Periodontitis and Cardiovascular Risk

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Atherosclerosis is a major component of the cardiovascular diseases and is centered by inflammation but its well-known predictors do not explain some of the atherosclerotic vascular disease events, generating the need to look for independent additional risk factors. Periodontitis, a chronic infection produced by oral bacteria and affecting the supporting structures of the teeth, seems to be linked with atherosclerosis and cardiovascular disease through several mechanisms, like genetic susceptibility, systemic inflammation, infection, and the molecular mimicry, the association being worsened in the presence of diabetes. The epidemiological studies revealed a modest but significant association between periodontal infections and cardiovascular disease, independent of the effect of confounding factors, but the definite effect of periodontitis and its treatment on the incidence of cardiovascular events requires further clarifications.

Keywords: cardiovascular disease, periodontitis, atherosclerosis

The cardiovascular diseases (CVD) are the most important cause of death in industrialized countries and one of the major causes of mortality worldwide [1]. Atherosclerosis, the major component of the cardiovascular diseases, is responsible for the majority of cases of coronary heart disease, cerebrovascular disease, and peripheral artery disease [2]. The risk scores for atherosclerotic vascular disease (ASVD) are based on the following predictors: age, diabetes, smoking, blood pressure, body mass index (BMI), total cholesterol, low-density lipoproteins (LDL), and high-density lipoproteins (HDL). However, these predictors cannot explain almost one-half of the ASVD events which are present in patients without these risk factors [3,4]. This variability in ASVD risk generated the need to look for independent additional risk factors who could explain some of the ASVD risk variation.

The atherosclerotic process is closely linked to inflammation – from endothelial cell expression of adhesion molecules, followed by the development of the fatty streak and, in the end, the plaque rupture. Periodontitis is a chronic infection produced by oral bacteria that affects the supporting structures of the teeth [5] and is the most studied oral infection. Oral pathogenic bacteria and their endotoxins can disseminate into the systemic circulation and be associated with systemic inflammation and damage to the distant organs [6]. There is increasing evidence that the bacterial pathogens, antigens, endotoxins, and inflammatory cytokines associated with periodontal and dental infections are also involved, in variable degrees, in the etiopathogenesis of atherosclerosis [7,8]. This hypothesis is also supported by the finding of systemically elevated levels of C-reactive protein (CRP) and other inflammatory mediators in patients with periodontal infection [9,10] and the effect of these on the pre-existing atherosclerotic lesions: increased inflammatory activity and ASVD event risk [11]. Besides the logical association between these two elements, there are several studies that confirm a connection between periodontal indexes (e. g. bone loss) and several direct markers of atherosclerosis (carotid intima-media thickness (IMT), increased calcium deposits in the carotid artery wall) [12,13]. On the other hand, there are studies that failed to find a solid association between oral health indicators and coronary heart disease deaths [14-16]. In 2012, the American Heart Association concluded that there are observational studies that support the existence of an association between periodontitis and ASVD, regardless of known confounders, but a causative relationship between the two pathological entities could neither be supported or dismissed. Also, there is no clear position if, on long term, periodontal interventions could prevent ASVD or modify its outcomes [17].

Periodontitis, Oral Infections and Proatherogenic Mechanisms

Atherosclerosis, as a major cause for CVD, is an inflammatory disease initiated by the injury of the vascular endothelium and its development is linked to an inflammatory process in the arterial wall. This inflammatory response may be modulated by chronic infectious diseases that directly supply bacteria into blood stream or indirectly modulate the systemic inflammation.

So far there are four hypothetical models trying to explain the complex association between periodontal disease and CVD, taking into account infection, inflammation, genetics, and the immune response of the body.

1. The *common susceptibility model* sustains that there is a genetically determined phenotype associated with exaggerated inflammatory responses. These susceptible persons will develop a periodontal disease associated with

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the periodontal pathogens and the atherosclerotic process will be accelerated [18].

2. The *systemic inflammation model* is based on the hypothesis that the systemic inflammation is associated with increased levels of cytokines and inflammatory mediators which lead to damage of the vascular endothelium and atherosclerosis [19].

