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Research Paper

Periodonitis and Hypertension: Interlinking pathways

Medical Science

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ABSTRACT

Chronic periodontitis is an inflammatory disease of the supporting tissues of the teeth caused by specific microorganism. Hypertension is one of the major causes of cardiovascular disease whereas periodontitis has recently drawn increasing attention because of its potential relationship with cardiovascular disease. This review is to examine the current literatures on the relationship between periodontitis and hypertension as well as to explore the possible biological pathways underlying the linkage between these health conditions. Hypertension is one of the major risk factors for cardiovascular diseases. Oxidative stress and endothelial dysfunction are among the critical components in the development of hypertension. Periodontitis, a chronic low-grade inflammation of gingival tissue, has been linked to endothelial dysfunction, with blood pressure elevation and increased mortality risk in hypertensive patients. Inflammatory biomarkers are increased in hypertensive patients with periodontitis.

Introduction

Periodontitis is the most common oral inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms [1]. *Porphyromonas gingivalis*, *Prevotella intermedia*, *Bacteroides forsythus*, *Campylobacter rectus*, *Actinobacillus actinomycetemcomitans* and the treponemes are among the most common organisms associated with periodontal diseases [2]. It is one of the most common chronic disorders of infectious origin with prevalence of 10% to 60% in adults depending on the diagnostic criteria [3].

Periodontal disease has been found to be associated with various cardiovascular diseases. It has been linked to systemic inflammatory markers and endothelial dysfunction as well [4]. It has also been recognized as a risk factor for atherosclerotic complications. Current epidemiological evidence also supports its potential association with increase in blood pressure and hypertension prevalence [5].

Although current epidemiological data are yet to provide sufficient evidence to prove a causal relationship between these two diseases, researchers have identified chronic inflammation as an independent link of periodontal disease in the development and progression of cardiovascular disease in some patients [6]. Both American Heart Association (AHA) and the American Academy of Periodontology (AAP) were in agreement that more thorough and long-term interventional studies should be carried out in order to gain an in-depth knowledge of the diseases' mechanism.

This article reviews the evidence and possible linking pathways of association between hypertension and periodontal disease.

Chronic immunosuppressive therapy with cyclophosphamide result in spontaneous depression of blood pressure (BP) in Okamoto spontaneously hypertensive rats (SHR) [7]. This finding supported the hypothesis regarding the involvement of inflammatory reaction in hypertension.

Kampus et al. [8] also found an increase in C-reactive proteins (CRP) and vascular wall stiffness in untreated hypertensive patients. More recently, a link between hypertension and inflammatory responses to oxidized low-density lipoprotein was reported in patients, further suggesting that BP is directly correlated to immunological milieu [9].

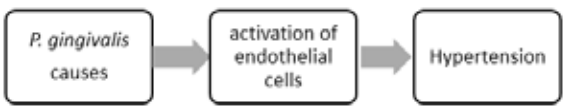
Possible Linking Pathways for the Association between Hypertension and Periodontitis

1. Hypertension and periodontitis are two diseases which seem to be profoundly unrelated. There is now evidence that supports periodontitis as an important risk factor for cardiovascular disease including stroke [10], peripheral artery disease, and coronary heart disease. Particularly, the inflammatory response accompanying periodontitis has been proposed as an important factor that may exert adverse effects on the regulation of BP. The level of serum high-sensitivity CRP (hs-CRP), an acute-phase reactant that has been reported to predict the outcome of cardiovascular disease, was found to be more increasing in patients with periodontitis than in control subjects, and it decreased significantly after periodontal treatment [11]. The association of CRP with hypertension in the setting of periodontitis has not been consistent, possibly due to many other factors that can elevate inflammatory markers, or simply hypertension itself is a multifactorial disease. However, it has recently been proposed that hs-CRP may be a useful marker linking periodontal disease and chronic inflammation which leads to endothelial dysfunction [12]. Periodontitis has been reported to attenuate endothelium-dependent vasodilatation in experimental rats. This ill-effect was due to the elevation of systemic inflammatory biomarkers (CRP and IL-6), worsening the lipid profile, and increased production of vascular superoxide radicals and reduction of vascular nitric oxide synthase-3 (NOS-3) expression [12]. Furthermore, periodontitis is not confined to a localized lesion but may contribute to an increased systemic immune response in patients [13]. Periodontitis may therefore be capable to induce vascular inflammation which leads to endothelial dysfunction, an initial step for cardiovascular disease. Serum levels of hs-CRP and IL-6 are usually elevated in patients with chronic periodontitis as compared to healthy control group. On the other hand, periodontal treatment reduces IL-6, CRP, and fibrinogen levels in patients having hypertension and severe periodontitis. Thus, it is getting clearer that inflammation might provide a potential link between hypertension and periodontitis.

