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Current Cardiology Reviews, **2014,** *10,* **355-361**

Is There an Association between Periodontitis and Hypertension?

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Abstract: Cardiovascular diseases are the leading cause of deaths. Also, cardiovascular risk factors start the atherosclerotic process, which leads to cardiovascular diseases. Nowadays, periodontal disease can also be considered another cardiovascular risk factor. It involves inflammatory, immunological and humoral activities, which induce the production of proinflammatory cytokines and the destruction of the epithelium. This allows the entry of endotoxins and exotoxins in the bloodstream, which may contribute to atherogenesis and thromboembolic events. There is also direct invasion of the vessel wall by oral pathogens, triggering an inflammatory response that produces endothelial dysfunction. In hypertension, changes in microcirculation can cause ischemia in the periodontium, which favors periodontal disease. Moreover, endothelial dysfunction promotes the formation of atherosclerotic plaque and the development of lesions in target organs. Periodontitis has also been associated with insulin resistance and a higher risk for the metabolic syndrome, which is characterized by oxidative stress. This seems to act as a common link to explain the relationship between each component of the metabolic syndrome (including hypertension) and periodontitis. This article will discuss clinical and experimental evidence, as well as possible pathophysiologic mechanisms and links involved in the relationship among periodontal disease, hypertension and cardiovascular disease.

Keywords: Atherogenesis, cardiovascular disease, cardiovascular risk, hypertension, metabolic syndrome, oxidative stress, periodontal disease, periodontitis.

INTRODUCTION

Periodontal disease (PD) or periodontitis is a destructive disease that affects the supporting structures of the teeth, including the periodontal ligament, cementum and the alveolar bone. It is characterized as a chronic mixed infection, which is caused by several microbial agents (Gram-negative and Gram-positive organisms). Recent studies have shown that PD affects over 50% of the general population [1]. In turn, cardiovascular disease (CVD) represents the main cause of deaths in developing and developed countries. In Brazil, CVD accounts for about 30% of the overall mortality rate and it is responsible for 1.2 million hospitalizations, with an approximate cost of one billion dollars/year [2]. Therefore, these clinical conditions are among the most prevalent diseases among adults, making CVD prevention and treatment an important strategy for global health. For over twenty years, these two conditions have not shown any correlation. Recent research on alternative risk factors for CVD has demonstrated that diseased periodontium is implicated in the development of atherosclerotic cardiovascular complications. Case-control and cross-sectional studies demonstrating associations between chronic periodontitis and CVD were followed by secondary analyses of the data available from existing longitudinal studies. These studies indicated that individuals with PD were at higher risk for CV events, namely, stroke, coronary heart disease (CHD), and possibly peripheral arterial disease [3-10]. Hypertension is the most prevalent of all cardiovascular diseases and affects about 30-40% of adults (over 70 million Americans and 36 million Brazilians) [11, 12]. In addition, hypertension is likely to be involved in 50% of the deaths due to CVDs [13, 14]. However, the association between hypertension and PD is not clear. Thus, this review will focus on clinical and experimental evidence, as well as on possible pathophysiologic mechanisms and links involved in the relationship among periodontal disease, hypertension and cardiovascular disease.

PERIODONTAL DISEASE AND CARDIOVASCULAR DISEASE

The atherosclerotic process, which is triggered by typical cardiovascular risk factors, constitutes the anatomic substrate for the development of major CVD [15] (Fig. **1**). However, despite all earlier recommendations for the prevention and treatment of the disease, atherosclerosis continues to advance, resulting in high rates of cardiovascular mortality. Today, there is a high prevalence of PD in the general population. Although PD is another cardiovascular risk factor, it has not been thoroughly studied by cardiologists. Approximately 35% of adults aged 30-90 years have moderate to severe PD [16]. The prevalence and severity of the disease increase with age. However, in the older age groups, the prevalence decreases and the percentage of edentulous subjects increases, which suggests that PD may be reduced with age due to tooth loss [17, 18]. Periodontitis affects bone and periodontal ligaments and it is characterized by bleeding, edema and increased crevicular fluid. It results in inflammatory activity (mediated by bacteria or endotoxins) and im-

