

The Link between Periodontal Disease, Inflammation and Atherosclerosis — an Interdisciplinary Approach

Theodora Benedek

University of Medicine and Pharmacy, Tîrgu Mureş, Romania

CORRESPONDENCE

Theodora Benedek

Str. Gheorghe Marinescu nr. 38
540139 Tîrgu Mureş, Romania
Tel: +40 265 215 551
E-mail: theodora.benedek@gmail.com

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ABSTRACT

Periodontal disease is a chronic inflammatory disease that results from the activity of altered oral microbiome, leading to altered immune reaction, destruction of tissues supporting the teeth, and oral bone loss. This disease is particularly associated with an expressed systemic inflammation, being considered nowadays an inflammatory disorder. At the same time, inflammation has been recognized to play a major role in the development of atherosclerotic lesions. Atheromatous plaque formation is triggered by alterations in the structure of the endothelium, which lead to the expression of adhesion molecules and recruitment of immune cells such as macrophages, in the arterial wall. While the association between periodontal disease, inflammation and cardiovascular diseases has been well established, the causality relation between these three entities has not been demonstrated so far. This review presents the most common advances in understanding the complex link between periodontal disease, inflammation and atherosclerosis, as a common pathway leading to increased cardiovascular risk.

Keywords: atherosclerosis, periodontal disease, inflammation

Atherosclerosis remains a major health problem, and atherosclerosis-related diseases continue to represent a significant burden for society. Atherosclerosis is a generalized process that affects the entire arterial system, being characterized by the presence of atheromatous plaques at different locations in the circulation.

According to the location of the atheromatous plaques, the most common presentations of this disease are represented by coronary artery disease (CAD) when the plaques are located in the coronary arteries, peripheral arterial disease (PAD) when the plaques are located in the circulatory system, or ischemic stroke resulting from severe atherosclerotic plaques in the carotid arteries. While the clinical manifestations are different in these three entities, the pathophysiological substrate is common in all clinical forms of atherosclerosis, relying mainly on the mechanisms of plaque formation and associated inflammation.

INFLAMMATION — A COMMON PATHWAY FOR PERIODONTAL DISEASE AND ATHEROSCLEROSIS

Periodontal disease is a chronic inflammatory disease that results from the activity of altered oral microbiome leading to altered immune reaction, destruction of tissues supporting the teeth, and oral bone loss.¹ This disease is particularly associated with an expressed systemic inflammation, being considered nowadays an inflammatory disorder. The activity of sub-gingival microbes accumulated in periodontal disease alters the cytokine and chemokine responses of the host, leading to an exacerbated systemic inflammation.² Lu *et al.* demonstrated that human gingiva is one of the sites of C-reactive protein production, proving the significant role of gingiva in the inflammatory pathways.³

At the same time, inflammation has been recognized to play a major role in the development of atherosclerotic lesions.⁴ Atheromatous plaque formation is triggered by alterations in the structure of the endothelium, which lead to expression of adhesion molecules and recruitment of immune cells such as macrophages, in the arterial wall. Once the endothelial surface is damaged, vascular adhesion molecules (VCAM) and intercellular adhesion molecules (ICAM) are expressed, allowing leucocytes to bind to the endothelium, thus favoring lipid accumulation and the production of chemokines, which in turn promote the accumulation of smooth muscle cells and, as a result of inflammatory stimulation, secretion of metalloproteinases and rupture of the fibrous cap, causing plaque rupture and acute coronary syndromes.⁵

In animal experiments, oral interventions were associated with increased release of biomarkers characterizing atherosclerosis. For instance, in a study by Li *et al.*, oral intervention in mice was associated with increased expres-

sion of matrix metalloproteinases in carotid arteries and higher levels of serum interleukin 6, biomarkers traditionally associated with atherosclerosis and, at the same time, powerful inflammatory markers.⁶ A case-control study led by Ramirez *et al.* proved that higher plasma levels of cardiovascular biomarkers such as E-selectin and myeloperoxidase were recorded in patients with chronic periodontal disease.⁷

The complex interaction between pro-inflammatory factors released by periodontal microbes and the vascular endothelium represents the pathophysiologic substrate of the link between the atherosclerotic process and periodontal disease (Figure 1). Table 1 presents the results of the main clinical studies that addressed the link between atherosclerosis and periodontal disease.^{8,9}

