

# Atherosclerosis and Periodontal Disease

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## ABSTRACT

Atherosclerosis is a chronic inflammatory disease of the arteries which initiate with the focal accumulation of lipids at the endothelium level. The prevalence of atherosclerosis has increased steadily due to aging population and it is one of the leading cause of mortality and morbidity worldwide. While the periodontal disease is a chronic, destructive and inflammatory condition of the oral cavity affecting a significant portion of the adult population and it is a major cause of tooth loss. To date, several epidemiological and meta-analysis studies have suggested that periodontitis infection is a risk factor for cardiovascular diseases and in particular of atherosclerosis.

The aim of this chapter was to summarize the pieces of the puzzle which identified the possible link between the atherosclerotic and the periodontal disease processes and, moreover, describe the possible double role of the periodontal disease treatment that may, interestingly, modulate both periodontitis and atherosclerosis.

**Keywords:** Atherosclerosis; Periodontal disease; Bacterial infection

# ATHEROSCLEROSIS

The prevalence of atherosclerosis has increased steadily due to aging population. Economic development and urbanization have promoted habits of diet rich in saturated fat and diminished physical activity, factors which favour atherosclerosis development [1]. Atherosclerosis is the leading cause of mortality and morbidity worldwide for the past 50 years [2-7]. Atherosclerosis and related Cardiovascular Diseases (**CVDs**) are not only a major cause of death in Western countries, but they also have a large impact on the quality of life of patients involved [8-10]. Atherosclerosis is a chronic inflammatory disease of the arteries which initiate with the focal accumulation of lipids into the vessel intima layer [11-13]. The atherosclerotic pathogenic process is initiated early in life, during postnatal development and maturation, and advances gradually throughout life [14,15]. Endothelial dysfunction is considered the initial step in the pathogenesis of atherosclerosis in the general population and may be a marker for future risk of cardiovascular events [1,3,16,17]. Dysfunctional lipid homeostasis plays a central role in the initiation and progression of endothelial alterations. High-Density Lipoproteins (**HDLs**) are inhibitors of the process, primarily through the process of reverse cholesterol transport, whereas Low-Density Lipoproteins (**LDLs**) are crucial to the development of atherosclerotic lesions [9,10,18,19] (Figure 1).

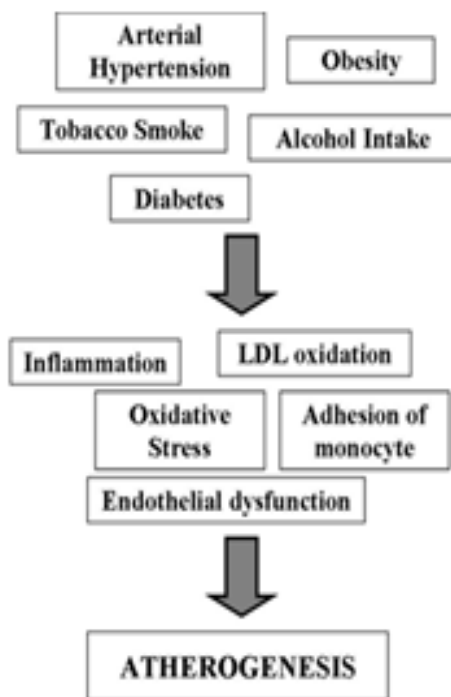


**Figure 1:** Proatherosclerotic alterations-Main alterations that induce the atherosclerotic plaque development.

LDL: low density lipoprotein.

In fact, oxidized-LDLs (**ox-LDLs**) are the major lipids found in the atherosclerotic lesion and they are considered the major causative factor in the development of atherosclerotic plaque [20,21]. Ox-LDLs also behave as potent inflammatory agents, they stimulate the expression of adhesion molecules on endothelial cells contributing, in turn, to the adhesion of monocytes and T lymphocytes to the arterial endothelium and their penetration into the subendothelial space and leading to endothelial dysfunction [14,22,23]. Thereafter, the monocyte-derived macrophages, by taking up ox-LDLs, become foam cells, which are typical cellular elements of the fatty streak, the earliest detectable atherosclerotic lesion [19,24]. Along with altered endothelium, these cells release various growth factors, leading to migration and proliferation of the smooth muscle cells of the tunica media layer, so forming the typical atherosclerotic plaque [1].

