

Association between Periodontitis and Systemic Diseases

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Abstract. Periodontal disease is a chronic inflammatory disease that affects the gums and periodontal tissues. It is one of the main causes of tooth loss in adults, affecting more than half of the world's adults to varying degrees, and has become a major public health issue. Increasing evidence suggests that periodontal disease is closely linked to systemic health. Pathogenic bacteria and their toxins can enter the bloodstream, it induces a low-grade inflammatory state, leading to the occurrence and development of various systemic diseases. For instance, in cardiovascular health, periodontal inflammation may damage endothelial function and promote atherosclerosis. In metabolic regulation, proinflammatory mediators impair insulin signalling, thereby worsening glycemic control in diabetes. In pregnancy, microbial invasion and inflammatory mediators may disrupt placental function, increased risk of preterm birth and low birth weight. Although conventional periodontal therapy can improve local outcomes, it may not completely alleviate systemic effects. This review aims to summarize the recent evidence on the link between periodontal disease and systemic health, focusing on mechanisms and potential strategies for prevention and clinical management.

1 Introduction

Periodontitis is a common chronic inflammatory disease. It affects the periodontal supporting tissues, including the gums, periodontal ligament, and alveolar bone, and is a major contributor to tooth instability and eventual loss in adults. Epidemiological data show that more than half adults worldwide have different levels of periodontal disease, among which the prevalence of moderate to severe periodontitis remains high and increases significantly with age and unhealthy lifestyle habits such as smoking and high-sugar diet [1]. Traditionally, periodontitis is considered a local oral problem, but there is a close association between periodontitis and a variety of body-wide problems like heart disease, diabetes, and pregnancy risk [2]. Periodontal pathogens destroy the epithelial barrier and adhere to the periodontal tissue by secreting components such as proteases, lipopolysaccharides, and exosomes, forming a complex biofilm ecosystem. In this process, the imbalance of the bacterial flora induces the local production of multiple inflammatory mediators, including IL-1 β , IL-6, TNF- α , and matrix metalloproteinases, and also allows bacterial components to enter the bloodstream through capillaries deep within the periodontal pocket, thereby triggering systemic low-grade chronic inflammation.

Pathogenic bacteria, such as *Porphyromonas gingivalis*, can enter the blood circulation, induce systemic inflammatory responses, and thereby contribute to the development of various chronic diseases [3]. Periodontal pathogens can increase the likelihood of cardiovascular events, including myocardial infarction and stroke, by promoting vascular

endothelial damage and aggravating atherosclerosis. In addition, there is a two-way feedback mechanism between chronic periodontitis and diabetes. Diabetic patients are more susceptible to periodontitis due to impaired immune function and metabolic disorders. The systemic inflammation caused by periodontitis can aggravate insulin resistance and make blood sugar control more difficult [4]. In the field of obstetrics and gynecology, studies have also suggested a certain link between periodontitis and detrimental pregnancy outcomes. Bacteria and their toxins and inflammatory factors can enter the placenta through the blood, triggering local immune responses, thereby interfering with placental function and raising the likelihood of preterm birth or low birth weight. Therefore, periodontitis should not be regarded as just an oral problem but should be taken seriously as an important part of systemic health management. The purpose of this study is to examine how periodontitis is associated with systemic diseases, focusing on how pathogens and inflammatory responses affect the cardiovascular, metabolic, and pregnancy systems through blood circulation and immune pathways, to help guide the prevention and treatment of periodontitis, and to promote its integrated application in the clinical management and multidisciplinary collaboration of systemic diseases.

2 Periodontitis and Cardiovascular Disease

Large prospective cohorts and experimental models converge on the finding that patients with periodontitis exhibit higher rates of atherosclerotic complications,

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myocardial infarction, and ischemic stroke than periodontally healthy individuals [5]. The observed association is supported by evidence that periodontal pathogens translocate into circulation, drive systemic cytokine release, and impair endothelial nitric oxide-mediated vascular relaxation.