The endothelial dysfunction associated with the periodontal inflammation can be revealed using two parameters:

- the flow-mediated dilatation or endothelial flow reserve (EFR), an index which is reduced in patients with severe periodontal disease and associated with high levels of CRP, interleukins (IL-1, IL-2, IL-6), tumor necrosis factor-α (TNF-α), and asymmetrical dimethylarginine (ADMA) – a plasma substance that inhibits the enzyme nitric oxide synthase [20] and high levels of ADMA are associated with endothelial dysfunction. This hemodynamic parameter is improved in patients included in intensive periodontal therapy group [21].

-the pulse wave velocity (PWV), a parameter related to the arterial wall rigidity. High PWV values are associated with ATS, increased cardiovascular events, and mortality. The periodontal treatment has been associated with lower levels of PWV, CRP, and IL-6 [22].

3.The *infection model* suggests that periodontal bacteria directly infect the endothelial cells. The pathogens are commonly reaching the bloodstream after dental treatments, during chewing food or after dental hygiene procedures, such as tooth brushing or dental flossing, and subsequently invade the endothelial cells producing endothelial dysfunction, inflammation, and at the end promote atherosclerosis process and plaque instability.

Porphyromonas gingivalis, a major periodontal pathogenic agent, has been demonstrated to induce platelet aggregation, expression of cell adhesion molecules (ICAM-1, VCAM-1, P-selectin), activate endothelial cells, and induce smooth muscle proliferation and impaired vasomotor function [23]. The extent of bacterial blood dissemination depends on the amplitude of tissue trauma, bacterial density in the dental plaque, and severity of local inflammation. Numerous studies have shown the presence of DNA of periodontal pathogens in atherosclerotic plaques [24-25]. Also, fresh atheromatous cells cultured with macrophages enabled the detection of *P. gingivalis* in culture [26]. It is still unclear if the oral bacteria are invading an already damaged arterial wall or they are at the origin of the atherosclerotic process.

4.The *molecular mimicry/cross-reactivity model* explains the progression of ATS as being associated with the immune response of the organism to the bacterial heat shock proteins (HSPs). All cells (endothelial, fibroblasts, and smooth muscle cells) are expressing HSPs when exposed to various forms of stress. Endogenous stress factors, as cytokines, bacterial lipopolysaccharides and mechanical stress are promoting the expression of protective HSP (hHSP60) on the surface of endothelial cells. The bacterial HSPs (GroEL) have a high degree of homology with hHSP60 proteins and antibodies to HSPs cross-reacts with periodontopathic bacterial GroEL. During the various periodontal infections, the bacterial HSPs (GroEL) are confounded by the immune system with self HSPs and thus cross-reactive T cells with self HSPs specificity may be activated [27]. This confounding mimicry is followed by the production of antibodies directed to bacterial HSPs who are generating also an autoimmune response to homologous structures of the host like hHSP60 [28] which may result in endothelial dysfunction and development of ATS [29]. These antibodies can lyse stressed but not unstressed endothelial cells [30]. Studies have also demonstrated that there is a correlation between elevated titers of anti-HSP60/65 antibodies and mortality due to ACVD [31,32].

Recent studies [33] suggest that there is also a pathophysiological link between periodontitis and hypertension. The systemic inflammatory response associated with periodontal disease is associated with vascular dysregulation (low levels of nitric oxide, increased lipid peroxidation [34], and reduced redox status, followed by increased arterial stiffness [35]. Finally, the concept of dental hypertension is being developed [33].

Diabetes and Periodontitis– A Bidirectional Relationship

Diabetes, a metabolic disease caused by a disturbance in the insulin production and peripheral resistance to insulin followed by hyperglycemia, abnormal lipid, glucose, and protein metabolism, which ultimately are associated with multiple system pathologies. The association between diabetes and periodontal disease is confirmed by numerous studies and it is widely accepted as a bidirectional relationship [79]. Diabetes is a risk factor for increased prevalence and severity of periodontitis [36,37] while the periodontal disease is an important trigger of increased diabetes complications, such as macroalbuminuria, end-stage renal disease, atheromatous plaque calcification, carotid intima-media thickening [38], and risk of worsening glycemic control [39].

Periodontitis is exacerbated by the diabetic state; patients with diabetes are carrying a two to three times higher risk for severe periodontitis and incidence of periodontal disease progression [39]. This association has been explained by several mechanisms:

·a hyper-responsive monocytic phenotype, associated with enhanced production of cytokines (IL-1β, IL6, TNFα, PGE2), very potent inductors of alterations in both connective and extracellular matrix tissues, as a result of the action of advanced glycation end-products (AGEs) [40-42]. The accumulation of AGEs in gingival tissue is associated with greater vascular permeability, greater breakdown of collagen fibers, and accelerated destruction of connective tissue and bone [43].

