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Review Article

The Oral-Systemic Axis: A Narrative Review of Inflammatory Mechanisms Linking Periodontitis to Cardiovascular Disease, Diabetes and Adverse Pregnancy Outcomes

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Abstract

Background: Periodontitis is a chronic inflammatory disease of the tooth-supporting structures that has been increasingly recognized as a contributor to systemic health beyond its local oral consequences. Through dysbiosis oral biofilms, sustained elevation of proinflammatory mediators and hematogenous dissemination of periodontal pathogens and their byproducts, periodontitis may amplify systemic inflammation and interact with the pathogenesis of cardiovascular disease, diabetes mellitus and adverse pregnancy outcomes.

Objective: To critically evaluate the current evidence linking periodontitis to systemic chronic disease, with emphasis on shared inflammatory mechanisms, bidirectional associations and the clinical implications of periodontal treatment on systemic outcomes.

Methods: A narrative review of the literature was conducted using PubMed, Google Scholar and the Cochrane Database of Systematic Reviews. Priority was given to systematic reviews, meta-analyses, randomized clinical trials and consensus reports published within the last ten years. Studies were selected based on relevance to the oral-systemic axis, with focus on cardiovascular disease, diabetes mellitus and adverse pregnancy outcomes.

Results: Periodontitis was consistently associated with increased systemic inflammatory burden through microbial dysbiosis, endotoxemia and upregulation of IL-1β, IL-6, TNF-α and C-reactive protein. Evidence supports an independent association between periodontitis and atherosclerotic cardiovascular disease, with periodontal pathogens detected in atheromatous plaques and periodontal treatment shown to reduce circulating inflammatory biomarkers, though hard cardiovascular endpoint reductions remain undemonstrated. A bidirectional relationship with diabetes mellitus is well-established: hyperglycemia promotes periodontal disease progression through advanced glycation end-product accumulation, while non-surgical periodontal therapy reduces HbA1c by approximately 0.5 percentage points. Maternal periodontitis is associated with increased risk of preterm birth, low birth weight and preeclampsia through both direct bacterial dissemination and systemic propagation of inflammatory mediators.

Conclusion: Periodontitis functions as a systemic risk modifier through chronic low-grade inflammation and shared pathobiological pathways with major chronic diseases. Clinical decisions should integrate periodontal evaluation into medical

management of cardiovascular disease, diabetes and high-risk pregnancies. Interdisciplinary collaboration between dental and medical providers is essential to optimally manage patients with co-existing periodontal and systemic disease.

Keywords: Periodontitis; Systemic Inflammation; Cardiovascular Disease; Diabetes Mellitus; Adverse Pregnancy Outcomes; Oral-Systemic Axis; Periodontal Treatment; C-Reactive Protein

Introduction The Mouth as a Window to Systemic Health

Among chronic oral conditions, periodontitis offers the most compelling illustration of the relationship between oral and systemic health. Beyond its local consequences; destruction of the gingiva, periodontal ligament and alveolar bone, periodontitis has been increasingly linked to a range of systemic conditions, including cardiovascular diseases, diabetes mellitus and adverse pregnancy outcomes [1,2]. This association is driven by three converging mechanisms: dysbiosis oral biofilms, in which a once-balanced microbial community shifts toward a pathogenic state; chronic low-grade systemic inflammation; and the hematogenous dissemination of periodontal pathogens and their byproducts to distant tissues and organs [3].

The oral-systemic hypothesis has matured considerably over the past two decades, supported by a growing body of evidence from epidemiological, microbiological and clinical research. It is now well established that inflammatory activity originating in the oral cavity can amplify systemic inflammation and, conversely, that systemic disease can exacerbate the local periodontal environment, a relationship that operates in both directions [2]. This bidirectional dynamic underscores why oral health can no longer be evaluated in isolation; it is an integral component of a patient's overall health status. Integrating oral health assessment into general healthcare programs is therefore not a clinical luxury but a public health necessity, one that supports multidisciplinary strategies aimed at achieving sustainable, whole-person well-being [3,4].

Periodontitis represents a significant global public health burden affecting individuals across all age groups and both sexes. It is the most common chronic inflammatory disease in humans: in its mild to moderate forms, it affects nearly half of adults worldwide, while severe forms impact approximately 10% to 15% of the global population [5]. In the United States, data from the National Health and Nutrition Examination Survey (NHANES) indicate that nearly 47% of adults aged 30 years and older have some form of periodontal disease, representing over 64 million individuals [6]. The condition carries significant epidemiological consequences beyond tooth loss, including masticatory dysfunction, nutritional compromise and reduced quality of life. Socioeconomic status is a recognized modifier of disease risk and periodontitis is consistently more prevalent in men than in women. Taken together, these factors establish periodontitis as a condition with far-reaching implications well beyond the oral cavity [4,5].