Intrusion of the plaque into the vessel lumen creates a region of low/disturbed flow downstream, which may account for the tendency of plaques to progress in a downstream direction [11,25]. Advanced lesions can grow sufficiently large to block blood flow and so develop an acute occlusion due to the formation of thrombus or blood clot resulting in the important and severe cardiovascular clinical events [24,26]. In Figure 2 is schematically represented the atherosclerotic plaque development.

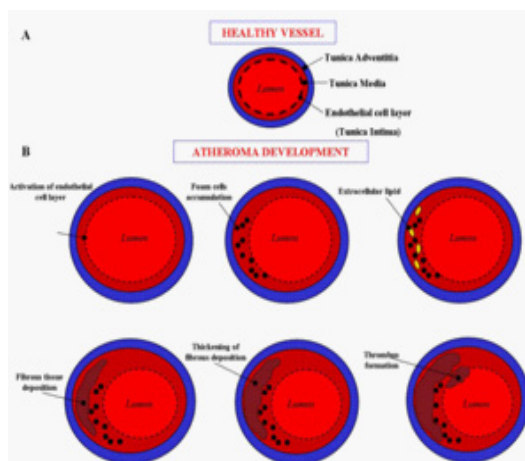


**Figure 2:** Healthy vessel vs atherosclerotic plaque - Schematic representation of a healthy vessel (A) and a vessel with the atherosclerotic plaque (B). In particular, the activation of the endothelial layer is the earliest histopathological change, and then macrophages accumulate lipids becoming foam cell. Thereafter, the lesion is defined by a relatively thin tissue separation of the lipid core from the arterial lumen, whereas the advance lesion exhibits a fibrous thickening of the cap. Finally, the lesion shows a complex plaque architecture culminating often in its rupture, fissuring or ulceration and so leading to atherosclerosis-related cardiovascular alterations. Modified from Stocker and Keane [155].

Atherosclerosis is a dynamic process that comprises continuous molecular and cellular activities within atherosclerotic plaques [4] and given the multifactorial and complex nature of atherosclerosis, further studies to clarify the understanding of the pathogenic process are needed to improve atherosclerosis diagnosis, management, prevention and treatment.

In addition to being a common and frequent CVDs, it seems to be link to periodontal disease. Several epidemiological and meta-analyses studies have also suggested that periodontal infection is a risk factor for acute myocardial infarction, peripheral vascular diseases and cerebrovascular disease [27-35]. In fact, the association between CVDs and periodontal diseases in meta-analysis literature is stronger when systemic inflammatory and serologic markers are used to determine the systemic bacterial exposure secondary to periodontitis.

## PERIODONTITIS

Periodontal disease is a chronic, destructive and inflammatory condition affecting a significant portion of the adult population. Over than the 47% of the population is affected of periodontitis. In particular, adults exhibited mainly moderate or severe periodontitis [36], whereas approximately 10% to 15% of the adult population has a more severe process with destruction of the teeth supporting tissues [37,38]. The periodontitis are defined by the anatomic destruction of the tissues that are sustaining the teeth [39]. In fact, periodontal disease is a major cause of tooth loss also because it leads to the irreversible destruction of connective tissue attachment and alveolar bone [40-43]. It is accompanied by conversion of the shallow gingival sulcus into a deep periodontal pocket and also a marked proliferation of a dysbiotic subgingival biofilm [32,44-48]. Periodontitis is usually defined as an asymptomatic disease because it not produce any clinical symptoms, even if periodontal pockets and alveolar bone loss are detectable [40,42,49] and, with radiographs, it is possible to identify also the destruction of the periapical tissues with possible reabsorption of root and bone [50].

The origin and progress of the inflammatory reaction in the periodontium are a result of the altered interplay of the defence mechanisms in the periodontal tissue to respond to the activity of dental plaque bacteria [49]. The cell infiltrate occupies an increasing proportion of the connective tissue and might cause a collagen degradation or a fibrotic reaction [51] by stimulative effects of inflammatory mediators of the connective tissue [52]. Periodontal disease is in fact characterized by a chronic infection that is the product of a polymicrobial perturbation of host homeostasis, at the level of soft and hard tissues that support the teeth [46,50,53-56], due to the presence of anaerobic bacteria in the dental biofilm [35]. A low redox potential, supply of nutrients in the crevicular fluid and limited amount of oxygen in the periodontal pocket characterize the optimal conditions for the occurrence of gram-negative anaerobic bacteria. The most frequent bacteria involved in pathogenesis of the periodontitis are *Porphyromonas gingivalis*, *Prevotella intermedia*, *Fusobacterium nucleatum*, *Tannerella forsythia*, *Treponema denticola*. Most of these pathogenic bacteria belong to gram negative bacteria that contain the lipopolysaccharides, a potent

