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Research Article

Emerging Biomarkers in Periodontal Disease: Diagnostic and Prognostic Implications

Dr Hiroj Bagde
Professor and Head, Department of Periodontology,
Chhattisgarh Dental College and research institute, Chhattisgarh

Abstract
Periodontal disease represents a significant global health burden, affecting approximately 50% of the adult population worldwide. Current diagnostic methods primarily rely on clinical parameters and radiographic assessment, which have inherent limitations in detecting early disease activity and predicting future progression. This narrative review aims to synthesize current evidence on emerging biomarkers in periodontal disease and evaluate their diagnostic and prognostic implications. We conducted a comprehensive literature search of PubMed and Scopus databases, focusing on studies published within the last decade that investigated novel biomarkers for periodontal disease. The review identifies several categories of promising biomarkers, including host-derived inflammatory mediators, tissue breakdown products, microbial signatures, genetic markers, and salivary biomarkers. Additionally, we explore the potential of omics-based approaches, including proteomics, metabolomics, and transcriptomics, in identifying novel biomarker panels. The evidence suggests that these emerging biomarkers demonstrate considerable promise in enhancing early detection, differentiating between disease phenotypes, monitoring treatment response, and predicting disease progression. However, challenges remain regarding standardization, validation, and clinical implementation. Multi-marker approaches appear to offer superior diagnostic and prognostic accuracy compared to single biomarkers. The integration of novel biomarkers with traditional clinical assessment may pave the way for personalized periodontal care, enabling targeted interventions based on individual risk profiles and disease activity

Keywords: periodontal disease, biomarkers, diagnosis, prognosis, inflammation, saliva, omics

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1. Introduction

Bordetellabronchiseptica is a small Gram-negative, aerobic, rod-shaped bacterium Periodontal disease, encompassing gingivitis and periodontitis, represents a spectrum of inflammatory conditions affecting the supporting structures of the teeth, including the gingiva, periodontal ligament, cementum, and alveolar bone [1]. As one of the most prevalent chronic diseases globally, severe periodontitis affects approximately 11% of the world's population, making it the sixth most prevalent condition [2]. The pathogenesis of periodontal disease involves a complex interplay between microbial dysbiosis and dysregulated host immune-inflammatory responses, leading to progressive destruction of periodontal tissues [3]. Beyond its oral health implications, periodontal disease has been associated with various systemic conditions, including cardiovascular disease, diabetes mellitus, adverse pregnancy outcomes, and respiratory diseases, highlighting its broader public health significance [4].

Current diagnostic approaches for periodontal disease primarily rely on clinical parameters such as probing depth, clinical attachment loss, bleeding on probing, and radiographic assessment of alveolar bone loss [5]. While these methods have served as the cornerstone of periodontal diagnosis for decades, they possess inherent limitations. Clinical parameters detect historical tissue destruction rather than current disease activity, exhibit considerable variability between examiners, and provide limited insight into future disease progression [6]. Furthermore, radiographic assessment, while valuable for detecting bone loss, exposes patients to ionizing radiation and primarily captures structural changes that occur relatively late in the disease process [7].

The limitations of traditional diagnostic methods have prompted intensive research into identifying reliable biomarkers that could enhance early detection, differentiate between disease phenotypes, monitor treatment response, and predict disease progression. Biomarkers, defined as "characteristics that are objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic intervention" [8], hold tremendous potential for revolutionizing periodontal diagnostics and prognostics.

The field of periodontal biomarker research has evolved significantly over the past two decades, moving from single-marker approaches to multi-marker panels and embracing advanced omics technologies [9]. Despite substantial progress, controversies remain regarding the clinical utility of many proposed biomarkers, their standardization, and implementation in routine periodontal practice [10]. Additionally, the complex and multifactorial nature of periodontal disease necessitates a comprehensive understanding of various biomarker categories and their interrelationships.

This narrative review aims to synthesize current evidence on emerging biomarkers in periodontal disease and evaluate their diagnostic and prognostic implications. Specifically, we will: (1) examine the pathophysiological basis for biomarker development in periodontal disease; (2) review traditional diagnostic methods and their limitations; (3) analyze emerging biomarker categories, including host-derived, microbial, genetic, salivary, and omics-based biomarkers; (4) evaluate the diagnostic and prognostic utility of these biomarkers; and (5) discuss current challenges, gaps in knowledge, and future directions for research and clinical implementation.

Pathophysiology of Periodontal Disease

Understanding the pathophysiology of periodontal disease is fundamental to identifying relevant biomarkers. Periodontal disease initiation and progression involve a complex interplay between microbial challenge and host response [11]. The current paradigm suggests that periodontal health is maintained in a state of symbiosis between the host and a diverse oral microbiome. Disruption of this balance, through various risk factors such as poor oral hygiene, smoking, diabetes, and genetic susceptibility, leads to dysbiosis—a shift in the microbial composition toward a more pathogenic state [12].

