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### The Impact of Periodontal Disease on Systemic Health: A Comprehensive Review

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#### **Abstract:**

Periodontal disease is a chronic inflammatory condition primarily affecting the supporting structures of the teeth. In recent decades, evidence has increasingly linked periodontal disease with various systemic conditions, including cardiovascular disease, diabetes mellitus, adverse pregnancy outcomes, and respiratory disorders. This comprehensive review synthesizes current research on how periodontal inflammation contributes to systemic pathophysiology. Mechanisms such as systemic dissemination of inflammatory mediators and periodontal pathogens are discussed. Understanding these connections has significant implications for public health and interdisciplinary patient care. Based on existing epidemiological and clinical evidence, periodontal management is recommended as part of strategies to improve overall systemic health.

**Keywords:** Periodontal disease, Systemic health, Inflammation, Cardiovascular disease, Diabetes mellitus, Pregnancy outcomes, Pathogenesis, Biomarkers

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#### **Introduction**

Periodontal disease, a chronic inflammatory condition affecting the tissues surrounding the teeth, has garnered attention for its potential link to various systemic health conditions. Recent studies have revealed that the implications of periodontal disease go beyond oral health, influencing overall systemic well-being. The inflammatory processes associated with

periodontal disease can contribute to the development or exacerbation of several systemic diseases, including heart disease, diabetes, respiratory diseases, and adverse pregnancy outcomes. These findings have sparked significant interest in understanding the mechanistic pathways through which oral health impacts systemic health. The underlying inflammation in periodontal disease is characterized by the presence of bacterial pathogens that stimulate the immune response, leading to the release of pro-inflammatory cytokines and markers. This persistent systemic inflammation is believed to play a key role in the onset and progression of systemic diseases. Additionally, the shared risk factors between periodontal disease and systemic conditions, such as smoking, poor diet, and diabetes, further complicate the relationship between oral and systemic health. This review seeks to explore the bidirectional relationship between periodontal disease and systemic health, with a focus on heart disease, diabetes, and other systemic conditions, emphasizing the importance of early diagnosis and intervention in both dental and medical settings.

### **Pathophysiology of Periodontal Disease**

#### **Formation of Dental Biofilm and Host Immune Response**

Periodontal disease begins with the accumulation of dental plaque, a sticky biofilm composed of bacteria, bacterial by-products, and extracellular matrix components. The formation of this biofilm is a multi-step process, starting with the attachment of initial colonizing bacteria (e.g., *Streptococcus* spp.) to the tooth surface. Over time, other bacterial species, including anaerobes and Gram-negative organisms, colonize the biofilm, creating a complex microbial community. The host immune system plays a critical role in defending against bacterial colonization. The initial immune response involves the activation of the innate immune system, where neutrophils are recruited to the site of infection. These immune cells attempt to phagocytize bacteria and release pro-inflammatory cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF- $\alpha$ ), to recruit additional immune cells. This early response is characterized by inflammation in the gingival tissues (gingivitis). However, in chronic gingivitis, the immune response becomes dysregulated, leading to persistent inflammation and tissue destruction.

#### **Progression from Gingivitis to Periodontitis**

Gingivitis is an initial, reversible stage of periodontal disease characterized by inflammation of the gingiva (gum tissue), usually in response to poor oral hygiene. At this stage, inflammation is confined to the gingiva, and there is no loss of attachment between the tooth and surrounding tissues. If untreated, gingivitis can progress to periodontitis, a more severe form of the disease. In periodontitis, the inflammation extends beyond the gingiva and involves the deeper periodontal structures, including the periodontal ligament and alveolar bone. This progression is facilitated by the sustained immune response, leading to tissue breakdown. A key feature of periodontitis is the formation of periodontal pockets, which are spaces between the tooth and the surrounding gum tissue. These pockets become filled with pathogenic bacteria and inflammatory mediators, leading to the loss of connective tissue attachment and alveolar bone resorption. The immune response in periodontitis shifts from an acute inflammatory reaction to a chronic one, with the activation of both innate and adaptive immune responses. Macrophages, T-cells, and B-cells are recruited to the site, and the production of inflammatory cytokines like IL-6, IL-17, and interferon-gamma (IFN- $\gamma$ ) increases. These mediators contribute to the destruction of connective tissue and bone through the activation of matrix metalloproteinases (MMPs), which break down collagen and extracellular matrix components. Over time, this results in the clinical symptoms of periodontitis, such as gum recession, tooth mobility, and potential tooth loss.

