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Periodontal inflammation and lipid metabolism – is it an overlooked interaction in progression of atherosclerotic disease?

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Abstract

Atherosclerotic Vascular Disease (ASVD) is one of the leading causes for Morbidity and mortality in the population. There are a multitude of known and established risk factors, but a significant portion of affected population does not exhibit any known risk factor. Periodontal disease is a widely prevalent condition in the Indian population. From being considered as an oral-limited disease, literature for the past few decades have explored potential systemic effects of it. In spite of research into the linkage, not much awareness exists on underlying mechanisms that influence pathogenesis of atherosclerosis. This short review aims at giving a peek into the way periodontal inflammation can affect lipid metabolism, and consequently have a role to play in atherosclerotic disease progression.

Keywords: Atherosclerotic vascular disease, periodontal disease, morbidity, mortality, inflammation

Mini review article **Corresponding Author*, e-mail: sumiraodas@gmail.com

1. Introduction

Periodontitis is a chronic inflammatory condition and caused by predominantly gram-negative anaerobes whose metabolites initiate and perpetuate inflammation, increasing the levels of pro-inflammatory cytokines which lead to the destruction of the periodontal ligament fibers and alveolar bone [1]. The microorganisms associated with periodontitis are predominantly gram-negative anaerobes [2] A Meta analysis in 2020 found the prevalence of Periodontitis in Indian population to be at 51% [3]. Earlier, periodontitis was considered as a stand-alone oral infection. Over the years, with the re-emergence of interest in Focal Sepsis, Periodontitis has been shown to affect and modify various Systemic diseases and conditions via its inflammatory response [4]. Atherosclerosis is one of the major causes for cardiovascular diseases (ASVD). Atheromatous plaque is an infectious lesion featuring blood clots [5]. The pathologic process is viewed as a progressive inflammatory process rather than as simply an accumulation of lipids involving various inflammatory signals and markers including high sensitivity C-Reactive Protein (hsCRP), fibrinogen, and various inflammatory cytokines, Interleukin-1 beta, 6 (IL-1β, IL-6), and tumor necrosis factor-alpha (TNF-α) [6]. ASVD is strongly associated with elevated Serum Lipids, especially oxidized lipids. Inflammation & increased circulatory mediators of inflammation such as IL-1β & TNF-α can alter lipid metabolism. Mechanisms by which this can happen are enhanced hepatic lipogenesis, increased adipose tissue lipolysis, increased synthesis and/or reduced clearance of low-density lipoprotein (LDL) due to reductions in lipoprotein lipase activity [7, 8]. Out of the different types of lipoproteins, high-density lipoprotein (HDL) is considered to be protective via multiple mechanisms, while LDL and very low-density lipoproteins (VLDL) are said to be pro-atherogenic. HDL aids in stabilizing atherogenic plaque and critical HDL functions may also include prevention of platelet activation and thrombus formation. Also, the oxidized forms of LDLs are more harmful when compared to the non-oxidized forms [8, 9, 10]. So, any mechanism that alters oxidation may also be a potential risk factor.

2.1 Systemic Bacteremia, Lipid Metabolism and Periodontal Inflammation

Systemic exposure to infectious challenges such as bacteria and/or their components such as lipopolysaccharides (LPS) can lead to increase in circulating cytokines such as IL - 1β, TNF – α, etc. can alter fat metabolism and lead to hyperlipidemia. This is mostly attributed to enhanced hepatic lipogenesis, increased adipose tissue lipolysis/blood flow, increased synthesis or reduced clearance of LDL due to reductions in lipoprotein lipase activity. Chronic local and acute systemic infections have been demonstrated to induce profound changes in the plasma concentration of cytokines and hormones leading to a catabolic state characterized by altered lipid metabolism. There exists evidence to suggest that a low-level chronic exposure to gram-negative microorganisms and/or their LPS can manifest the same response.

