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Autoimmune Inflammation - As a Causal Relationship between Periodontitis and Atherosclerosis

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Abstract Over the past few years, a sufficient number of randomized clinical trials have been aimed at finding links between periodontal diseases, in particular, periodontitis of varying severity with chronic coronary heart disease, acute coronary syndrome, arterial hypertension and metabolic syndrome. Almost all of these cardiac diseases develop against the background of atherosclerosis. The commonality between periodontitis and atherosclerosis of various localizations remains to be elucidated, and this review is intended to summarize the research to date and that is still to come in the future.

Keywords Periodontitis, Atherosclerosis, Pro-inflammatory cytokines

The main cause of almost all cardiovascular diseases is atherosclerosis. Atherosclerosis is a chronic inflammatory vascular disease that leads to the deposition of lipids in the intima to form an atherosclerotic plaque [1,3]. The increase and growth of plaques leads to a decrease in the lumen of the vessel, and hence, blood flow, which leads to ischemia of almost all organs and tissues. Ruptures or tears of plaques can lead to vascular thrombosis and irreversible processes in the body. Major heart diseases associated with atherosclerosis include myocardial infarction [fatal and non-fatal], angina pectoris, acute coronary syndrome, arrhythmias, chronic heart failure, valvular disease, and cardiomyopathy [2]. The main vessels affected by atherosclerosis are coronary, carotid, peripheral arteries.

Throughout the world, cardiovascular diseases are the main cause of death twenty years ago, and now, despite the high adherence to the treatment of patients, a large number of different medications and various interventional interventions - vascular stenting and coronary artery bypass grafting. Many risk factors that we can change, in particular, increased body mass index, obesity, blood sugar, insulin, high blood pressure, sedentary lifestyle, high cholesterol and lipoproteins, measurable and non-modifiable, dependent on atherosclerosis - age, sex, genetics.

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Atherosclerosis itself is accompanied by constant inflammation, and it is necessary to find out how periodontal diseases that are not directly related to the vessels constantly support autoimmune inflammation in the body. Atherosclerotic disease is a focal thickening of the vascular intima located between the endothelial lining and smooth muscle cell (SMC) layers of blood vessels in response to an immune response [14]. Endothelial dysfunction is the earliest change in atherosclerotic formation. The primary etiology of atherosclerosis is unknown [15]. However, other risk factors contribute significantly to the development and progression of this pathology, such as an abnormal plasma cholesterol profile, smoking, hypertension, diabetes mellitus, and elevated levels of inflammatory mediators, including C-Reactive Protein (CRP), and cytokines [15]. In recent years, researchers have been increasingly interested in the role of immune factors, in particular the cytokine cascade, in the development of the most formidable complication of atherosclerosis, myocardial infarction [4,13]. The commonality of inflammation and atherosclerosis is quite natural, since both syndromes form the same cells of loose connective tissue: endothelial and smooth muscle cells (SMCs), fibroblasts, monocytes and macrophages, neutrophils, platelets, and to a lesser extent T- and B-lymphocytes [3]. In recent years, researchers have been increasingly interested in the role of immune factors, in particular pro-inflammatory cytokines, in the development of the most severe complication of atherosclerosis, myocardial infarction [8].

Atherosclerosis begins with the accumulation of low-density lipoprotein (LDL) in the intima, where they are oxidized. This in turn activates increased expression in nearby endothelial cells of cell surface proteins such as inter-Cellular Adhesion Molecule 1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and selectins [15]. The adhesion of circulating inflammatory cells [monocytes, lymphocytes] to these adhesion molecules increases due to their diapedesis into the inflamed area of the intima [15]. The initial development of an atherosclerotic lesion occurs by differentiation of monocytes into macrophages, which engulf low-density lipoprotein (LDL) to form foam cells and then fat streaks [15,16]. Later, T-leukocytes induce a cell-mediated immune response with increased levels of inflammatory cytokines such as interferon gamma (INF-Y), tumor necrosis factor alpha (TNF-a), and interleukin-1 (IL-1e), further accelerating atherogenesis [17]. T-cell-associated mediators stimulate migration and mitosis of smooth muscle cells (SMCs) with the formation of a fibrous pseudocapsule around the lesion [17]. Lipid-laden macrophages undergo apoptosis, leading to the formation of a necrotic nucleus under the fibrous cap, making it susceptible to rupture, leading to the formation of a fatal thrombosis [14].

Periodontal disease [including gingivitis] resulting from various types of plaque is estimated to affect 47.2% of adults in the United States aged 30 years and older [1]. This figure increases to 70% after age 65 [4]. In addition to oral care habits, factors that contribute to periodontal disease include socioeconomic status, gender [male > female], education, diet, and smoking [4,5]. Based on data from 2009 and 2010, it is estimated that severe periodontal disease affects 11% of adults worldwide and is the sixth most common disease [number of cases at a given time] [5]. Periodontal disease and cardiovascular disease (CVD) [probability of new cases] increases with age [3,5].

