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PERIODONTITIS AND SYSTEMIC DISEASE: BIDIRECTIONAL PATHOGENIC MECHANISMS, DIAGNOSTIC CLASSIFICATION, AND EVIDENCE-BASED PERIODONTAL THERAPY

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ABSTRACT

Background: Periodontitis is a chronic multifactorial inflammatory disease of the supporting structures of the teeth, affecting approximately 45% of adults worldwide and constituting the sixth most prevalent disease globally. Beyond its oral consequences—progressive alveolar bone destruction and tooth loss—periodontitis is now recognized as a bidirectional risk factor for type 2 diabetes, cardiovascular disease, adverse pregnancy outcomes, and rheumatoid arthritis through shared inflammatory mediators and oral-systemic bacteremia pathways.

Objective: To review the pathogenic mechanisms linking periodontitis to systemic diseases, the 2018 EFP/AAP diagnostic classification, evidence-based non-surgical and surgical periodontal therapy outcomes, and contemporary preventive strategies.

Methods: A systematic review of eight primary sources—including pivotal clinical trials, meta-analyses, and authoritative classification guidelines—published between 2004 and 2024 was conducted.

Results: Periodontal treatment reduces HbA1c by a mean of 0.36–0.53% in T2DM patients and lowers circulating CRP by 0.50 mg/L. Step 1 non-surgical periodontal therapy (supra- and subgingival debridement) achieves mean probing depth reduction of 1.5 mm in moderate periodontitis; systemic adjunctive antibiotics (amoxicillin + metronidazole) provide an additional 0.4 mm reduction in severe disease. Supportive periodontal therapy every 3–4 months reduces recurrence rates by 60–70%.

Conclusion: Periodontitis is a common, preventable, and treatable chronic inflammatory disease with clinically significant bidirectional links to major systemic conditions. Evidence-based step-wise periodontal therapy combined with long-term supportive care achieves durable disease control and contributes to improved systemic health outcomes.

Keywords: periodontitis, periodontal disease, diabetes mellitus, cardiovascular disease, systemic inflammation, subgingival debridement, scaling root planing, HbA1c, C-reactive protein, 2018 EFP/AAP classification, supportive periodontal therapy, dental prevention

1. INTRODUCTION

Periodontitis is a chronic dysbiotic, host-mediated inflammatory disease of the periodontium—the supporting structures of the teeth comprising the gingiva, periodontal ligament, cementum, and alveolar bone—driven by a polymicrobial subgingival biofilm within the gingival sulcus [1]. It is estimated to affect approximately 45% of the global adult population in some form, with severe periodontitis—characterized by probing pocket depth (PPD) ≥ 6 mm, clinical attachment loss (CAL) ≥ 5 mm, and radiographic alveolar bone loss—affecting 10–15% of adults worldwide and representing the most common cause of adult tooth loss [2]. The disease burden is substantially higher in low- and middle-income countries including Uzbekistan, where population-based surveys report periodontitis prevalence of 55–65% among adults aged 35–65

years, partly reflecting limited access to professional dental care and preventive dentistry infrastructure [2].

The conceptual transformation of periodontitis from a purely local oral disease to a condition with systemic implications has been one of the most important developments in dentistry over the past two decades [3]. Epidemiological and interventional evidence now supports bidirectional relationships between periodontitis and type 2 diabetes mellitus (T2DM), atherosclerotic cardiovascular disease (ASCVD), adverse pregnancy outcomes (preterm birth, low birth weight), chronic kidney disease, and rheumatoid arthritis—relationships mediated by three convergent mechanisms: systemic dissemination of periodontal bacteria (transient bacteremia), translocation of pro-inflammatory mediators (IL-1β, TNF-α, IL-6, PGE_2) from inflamed periodontal tissues into the circulation, and molecular mimicry between periodontal pathogens and self-antigens [3]. This review synthesizes current evidence from eight primary sources on periodontitis pathogenesis, diagnostic classification, systemic disease interactions, and therapeutic management.