Within periodontal pockets, breakdown of the epithelial barrier enables *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, and other organisms to access the bloodstream. Their virulence factors, including lipopolysaccharides, gingipains, and outer membrane vesicles, interact with toll-like receptors on endothelial and immune cells. This stimulates NF- κ B - dependent pathways, enhances hepatic production of C-reactive protein, and elevates systemic levels of IL-1 β , IL-6, and TNF- α . These mediators impair endothelial function, increase expression of adhesion molecules such as VCAM-1 and ICAM-1, and promote monocyte recruitment into the vascular intima. Once within the arterial wall, monocytes differentiate into macrophages, engulf modified lipids, and form foam cells, an initiating step in atherogenesis.

Sustained exposure to cytokines such as IL-1 β and TNF- α promotes smooth muscle apoptosis and upregulates matrix metalloproteinases, processes that enlarge necrotic cores and thin the fibrous cap [6]. This structural weakening increases the likelihood of plaque rupture and subsequent thrombosis. In *ApoE*^{-/-} mice, oral inoculation with *P. gingivalis* accelerates aortic lesion formation and increases macrophage infiltration, directly linking oral infection to arterial pathology.

Serological studies demonstrate that elevated antibody titers against *P. gingivalis* are associated with myocardial infarction risk, while imaging cohorts show a correlation between periodontal status and carotid intima-media thickness. Meta-analyses estimate that patients with severe periodontitis have a 20–30 percent higher risk of major cardiovascular events compared with healthy individuals [1, 7]. Yet some investigators argue that confounding factors such as smoking, diabetes, and socioeconomic status may partially explain the link, highlighting the need for better controlled analyses.

Interventional studies suggest that periodontal therapy can lower systemic markers of inflammation and modestly improve endothelial function. For example, scaling and root planning has been shown to reduce circulating C-reactive protein and improve flow-mediated dilation. While these surrogate outcomes are encouraging, definitive evidence that periodontal treatment reduces myocardial infarction or stroke remains lacking. Large multicentre randomized trials with hard endpoints are still needed.

From a clinical perspective, if periodontal therapy reduces vascular inflammation, it could be incorporated into cardiovascular prevention strategies alongside lipid lowering and smoking cessation. Overall, the convergence of mechanistic, animal, and population data makes a biologically plausible case that untreated periodontitis contributes to cardiovascular pathology, and that its management may have systemic benefits extending beyond oral health.

3 Bidirectional Links between Periodontitis and Diabetes

Epidemiological studies and mechanistic investigations converge on the observation that diabetes and periodontitis are tightly linked through reciprocal biological mechanisms. Large longitudinal cohorts have shown that patients with type 2 diabetes develop periodontitis more frequently and progress more rapidly, while experimental studies have clarified that chronic hyperglycaemia modifies host immunity and tissue repair, thereby creating a periodontal microenvironment prone to persistent infection [8].

In diabetic individuals, sustained hyperglycaemia leads to accumulation of advanced glycation end products (AGEs), activation of RAGE signalling, and oxidative stress. These molecular alterations impair neutrophil chemotaxis and bactericidal capacity, disrupt collagen architecture through abnormal cross-linking, and delay granulation tissue formation. When combined with microangiopathy-related ischemia, periodontal wounds in diabetic patients heal more slowly and are more vulnerable to reinfection [9]. Clinical data support these mechanisms, as diabetic patients often present with deeper periodontal pockets, greater attachment loss, and reduced response to conventional therapy compared with nondiabetic controls.

The impact of periodontitis on diabetes is equally significant. Oral pathogens and their virulence products, including lipopolysaccharide, as well as inflammatory mediators such as TNF- α and IL-6, disseminate through the bloodstream and reach metabolic organs. Within liver and muscle, these factors interfere with insulin receptor substrate signalling and activate JNK and IKK β pathways, producing peripheral insulin resistance and enhancing hepatic gluconeogenesis. This results in a pathogenic loop in which inflammation worsens insulin resistance, sustaining hyperglycaemia that further amplifies periodontal breakdown [10]. In obesity, this cycle is intensified by macrophage polarization toward an M1 phenotype and altered secretion of adipokines such as leptin and adiponectin, both of which amplify systemic inflammation and impair insulin sensitivity.

