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REVIEW ARTICLE

Role of periodontal pathogens in atherosclerotic plaque development and progression: An overview

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ABSTRACT

Atherosclerosis is a progressive disease marked by the accumulation of lipids and fibrous components in the large arteries. It is one of the primary causes of heart disease and stroke. Periodontal diseases encompass conditions like gingivitis and periodontitis, which are multifactorial diseases associated with dysbiotic plaque biofilms that trigger an immune-inflammatory host response, eventually resulting in the destruction of periodontal tissues. Links between periodontal disease and atherosclerosis may be based on direct invasion of periodontal pathogens or inflammatory mechanisms triggered by bacteria related to periodontal lesions, locally or systemically, that may impact the initiation of the atherosclerotic lesion. The presence of periodontal pathogens within an atheromatous lesion implies hematogenous dissemination. The invasion of atheroma by periodontal pathogens results in changes in the proatherogenic and proinflammatory properties of endothelial cells, leading to endothelial dysfunction, which is a hallmark of atherosclerosis. Clinical and epidemiological studies have offered sufficient evidence of periodontitis having an adverse effect on systemic health, including atherosclerosis; however, a direct causal effect has not yet been proved. This review aims to analyse scientific results regarding the mechanism by which periodontal pathogens may cause atherosclerosis as well as to describe the role of *Porphyromonas gingivalis* in atherosclerotic plaque development and progression.

KEYWORDS

atherosclerosis, periodontitis, cardiovascular disease, *Porphyromonas gingivalis*

INTRODUCTION

Atherosclerosis is a progressive disease marked by the deposition of lipids and fibrous components in the large arteries and eventually leading to clinical complications like myocardial infarction and stroke. Atherosclerotic plaque formation occurs over a series of stages, starting from the initial damage to the blood vessel wall and culminating in the development of a mature plaque. Numerous risk factors for atherosclerosis like high cholesterol and low-density lipoprotein (LDL) in the blood, smoking, hypertension, diabetes mellitus (DM), obesity and sedentary lifestyle have been identified [1, 2]. They, however, do not account for all the cases reported and cardiovascular disease (CVD) can occur even in the absence of these risk factors. Globally there were 12.1 million CVD-related deaths in 1990 and 18.6 million in 2019 [2]. There is evidence indicating that infection contributes to the chronic inflammatory processes either directly or indirectly and increases the risk of developing atherosclerosis [3]. Research conducted over the past few years have reported that individuals with periodontitis have an increased risk of developing coronary artery disease, atherosclerosis and myocardial infarction even after adjusting for cardiovascular risk factors [4]. Periodontitis, a chronic inflammatory disease, is characterized by the gradual

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destruction of the tooth-supporting structures. It primarily begins as a protective response to plaque biofilm; however, periodontal inflammation fails to resolve in susceptible individuals, resulting in a chronic condition which may have systemic effects. Studies have revealed striking differences in the periodontal microbiota composition in healthy and diseased individuals [5, 6]. Increased levels of Gram-negative bacteria primarily anaerobic bacteria including *Porphyromonas gingivalis* (*P. ginigvalis*), *Aggregatibacter actinomycetemcomitans, Tannerella forsythia, Treponema denticola* and other spirochetes, in the subgingival biofilm are a defining feature of periodontitis [7]. *P. gingivalis* is a Gram-negative bacterium and has been hypothesized to be a keystone pathogen that dysregulates the host immune response to lead to an inflammatory condition by remodelling a normal healthy microbiota into a dysbiotic one. It is found in sites with advanced and active chronic periodontitis [8]. Numerous *in vivo* and *in vitro* studies indicate that chronic inflammation caused by periodontal bacteria could compromise the integrity of the epithelial barrier, allowing periodontal pathogens to infiltrate the underlying connective tissue and exposed blood vessels [9–11]. A systemic inflammatory reaction may be brought on by the release of bacteria and bacterial by-products into the circulation. Hence the link between periodontal disease and atherosclerosis can be based on direct invasion of periodontal pathogens or indirectly based on inflammatory mechanisms triggered by bacteria associated with periodontitis, that may affect the initiation or progression of the atherosclerotic lesion. The detection of certain periodontal pathogens, in particular *P. gingivalis* has been the focus of various studies and has been implicated in systemic diseases, such as CVD, DM, rheumatoid arthritis, pre-term low birth weight and myocardial infarction [12–14].

The role of periodontal pathogens in the onset and progression of atherosclerosis has been highlighted in numerous studies but the results have been inconclusive so far and evidence regarding the causal mechanisms is still lacking. The aim of this review is to summarise the possible mechanism by which periodontal pathogens can influence the onset or progression of atherosclerosis.