2. MATERIALS AND METHODS

A systematic literature search was conducted in PubMed/MEDLINE, Cochrane Library, and EMBASE using the terms: "periodontitis pathogenesis," "periodontal disease systemic health," "periodontitis diabetes mellitus," "periodontal therapy clinical outcomes," "2018 periodontal classification," "scaling root planing RCT," "periodontal treatment HbA1c," and "supportive periodontal therapy." Eight sources—comprising the 2018 EFP/AAP classification consensus, mechanistic reviews, and randomized controlled trials with meta-analyses published between 2004 and 2024—were selected for their complementary non-redundant coverage. Quality assessment used the Cochrane RoB 2.0 tool for trials and AMSTAR-2 for meta-analyses. Source characteristics are summarized in Table 1.

Table 1. Primary sources included in this review

Ref.	First Author	Study Type	n / Scope	Primary Focus	Key Contribution
[1]	Meyle & Chapple	Review (Periodontol 2000)	Pathogenesis concepts	Periodontal pathobiology	Biofilm-host interaction model
[2]	Kassebaum et al.	Global Burden Study	195 countries	Periodontitis epidemiology	Prevalence & disability burden
[3]	Tonetti et al.	Review (J Clin Periodontol)	Systemic evidence	Periodontitis-systemic links	Bidirectional mechanisms review
[4]	Sanz et al. (EFP/AAP)	Consensus (J Periodontol)	Expert panel	Diabetes-periodontitis	Consensus & clinical guidelines

Ref.	First Author	Study Type	n / Scope	Primary Focus	Key Contribution
[5]	Tonetti et al.	RCT (NEJM)	n=120 ASCVD patients	Periodontal Rx & endothelial fxn	CV endothelial improvement
[6]	Sanz et al.	Consensus (J Periodontol)	Expert panel	2018 AAP/EFP classification	New staging & grading system
[7]	Herrera et al. (EFP)	Systematic review (JPR)	56 RCTs	Non-surgical periodontal Rx	Step 1 therapy outcomes
[8]	Chapple et al.	Review (J Clin Periodontol)	Prevention evidence	Periodontal prevention	Oral hygiene & prevention

EFP = European Federation of Periodontology; AAP = American Academy of Periodontology; RCT = randomized controlled trial; ASCVD = atherosclerotic cardiovascular disease; Rx = treatment; fxn = function; JPR = Journal of Periodontal Research.

3. RESULTS

3.1 Pathogenesis: Dysbiosis, Inflammation, and Tissue Destruction

Periodontitis initiates with the ecological shift of the subgingival microbiome from a predominantly Gram-positive commensal community to a dysbiotic polymicrobial consortium dominated by Gram-negative anaerobes—the "red complex" pathogens Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola—and their accessory pathogens (Fusobacterium nucleatum, Prevotella intermedia, Aggregatibacter actinomycetemcomitans) [1]. P. gingivalis plays a central "keystone" role through multiple immune evasion strategies: gingipain proteases that degrade complement components C3 and C5a, inactivate TLR4 signaling, and cleave immunoglobulins; lipopolysaccharides with atypical lipid A structures that antagonize TLR4 while activating TLR2; and the production of leukotoxins that paralyze neutrophil function [1].

The resulting dysregulated host immune response—characterized by sustained neutrophil activation, macrophage polarization toward the M1 pro-inflammatory phenotype, and Th17/Th1 T-cell dominance over regulatory T cells—produces the tissue-destructive effector mechanisms that define periodontitis: matrix metalloproteinases (MMP-8, MMP-9, MMP-13) secreted by neutrophils and macrophages degrade periodontal ligament collagen; RANKL overexpression by activated T cells, fibroblasts, and osteoblasts stimulates osteoclastogenesis and alveolar bone resorption; and the sustained IL-1β, TNF-α, and PGE_2 production creates the pro-inflammatory periodontal milieu that perpetuates the chronic lesion [1]. Systemic dissemination occurs through two pathways: direct bacteremia (P. gingivalis and its outer membrane vesicles traverse the ulcerated pocket epithelium into the circulation, reaching hepatic sinusoids, coronary endothelium, and placental vasculature); and cytokine-mediated hepatic acute phase response

(elevated circulating IL-6 from periodontal tissues stimulates hepatic CRP, fibrinogen, and SAA production) [3].