The systemic consequences of periodontitis are mediated through shared inflammatory pathways that connect it to conditions such as diabetes mellitus, cardiovascular diseases and pregnancy-related complications. These pathways involve dysregulation of proinflammatory cytokines, activation of innate and adaptive immune responses and the direct or indirect effects of periodontal microorganisms on systemic physiology. Host factors including age and sex further shape the clinical expression of periodontitis, with older adults bearing a disproportionate burden due to cumulative pathogen exposure and age-related immune senescence [5,7].

At the mechanistic level, periodontitis triggers a well-characterized inflammatory cascade. Dysbiotic oral communities dominated by keystone pathogens, including Porphyromonas gingivalis, Treponema denticola and Tannerella forsythia, induce a surge in proinflammatory mediators such as Tumor Necrosis Factor-Alpha (TNF-α), Interleukin-1β (IL-1β), Interleukin-6 (IL-6), prostaglandin E_2 and C-Reactive Protein (CRP). The breakdown of the epithelial barrier lining the periodontal pocket allows bacterial lipopolysaccharides and viable organisms to enter the bloodstream, producing transient or sustained bacteremia. Over time, this repeated systemic exposure sustains a state of chronic low-grade inflammation that has been implicated in the development and progression of cardiovascular disease, dysglycemia and adverse obstetric outcomes such as preterm birth, low birth weight and preeclampsia [7,8]. This Narrative synthesizes the current evidence linking periodontistis to three major systemic conditions for which the biological and clincal evidence is strongest: cardiovascular disease, diabetes mellitus and pregnancy outcomes. It is organizaed as follows: Shared pathobiology: Periodontitis and Cardiovascular Disease; The Periodontal-Diabetes Bidirectional Relationship; Adverse Pregnancy Outcomes and Conclusion.

Shared Pathobiology: Inflammatory and Immunological Mechanisms Linking Periodontitis to Systemic Disease

The association between periodontitis and systemic disease is not merely epidemiological; it rests on a well-defined biological framework involving immune dysregulation, microbial dissemination and the sustained amplification of inflammatory signals far beyond the oral cavity. Understanding these mechanisms is essential for appreciating why treating periodontal disease is not simply a matter of oral hygiene, but a genuine systemic health intervention [8].

Biological Plausibility

Periodontitis is now understood as a chronic inflammatory disease driven by a dysbiotic microbial community that disrupts the finely balanced relationship between the oral microbiome and the host immune system [9]. This disruption produces an exaggerated and poorly regulated immune-inflammatory response, one that does not remain confined to the periodontium. Normally, the host maintains a state of homeostasis with the oral microbiome; when this balance is disturbed by an aberrant or hyper-responsive host immune reaction, unresolved inflammation becomes the primary driver of tissue destruction [10]. Breakdown of the ulcerated pocket epithelium then creates a pathway through which bacteria and their toxic byproducts most notably Lipopolysaccharide (LPS) gain access to the systemic circulation.11 Once in the bloodstream, these microbial signals trigger the release of proinflammatory mediators including IL-1β, TNF-α and the acute-phase reactant C-Reactive Protein (CRP), sustaining a state of chronic low-grade systemic inflammation [9]. It is precisely this persistent, subclinical inflammatory burden that provides the biological basis for periodontitis as a driver of systemic disease [9,10].

Periodontal Pathogens and Immune Modulation

The pathogenesis of periodontitis centers on the so-called red complex bacteria, *Porphyromonas gingivalis*, *Treponema denticola* and *Tannerella forsythia*, which act in concert through a suite of virulence factors that promote inflammation, facilitate immune evasion and enable epithelial colonization [11]. Among these, *P. gingivalis* has earned the designation of 'keystone pathogen', not because of its numerical dominance in the biofilm, but because of its outsized ability to subvert microbial homeostasis and hijack host immune signaling, promoting dysbiosis and amplifying the overall inflammatory cascade [9]. These pathogens engage neutrophils, macrophages and dendritic cells in ways that skew the immune response away from effective pathogen clearance and toward a chronically proinflammatory phenotype [10,12]. The result is a self-perpetuating inflammatory environment in which the host's own immune cells become inadvertent mediators of tissue destruction, both locally and, over time, systemically.

