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Periodontal Disease: Pathogenesis, Diagnosis, Biomarkers, Systemic Associations, and Emerging Adjunctive Therapies

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Abstract

A serious global public health concern, periodontal disease constitutes a continuous inflammatory disorder that affects the teeth's supporting structures. Traditionally considered a localized oral disease, periodontitis is becoming more well acknowledged as a broad inflammatory condition with wide-ranging effects on overall health. The disease is initiated by a dysbiotic oral biofilm; however, the host immune-mediated inflammatory response plays a major role in determining the severity and course. This review comprehensively discusses the etiopathogenesis, classification, diagnostic criteria, and global burden of periodontal disease, with special emphasis on inflammatory pathways, biomarkers of tissue destruction and bone remodeling, and emerging diagnostic strategies. Additionally, a comprehensive analysis is conducted of the reciprocal association between periodontal conditions and systemic problems such rheumatoid arthritis, obesity, diabetes mellitus, cardiovascular disease, respiratory illnesses, unsuccessful pregnancies, and neurodegenerative disorders. In addition, emerging adjunctive therapeutic approaches, particularly phytotherapeutic agents like curcumin, are reviewed for their potential role in host modulation and inflammation control. By integrating evidence from clinical, epidemiological, and mechanistic studies, this review highlights current limitations, research gaps, and future directions aimed at personalized and multidisciplinary periodontal care.

Keywords

Periodontal disease, inflammation, biomarkers, systemic diseases, diagnosis, curcumin, host modulation

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1. INTRODUCTION

One of the most common oral health issues in the world, periodontal disease is a collection of chronic inflammatory conditions that affect the gingiva, cementum, periodontal ligaments, and alveolar bone (1). It is one of the main causes of adult tooth loss and has a major impact on speech, mastication, appearance, and general quality of life (2). The disease spectrum ranges from reversible gingivitis to irreversible periodontitis, characterized by progressive loss of fibrous tissue attachment and alveolar bone deterioration (3).

Despite improvements in dental hygiene awareness and access to dental treatment in many regions, periodontal disease continues to pose a major challenge due to its chronic nature and high recurrence rate (4).

From a scientific standpoint, the development of a complex bacterial film on the tooth surface causes periodontal disease; however, the human immune-

inflammatory response, rather than the microbial burden alone, largely controls the degree and course of tissue loss (5).

Pro-inflammatory chemokines, cytokines, prostaglandins, and matrix proteins are released as a result of prolonged immunological activation brought on by dysbiosis of the oral microbiota, all of which contribute to the degradation of periodontal tissue. This change from a symbiotic to a pathogenic microbiological community highlights the importance of host–microbe interactions in periodontal pathogenesis (6).

In recent years, periodontal disease has been increasingly recognized as a condition with systemic relevance rather than a localized oral infection. With an emphasis on the reciprocal association between inflammation in the periodontal tissues and systemic diseases such diabetes, heart disease, mellitus, obesity, rheumatic arthritis, adverse birth outcomes, and neurodegenerative disorders, the idea of periodontal medicine has arisen (7). A persistent minimal systemic inflammatory load is exacerbated by chronic periodontal disease, which may exacerbate or modify the course of systemic diseases through shared inflammatory and immune-mediated pathways (8).

Given the growing body of evidence linking periodontal disease to overall health, there is an urgent need for comprehensive reviews that integrate current knowledge on its etiopathogenesis, diagnostic strategies, biomarker research, systemic associations, and emerging therapeutic approaches (9). This review aims to provide an in-depth and up-to-date synthesis of periodontal disease, with particular emphasis on inflammatory mechanisms, diagnostic limitations, biomarker-based advancements, and novel adjunctive therapies such as curcumin. By consolidating evidence from clinical, epidemiological, and mechanistic studies, this review seeks to support a multidisciplinary and personalized approach to periodontal disease management (10).

2. Etiology and Risk Factors

Dental plaque is the main cause of periodontal disease, a complex biofilm composed of diverse microbial communities. However, the mere presence of plaque is insufficient to explain disease severity, indicating the importance of host-related and environmental risk factors (11).

2.1 Microbial Factors

Periodontal pathogens are predominantly Gram-negative anaerobic bacteria. The transition from a symbiotic to a dysbiotic biofilm is marked by an increased abundance of keystone pathogens such as Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola. These microbes have virulence factors that cause persistent inflammation and interfere with host immunological control (8).