2. Oral Infection. Periodontal bacterial infection may also be involved, at least in part, in the development of hypertension. Periodontitis results from the accumulation of bacterial species in subgingival biofilm, particularly by Gram-negative anaerobic and microaerophilic bacteria, such as *P. gingivalis, Prevotella intermedia, Prevotella nigrescens, Tannerella forsythia, Treponema denticola, Fusobacterium nucleatum, Aggregatibacter actinomycetemcomitans,* and *Campylobacter rectus*. These periodontal pathogens are able to destruct and invade gingival tissues by proteolysis then enter the systemic circulation, causing transient bacteraemia [14]. Subsequently, the periodontal microbes may directly invade the arterial wall and lead to vascular inflammation and atherosclerosis [14]. *P. gingivalis* is the most prevalent

bacterium harboured in atheromas, with its presence found in 50% of the atheroma samples obtained from patients with periodontitis. Infection of macrophages with *P. gingivalis* itself, and its outer membrane vesicles, is able to induce higher levels of foam cell formation.

P. gingivalis has been demonstrated to induce the expression of cell adhesion molecules including ICAM-1, VCAM-1, P-selectin, and E-selectin [15]. *P. gingivalis* can cause activation of endothelial cells. Therefore, periodontopathogens from periodontal lesions into the circulation may deliver virulent factors to the arterial wall to initiate and/or promote foam cell formation in macrophages, thus contributing to development of cardiovascular disease.



3. Oxidative Stress. Reactive oxygen species (ROS) such as superoxide anions and hydrogen peroxides are chemically reactive molecules. They damage cellular components including lipid membranes, nucleic acids, and proteins. ROS are formed as natural by-products during physiological processes in cell membranes, mitochondria, and endoplasmic reticulum. In addition, ROS can be generated from tobacco, pollutants, drugs, and ionizing radiation. However, excessive production of ROS leads to oxidative stress with an increase in the formation of free radicals as well as a decrease in antioxidant levels.

Periodontal disease also induces excessive production of ROS in periodontal tissues. Therefore, oxidative stress is suggested to be involved in the pathogenesis of periodontal tissue destruction. As the periodontal disease worsens, the production of ROS increases in response to periodontal inflammation; excessive increase in ROS can result in entry of ROS species in systemic circulation. Thus these ROS may prove detrimental to systemic health. Oxidative stress has been implicated in the development of hypertension. ROS are widely accepted as the mediators for vasoconstriction and vascular inflammation, and bioavailability of NO is strongly related to hypertension [16].

Periodontal disease may contribute to endothelial dysfunction, which eventually increases the risk of hypertension. NO deficiency is strongly related to the redox imbalance. Inducible nitric oxide synthase (iNOS), which is expressed exclusively under inflammatory condition to produce large amounts of prooxidative NO, is prominently expressed in gingival tissues with periodontitis. Furthermore, given that inflammation or even oxidative stress can destruct extracellular matrix [17], it is possible that periodontitis may link to adverse vascular remodelling. Damage to the extracellular matrix has been shown to cause structural and functional alterations, consequently affecting cell adhesion, proliferation, and signalling pathway. Hence, this impairment of elastic properties of large arteries plays a significant part in the development and progression of hypertension. Various studies documented the involvement of endothelial dysfunction in periodontitis with the presence of inflammatory biomarkers.

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