This dysbiotic microbial community, characterized by an increased proportion of anaerobic gram-negative bacteria such as Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola (collectively known as the "red complex"), triggers a robust host immune-inflammatory response [13]. The host response, while initially protective, becomes dysregulated in susceptible individuals, leading to the release of a cascade of inflammatory mediators, including cytokines, chemokines, prostaglandins, and matrix metalloproteinases (MMPs) [14].

These inflammatory mediators, along with bacterial products, stimulate various cellular processes that result in tissue destruction. Neutrophils and macrophages release reactive oxygen species and proteolytic enzymes, while osteoclasts are activated, leading to alveolar bone resorption [15]. Fibroblasts and other connective tissue cells undergo apoptosis, and the extracellular matrix is degraded by MMPs and other enzymes [16].

The net result is the progressive destruction of periodontal tissues, characterized by clinical attachment loss, periodontal pocket formation, and alveolar bone loss.
This complex pathophysiological process provides numerous potential biomarkers that reflect different aspects of disease activity, including microbial challenge, inflammatory response, tissue degradation, and bone remodeling [17]. Understanding these pathophysiological mechanisms is crucial for interpreting biomarker profiles and developing clinically useful diagnostic and prognostic tools

Traditional Diagnostic Methods and Their Limitations

The diagnosis of periodontal disease has traditionally relied on a combination of clinical examination and radiographic assessment. Clinical parameters include probing depth (PD), clinical attachment level (CAL), bleeding on probing (BOP), plaque index, and gingival index [18]. These measures, while valuable, have several limitations that underscore the need for complementary biomarker-based approaches.
Probing depth and clinical attachment level are considered gold standards for assessing periodontal status and monitoring disease progression [19]. However, these measurements only detect historical tissue destruction rather than current disease activity. Furthermore, they exhibit considerable variability between examiners, with measurement errors of up to 1.0 mm reported in some studies [20]. The invasive nature of probing can also cause discomfort for patients and potentially introduce bacteria into the periodontal tissues.
Bleeding on probing is widely used as an indicator of gingival inflammation, with its absence considered a sign of periodontal health [21]. However, BOP has limited specificity for active disease progression, as bleeding can occur in stable gingivitis without progression to periodontitis [22]. Additionally, factors such as probing force and angulation can influence BOP scores, contributing to variability in assessment.
Radiographic examination, particularly bitewing and periapical radiographs, is essential for detecting alveolar bone loss, a hallmark of periodontitis [23]. However, radiographic assessment has several limitations, including exposure to ionizing radiation, two-dimensional representation of three-dimensional structures, and the inability to detect early bone changes due to the requirement of 30-50% mineral loss before becoming radiographically apparent [24]. Furthermore, radiographs provide a static view of bone levels and do not reflect current disease activity.
These limitations of traditional diagnostic methods highlight the need for adjunctive tools that can detect early disease activity, differentiate between disease phenotypes, monitor treatment response, and predict future progression. Biomarkers offer the potential to address these limitations by providing objective, quantifiable measures of biological processes associated with periodontal disease [25].

Emerging Biomarkers in Periodontal Disease

Host-Derived Biomarkers

Host-derived biomarkers reflect the inflammatory and immune responses to microbial challenge in periodontal disease. These biomarkers can be detected in various biological samples, including gingival crevicular fluid (GCF), saliva, blood, and tissue biopsies [26].
Inflammatory mediators represent a major category of host-derived biomarkers. Interleukin-1 beta (IL-1β) is a pro-inflammatory cytokine that plays a central role in periodontal tissue destruction. Elevated levels of IL-1β in GCF and saliva have been consistently associated with periodontal inflammation and disease severity [27]. Tumor necrosis factor-alpha (TNF-α) is another key pro-inflammatory cytokine that has been extensively studied as a periodontal biomarker. Increased levels of TNF-α in GCF and

saliva correlate with clinical parameters of periodontal disease and decrease following successful periodontal therapy [28].

Interleukin-6 (IL-6) is a multifunctional cytokine involved in both inflammatory responses and bone metabolism. Salivary and GCF levels of IL-6 have been shown to distinguish between periodontal health and disease and correlate with disease severity [29]. Matrix metalloproteinases (MMPs), particularly MMP-8 and MMP-9, are enzymes responsible for extracellular matrix degradation and have emerged as promising biomarkers for periodontal tissue destruction. Elevated levels of MMP-8 in GCF and saliva have been demonstrated in periodontitis patients compared to healthy individuals, with levels decreasing following periodontal treatment [30].