Bacteremia, Endotoxemia and Systemic Dissemination

In established periodontitis, the degraded epithelium lining the periodontal pocket becomes highly permeable, allowing subgingival bacteria and their products to enter the systemic circulation [13]. This produces episodes of transient bacteremia and a more sustained state of low-grade endotoxemia, driven by the continuous seeding of LPS into the bloodstream [11]. Vitkov, et al., demonstrated that this periodontitis-induced endotoxemia promotes neutrophil hyper-responsiveness and exaggerated formation of Neutrophil Extracellular Traps (NETs), which have been implicated in vascular injury and the pathogenesis of atherosclerosis [11]. Schenkein, et al., further elaborated the mechanisms connecting this systemic bacteremia to atherogenesis, including direct bacterial invasion of arterial walls, immune complex deposition and molecular mimicry between bacterial antigens and host endothelial epitopes [14]. Once circulating, these microbial signals activate innate immune pathways and amplify cytokine release through a self-reinforcing loop. The chronic, recurring nature of this process, unresolved over months to years, distinguishes it from an acute infection and explains its capacity to influence distant organ systems [14,15]. The rational for detailing these mechanism is that bacteremia and endotoxemia costitute the primary biological bridge between localized periodontal infection and systemic disease: without this sustained microbial dissemination, the oral-sytemic axis would lack a direct pathophysiological pathway capable of influencing distant organ systems.

Chronic Inflammation and Systemic Impact

The sustained elevation of proinflammatory mediators TNF-α, IL-1β, IL-6 and CRP, constitutes the shared pathobiological thread connecting periodontitis to cardiovascular disease, insulin resistance and adverse pregnancy outcomes [9,12]. Critically, this relationship appears to be modifiable. D'Aiuto, et al., demonstrated that effective periodontal treatment produces measurable reductions in circulating CRP and other systemic inflammatory markers, lending direct mechanistic support to the hypothesis that controlling oral inflammation can reduce the systemic inflammatory burden [13]. This finding carries significant clinical implications: it positions the periodontist not only as an oral health specialist, but as an active contributor to the management of systemic inflammatory disease. The sections that follow explore this link in the context of three conditions; cardiovascular

disease, diabetes mellitus and adverse pregnancy outcomes, where the biological evidence is strongest and the clinical implications are most immediate. The rationale for foregrounding chrinic systemic inflammation as the unifying mechanism is that it explains not merely the co-occurrence of periodontitis with cardiovascular disease, diabetes and adverse pregnancy outcomes, but their bidirectionality: a persistently elevared inflammatory milieu creates premissive conditions for multiple pathological process simultaneously, making periodontal disease not a bystander but an active upstream driver of systemic risk.

Periodontitis and Cardiovascular Disease: Evidence, Mechanisms and Clinical Relevance

Atherosclerotic Cardiovascular Disease (ASCVD) remains the leading cause of death in the United States, accounting for approximately 30% of all mortality. In 2020 alone, nearly 929,000 deaths were attributed to ASCVD and an estimated 605,000 new myocardial infarctions and 795,000 strokes occurred that year [15,16]. Against this backdrop, identifying modifiable upstream contributors to cardiovascular risk has become a public health priority and periodontitis has emerged as one such factor deserving serious clinical attention.

Epidemiological Evidence

The association between periodontal disease and cardiovascular disease has been documented across a substantial body of epidemiological evidence spanning prospective cohort studies, case-control designs, and, more recently, Mendelian randomization analyses. The 2020 consensus report jointly authored by the European Federation of Periodontology (EFP) and leading cardiologists concluded that periodontitis is independently associated with increased risk of ASCVD, including coronary artery disease and stroke, even after adjustment for shared risk factors such as smoking, diabetes and obesity [16]. Herrera, et al., in a comprehensive review of the epidemiological literature, confirmed this association across multiple populations, noting that individuals with severe periodontitis face a meaningfully higher relative risk of major cardiovascular events compared with periodontally healthy controls [17]. Importantly, these shared risk factors; diabetes, hypertension, obesity and smoking, are not merely confounders but likely act synergistically with periodontal inflammation to amplify cardiovascular risk, making high-risk patients particularly important targets for integrated oral and medical care [17,18].

Biological Mechanisms: From Pocket to Plaque

The pathways linking periodontitis to ASCVD are both direct and indirect and neither operates in isolation [17]. On the direct side, periodontal pathogens, in particular *Porphyromonas gingivalis* have been detected within carotid and coronary atheromatous plaques, suggesting that hematogenous bacterial seeding of the arterial wall is not merely theoretical [19]. Once in the systemic circulation, these organisms and their LPS byproducts trigger endothelial dysfunction through upregulation of adhesion molecules (ICAM-1, VCAM-1), promotion of foam cell formation and facilitation of monocyte infiltration into the subintimal space, all early steps in atherogenesis [18,19].