activator of B lymphocytes. *Porphyromonas gingivalis* is one of the more important periodontal disease pathogen (Bartova et al., 2014) together with *Aggregatibacter actinomycetemcomitans* [35,42,57,58]. Pathology occurs when *Porphyromonas gingivalis* binds to and accumulates on the tooth surface, leading to the development of a mixed biofilm, the expansion of the bacteria into the gingival sulcus and so the formation of a periodontal pocket [59]. In particular, *Porphyromonas gingivalis* invades gingival epithelial cells binding its fimbriae to integrin on the host cell surface and follow a rearrangement of the host actin cytoskeleton [60]. This pathological mechanism induces also a delay in neutrophil recruitment, which allows the proliferation of bacteria in this new niche, leading to an alteration of the subgingival microbiota with respect to its composition and total bacterial count [59,61,62]. Although, it is important to underline that the presence of subgingival microbiota is a necessary condition for the disease to progress, it is not the only cause [49] (Figure 3).

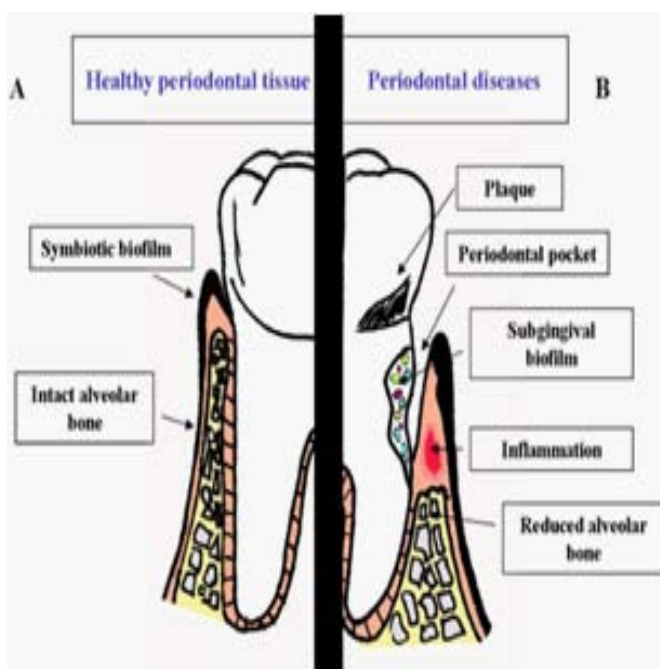


**Figure 3:** Healthy periodontal tissue vs periodontal disease - Schematic representation of healthy periodontal tissue (A) representation compared to periodontal disease (B), underlining the formation of periodontal pocket ( $\geq 4$  mm), plaque, dysbiotic biofilm, inflammatory response and alveolar bone reabsorption.

Interestingly, many studies have, in particular, analyzed the potential impact of the *Porphyromonas gingivalis* on general health and especially on cardiovascular problems [38,63,64] and so chronic periodontitis has become the focus of increasing interest, owing to its rising prevalence and its association with life-threatening systemic disorders such as atherosclerosis,

autoimmune disease, cancers, diabetes mellitus, rheumatoid arthritis and Alzheimer's disease [41,65-67]. To date, chronic infectious diseases, including gingival inflammation and periodontal disease, have been shown to be involved in the development and progression of CVDs [32,68-72]. Periodontal bacteria from the biofilm at the interface with the ulcerated periodontal pocket epithelium enter the circulation during speech, eating and tooth brushing and disseminate throughout the body via the blood circulation [73-76]; so bacterial infections promote the onset and progression of atherosclerosis by injuring the vascular endothelium and by activating systemic and local inflammatory immune responses [74,77,78]. Many bacterial species have been suspected of playing an important role also in atheroma development [79] together with the fact that the global prevalence of periodontal diseases is extremely high and, moreover, periodontitis may induce a chronic inflammatory response [38, 80]. Susceptibility to periodontitis and other inflammatory diseases appears to change in response to complex interactions of genetic, environmental and stochastic factors throughout the lifespan [36]. All these observations have increased the interest to study in deep the link between atherosclerotic and periodontal pathogenic processes. However, the causal relationship and pathological mechanism(s) still remain to be elucidate also because periodontal disease and many chronic systemic diseases are multifactorial with a large number of causes and modifying endogenous and exogenous factors [81].