2.2 Host Factors

The development of periodontal disease is significantly influenced by host vulnerability. Genomic tendency, immune system variation, and systemic inflammatory status influence disease expression (12). Polymorphisms in cytokine genomes, notably those encoding interleukins, and tumor- necrosis factor-alpha, among others have been related with greater periodontal risk (13).

2.2.1 Genetic and Epigenetic Determinants

Genetic susceptibility plays a significant role in determining individual risk and disease severity in periodontitis. Polymorphisms in genes encoding inflammatory mediators, such as interleukin-1, tumor necrosis factor-α, and Fc-gamma receptors, have been associated with exaggerated inflammatory responses and accelerated periodontal tissue destruction (14). Beyond genetic variation, emerging evidence suggests that epigenetic mechanisms, including DNA methylation and histone modification, may influence host immune responses to dysbiotic biofilms. These mechanisms provide a potential explanation for inter-individual variability in disease expression among patients with similar microbial exposure and environmental risk factors (15).

2.3 Environmental and Lifestyle Factors

One of the biggest modifiable causes for dental disease is smoking. It alters immune function, reduces vascularity, and impairs healing. Other contributing factors include poor oral hygiene, stress, nutritional deficiencies, and socioeconomic status (16).

3. Pathogenesis of Periodontal Disease

Microbial assault and host the immune system's reaction interact intricately in the pathophysiology of periodontal disease. Although the illness process is started by bacteria, the host inflammation plays a major role in tissue loss (17).

3.1 Microbial Dysbiosis and Keystone Pathogens

The initiation of periodontal disease is closely linked to a shift from a symbiotic oral microbiome to a dysbiotic biofilm dominated by keystone pathogens. *Porphyromonas gingivalis* plays a central role by subverting host immune responses and altering the microbial community structure, enabling persistence of inflammation without effective bacterial clearance (18). The major periodontal pathogens and the specific pathogenic role in disease initiation and progression are summarized in **Table 1**. This dysbiotic environment sustains chronic immune activation and tissue damage rather than acute infection resolution (19).

Table 1: Major Periodontal Pathogens and Their Pathogenic Roles

Pathogen	Classification	Key Virulence Factors	Role in Periodontal Pathogenesis
Porphyromonas gingivalis	Gram-negative anaerobe	Gingipains, LPS, PAD enzyme	Immune subversion, dysbiosis initiation, systemic inflammation
Tannerella forsythia	Gram-negative anaerobe	Proteases, BspA protein	Tissue invasion and chronic inflammation
Treponema denticola	Spirochete	Dentilisin, motility	Connective tissue degradation
Aggregatibacter actinomycetemcomitans	Gram-negative facultative	Leukotoxin, CDT	Aggressive periodontitis, immune evasion

3.1.1 Role of the Commensal Oral Microbiome

While keystone pathogens play a critical role in periodontal dysbiosis, the broader oral microbiome significantly influences disease initiation and progression. Health-associated commensal species contribute to immune tolerance and microbial homeostasis, whereas loss of microbial diversity predisposes the host to inflammatory breakdown (20). Periodontitis therefore reflects a community-wide ecological shift rather than the overgrowth of a single pathogen. This polymicrobial synergy underscores the importance of therapeutic strategies aimed at restoring microbial balance rather than indiscriminate antimicrobial suppression (17).

3.2 Innate Immune Response

The innate immune system constitutes the first defensive barrier against periodontal pathogens, primarily mediated by neutrophils, macrophages, and dendritic cells. Although neutrophils are essential for microbial control, dysregulated neutrophil activity leads to excessive release of reactive oxygen species and proteolytic enzymes, contributing to collateral periodontal tissue destruction (21).

3.3 Adaptive Immune Response

Persistent antigenic stimulation activates the adaptive immune response, characterized by infiltration of T and B lymphocytes. Th1 and Th17 cells promote sustained production of pro-inflammatory cytokines such as interleukin-1β and tumor necrosis factor-α, which stimulate osteoclast differentiation and connective tissue degradation. Failure of immune resolution mechanisms perpetuates chronic inflammation (22).

Innate immune responses dominated by neutrophils represent the first line of defense against periodontal pathogens; however, functional abnormalities in neutrophil chemotaxis and phagocytosis contribute to collateral tissue damage (14). Chronic antigenic stimulation activates the adaptive immune system, particularly Th1 and Th17 cell subsets, which further amplify inflammation and osteoclastogenesis. The imbalance between pro-inflammatory and pro-resolving mediators prevents resolution of inflammation, establishing periodontitis as a chronic non-resolving inflammatory disease (21).

