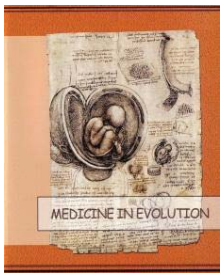
Chronic inflammation – the link between periodontal and cardiovascular disease



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Abstract

Coronary heart disease (CHD) is the leading cause of death and morbidity in many developed countries. Many risk factors for CHD have been identified, but a significant proportion of CHD is not explained by traditional risk factors. Recently, several lines of evidence have implicated chronic inflammation etiologically in CHD and cardiovascular disease (CVD). Periodontal disease is a chronic gram-negative anaerobic infection of the tooth-supporting structures. Periodontal disease is associated with elevations of several markers of chronic inflammation, and because of evidence implicating chronic inflammation in the etiology of CHD, an etiologic relationship between periodontal disease and CVD has been hypothesized. For these reasons, there has been strong interest in evaluating whether periodontal disease is independently associated with CVD.

Keywords: periodontal disease, cardiovascular disease, coronary heart disease, chronic inflammation, oral health

INTRODUCTION

Periodontitis is a family of diseases that affect dental supporting tissues, caused by infections sustained by periodontal pathogens such as Porphyromonas gingivalis, Prevotella intermedia, Tannarella forsythia, and Aggregatibacter actinomycetmcomintans, which lead to soft and hard tissue destruction, dental mobility, and the loss of dental elements [1]. Susceptibility to these diseases is highly variable and depends on host responses to periodontal pathogens. Although bacteria cause plaque-induced inflammatory periodontal disease, the progression and clinical characteristics of these diseases are influenced by both acquired and genetic factors that can modify susceptibility to infection [2].

Periodontal disease is a chronic gram-negative anaerobic infection of the tooth-supporting structures with an estimated prevalence of as high as 75% in adults in the US, among whom approximately 20–30% have severe forms of the disease [3-5] Alveolar bone resorption is both a measure and a consequence of severe periodontal disease. Common signs of periodontal disease that are identified by dentists and may be noted by primary care providers include: tooth loss, gingivitis with gum inflammation and bleeding, excess tartar, infection, decay, tooth mobility, and gum recession with bone loss. [boala paro]

Periodontitis depends on host responses to periodontal pathogens. The initial increased presence of neutrophils at the site is followed by the release of cytokines by neutrophils and macrophages; the chemical mediators released include tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and prostaglandins.

The inflammatory process includes the stimulation of fibroblasts by IL-1 and the secretion of matrix metalloproteinases (MMP), of which collagenase is the most prominent, by polymorphonuclear neutrophils. MMPs are responsible for increased collagen breakdown, and TNF-α is primarily responsible for increased osteoclast activity resulting in bone resorption. T-lymphocytes secrete receptor activator of nuclear factor kappa-B ligand (RANKL), which is involved in osteoclast activity and, therefore, bone resorption [6].

Periodontitis has also been associated with elevations in circulating levels of IL-6 and C-reactive protein (CRP). IL-6 is an important pro-inflammatory cytokine involved in the regulation of host response to tissue injury and infection. It is produced by a variety of cells, such as monocytes, fibroblasts, osteoblasts, and vascular endothelial cells, in response to inflammatory challenges. Moreover, it is widely accepted that IL-6 induces CRP production.

In addition, a significant overexpression of IL-21, IL-1β, IL-17, and IL-23p19 has been detected in tissues affected by periodontal disease compared with healthy gingival tissues. In particular, IL-21 is overexpressed in chronic periodontitis gingival tissues and is correlated with the clinical parameters of periodontal destruction and with pro-inflammatory cytokines [10]. A negative modulatory role of IL-4 and IL-13 in osteotropic cytokine production could be a mechanism that plays an important inhibitory role in inflammation induced periodontitis. In facts the activation of STAT6 by IL-4 and IL-13, through type 2 IL-4 receptors, seems to inhibit the production of IL-11 and leukemia inhibitory factor stimulated by IL-1β and TNF-α in human gingival fibroblasts [7].

Also, IL-10 and tumour growth factor-β1 (TGF-β1) are down-regulated in periodontal lesions. Generalized aggressive periodontitis subjects are characterized by a higher IL-1β/IL-10 ratio than are periodontal healthy subjects, suggesting an imbalance between pro- and anti-inflammatory cytokines in generalized aggressive periodontitis. IL-10 is also associated with periodontal health and seems to be a regulator of inflammation and alveolar bone loss in periodontal diseases. It might be involved in controlling the inflammatory process at periodontal healthy sites [7].