#### **Role of Bacterial Virulence Factors and Host Cytokines**

The progression from gingivitis to periodontitis is heavily influenced by bacterial virulence factors and the host's immune response. Several bacterial species, particularly *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola*, are strongly

associated with periodontitis. These bacteria produce various virulence factors that enable them to evade the host immune response and contribute to tissue destruction. *P. gingivalis* produces proteases (gingipains) that can degrade host proteins, including immune molecules such as antibodies and complement components, allowing the bacteria to persist in the periodontal tissues. Additionally, *P. gingivalis* can induce the expression of pro-inflammatory cytokines through the activation of nuclear factor-kappa B (NF- $\kappa$ B), which is a key pathway in the host immune response. Host cytokines also play a central role in periodontal disease pathogenesis. Cytokines like IL-1, IL-6, and TNF- $\alpha$  are critical in initiating and amplifying the inflammatory response in periodontal tissues. These cytokines not only recruit immune cells to the site of infection but also stimulate osteoclasts to resorb bone and activate MMPs to degrade extracellular matrix proteins. The balance between pro-inflammatory and anti-inflammatory cytokines is crucial in determining the progression of periodontal disease. In patients with uncontrolled or chronic periodontal inflammation, there is often an overproduction of pro-inflammatory cytokines, which leads to increased tissue damage and bone loss.

### **Biological Mechanisms Linking Periodontal and Systemic Inflammation Inflammatory Mediator Spill-Over**

One of the key mechanisms linking periodontal disease to systemic inflammation is the spill-over of inflammatory mediators from the oral cavity into the systemic circulation. Periodontal disease is characterized by chronic inflammation, which leads to the release of various cytokines and inflammatory mediators, including interleukins (IL-1 $\beta$ , IL-6), tumor necrosis factor-alpha (TNF- $\alpha$ ), and C-reactive protein (CRP). These molecules are produced by both immune cells in the periodontal tissues (such as macrophages and neutrophils) and the surrounding gingival cells. When these inflammatory mediators are released into the bloodstream, they can travel to distant tissues and organs, contributing to the systemic inflammatory response. The spill-over of these mediators can have profound effects on various organs. For example, elevated levels of IL-6 and TNF- $\alpha$  have been linked to the development of atherosclerosis, a common cardiovascular condition. Additionally, systemic inflammation can exacerbate insulin resistance, a key feature in the development of type 2 diabetes. The chronic low-grade systemic inflammation resulting from periodontal disease is thought to act as a contributing factor to the development and progression of various systemic diseases, including cardiovascular disease, diabetes, and even certain cancers.

### **Bacterial Translocation into Systemic Circulation**

In addition to the inflammatory mediators, periodontal disease also facilitates the translocation of bacteria and their by-products from the oral cavity into the bloodstream. This process, often referred to as "bacterial dissemination," occurs when pathogenic bacteria from infected periodontal pockets enter the bloodstream through ulcerated gum tissues. The most well-known bacteria involved in this process include *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola*, which are commonly found in periodontally diseased tissues. Once in the bloodstream, these bacteria can travel to distant organs, where they may trigger localized inflammatory responses or directly contribute to the pathology of various diseases. For instance, *P. gingivalis* has been implicated in the pathogenesis of atherosclerosis, where it is thought to accelerate plaque formation and contribute to endothelial dysfunction. Furthermore, bacterial translocation has been linked to respiratory infections, particularly in individuals with compromised immune systems or underlying respiratory conditions, where the bacteria can lead to pneumonia or exacerbations of chronic obstructive pulmonary disease (COPD). The continuous presence of bacteria in the bloodstream also exacerbates systemic inflammation, creating a vicious cycle of immune activation and tissue damage.

### **Activation of Acute Phase Response**

The acute phase response (APR) is a systemic reaction that occurs in response to infection, injury, or inflammation. It is characterized by an increase in the production of acute-phase proteins such as C-reactive protein (CRP), fibrinogen, and serum amyloid A (SAA) from the liver. In the case of periodontal disease, the chronic oral infection leads to the activation of the APR. The systemic release of pro-inflammatory cytokines such as IL-1, IL-6, and TNF- $\alpha$  triggers the liver to synthesize and release these acute-phase proteins into the bloodstream.