The aim of this chapter was to summarize the many pieces of the puzzle which identified the possible link between the atherosclerotic and the periodontal disease processes and, moreover, describe the possible double role of the periodontal disease treatment that may, interestingly, modulate both periodontitis and atherosclerosis.

## **ATHEROSCLEROSIS AND PERIODONTAL DISEASES**

In recent years the concept of focal infection has changed and mostly shows the correlation between systemic diseases and chronic periodontal inflammation [50,55,56,82]. Interestingly, there is an important association between periodontal infection and increased risk of atherosclerotic vascular disease development [27-29,32,35,45,83,84]. The main underlying mechanisms are due to the effect of bacterial invasion (direct mechanism) and inflammatory responses (indirect mechanism) [42,49,81,85,86].

Epidemiological studies have established that periodontitis is a risk factor for myocardial infarction, peripheral vascular disease and cerebrovascular disease [32,87,88], lung diseases [89], nephropathies [49,90], autoimmune diseases, cancers, rheumatoid diseases [41,65-67] and low birth weight in children [49,90]. So, it may be assumed that dental plaque bacteria not only influence the oral cavity locally, but may also contribute to the development of some serious systemic diseases. The prevalence of CVDs in patients with periodontitis is 25-50% higher than in healthy individuals. Moreover, poor self-reported oral health, as a possible risk factor for periodontitis, and tooth loss, as a possible consequence of periodontitis, are positively

associated with a coronary atherosclerotic burden [91]. Moreover, severe tooth loss may be a predictor of cerebrovascular disease-silent cerebral infarct [49,92]. However, it should be noted that much of the evidences that confirmed the link between CVDs and periodontal disease were generated by observational studies and so further studies with more robust designs should be carried out to provide answers regarding the real association between periodontitis and CVDs, like atherosclerosis.

A large number of studies published over the last two decades have examined the association of poor periodontal status and clinical atherosclerotic vascular disease-related outcomes, including coronary heart disease, myocardial infarction and stroke. Despite a substantial variability in the findings, many studies reported statistically significant associations and so confirmed that periodontal disease is a risk factor for CVDs development after adjustment for covariates and potential confounders [39,42,46,93-96]. A metaanalysis of Bahekar et al. [68] has shown increased incidence of coronary heart disease in patients with periodontal disease, even after the removal of confounding factors such as smoking, diabetes, alcohol intake, obesity and arterial hypertension.

In the late 1990s, periodontitis-atherosclerosis syndrome was firstly described and the number of studies devoted to periodontitis-atherosclerosis syndrome has increased every year. Oral diseases, periodontal inflammation and especially poor oral hygiene may act as risk factors for the development of atherosclerosis via chronic infection. In particular, chronic microbial infection, including several periodontal pathogens, may play an important role in the development of atherosclerotic disease [41,95-97]. However actually, it is unclear how periodontal disease causes thickening of the arterial intima-media wall, which is an important predictor of sub-clinical atherosclerosis [96,98,99]. Furthermore, it is important to consider that among the studies there are considerable variations in the criteria defining periodontitis, in the anatomic sites for arterial stiffness measurement, meaning that each study measured separate segments of the arterial tree and so these studies are thus not directly comparable.

*Porphyromonas gingivalis*, previous described as the microorganism closely connected with chronic periodontitis, should be considered also as one of the possible causes of eliciting general inflammation [59,100,101]. Some investigated the effect of repeated systemic inoculations with *Porphyromonas gingivalis* on the progression of atherosclerosis in hypercholesterolemic apolipoprotein E null mice, a model that spontaneously develops hypercholesterolemia and atherosclerotic lesions in the aorta in a time dependent manner [102,103], observing that chronic *Porphyromonas gingivalis* infection accelerate atherogenic plaque progression [38,49,104,105]. However, injection of *Porphyromonas gingivalis* is not the same as the condition where human periodontitis affects the pathogenesis of atherosclerosis. Therefore, we cannot translate these results as the perfect simulation of human periodontitis. There are several mechanisms by which dental plaque bacteria may initiate or worsen atherosclerotic processes: activation of innate immunity, bacteremia, direct involvement of mediators activated by dental plaque antigens in atheroma processes and involvement of cytokines and heat shock proteins from dental plaque

bacteria [49]. The anaerobic bacteria of the oral infection are able to colonize the periodontal pocket and establish a severe infection, resulting in significant gingival inflammation, alveolar bone resorption and systemic dissemination in bloodstream. Bacteria in the bloodstream interact with arterial tissues and so stimulating local vascular inflammation, which in turn can cause oxidation of LDLs and promote endothelial dysfunction [84].