3.4 Failure of Inflammation Resolution in Periodontitis

Recent advances indicate that periodontitis is not merely a consequence of excessive inflammation but rather a failure of active inflammatory resolution. Specialized pro-resolving mediators, including resolvins, protectins, and lipoxins, play a critical role in terminating inflammatory responses and restoring tissue homeostasis (23). In periodontal disease, impaired production or function of these mediators results in persistent neutrophil recruitment, prolonged cytokine release, and continued osteoclast activation. This concept reframes periodontitis as a chronic non-resolving inflammatory disease rather than a classical infection-driven condition, providing a mechanistic rationale for host modulation therapies aimed at restoring resolution pathways rather than suppressing immunity outright (24),

4. Classification and Staging of Periodontal Diseases

The classification of periodontal diseases has undergone substantial evolution over the past decades, reflecting advances in the understanding of disease pathogenesis, progression patterns, and patient-specific risk factors (25). Earlier classification systems, including the 1999 Armitage classification, primarily relied on clinical presentation and disease extent but were limited in their ability to capture disease complexity and future risk (26). To address these shortcomings, the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions introduced a unified framework that emphasizes disease severity, complexity of management, and biological risk (27).

The contemporary classification system conceptualizes periodontal diseases as a continuum

rather than distinct entities, integrating gingival health, gingivitis, and periodontitis within a single diagnostic spectrum (28). This approach recognizes that disease expression is influenced not only by microbial burden but also by host susceptibility, environmental exposures, and systemic conditions. By incorporating staging and grading, the system provides a structured and clinically relevant method for diagnosis, prognosis, and individualized treatment planning (25).

4.1 Gingivitis

Gingivitis is defined as a reversible inflammatory condition confined to the gingival tissues without evidence of clinical attachment loss or alveolar bone destruction. It is most commonly induced by dental plaque accumulation and is characterized clinically by erythema, edema, bleeding on probing, and changes in gingival contour (29). Importantly, gingivitis may occur on an intact periodontium or on a reduced but stable periodontium, highlighting the need for careful clinical assessment (30).

Although gingivitis does not result in permanent tissue damage, it represents a critical precursor to periodontitis in susceptible individuals (31). Longitudinal studies demonstrate that untreated gingival inflammation can progress to irreversible periodontal breakdown when host immune dysregulation and persistent microbial dysbiosis are present. Consequently, early identification and management of gingivitis are central to preventive periodontal care (14).

4.2 Periodontitis

Periodontitis is defined as a chronic, multifactorial inflammatory disease associated with dysbiotic plaque biofilms and characterized by progressive destruction of the tooth-supporting apparatus (32). The diagnosis of periodontitis is based on the presence of interdental clinical attachment loss at two or more non-adjacent teeth, or buccal or oral attachment loss with pocketing greater than 3 mm, in the absence of non-periodontal causes (33).

The staging component of the classification system reflects the severity and extent of tissue destruction as well as the complexity of disease management. Stage I represents initial periodontitis with mild attachment loss, whereas Stage II denotes moderate disease with increased probing depths and bone loss (34). Stages III and IV correspond to severe and advanced periodontitis, respectively, characterized by extensive attachment loss, vertical bone defects, tooth mobility, occlusal dysfunction, and potential tooth loss. This stratification assists clinicians in selecting appropriate therapeutic strategies and anticipating treatment challenges (35).

Grading complements staging by estimating the rate of disease progression and assessing the impact of systemic and behavioral risk factors. Grade A indicates slow progression, Grade B reflects moderate progression, and Grade C denotes rapid disease progression, often associated with smoking, poorly controlled diabetes, or pronounced inflammatory burden (36). This dynamic component acknowledges that patients with similar clinical presentations may exhibit markedly different biological behavior and long-term outcomes (37).

4.3 Clinical Relevance of the Staging and Grading System

The integration of staging and grading represents a paradigm shift in periodontal diagnosis by moving beyond descriptive assessment toward a risk-based and personalized model of care (38). This framework facilitates improved communication among clinicians, enhances prognostic accuracy, and supports shared decision-making with patients. Furthermore, it aligns periodontal diagnosis with broader medical classification systems that incorporate disease severity and progression risk (39).

From a research perspective, the standardized classification enables more consistent patient stratification in epidemiological and clinical studies, improving comparability across investigations (40). Despite these advantages, challenges remain regarding implementation in routine practice, particularly in relation to clinician training and integration with biomarker-based diagnostics. Ongoing refinement and validation of the classification system are therefore essential to fully realize its potential in both clinical and public health settings (41).

