The Bi-Directional Relationship between Periodontal Disease and Hyperlipidemia

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ABSTRACT

It has been proposed for several decades that infections may be responsible for the accelerated development of atherosclerosis. The initiation of the atherosclerotic plaque is ascribed to focal accumulation of lipids. This explains the importance of plasma lipids in the development of atherosclerosis. Recent reports point towards a possible association between periodontal disease and increased risk for cardiovascular disease. Thus, periodontitis and cardiovascular disease may share common risk factors, and association between periodontitis and coronary heart disease may be due to the elevated levels of plasma lipids. Epidemiological and clinical studies have also suggested that there is a relationship between periodontal disease and impaired lipid metabolism. In this review, we summarized the potential link mechanisms in the association between periodontal infection and serum lipids. (Eur J Dent 2008;2:142-149)

Key words: Periodontal disease; Hyperlipidemia; Lipid metabolism.

INTRODUCTION

Periodontal diseases are a group of inflammatory diseases in which Gram-negative microorganisms and their products are the principal etiologic agents.[1] These microorganisms, particularly *Porphyromonas gingivalis (P. gingivalis),* produce endotoxins in the form of lipopolysaccharides (LPS) that are instrumental in generating a host-mediated tissue destructive immune response.[2] Recent studies indicate that periodontal disease may have profound effects on systemic health. Subjects with periodontal disease may have a higher risk for cardiovascular disease when compared to subjects with a healthy periodontium.[3]

The biological plausibility for a periodontal infection-systemic disease link can be briefly explained as follows. Periodontal infection causes bacteraemia and endotoxaemia and promotes systemic inflammatory and immune responses that may roles in systemic disease. Periodontal pathogens express specific virulence factors that can affect atherogenic events. Finally, periodontal pathogens have also been isolated from non-oral

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tissues like atheromatous plaques.[4]

The consequence of these findings, recent researches have been focused the association of periodontal infection and systemic disease, and in this relationship in the alterations of lipid metabolism have been revealed as a potentially inductive factor.[5]

A. POTENTIAL MECHANISMS IN THE ASSOCIATION BETWEEN PERIODONTAL DISEASE AND HYPERLIPIDEMIA

1.   Infection and hyperlipidemia

Previously, it was thought that serum lipid alterations were related to the underlying pathological conditions rather than the infectious process. However, recent studies have demonstrated that lipid metabolism may be altered by chronic local and acute systemic infections which are involved in the plasma concentrations of unregulated cytokines and hormones. The main features of this catabolic state are lipid oxidation and elevated free fatty acids, triglycerides and low density lipoprotein (LDL) cholesterol.[6,7]

Studies in humans and animals have shown a number of cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin-1 beta (IL-1β) are produced in response to systemic Gram-negative LPS exposure. It is believed that these cytokines exert effects on lipid metabolism by influencing production of other cytokines, altering hemodynamics/aminoacid utilization of various tissues involved in lipid metabolism,[8,9] or modifying the hypothalamic-pituitary-adrenal axis increasing plasma concentrations of adrenocorticotropic hormone, cortisol, adrenaline, noradrenaline, and glucagon.[10-12] Thus, through action of TNF-α and IL-1β, exposure to microorganisms/endotoxin results in elevated levels of free fatty acids, LDL and triglyceride. These elevations in serum lipids are thought to arise from enhanced hepatic lipogenesis,[13,14] increased adipose tissue lipolysis/blood flow, increased synthesis or reduced clearance of triglyceride, and reduced clearance of LDL due to reductions in lipoprotein lipase activity.[15,16] Thus, any condition producing elevations in serum TNF-α and IL-1β has potential to cause hyperlipidemia.

Lipids may interact directly with the macrophage cell membrane, interfering with membrane-bound receptors and enzyme systems, altering macrophage gene expression for pro-inflammatory cytokines such as TNF-α and IL-1β and essential polypeptide growth factors such as platelet-derived growth factor (PDGF), transforming growth factor beta 1 (TGF-β1) and basic fibroblast growth factor (bFGF).[17,18] Additionally, serum lipids, whether induced by diabetes, or diet increase polymorphonuclear leukocyte (PMN) production of pro-inflammatory cytokines and inhibit macrophage production of essential polypeptide growth factors impairing the wound healing process. Furthermore, hyperlipidemia may be more important than hyperglycemia relative to the hyper-responsive monosytic phenotype[19-21] and development of many diabetic complications.[22]