The ability of *Porphyromonas gingivalis* to actively invade aortic and heart endothelial cells is just an example of the relationship between periodontitis and atherosclerosis. The presence of *Porphyromonas gingivalis* in atherosclerotic plaques also after surgical reconstruction of venous system was established [49,106]. These observations were confirmed also in many clinical trials in which the *Porphyromonas gingivalis* DNA was detected in atherosclerotic plaques of patients with also chronic periodontitis. Toyofuku, et al. [107] detected the *Porphyromonas gingivalis* DNA in 52% of arterial samples obtained from atherosclerosis patients. Marcelino et al. [108] collected and analyzed DNA of periodontal pathogens in human atheromatous and observed that the samples were positive for all bacteria, except for *Fusobacterium nucleatum*, and that *Porphyromonas gingivalis* DNA was present in 50% of the atheromatous plaque investigated. Furthermore, Ishihara et al. [109] analyzed atheromatous plaques of coronary arteries of 51 patients and detected in 21.6% of the samples the DNA of *Porphyromonas gingivalis*. Similar results were showed also by Mahendra, et al. [110], who examined the atheroma of coronary arteries of patients with chronic periodontitis and observed, in 45.1% of samples, the presence of *Porphyromonas gingivalis* DNA. Gaetti-Jardim, et al. [111] detected the 53.8% of *Porphyromonas gingivalis* DNA evaluating the atherosclerotic coronary arteries of patients with chronic periodontitis and also Szulc, et al. [38] observed the presence of *Porphyromonas gingivalis* DNA in the vessels of patients with carotid atherosclerosis. Furthermore, Ford, et al. [112] in the 31 carotid endarterectomy specimens evaluated detected the presence of *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Tannerella forsythia*, *Prevotella intermedia* and *Aggregatibacter actinomycetemcomitans*. Interestingly, recent studies have shown that invasion by *Porphyromonas gingivalis* induces also the expression of endothelial cell adhesion molecules, interleukins, monocyte chemotactic protein and toll-like receptors [113]. *Porphyromonas gingivalis* induces in fact toll-like receptor-2 and -4 expression on the surface of endothelial cells [114], suggesting that also autoimmune mechanisms secondary to periodontal infections could play a role in the progression and development of atherosclerosis [30]. Despite the presence of these bacteria in vascular endothelial cells, detection of their DNA in the filtrate obtained from stable plaque covered with a layer of fiber is difficult or not always possible [38]. Importantly, the detected bacterial DNA is derived from only live bacteria, because only live microorganisms are able to invade endothelial cells other than phagocytes [115,116]. These observations suggested that the oral microbiota may be causal in the etiology of atherosclerosis. On the other hand, Cairo, et al. [117] and also Aimetti, et al. [118] examined samples of atherosclerotic plaques of patients with periodontitis and did not detect the presence of any periodontal pathogenic bacteria. This and

the above cited discrepancies in the results from different studies may be associated with different conditions and testing methods of laboratory analysis. Furthermore, most people with a given disease suffer from more than one pathology or condition, complicating both study participant enrollment and statistical analyses of the data collected. Confirming these discrepancies, it was observed that some periodontopathic bacteria have been detected in the cardiac valve [119] and in aortic aneurysm cases [42,120], but in a meta-analysis of cohort study the risk of stroke did not vary significantly with presence of gingivitis [72].

Besides *Porphyromonas gingivalis* also *Aggregatibacter actinomycetemcomitans* is a key microbe in periodontitis and it is considered to be a potential risk factor for atherosclerosis [35,66], therefore also adding more supportive evidence how the two diseases are associated with each other. Hulthe and Fagerberg [121] observed that *Aggregatibacter actinomycetemcomitans* infection of Apolipoprotein E null mice promoted LDL oxidation at aorta level, so leading to the atherosclerotic plaque development. In this context, Blasco-Baque et al. [122] also reported that one month of colonization with periodontal pathogens such as *Porphyromonas gingivalis*, *Prevotella intermedia* and *Fusobacterium nucleatum* aggravated high-fat diet-induced metabolic alteration as well as systolic and diastolic arterial pressure in diabetic mice. Furthermore, *Porphyromonas gingivalis* increased oxidative modification of LDL [123,124] and promote the rupture of atherosclerotic plaque through induction of matrix metalloproteinases [42, 125]. Interestingly, Miyakawa, et al. [126] and Kuramitsu, et al. [127] showed that co-incubation of a murine macrophage cell line with *Porphyromonas gingivalis* in the presence of LDLs resulted in the formation of foam cells in a dose-dependent manner. Furthermore, patients with periodontitis also have increased levels of lipid peroxidation and pro-inflammatory cytokines in plasma, saliva and gingival crevicular fluid [50] and these levels have been correlated with the severity of periodontal disease [42,128].