Indirectly, the chronic systemic inflammation driven by periodontal disease amplifies cardiovascular risk through several converging pathways. Persistently elevated CRP, IL-6, IL-18 and soluble CD40 ligand (sCD40L), a platelet-derived mediator with thrombogenic properties, have each been independently associated with incident coronary heart disease and are consistently elevated in patients with severe periodontitis [16,17]. Beyond inflammation, periodontitis-associated endotoxemia promotes platelet hyper-reactivity and aberrant coagulation, contributing to a prothrombotic state that may lower the threshold for acute coronary events [18]. Molecular mimicry between periodontal bacterial antigens and host endothelial proteins has been proposed as an additional mechanism by which the host immune response, initially directed at oral pathogens, inadvertently promotes vascular injury (Table 1) [14].

Pathway Type	Key Organisms / Mediators	Mechanism of Action	Cardiovascular Effect
Direct — Hematogenous Bacterial Seeding	*P. gingivalis*, LPS, bacterial byproducts	Periodontal pathogens enter bloodstream via ulcerated pocket epithelium and colonize arterial walls; detected in carotid and coronary atheromatous plaques	Endothelial dysfunction; upregulation of ICAM-1, VCAM-1; foam cell formation; monocyte infiltration → early atherogenesis. [18, 19]

Pathway Type	Key Organisms / Mediators	Mechanism of Action	Cardiovascular Effect
Indirect — Systemic Inflammation	CRP, IL-6, IL-18, TNF-α, sCD40L	Persistent elevation of proinflammatory cytokines amplifies vascular inflammation; each mediator independently associated with incident coronary heart disease	Accelerated plaque formation; monocyte adhesion; increased cardiovascular event risk. [16, 17]
Indirect — Prothrombotic State	LPS, endotoxin (sustained endotoxemia)	Periodontitis-associated endotoxemia promotes platelet hyper-reactivity and aberrant coagulation, lowering threshold for acute coronary events	Increased thrombotic risk; potential trigger for acute MI and unstable angina [18]
Molecular Mimicry	Bacterial antigens (cross-reactive epitopes)	Host immune response initially targeting oral pathogens cross-reacts with structurally similar endothelial proteins, promoting autoimmune-mediated vascular injury [19]	Vascular inflammation independent of microbial load; contributes to chronic arterial wall damage

Table 1: Mechanistic pathways linking periodontitis to atherosclerotic cardiovascular disease.

Critical Appraisal: Does Treating Periodontitis Reduce Cardiovascular Risk?

This is where the evidence becomes more nuanced and where intellectual honesty demands some caution. Several randomized controlled trials and meta-analyses have demonstrated that successful periodontal treatment reduces systemic inflammatory biomarkers, including CRP, IL-6 and endothelial dysfunction markers such as flow-mediated dilation, within three to six months of intervention [13]. These findings are biologically coherent and clinically encouraging. However, as Gianos, et al. and Kim, et al., have separately emphasized, surrogate marker improvements do not yet translate into demonstrated reductions in hard cardiovascular endpoints, that is, we do not yet have trial evidence showing that treating periodontitis prevents myocardial infarction or cardiovascular death [13,20]. Furthermore, Mendelian randomization studies, which use genetic variants as proxies to test causal hypotheses; have not found evidence of genetic causality between periodontitis and ASCVD, introducing important questions about the direction of the relationship and the role of shared genetic susceptibility [20]. This does not diminish the clinical relevance of the association. It does, however, mean the field must be careful not to overstate the case. The current evidence supports periodontitis as an independent risk indicator for ASCVD and as a target for risk reduction within an integrated care framework, not yet as a proven, modifiable causal risk factor in the cardiovascular sense [16,20]. Regular dental screening and referral to a periodontist remain particularly important for patients who already carry multiple cardiovascular risk factors, as the combined burden of oral and systemic inflammation in these individuals is likely additive [18].

The Periodontal-Diabetes Bidirectional Relationship: A Two-Way Street

Diabetes Mellitus (DM) has emerged as one of the defining chronic disease challenges of the 21st century. According to the International Diabetes Federation, global prevalence is projected to reach 783 million individuals by 2045, affecting approximately one in eight adults worldwide [21]. DM encompasses two major forms: Type 1 (T1DM), an autoimmune condition characterized by destruction of pancreatic beta cells and absolute insulin deficiency, which predominantly manifests in children and adolescents; and Type 2 (T2DM), the more prevalent form, driven by progressive insulin resistance and relative beta-cell dysfunction [21]. The clinical and epidemiological overlap between DM and periodontitis is now among the most robustly established associations in the oral-systemic literature, with evidence accumulating that each condition not only coexists with the other but actively worsens it [21,22].