2.2. Potential Mechanisms

As early as almost forty years ago, three mechanisms or pathways linking oral infections to secondary systemic effects were proposed [11]. These were Metastatic spread, metastatic injury, and metastatic inflammation. Metastatic infection – oral infections and dental procedures can cause transient bacteremia [12]. The microorganisms potentially enter systemic circulation via the ulcerated sulcular epithelium inside the pocket and can are usually eliminated by the reticuloendothelial system within minutes (transient bacteremia). However, under certain favorable conditions, these microorganisms can attach to specific sites, such as blood vessel walls or an area of existing injury. Metastatic injury – Bacteria may produce cytolytic enzymes with specific pharmacological actions and endotoxin (LPS) that, when introduced into the host, gives rise to a large number of pathological manifestations. LPS is continuously shed from periodontal gram-negative rods during their growth in vivo and can contribute to injury. When attached to endothelial wall, after a given time, they start to multiply. Metastatic inflammation – Soluble antigen may enter the bloodstream, react with circulating specific antibody, and form a macromolecular complex. These immunocomplexes also further acute and chronic inflammatory reactions at the sites of deposition. These three mechanisms, acting in tandem can trigger potential atheroma formation, increase or rupture, in that order. A pathogenesis model has also been derived that underlines the periodontal-atherosclerosis link – "Periodontitis-atherosclerosis Syndrome" [13].

2.3 Effects on Lipid Metabolism

Inflammation and infections have been associated with altered lipid metabolism, with minimal to no changes seen in acute states, but associated with significant variations in chronic states, potentially contributing to the increased risk of atherosclerosis. The most common changes noted are decrease in serum HDL and increases in triglycerides. The increase in serum triglycerides is due to both an increase in hepatic VLDL production and secretion and a decrease in the clearance of triglyceride rich lipoproteins.

In the case of periodontitis, elevations of pro-inflammatory cytokines may be mediated by "systemic dumping" of locally produced IL-1β/TNF-α and/or low-level "asymptomatic bacteremia/endotoxemia" [12,14]. With inflammation there is also a consistent increase in lipoprotein-a levels due to increased apolipoprotein-a synthesis. LDL levels are frequently decreased but the prevalence of small dense LDL is increased due to exchange of triglycerides from triglyceride rich lipoproteins to LDL followed by triglyceride hydrolysis [8]. In addition to affecting serum lipid levels, inflammation also adversely effects lipoprotein function. LDL is more easily oxidized as the ability of HDL to prevent the oxidation of LDL is diminished. Moreover, there are a number of steps in the reverse cholesterol transport pathway that are adversely affected during inflammation. The changes in lipids and lipoproteins that occur during inflammation and infection are part of the innate immune response and therefore are likely to play an important role in protecting the host. Studies researching the link between periodontal inflammation and lipid metabolism and levels have found varing results. An observational study revealed that untreated periodontitis is associated to the alteration of important lipid markers related to cardiovascular disease [15]. Other reviews have also explored studies associating these two [16].

3. *Conclusions*

In 2012, the AHA published a position paper on the potential relation between periodontitis and atherosclerotic vascular disease that covered all the potential mechanisms involved and/or proposed. Findings were mixed. They stated that existing studies suggested a link that met standards for Level of Evidence A, but causation of ASVD by PD is not supported by either level A or level B evidence. They found that the linkage was noted independent of known cofounding variables, including smoking, but causation could not be established. The review also highlighted significant lacunae in research and inconsistent methodologies which were unable to be replicated or were not sustainable, with a few studies even claiming that periodontal therapy causes a transient worsening of markers of endothelial dysfunction [17]. Since then many other studies have tried to analyze this relationship in various ways with highly varying, and sometimes non-conclusive results. Atherosclerosis, cardio-vascular diseases are highly prevalent among the Indian population and are seen as a hidden menace in the younger age groups and can lead to significant morbidity and mortality. Well-established protocols do not account for a significant number of cases where traditional factors are absent. When the relationship between periodontal infection and lipid metabolism has been investigated in numerous studies and data available on this, ignoring the ramifications of this might not just harm the patient, but also mire the treating doctors in potential legal situations [18]. Some authors have argued that blaming oral focus for systemic sepsis post dental treatment is baseless and can be misused while some have argued for considering the relation for identifying as a potential risk indicator. As stated in multiple studies, the foundation of this link is the presence of similar inflammatory pathways and inflammation-mediated destruction in both conditions. The very existence of the possibility warrants further investigations, especially long-

term follow-up studies to prevent further unexplained morbidity and mortality in future populations.

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