Evaluating periodontal risk for patients at risk of or suffering from atherosclerosis: Recent biological hypotheses and therapeutic consequences

Olivier Huck, Kenza Saadi-Thiers, Henri Tenenbaum, Jean-Luc Davideau, Christine Romagna, Yves Laurent, Yves Cottin, José G. Roul

Service de parodontologie, faculté de chirurgie dentaire, 1, place de l'Hôpital, 67000 Strasbourg, France
Inserm UMR 977, Strasbourg, France
CHU Dijon, Dijon, France
Service de cardiologie, hôpitaux universitaires de Strasbourg, Strasbourg, France

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Summary
Cardiovascular disease, such as atherosclerosis, is the main cause of mortality in developed countries. Most atherosclerosis risk factors have been identified and are treated, improving patient cardiovascular status and reducing mortality, but some remain unknown. Periodontal disease is generally defined as inflammatory disease initiated by accumulation of dental bacterial plaque, leading to the destruction of tissues that support the teeth. Severe forms have a high prevalence (15% of the population) and are associated with the presence of virulent pathogens such as Porphyromonas gingivalis. Epidemiological studies have shown that severe periodontal disease negatively influences cardiovascular status. The aim of this review is to summarize and discuss recent biological hypotheses on the relationship between periodontal disease and cardiovascular disease, and to provide an overview of potential therapeutic consequences.
Biological data linking periodontal disease and atherosclerosis

Introduction

Cardiovascular disease, including atherosclerosis, is a major public health concern. To ensure optimal treatment it is important for cardiologists to be aware of all of the potential risk factors for these pathologies. For more than 20 years it has been proposed that periodontal disease could influence the development of systemic disorders, increasing cardiovascular disease and diabetes severity as well as the rate of preterm birth [1–3]. Since then, many clinical and experimental studies have investigated the link between atherosclerosis and periodontal disease, with variable conclusions [4]. A recent meta-analysis from five prospective cohorts with coronary heart disease (CHD) concluded that individuals with periodontitis had a 1.14-time-higher risk of developing CHD than subjects without periodontitis. The case-control and cross-sectional studies included in this meta-analysis showed a greater association (odds ratio 2.2) [5]. These data were confirmed by Mustapha et al. whose meta-analysis suggested a 1.75 average odds ratio [6]. However, some studies consider that this relationship is relatively weak and argue that additional controls are needed to verify the relationship between these two diseases [7]. Nevertheless, it is generally accepted that periodontal disease may contribute to cardiovascular events or stroke as shown by the recent consensus reports in dental and cardiology journals [8–10].

Periodontal disease

Periodontal disease is defined as inflammatory and infectious diseases of the gum and tooth-supporting tissues caused by long-term accumulation of dental biofilm and calculus [11]. Periodontal disease can be classified as either gingivitis, which is superficial, reversible and relatively harmless, or as periodontitis, which is profound and irreversible [11]. The main clinical signs of periodontitis are gingival bleeding, gingival retraction, long appearance of the teeth, tooth mobility, halitosis, abscess, periodontal pocket formation, bone loss, tooth mobility and, in the most severe cases, spontaneous tooth loss [12]. Periodontitis is more prevalent in men and the peak of incidence is at around 60 years of age. The disease progresses slowly for decades, displaying successive phases of activity that are more or less destructive [11]. Severe periodontitis affects almost 15–20% of the general population [11]. Periodontitis is characterized by a strong inflammatory response and a rapid, profound and generalized destruction of periodontal tissues associated with the presence of virulent bacteria such as Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans and Treponema denticola [13]. In addition to a notably impaired oral status, the negative influence of periodontal disease on general health is revealed in cases of severe periodontitis [14,15]. The diagnosis of periodontitis is generally based on the clinical symptoms described above, and many studies based on self-report have shown that patients were able to evaluate correctly but grossly their periodontal status [16]. However, the evaluation of periodontitis severity requires a specific clinical examination including periodontal pocket probing and radiological examinations performed by a periodontist or general dentist (Fig. 1). X-ray bone level measurements reflect the history and severity of the periodontitis, but do not necessarily correlate with clinical parameters [11].

Periodontal treatments consist of the mechanical (dental hygiene, scaling and root planning, surgery) and chemical (antiseptic, antibiotic) suppression of periodontal biofilms.
They efficiently decrease periodontal tissue inflammation and infection [17]. Furthermore, they improve some systemic conditions (glycaemia, lipid metabolism, endothelial functions) [18]. However, a large part of the French population is apparently not treated, especially patients at risk for systemic disease [19].

**Cardiovascular disease**

Atherosclerosis corresponds to the formation of atheromatous plaques, which are responsible for CHD, acute coronary syndromes (ACS) and ischaemic strokes, and represent approximately half of all cases of cardiovascular disease. They are the second highest cause of mortality in France. An annual rate of 120 000 ACS and strokes leads to 40 000 and 30 000 deaths, respectively. Men are more vulnerable than women and the highest incidence is at approximately 65 years of age [20].