Diabetes as a Risk Factor for Periodontitis

The impact of hyperglycemia on periodontal health is both direct and multifactorial. Cross-sectional studies have consistently demonstrated a striking prevalence disparity: while periodontitis affects approximately 15% of normoglycemic controls, prevalence rises to nearly 58% in diabetic patients and is most severe in those with uncontrolled glycemic levels [23,24]. Among patients with T1DM specifically, approximately 20% develop clinically significant periodontal disease, with increased indices of plaque accumulation, gingival inflammation and Clinical Attachment Loss (CAL) compared to matched non-diabetic controls [22]. The molecular mechanisms driving this susceptibility are increasingly well understood. Under hyperglycemic conditions, the non-enzymatic glycation of proteins, lipids and nucleic acids generates irreversible compounds known as Advanced Glycation End-products (AGEs). These molecules accumulate in periodontal tissues and mediate their destructive effects; both directly and through binding to their receptor, RAGE (Receptor for Advanced Glycation End-Products), across all cell types of the periodontal ligament, including osteocytes, gingival fibroblasts, epithelial cells and stem cells [23]. When combined with lipopolysaccharides from Porphyromonas gingivalis, AGE activity is further amplified, accelerating connective tissue degradation and bone resorption [23]. Beyond the AGE/RAGE axis, DM impairs neutrophil chemotaxis and phagocytic function, blunts the host's capacity to resolve local infection and alters the subgingival microbiome toward a more pathogenic composition, effects that collectively create a permissive environment for periodontitis progression [21,23].

Periodontitis as a Worsening Factor for Glycemic Control

The relationship is not unidirectional. There is substantial and growing evidence that active periodontitis exacerbates glycemic dysregulation in diabetic patients and may even impair glucose metabolism in otherwise normoglycemic individuals. The chronic systemic inflammatory burden produced by periodontal infection, driven by elevated TNF-α, IL-1β and IL-6, promotes insulin resistance at the tissue level, interfering with insulin receptor signaling in a manner analogous to that observed in obesity-related inflammation [25]. These mechanisms collectively provide the biological rationale for including the DM-periodontitis relationship in this review: glycemic dysregulation does not merely coexist with periodontal disease but mechanistically accelerates it, making glycemic control a direct therapeutic target in periodontal management of diabetic patients.

Periodontal Treatment and Glycemic Outcomes: What the Evidence Shows

The most clinically compelling aspect of this bidirectional relationship is the evidence that treating periodontitis improves metabolic control in diabetic patients. At least 26 systematic reviews and meta-analyses have examined this question and their pooled findings consistently demonstrate that non-surgical periodontal therapy; Scaling and Root Planning (SRP), reduces glycated Hemoglobin (HbA1c) by approximately 0.5 percentage points over a period of three to twelve months [24]. To place this in clinical context: a reduction of one percentage point in HbA1c has been associated with a 21% decrease in diabetes-related mortality, a 14% reduction in myocardial infarction risk and a 37% reduction in microvascular complications, making even a 0.5% improvement clinically meaningful [24]. Borgnakke, summarized the weight of this evidence compellingly, arguing that these findings are now sufficiently robust to justify formal inclusion of periodontitis screening and treatment within standard diabetes management protocols [24].

Clinical Implications: Closing the Loop Between Dental and Medical Care

The bidirectional nature of this relationship demands a bidirectional clinical response. Dental providers treating patients with DM should be alert to the possibility that poor glycemic control is actively fueling periodontal disease progression and conversely, that uncontrolled periodontitis may be a contributing barrier to glycemic stability [24,25]. Dentists are uniquely positioned to screen for undiagnosed or poorly controlled diabetes through chairside HbA1c testing and to refer patients to physicians when metabolic red flags are detected. Physicians, in turn, must recognize that untreated periodontal infection represents a modifiable source of systemic inflammation with measurable effects on their patients' glycemic trajectories [25]. An umbrella review by Arbildo-Vega, et al., synthesizing evidence across multiple systematic reviews, confirmed this association with high confidence and underscored the importance of integrated interdisciplinary protocols [26]. Ultimately, the shared inflammatory pathobiology of DM and periodontitis makes collaborative dental-medical management not a complementary nicety but a clinical imperative.

Adverse Pregnancy Outcomes and Emerging Systemic Associations

Among the most clinically consequential extensions of the oral-systemic axis is the mounting evidence linking maternal periodontitis to adverse pregnancy outcomes, specifically Preterm Birth (PTB), Low Birth Weight (LBW) and preeclampsia. Bobetsis, et al., in a comprehensive review published in Periodontology 2000, provided the most thorough synthesis of this

literature to date, concluding that periodontal diseases should be considered both a risk factor for and a potential contributor to these outcomes through well-defined biological pathways [29]. These complications collectively represent a significant perinatal burden: PTB is the leading cause of neonatal morbidity and mortality, affecting approximately one in ten pregnancies globally, while preeclampsia complicates 5-7% of pregnancies and remains a major driver of maternal death and long-term cardiovascular morbidity in both mother and child [30]. Low birth weight, the second leading contributor to perinatal mortality, has also been independently associated with elevated risk of type 2 diabetes in later life [29]. The clinical urgency of understanding what drives these outcomes and whether oral inflammation is one modifiable upstream factor, is therefore self-evident.