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1875-6557/14 $58.00+.00

Major Risk Factors
• Smoking
• Dyslipidemia
• Diabetes Mellitus
• Nephropathy
• Age > 60 years-old
• Familiar History of Cardiovascular Disease
➢ Women < 65 years-old
➢ Men < 55 years-old
Others Factors
• Waist-to-hip ratio
• Abdominal waist circumference
• Microalbuminuria
• Reduced glucose tolerance / impaired fasting glucose
• Hyperuricemia
• Elevated C-Reactive Protein

Fig. (1). Cardiovascular risk factors.

munological and humoral response (mediated by polymorphonuclear leukocytes, lymphocytes, immunoglobulins and complement system). These responses lead to the production of proinflammatory cytokines and markers, such as interleukin-6, interleukin-1 beta, interferon gamma, alpha-tumor necrosis factor (TNF-α), plasminogen-activator-inhibitor 1, fibrinogen, C-reactive protein (CRP), prostaglandin E2 and matrix metalloproteinase [19-24]. There are several common risk factors for CVD and PD, which may act on both diseases. They provide a pathophysiological link, regardless of PD being a direct etiological factor [3]. Thus, it appears that periodontal disease is a potential risk factor for CVD and we will discuss this association.

In periodontitis, the bacterial plaque destroys the epithelium of the periodontal pocket and breaks the barrier that isolates the tissue and circulation, allowing the entry of harmful elements in the bloodstream (endotoxins and exotoxins). There is also direct invasion of the vessel wall by oral pathogens, triggering an inflammatory response that leads to endothelial dysfunction. Oral hygiene, chewing or dental procedures can cause transient asymptomatic bacteremia and allow microorganisms to have direct contact with the bloodstream and, consequently, with the coronary endothelium. This is demonstrated by periodontal pathogens found in atherosclerotic lesions. As previously described, PD leads to increased local inflammatory mediators, which promote chronic endothelial inflammation (manifested by elevated CRP and proinflammatory cytokines). This fact suggests that the inflammatory process may contribute to vasospasm, thrombosis and CVD [8]. The systemic invasion by bacteria or endotoxins can induce infiltration of inflammatory cells in large arteries and proliferation of vascular smooth muscle, which constitute main features in the natural history of atherogenesis. On the other hand, cytokines can cause the endothelium to produce vasoconstrictors and promote leukocyte adhesion and aggregation, which could predispose to thrombogenesis [6]. So, the systemic inflammatory response that may accompany periodontitis seems to be a connection among PD, atherosclerosis and its cardiovascular complications. However, a recent Scientific Statement from the American Heart Association discussed that although the current body of scientific evidence (observational studies) does not support a causal relationship between atherosclerotic vascular disease events and periodontitis, it has observed that an association between the two conditions is supported by level A evidence (derived from multiple randomized clinical trials or meta-analyses), regardless of well-known confounding variables [3-5, 25].

PERIODONTITIS AND HYPERTENSION

Hypertension appears to be associated with PD [26-33]. More recent studies have shown that systolic and diastolic pressures are higher among PD patients than in individuals without periodontitis [32, 33]. The 3rd National Health and Nutrition Examination Survey (NHANES III) conducted a large study of almost 12.000 dentate adults to examine associations between PD and blood pressure (BP) levels. A positive linear relationship was found between systolic BP and severe periodontitis in middle-aged individuals [33]. Other studies have also suggested higher BP values in individuals with missing teeth [18, 34], once periodontitis is the major cause of tooth extraction and tooth loss among adults. The (Fig. **2**) shows the possible pathophysiologic mechanisms between periodontitis and hypertension.