5. Global Burden and Epidemiology

A large percentage of people worldwide suffer from periodontal disease, which is a leading cause of oral impairment. Epidemiological studies indicate wide variations in prevalence influenced by age, geographic region, and socioeconomic factors (42).

The worldwide load of periodontal illness extends beyond oral health, contributing to healthcare expenses and a lower standard of living. From a public health perspective, More and more people believe that periodontal disease is a preventable risk factor for the development of chronic illnesses and systemic inflammation (43).

6. Diagnostic Approaches in Periodontology

Traditionally, radiographic and clinical evaluations have been used to diagnose periodontal disease (44).

6.1 Clinical Diagnostic Parameters

Clinical periodontal examination remains the foundation of diagnosis and includes assessment of

probing pocket depth, clinical attachment level, bleeding on probing, and plaque indices. These parameters provide valuable information regarding disease severity and extent; however, they primarily reflect past tissue destruction rather than current disease activity (45).

6.2 Radiographic Assessment

Radiographic imaging is used to evaluate alveolar bone loss and periodontal architecture. Conventional radiographs detect bone loss only after significant mineral depletion has occurred, limiting sensitivity for early disease detection. The types of radiographs with their properties are mentioned in **Table 2** Advanced imaging techniques offer improved visualization but are not routinely used due to cost and radiation considerations (46).

Table 2: Types of Radiographs with their Parameters, Coverage area and Diagnostic application

S. No.	Radiograph Types	Parameters	Area Of Coverage	Primary Diagnostic Application
1.	Horizontal bitewings radiograph	• Use for caries detection. • Alveolar crest can be visualized. • Provides good quality of image for bone loss.	Crowns of maxillary and mandibular posterior teeth and the interproximal contact areas with minimal visualization of alveolar bone.	Primarily used for detection of interproximal caries, evaluation of existing restorations, and assessment of marginal integrity of fillings and crowns.
2.	Panoramic radiograph	• All teeth seen in one image or film. • Newer machine generated for good quality of images. • Details are much fine as compared to intraoral radiographs.	Entire maxilla and mandible, including all the teeth, alveolar bone, temporomandibular joints, maxillary sinuses, and surrounding anatomical structures.	Used for overall assessment of dentition, detection of impacted pr unerupted teeth, evaluation of jaw fractures, cysts and tumours, developmental anomalies, and assessment of temporomandibular joint conditions.
3.	Periapical radiograph	• Long cone parallel technique. • Good clarity of images as compared to horizontal radiograph. • Times consuming process.	Entire tooth from crown to root apex along with the surrounding periapical bone and periodontal ligament space.	Used for detection of periapical pathology, assessment of root morphology, evaluation of endodontic treatment, and diagnosis pf apical infections, abscesses, or cystic lesions.
4.	Vertical bitewing radiograph	• Shows 90◦ angle bitewing film image. • Better quality of image for extensive bone loss.	Crowns and maxillary and mandibular posterior teeth along with a larger portion of the supporting alveolar bone.	Primarily indicated for evaluation of periodontal bone loss and assessment of the level of alveolar bone in the patients with moderate to severe periodontal disease.

6.3 Emerging Diagnostic Strategies

The limitations of conventional diagnostics have driven interest in biologically active diagnostic tools, including salivary and gingival crevicular fluid analysis. These approaches aim to identify active inflammation and predict disease progression, thereby supporting personalized periodontal care (47).

Despite their widespread use, traditional diagnostic parameters have inherent limitations, as they do not adequately reflect current disease activity or predict future progression. Radiographic techniques detect

alveolar bone loss only after significant mineral loss has occurred, limiting their utility for early diagnosis (48). These limitations have driven interest in adjunctive diagnostic approaches that incorporate biological markers capable of identifying active disease and individual (49).

Recent advances in point-of-care diagnostic technologies have enabled the development of chairside tests capable of detecting periodontal biomarkers such as active matrix metalloproteinase-8 and inflammatory cytokines in saliva and gingival crevicular fluid (50). These rapid assays offer real-time assessment of disease activity and treatment response, overcoming the retrospective limitations of traditional clinical parameters. Although promising, widespread clinical adoption remains limited due to variability in biomarker thresholds and the need for large-scale validation studies (51).

7. Biomarkers in Periodontal Disease

Biomarkers offer promising opportunities for early diagnosis, disease monitoring, and risk prediction in periodontal disease (47).