Mechanisms: How Periodontal Inflammation Reaches the Fetoplacental Unit

Two non-mutually exclusive biological theories have been proposed to explain how periodontal infection might trigger or accelerate adverse pregnancy outcomes. The first implicates direct bacterial dissemination: periodontal pathogens entering the bloodstream through the ulcerated pocket epithelium may travel hematogenously to the embryo-placental unit, provoking a localized inflammatory response capable of disrupting normal placental function and triggering premature uterine contractions [27,29]. Indeed, *P. gingivalis* and other periodontal organisms have been detected in placental tissues and animal studies have demonstrated that systemic administration of periodontal pathogens can induce fetal growth restriction and preterm delivery in pregnant mice [29]. The second theory emphasizes systemic propagation of inflammatory mediators, particularly Prostaglandin E_2 (PGE_2), IL-1β, IL-6 and TNF-α, which, once in circulation, may reach the fetoplacental interface and amplify local inflammation in ways that promote preeclampsia or premature cervical ripening [27,28]. During normal pregnancy, amniotic fluid levels of PGE_2 and TNF-α naturally rise toward term until reaching a threshold that initiates labor; the concern is that periodontitis-driven systemic inflammation may accelerate this process, lowering the biological threshold for early labor onset [29].

Preterm Birth and Low Birth Weight: The Clinical Evidence

Dörtbudak et al. provided one of the earliest direct demonstrations of this link, performing periodontal examinations and amniotic fluid collection between 15 and 20 weeks of gestation in 36 high-risk pregnant women [27]. Periodontitis was diagnosed in 20% of women who delivered at term, compared with 83% of those who experienced preterm delivery; a clinically striking disparity. Amniotic IL-6 and PGE_2 levels correlated significantly with subgingival bacterial burden, supporting a direct biological relationship between periodontal pathogens and fetoplacental inflammatory activation, with an odds ratio for preterm delivery in the context of periodontitis of 20.0 (95% CI: 2.0-201.7) [27].

These findings were reinforced by Perunovic, et al., in a cross-sectional study of 120 women, 60 with preterm and 60 with full-term deliveries [28]. Women with preterm birth presented with significantly worse periodontal parameters and elevated Gingival Crevicular Fluid (GCF) levels of IL-6 and PGE_2 compared to the full-term group, while serum levels showed no significant difference, a finding consistent with the hypothesis that the periodontium itself acts as the primary reservoir for the inflammatory mediators that ultimately reach the fetoplacental unit [28]. Bobetsis, et al., further synthesized interventional data, noting that while some trials of periodontal therapy during pregnancy have shown reductions in preterm birth rates, results remain inconsistent, largely due to heterogeneity in study design, periodontal case definitions and timing of treatment [29].

Preeclampsia: Epidemiological Association and Mechanistic Inconsistency

The epidemiological evidence linking periodontitis to preeclampsia is substantial. Sgolastra, et al., in a PRISMA-compliant meta-analysis of 15 studies encompassing over 5,100 participants, found that periodontal disease was associated with a statistically significant twofold elevation in preeclampsia risk (OR 2.17; 95% CI 1.38-3.41) [31]. This association is biologically plausible: periodontal bacteria and their byproducts may directly promote endothelial dysfunction, a hallmark of preeclampsia pathophysiology; through LPS-mediated inflammatory signaling, while the shared systemic inflammatory milieu driven by cytokines like TNF-α and IL-6 may amplify the exaggerated maternal inflammatory response characteristic of this condition [29,30].

However, an important inconsistency must be acknowledged. The systematic review by Kunnen, et al., which examined twelve epidemiological studies and three randomized intervention trials, found that while eight observational studies demonstrated a positive association between periodontitis and preeclampsia, none of the three intervention trials showed a statistically significant reduction in preeclampsia risk following periodontal treatment during pregnancy [32]. This gap consistent with patterns observed in Section 3 for cardiovascular disease, serves as an important reminder that observational associations do not

automatically translate into modifiable risk and that confounders including socioeconomic status, BMI, smoking and pre-existing hypertension must be rigorously controlled in future interventional designs [31,32].