Coronary heart disease (CHD) is the leading cause of death and morbidity in many developed countries. Worldwide, CHD kills more than 7 million people each year [8]. Many risk factors for CHD have been identified, but a significant proportion of CHD is not

explained by traditional risk factors. Recently, several lines of evidence have implicated chronic inflammation etiologically in CHD and cardiovascular disease (CVD) [9].

Aim and objectives

In this systematic review, we evaluate the epidemiologic literature evaluating the possible link between periodontal disease and associated measures of oral health, and CHD. Identifying individuals at higher risk for CVD than predicted by traditional risk factors could facilitate more aggressive treatment of risk factors known to decrease CHD in high-risk individuals, such as those with hyperlipidaemia.

MATERIAL AND METHODS

CARDIOVASCULAR DISEASE AND PERIODONTITIS

Cardiovascular diseases are a leading cause of morbidity and mortality in developed countries. The disease process that underlies the majority of cardiovascular events is atherosclerosis, an inflammatory disease of the blood vessel wall. The earliest physical evidence of atherosclerosis are fatty streaks, which are typically present in childhood.

In the presence of arterial endothelial dysfunction, which is involved in the initiation and progression of atherosclerosis, these early lesions progress through to complex atheromatous lesions in adulthood, finally resulting in occlusion, plaque rupture and ischaemic events [10].

Periodontal disease is inflammation of the tissues surrounding teeth and results from a complex interplay between bacteria and host risk factors such as long-term smoking, poor oral hygiene, poorly controlled diabetes, stress and genetic predisposition [11]. Not only have periodontal organisms adapted to survive within an environment that is constantly besieged by host defences, but they flourish in the presence of inflammation, enabling their capacity to invade host tissues and gain direct access to the circulation [12]. Repeated bacteremias and endotoxemias are characteristic of periodontal infection, and periodontal organisms have been found to co-localise within atheromatous plaques [13]. The constant exposure of the vasculature to these pathogens provides an opportunity for endothelial inflammatory activation and functional impairment. Clinically, periodontal disease manifests as deepening of the epithelial attachment around teeth, loss of periodontal attachment and, ultimately, tooth loosening.

Periodontal disease has been associated with atherosclerosis [14], cardiovascular disease [15], diabetes [16], pre-term low birth weight [17], stroke [18], and premature death [19]. Accordingly, periodontal disease may account for a portion of the risk for cardiovascular disease via a shared pathogenic underlying inflammatory response [10].

Treating periodontal disease results in a functional improvement in cardiovascular status [20-23]. These studies are consistent with the concept that periodontal disease may be an important source of infectious and inflammatory vascular stress, and that periodontal therapy may be of particular clinical relevance in populations with high prevalence of both periodontal disease and cardiovascular disease.

HYPERTENSION AND PERIODONTITIS

Hypertensive patients suffering from metabolic syndrome show increased oxidative stress and compromised antioxidant activity in plasma and cells [24,25]. In addition, obesity and overweight are strictly related to hypertension. In fact, weight loss determines a diminished blood pressure independent from sodic diet [95]. Moreover, hyperglycemia and hypertension are strictly related. Hyperglycemia provokes an increased stimulation of a sympathetic nervous system that causes vasoconstriction and increased sodium reabsorption with consequent water attraction and insurgence of hypertension, which damages the endothelium integrity of vessels [26]. Augmented endothelial permeability allows the passage of lipoproteins and platelet-derived growth factors (PDGF), which give rise to the

proliferation of muscular smooth cells in the intima, which occludes vessel lumen and causes emboli, hypoxia, and consequent cellular death [27].

It also seems that periodontitis can influence some types of hypertension [28]. Several studies have taken into consideration the relationship between hypertension and periodontitis, although an association between periodontal disease measures and incident hypertension in cohort studies has not yet been evidenced. In a sample of 31,543 participants of the Health Professionals' Follow-Up Study, based on a prospective cohort of 40- to 75-year-old men at baseline, with no prior hypertension history and complete baseline information on oral health, an incidence of 10,828 cases of hypertension over 20 years of follow-up was identified, with no significant association between incident hypertension and periodontal disease [29].

Although statistical evidence is lacking, a clinical relation between high blood pressure and aggressive periodontitis has been deduced, as patients with poor oral hygiene have higher blood pressure problems than do healthy subjects with good oral hygiene condition [30].