Materials and methods

A systematic search was carried out using various databases like “Google scholar”, “Scopus” and “PubMed” by using the keywords like atherosclerosis, *P. gingivalis,* CVD and periodontal pathogens. A thorough evaluation of systematic reviews, consensus reports, cross-sectional studies relevant to the review was done.

ANALYSIS OF LITERATURE

Periodontal pathogens and atherosclerotic plaque formation

Atherosclerotic plaque formation occurs over a series of stages, starting from the initial damage to the blood vessel wall and culminating in the development of a mature plaque. In the development of atherosclerosis, the primary trigger, is the build-up of LDL in the subendothelial matrix of blood vessels; this build-up is exacerbated by elevated levels of circulating LDL. Subendothelial retention of LDL in the vessel wall involves interactions between the LDL constituent apolipoprotein B and matrix proteoglycans and appears to be a crucial process involved in atherosclerosis [15]. Studies have indicated that patients with periodontitis, exhibit increased levels of LDL, very low-density lipoprotein and triglycerides [16]. Additionally, increased levels of lipid peroxidation, a process involving the oxidative damage of lipids, have been observed in plasma, gingival crevicular fluid and saliva of individuals with periodontitis and these increased levels have been linked with the severity of the periodontal disease [17, 18].

Invasion of endothelial cells by bacteria can cause endothelial dysfunction which is one of the initial stages in atherosclerosis formation. Periodontal pathogen like *P. gingivalis* can invade endothelial cells, causing changes in the pro-inflammatory properties of the cell and triggering a cascade of events that eventually leads to programmed cell death. An *in vitro* study has reported that certain bacterial strains that express *P. gingivalis* hemagglutinin A have the ability to adhere and penetrate human coronary artery endothelial cells [19]. Infected endothelial cells express an abundance of adhesion molecules on their surface, along with the release of inflammatory mediators like IL-8, IL-6, Monocyte chemotactic protein (MCP)-1, and cyclooxygenase-2 which enhance monocyte migration and adhesion [20–22]. The inflammatory response is amplified by the secretion of inflammatory mediators, which further advances the endothelial dysfunction. *P. gingivalis* secretes enzymes like gingipains, that can degrade vascular endothelial-cadherin and platelet endothelial cell adhesion molecule, disrupting the endothelial barrier. Additionally, *P. gingivalis* infected human endothelial cells have been reported to exhibit disrupted cell–cell junctions, increased endothelial cell permeability and decreased cell surface expression of platelet endothelial cell adhesion molecule-1 and VE-cadherin [21–23].

Periodontal pathogens stimulate the expression of adhesion and chemoattractant molecules on the surface of endothelial cells, which promotes the adherence of monocytes and other leukocytes [24–26]. It has been demonstrated that *P. gingivalis* can penetrate and survive in monocytes and macrophages, a process that could contribute to the spread of the bacteria from the subgingival area to other inflamed sites in the body [27]. Early atherosclerosis is characterized by recruitment of monocytes on the endothelial surface, which precedes their trans-endothelial migration to the arterial intima and further differentiation to macrophages (Fig. 1). *P. gingivalis* lipopolysaccharide (LPS) mediates monocyte adhesion through Toll like receptor 2-dependent mechanism [28, 29].

Anti-coagulant and anti-adhesion properties can be observed in a normal arterial endothelium however, proteolytic degradation of endothelial thrombomodulin by