### **Cardiovascular Disease and Periodontal Health**

#### **Epidemiological Associations**

Numerous epidemiological studies have identified significant associations between periodontal disease and cardiovascular disease (CVD). Research has consistently shown that individuals with periodontal disease are at a higher risk of developing atherosclerosis, coronary artery disease, and other cardiovascular conditions. The strength of these associations is particularly evident in individuals with severe periodontal disease, where the risk of cardiovascular events such as heart attacks and strokes is elevated. Studies suggest that the chronic inflammation caused by periodontal disease contributes to systemic inflammation, which is a known risk factor for cardiovascular disease. The connection between periodontal disease and CVD is also supported by findings that individuals with poor periodontal health often have elevated levels of inflammatory biomarkers, such as C-reactive protein (CRP) and interleukin-6 (IL-6), which are implicated in both periodontal disease and cardiovascular disease. Several large cohort and case-control studies have demonstrated that periodontal disease is an independent risk factor for cardiovascular disease, even after adjusting for traditional cardiovascular risk factors such as smoking, hypertension, and diabetes. These studies suggest that the inflammation and bacterial factors associated with periodontal disease contribute to the development and progression of cardiovascular conditions, reinforcing the notion that oral health should be considered an integral part of overall cardiovascular health.

#### **Endothelial Dysfunction and Atherogenesis**

One of the key mechanisms by which periodontal disease influences cardiovascular health is through the induction of endothelial dysfunction and atherogenesis. Endothelial cells line the blood vessels and play a crucial role in maintaining vascular tone, blood flow, and the regulation of inflammatory processes. Periodontal disease contributes to endothelial dysfunction through the release of inflammatory mediators, including cytokines and bacterial products, into the bloodstream. These inflammatory mediators, such as TNF- $\alpha$  and IL-1 $\beta$ , promote the activation of endothelial cells, which in turn increases the expression of adhesion molecules that facilitate the recruitment of immune cells to the vessel walls. In response to these inflammatory signals, endothelial cells undergo structural changes that impair their ability to regulate vascular tone and blood flow. This dysfunction contributes to the early stages of atherosclerosis, where fatty streaks begin to form in the arterial walls. Additionally, periodontal pathogens, particularly *Porphyromonas gingivalis*, have been shown to invade endothelial cells and promote the formation of plaque within the arteries, further exacerbating the process of atherogenesis. As a result, individuals with periodontal disease have a higher burden of atherosclerotic plaques and an increased risk of plaque rupture, which can lead to heart attacks and strokes.

#### **Outcomes of Periodontal Therapy on Cardiovascular Biomarkers**

Recent studies have explored the potential benefits of periodontal therapy in improving cardiovascular health by reducing systemic inflammation and improving endothelial function. Periodontal therapy, including non-surgical treatments like scaling and root planing, has been shown to reduce levels of inflammatory markers such as CRP and IL-6, which are linked to both periodontal disease and cardiovascular risk. These treatments can lead to a reduction in periodontal pocket depth, less gingival bleeding, and a decrease in the

number of periodontal pathogens in the mouth, all of which contribute to the resolution of local and systemic inflammation.

### **Diabetes Mellitus and Periodontal Disease**

#### **Bidirectional Relationship**

The relationship between diabetes mellitus and periodontal disease is bidirectional, meaning that not only can periodontal disease exacerbate diabetes, but poor glycemic control can also increase the risk and severity of periodontal disease. This bidirectional relationship is grounded in the chronic inflammation present in both conditions. In individuals with diabetes, particularly those with poor glycemic control, hyperglycemia can lead to immune dysfunction, which impairs the body's ability to respond to infections, including those caused by periodontal pathogens. As a result, individuals with diabetes are more susceptible to developing periodontal disease and often experience more severe forms of the condition. On the other hand, the persistent inflammation and infection caused by periodontal disease can worsen glycemic control by increasing insulin resistance. The inflammatory mediators released from infected periodontal tissues, such as interleukins (IL-1 $\beta$ , IL-6) and tumor necrosis factor-alpha (TNF- $\alpha$ ), are known to interfere with insulin signaling pathways and contribute to insulin resistance, thereby worsening blood sugar levels. This two-way interaction makes the management of both conditions crucial for overall health. Effective control of one condition may help improve the outcomes of the other. For instance, controlling periodontal disease may help improve blood glucose control in diabetic patients, and conversely, maintaining stable blood glucose levels can reduce the risk and progression of periodontal disease.

