

# Association of Periodontitis and Aging-Related Diseases: A Review of Mechanistic Studies

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## Abstract

**Background and Aim:** Periodontitis, as the most prevalent cause of tooth loss, affects 20-50% of individuals throughout the world. One factor involved in the severity and incidence of periodontitis is aging, which is a substantial risk factor for mortality and morbidity. It is stated that some disorders are common in older population, like cardiovascular diseases, osteoporosis, chronic kidney disease, and Alzheimer's disease. Understanding the changes related to aging may provide a better insight into age-related diseases. Hence, this study aimed to review and summarize evidence regarding periodontitis and aging-related disorders with a mechanistic insight.

**Materials and Methods:** Data were obtained from the scientific databases, including PubMed, Google Scholar, and Scopus in English between 1993 and 2021.

**Results:** Cardiovascular diseases, osteoporosis, chronic kidney disease, and Alzheimer's disease are associated with periodontitis directly or indirectly, and pro-inflammatory cytokines are the key mediators in such relationships. For instance, interleukin (IL)-1 $\beta$ , tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and IL-6 have a substantial role in pathogenesis of periodontitis in the majority of such diseases. These agents, particularly IL-1 $\beta$  and TNF- $\alpha$ , can also lead to leukocyte migration and subsequently form reactive oxygen species (ROS), reactive nitrogen species, and matrix metalloproteinases (MMPs).

**Conclusion:** It seems that periodontitis is linked to aging-related diseases, namely cardiovascular diseases, osteoporosis, chronic kidney disease, and Alzheimer's disease by the mediation of pro-inflammatory agents such as IL-1 $\beta$ , TNF- $\alpha$ , and IL-6.

**Key Words:** Alzheimer's Disease; Renal Failure; Osteoporosis; Cardiovascular Diseases; Periodontitis

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## Introduction

Periodontitis is described as an infectious-inflammatory disorder affecting tooth-supporting structures, and is the most common reason for tooth loss in the adult population of industrialized societies (1). The disease involves 20–50% of subjects around

the world (2). Pathological manifestations of this oral condition are characterized by degradation of soft tissue and loss of alveolar bone in connection with oral microbial dysbiosis (3). Unfortunately, the common treatments cannot regenerate the lost alveolar bone (4). Currently, the etiology of

periodontitis is known to be the oral microbiota and host dysbiosis (5). The oral microbiota is heterogeneous and complex, and is composed of Gram-positive and Gram-negative bacteria (6). Periodontal tissue destruction occurs due to the reaction of host immunity and inflammatory system resulting from periopathogenic microorganisms (7). T and B lymphocytes, macrophages, neutrophils, and monocytes are involved in the immune responses. They are activated in order to induce inflammatory factors, such as proteolytic enzymes, arachidonic acid metabolites, chemokines, and cytokines. These factors can take part in bone resorption and tissue destruction through stimulation of different degradation-related pathways (8). Aging is another factor that affects the severity and incidence of periodontitis (9). Aging is a biologic, degenerative, and time-dependent occurrence and is known as one of the most important risk factors for mortality and morbidity (10). Investigation of changes related to aging, e.g., in immune cells that regulate inflammation, may result in better understanding of age-related ailments and also can be effective in treatment planning for management of aging-related disorders and periodontal diseases (11). In this line, some illnesses have a high prevalence in the older population, such as chronic kidney disease, cardiovascular diseases, osteoporosis, and Alzheimer's disease (12-15). In this narrative review, we aimed to explain the association of periodontitis with these aging-related diseases with a focus on the involved mechanisms.

#### ***Risk factors and pathogenic process of periodontitis***

In the past three decades, our knowledge has been considerably enhanced about the risk factors of periodontitis. Many risk factors have been investigated, including aging-specific bacteria, smoking, alcohol consumption, nutrition, stress level, socioeconomic status, systemic diseases (such as diabetes mellitus),