2. Interactions between bacterial lipopolysaccharides and serum lipoproteins

a. Bacterial infections, lipoprotein levels and lipoprotein metabolism

The most commonly observed infection-induced lipid abnormalities in man and experimental animals are increased triglyceride and very low density lipoprotein (VLDL) levels[23] and decreased high density lipoprotein (HDL) cholesterol levels.[24] A decrease in total and LDL cholesterol levels has also been reported during severe bacterial infections.[25] However, in rodents and rabbits administration of LPS often leads to hypercholesterolemia.[23] Hepatic and lipoprotein lipase activity levels decreased during acute infections.[26, 27]

b. Abnormalities in lipid and lipoprotein levels: cytokine mediated effects

Tumor necrosis factor (TNF) induces a rapid increase in serum triglyceride, VLDL and cholesterol levels. Although the mechanism by which TNF increases serum cholesterol levels is unknown, the increase in hepatic cholesterol synthesis may be due to an increase in the activity of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase.[13]

c. LPS-LDL interactions: effects on lipoprotein metabolism

Low concentrations of LPS inhibit the

expression of scavenger receptor activity on human monocyte-derived macrophages but had no effect on LDL receptor activity.[28] Furthermore, when LPS is complexed with LDL the inhibitory effect of LPS on scavenger receptor activity is markedly enhanced.[29] Besides affecting scavenger and LDL receptors, LPS affects LDL metabolism by precluding its hydrolysis. Furthermore, LPS binds to lipoproteins in direct proportion to their cholesterol content and that the LDL-LPS complex once taken by macrophages is not degraded.[29]

d. LPS, release of cytokines and LDL modification

Though it was demonstrated that LPS causes widespread endotelial damage, in hypercholesterolemic status this damage seems to be more severe and persistent.[30] In animals maintained on high cholesterol diets for the duration of the experiment, arteriosclerotic lesions may not be detectable until 3 months after administration of a single small dose of LPS, even so, LPS cause the initial endothelial damage, and hypercholesterolemia may interrupt the normal repair process.[31]

Another possible mechanism by which LPS contributes to the development of atherosclerosis is the oxidative modification of LDL induced during macrophage activation. Several possible pathogenic roles with marked importance in the development of atherosclerosis may be attributed to oxidized LDL (ox-LDL). First, ox-LDL is taken up by macrophage scavenger receptors[32,33] leading to the transformation of macrophages into foam cells, the hallmark of the atherosclerotic process. Second, ox-LDL is cytotoxic for endothelial cells[34] and is a potent chemo-attractant for circulating human monocytes.[33]

3. Lipoprotein-associated inflammatory proteins: mediators of cardiovascular disease

Plasma lipoproteins are largely involved in the transport of acute phase reactant proteins such as C-reactive protein (CRP), serum amyloid A and secretory phospholipase A_2 which greatly increases the risk of atherosclerosis.[35]

The acute phase reactions, associated with injury, inflammation, or sepsis, markedly affect the concentration and composition of plasma lipids and lipoproteins. Hepatic production of triglycerides and LDL formation are increased, but do not necessarily result in high plasma triglyceride levels. In contrast, all conditions lower plasma cholesterol by decreasing its content in both low-density and high-density lipoproteins. In addition, substantial changes in protein and lipid composition of lipoproteins are observed that may redefine the function of these particles, but also increase their atherogenic and inflammatory properties.[36]

4. Modulatory effects of dietary lipids on immune system functions

The immune response of both humans and animals may be influenced by several essential nutrients, which modify the immune system functions. Dietary lipids or free fatty acids may be modulate the immune system through a great number of mechanisms that include reduction of lymphocyte proliferation, reduction of cytokine synthesis, increase of phagocytic activity, modification of natural killer (NK) cell activity and so on. This modulation may be associated with changes in the cell membrane due to dietary fatty acid manipulation. Fatty acids may be incorporated into the plasma membrane after dietary lipid administration, so that the composition of lipids in this cellular structure will reflect the composition of dietary lipids.[37] Because of this incorporation, the phospholipid profiles associated with plasma membrane of lymphocytes, monocytes/macrophages or polymorphonuclear cells may be altered by dietary lipids.[38,39]

Diets including polyunsaturated fatty acids, such as eicosapentaenoic or docosahexaenoic acids, suppress the mitogenic response of lymphocytes to a greater extent than diets rich in saturated fatty acids.[40]

Fatty acids may regulate cytokine production and in fact cytokine modulation by fatty acids seems to be responsible for the reduction of lymphocyte proliferation in both animals and humans. Cytokines such as IL-1 and TNF are important mediators of inflammation and dietary fatty acids have been demonstrated to be substances capable of reducing the pro-inflammatory response induced by IL-1 and TNF.[41-43] The mechanisms involved in the modification of cytokine synthesis remain unclear as yet, but a possible explanation could be found

in the regulation at the transcriptional level, that is, reduction of cytokine mRNA production by polyunsaturated fatty acids.[44] Dietary fatty acids may also be able to modulate activity of NK cells participating in protection against virus, intracellular bacteria or tumoral cells. Diets containing fish oil or olive oil produce the greatest percentage of NK cell activity inhibition in comparison with diets rich in saturated fatty acids or n-6 polyunsaturated fatty acids.[45, 46] However, there are several reports are found, eicosanoids such as prostaglandins, leukotrienes or lipoxins may play important role in this mechanism.[47-49] It has been reported that unsaturated fatty acids increase phagocytosis which is an important mechanism in many cells for the elimination of microorganisms or foreign particles.[42,50]