#### **Glycemic Control and Periodontal Inflammation**

Glycemic control plays a critical role in both the progression of periodontal disease and the effectiveness of periodontal treatment. Elevated blood glucose levels in individuals with diabetes create an environment conducive to the growth of periodontal pathogens, which thrive in the inflammatory conditions associated with hyperglycemia. High glucose levels also impair neutrophil function, which is essential for controlling bacterial infections. This impaired immune response leads to increased plaque formation and deeper periodontal pockets, accelerating the progression from gingivitis to periodontitis. Furthermore, chronic hyperglycemia exacerbates the inflammatory response in periodontal tissues. Increased blood sugar levels promote the production of advanced glycation end-products (AGEs), which bind to receptors on immune cells and trigger the release of additional inflammatory mediators. These mediators, including cytokines and reactive oxygen species, can further damage the periodontal tissues and contribute to tissue breakdown, leading to tooth mobility and potential loss. On the other hand, well-controlled glycemia, typically defined as maintaining HbA1c levels below 7%, can reduce the severity of periodontal disease. Lower blood glucose levels support the immune system's ability to manage periodontal infections, reduce the inflammatory response, and enhance the effectiveness of periodontal treatments.

#### **Impact of Periodontal Therapy on HbA1c**

Periodontal therapy has shown promise in improving glycemic control in diabetic patients. Clinical studies have demonstrated that after receiving periodontal treatment, such as scaling and root planing, diabetic patients often experience a reduction in HbA1c levels, a key marker of long-term blood glucose control. The mechanism behind this improvement is believed to be the reduction in periodontal inflammation and bacterial load. By treating the infection and inflammation in the periodontal tissues, the body's overall inflammatory burden is reduced, which can lead to improved insulin sensitivity and better glycemic control. The reduction in HbA1c following periodontal therapy is particularly noticeable in patients with poorly controlled diabetes. Studies have reported that after periodontal treatment, patients can experience a 0.4% to 1.0% reduction in HbA1c, which is clinically significant and can help prevent complications related to diabetes. Additionally, improvements in

periodontal health can lead to better overall health outcomes, as managing one chronic condition like periodontal disease can reduce the strain on the immune system and improve the body's ability to handle other comorbidities associated with diabetes. However, it is important to note that while periodontal therapy can aid in glycemic control, it should not be considered a substitute for proper diabetes management. Diabetic patients must continue to adhere to their prescribed medication regimens, dietary guidelines, and exercise plans. Periodontal therapy, however, can be an important complementary treatment that helps reduce the systemic inflammatory burden and improve the overall management of diabetes.

#### **Other Systemic Conditions Associated with Periodontal Disease**

##### **Adverse Pregnancy Outcomes (Preterm Birth, Low Birth Weight)**

Periodontal disease has been implicated in adverse pregnancy outcomes, including preterm birth and low birth weight, which are significant risk factors for infant morbidity and mortality. Pregnant women with periodontal disease have been shown to have an increased risk of delivering prematurely and of having infants with low birth weight. The mechanism behind this association is thought to involve the systemic inflammation caused by periodontal infection. Infected periodontal tissues release inflammatory cytokines and prostaglandins into the bloodstream, which can trigger uterine contractions and premature labor. Additionally, these inflammatory mediators can affect placental function, impairing nutrient and oxygen delivery to the fetus, which may contribute to intrauterine growth restriction and low birth weight. Several studies have demonstrated that treating periodontal disease during pregnancy can help reduce the risk of preterm birth and low birth weight. Periodontal therapy, such as scaling and root planing, can lower the levels of pro-inflammatory mediators in the bloodstream, thereby improving pregnancy outcomes. However, while there is growing evidence linking periodontal disease to adverse pregnancy outcomes, it remains essential for pregnant women to receive regular prenatal care and adhere to guidelines for managing periodontal health.