The oxidative stress and ox-LDL levels were increased in the blood and local sites of periodontal or atherosclerotic patients and in the mouse model suggest that lipid peroxidation activates the Nod-like receptor family pyrin domain containing 3 (**NLRP3**) inflammasome and contributes to the activation of interleukines-producing T helpers [42]. In this respect, the NLRP3 inflammasome may play an important role in interleukins production in response to several bacterial ligands [42,129]. Dysregulation of the inflammasome plays a significant role in various pathological processes. In fact, NLRP3 proteins were upregulated in the aorta of coronary atherosclerosis patients [130] and gingival tissues of periodontitis patients [131]. It is possible that the NLRP3 inflammasome is activated through reactive oxygen species and ox-LDL produced due to infection, as well as through direct inflammasome activation due to infection by periodontal bacteria. Interestingly, all these observations suggest that periodontopathic bacteria contribute significantly to lipid oxidation and further inflammatory induction in remote structures as well as the oral cavity [42] corroborating the link between periodontal disease and atherosclerosis.

Kimak, et al. [50] involved in their study patients with chronic apical periodontitis, but generally in good health condition without acute periodontal diseases and infections, caring for oral hygiene. This clinical trial demonstrated that the inflammatory markers, like interleukin-6, tumor necrosis factor- $\alpha$  and high-sensitive C-reactive protein and size of chronic apical periodontitis lesion were significantly lowest in patients under 50 years of age; whereas after 50 years of age greatly increased, confirming that the patient's age has a fundamental impact on systemic healing [50]. Furthermore, a meta-analysis study of Kapellas, et al. [132] observed that the presence of periodontitis is associated with an increased carotid intima-media thickness and a decreased flow-mediated dilation, measures of endothelial dysfunction. Importantly, the Authors also concluded that periodontal treatment leads to improve the endothelial function and decreased intima-media thickness of the carotid artery, the possible beneficial effects of periodontal treatment are better explain in the last paragraph of this chapter. Also another study postulated that poor oral hygiene may be an insidious cause of endothelial dysfunction and future cardiovascular events [96,133]. Oral bacterial spread into the bloodstream also may be the origin of periodontal disease-induced endocarditis and myocardial and/or cerebral infarction, especially in patients with heart valve dysfunction, as the result of uncontrolled bacteremia [134,135].

Interestingly, a number of traditional cardiovascular risk factors are linked to intima-media thickness progression: age, gender, systolic blood pressure, LDLs, HDLs, smoking, diabetes, hypertension treatment and total cholesterol. Clearly periodontal disease shares most of these risk factors with atherosclerosis and therefore it is difficult to discern the potential impact of periodontal disease alone on the progression of intima-media thickness. The lack of a uniform adjustment for all these confounders in clinical trials, as reported also by Orlandi, et al. [45] meta-analysis review, could have reduced the accuracy of the results about the association between periodontal disease, increased intima-media thickness and impaired flow-mediated dilatation. Despite these limitations of clinical trials, several pathways have been proposed to support a potential involvement of periodontitis in the development and progression of atherosclerosis [27-29,32, 34,35,45,83]. Firstly, a direct role of oral bacteria has been hypothesized following pathogen's DNA being detected in atheromas [86]. Periodontal bacteria could directly invade endothelial cells and promote a vascular inflammatory state. In addition, bacterial end-products could trigger an innate- [45,136] or auto-immune response [83]. Secondly, patients suffering of periodontitis exhibit higher systemic inflammation than controls [85]. Locally produced inflammatory products into the systemic circulation coupled with a systemic low-grade hepatic acute phase response to periodontitis could result in a state endothelial dysfunction and further promote the atherosclerotic inflammatory process [137,138]. Lastly, cases with periodontitis tend to show a proatherogenic lipid profile including alterations of lipoprotein function and chronic vascular inflammation [32,45,139,140]. Interestingly, periodontitis and atherosclerosis are multifactorial diseases with an onset in early childhood, although first symptoms may appear in adulthood. In fact, preatheroma and atheroma are usually diagnosed in patients aged 20-30

years, similar to the age which aggressive periodontitis (early onset periodontitis) is diagnosed. Fibroatheroma is diagnosed in patients aged 40 years and over, in the similar age group where periodontitis is diagnosed in more than 50% of patients [49].