PATHOPHYSIOLOGIC MECHANISMS THAT COULD EXPLAIN THE ASSOCIATION BETWEEN PERIODONTITIS AND HYPERTENSION

Endothelial Dysfunction

An important mechanism that could explain the association between hypertension and PD is endothelial dysfunction, which plays an important role in the genesis of hypertension. Endothelial dysfunction is the initial step in the de-

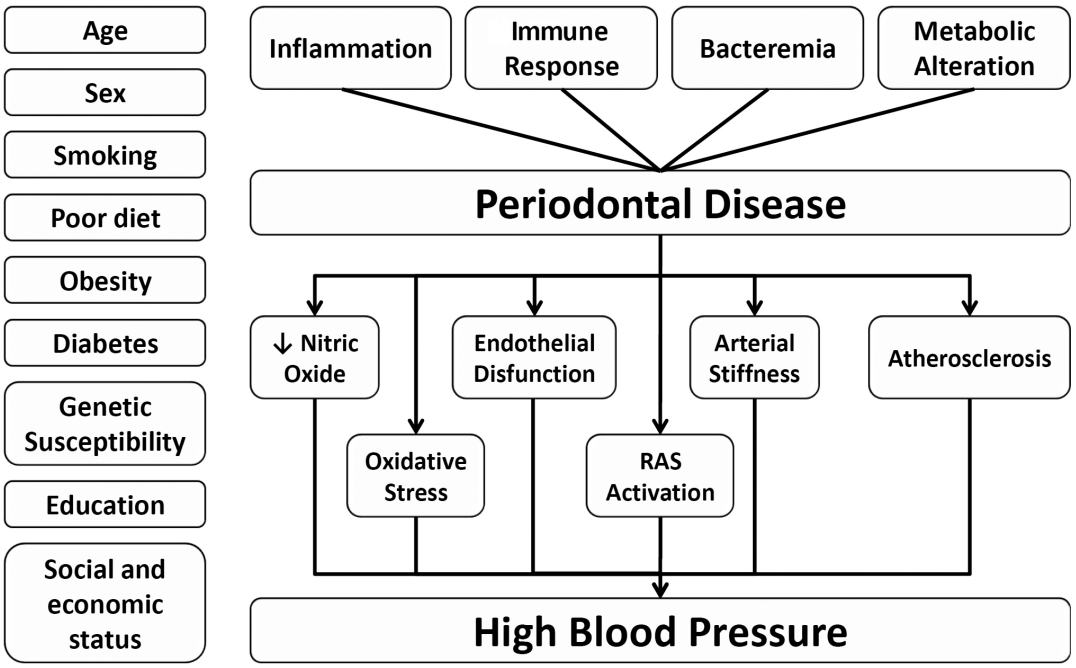

Fig. (2). Possible pathophysiologic mechanisms between the periodontal disease and high blood pressure. Specific conditions (inflammation, bacteremia, imune response and metabolic syndrome) associated with classical risk factors contribute to development of the periodontal disease. In turn, the periodontal disease can also present endothelial and vascular dysfunction that may lead to increased blood pressure. It is interesting to observe that both diseases (periodontal disease and hypertension) share common cardiovascular risk factors, which enhance the association between both disorders. RAS = renin-angiotensin system.

velopment of atherosclerosis, leading to CVD [35]. There is a probable association between the inflammation caused by periodontitis and endothelial dysfunction [19, 20]. Therefore, there might also be an interaction between PD and hypertension, with the underlying inflammatory process interfering with the endothelial function. This could have implications for blood pressure control and the development of lesions in target organs. A cross-sectional study identified impaired brachial artery endothelium-dependent, flow-mediated dilation in otherwise healthy patients with severe periodontitis, which was comparable to that observed in patients with hypertension [36]. In normotensive and hypertensive patients, pre-existing impaired endothelium dependent vasodilation worsens with the presence of mild-to-moderate periodontitis [37]. This suggests that PD is associated with endothelial dysfunction in normotensive subjects without cardiovascular risk factors and in hypertensive patients, as there is a reduction of NO bioavailability as well as the promotion of systemic inflammation in these patients. Also, periodontal therapy improves endothelium-dependent vasodilation in normotensive and hypertensive patients [36-38]. Patients with PD present higher levels of endothelin-1 compared with those without PD [39, 40]. A nitric oxide synthase inhibitor level (asymmetric dimethylarginine) associated with endothelial dysfunction was higher in hypertensive patients with PD [41]. As previously observed, altered elastic properties of the large arteries are involved in the pathogenesis of hypertension. Apparently, there is a relationship between PD and alterations of arterial distensibility (arterial stiffness and reduced wave reflections) in patients with periodontitis [42, 43].

