Association of Periodontal Disease with Systemic Diseases – Update

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Abstract: Periodontitis is a state of inflammation caused by bacteria in the oral cavity. Typical clinical symptoms of periodontitis include gum inflammation, alveolar bone loss, clinical attachment loss and periodontal pocket formation.Through the years, the association of periodontal disease with other non-infectious systemic diseases has been brought to attention.A growing body of scientific evidence has shown that severe periodontitis may enhance susceptibility to certain important systemic diseases and conditions, for example, cardiovascular disease, diabetes mellitus, adverse pregnancy outcomes, chronic kidney disease, cancer and pulmonary infections. Here, we give a review of the available evidence supporting this association, and the possible mechanisms involved.

Keywords: Periodontal Disease; Systemic Disease; Inflammation; Diabetes Mellitus

1. Periodontal disease and diabetes

Diabetes is a complex chronic disease that requires continuous and repeated correction of glycemic parameters and cardiovascular risk factors to prevent acute and chronic complications. According to the current World Health Organisation (WHO) classification. Diabetes is classified into two types: type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus. (T2DM, type 2 diabetes) T2DM accounts for 90-95% of all diabetics, with beta cell insufficiency and insulin resistance in the muscle and liver being the predominant pathophysiological abnormalities. [10]. A number of studies have now pointed to a bidirectional association between periodontal disease and diabetes mellitus. The main mechanisms of the association between diabetes and periodontal diabetes are the release of late glycosylation end products as a consequence of hyperglycemia and several genetic factors, etc., and microbial and lifestyle factors which are common triggers. Current research suggests that in some cases there is a link between diabetes and periodontal disease and/or bone resorption. Recently, it has been shown that periodontal treatment can improve metabolic control in diabetic patients, and uncontrolled diabetes also appears to affect the response to periodontal treatment and may lead to peri-implant disease. As a result, examining the association between diabetes and periodontal disorders may aid in better understanding of the role of diabetes in periodontal disease and the risk factors associated with it, leading to better oral health care. with the highest prevalence reported in patients with severe periodontal disease. Mechanistic studies have shown that T2DM induces a high inflammatory response in the periodontal microbiota, which influences inflammatory resolution and recovery and accelerates periodontal tissue damage[11]. Based on the above results, we believe that periodontal disease is caused by high oxidative stress due to insulin resistance in hyperglycemic states. Mechanistic studies have shown that T2DM induces a high inflammatory response in the periodontal microbiota, which influences inflammatory resolution and recovery and accelerates periodontal tissue damage[12]. Periodontal treatment may improve glycemic control by reducing serum inflammatory marker levels and improving insulin resistance[13]. These recent scientific data confirm that routine clinical periodontal care has a direct positive impact on the prognosis of patients with T2DM[14]. There is also considerable evidence that younger T1DM patients with poor metabolic control, especially as measured by glycemic haemoglobin levels, have worse periodontal disease status than healthy individuals[15].

2. Periodontal disease and cardiovascular disease

Cardiovascular disease (CVD) refers to a group of atherosclerotic diseases, including coronary heart disease, cerebrovascular disease, and peripheral vascular disease. Many chronic infectious, inflammatory, and immunological illnesses have been linked to an elevated risk of cardiovascular disease.[16]. The most frequent risk factors for

cardiovascular disease include lifestyle variables such as smoking, dyslipidemia, hypertension, and alterations in glucose metabolism [17]. The main traditional risk factor for cardiovascular disease is lifestyle, mainly characterised by smoking. Recent research has found that patients with hypertension or other cardiovascular disorders are more likely to experience significant adverse events such as stroke and myocardial infarction after therapy than the general population. Some studies have found that people with periodontal disease had a higher risk of cardiovascular death. Periodontitis and its potential repercussions, edentulism, were linked to higher mortality from cardiovascular disease, coronary heart disease, in a recent thorough systematic review and meta-analysis.[18]. Cross-sectional data from 6017 participants in the Risk of Atherosclerosis in Communities study showed that the development of severe periodontitis was associated with an increase in medial carotid artery thickness, influenced by confounding factors, suggesting a possible role of periodontitis in cardiovascular disease[19]. Simultaneously, periodontal disease is regarded as a separate risk factor for the evolution of atherosclerotic vascular disease, and systemic inflammation has been recognized as a potentially relevant pathogenetic process [20]. In a recent large cohort study in the USA and Korea with >year follow-up, patients with severe periodontal disease had a twofold increased risk of stroke and a twofold increased risk of myocardial infarction and stroke, respectively[21]. A recent meta-analysis showed that tooth loss was associated with an increased risk of cardiovascular disease and stroke, as well as a dose response [22]. Clinical research have demonstrated that specialist oral prophylaxis and comprehensive periodontal treatment can result in short-term improvements in surrogate markers of cardiovascular disease, such as 1.7% and 3.7% increases in endothelial function and blood pressure reductions of 7 mmHg and 12 mmHg[23]. More importantly, periodontal treatment reduced the incidence of major cardiovascular events by 14-10% during more than 10 years of follow-up[24].People who brushed regularly (twice a day) were 70% more likely to develop coronary heart disease compared to those who never/rarely brushed their teeth[25]. More recently, in a national cohort study of a Korean population, frequent tooth brushing (≥3 times per day) was associated with a 10% and 12% reduction in the risk of atrial fibrillation and heart failure [26].