-an increased production of cytokines (IL-1β, IL-6, IL-8, TNFα) in monocytes/macrophages and endothelial cells due to up-regulation of the nuclear factor KB, a protein transcription factor [44]; there is also evidence of the matrix metalloproteinases involvement (MMPs, mainly MMP-8, MMP-9, and MMP-13) [39]. This up-regulation can be secondary to the production of advanced glycation end-products (AGEs) and their ligation to cell surface receptors (RAGEs).

-alterations in connective tissue metabolism and impaired wound healing [445].

The influence of diabetes on periodontal disease is confirmed by cross-sectional, case-control, and longitudinal studies indicating that diabetes is a prominent risk factor for periodontitis [46].

Furthermore, acute infections act like a metabolic stress factor associated with an increased demand for insulin, glucose, and lipids [47-49]. Acute infections are also associated with elevated systemic levels of pyrogenic cytokines (IL-1β, TNF-α, IL-6) caused by bacteremia and/or endotoxemia which block lipoprotein lipase activity, followed by decreased transfer of blood lipids from circulation into cells and hyperlipemia (increased LDL and total cholesterol) [50-52]. Acting on glucose transport receptors expression, these cytokines are also promoting glycogenolysis and impaired glucose uptake by the

peripheric cells. Inhibiting the insulin receptor tyrosin-kinase and other signaling proteins, these cytokines also induce insulin resistance. Recent experimental studies suggest that IL-1β and TNF-α are participating in the damage of β cells in animal obesity models of type 2 diabetes [53].
These mechanisms can explain the reversible diabetes metabolic state associated with the acute infectious episodes. When the infectious process is chronic, the associated metabolic changes are not well known, but periodontitis is a chronic inflammatory condition associated with the production of cytokines that may represent a metabolic stress in diabetic patients, with increasing insulin resistance and reduced insulin secretion, further leading to increased diabetes morbidity and complications. Although meta-analyses showed no clear results about the effect of periodontal disease treatment on the improvement of the glycemic control. It seems that a beneficial effect on glycemic control is seen mainly in type 2 diabetes, supporting the role of a closer collaboration between physicians involved in diabetes healthcare and oral healthcare professionals [54, 55].

Periodontal Disease and Cardiovascular Risk – Epidemioligical Studies

The identification of the physiopathological link between periodontal disease and cardiovascular morbidity was followed by studies to identify the independent association with cardiovascular clinical endpoints. This is not an easy task, mainly due to the presence of various confounding factors who interfere with both periodontal disease and atherogenesis: age, educational level, obesity, hypertension, hypercholesterolemia, smoking, diabetes; there are also confounding factors not usually included in statistical modeling, like lifestyle factors-diet and health awareness [56].

A large Danish cohort study [57] included more than 17,000 patients with a hospital diagnosis of periodontitis. The patients with periodontitis had increased overall comorbidity and risk factors for both periodontitis and CVD: smoking, low socioeconomic status, diabetes, and arterial hypertension. After the adjustment for age, gender, socioeconomic status, smoking, comorbidities, and medication, the risk for all cardiovascular outcomes (myocardial infarction, ischemic stroke, and cardiovascular death) and all-cause mortality was significantly higher in patients with periodontitis [57]. The association between periodontitis and cardiovascular disease was confirmed by another large study [58] showing that patients aged > 60 years, treated for severe periodontitis, had an increased risk of major adverse cardiovascular events (MACE) with an IRR = 1.26. Several recent studies and meta-analysis confirmed the association between periodontitis and cardiovascular disease [59-61].

Moreover, a recent meta-analysis [62] confirms the association between periodontitis and an increased risk for stroke, 1.47 to 2.63 times higher when compared with subjects without periodontitis, depending on the type of analyzed study (prospective or retrospective). A research done by Watt et al. [63] reported a correlation between tooth loss and overall CVD mortality that was mainly driven by lethal cerebrovascular events. It is still unknown why periodontitis is associated with a stronger risk factor for stroke than for CAD [64], most of the studies reporting a low to moderate positive association between periodontitis and CVD, with an odds ratio ranging between 1.03 and 8.5 [65].