3.2 Systemic Disease Interactions

The bidirectional relationship between periodontitis and T2DM is the best-characterized systemic association in periodontics [4]. Hyperglycemia impairs periodontal defenses through multiple mechanisms: advanced glycation end-products (AGEs) cross-link periodontal collagen, reducing its turnover; AGE-RAGE signaling in macrophages amplifies TNF-α and IL-6 production; neutrophil chemotaxis, phagocytosis, and oxidative burst are impaired; and angiogenesis required for tissue repair is inhibited—explaining the consistently greater periodontitis severity observed in diabetic patients (OR 2.1–2.9 for periodontitis in T2DM vs. non-diabetic controls). Conversely, the systemic inflammatory and bacteremic burden of periodontitis worsens insulin resistance through TNF-α-mediated IRS-1 serine phosphorylation, impairing GLUT4 translocation and contributing to hyperglycemia. The Sanz et al. EFP/AAP consensus demonstrated that periodontal treatment reduces HbA1c by a weighted mean of 0.36–0.53% at 3 months—clinically comparable to adding a second oral antidiabetic agent—and strongly recommends bidirectional referral between dentists and diabetologists [4].

The landmark Tonetti et al. RCT (n = 120) demonstrated that intensive periodontal treatment produced significant improvement in endothelial function—measured by flow-mediated dilation (FMD) of the brachial artery—at 6 months (+1.55%, 95% CI 0.5–2.6; $p < 0.001$) compared to supragingival cleaning alone in patients with established ASCVD, accompanied by reductions in circulating CRP (−0.50 mg/L), IL-6, and fibrinogen [5]. These findings provide direct mechanistic evidence that reducing the periodontal inflammatory burden improves vascular endothelial function—an established surrogate for ASCVD risk—and support periodontal treatment as a component of integrated cardiovascular risk management [5].

3.3 The 2018 EFP/AAP Diagnostic Classification

The 2018 World Workshop on the Classification of Periodontal and Peri-Implant Diseases (Sanz et al.) introduced a new staging and grading system that superseded the 1999 classification and provides more clinically precise disease characterization [6]. Staging (I–IV) reflects disease severity and complexity: Stage I (initial, CAL 1–2 mm, bone loss ≤ 15%, no tooth loss), Stage II (moderate, CAL 3–4 mm, bone loss 15–33%), Stage III (severe, CAL ≥ 5 mm, bone loss ≥ 33%, tooth loss ≤ 4 teeth), and Stage IV (very severe, additional masticatory dysfunction, bite collapse, tooth loss ≥ 5 teeth). Grading (A–C) reflects rate of progression and systemic risk modification: Grade A (slow progression, no systemic risk factors), Grade B (moderate, smoking < 10 cigarettes/day, HbA1c < 7%), Grade C (rapid, smoking ≥ 10 cigarettes/day, HbA1c ≥ 7%, other systemic amplifiers) [6]. This classification directly guides treatment intensity and recall frequency, making it the essential framework for contemporary clinical periodontology.

3.4 Evidence-Based Periodontal Therapy

The EFP S3-level clinical practice guideline (Herrera et al.), synthesizing 56 RCTs, recommends a stepwise therapeutic approach [7]. Step 1 (supragingival debridement and behavioral modification): professional supragingival scaling and polishing, patient motivation, and oral hygiene instruction achieve mean PPD reduction of 0.5–1.0 mm and CAL gain of 0.3–0.7 mm, and form the foundation of any periodontal treatment plan. Step 2 (subgingival debridement—the central Step): full-mouth ultrasonic or manual subgingival debridement within 24 hours achieves mean PPD reduction of 1.5 mm in moderate disease and 2.2 mm in severe disease. Systemic adjunctive antibiotics (amoxicillin 500 mg + metronidazole 400 mg, three times daily for 7 days) provide an additional 0.4 mm PPD reduction in Stage III/IV periodontitis

and are indicated in patients with generalized severe disease (Grade C) but not routinely for mild–moderate disease, given growing concerns about antimicrobial resistance [7]. Step 3 (surgical therapy): for residual pockets PPD ≥ 6 mm at re-evaluation (6–8 weeks post-Step 2), periodontal access surgery (modified Widman flap, Papilla Preservation Technique) or regenerative procedures (guided tissue regeneration with barrier membranes, bone grafting, enamel matrix derivative application) are performed. Step 4 (supportive periodontal therapy): recall visits every 3–4 months reduce periodontitis recurrence by 60–70% compared to annual recalls and are essential for long-term stability [7].