3. Periodontal disease and respiratory disease

Respiratory illnesses affect the trachea, bronchi, lungs, and chest. Coughing, chest pain, and difficulty breathing are frequent in moderate cases, but breathing difficulties, a lack of oxygen, and even respiratory failure can lead to death in severe cases. Respiratory disorders are the leading cause of morbidity and mortality in the general population. The widespread prevalence of these diseases affects the overall health of the population and health care costs. Respiratory diseases such as pneumonia, bronchitis and emphysema are the most significant risks. According to a recent analysis, lower respiratory tract infections were the third largest cause of death worldwide in 1990, with chronic obstructive pulmonary disease ranking sixth. In developed countries, where lung illness is the major cause of death, the greatest challenge for dentists is to prevent and cure infectious diseases caused by numerous harmful germs. The structural connection between the lungs and the mouth cavity marks the latter as a probable host for respiratory infections. Because periodontal tissue is vital in bacterial translocation, the study of oral germs is strongly related to infectious disorders of the respiratory system. The surface plaque biofilm serves as a reservoir for respiratory pathogens, and periodontal pathogenic bacteria can be inhaled into the respiratory tract, colonize it, and cause respiratory inflammation, becoming a risk factor for respiratory infections and an important contributor to the development of aspiration pneumonia.[27]. This is again a key factor in the development of aspiration pneumonia. An inflammatory reaction is also detected in the early stages of infection. Porphyromonas gingivalis et al, Clostridium perfringens and Actinomyces may contribute to the invasion of the airway epithelium by Pseudomonas aeruginosa, the production of cytokines, and apoptosis [28]. The results of this study are discussed below. Inflammatory cytokines present in periodontal tissues can enter the airways, damage airway epithelial cells and promote colonisation of respiratory pathogens. The periodontal pathogen virulence factor protease also penetrates the airways, preventing the airway mucosa from removing respiratory pathogens adhering to the mucosal surface, and promoting respiratory pathogen adhesion and colonisation [29]. Porphyromonas gingivalis gingivalis can exacerbate the host's immune response and cause an excessive inflammatory response, resulting in bronchopneumonia, lung abscesses, haemorrhage and even necrosis.

4. Periodontal disease and chronic kidney disease

Chronic kidney disease is described as a structural or functional abnormality of the kidney that has been present for more than three months and has a negative impact on health[30]. The great majority of those affected are asymptomatic and may never be aware of their ailment. More than 1,000 people worldwide have stage 5 or end-stage renal illness, and around 30,000 people rely on renal replacement therapy such as central haemodialysis,

peritoneal dialysis, or kidney transplantation.[31]. The incidence of chronic kidney disease is increasing and the medical costs of treatment, particularly renal replacement therapy, are high. Periodontal pathogenic bacteria can promote the release of a number of inflammatory cytokines associated with endothelial dysfunction and exacerbate the systemic inflammatory response, thereby inducing renal inflammation and becoming a trigger for chronic kidney disease [32]. Periodontal pathogenic bacteria can survive and colonise renal cells, releasing inflammatory cytokines that activate the expression of trigger receptor 1 and its ligand peptidoglycan recognition protein 1 expressed by myeloid cells, contributing to the formation of atherosclerotic plaques in the renal vasculature[33]. Studies have shown that elevated levels of serum IgG antibodies against periodontal pathogens are associated with renal insufficiency [34]. The detection of Porphyromonas gingivalis, Tartaris densa spirochetes and Fosetanella spp. in subgingival plaque was increased in patients with chronic kidney disease compared to healthy controls.