Some studies revealed the association between periodontitis and abnormal levels of serological markers for CVD – glucose, CRP, IL-18 and HDL cholesterol [66], which may explain the increased risk for CVD associated with periodontitis. Other studies [67,68] are supporting the association between periodontitis severity and carotid atherosclerosis, including subclinical disease, suggesting that periodontal disease may be a risk factor for atherosclerotic disease. This hypothesis is supported by a study of Petersen et al. which concluded that patients with at least one apical periodontitis are having a higher atherosclerotic burden in the abdominal aorta, as evaluated by CT total body examination [69].

On the other hand, some studies failed to demonstrate a positive association between periodontitis and an increased risk for adverse cardiovascular events [70-72]. There are several reasons for the controversial results reported in the literature: variable design of the studies, mainly regarding inclusion and exclusion criteria, important variations concerning the number of the patients included, large variations in the cardiovascular outcome parameters, and the absence of a proper consensus on the *periodontitis* diagnosis, many studies using clinical parameters like bleeding on probing, pocket depth, tooth loss, as well as radiographic markers as surrogate markers of periodontitis. Some researchers are explaining the absence of an association between oral health indicators and CVD death when multivariate analysis is used mainly by the role of the factors relating to health behavior [73].

Is Periodontitis Treatment Changing the Cardiovascular Profile of the Patient?

As elements proving the association between periodontitis and CVD/ASVD started to emerge, many studies investigated the effect of periodontal therapy (PT) on cardiovascular events, atherosclerosis risk factors, and markers of inflammation. A recent large meta-analysis [52] screened 3928 studies and found 25 trials meeting the eligibility criteria; it concluded that periodontal treatment improves endothelial function and reduces biomarkers of atherosclerotic disease (CRP, IL-6, TNF-α, fibrinogen, triglycerides, total cholesterol, HDL-Cholesterol, and HbA_{1c}), especially in patients already suffering from CVD and/or diabetes. This effect is visible better over 6-months after therapy and is amplified in individuals suffering from both periodontitis and diabetes.

The PAVE (Periodontitis and Vascular Events) study confirmed the effect of a 6-months periodontal treatment on lowering hs-CRP levels but to a lesser extent in obese patients, suggesting a critical role of the obesity [74]. An arm of the same study failed to confirm that the periodontal treatment (scaling and root planning) in patients with myocardial infarction or angina symptoms is associated with a reduced risk of future cardiovascular events [75].

Small pilot trials were developed to optimize the treatment regimen for maximal improvement of systemic parameters. Intensive periodontal therapy, comprising combined application of oral hygiene instructions, extraction of hopeless teeth, scaling, root planning under local anesthesia performed over a 24-hour period, and controlled local delivery of minocycline at all pockets of minimum 4 mm, was associated with better and earlier improvement when compared with mechanical debridement alone [76].

The periodontal therapy is associated with beneficial effects on carotid IMT and endothelial dysfunction. When treated with root debridement, a group of healthy individuals showed after a period of 6 to 12 months a significant decrease of IMT at different locations in the carotid artery [77]. Healthy subjects with severe generalized periodontitis who were submitted to an intensive periodontal therapy

(oral hygiene instruction, scaling and root planning, and extraction of hopeless teeth) had significantly better results on flow-mediated dilatation of the brachial artery when compared with a control group, signifying that the periodontal therapy is associated with an improvement of the endothelial dysfunction [78].

Conclusions

Periodontitis is a multifactorial disease sharing multiple risk factors with atherosclerotic disease. The poor oral health, including consequent periodontitis, is associated with chronic inflammation and bacteremia, both important pathogenic factors in the genesis of the atherosclerotic lesions. There is a clear evidence about the association between periodontitis and serological markers of cardiovascular diseases and about a modest but significant association between periodontal infections and CVD, independent of the effect of confounding factors. The definite effect of periodontitis on the incidence of cardiovascular events requires further clarifications.

The treatment of periodontitis is associated with an improvement of the endothelial function and normalization of the biomarkers of the atherosclerotic process but there is no clear evidence that the treatment is also associated with an improvement of the clinical cardiovascular endpoints. Available data confirm the importance of oral health as an important element to be taken into account when the comprehensive profile of the cardiovascular patients is made.

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Manuscript received:12.07.2017