Emerging Systemic Associations: Rheumatoid Arthritis, Alzheimer's Disease and Beyond

The oral-systemic hypothesis has increasingly extended beyond the three core conditions covered in this review. Tsikouras, et al., situate periodontal pathology within a wider network of systemic associations spanning chronic kidney disease, rheumatoid arthritis, respiratory disease, Parkinson's disease, dementia and several cancers [32,33]. Among these, two emerging links deserve particular attention for the strength of their mechanistic underpinning.

The association with Rheumatoid Arthritis (RA) is perhaps the most mechanistically compelling. Potempa, Mydel and Koziel, in a landmark review published in Nature Reviews Rheumatology, outlined the case for periodontitis in RA pathogenesis via the citrullination hypothesis: *P. gingivalis* uniquely expresses a bacterial Peptidylarginine Deiminase (PPAD) that citrullinates host proteins in the inflamed periodontium, potentially generating the autoantigenic epitopes; recognized by Anti-Citrullinated Protein Antibodies (ACPAs), that are a hallmark of seropositive RA [34]. This mechanism positions the periodontium as a plausible site for the breakdown of immune tolerance that initiates RA in genetically susceptible individuals. Supporting this mechanistic framework, descriptive epidemiological studies have consistently found a twofold to threefold higher prevalence of periodontitis in patients with established RA compared with age- and sex-matched controls, with greater periodontal attachment loss correlating with higher Disease Activity Scores (DAS28) and seropositivity for ACPAs [34,35]. Conversely, patients with severe periodontitis have a significantly higher prevalence of subclinical synovitis and elevated anti-CCP antibody titers compared with periodontally healthy controls, suggesting that the oral-joint inflammatory axis operates in both directions at the clinical level [35].

The link with Alzheimer's disease has also gained substantial traction. In a landmark Science Advances study, Dominy, et al., identified *P. gingivalis* and its toxic gingipain proteases in the brain tissue of Alzheimer's disease patients, gingipain levels correlated with tau and ubiquitin pathology and oral *P. gingivalis* infection in mice resulted in brain colonization and increased production of amyloid-β_{1-42} [33]. While these findings do not establish causality, they provide the most direct biological evidence to date that periodontal pathogens can access and damage neural tissue, lending credibility to the emerging concept of an oral-brain axis.

Across these emerging associations and including the growing evidence for periodontitis as a contributor to chronic kidney disease progression and non-alcoholic fatty liver disease; the strength of evidence varies considerably [7,36]. Some associations, such as RA and Alzheimer's disease, are well-supported at both epidemiological and mechanistic levels. Others remain largely epidemiological, with the underlying biological pathways still being characterized. What is consistent across all of them is the common inflammatory thread: a systemic low-grade inflammatory state, perpetuated by chronic periodontal infection, that creates permissive conditions for disease progression in multiple organ systems. The field is advancing rapidly and what is considered speculative today may be well-established within a decade, making ongoing investment in this area of research both scientifically justified and clinically important [36].

Conclusion: Periodontitis As a Systemic Risk Modifier-Evidence, Implications and The Path Forward

Clinical Implications

The evidence presented supports several concrete clinical recommendations. First, periodontal evaluation should be integrated into routine medical workups for patients with established cardiovascular disease, type 2 diabetes and for pregnant women at risk of obstetric complications [36]. Second, scaling and root planning should be formally recognized; in clinical guidelines, as an intervention capable of reducing the systemic inflammatory burden, beyond its traditional indication as local oral treatment alone [13,25]. Third, interprofessional collaboration among periodontists, cardiologists, endocrinologists and obstetricians is not optional but essential: the shared inflammatory pathobiology of periodontitis and each of these systemic conditions means that neither specialty can optimally manage their patients without awareness of the other [36]. Structured referral pathways and joint screening protocols, already advocated in principle by the EFP/WONCA Europe consensus, need to be operationalized at the level of clinical practice guidelines in medicine and dentistry alike [36].

Limitations of This Review

Several limitations must be acknowledged honestly. The majority of studies included in this review are observational in design, which limits the strength of causal inference. Heterogeneity in periodontal case definitions with varying thresholds for probing depth, clinical attachment loss and radiographic bone loss, across studies likely contributes to variability in effect size estimates and makes cross-study comparisons challenging. Randomized controlled trials with hard clinical endpoints; myocardial infarction, stroke incidence or preeclampsia, are both scarce and methodologically difficult to design and fund. Additionally, potential publication bias and confounding by shared risk factors (smoking, socioeconomic status, obesity and age) cannot be fully excluded from observational data. Despite these constraints, the consistency of the association across diverse populations and study designs, the biological plausibility of the proposed mechanisms and the positive, if modest; effects of periodontal intervention on systemic inflammatory markers collectively support a causal role for periodontitis as a systemic risk modifier.