GINGIVAL MICROBIOTA AND ATHEROSCLEROTIC PLAQUE COMPOSITION

Recent evidence suggest that among the multitude of factors involved in the development of atherosclerotic plaques, microbiota and associated inflammation in the periodontium could play a role in the pathophysiology of atheromatous plaque formation, via increasing the inflammatory level in the body of the host. Immune dysregulation mediated by the oral microbiome has been proposed to represent the pathway between periodontitis and chronic inflammation, which in turn triggers and augments the development of the atherosclerotic process.¹ Oral infection leads to an increased release of inflammatory cytokines, which enter the systemic circulation and reach various distant locations, favoring the development of atherosclerosis at these sites.¹⁰ However, the immune mechanisms via which periodontal pathogens exacerbate plaque progression are not elucidated yet. At the same time, Carrion *et al.* demonstrated that blood myeloid DCs

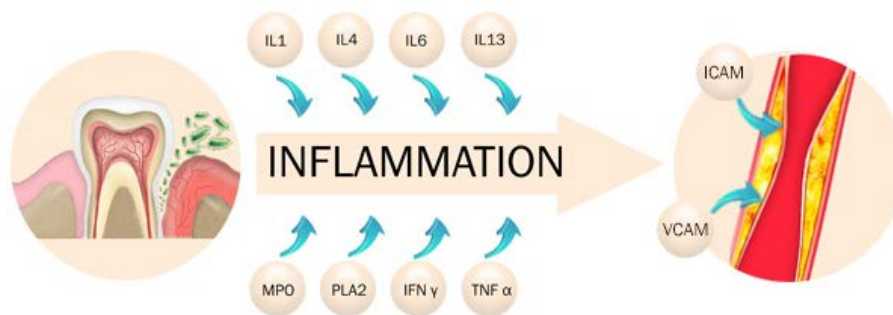


FIGURE 1. The pathophysiologic substrate of the link between the atherosclerotic process and periodontal disease

TABLE 1. Recent studies on the link between atherosclerosis and periodontal disease

Study	Year	Number of participants	Conclusions
Gomes <i>et al.</i> ³²	2016	278 dental patients	Endodontic burden is an independent predictor of CVD
Bengtsson <i>et al.</i> ³⁵	2016	499 dental patients	Periodontitis is significantly associated with carotid calcification
Ketabi <i>et al.</i> ³⁴	2016	59 patients with coronary artery disease 23 patients without coronary obstruction	Periodontal disease and dental parameters correlates with the severity of coronary artery disease
Mahendra <i>et al.</i> ¹³	2015	51 patients with CV disease 51 controls	Study lot had higher number of bacteria in the subgingival plaques Number of bacteria in the subgingival plaques correlates with number of bacteria in atherosclerotic plaques
Groves <i>et al.</i> ³³	2015	473 diabetic patients 548 non-diabetic patients	Periodontal disease is a direct predictor of CVD in type 1 diabetic patients
Soder <i>et al.</i> ³⁹	2015	1676 participants randomly selected	Gingival inflammation correlates with stroke
Ramirez <i>et al.</i> ⁷	2014	22 patients with moderate/severe periodontitis 22 controls	E-selectin and myeloperoxidase levels significantly increased in patients with moderate/severe periodontitis
Rathnayake <i>et al.</i> ⁴⁸	2015	200 patients with acute myocardial infarction	Salivary levels of Matrix Metalloproteinase-8 and 9 and myeloperoxidase (biomarkers of CV risk) are associated with periodontal status
Gupta <i>et al.</i> ⁴⁹	2015	30 patients with severe chronic periodontitis 50 healthy controls	CV risk markers are increased in patients with periodontal disease
Etemadifar <i>et al.</i> ⁵⁰	2015	30 patients with severe periodontal disease 30 healthy controls	High levels of C-reactive protein is associated with periodontal disease
Armingohar <i>et al.</i> ⁴⁷	2014	40 patients with peripheral arterial disease	Higher bacteria levels in vascular biopsies from patients with periodontal disease
Carrion <i>et al.</i> ¹¹	2012	40 patients with acute coronary syndrome 25 healthy controls	Blood myeloid DCs play a role in harboring and disseminating oral pathogens to atheromatous plaques
Koren <i>et al.</i> ²⁹	2011	15 patients with atherosclerosis 15 healthy controls	Levels of plaque, oral and gut microbiota correlate with biomarkers of atherosclerosis
Figuro <i>et al.</i> ³⁸	2011	42 patients undergoing carotid endarterectomy	DNA of at least 1 bacteria was present in all 42 samples

play a role in harboring and disseminating oral pathogens to atheromatous plaques, suggesting also a direct effect of bacterial contamination in the determination of atherosclerotic lesions.¹¹