It is important to underline that the association of tooth loss with atherosclerosis may be a statistical epiphenomenon reflecting dental infection sufficiently serious to result in extraction. However, the possibility remains that tooth loss itself influences propensity for vascular disease, independent of preceding dental infection. Possible mechanisms for such a direct effect of tooth loss include consumption of a proatherogenic diet with reduced chewing efficiency and chronic denture-associated infection [141].

In summary, current evidence supports a plausible association between atherosclerosis and periodontal disease (Figure 4).

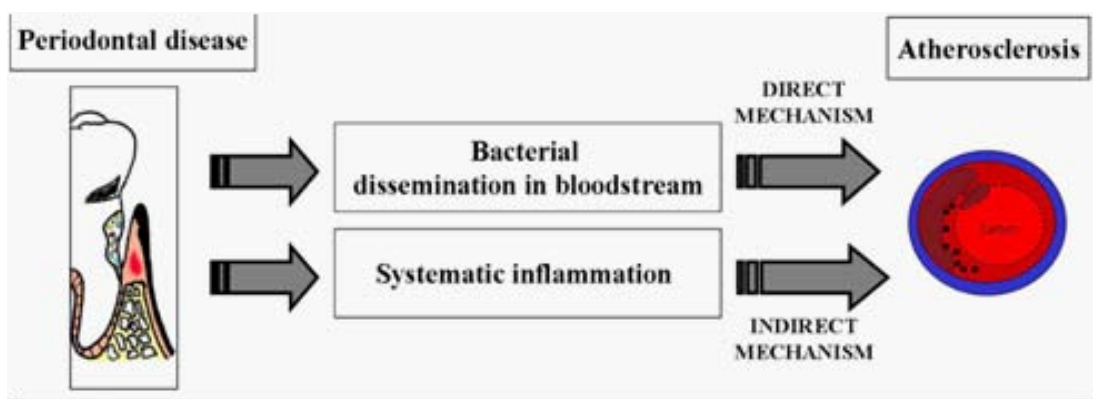


**Figure 4:** Periodontal disease and atherosclerosis association - Biologically plausible mechanisms linking periodontal disease to atherosclerotic plaque formation. Certain periodontitis-bacteria, including *Porphyromonas gingivalis*, have been detected in circulating leukocytes and in atherosclerotic lesions, where they may act as proatherogenic stimuli (direct mechanism). Furthermore, the periodontal disease locally produced pro-inflammatory cytokines that can enter the systemic circulation and contributing to induce atherosclerosis (indirect mechanism).

However, the evidence obtained from observational studies is still controversial, probably due to selection biases that have resulted in weaker association strengths. Currently, few studies have investigated whether treatment of periodontal disease improves arterial function and, in the next paragraph, we summarized the actually knowledge about this interesting point.

## Treatment of Periodontitis and Atherosclerotic Pathogenic Process

Mechanical removal of supra- and sub-gingival bacterial plaque deposits and intensive oral hygiene instructions are needed to reduce or eliminate periodontitis lesions [48]. Successful periodontal intervention may not only reduce periodontal disease and extend tooth survival, but

interestingly also prevent the initiation or progression, as well as ameliorate, of several chronic systemic diseases [81]. In detail, treatments against periodontitis consist mainly on reducing the formation of bacterial plaque in the oral cavity using physical and/or chemical forces. Antibiotics may be given as a short course, but they usually only accompany periodontal treatment, as they have difficulties to penetrate periodontal biofilms [59]. A reduction in the oral infectious burden can result in a reduction in the overall inflammatory load, with positive effects demonstrated on surrogate measures of atherosclerosis [48,142,143] and on glycaemic control, as evidenced by several meta-analyses [75,144-146]. Intensive periodontal treatment involving periodontal therapy and removal of teeth combined with localized antibiotic administration improved endothelial function at 60 and 180 days post-intervention, as observed by Tonetti, et al. [147]. Such improvements in endothelial function are consistent with slower progression of carotid intima-media thickness [148] and reduced risk of cardiovascular events [132,149]. Furthermore, in a randomized and controlled trial on Aboriginal Australians with periodontitis, the nonsurgical periodontal therapy significantly reduced progression of carotid intima-media thickness in one year [132]. However, another study including extraction of hopeless teeth for the secondary prevention of cardiovascular disease reported no benefit for subsequent CVDs [150].