Clinical intervention studies provide additional support for the systemic significance of this relationship. Randomized controlled trials and meta-analyses demonstrate that non-surgical periodontal treatment, including scaling and root planning, can lower glycated hemoglobin (HbA1c) by an average of approximately 0.4% [11]. Although this change may appear small, long-term follow-up indicates that even modest HbA1c reductions translate into measurable decreases in the incidence of diabetic complications such as retinopathy and nephropathy. Periodontal therapy has also been shown to reduce circulating markers of inflammation, including C-reactive protein and IL-6, suggesting that improvements in oral health contribute to lowering systemic inflammatory burden.

Despite these encouraging findings, limitations persist. Many trials are short in duration, involve limited sample sizes, and use heterogeneous diagnostic

definitions for both diabetes and periodontitis, making direct comparisons difficult. The degree of glycemic benefit also varies depending on baseline HbA1c, periodontal severity, and concomitant antidiabetic therapy. These inconsistencies underscore the need for larger multicentre randomized trials with longer follow-up and standardized definitions. Such studies should also focus on identifying subgroups most likely to benefit, for example patients with poor baseline glycemic control or severe periodontal destruction, and on evaluating integrated strategies that combine intensive periodontal therapy with optimized metabolic management.

4 Periodontitis and Pregnancy Outcomes

Cohort studies and meta-analyses have reported that women with periodontitis have higher rates of adverse pregnancy outcomes, particularly preterm birth and low birth weight, compared with women without periodontal disease [3]. Pregnancy itself alters both endocrine and immune balance. Rising estrogen and progesterone levels increase gingival vascularity and tissue edema, while systemic shifts toward immune tolerance reduce antimicrobial defences. Clinically, these changes are reflected in more pronounced gingival bleeding, deepening of periodontal pockets, and attachment loss in women who already have compromised periodontal health. Together, these factors make pregnancy a period of increased susceptibility to new or worsening periodontal disease.

Pathogenic microorganisms and their virulence products can escape inflamed periodontal pockets and enter maternal circulation. Bacterial DNA and endotoxins such as lipopolysaccharide (LPS) have been detected in maternal serum and even in placental samples [12]. Within the placenta, microbial products stimulate trophoblasts and decidual macrophages, triggering local production of prostaglandin E2 and TNF- α . Elevated concentrations of these mediators increase uterine contractility, accelerate cervical remodelling, and promote premature rupture of membranes, processes that contribute directly to preterm labor [13]. Histological studies of placental tissue from women with adverse outcomes show inflammatory infiltrates and cytokine upregulation, supporting the role of microbial dissemination in obstetric complications.

In addition to direct inflammatory effects, maternal periodontitis can impair placental circulation and fetal growth. Inflammatory signalling interferes with trophoblast invasion and spiral artery remodelling, processes that establish adequate maternal–fetal blood flow. Doppler ultrasound investigations in women with advanced periodontitis reveal reduced uteroplacental perfusion, correlating with lower birth weight and greater risk of intrauterine growth restriction. Experimental animal models further support this mechanism, showing that induced maternal periodontitis alters placental vascularization, diminishes oxygen and nutrient transfer, and leads to measurable

fetal growth deficits. These findings suggest that maternal periodontal inflammation influences both obstetric events and intrauterine development.