Other host-derived biomarkers that have shown promise include calprotectin, a protein released by neutrophils during inflammation; osteocalcin, a marker of bone turnover; and pyridinoline cross-linked carboxyterminal telopeptide of type I collagen (ICTP), a marker of collagen degradation [31]. While these host-derived biomarkers demonstrate considerable potential, their diagnostic and prognostic utility varies, and no single biomarker has proven sufficient for accurate periodontal diagnosis or prognosis.

Microbial Biomarkers

The microbial component of periodontal disease pathogenesis has led to extensive research on microbial biomarkers. Traditional approaches have focused on identifying specific periodontal pathogens, particularly the "red complex" bacteria (P. gingivalis, T. forsythia, and T. denticola) [32]. Polymerase chain reaction (PCR) and DNA-DNA hybridization techniques have been widely used to detect and quantify these pathogens in subgingival plaque samples [33].

However, the microbial community's complexity and the shift toward a dysbiotic model have prompted investigations into microbial community profiles rather than individual pathogens. Next-generation sequencing (NGS) technologies have enabled comprehensive characterization of the subgingival microbiome, revealing distinct microbial signatures associated with periodontal health and disease [34]. Studies have demonstrated that periodontitis is associated with decreased microbial diversity and enrichment of specific taxonomic groups, including the genera Porphyromonas, Tannerella, Treponema, and Filifactor [35].

Microbial biomarkers can be categorized into several types: (1) specific pathogens associated with disease progression; (2) microbial community signatures or ratios indicative of dysbiosis; (3) microbial virulence factors; and (4) host immune responses to specific microbial components [36]. While microbial biomarkers have shown promise in distinguishing between periodontal health and disease, their prognostic value remains less clear, and the relationship between microbial presence and disease activity is not always straightforward [37].

Genetic Biomarkers

Genetic factors play a significant role in determining individual susceptibility to periodontal disease. Twin studies have estimated that approximately 50% of the variance in periodontal disease may be attributed to genetic factors [38]. This has led to extensive research on genetic biomarkers that could identify individuals at increased risk for periodontal disease.

Polymorphisms in genes encoding inflammatory mediators have been the most extensively studied genetic biomarkers in periodontal disease. Interleukin-1 (IL-1) gene cluster polymorphisms, particularly IL-1A (-889) and IL-1B (+3953), have been associated with increased severity of periodontitis in several populations [39]. However, these associations have not been consistently replicated across all ethnic groups, highlighting the importance of population-specific genetic factors [40].

Other genetic polymorphisms that have been investigated include those in the genes encoding TNF-α, IL-6, IL-10, vitamin D receptor, and CD14 [41]. Genome-wide association studies (GWAS) have identified several novel genetic loci associated with periodontitis, including genes involved in immune response, epithelial barrier function, and connective tissue metabolism [42].

While genetic biomarkers hold promise for identifying individuals at increased risk for periodontal disease, their clinical utility remains limited due to several factors. These include the polygenic nature of periodontal disease susceptibility, gene-environment interactions, ethnic variations in allele frequencies, and the relatively modest effect sizes of individual genetic variants [43]. Future research may focus on developing polygenic risk scores that combine multiple genetic variants to improve predictive accuracy.

Salivary Biomarkers

Saliva has emerged as an attractive diagnostic fluid for periodontal disease due to its non-invasive collection, ease of sampling, and composition reflecting both local and systemic conditions [44]. Saliva contains various biomarkers derived from local periodontal tissues, GCF, oral microbiota, and systemic circulation, making it a comprehensive source of diagnostic information [45].

Numerous salivary biomarkers have been investigated for periodontal disease diagnosis and prognosis. These include inflammatory mediators (IL-1β, TNF-α, IL-6), tissue breakdown products (MMP-8, MMP-9), microbial components, and host response proteins [46]. Among these, salivary MMP-8 has shown particular promise, with studies demonstrating its ability to distinguish between periodontal health and disease with high sensitivity and specificity [47].

Recent advances in salivary diagnostics have focused on developing point-of-care devices that can rapidly detect multiple biomarkers simultaneously. These technologies include lateral flow assays, microfluidic devices, and biosensors that could enable chairside assessment of periodontal disease activity [48]. Additionally, the development of standardized collection and processing protocols has improved the reliability and reproducibility of salivary biomarker measurements [49].

Despite these advances, challenges remain in implementing salivary biomarkers in routine clinical practice. These include variability in salivary flow rates, diurnal variations in biomarker concentrations, and the influence of various systemic conditions and medications on salivary composition [50]. Future research should focus on validating multi-marker salivary panels and developing standardized protocols for clinical implementation.