It has been demonstrated that treatments-oral hygiene plus mechanical periodontal instrumentation were effective in improving clinical periodontal parameters and also promote endothelial functions and the reduction of the carotid intima-media thickness already at 6 months [147,151]. Kapellas, et al. [152] observed that modest improvements to periodontal status can be achieved and maintained for  $\leq 3$  months after one stage of periodontal therapy, irrespective of oral hygiene. However, without periodontal maintenance to remove newly formed deposits of calculus and disturb the dental biofilm, the short-term response to the periodontal tissues has a tendency to regress. Moreover, a single session of non surgical periodontal therapy may be insufficient to alter the functional aspects of vascular [132, 152]. The Authors attributed this effect to reduction in at least one microbial species associated with chronic periodontitis [151]. Furthermore, periodontal treatment reduces the risk for CVDs development by improving plasma levels of inflammatory (interleukins, tumour necrosis factor- $\alpha$ ), thrombotic (fibrinogen), adhesion molecules (VCAM-1, ICAM-1, P-selectin) and metabolic (triglycerides, HDLs) markers and endothelial functions. This improvement is sustained well over 6 months after therapy and it is greater in those individuals suffering from both periodontitis and co-morbidities like CVDs and/or diabetes mellitus [32,48]. However, risk factors for CVDs, like overweight and smoking habits may frustrate these favourable effects.

Together with traditional periodontal treatment, in the last year is emerging also “unconventional” treatment with antioxidants. An interesting study of Maruyama et al. [153] showed that topical application of a dentifrice containing green tea catechin, important polyphenol with antioxidant, antiinflammatory, and antithrombotic properties, in an induced periodontitis rat model reduced inflammatory cell infiltration in the periodontal lesions to a greater extent than did the control

dentifrice. Catechins perform antioxidant activity by scavenging free radicals, inhibiting redox active transcription factors, inhibiting pro-oxidant enzymes and inducing antioxidant enzymes. It is important to underline that these effects are critical in influencing also the progression of atherosclerotic lesions and amelioration of CVDs with improved endothelial function. Therefore, catechin consumption or supplementation may be useful in preventing gingival and periodontal inflammation as well as pathogen-accelerated vessel atherosclerosis [42]. Moreover, Murakami, et al. [153] reviewed that chronic infection induced by *Porphyromonas gingivalis* may be prevented by melatonin, pineal indoleamine with multiple and intersingly properties [14,103]. The cytoprotective activity of melatonin may be derived from its high endogenous radical-scavenging activity, which in turn could explain its antiinflammatory property; so it may be applicable clinically for the prevention of oral diseases and chronic infections in the body induced by periodontopathic bacteria.

In addition to the beneficial effects even at vascular level of periodontitis treatment, it is important also evaluate the possible reverse effects of treatment against CVDs. During the last years calcium antagonists reached the class I, a level of evidence recommendation in treating Coronary Heart Disease (**CHD**), the most fearful and most frequent expression of atherosclerosis. Balan, et al. [39] demonstrated a causal link between periodontal disease and CVDs and, interestingly, evaluated, besides their benefic effects against CHD that calcium antagonism, could have a deleterious effect on the oral cavity. The Authors observed, in particular, that calcium antagonism can have a very important impact on the periodontium, on the cement and on the alveolar bone. The most frequent adverse effect that is associated with calcium antagonists is represented by gingival overgrowth, an increase of the volume of the extra-cellular gingival tissue. This side effect can be observed after few weeks or after few years from the beginning of the treatment, being reversible after interruption of the drug underlining that are necessary periodic and specialized examinations [39].

Further investigations may determine whether a more intensive approach to periodontal therapy, including regular periodontal maintenance schedules, may result in marked improvements in vascular structure and further intervention trials are needed to evaluate implementation of oral health in cardiovascular care on prevention of hard clinical outcomes, like secondary cardiovascular events or death.

## CONCLUSION

The World Health Organization (**WHO**) has been strongly advocated for a good oral health, for integrating the prevention and health promotion policies between oral and general health [154]. Keeping the teeth as clean as possible may help lower the risk for heart attacks, stroke, some cancers and other diseases. In fact, cleaning the teeth is necessary for having a healthy body, because the mouth is part of the body and, in turn, a healthy mouth increases the quality of life [81].

The literature strongly supports the suggestion that periodontal disease contributes to atherosclerosis and the plausible mechanisms are summarized in this chapter. However, further intervention trials are needed to evaluate implementation of oral health in cardiovascular care on prevention of hard clinical outcomes.

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