Oxidative Stress

Oxidative stress, a condition in which the balance between the production and the inactivation of reactive oxygen species (ROS) becomes disrupted, participates in the inflammatory process of periodontitis. ROS produced by locally infiltrating neutrophils contributes to periodontal tissue destruction. An imbalance between the oxidant/antioxidant activity within the oral cavity adversely influences systemic oxidant status, as reflected by increased serum levels of ROS metabolites and reduced antioxidant scavengers [44, 45]. On the other hand, oxidative stress is implicated in the development of hypertension, since ROS may be regarded as mediators of vasoconstriction and vascular inflammation. Furthermore, bioavailability of nitric oxide is strongly related to the redox state [39, 46]. Experimental data have also suggested that periodontitis-induced aortic lipid peroxidation may be a trigger of early atherosclerosis [47].

Inflammatory and Biologic Pathways

Several inflammatory mediators can be associated with the development of hypertension [48, 49]. The systemic inflammatory response that may accompany PD has been proposed as a connection among periodontal disease, atherosclerosis and its cardiovascular effects [19-24]. Studies have demonstrated that serum CRP is able to predict the development of hypertension, independently of baseline BP and traditional risk factors. It has also been consistently reported as mildly elevated in patients with PD [48]. It seems that slightly elevated serum CRP concentrations in individuals with PD, compared with controls, would be enough to increase the risk for incident hypertension [48, 50]. Other in-

flammatory markers, such as interleukin-6 and TNF-α levels are elevated in patients with periodontitis, when compared with healthy controls [20, 21]. Patients with PD exhibit a higher white blood cells count albeit within normal range, though not necessarily associated with BP levels [20, 30]. Also, higher levels of plasminogen-activator inhibitor 1 and fibrinogen have been observed in PD patients, compared with controls, suggesting an increased procoagulant state [22, 23]. Both the crevicular fluid and serum levels of matrix metalloproteinases are also altered [24]. Studies have also shown the participation of the local renin–angiotensin-system in gingival tissue, which may be another pathogenic correlation between the two conditions under study [51, 52]. Moreover, in order to confirm the importance of the participation of inflammatory markers in the association of PD and hypertensionn, there is evidence that periodontal treatment significantly reduced blood levels of fibrinogen CRP and IL-6 in refractory hypertensive patients [53].

Local bacteria, Bacteremia and Immune Response

Periodontal pathogens are able to invade gingival tissues and promote transient bacteremia, even during tooth brushing [54]. Periodontal microbes may directly invade the arterial wall and colonize atherosclerotic plaques [55, 56]. Porphyromonas gingivalis, a major periodontal pathogen, has been shown to aggregate platelets, induce expression of cell adhesion molecules, including ICAM-1 (intercellular adhesion molecule), VCAM-1 (vascular cell adhesion molecule), and p-selectin. It also activates endothelial cells, triggers smooth muscle cell proliferation, and therefore impairs vasomotor function [57-60]. The cell-mediated immune response in the gingiva is primer for the disruption of local periodontal tissues, favoring microbes, bacterial endotoxins (lipopolysaccharides) and various microbial antigens to spread through the circulation. On the other hand, endothelial dysfunction could be modulated by immunoreactive mechanisms [10].