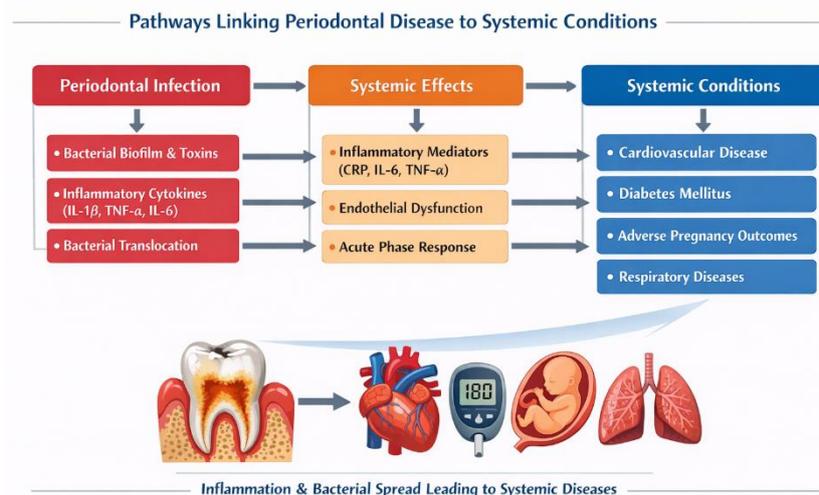
##### **Respiratory Diseases (e.g., COPD, Pneumonia)**

Periodontal disease has also been linked to an increased risk of respiratory diseases, including chronic obstructive pulmonary disease (COPD) and pneumonia. The primary mechanism behind this association is the aspiration of periodontal bacteria into the lungs. Bacteria from infected periodontal tissues can be aspirated during sleep or while eating and drinking, especially in individuals with compromised oral hygiene. Once in the lungs, these bacteria can contribute to inflammation, respiratory infections, and the exacerbation of chronic lung diseases such as COPD. In individuals with existing respiratory conditions, periodontal disease can worsen symptoms and increase the frequency of exacerbations. Studies have shown that individuals with periodontal disease are more likely to experience acute respiratory events, including pneumonia, and may have a higher risk of developing severe complications from these infections. In people with COPD, the chronic inflammation caused by periodontal disease can further compromise lung function, leading to more frequent hospitalizations and a decline in overall health. Preventing and managing periodontal disease in individuals with respiratory conditions is crucial for improving respiratory health and reducing the burden of respiratory diseases.

##### **Chronic Kidney Disease and Rheumatoid Arthritis**

Chronic kidney disease (CKD) and rheumatoid arthritis (RA) are two systemic conditions that are also strongly associated with periodontal disease. In CKD, the kidneys' ability to filter waste and regulate fluid balance is impaired, leading to the accumulation of toxins and the potential for systemic inflammation. Periodontal disease exacerbates this inflammatory burden, as the bacteria and inflammatory mediators from infected periodontal tissues enter the bloodstream, contributing to the progression of kidney dysfunction. Additionally, individuals with CKD often experience an increased risk of infections, and the presence of periodontal disease can further increase susceptibility to infections such as sepsis, which can

worsen kidney function. Managing periodontal disease in CKD patients may help reduce systemic inflammation and prevent further deterioration of kidney function. Rheumatoid arthritis, periodontal disease shares common inflammatory pathways, as both conditions involve immune system dysfunction. RA is characterized by chronic inflammation of the joints, and periodontal disease is marked by inflammation of the gums and supporting tissues of the teeth. Research has shown that the systemic inflammation associated with periodontal disease may exacerbate the joint inflammation seen in RA, leading to more severe symptoms and increased pain. Additionally, the bacteria involved in periodontal disease, particularly *P. gingivalis*, have been implicated in triggering autoimmune responses that may contribute to the development of RA. Therefore, treating periodontal disease in individuals with RA may help reduce systemic inflammation and improve the management of joint symptoms.



## Summary:

Periodontal disease, characterized by inflammation of the gums and surrounding tissues, has been increasingly linked to various systemic health issues. Research suggests that the chronic inflammation seen in periodontal disease can contribute to the development of systemic conditions such as cardiovascular disease, diabetes, and respiratory illnesses. The mechanisms behind these connections include the spread of inflammatory cytokines and bacterial byproducts from the oral cavity into the bloodstream, leading to systemic inflammation and endothelial dysfunction, which are critical factors in heart disease and diabetes. Studies have shown that periodontal disease can worsen blood sugar control in diabetic patients, potentially accelerating the progression of diabetes. Moreover, the inflammatory response triggered by periodontal pathogens has been linked to increased risk for heart disease, as it can lead to the development of atherosclerosis and other cardiovascular complications. Interventions targeting periodontal disease, such as professional cleanings, anti-inflammatory therapies, and proper oral hygiene practices, may not only improve oral health but also reduce the risk of systemic diseases. Understanding the connection between periodontal disease and systemic health highlights the need for integrated healthcare approaches where dental health is considered a vital component of overall well-being.

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