7.1 Inflammatory Biomarkers

Inflammatory biomarkers reflect active periodontal tissue breakdown and host immune response. Elevated levels of interleukin-1β, interleukin-6, tumor necrosis factor-α, and C-reactive protein have been consistently associated with periodontal disease severity and progression. These markers are detectable in saliva, gingival crevicular fluid, and serum, offering non-invasive diagnostic potential (26, 47).

7.2 Biomarkers of Connective Tissue Degradation

Matrix metalloproteinases, particularly MMP-8 and MMP-9, are key enzymes involved in collagen degradation within periodontal tissues. Increased MMP activity correlates with active periodontal destruction and may serve as an indicator of disease activity and treatment response (52).

7.3 Bone Metabolism Biomarkers

Bone turnover biomarkers such as RANKL, osteoprotegerin, alkaline phosphatase, and osteocalcin provide insight into alveolar bone resorption and formation. An increased RANKL/OPG ratio is strongly associated with enhanced osteoclastic activity and periodontal bone loss (53).

In addition to inflammatory markers, biomarkers of connective tissue degradation and bone turnover provide insight into disease progression. Elevated levels of matrix metalloproteinases, particularly MMP-8 and MMP-9, reflect collagen breakdown, while increased RANKL/OPG ratios indicate enhanced osteoclastic activity and bone resorption. Integration of biomarker profiling with clinical parameters represents a promising step toward personalized periodontal care (54).

8. Periodontal Disease and Systemic Health

Chronic periodontal inflammation has been connected to several systemic illnesses and adds to the systemic inflammatory burden.

Table 3: Bidirectional Mechanisms Linking Periodontal Disease and Systemic Conditions

Systemic condition	Periodontal contribution	Systemic feedback on periodontium	Key references
Diabetes mellitus	Cytokine-mediated insulin resistance	Hyperglycemia amplifies inflammation	Genoc et al., 2000; Chapple & Genco, 2013
Cardiovascular disease	Endotoxemia, endothelial dysfunction	Vascular inflammation worsens healing	Lockhart et al., 2012; Tonetti &Van Dyke, 2013
Rheumatoid arthritis	Citrullination by P. gingivalis	Autoimmune inflammation	Bartold et al., 2010; Potempa et al., 2017
Obesity	Adipokine-driven inflammation	Impaired immune response	Preshaw et al., Linden et al., 2013

8.1 Cardiovascular diseases

Periodontal disease has been consistently associated with an increased risk of atherosclerotic cardiovascular diseases, including coronary artery disease, myocardial infarction, and stroke. The proposed mechanisms include systemic dissemination of periodontal pathogens, particularly *Porphyromonas gingivalis*, and their virulence factors such as lipopolysaccharides, which promote endothelial dysfunction and atheroma formation(19). Additionally, periodontitis contributes to elevated systemic inflammatory markers such as C-reactive protein, interleukin-6, and tumor necrosis factor-α, all of which play established roles in cardiovascular pathology. Clinical and epidemiological studies suggest that periodontal therapy can lead to modest improvements in endothelial function and systemic inflammatory burden, supporting a causal biological link (55).

8.2 Diabetes Mellitus

Diabetes mellitus and periodontitis exhibit a well-established bidirectional relationship. Chronic hyperglycemia enhances periodontal tissue destruction by impairing neutrophil function,

increasing oxidative stress, and promoting the accumulation of advanced glycation end products that amplify inflammatory responses (56). Conversely, periodontal inflammation exacerbates insulin resistance through systemic dissemination of pro-inflammatory cytokines, thereby worsening glycemic control. Meta-analyses of interventional studies demonstrate that non-surgical periodontal therapy can result in significant reductions in glycated hemoglobin levels, underscoring the clinical relevance of periodontal management in diabetic patients (57).

8.3 Obesity and Metabolic Syndrome

Obesity is recognized as an independent risk factor for periodontal disease due to its association with a chronic low-grade inflammatory state. Adipose tissue functions as an active endocrine organ, releasing adipokines such as leptin, resistin, and adiponectin, which modulate immune and inflammatory responses (58). Elevated levels of pro-inflammatory adipokines in obese individuals may intensify periodontal tissue breakdown and impair healing responses. The coexistence of obesity, insulin resistance, dyslipidemia, and hypertension in metabolic syndrome further amplifies periodontal susceptibility and disease severity (59).