Interaction Among Insulin Resistance, Diabetes, Metabolic Syndrome and Oxidative Stress

There is a symbiotic relationship between diabetes and periodontitis, since diabetes is associated with an increased incidence and progression of PD; and periodontal infection is associated with poor glycemic control in diabetes [61]. Also, PD has been associated with insulin resistance and a higher risk factor for the metabolic syndrome (MS) [62]. MS is characterized by oxidative stress and it may act as a common link to explain the relationship between each component of MS and periodontitis [63]. Reactive oxygen species can contribute to cellular dysfunction and damage. On the other hand, oxidative damage promotes a proinflammatory state. Moreover, adipocytokines, produced by the cells of adipose tissue, might modulate the balance between oxidant and antioxidant activities. In patients with MS, an increased caloric intake can cause an increased production of ROS, inducing insulin resistance and hyperinsulinemia, which can evolve into type 2 diabetes. Oxidation products can increase neutrophil adhesion, chemotaxis and advanced glycation end-products, which could also be implicated in the degeneration and damage of periodontal tissue [64]. Recent systematic review and meta-analysis showed evidence for an association between MS and PD [65]. Oxidative stress is also associated with the development of hypertension [39, 46]. Individuals with moderate to severe PD show higher blood pressure levels [66, 67]. Thus, insulin resistance and oxidative stress seem to be common elements present in MS, periodontitis, CVD and hypertension [61-64]. The (Fig. **3**) shows the pathophysiological mechanisms linking insulin resistance, metabolic syndrome, stress oxidative and periodontitis.