Regarding the biological mechanism of this relationship, a recent study evaluated endothelial function in patients with periodontitis. Circulating levels of CRP and IL-6 were significantly higher in the periodontitis subjects with hypertension, than in the control group. Periodontal therapy seems to reduce serum concentrations of CRP and IL-6 [31].

PERIODONTAL DISEASE AND METABOLIC SYNDROME

As already mentioned, metabolic syndrome is a syndrome characterized by several signs that together seriously compromise the health of an individual. It is clear that the common denominator of the member pathologies of Metabolic syndrome is oxidative stress and the consequent hyperinflammation that primes chain interactions and leads to grave systemic complications, such as CVD, or local complications, such as periodontitis. Metabolic syndrome allows a pro-oxidative state in periodontal tissue, altering antioxidant defense mechanisms. This adversely affects tissular response against bacterial plaque attack.

On the contrary, periodontitis, being a great source of oxidative markers, promotes the onset of insulin resistance and metabolic syndrome in a vicious circle [32]. Chronic inflammation during old age periodontitis causes increased neutrophil defense activity, which involves increased oxidative activity, resulting in peroxidation and oxidative stress. In fact, both metabolic syndrome and periodontitis show increased serum rates of oxidative stress markers [33,34]. Regarding the oxidative stress markers found in periodontitis, individuals with periodontal disease exhibit a significant increase in the activities of oxidative stress markers. The increase in glutathione peroxidase may represent possible antioxidant compensation in detoxification reactions of organic peroxides produced during oxidative stress in gingival tissue. Since glutathione S-transferase (GST) has a direct role in the neutralization of hydroperoxides derived from the lipoperoxidation processes, increases in GST activities are probably related to the oxidative stress caused by the periodontal inflammatory process. GST comprises a group of enzymes that are also able to detoxify a variety of compounds, including xenobiotics derived from pathogenic microorganisms. Hence, increases in GST activities are excellent indicators of endogenous detoxification from exogenous sources. Myeloperoxidase activity in gingival tissue has shown a significant increase in patients with periodontal disease when compared with controls: this seems indicative of a chronic inflammatory process also reflected at a systemic level. A significant increase in oxidized glutathione (GSSG) concentrations has been detected in periodontitis patients, which is a clear biomarker of oxidative stress detected in inflammatory processes linked to periodontitis.

Consistent with the results for GSSG, tissue lipoperoxidation, measured as thio-barbituric acid reactive substances, seems to increase in the gingival tissue of periodontitis [35]. Periodontal diseases seem related to pathologies and conditions characterized by high

oxidative stress and by the presence of AGE, such as diabetes and physiologic aging. AGEs are able to favour chemotaxis and the production of proinflammatory mediators, to inhibit fibroblasts and osteoblasts, and to accelerate periodontal damage directly or binding their receptors RAGE [36]. Periodontitis is strictly correlated to hyperglycemia; in fact, it is also considered the sixth complication of diabetes mellitus [37]. Predialysis and hemodialysis in chronic kidney diseases are also associated with a higher prevalence of severe periodontitis compared with healthy individuals.

Chronic kidney failure is a clinical syndrome due to the slow, progressive, and irreversible loss of the glomerular filtration rate, and may be associated with several oral manifestations, such as xerostomia, uremic stomatitis, and periodontitis, diagnosed as clinical attachment loss.

Recent studies have shown an association between high levels of CRP and IL-6 and periodontitis, an association that decreases after periodontal treatment. Due to this association with the systemic inflammatory response, chronic periodontitis has recently been included as a non-traditional risk factor for chronic kidney failure [38].

In synthesis, metabolic alterations related to metabolic syndrome component diseases cause an augmented response to bacterial plaque, which favours periodontitis insurgence. It has been pointed in many studies out how periodontal treatment can reduce inflammatory mediators related to endothelial and cardio-circulatory dysfunctions [39]. A very recent work reported a real relationship between periodontitis and Metabolic syndrome, especially in women, while abdominal obesity was the largest contributory factor in both genders [40]. On the contrary, another new work about metabolic syndrome and periodontal diseases and caries did not find a strong association between metabolic syndrome and periodontal infections [41].

CONCLUSIONS

The role of dentists in the diagnosis, therapy, and management of cardiovascular patients is fundamental, but an improvement of collaboration among dentists, cardiologists, endocrinologists, nutritionists, etc., is needed.

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