8.4 Respiratory Diseases

Periodontal disease has been implicated in the pathogenesis of respiratory conditions, including chronic obstructive pulmonary disease and aspiration pneumonia. Oral pathogens residing in periodontal pockets may be aspirated into the lower respiratory tract, particularly in hospitalized or elderly individuals, leading to pulmonary infections (60). Inflammatory mediators originating from periodontal tissues may also alter respiratory epithelium integrity, increasing susceptibility to infection. Improved oral hygiene and periodontal care have been shown to reduce the incidence of ventilator-associated and nosocomial pneumonia (61).

8.5 Rheumatoid Arthritis

Rheumatoid arthritis and periodontitis share common pathogenic mechanisms, including dysregulated immune responses and excessive production of pro-inflammatory cytokines. *Porphyromonas gingivalis* is unique among periodontal pathogens in its ability to express peptidylarginine deiminase, an enzyme that promotes protein citrullination, a key process in the generation of rheumatoid arthritis–associated autoantibodies (62). Clinical studies demonstrate higher prevalence and severity of periodontitis in patients with rheumatoid arthritis, suggesting a biologically plausible and clinically relevant association (63).

8.6 Adverse Pregnancy Outcomes

Maternal periodontal disease has been associated with adverse pregnancy outcomes such as preterm birth, low birth weight, and preeclampsia. Periodontal pathogens and inflammatory mediators may reach the fetal–placental unit via hematogenous spread, triggering inflammatory cascades that interfere with normal fetal development (64). Elevated levels of prostaglandins and cytokines linked to periodontal inflammation have been detected in amniotic fluid and placental tissues, supporting a mechanistic connection (65).

8.7 Neurodegenerative Disorders

Emerging evidence suggests that chronic periodontal inflammation may contribute to neurodegenerative disorders, including Alzheimer's disease. Periodontal pathogens and their toxic products have been identified in brain tissues, where they may induce neuroinflammation and amyloid-beta accumulation (66). Systemic inflammation originating from periodontal disease may also compromise the blood–brain barrier, facilitating microbial and inflammatory insult to neural tissues. Although causality remains under investigation, these findings highlight the potential neurological implications of long-standing periodontal disease (67).

9. Therapeutic Approaches in Periodontal Disease

The main goals of traditional periodontal therapy are infection prevention and mechanical plaque eradication. The pathophysiological pathway of periodontal disease is well explained in **Figure 1**.

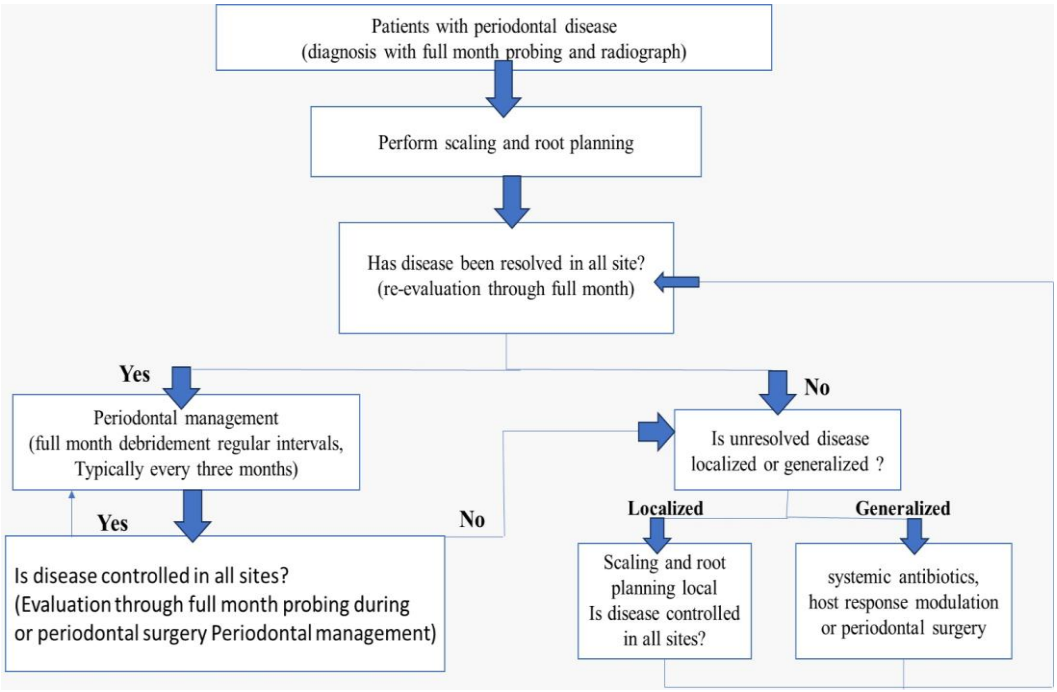

Figure 1: Integrated Pathophysiological Pathway of Periodontal Disease: From Microbial Dysbiosis to Systemic Inflammation

9.1 Non-Surgical Periodontal Therapy

Scaling and root planning remains the cornerstone of periodontal treatment and aims to disrupt subgingival biofilm and reduce microbial load. Clinical studies consistently demonstrate significant reductions in probing depth and inflammation following non-surgical therapy, particularly when combined with effective plaque control and patient compliance (68).