genetic disorders which usually occur in the form of polymorphisms, and inflammatory responses (16-18). Among the various bacteria that colonize the oral cavity, *Porphyromonas gingivalis* (*P. gingivalis*), *Tannerella forsythia*, and *Aggregatibacter actinomycetemcomitans* have been implicated as initiators to induce inflammatory responses in periodontitis (17). In periodontitis, especially in periodontitis related to aging, pro-inflammatory cytokines, like interleukin (IL)-1 $\beta$ , tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and IL-6, also increase the activity of osteoclasts as a result of stimulation of innate immune pathways (19). Other pro-inflammatory cytokines involved in periodontitis pathogenesis include IL-2, IL-8, IL-11, IL-12, IL-15, IL-17, interferon gamma, IL-18, IL-21, IL-32, IL-35, and IL-37 (20). TNF- $\alpha$  and IL-1 $\beta$  stimulate adhesion molecule upregulation in the endothelium and chemokine formation resulting in leukocyte migration into the periodontal tissue (21). Migrated leukocytes form some factors, like matrix metalloproteinases (MMPs), reactive nitrogen species, and reactive oxygen species (ROS) (22, 23). Recently, several lines of evidence indicate that smoking affects the development of periodontitis in a dose-dependent manner (24). Smoking was reported to be associated with elevated level of TNF- $\alpha$  in gingival crevicular fluid of patients with moderate to severe periodontitis. Psychological stress is another risk factor for periodontitis (25). Although no longitudinal or interventional studies have confirmed psychological stress as a risk factor for periodontitis, some case-control and cross-sectional studies have shown a possible link in this regard (26-28). This correlation may be related to enhancement of IL-6 production in response to the increased level of psychological stress, defects in the immune system responses of the host to *P. gingivalis* infection, and poor oral hygiene and prophylaxis in individuals under stress

(25, 26, 29).

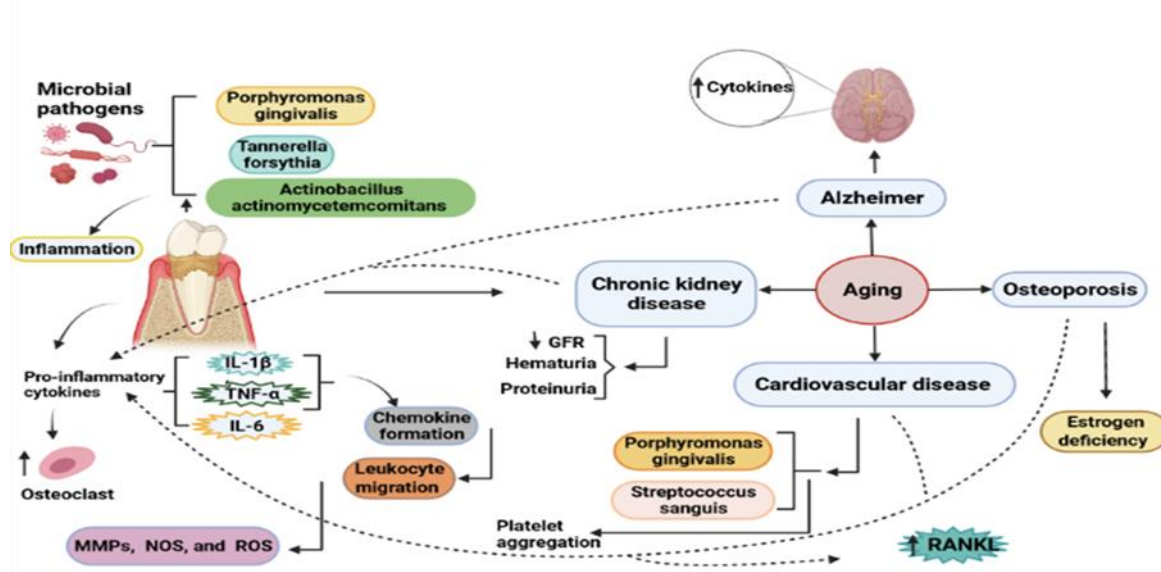
A currently widely held view based on a large body of evidence is that genetic disorders play an important role in the pathogenesis of periodontitis (18). In line with the role of genetic disorders in disease predisposition, it is suggested that periodontitis is correlated to N-formyl-L-methionyl-L-leucyl-L-phenylalanine (FLMP) and FC receptor gene polymorphisms (18, 30).

Several diseases are caused by defects in neutrophil function, including cyclic neutropenia, Chediak-Higashi syndrome, leukocyte adhesion deficiency, agranulocytosis, and Down syndrome (17). Regarding the fact that localized periodontitis is associated with defects in neutrophil function, it is thought that there is a possible relationship between such diseases and localized periodontitis. However, it has not yet been well documented (31).