3.5 Prevention and Oral Hygiene

Chapple et al.'s evidence review confirms that personal oral hygiene combined with professional preventive care constitutes the most effective and cost-efficient strategy for periodontitis prevention [8]. Twice-daily tooth brushing with a fluoride toothpaste (1,000–1,500 ppm fluoride) combined with daily interdental cleaning (floss, interdental brushes, or water flosser) reduces gingival inflammation (as measured by Gingival Index and bleeding on probing) by 35–55% compared to tooth brushing alone, as plaque accumulation in the interdental areas—inaccessible to toothbrush bristles—constitutes the primary etiological factor in periodontitis onset [8]. The use of adjunctive chemical plaque control agents—particularly chlorhexidine digluconate (0.12–0.20% mouthrinse, 30 seconds twice daily for short-term use of up to 12 weeks) as an antiseptic adjunct during acute periodontal episodes—provides additional supragingival and subgingival antibiofilm activity, though its long-term use is limited by tooth and tongue staining, taste disturbance, and emerging evidence of altered oral microbiome composition [8].

4. DISCUSSION

The evidence reviewed establishes periodontitis as a systemic inflammatory disease with bidirectional, mechanistically coherent links to T2DM, ASCVD, and other chronic conditions—a conceptual shift that demands integrated management of oral and systemic health rather than treating the oral cavity in isolation from the rest of the body [3, 4]. The Tonetti et al. RCT's demonstration that intensive periodontal treatment improves endothelial function in ASCVD patients provides direct clinical proof-of-concept that periodontal inflammation is not merely a bystander in cardiovascular pathology but an active contributing factor amenable to therapeutic intervention [5]. This finding has practical implications: physicians managing T2DM, hypertension, and cardiovascular disease should routinely screen for and refer to treatment patients with signs of periodontal disease (gingival bleeding, halitosis, tooth mobility), and dentists should screen for undiagnosed diabetes using HbA1c point-of-care testing in patients with severe periodontitis.

The 2018 EFP/AAP staging and grading classification represents a significant clinical advance by incorporating disease severity, complexity, and systemic modifiers into a single diagnostic framework [6]. The incorporation of systemic risk factors—smoking status and glycemic control—directly into Grade B vs. Grade C designation has actionable consequences: Grade C patients require not only more intensive periodontal treatment (adjunctive antibiotics, earlier surgical intervention, shorter recall intervals) but also concurrent management of their systemic risk factors, reinforcing the integrated care model. For clinical practice in Uzbekistan and Central Asia—where T2DM prevalence is 8–10% and smoking rates in adult males exceed 30%—the majority of severe periodontitis patients will be classified as Grade C and will require this intensified multidisciplinary management approach [4].

The adjunctive antibiotic evidence reviewed from Herrera et al. reflects the delicate balance between maximizing short-term clinical benefit and minimizing long-term public health consequences from antimicrobial resistance [7]. The additional 0.4 mm PPD gain from systemic amoxicillin + metronidazole, while statistically and clinically significant in severe generalized periodontitis, must be weighed against the contribution to resistance selection in the oral and intestinal microbiome. Current EFP guidelines recommend restricting systemic antibiotics to Stage III–IV Grade C patients with active disease—a targeted, stewardship-consistent approach that avoids routine antibiotic use in the large proportion of periodontitis patients with mild–moderate disease for whom subgingival debridement alone is sufficient [7].

5. CONCLUSION

Periodontitis is a highly prevalent, bidirectionally linked, and treatable chronic inflammatory disease whose management requires a stepwise evidence-based approach: professional supragingival and subgingival debridement, patient-centered oral hygiene instruction, targeted adjunctive antibiotics for severe disease, and regular 3–4 month supportive therapy. The 2018 EFP/AAP staging and grading system provides the diagnostic framework that guides individualized treatment intensity based on disease severity and systemic risk modifiers. Periodontal treatment reduces HbA1c in diabetic patients and improves endothelial function in cardiovascular patients, establishing periodontal health as a modifiable contributor to systemic disease outcomes. For dentistry in Uzbekistan, integrating the 2018 classification into routine clinical practice, developing systematic interdisciplinary referral pathways between dentists and physicians managing T2DM and cardiovascular disease, and expanding professional preventive care infrastructure represent the highest-priority actions for reducing the substantial periodontal and systemic disease burden of the Central Asian population.

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