9.2 Surgical Periodontal Therapy

Surgical interventions are indicated in advanced cases to improve access for debridement and to regenerate lost periodontal structures. Techniques such as guided tissue regeneration, bone grafting, and use of biologic modifiers have demonstrated favorable outcomes in selected cases, although results are influenced by patient-related and site-specific factors (69).

9.3 Adjunctive Antimicrobial Therapy

Systemic and local antimicrobial agents may be used as adjuncts in aggressive or refractory periodontitis. While adjunctive antibiotics can enhance short-term clinical outcomes, their use must be carefully controlled to prevent antimicrobial resistance and adverse effects (70).

In cases of advanced periodontal destruction, surgical interventions may be required to gain access to deep periodontal pockets, regenerate lost tissues, and restore functional architecture. Regenerative approaches employing bone grafts, guided tissue regeneration, and biologic modifiers such as enamel matrix derivatives have shown variable but promising outcomes (71). Adjunctive use of systemic or local antimicrobials may be beneficial in selected cases but must be judiciously applied to minimize antimicrobial resistance (72).

10. Emerging Adjunctive Therapies

Adjunctive therapies aim to modulate host response and enhance treatment outcomes.

Table 4: Therapeutic Approaches in Periodontal Disease

Therapy type	Target	Key Benefit	Limitation	Examples/Agents Used
Scaling & Root Planning (SRP)	Subgingival biofilm	Reduces microbial load and inflammation	Does not address host-mediated tissue destruction	Hand instruments, ultrasonic scalers
Surgical Therapy	Periodontal defects	Pocket reduction and regeneration	Technique-sensitive, invasive	Flap surgery, bone grafts, GTR membrane

Antimicrobial Therapy	Periodontal pathogens	Suppresses pathogenic bacteria	Risk of resistance, limited long-term efficacy	Tetracyclines, metronidazole, chlorhexidine
Host Modulation Therapy	Host inflammatory response	Reduces tissue destruction and bone loss	Limited long-term clinical data	Sub-antimicrobial dose doxycycline, NSAIDs
Phytotherapy/Adjunctive Therapy	Inflammatory signaling pathways	Anti-inflammatory and antioxidant effects	Bioavailability and standardization issues	Curcumin, green tea polyphenols, resveratrol

10.1 Host Modulation Therapy

Host modulation therapy is an adjunctive periodontal treatment approach that focuses on modifying the host immune and inflammatory responses responsible for periodontal tissue destruction, rather than directly eliminating microbial biofilm. The biological basis of this strategy lies in evidence demonstrating that an exaggerated and persistent host inflammatory response is the primary mediator of connective tissue breakdown and alveolar bone resorption in periodontitis (73). Among the most extensively studied agents is sub-antimicrobial dose doxycycline, which inhibits matrix metalloproteinases involved in collagen degradation without exerting antibacterial effects, thereby reducing the risk of antimicrobial resistance. Clinical studies have shown that its adjunctive use with scaling and root planning results in significant improvements in clinical attachment levels and probing depth reduction (74). In addition, non-steroidal anti-inflammatory drugs and emerging endogenous pro-resolving lipid mediators, such as resolving and lipoxins, have demonstrated potential in suppressing pro-inflammatory cytokine activity while actively promoting resolution of inflammation and restoration of periodontal tissue homeostasis. Collectively, host modulation therapy represents a scientifically validated and patient-centred approach that complements conventional mechanical therapy by targeting the underlying inflammatory mechanisms of periodontal disease rather than solely focusing on microbial (75).

10.2 Phytotherapeutic Agents: Curcumin

Curcumin, a polyphenolic compound derived from *Curcuma longa*, has gained considerable attention as an adjunctive agent in periodontal therapy due to its anti-inflammatory, antioxidant, and antimicrobial properties (76). Experimental and clinical studies demonstrate that curcumin can inhibit nuclear factor-kappa B signaling, suppress pro-inflammatory cytokine production, and reduce oxidative stress within periodontal tissues. When used as a local delivery agent or systemic supplement alongside scaling and root planing, curcumin has been shown to improve clinical periodontal parameters such as probing depth reduction and clinical attachment gain (77). However, limitations related to poor bioavailability necessitate the development of novel formulations, including nanoparticles and adjuvant carriers, to enhance its therapeutic efficacy (78).

