that periodontal therapy can decrease the levels of CRP, TNF-α, and IL-6.[62] An association between macrophage activation stimulated by serum LPS and periodontal inflammation have been observed in periodontitis patients with noncontributory medical history. An increase in the ratio of HDL/LDL following periodontal therapy was also noted.[34] It was observed that periodontal infection may weaken the anti-atherogenic effect of HDL thereby enhancing the risk of CHD.[63] Several studies have shown an improvement in serum lipid levels and a decrease in serum proinflammatory cytokine levels in patients with periodontitis and hyperlipidemia following periodontal therapy,[14] while some studies failed to show beneficial effects of periodontal treatment on lipid metabolism. It was reported that nonsurgical periodontal therapy is unlikely to alter serum levels of inflammatory markers such as CRP, fibrinogen, or inflammatory cytokines, 6 weeks after treatment.[64] Yamazaki *et al*. reported that specific populations responded differently to treatment suggesting an ununiformed relationship between periodontitis and CVD[65] which indicate a need for further studies regarding the impact of periodontal therapy on CVD.

2. Effect of lipid lowering drugs on periodontal disease

Statins are a group of medicines that lower the level of LDL in the blood. Apart from lipid-lowering action, studies provide evidence for anti-inflammatory[66] and potential pleiotropic effects of statins (immunomodulatory, antioxidant, antithrombotic and endothelium stabilization actions, angiogenesis promotion and increase of osteoblastic differentiation, including bone formation)[67] which can elicit a positive impact on periodontal diseases. As evidenced in a recent systematic review, statins could be an adjunctive in promoting periodontal health following nonsurgical therapy and simvastatin was the only drug that showed additional benefits in all evaluated parameters (probing pocket depth, clinical attachment level, and intrabony defect) when compared to groups without statin.[68] Simvastatin treatment inhibits LPS-induced gingival inflammation, osteoclastogenesis, and reduce alveolar bone loss[69] Statins interact with immune response of host by inhibiting adhesion and extravasation of leukocytes in inflammatory sites which in turn diminishes the co-stimulation of T-cells and decrease inflammatory cytokines such as IL-1β, IL-6, and TNF-α.[70,71] Fentoğlu *et al*. evaluated the effect of statins on the level of inflammatory cytokines in GCF[18] and found that the level of TNF-α was reduced in GCF of periodontitis patients after 3 months of systemic administration of statins.

Subgingivally delivered simvastatin gel in chronic periodontitis could enhance the beneficial effect of scaling and root planing (SRP) in pocket reduction, gain in CAL, and bone loss.[72] The effect of different concentrations of local Rosuvastatin (0.1 and 1 mg) in calvarial bone defects was studied, and it was observed that local administration of 1 mg of Rosuvastatin enhanced bone regeneration in calvarial rat defect.[73] Systematic review and meta-analysis find that adjunctive use of locally delivered statins to mechanical SRP is beneficial to increasing bone fill percentage. Improved inflammatory and bleeding control as well as probing depth reduction and CAL gain are possible advantages of these drugs in treating patients with periodontal intrabony defects.[74]

However, some studies failed to prove the beneficial effects of statins on periodontium. In a systematic review

done it was concluded that statins have a beneficial effect on bone formation, reducing inflammation, and immunomodulatory effect, however, it was emphasized that statins could not be used as an alternative for standard periodontal treatment.[71] Hence, further studies have to be conducted on the impact of statins on periodontium.

Role of dietary lipids

Dietary lipids play a role in modulating the immune system. Lymphocyte proliferation and cytokine synthesis are established to be reduced by dietary lipids high in saturated fat and an increase of phagocyte activity, and modification of natural killer cell-cell activity are also observed. Fatty acids obtained from dietary lipids gets incorporated to the plasma membrane which alter the phospholipid profiles of lymphocytes, monocytes/macrophages, or polymorphonuclear cells.[75] Diet rich in polyunsaturated fatty acids can suppress the mitogenic response.[76] Immunomodulation induced by IL-1β and TNF-α can be suppressed by dietary lipids.[77] Fatty acids cause a reduction in cell proliferation by inducing apoptosis. Dietary fatty acids can also decrease antioxidant enzyme mRNA levels and enhance radicle induced tissue damage. Enzymatic degradation of these fatty acids can depress the immunocompetence of prostaglandin, leukotrienes, or lipoxins.[78] Circulating lipids above the threshold level have a negative impact on gingival mucosa and elsewhere.[79]

Conclusion

Recent literatures and studies have demonstrated a cyclic link between periodontal disease and hyperlipidemia. Both are chronic inflammatory diseases with common risk factors. Periodontopathogenic bacteria-induced inflammatory mechanisms and it is influence on atherosclerosis strengthen the premise that periodontitis and hyperlipidemia are bi-directionally linked. Up-regulated cytokines such as IL-1β and TNF-α are common to both diseases. Periodontal therapy has a positive effect on lipid metabolism, and statins are shown to reduce periodontitis.

Although there is evidence to support the concept of association between periodontitis and hyperlipidemia more studies with case–control or cohort designs need to be conducted to fully understand the actual relationship that exists between high lipid profile and periodontitis.

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Conflicts of interest

There are no conflicts of interest.

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