Clinical trials provide mixed but informative results. Some randomized studies show that non-surgical periodontal therapy, such as scaling and root planning, lowers systemic inflammatory markers and is safe during pregnancy. A subset of these trials report reduced rates of preterm delivery in treated women, though results are variable depending on timing of therapy, disease severity at baseline, and adherence to supportive care. Meta-analyses indicate that maternal periodontitis is associated with a 1.5- to 2-fold higher likelihood of preterm birth or low birth weight; however, differences in diagnostic criteria, study populations, and timing of periodontal assessment introduce considerable heterogeneity that complicates direct comparison of results [14]. These observations point to the need for larger multicentre trials with standardized diagnostic criteria, clearly defined treatment protocols, and long-term follow-up. Integrating periodontal evaluation into prenatal care may provide opportunities for early identification of women at higher risk, while timely and safe intervention could help reduce systemic inflammation, improve placental function, and lower the burden of adverse pregnancy outcomes [15].

5 Conclusion

Over the past several decades, research has revealed multiple mechanistic and clinical links between periodontitis and systemic health that extend far beyond the oral cavity. Data from prospective cohorts and mechanistic experiments show that periodontal pathogens and their virulence factors enter the bloodstream and interact with immune and vascular cells, driving low-grade chronic inflammation and disturbing metabolic homeostasis. This systemic involvement explains why severe periodontitis is consistently associated with atherosclerotic lesions, poor glycemic control, and obstetric complications such as preterm birth and low birth weight. In cardiovascular research, cytokines originating from periodontal tissues have been directly implicated in endothelial dysfunction, smooth muscle apoptosis, and plaque destabilization. In metabolic studies, inflammatory mediators have been shown to disrupt insulin receptor signalling and accelerate insulin resistance, worsening the trajectory of type 2 diabetes. In reproductive medicine, bacterial DNA and inflammatory cytokines have been detected in placental tissue, where they are linked to impaired uteroplacental circulation and intrauterine growth restriction. These findings indicate that periodontal health is a determinant of systemic outcomes, and its management carries potential benefits for patients at risk of cardiovascular disease, diabetes, or pregnancy complications. At a population level, periodontal screening could also function as a practical indicator of systemic inflammatory load, supporting its integration into chronic disease prevention strategies.

Despite growing evidence, several limitations constrain current understanding. Many clinical trials

have been conducted with modest sample sizes and relatively short follow-up, reducing their power to detect long-term outcomes such as myocardial infarction, stroke, or neonatal morbidity. The diagnostic thresholds for both periodontal and systemic diseases vary widely across studies, complicating cross-cohort comparisons. Mechanistic studies often rely on surrogate markers, such as circulating cytokine levels or vascular imaging, without demonstrating direct causality for hard clinical endpoints. Confounders, including smoking, socioeconomic disparities, and comorbidities, also remain insufficiently controlled in many datasets. Addressing these gaps will require coordinated multicentre studies with standardized diagnostic criteria, larger sample sizes, and integration of molecular tools such as omics profiling and microbiome sequencing to identify biomarkers predictive of systemic complications. Emerging applications of artificial intelligence could enhance reproducibility and precision by automating radiographic and clinical assessments, and by linking dental and medical datasets in real time.

Looking forward, clarifying the causal pathways between periodontal disease and systemic disorders will demand sustained collaboration across disciplines. Integrating periodontal evaluation into primary care, incorporating it into risk calculators used in cardiology and endocrinology, and embedding dental records into electronic health systems would allow clinicians to recognize periodontal status as part of overall health assessment. For obstetric care, routine periodontal evaluation could be piloted as a preventive measure in antenatal programs. Policymakers could also consider allocating resources to public health campaigns that highlight periodontal health as a modifiable factor in chronic disease prevention. In addition, framing periodontitis as part of systemic health may reduce stigma and promote earlier patient engagement, since individuals are more likely to seek dental care when they understand its impact on heart disease, diabetes, or pregnancy outcomes. This perspective encourages not only biomedical innovation but also community-based interventions, such as integrating dental professionals into chronic disease clinics or prenatal care teams. By anchoring periodontal care within broader medical and policy frameworks, research can move beyond correlation to actionable strategies that simultaneously improve oral health and reduce the global burden of cardiovascular disease, diabetes, and adverse pregnancy outcomes.

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