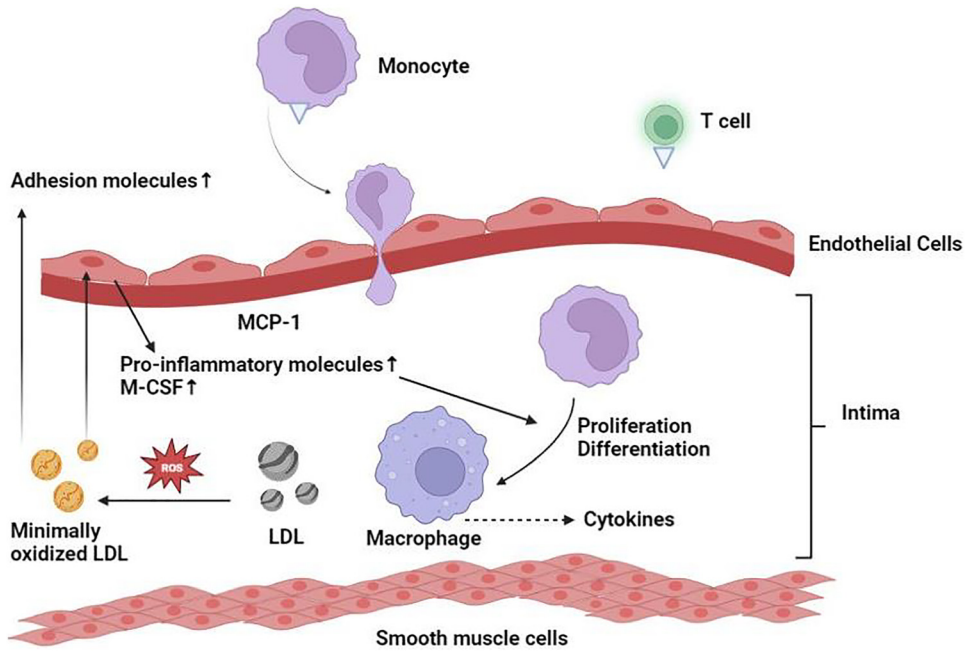

Fig. 1. Bacterial invasion of endothelial cells leads to upregulation of inflammatory mediators, adhesion molecules and Monocyte chemoattractant protein (MCP)-1 causing increased adhesion and migration of the monocytes into the subendothelial layer causing endothelial dysfunction

gingipains secreted by *P. gingivalis* can induce procoagulant properties in endothelial cells [30]. The combined effects of *P. gingivalis* invasion, the release of inflammatory mediators, increased expression of P-selectin, and E-selectin on endothelial cells, altered protein expression, and induction of endothelial cell apoptosis contribute to endothelial dysfunction and enhance monocyte migration and adhesion [22]. By disrupting the normal functioning of endothelial cells, *P. gingivalis* infection can promote the formation of atherosclerotic plaques and contribute to the pathogenesis of CVD.

FOAM CELL FORMATION

Macrophages play a crucial role in controlling serum lipoprotein and cholesterol levels by efficiently absorbing and expelling lipids into the circulation [31]. Endotoxins produced by periodontal pathogens can disrupt lipid metabolism in macrophages, leading to lipid build-up. *P. gingivalis* has been shown to promote oxidative modification of LDL [32]. Endothelial cells and macrophages produce reactive oxygen species that are involved in oxidative modification of LDL particles, along with enzymes, like myeloperoxidase and sphingomyelinase [33]. This increases LDL susceptibility to macrophage uptake, leading to foam cell formation, which are lipid-laden macrophages commonly found in atherosclerotic plaques. *P. gingivalis*-derived LPS has also been found to upregulate the expression of CD36, a scavenger receptor responsible for the uptake of LDL and oxidized (Ox)- LDL by macrophages [13, 34]. As a result of suppression of both lipid catabolism and efflux by bacterial LPS, LDL cholesterol and oxidized LDL start accumulating in macrophages.

FIBROUS PLAQUES FORMATION

The smooth muscle cells (SMC) migrate from the middle layer into the intima of the blood vessel as the atherosclerotic lesion progresses resulting in fibrosis which is a major event in the development of atherosclerosis [35]. The cytokines and growth factors produced by macrophages and T cells aid in SMC migration, proliferation and extracellular matrix production. Degradation of the extracellular matrix by matrix metalloproteinases (MMPs) and other proteases promotes SMC migration [36]. Periodontal pathogens like *Porphyromonas intermedia, P. gingivalis* and *A. actinomycetemcomitans* upregulate the synthesis and matrix-degrading activity of distinct MMPs in endothelial cells, monocytes, macrophages, and fibroblasts [37]. *P. gingivalis* gingipains influence SMC migration by upregulating angiopoietin 2 which regulates vascular maturation and stability [38].

Fibrous plaques are characterized by an increasing mass of extracellular lipid, largely cholesterol and its ester, and by the accumulation of SMC and extracellular matrix. The mature atherosclerosis plaque which is characterized by fibrosis and calcification bulges into the channel and reduces the vessels blood supply [39]. The composition and vulnerability of a plaque are thought to be the primary determinants that influence the occurrence of thrombus-mediated acute coronary events with vulnerable plaques having a thin fibrous cap with increased numbers of inflammatory cells. The presence of tissue factor, a protein responsible for initiation of the coagulation cascade is likely to play a key role in the thrombogenicity of the lesion. Bacterial infection and Ox-LDL have an impact on the synthesis of tissue factor by endothelial cells and macrophages [40].