The formation of an atheromatous plaque or atherosclerosis is a slow phenomenon, more or less reversible initially due to the transport and oxidation of lipids from low-density lipoprotein (LDL) on the arterial wall [21]. Classically, various anatomopathological forms of atheromatous plaque have been defined (fatty streak, fibrous cap) [22]. Recently, the notion of stable or unstable/vulnerable plaque has been proposed, to reflect the clinical consequences of atherosclerosis, such as ACS [23]. ACS is triggered by rupture of the atherosclerotic plaque, and reduced blood flow leading to an ischaemic lesion of the myocardium [22]. Plaque rupture is still not considered as a natural evolution of the atherosclerosis process, but depends on specific pathogenic pathways [23]. The major risk factors for atherosclerosis are dyslipidaemia, high blood pressure, tobacco smoking, diabetes, socioeconomic stress, and advanced age, but around 10% of patients with cardiovascular disease have no conventional risk factors [24]. With the exception of unstable angina, ACS and stroke, symptoms of atherosclerosis often remain subclinical, and its diagnosis is based initially on screening for the main risk factors. In order to evaluate the severity of atherosclerosis, and in addition to new non-invasive techniques, considerable research has been undertaken in the field of biochemical markers that are characteristic of the status of atheromatous plaques [25]. Among these, inflammatory markers such as C-reactive protein (CRP) are routinely used to evaluate the evolution of atherosclerosis and cardiovascular risk. Indeed, the inflammatory response to trapped lipids in arteries plays an important (even predominant) role in the formation, and especially in the rupture, of the atherosclerotic plaque [23,26]. The experimental (mice ApoE−/−) and the clinically observed (associated with diabetes, obesity, autoimmune disease, infection) modifications of the inflammatory response encourage the formation of atherosclerotic plaques [27].

Similar to periodontal disease, the treatment of atherosclerosis is based mainly on the underlying causes, including improved regimens of lifestyle and diet, hypolipidaemic drugs and corrective vascular surgery [26]. Since 1980, a 20% decrease in ACS incidence has been observed in France, due to the development of cardiovascular disease prevention and treatments and adherence to guidelines [28]. However, during the past 5 years, this decrease has declined, possibly due to the increasing incidence of diabetes and obesity. Furthermore, these data also highlight the limits of the current atherosclerosis treatments and the importance of the investigation of new risk factors [26].

**Biological mechanisms**

To explain the relationship between periodontal disease and cardiovascular disease, and in particular atherosclerosis, three major biological theories have been proposed: the bacteriological theory, the inflammatory theory [27] and the immune theory [29].

**The bacteriological theory**

This theory refers to the concept of focal infection that shows an association between oral flora and systemic disease, especially endocarditis. It appears that some virulent periodontal pathogens such as *P. gingivalis* can disseminate from periodontal pockets to the general circulation [30] and are found in the atheromatous plaque and in unaffected vessels [31]. *P. gingivalis* produces numerous virulence factors including gingipains, lipopolysaccharide or fimbriae [32] and may promote the development or evolution of atheromatous plaque through different pathways. These bacteria can activate endothelial cells through Toll-like receptor 4 [33] and can induce apoptosis of endothelial cells through different pathways or disrupt adhesion structures including integrin β1-cadherin complexes [34]. In vivo studies on apolipoprotein E-deficient mice, which eventually develop atherosclerosis, show that oral or systemic infection with *P. gingivalis* accelerates the development of atherosclerosis [35]. It is important to notice that the amounts of some periodontal pathogens, such as *P. gingivalis* and *A. actinomycetemcomitans*, vary depending on the form of periodontitis [31]. The deeper the periodontal pockets, the more important is the exchange surface between bacterial biofilms and blood circulation (15–20 cm² in the most
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Figure 2. Bacterial theory: periodontal bacteria such as *P. gingivalis* promote the development of atheromatous plaque via virulence factors. The effects of bacteria on the atheromatous plaque are dependent on the presence of other cardiovascular risk factors.

Severe cases) [36]. Patients suffering from severe forms of periodontitis have higher concentrations of *P. gingivalis* and *A. actinomycetemcomitans* in periodontal pockets than patients presenting moderate forms [37,38]. Many in vitro [33], in vivo [35], and clinical [31] studies have suggested that higher concentrations of these bacteria may increase periodontal pathogen effects on endothelial cells and the evolution of atheromatous plaques (Fig. 2).

The inflammatory theory

In periodontal disease, gingival cells produce proinflammatory factors such as tumour necrosis factor (TNF-α), interleukin (IL)-1β, prostaglandin E2 (PGE)-2, matrix metalloproteinases and cathepsins [37,38]. Locally, these cytokines induce the destruction of periodontal tissues and may also have systemic effects after entering the blood stream. Stimulated endothelial cells in turn produce other mediators of inflammation, including monocyte chemotactic protein (MCP)-1, macrophage colony-stimulating factor (M-CSF), intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), P-selectin and E-selectin. These cytokines accelerate the formation of atheromatous plaques [39]. The production of VCAM, P-selectin and E-selectin promotes the transformation of leukocytes into macrophages. MCP-1 plays a role in the migration of monocytes, whereas M-CSF promotes their transformation into macrophages [39] (Fig. 3).