11. Limitations and Research Gaps

11.1 Diagnostic and Methodological Limitations

Variability in diagnostic criteria, study design, and outcome measures remains a major challenge in periodontal research. The lack of standardised thresholds for biomarker-based diagnosis limits their translation into routine clinical practice (79).

11.2 Therapeutic Evidence Gaps

Although adjunctive and host-modulatory therapies show promise, high-quality long-term randomized controlled trials are limited. Inconsistent reporting of clinical endpoints further complicates evidence synthesis and guideline development (80).

11.3 Future Research Directions

Future research should focus on longitudinal cohort studies, validation of diagnostic biomarkers, and integration of periodontal care within systemic disease management frameworks. Interdisciplinary collaboration between dental and medical professionals is essential to fully elucidate the systemic impact of periodontal disease (26).

12. Future Perspectives

The future of periodontal care is moving toward precision and personalized medicine, emphasizing early diagnosis, risk stratification, and targeted therapeutic interventions. Advances in biomarker discovery, digital diagnostics, and artificial intelligence-driven risk assessment tools hold promise for identifying susceptible individuals before irreversible tissue destruction occurs (81). Integration of periodontal care with medical management of systemic diseases such as diabetes and cardiovascular disorders is expected to enhance patient outcomes through coordinated, multidisciplinary approaches (82). Additionally, emerging host-modulatory and regenerative therapies may shift the focus from disease control to true periodontal tissue regeneration. Continued

investment in translational research and public health initiatives will be critical for reducing the global burden of periodontal disease (83). A structured comparison of historical perspectives and recent advances in periodontal disease is provided in **Table.5**, emphasizing clinical implications and areas requiring further investigation.

Table 5: Evaluation of Conceptual Understanding of Periodontal Disease Across Key Disease Dimensions

Disease dimension	Conventional understanding	Emerging insight (Novel contribution)	Clinical implication	Research gaps/ future directions
Etiology	Plaque-induced infection	Dysbiosis with keystone pathogen dominance	Encourages personalized prevention strategies	Need for longitudinal microbiome studies
Pathogenesis	Local tissue inflammation	Non-resolving inflammation with systemic spillover	Supports targeted anti-inflammatory therapy	Identification of reliable molecule biomarkers
Diagnosis	CAL, PPD, radiographs	Biomarker-based activity assessment	Earlier disease detection possible	Validation of chairside diagnostic tools
Systemic link	Association-based	Shared inflammatory and immune pathways	Multidisciplinary management required	Mechanistic studies on oral-systemic axis
Therapy	Mechanical plaque control	Host modulation + phytotherapy	Improved treatment outcomes	Long-term clinical trials needed
Prognosis	Tooth survival	Systemic health impact	Better patients' stratification	Development of predictive models

12.1 Clinical Implication

The expanding understanding of periodontal disease as a systemic inflammatory condition has important clinical implications. Periodontal assessment should be integrated into routine medical evaluations for patients with diabetes, cardiovascular disease, and autoimmune disorders (84). Early diagnosis, risk stratification, and host-modulatory interventions may not only preserve periodontal health but also contribute to improved systemic outcomes. This integrated care model reinforces the need for closer collaboration between dental and medical professionals in managing chronic inflammatory diseases (85).

13. CONCLUSION

Periodontal disease is a complex, chronic inflammatory condition characterized by dysbiotic microbial communities and an exaggerated host immune response, resulting in progressive destruction of the tooth-supporting tissues. The expanded evidence presented in this review highlights that periodontitis should no longer be regarded as an isolated oral disease but rather as a condition with significant systemic implications, sharing common inflammatory pathways with metabolic, cardiovascular, autoimmune, and neurodegenerative disorders. Advances in classification systems, diagnostic strategies, and biomarker research have improved disease characterization and risk assessment, while emerging adjunctive and host-modulatory therapies offer promising avenues for enhancing treatment outcomes. Despite these advances, substantial research gaps remain, particularly in biomarker validation and long-term therapeutic efficacy. A comprehensive, interdisciplinary, and personalized approach that integrates preventive care, early diagnosis, and targeted therapy is essential for improving periodontal and overall health outcomes. Continued collaboration between dental and medical disciplines will be pivotal in addressing the growing global burden of periodontal disease

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