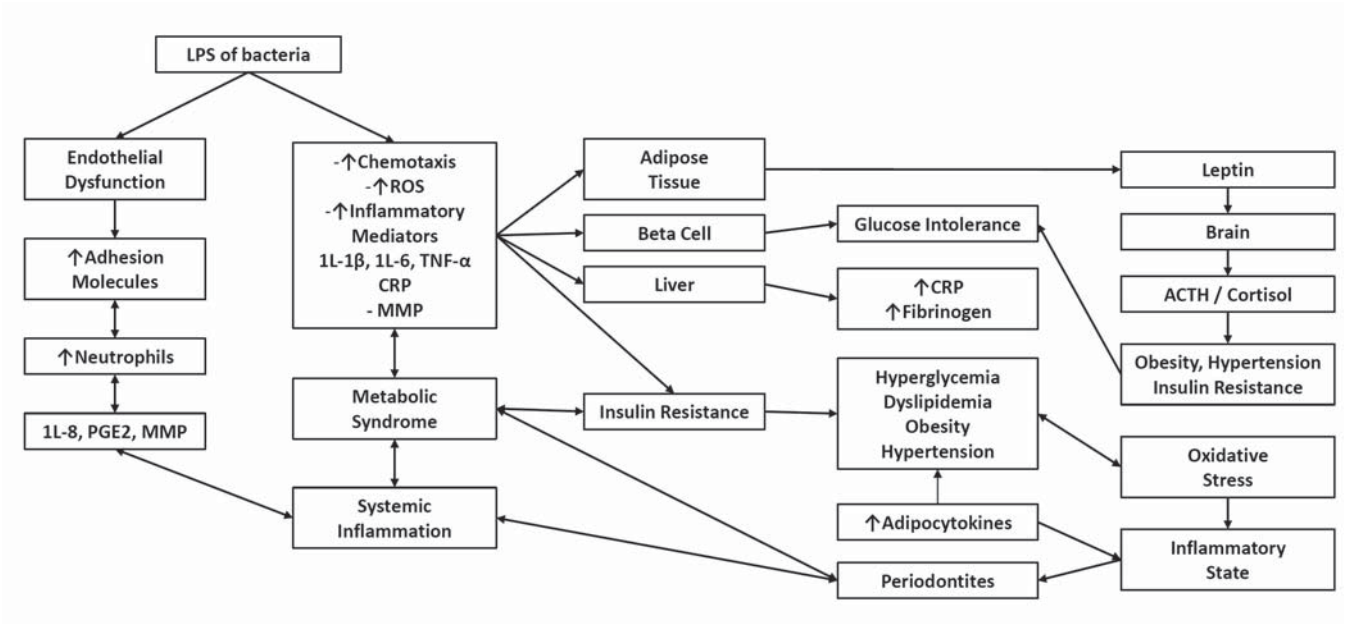

Fig. (3). Pathophysiological mechanisms which link insulin resistance, metabolic syndrome, oxidative stress, hypertension, and periodontitis. This figure explains how periodontitis could contribute to systemic inflammation, impairing sugar balance, as well as leading to insulin resistance, diabetes and others components of metabolic syndrome. Adhesion molecules [ICAM-1 (intercellular adhesion molecule), VCAM-1 (vascular cell adhesion molecule) and p-selectin]; LPS = lipopolysaccharide; IL-8, IL-1β, IL-6 = interleukine-8, -1β, -6; TNF-α = tumoral necrosis factor-α; PGE2 = prostaglandin E2; MMP = matrix metalloproteinase; ROS = reactive oxygen species; CRP = C-reactive protein; ACTH = adrenocorticotropic hormone.

Pressure Overload

Pressure overload can also be involved in the development of PD by promoting changes in microcirculation (proliferation of the intima and the elastic layers with lumen reduction of vessels feeding the periodontal membrane). This can lead to arteriolar and capillary rarefaction and subsequent ischemia in the periodontium, which favors periodontitis [26-29].

LIMITATIONS INVOLVED IN THIS ASSOCIATION

As in the case of the association between periodontitis and cardiovascular complications, several explanatory and causal factors should also be considered, when evaluating the association between BP and teeth [1, 6, 10]. Heterogeneity in study populations, diverse research designs, definition of periodontal and cardiovascular diseases or events, appropriateness of surrogate markers of disease, frequent lack of adjustment for socioeconomic status and confounders of chronic diseases further complicate the interpretation of study findings [25]. In addition, age, sex, lifestyle parameters (smoking and nutrition), educational status, metabolic diseases (obesity and diabetes) have all been implicated in both conditions. Also, issues regarding study methodologies should be considered. Most studies have assessed BP levels with a single office BP measurement or even reported BP medication. Only a few studies have utilized ambulatory blood pressure monitoring, which presents better correlation with daily life blood pressure and hypertension-related target organ damage [10, 68].

Moreover, periodontitis can show periods of acute inflammation superimposed on chronic disease progression or can appear stable with evidence of past periodontal tissue destruction, which may influence the credibility of a causal relationship. Gingival bleeding marks ongoing inflammation, whereas other measures, such as bone loss and attachment loss, are more indicative of past exposure.

Recently, Leong *et al*. [69] summarized the main limitations this association: "the epidemiological studies to date have shown an association between hypertension and periodontitis. Nevertheless, the related studies were mostly cross-sectional, with varied numbers of subject and assessment methods. For instance, earlier investigations depended on surrogate markers of exposure, including depth of periodontal pocket, attachment loss, and dental indices, or based on the number of missing tooth or self-reported periodontal status such as oral hygiene practice. As a result, data obtained from early studies need to be interpreted with caution, emphasizing the need for further research, as suggested by Tsioufis *et al*. [10]".

CONCLUSIONS

In conclusion, periodontal disease and hypertension share multiple common risk factors, which should be readily controlled in case of assessment of a possible association [10, 25]. In patients with signs and symptoms of poor oral health, it is reasonable to recommend a medical evaluation (including blood pressure measurement) and comprehensive periodontal examination, especially when unexplained increased CRP levels are identified.

Therefore, in the face of two highly prevalent diseases (or cardiovascular risk factors) in the population (hypertension and PD), we strongly believe that simple periodontal evaluation should be a new useful tool for assessing cardiovascular risk in the general and especially in the hypertensive population.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose. There has been no financial support.

ACKNOWLEDGEMENTS

We thank the reviewer for correcting both spelling and grammar of the English text.

DISCLOSURE

The authors have declared no conflict of interest. There is not grant support.

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Received: February 20, 2013 Revised: March 29, 2014 Accepted: April 14, 2014