5. Periodontal disease and cancer

There are few epidemiological studies on periodontitis and cancer, and most of them show a positive association. The study, conducted in early 2008, included 48 375 US male health professionals and had an average follow-up of 17.7 years. The authors report that a history of periodontal disease was associated with a statistically significant increase in the risk of overall, individual lung, kidney, pancreatic and haematological cancers. However, the positive association between overall cancer risk and blood cancers persisted only in the context of a reduction in non-smokers. The presence of an inflammatory response in the early stages of the disease was also found. In a population-based cohort study of 15,333 Swedish twins, researchers adjusted for known risk factors, including smoking, and found an increased overall cancer risk in more than half of the participants who self-reported dental activity[35]. Statistical associations were also found for gastrointestinal cancer, colorectal cancer, pancreatic cancer, prostate cancer and uterine cancer, and in people over 51 years of age. This suggests that reducing cancer risk by reducing oral hygiene behaviour among smokers may be an effective prevention strategy. The association between periodontal disease and cancer was weaker in those who reported less tooth loss or were under 51 years of age. These results suggest that periodontal disease may be a potential factor contributing to the development of some cancers. A big case-crossover study in Japan looked at cancer risk in 14 different body regions and discovered that tooth loss was connected with a higher risk of head and neck cancer, esophageal cancer, and lung cancer, however lung cancer was not observed in those who had never smoked[36]. Pathogenic bacteria in the periodontal system can contribute to the development of oral squamous cell carcinoma and metastases. Dentists believe that these bacteria can cause periodontal tissue diseases. Pathogenic bacteria in periodontitis are also associated with gastrointestinal tumours. Periodontal patients have increased serum expression of several cytokines involved in the body's immune defence against tumours and in inflammatory processes. High levels of Porphyromonas gingivalis in the oral cavity have also been shown to be involved in the development of pancreatic and oesophageal cancer.

6. Periodontal disease and other diseases

Alzheimer's disease is a neurodegenerative disease in which neuroinflammation is an important factor in its pathogenesis. Peripheral infections caused by periodontal pathogenic bacteria may affect the inflammatory state of the central nervous system. Periodontal pathogenic bacteria and inflammatory mediators may also cross the blood-brain barrier into the brain, causing a local immune response and influencing the development of the Alzheimer's disease process [37]. Inflammatory bowel disease is closely linked to oral disease. As early as 1945, Bergen demonstrated that a group of bacteria present in dental lesions, non-haemolytic streptococci, could cause colitis, which subsided rapidly after removal of the dental lesion and administration of an appropriate amount of autologous vaccine to the patient[38]. Inflammatory bowel disease often has significant extra-intestinal clinical manifestations, with the prevalence of oral diseases such as mouth ulcers and gingivitis ranging from 20% to 50%[39]. The development of SLE is associated with dysbiosis. Patients with SLE have a low subgingival microbial diversity, with a large number of periodontopathogenic bacteria (e.g. Porphyromonas gingivalis, dense spirochetes of dental tartar and Bacillus actinomycetemcomitans) dominating the microecology, and a reduced normal periodontal flora. The increased number of periodontopathogenic bacteria exacerbates the systemic inflammatory response, upregulates blood levels of inflammatory cytokines and promotes the development of SLE [40]. The increase in periodontal pathogenic bacteria can increase the systemic inflammatory response, upregulate blood levels of inflammatory cytokines and promote the development of SLE. Periodontopathogenic bacteria can adversely affect pregnancy by two mechanisms: firstly, they pass directly through the circulatory system and enter the placenta to reach the amniotic fluid and the fetus; secondly, inflammatory mediators from periodontal tissue enter the circulatory system and cause an acute phase response in the liver, with negative consequences for the placenta and

the fetus. In both ways, periodontal pathogens may cause an inflammatory response in the placental tissue of the pregnant woman, elevating prostaglandin E2 and TNF-α levels in the amniotic fluid and leading to preterm labour[41].

7. Challenges and future perspectives

A growing body of research has shown that periodontal pathogens can have a variety of direct and indirect effects on the health of the body. Periodontal pathogens may cause bacteremia and systemic inflammation, disrupting microbial homeostasis in the body, and maintaining periodontal health can effectively reduce the development of disease and improve quality of life. The connections between oral illness and overall health are numerous and intricate. While data relating periodontal disease to many systemic disorders is still emerging, new discoveries indicate a substantial association. The link between oral infections and major systemic diseases may drive stakeholders to collaborate to establish patient-centered, sustainable strategies for the management of co-morbid dental and medical conditions.

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