#### ***Periodontitis and disorders associated with the cardiovascular system:***

Cardiovascular diseases (CVDs) include coronary heart disease, myocardial infarction, angina, congenital heart disease, and stroke (32, 33). CVD is associated with tobacco consumption, stress level, low socioeconomic status, and diabetes; all of these parameters are also risk factors for periodontitis (34). There are several similarities between patients with periodontitis and CVD. Based on these similarities, it is believed that periodontitis is correlated with CVD. The most common systemic disorder in patients with periodontitis is CVD (35). A relationship between periodontitis and heart disease has also been reported (36). Despite the role of oral infections in coronary heart disease and stroke, possible mechanisms involved in the pathogenesis of CVD remain unknown. Several mechanisms have been proposed for the relationship between periodontitis and systemic conditions such as CVD, including (I) common susceptibility, (II) changes in immune cell functions with increased pro-inflammatory

cytokines and mediators, and (III) direct infection and cross-reactivity or molecular mimicry between pathogenic antigens and self-antigens (37-39). For instance, in patients with periodontitis, lipopolysaccharides and other substances from Gram-negative bacteria can lead to a series of changes in immune cell functions and mechanisms involving pro-inflammatory cytokines that cause metabolic dysregulation. Therefore, elevated serum levels of lipids and/or pro-inflammatory cytokines may be a contributing risk factor for heart disease (40, 41). Some studies have shown that periodontal pathogens may enhance the risk of myocardial infarction (42, 43). Oral bacteria can be found in carotid atheromas; while some of these bacteria (*P. gingivalis* and *Streptococcus sanguis*) are associated with platelet aggregation (Figure 1), an important event for thrombosis (36). Although there is increasing evidence that oral infections participate in initiation and development of CVD, legitimate concerns have arisen about the nature of this association. As already mentioned, there are multiple independent risk factors that are common to both periodontitis and CVD. Several authors have proposed that the relationship between periodontitis and CVD is due to the insufficient statistical adjustment for confounders, especially age and smoking (44, 45). It has been suggested that periodontitis may act as an independent risk factor for CVD, even after adjusting for risk factors such as smoking (46). This relationship can occur through systemic lipopolysaccharides and bacterial exposures posed by periodontitis which lead to platelet aggregation, atherogenesis, and thrombi formation. These events act as a trigger for stroke, atherosclerosis, and coronary heart disease (47). Therefore, it should be noted that future studies are required to evaluate the impacts of cytokines on the association between periodontitis and CVD.



**Figure 1.** Some of the pathogenic events in aging-related disorders that are linked to periodontitis. GFR: Glomerular filtration rate; RANKL: Receptor activator of nuclear factor kappa-B ligand; IL-1 $\beta$ : Interleukin-1 $\beta$ ; IL-6: Interleukin-6; TNF- $\alpha$ : Tumor necrosis factor  $\alpha$

### ***Periodontal disease and osteoporosis***

Osteoporosis is a skeletal disorder caused by an imbalance between bone resorption and formation, favoring resorption. This disorder is characterized by reduced strength of bone and increased risk of bone fracture (48).

Periodontitis is characterized by the breakdown of alveolar bone around the teeth and loss of connective tissue surrounding the teeth. Thus, bone loss is a common feature that occurs in both periodontitis and osteoporosis. It is believed that periodontitis and osteoporosis have similar outcomes (49). The effects of cytokines and local cells are considered as the mechanisms which affect bone destruction in periodontitis and osteoporosis (50). As mentioned earlier, in patients with periodontitis, dense infiltrates of periodontal pathogens in the gingiva cause the activation and recruitment of mononuclear leukocytes to the infective sites (21). Pro-inflammatory cytokines produced by the recruited immune cells and some local cells, either alone or through synergistic interactions, enhance the expression of receptor activator of nuclear factor- $\kappa$ B ligand (RANKL) (Figure 1) by activated T

lymphocytes. RANKL binds to its receptor, RANK, on monocyte/osteoclast precursor cells (51, 52). This cell-to-cell contact results in osteoclast differentiation and bone loss in periodontitis and osteoporosis. Pro-inflammatory cytokines also inhibit bone formation by inhibiting osteoblast differentiation (21). In addition to T lymphocytes, other immune cells such as B lymphocytes may affect the pathophysiology of bone disorders either by serving as osteoclast progenitor cells themselves or expressing RANKL (53). Osteoprotegerin released from stromal and osteoblast cells reduces bone destruction by inhibiting the activation of osteoclasts. According to studies on periodontal patients, the mRNA level of RANKL increases in the periodontal tissues of patients with advanced periodontitis. In contrast, the level of osteoprotegerin mRNA is downregulated (54).

Extensive data from the literature have indicated that estrogen deficiency is a common risk factor for both osteoporosis and periodontitis. Estrogen, either directly or indirectly, modulates the levels of TNF- $\alpha$ , IL-1 $\beta$ , and monocyte colony-stimulating factor that

play critical roles in regulation of inflammatory response and bone metabolism (55). In estrogen deficiency, the inhibitory effects of estrogen on inflammatory cytokines are removed, and thereby the balance between bone resorption and formation is disrupted (51, 55). Hence, estrogen deficiency may act as a linker to the correlation of periodontitis with osteoporosis.