Table 1. Summary of studies that have detected periodontal pathogens in the atherosclerotic plaque

Author	Methodology	Significant Findings
Kazarov et al. (2006) [42]	129 samples from 29 patients divided into two groups and were examined for presence of bacterial 16SrDNA from 10 different species using real time PCR.	Species from the Bacteroides family was found in 17% of the young but about 80% of the elderly patients group. Found an association between periodontal organisms and vascular inflammation.
Gaetti-Jardin et al. (2009) [43]	Detection of 6 pathogenic bacteria in 44 patients (39 periodontitis patients and 5 healthy patients) with CVD by quantitative PCR.	*P. intermedia, P. gingivalis* and *A. actinomycetemcomitans* were the most prevalent bacteria in the atheromas from patients with periodontitis. Periodontal bacterial DNA was found in atheromatous plaques of periodontitis patients.
Ziebolz et al. (2018) [44]	Detection of 11 pathogenic bacteria in atrial and myocardial samples using PCR in 30 patients and to investigate the connection between periodontal status and cardiac tissue inflammation.	Pathogenic bacteria comprising of *A. actinomycetemcomitans* and red complex were present in the cardiac tissues in 42% of the patients. 76% of the patients had severe form and 17% had moderate form of periodontitis.
Brun et al. (2019) [45]	A cross-sectional study where 45 patients scheduled for endarterectomy were examined. The levels of antibodies against periodontal bacteria were determined in sera and the markers of neutrophil recruitment, activation and cytokines were also measured. The oral microbiota was evaluated using microbial whole-genome sequencing, nested PCR, and immunostaining in carotid plaque samples.	*P. gingivalis* DNA were identified in 24% of the samples. Periodontitis associated genera (*Porphyromonas, Prevotella, Campylobacter, Fusobacterium, Capnocytophaga*) were detected in 21% of the samples. Periodontitis was significantly associated with neutrophil activation markers and plaque vulnerability to rupture. A strong association between high total and LDL cholesterol and deep pockets.
Szulc et al. (2015) [46]	91 patients with CAD or scheduled for carotid endarterectomy were examined. Presence of *P. gingivalis* DNA in subgingival and atheromatous plaques was determined by PCR.	Bacterial DNA was detected in 21 of 91 samples taken from vessels and *P. gingivalis* was identified in the vessel samples of patients with periodontitis.

EVIDENCE OF DIRECT BACTERIAL INVASION

Invasion of endothelial cells by periodontal pathogens may affect their proinflammatory and proatherogenic properties and lead to programmed cell death, which are all indicative of endothelial dysfunction. Periodontal pathogens, like *A. actinomycetemcomitans*, *P. gingivalis*, *T. denticola* and *T. forsythia*, have been detected in human atheromatous plaque which implies invasion of the atheroma's. A summary of the studies where periodontal pathogens were detected in atheromatous plaques of patients with CVD is shown in Table 1. Workshop on Periodontitis and Systemic Diseases conducted by the European Federation of Periodontology/American Academy of Periodontology reported that there is epidemiologic data that periodontitis may increase the risk for future CVD and the influence of periodontitis on CVD is plausible: translocated oral bacteria may induce systemic inflammation and lead to the progression of atherosclerosis [41].

INDIRECT MECHANISM OF PERIODONTAL PATHOGENS CAUSING ATHEROSCLEROSIS

Inflammation is a major driver of plaque maturation and rupture and various types of inflammatory cells have been identified in atherosclerotic plaques [47]. Endotoxin produced by bacteria have been shown to be potent activators of various inflammatory responses, stimulating monocytes, and triggering the production of several cytokines [48]. The cytokines and inflammatory mediators released during periodontal disease have been hypothesized to act systemically to induce systemic disease. It has been observed that healthy individuals with periodontitis had higher serum levels of acute-phase reactants, C-reactive protein (CRP), and inflammatory cytokine concentration than periodontally healthy controls [49]. CRP promotes foam cell formation by stimulating increased expression of cell adhesion molecules, enhancing monocyte recruitment to the arterial wall, and promoting LDL uptake by macrophages [47]. Numerous studies have reported that patients with severe periodontitis have elevated levels of systemic inflammatory markers like IL-6, CRP and haptoglobin and these increased levels can intensify the atherosclerosis and its associated complications [50–52].

CONCLUSION

Clinical and epidemiological studies have offered sufficient evidence of periodontitis having an adverse effect on systemic health including atherosclerosis, however, a direct causal effect has not yet been proved. Further longitudinal

and randomized controlled trials would be needed to establish the role of periodontal pathogens in the development of atherosclerosis. Several risk factors for CVD have been recognized, however, there has still been an alarming increase in the prevalence of cardiovascular disease. Thus, efforts to prevent atherosclerosis are an important public health issue. If a link between periodontal pathogens and development of atherosclerosis is established, it would lead to a better understanding of the mechanisms of infectious atherosclerosis and may also hold the key to develop novel and effective treatment and preventive approaches. Targeted therapy against specific micro-organisms would then be beneficial and the mortality rate from cardiovascular diseases can be reduced.

Conflict of interest: There was no conflict of interest.

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