In the Oral Infection and Vascular Disease Epidemiology Study, 4,561 biofilm samples were collected from 593 patients for the assessment of bacterial species and found significantly increased levels of secretory phospholipase A2 and lipoprotein-associated PLA2, two inflammatory enzymes associated with atherosclerosis.¹² At the same time, Mahendra *et al.* proved that patients with cardiovascular diseases (CVD) exhibit higher levels of periodontal pathogens in subgingival biofilms, and that the amount of subgingival bacteria was significantly associated with the amount of bacteria identified in the atherosclerotic plaques.¹³

Various pathogens such as *Chlamidia pneumoniae*, *Porphyromonas gingivalis* or *Helicobacter pylori* were identified

in human atheromatous plaques, suggesting that infectious agents present in the systemic circulation could penetrate the vascular endothelium and accumulate within the atheromatous plaques, favoring plaque progression.^{1,14-21} Table 2 presents the main types of bacteria from oral microbiota, identified by different studies as related to atheromatous plaque formation. In a study on 91 patients with carotid artery disease, the DNA of atheromatous plaques was assessed following carotid or coronary atherectomy (an interventional technique used for in vivo plaque removal using a cutting device introduced percutaneously via the femoral artery and guided under fluoroscopic control to the site of the carotid or coronary plaque). This technique succeeded to identify the DNA of *Porphyromonas gingivalis* in atheromatous plaques of patients with periodontitis.^{22,23}

Filardo *et al.* isolated a *Chlamidia pneumoniae* strain from the gingival cervicular fluids and demonstrated that this isolate significantly increased the number of foam cells

TABLE 2. Main types of bacteria from oral microbiota identified by different studies as related to atheromatous plaque formation

Study	Year	Bacteria
Haraszthy <i>et al.</i> ¹⁶	2000	Porphyromonas gingivalis Tannerella forsythensis Proteolla intermedia
Figuero <i>et al.</i> ³⁷	2011	Porphyromonas gingivalis Aggregatibacter actinomycetemcomitans Tannerella forsythensis Eikenella corrodens Fusobacterium nucleatum Campylobacter rectus
Koren <i>et al.</i> ²⁸	2011	Chryseomonas Veillonella Streptococcus
Carrion <i>et al.</i> ¹⁰	2012	Porphyromonas gingivalis Burkholderia cepacia
Szulc <i>et al.</i> ²¹	2015	Porphyromonas gingivalis
Fak <i>et al.</i> ²⁷	2015	Anaeroglobus Parvimonas Catonella Lactobacillus Capnocytophaga
Filardo <i>et al.</i> ²³	2015	Chlamydia pneumoniae
Chukkapalli <i>et al.</i> ²⁴	2015	Porphyromonas gingivalis Treponema denticola Tannerealla forsythis Fusobacterium nucleatum

and the levels of interleukin-1 and interleukin-6, all these factors playing major roles in the development of atherosclerotic plaques.²⁴

In a study by Chukkapali *et al.*, the oral cavity of ApoE^{null} mice was infected with various microbial species such as *Porphyromonas gingivalis*, *Treponema denticola*, *Fusobacterium nucleatum* and *Tannerealla forsythis*, agents that have been identified in the atherosclerotic plaques collected from humans. The study demonstrated an increased release of inflammatory cytokines such as IL-13, IFN gamma and IL-4 at 24 weeks after infection. At the same time, polybacterial infection was associated with altered lipid profiles and increased plaque formation in the aorta, proving that these oral cavity infections could induce atherosclerosis via inflammatory pathways.^{25,26}

In a study on pigs exposed orally to *P. gingivalis*, Paquette *et al.* demonstrated that exposed pigs exhibited higher levels of systemic C-reactive protein (a strong inflammatory marker) and increased atheroma burden as compared to controls.²⁷ In humans, Fak *et al.* proved that atherosclerotic patients had higher levels of *Anaeroglobus*

as compared to controls, and that the presence of *Lactobacillus*, *Catonella* and *Capnocytophaga* in the periodontal space was associated with elevated levels of serum lipids.²⁸ Other bacteria isolated from atherosclerotic plaques were *Chryseomonas*, *Veillonella* and *Streptococcus*.²⁹

PERIODONTAL DISEASE AND CARDIOVASCULAR RISK

The association between periodontitis and CVD has been recognized for many years, and since then, many studies tried to elucidate the role of periodontal disease as a cardiovascular risk factor. Buhlin *et al.*, using a nationwide questionnaire in Sweden, reported a significantly increased risk of CVD if the patient had experienced untreated dental problems (OR 2.45, 95% CI 1.066–5.625).³⁰

Various clinical biomarkers have been used to validate the hypothesis that periodontal disease could independently predict the development of clinical atherosclerosis. One of these biomarkers is the carotid-intima thickness, a strong indicator of cardiovascular risk significantly associated with the severity of the atherosclerotic process. In a study by Toregeani *et al.*, the treatment of periodontitis significantly decreased the carotid-intima thickness at 6 months after initiation. The reduction of carotid-intima thickness following periodontitis treatment could be considered a direct expression of the relation between this disease and atherosclerotic disease.³¹