#### ***Periodontitis and chronic kidney disease***

Chronic kidney diseases (CKDs) include reduced kidney activity, hematuria, and proteinuria. CKD has an adverse effect on the quality of life by increasing the risk of pathological disorders such as diabetes, systemic inflammation, urinary tract infections, and autoimmune conditions (56, 57). Periodontitis is a new risk factor for CKD and decreases kidney activity gradually (58). Periodontal pathogens related to periodontium can transfer through the blood flow and affect endothelial activity of nephrons (58). Chen et al. indicated that 18.2% of individuals with periodontitis had a reduction in estimated glomerular filtration rate, hematuria, and proteinuria (Figure 1). Moreover, periodontitis may increase pathological alterations in the kidney of obese mice, probably through reducing MMP2 and increasing TGF- $\beta$ 1, tissue inhibitor of matrix metalloproteinase 1, and MMP inhibitor expressions (59). The renal endothelium can be injured by circulating periodontal bacteria probably due to changes in renal endothelium that decreases the bloodstream in the kidney and negatively affects renal activities. In CKD patients, periodontal treatment has a positive impact on glomerular filtration rate (60). Many cross-sectional studies have provided convincing evidence indicating that the association of CKD with periodontitis is a two-way link, and diabetes and hypertension are involved in this relationship (61, 62). Besides the effects of periodontal pathogens on renal endothelium, which can lead to CKD, the increased risk of

CKD in patients with periodontitis may be attributed to inflammatory mediators such as thromboxane B2, TNF- $\alpha$ , and IL-6 (63). Vilela et al. studied the effect of periodontal treatment on IL-6 and C-reactive protein levels in CKD patients. The authors reported that periodontal treatment decreased these inflammatory agents after 3 months, confirming the link between CKD and chronic periodontitis (64). Although there are several studies showing the relationship between CKD and periodontitis, additional studies are needed to confirm this association.

#### ***Periodontitis and Alzheimer's disease***

Neurodegenerative disorders are characterized by defects in performance and lack of neurons with the participation of various functional systems (65). Among neurodegenerative diseases, Alzheimer's disease has the highest prevalence (66). Several studies established some risk factors for Alzheimer's disease, including low physical activity, smoking, diabetes mellitus, and depression. Recently, periodontitis, as an environmental agent, has been mentioned as a risk factor for Alzheimer's disease (67-69). Based on previous studies, it is likely that periodontitis prevention and its treatment can help inhibit the progression of Alzheimer's disease (70, 71). The oral cavity contains more than 700 bacterial strains, some of which have the ability to access the brain through peripheral nerves and blood flow, thereby inducing inflammatory responses in the central nervous system. Patients with Alzheimer's disease and periodontitis have defects that may contribute to the secretion of pro-inflammatory cytokines (72). In addition to the local production of pro-inflammatory cytokines in the central nervous system mediated by bacterial pathogens, the cytokines originating from periodontium may enter the brain through neural or systemic pathways and enhance cytokine levels in the brain (Figure 1) (72, 73). Parkinson's disease is another neurodegenera-

tive disorder that chronic periodontitis may participate in its progression. This participation may result in systemic inflammation accompanied by an increase in the number of periodontal microorganisms. In line with the association of periodontitis with neurodegenerative disorders, a longitudinal cohort study on 152 individuals indicated that in individuals with less than 10 lost teeth, increased prevalence of periodontitis was related to a reduction in cognitive levels (74).

### Conclusion

Periodontitis is the main cause of tooth loss, and there is no effective definite treatment option for it. Aging, as one of the most important causes of morbidity and mortality, is often associated with serious diseases such as CVD, osteoporosis, CKD, and Alzheimer's disease. Thus, identifying processes involved in aging and aging-related diseases can be effective in treating both periodontitis and these disorders. The mentioned diseases are linked to periodontitis directly or indirectly. Pro-inflammatory cytokines have a substantial role in such relationships. For example, IL-1 $\beta$ , TNF- $\alpha$ , and IL-6 play a pivotal role in the pathogenesis of periodontitis and most of these disorders. These cytokines (IL-1 $\beta$  and TNF- $\alpha$ ) can also cause leukocyte migration and subsequently produce ROS, reactive nitrogen species, and MMPs. Further investigations are required to show other possible mechanisms involved in the relationship of periodontitis and other diseases.

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Figure 1 was created by BioRender.com

### Conflict of interest

The authors report no conflict of interest.

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