Numerous epidemiological studies have shown an association between periodontitis [with the exception of gingivitis] and cardiovascular disease [8-14]. In 2012, after more than 10 years of epidemiological evidence supporting an association between periodontitis and cardiovascular disease (CVD), the American Heart Association published a scientific statement confirming an association between the two diseases, but emphasizing the absence of a causal relationship [15].

Cumulative data from the literature over the past decades support the role of periodontitis as an independent risk factor for atherosclerosis [18]. The presence of some periodontal pathogens, in particular Gram-negative anaerobes, in subgingival biofilm has been associated with an increased risk of myocardial infarction; the odds ranged from 2.52 to 2.99 with T. forsythia and P. gingivalis, respectively, compared with controls [19]. The hallmark of periodontitis is an increase in gram-negative bacteria, which are characterized by their ability to elicit an intense immune response through a pathogenicity mechanism such as lipopolysaccharide (LPS) [20]. What's more, some of these bacterial species have the ability to penetrate deeper tissues, reaching the circulation and triggering a systemic immune response away from their original habitat [21]. Several in vivo and in vitro studies have shown that periodontal bacteria associated with chronic inflammation can impair epithelial barrier function through the epithelial-mesenchymal transition [22-24].

The epithelial-mesenchymal transition includes cellular events beginning with the loss of polarity, cytoskeletal proteins, and adhesion, ending in the loss of the epithelial phenotype and the acquisition of mesenchymal-like characteristics [25]. This leads to a loss of synchronization of the epithelial layer and the formation of microulcers; thus, facilitating the entry of motile periodontal pathogens or virulence factors into the underlying connective tissue and exposed blood vessels. On the other hand, periodontal bacteria can invade host cells as part of their defensive strategy of evading the host's immune response [26]. This intracellular localization provides not only protection from the body's defense mechanisms, but also shelter from the action of antimicrobials [26]. Periodontopathogens such as P. gingivalis that reside inside cells either remain dormant or proliferate by modulating the cellular machinery [27]. After replication, P. gingivalis leaves the epithelial cells via the endocytic recirculation pathway to infect other cells or gain access to the circulatory system [28]. The bacterial load on the penetration of P. gingivalis into endothelial cells increases. In addition, P. gingivalis invasion of gingival epithelial and endothelial cells may be enhanced by Fusobacterium nucleatum [30] and T. forsythia [31]. It has been proven that P. gingivalis can cause the formation of foam cells or their persistence inside the cells and thereby induce a state of secondary inflammation, leading to endothelial dysfunction. Also, periodontal disease, in particular periodontitis, stimulates a systemic inflammatory response that leads to chronically elevated levels of various cytokines also associated with atherosclerotic vascular disease, such as interleucin-6 (IL-6) , interleukin-8 (IL-8), tumor necrosis factor alpha (TNF-a). Some of them may increase rapid hepatic synthesis and secretion of intravascular plasma proteins such as C-reactive protein [CRP] and fibrinogen [36,37]. In addition, bacterial products such as lipopolysaccharides can enter the bloodstream and trigger a strong immune response. These aforementioned factors can initiate atherosclerosis by acting on endothelial cells, modulating lipid metabolism and increasing oxidative stress [38].

Several studies have linked periodontitis to endothelial dysfunction, and this association is supported by several common biomarkers of periodontitis, atherosclerotic cardiovascular disease, and endothelial dysfunction [47]. Despite the potential of these biomarkers to determine the strength of this correlation, they are still not considered "gold standard" diagnostic markers [47]. When periodontitis is initiated, the expression of inflammatory cytokines increases markedly along with a change in the lipid profile, which can contribute to the development and aggravation of thrombus

formation and thromboembolic complications [57]. Periodontal disease (PD) has been reported to be significantly associated with the activation of biomarkers responsible for endothelial dysfunction and dyslipidemia such as C-Reactive Protein(CRP), tissue plasminogen activator [t-PA] and LDL cholesterol (C), tumor necrosis factor alpha (TNF-α) [58]. In addition, periodontitis is associated with higher serum levels of other inflammatory biomarkers, including von Willebrand factor (vWF), fibrinogen, and endothelial progenitor cells [58]. Interestingly, serum levels of these biomarkers decrease after periodontal therapy [59,60].

A systematic review examined the serum level of a group of common biomarkers to determine the strength of the evidence regarding periodontal disease (PD), cardiovascular disease (CVD), and endothelial dysfunction. Analysis of the results showed that the levels of various inflammatory markers, in particular interleukin-6 (IL-6) and C-Reactive Protein(CRP), were elevated. These results of this systematic review suggest that endothelial dysfunction may be a link between periodontal disease and atherosclerotic cardiovascular disease [61]. In addition, atherosclerotic CVD has been found to be associated with more severe periodontitis, and this has been noted by higher serum levels of highly sensitive [hs]-CRP [62]. Elevated and highly sensitive (hs) hs-CRP associated with periodontitis puts additional stress on the pre-existing inflammatory activity of the atherosclerotic lesion; hence increasing the risk of an even greater risk of ASCVD [63]. It has recently been found that periodontitis is associated with high levels of interltucin-6 (IL-6) , pentraxin-related protein 3 (PTX3), and soluble tumor necrosis factor-like weak inducer of apoptosis (sTWEAK) in patients with cerebral small vessel disease, which increases the likelihood of having this type of atherosclerotic cardiovascular disease (ACVD) by almost 3 times [64]. This was confirmed by the results of an in vivo study that showed changes in the vascular inflammation biomarkers, of interltucin-6 (IL-6), pentraxin-related protein (PTX3) and soluble tumor necrosis factor-like weak inducer of apoptosis (sTWEAK), in the systemic circulation after injection of LPS from P. gingivalis in rats [65].