Mechanisms involved in fatty acid modulation are membrane fluidity, production of lipid peroxides, eicosanoid synthesis and influence on gene regulation. As a result of changes in the phospholipids fatty acid composition due to dietary lipid manipulation, the fluidity of the cell membrane may change. Fatty acids have inhibitory effects on cellular proliferation due to lipid peroxidation which are toxic to cells. Dietary fats have an important role in decreasing antioxidant enzyme mRNA levels and enhancing free radical-induced tissue damage. Fatty acids undergo enzymatic degradation to yield eicosanoid family (prostaglandins, leukotrienes or lipoxins) participating in inflammatory processes and are also related to immunomodulatory effects, which act as lipid mediators.[51]

B. PERIODONTITIS AND HYPERLIPIDEMIA

The alterations in immune cell phenotype due to serum lipids and elevation in serum pro-inflammatory cytokines such as TNF-α and IL-1β through periodontitis as a chronic gram (-) infection verified substantial evidences supporting this bidirectional relationship.

Hyperlipidemia, arising from a high-fat diet or metabolic disorders such as type 2 diabetes, has a dysregulatory effect on immune system cells and on wound healing and as a result, it increases the susceptibility to periodontitis and other infections. This condition needs a particular threshold level of circulating lipids for every individual, above which can lead to this dysregulatory effect within the gingival mucosa and elsewhere.[5]

It has been reported that consumption of a typical high-fat American breakfast (fried eggs, bacon, potatoes) or a defined saturated-fat-rich meal (i.e. ice cream) leads to functional abnormalities in PMNs.[52] A protective role for PMNs in the early response to periodontal infection is supported by compelling experiments in nature, wherein subjects with impairments of PMN function[53] or number[54] have more acute and severe periodontitis. So, PMNs primed by endotoxin or other activating agents, including dietary lipids may play a major role in the pathogenesis of periodontitis.[55] A possible role of hyperlipidemia for periodontitis is also obvious from several studies. Hyperlipidemia is known to cause a hyperactivity of white blood cells.[56,57] Hyperactivity of white cells, e.g., increased production of oxygen radicals, have been shown to be frequently associated with progressive periodontitis in adults.[58] In animals feeding a cholesterol-rich diet have caused to periodontitis.[59]

In an animal model, Maglakelidze et al[60] have reported significant changes in extracellular matrix and gingival mucous cells as well as in microcirculatory bed components in hypercholesterolemia. Hypercholesterolemia damages endotheliocytes, subendothelial zone and basal membrane permeability. The contact of lymphocytes and plasmocytes with the vascular wall confirms the trigger role of the vascular factor in damaging of periodontal complex.

There are several studies which report significant association between plasma lipid levels and the severity of the periodontal disease.[61-63] While some authors mentioned that there were significant correlations between periodontal status and cholesterol levels,[64-69] others indicate that there were significant associations between triglyceride level and periodontal disease.[70-72]

The studies which trying the effect of periodontal therapy on serum lipids and lipoprotein associated inflammatuar mediators[73-76] also suggested that the treatment of periodontal disease have beneficial effects on lipid metabolism. In one study conducted in systemically healthy subjects with periodontitis, Pussinen et al[73] stated that periodontitis is associated with macrophage

activation via increased serum LPS concentration. Additionally, there was a significant increase in the ratio of HDL/LDL after periodontal treatment in this study. In another study, Pussinen et al[74] reported that there were statistically significant decreases in CRP and serum amyloid A levels after periodontal treatment in systemically healthy subjects with periodontitis. That study also suggested that periodontitis diminishes the anti-atherogenic potency of HDL and increase the risk for coronary heart disease.

Lösche et al[75] evaluated 32 patients with moderate to severe periodontitis before and 3 months after local periodontal treatment and they reported that treatment of periodontitis caused a significant reduction in the serum activity of lipoprotein-associated phospholipase A_2 which is believed to be an independent cardiovascular risk factor. In a similar study, 65 subjects presenting with severe (probing pocket depth greater than 6 mm and marginal alveolar bone loss greater than 30%), generalized (at least 50% of teeth affected) periodontitis were assessed and the 3 groups consisted of untreated control; standard periodontal therapy; and an intensive periodontal treatment including standard periodontal treatment with adjunctive local delivery of minocycline. In that study both standard periodontal therapy and intensive periodontal therapy resulted in significant reductions in serum CRP compared with the untreated control and the intensive periodontal therapy group also showed a decrease in total and LDL cholesterol after 2 months following the periodontal treatment.[76]

Higher serum levels of total cholesterol, LDL-C and triglycerides have been found in subjects with periodontal disease,[71,77,62] and hyperlipidemic patients have a significantly higher percentage of sites with probing depth greater than 3.5 mm than subjects with normal metabolic status.[78] The interrelationship between periodontitis and hyperlipidemia provides an example for systemic disease predisposing to oral infection, and once the oral infection is established, it exacerbates systemic disease.

CONCLUSIONS

However, it is unclear whether the association of periodontal disease and impaired lipid metabolism is a cause-effect interrelationship, namely whether periodontitis induces higher serum lipid levels or higher serum lipid levels are predisposing factors for periodontitis, the association of these two phenomenons is widely discussed in the periodontal literature.

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