In vitro studies show that endothelial cells produce CRP in response to infection with *P. gingivalis* [39]. CRP affects macrophages in atherosclerotic plaques in the presence of oxidized LDL-cholesterol, facilitating their transformation into foamy macrophages that are widely present in atherosclerotic plaques [40]. CRP has been demonstrated in vivo to be localized at a high level in foamy macrophages.

Figure 3. Process of atherogenesis and role of direct and indirect periodontal factors.

Periodontal pathogens may directly and indirectly affect blood cells and blood vessels, resulting in foam-cell formation. CRP: C-reactive protein; Hsp: heat shock protein; IL-1β: interleukin-1β; MCP-1: monocyte attractant protein-1; M-CSF: macrophage colony-stimulating factor; oxLDL: oxidized low-density lipoprotein; PGE2: prostaglandin E2; ROI: rate of infection; TNF-α: tumour necrosis factor-α; VCAM: vascular cell adhesion molecule [39].
cells, degrade connective tissue and induce bone destruction; from the cardiovascular perspective, these patients are at risk of cardiovascular disease due to the over-expression of proinflammatory cytokines and dissemination through blood flow [43].

The second mechanism is an immunological phenomenon of cross-reactivity due to molecular mimicry. This phenomenon describes the possibility that antibody responses targeted against bacterial antigens can essentially function as autoimmune responses, due to the high degree of homology between specific bacterial antigenic peptides and mammalian proteins. It has been considered as a biologically plausible mechanism linking infection and atherosclerotic vascular disease [4]. During the atherosclerotic process, endothelial cells in response to stress, such as in hypertension, hypercholesterolemia or stimulation by the lipopolysaccharide of P. gingivalis, produce Hsp60 [29]. Antibodies against bacterial heat-shock proteins, such as HSP60-related GroEL, may autoreact with human HSP60 expressed by activated endothelium, resulting in cell destruction and therefore promoting the development of atherosclerosis. Some studies revealed a high rate of anti-Hsps 60, 65 and 70 in the arterial lesions [44]. This high rate of anti-Hsp production can be explained by endothe-
lial injury, cell apoptosis or necrosis inside atheromatous plaques. Molecular mimicry contributes to maintaining the autoimmune response and may have an important role in the physiopathology of atherosclerosis, especially during the early stages of the disease [45] (Fig. 5).

Effects of periodontal treatment: the vascular point of view

In general, periodontal treatment consists of professional hygiene education, scaling and root planning with or without antibiotics, and may include surgical procedures for severe forms [46]. Locally, periodontal therapy efficiently reduces tissue inflammation and the concentration of cytokines, including matrix metalloproteinase (MMP)-9, MMP-8, tissue inhibitor of metalloproteinases (TIMP)-2 and myeloperoxidase [47]. At the systemic level, a reduction in concentration of inflammatory markers such as CRP, TNF-α, E-selectin, IL-18 and interferon-γ was also observed, notably in patients with cardiovascular disease [48]. Endothelial function was also improved 6 months after periodontal treatment, especially when antibiotics were used in conjunction with mechanical treatment [49]. Treatment in a single session appeared to give better results than treatment made by quadrant, especially regarding the levels of IL-6 and thrombomodulin [50]. Studies have observed beneficial effects on systemic disease such as diabetes or rheumatoid arthritis [18]. Elimination of bacterial factors and lower rates of proinflammatory cytokines may improve the vascular status [46].

In response to the publication of recent studies, a consensus between the American Journal of Cardiology and the Journal of Periodontology was published in 2009 [9]. For these authors, patients with periodontitis should be informed that gum disease can increase the risk of atherosclerosis, and patients with periodontitis who had a
history of cardiovascular disease were prompted to attend a medical examination. The most important part of this consensus concerns patients suffering from both atherosclerosis and periodontitis. For these patients, a reinforced collaboration between cardiologists and periodontologists is recommended to optimize periodontal care and reduce cardiovascular disease risk. However, many aspects of the link between cardiovascular and periodontal disease, as well as the real impact of periodontal interventions on cardiovascular events, remain to be clarified or assessed [48]. Oral infection and inflammation are detrimental to health and having a healthy mouth is important for a healthy lifestyle; periodontal treatment can improve both oral health and cardiovascular outcomes [10].

Conclusion
Considering epidemiological and biological studies, it seems important to consider periodontal disease as a risk factor for cardiovascular disease and atherosclerosis. Clinical or in vitro studies show that periodontal monitoring and treatment of patients with a risk of atherosclerosis or cardiovascular disease may have positive effects. Collaboration between cardiologists and periodontologists should be encouraged, especially for patients with a history of a cardiovascular event presenting with severe forms of periodontitis. For these patients, but also for all patients suffering from severe periodontitis, periodontal treatment may be positive in terms of reducing the levels of inflammatory cytokines and improving quality of life.

Disclosure of interest
The authors declare that they have no conflicts of interest concerning this article.

References