The Baltimore Longitudinal Study of Ageing, carried out on 278 patients, proved that apical periodontitis is independently associated with the incidence of cardiovascular events.³²

While the association between periodontal disease and atherosclerosis has been well established for many years, the role of periodontal disease as an independent risk factor for cardiovascular disease is not clearly supported by current evidence so far. There is accumulating evidence suggesting that the treatment of periodontitis could reduce atherosclerosis progression. However, larger longitudinal studies are needed in order to prove the power of this new risk factor in the complex family of CV risk factors.

PERIODONTAL DISEASE AND CORONARY ARTERY DISEASE

Groves *et al.*, in a study on 1,021 individuals out of which 473 diabetics, demonstrated that periodontal disease is significantly associated with the accumulation of calcium in the coronary artery wall in diabetic patients, proving that the presence of periodontal disease could be considered an

independent predictor of atherosclerosis development in a diabetic population.³³

In a study on 82 patients undergoing coronary angiography, Ketabi *et al.* proved that parameters expressing periodontal disease, such as pocket depth, gingival recession, clinical attachment level, and bleeding on probing were significantly higher in patients with CAD as compared to patients with no coronary obstruction on angiography. Furthermore, they found a significant correlation between these parameters and the severity of CAD at angiography, proving that a direct link exists between periodontal disease and coronary atherosclerosis.³⁴

At the same time, the treatment of periodontal disease seems to reduce the atherosclerotic burden along with the level of inflammation. A recent meta-analysis demonstrated that the treatment of established periodontitis led to an improved endothelial function and a significant reduction in the levels of CRP, Il-6, TNF-alpha and total cholesterol.^{35,36}

However, it should be noted that according to the level of stability of coronary plaques, coronary artery disease has two different forms: (1) stable coronary artery disease, characterized by stable coronary plaques, which is associated with a chronic low-grade inflammation, and (2) acute coronary syndromes, triggered by the rupture of a vulnerable coronary plaque, process in which a suddenly exacerbated inflammation plays a major role.³⁷ While a large number of studies addressed the link between periodontal disease and chronic atherosclerosis, no study reported a clear correlation between this disease and acute coronary syndromes.

PERIODONTAL DISEASE AND CAROTID ARTERY DISEASE

The presence of DNA from bacteria causing periodontal disease has been identified in a large proportion of samples of carotid plaques obtained using endarterectomy.³⁸ Soder *et al.* proved a strong association between gingival inflammation and stroke and demonstrated, in a multiple regression analysis, an odds ratio of 2.2 (95% CI 1.02–4.74) for gingival inflammation for predicting stroke.³⁹

A very large meta-analysis on 17,330 patients, designed to identify the association between carotid atherosclerosis and periodontal disease, proved that the presence of periodontal lesions is associated with a significant risk for carotid atheromatous plaque formation (OR: 1.08, $p = 0.05$).⁴⁰ Another study, conducted on 499 individuals, proved that patients with periodontitis had a significantly higher prevalence of carotid calcifications compared to patients with no periodontal disease.⁴¹ All these data suggest

that the mechanisms of endothelial plaque formation and progression, in relation to periodontal disease, are common both for carotid and coronary locations.

PERIODONTAL DISEASE AND PERIPHERAL ARTERY DISEASE

PCR analysis of the DNA and RNA of various oral bacterial species demonstrated the presence of *P. gingivalis*, *T. forsythia*, *F. nucleatum* and others in atherosclerotic plaques extracted from the peripheral arteries.^{42–44} It has also been proved that the presence of *P. gingivalis* in atherosclerotic plaques accelerates the progression of abdominal aortic aneurysms,^{42,43} and Kowalski *et al.* demonstrated that infection with oral pathogens is associated with a significantly greater lumen loss at 6 months after stent implantation, proving that periodontal disease and associated bacteria can also be involved in the complex mechanism of in-stent restenosis.⁴⁵ Armingohar *et al.* extracted DNA from vascular biopsies obtained from patients with peripheral vascular disease and found a significantly higher bacterial load in patients with vascular disease associating periodontal disease as compared to those without periodontal disease.^{46,47}

CONCLUSIONS

The link between periodontal disease, inflammation and CVD has been well established. However, the relation of causality between these three entities has not been demonstrated so far. Further research is still needed in order to elucidate whether periodontal disease causes atherosclerotic plaque formation or they are rather common manifestations of the same inflammatory disease.

CONFLICT OF INTEREST

Nothing to declare.

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