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Mini Review

Keywords

Porphyromonas gingivalis,
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Cardiovascular disease,
Periodontal disease

Cooperation of the oral microcirculation and systemic circulation in the peripheral vascular disorder

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Abstract

Periodontal disease is characterized by both inflammation and bone resorption. This relationship has resulted in a new field of study and provides a context for better understanding of the pathogenesis of periodontal disease. We can infer that the involvement of reactive oxygen species (ROS) may be the pathological mechanism linking periodontal disease and cardiovascular disease. Therefore, we recommend further studies using antioxidants to characterize the ROS pathway involved in periodontal disease and cardiovascular disease.

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1. Association between cardiovascular diseases and periodontal diseases

The significant association between cardiovascular and periodontal diseases is receiving increasingly more attention. Epidemiological studies show periodontal disease may be a risk factor for systemic diseases, such as hypertension and diabetes[1-4]. Periodontal diseases can significantly affect systemic diseases, which can inversely be risk factors for periodontal diseases. The relationship between periodontal and systemic diseases is a basic concept in periodontal medicine[5], increasing the prevalence of this field[6, 7].

Periodontal diseases are bacterially-induced inflammatory diseases of the supporting tissues of teeth and have also been recognized as a lifestyle-related disease. *Porphyromonas gingivalis* (*P. gingivalis*) is one of the prominent periodontal pathogens, and is the most important bacteria involved in the onset and exacerbation of periodontitis[8]. *P. gingivalis*, which is an anaerobic Gram-negative coccobacillus, has been shown to play a role in the progression of periodontal disease including bone and tissue destruction[9]. *P. gingivalis* possesses fimbriae on its cell surface[10], which induce cytotoxicity and enhance aggregation and bacterial adhesion to cells as well as invasiveness[11].

2. Relationship between oxidative stress and periodontal disease

Oxidative stress occurs when the production of reactive oxygen species (ROS) exceeds the capacity of the cell to detoxify these potentially injurious oxidants using endogenous antioxidant defense systems.

Conditions that are associated with oxidative stress induced by ROS include hypertension and stroke. We previously developed an electron spin resonance-based technique to assess oxidative stress, including ROS, in biological systems[12-19]. We demonstrated that the generation of ROS was increased in the brain of the stroke-prone spontaneously hypertensive rat (SHRSP), and ultimately contributed to the mechanisms causing hypertension or stroke[12,16-18]. We also reported that periodontal disease-reduced gingival vascular reactivity was accelerated by diabetes due to an increase in oxidative stress in the microcirculation of the oral and maxillofacial regions of a rodent model[19].

Periodontal disease is characterized by inflammation and bone resorption; the study of the relationship between inflammation and bone resorption has resulted in a new field of study, providing context for a better understanding of the pathogenesis of periodontal disease[20]. Garrett *et al*. demonstrated that the formation of osteoclasts was stimulated in the bone by the generation of ROS, and that bone resorption occurred both *in vivo* and *in vitro*[21]. Furthermore, ROS are generated predominantly by polymorphonuclear leukocytes (PMN) during an inflammatory response, and are regarded as being highly destructive; they are known to induce lipid peroxidation in cell membranes[14,22]. It has been observed that invading *P. gingivalis* bacteria trigger the release of cytokines such as interleukin-8 and tumour necrosis factor alpha, leading to elevated numbers and activity of PMNs[23]. As a result of stimulation by bacterial antigens, PMNs produce the ROS superoxide *via* the respiratory burst as part of the host response to infection[14,16]. Lipopolysaccharide (LPS) enhances ROS production, as well as expression of pro-inflammatory cytokines such as interleukin-1 beta, interleukin-6, interleukin-8 and tumour necrosis factor alpha, and the production and activation of Matrix metalloproteinase (MMP)-2. *N*-acetyl-L-cysteine (NAC) suppressed all LPS-induced inflammatory responses examined suggesting that LPS-induced ROS may play a major regulatory role in these responses in gingival fibroblasts[24]. Previous clinical and epidemiological studies have shown that periodontal disease is an infection of the oral cavity caused by Gram-negative coccobacilli, and is a risk factor for cardiovascular disease[25-27]. In addition, a recent study suggested that periodontitis may be associated with endothelial dysfunction in individuals without cardiovascular risk factors, as well as in hypertensive patients[28]. Therefore, we hypothesized that oxidative stress induced by ROS may play a critical role in the resorption of bone due to periodontal disease caused by *P. gingivalis*. However, the relationship between bone resorption due to periodontal disease and a vascular disease model such as SHRSP, which is a model associated with increased oxidative stress, has not yet been examined.

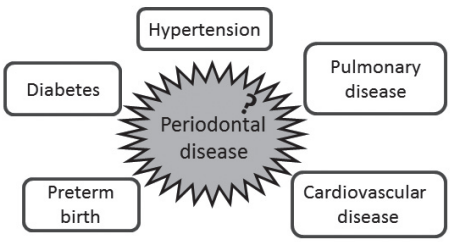

Fig. 1 The relationship between periodontal disease and systemic disease

3. Role of ROS in lifestyle-related disease and periodontal disease

Our previous results suggested that *P. gingivalis*-induced alveolar bone loss could occur in periodontitis and also "hypertension and stroke" animal models, such as SHRSP[29]. Furthermore, another report investigated the effects of *P. gingivalis* in the SHRSP rodent model, representing hypertension or stroke[30]. By measuring reactive hyperemia in the oral microcirculation, we examined *in vivo* endothelial function and gingival blood flow in the oral microcirculation animal models of lifestyle-related diseases, such as periodontitis or stroke. Furthermore, we measured isometric contraction changes using ring preparations that we extracted from these model animals *in vitro*. We examined *P. gingivalis*-induced alteration of oral vascular function in both SHRSP and control model, and found that vascular function changed in SHRSP infected with *P. gingivalis*.

Furthermore, the reactivity of blood vessels in the oral cavity was modulated by *P. gingivalis* infection in this experiment. *P. gingivalis* is found in the lesions of atherosclerosis and can also penetrate the vascular endothelium[31]. In addition, vascular contraction is affected by ROS[32,33]. Therefore, *P. gingivalis* invasion into blood vessels may induce modulation in vascular function. Interestingly, the effects on vascular functions

were noted in specimens removed from the descending aorta, as well as the intraoral vessels, suggesting that *P. gingivalis* infection in the oral cavity may show systematic effects[30].

As can be seen from the above, if patients predisposed to any systemic lifestyle related diseases are infected with *P. gingivalis*, periodontal tissue and other systemic vascular dysfunctions and failures may also slowly progress (Fig. 1). We can infer that the involvement of ROS may be the pathological mechanism linking periodontal disease and cardiovascular disease. Thus, we recommend further studies using antioxidants to characterize the ROS pathway involved in periodontal disease and cardiovascular disease.

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