Indeed, the current literature has provided valuable information on common biomarkers for periodontal disease (PD) and a atherosclerotic cardiovascular disease (ACVD), which may offer prognostic and diagnostic potential to significantly reduce the risk of early adverse cardiac and vascular events. However, further research is needed in this regard, as precise signaling other than atherosclerotic cardiovascular disease (ACVD) and periodontal disease (PD) biomarkers has not yet been fully elucidated [66,67].

At a joint workshop of the European Federation of Periodontology (EFP) and the American Academy of Periodontology [AAP] in 2012, evidence was presented for an association between periodontal disease (PD) and atherosclerotic cardiovascular disease (ACVD) [45]. Evidence included the role of periodontopathogenic bacteria in atherosclerotic cardiovascular disease (ACVD) and clinical [epidemiological and interventional] studies supporting an association between the two diseases [46]. Clinically, it is very difficult to find the causative agents of atherosclerosis. First, endothelial injury usually develops and progresses asymptomatically, potentially masking the initiating agent. Second, several factors can lead to a common inflammatory response, such as an atherosclerotic lesion, and these factors can coexist, further complicating the identification of a causative factor. In addition, studies regarding interventions performed in this regard have reported mixed results such as no change, temporary worsening of symptoms after periodontal treatment, or improvement in symptoms [65,67]. The main goal of periodontal therapy (PT) is to reduce the number of pathogenic bacteria and thus reduce the likelihood of progressive inflammation and recurrence of periodontitis [16]. Systematic review and meta-analysis of 10 clinical studies by Roca-Millan et al. summarized the effect of periodontitis therapy on the risk of cardiovascular disease. Therapy has been shown to result in: decreased levels of C-Reactive Protein (CRP), tumor necrosis factor-α, interleukin-6, and leukocytes. Fibrinogen levels also improved significantly after therapy. Moreover, after treatment of periodontitis, there was a significant decrease in low-density lipoprotein (LDL) levels and an increase in high-density lipoprotein (HDL). A meta-analysis showed that non-surgical treatment of periodontitis, in contrast to no treatment at all, leads to a significant reduction in C-Reactive Protein (CRP). Among the various drugs used to treat and prevent atherosclerotic cardiovascular disease (ACVD), statins have shown therapeutic potential in the treatment of periodontal disease [47,48]. Statins are inhibitors of 3 hydroxymethyl glutaryl coenzyme A reductase [HMG-CoA reductase]. These drugs have different ring structures and are known to lower blood levels of LDL and cholesterol to prevent atherosclerotic disease [49,50]. In addition to their primary lipid-lowering action, statins have several pleiotropic effects, including anti-inflammatory, antioxidant, antibacterial, and immunoregulatory functions [51,52].

The anti-inflammatory effect of statins is due to their ability to inhibit pro-inflammatory cytokines and increase anti-inflammatory activity. This effect is primarily associated with the activation of extracellular signal-regulated protein kinases (ERK), mitogen-activated protein kinase (MAPK), protein kinase signaling pathway 7(PI3-Akt). In addition, statins are able to modulate the host response to bacterial attack; thereby preventing inflammation-mediated bone resorption and stimulating new bone formation [53]. Topical administration of statins using experimental animal models contributed to the prevention of alveolar bone resorption as a result of their anti-inflammatory, antimicrobial, and bone remodeling properties, in addition to their inhibitory effects on metalloproteinases [54].

A 5-year, population-based, competitive follow-up study examined the effect of systemically administered statins on the rate of tooth loss compared to participants not taking

statins. A study reported a reduction in the incidence of tooth loss in patients treated with statins compared to controls [55]. In addition, a significant improvement in the clinical signs of periodontitis leads to a prolongation of the preclinical course of atherosclerotic cardiovascular disease (ACVD) and the prevention of fatal outcomes of heart attack, stroke, and thrombosis. Further intervention studies are needed to further elucidate the relationship between periodontal disease (PD) and atherosclerotic cardiovascular disease (ACVD), especially in terms of the biological impact of periodontal disease (PD) on the atherogenic cascade through effects on the vascular endothelium. In general, there will undoubtedly be a need for further research on the effect of statins on the course of periodontitis in complex standard treatment, especially its topical application. Despite the promising results of statins, their effect on various aspects of soft and hard tissue healing needs further study, especially in relation to wound healing and regeneration.

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