Critical Gaps and Future Directions

Large-scale randomized trials with standardized periodontal case definitions and pre-specified hard clinical endpoints remain the field's most urgent methodological priority. Concurrently, periodontitis must be formally recognized in systemic disease management guidelines, across cardiology, endocrinology and obstetrics, not as a footnote, but as a modifiable systemic risk factor in its own right [37-41].

Conclusion

This narrative review synthesized current evidence on the inflammatory mechanisms linking periodontitis to cardiovascular disease, type 2 diabetes mellitus and adverse pregnancy outcomes, drawing on a body of literature spanning epidemiology, molecular biology, interventional trials and emerging mechanistic research. The following conclusions are supported by the evidence presented.

The central finding of this review is unambiguous: periodontitis is not a localized disease but a source of sustained, chronic low-grade systemic inflammation. Periodontal pathogens most notably Porphyromonas gingivalis, translocate into the bloodstream via the ulcerated pocket epithelium, while proinflammatory mediators including IL-6, TNF-α, IL-1β and CRP enter the systemic circulation, constituting what has been termed the oral-systemic axis. This biological highway explains how a chronic oral infection can influence distant organs and systems, contributing to vascular endothelial dysfunction, impaired insulin signaling and fetoplacental inflammatory activation, among other consequences.

The evidence linking periodontitis to atherosclerotic cardiovascular disease is among the most mature in the field. Multiple consensus reports including the landmark joint EFP/AAP report Sanz, et al. and the more recent EFP/WONCA Europe workshop, Herrera, et al., have concluded that periodontitis is independently associated with increased cardiovascular risk, even after adjustment for shared traditional risk factors. A meta-analysis by Gupta, et al., examining cardiovascular biomarker profiles across 36 studies, confirmed significantly elevated oxidative stress indices and reduced HDL cholesterol in periodontitis patients compared to periodontally healthy controls, findings consistent with accelerated atherogenesis. Mechanistically, IL-6 and CRP activate vascular endothelium, promote monocyte adhesion and accelerate plaque formation, while periodic bacteremia contributes to thrombotic risk through platelet hyper-reactivity. Randomized interventional evidence indicates that successful periodontal treatment reduces systemic inflammatory biomarkers, though hard endpoint reductions in myocardial infarction or stroke have yet to be demonstrated.

The periodontitis-diabetes relationship is bidirectional and has perhaps the strongest interventional evidence of any oral-systemic association. Periodontal inflammation elevates circulating TNF-α, impairing insulin receptor signaling in peripheral tissues; hyperglycemia in turn drives AGE accumulation in the periodontium, perpetuating a self-amplifying inflammatory cycle. Meta-analyses aggregating over 26 systematic reviews have consistently demonstrated that non-surgical periodontal therapy (scaling and root planing) reduces HbA1c by approximately 0.5 percentage points over three to twelve months a clinically meaningful improvement given that a one-point HbA1c reduction is associated with a 21% reduction in diabetes-related mortality. This finding positions periodontal intervention as a genuinely complementary, low-cost strategy in diabetes management and supports the formal inclusion of periodontal screening in standard diabetes care protocols.

Pregnant women with periodontitis consistently exhibit elevated GCF and serum levels of PGE_2, IL-1β, IL-6 and matrix metalloproteinases mediators capable of reaching the fetoplacental unit and disrupting normal placental function. These inflammatory signals have been associated with preterm birth, low birth weight and preeclampsia through two non-mutually exclusive pathways: direct hematogenous seeding of the fetoplacental interface by periodontal pathogens and systemic propagation of periodontitis-derived cytokines that lower the threshold for early labor onset. While epidemiological evidence for these associations is robust, the gap between observational data and interventional outcomes, particularly for preeclampsia, underscores the need for rigorously designed randomized trials with standardized periodontal case definitions and hard obstetric endpoints.

While this review has focused on marginal periodontitis, emerging evidence reviewed by Venugopal, et al., indicates that apical periodontitis; inflammatory lesions of endodontic origin, shares analogous systemic consequences, with moderate-certainty evidence linking it to increased cardiovascular risk and poorer glycemic control in diabetic patients. This broadens the clinical scope of the oral-systemic axis and suggests that endodontic disease should be incorporated into future research frameworks examining the relationship between oral infection and systemic health.

The biological and clinical evidence reviewed here collectively supports periodontitis as a true systemic risk modifier. The oral cavity is not an island. It is connected, immunologically, microbiologically and clinically, to the cardiovascular system, the metabolic axis and the reproductive environment. Translating these findings into improved patient outcomes will require structured interprofessional collaboration, standardized diagnostic frameworks and a shared commitment among medicine and dentistry to treat the patient as a whole rather than as a collection of isolated organs.

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The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Authors' Contributions
All authors contributed equally to this paper.

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