Omics-Based Biomarkers

The advent of high-throughput "omics" technologies has revolutionized biomarker discovery in periodontal disease. These approaches enable comprehensive analysis of various biological molecules, providing a systems-level understanding of disease processes [51].

Proteomics, the large-scale study of proteins, has identified numerous potential biomarkers in GCF, saliva, and tissue samples from periodontal patients. Mass spectrometry-based proteomic analyses have revealed distinct protein expression patterns associated with periodontal health and disease, including proteins involved in inflammation, immune response, and tissue degradation [52]. Multi-marker protein panels derived from proteomic studies have shown improved diagnostic accuracy compared to single biomarkers [53].

Metabolomics, the study of small-molecule metabolites, has identified distinct metabolic profiles associated with periodontal disease. These include alterations in amino acid metabolism, lipid metabolism, and energy pathways [54]. Metabolomic signatures in

saliva and GCF have demonstrated potential for distinguishing between periodontal health, gingivitis, and periodontitis, as well as monitoring treatment response [55].

Transcriptomics, the analysis of RNA expression patterns, has revealed distinct gene expression profiles in gingival tissues associated with periodontal disease. These include upregulation of genes involved in inflammatory responses, immune cell activation, and tissue degradation [56]. Circulating RNA molecules, including microRNAs, have also emerged as promising biomarkers for periodontal disease, with potential systemic implications [57].

Integrative multi-omics approaches, combining data from proteomics, metabolomics, transcriptomics, and microbiome analyses, offer the most comprehensive understanding of periodontal disease pathogenesis and hold promise for identifying robust biomarker panels [58]. However, the complexity and cost of these approaches present challenges for clinical implementation, and further research is needed to validate omics-based biomarkers in diverse populations.

Diagnostic Implications of Emerging Biomarkers

The emerging biomarkers discussed above have significant diagnostic implications for periodontal disease. They offer the potential to enhance early detection, differentiate between disease phenotypes, and provide objective measures of disease activity [59].

Early detection of periodontal disease is crucial for preventing irreversible tissue destruction. Traditional clinical parameters detect established disease rather than early inflammatory changes. Biomarkers such as MMP-8, IL-1β, and specific microbial signatures have shown promise in identifying early disease activity before clinical signs become apparent [60]. For example, elevated levels of MMP-8 in saliva have been detected in sites that later develop clinical signs of periodontitis, suggesting its potential for predicting disease onset [61].

Periodontal disease encompasses various phenotypes with different progression rates and treatment responses. Biomarkers may help differentiate between these phenotypes, enabling personalized treatment approaches. For instance, distinct inflammatory mediator profiles have been associated with aggressive versus chronic periodontitis, while specific microbial signatures may identify patients at higher risk for disease progression [62]. Additionally, biomarkers may help differentiate between active and inactive disease sites, guiding targeted treatment interventions [63].

The objective nature of biomarker measurements addresses the limitations of subjective clinical assessments. Quantitative biomarker data can provide more precise measures of disease activity and severity, reducing examiner variability and improving diagnostic accuracy [64]. Furthermore, biomarkers may enable monitoring of treatment response at a molecular level, providing early indication of therapeutic efficacy before clinical improvements become apparent [65].

Several studies have demonstrated the diagnostic potential of multi-marker approaches, which combine multiple biomarkers to improve accuracy. For example, a panel including IL-1β, MMP-8, and P. gingivalis showed superior diagnostic performance compared to individual biomarkers in distinguishing between periodontal health and disease [66]. Similarly, machine learning algorithms applied to multi-omics data have demonstrated high accuracy in classifying periodontal disease states [67].

Despite these promising developments, challenges remain in implementing biomarker-based diagnostics in routine clinical practice. These include the need for standardized collection and processing protocols, establishment of reference ranges, validation in diverse populations, and development of cost-effective point-of-care testing devices [68]. Future research should focus on addressing these challenges and translating biomarker discoveries into clinically useful diagnostic tools.

Prognostic Implications of Emerging Biomarkers

Beyond diagnosis, emerging biomarkers offer significant prognostic value in periodontal disease, enabling prediction of disease progression, treatment outcomes, and systemic complications [69].

Predicting disease progression is a major challenge in periodontal practice, as only a subset of patients or sites experience progressive tissue destruction. Biomarkers may help identify individuals or sites at higher risk for progression, enabling targeted preventive interventions. Longitudinal studies have demonstrated that elevated levels of certain inflammatory mediators, tissue breakdown products, and microbial pathogens are associated with future disease progression [70]. For example, persistently elevated levels of IL-1β and MMP-8 in GCF have been shown to predict future attachment loss with reasonable accuracy [71].

Treatment response varies considerably among periodontal patients, with some showing excellent outcomes while others experience limited improvement or recurrence. Biomarkers may help predict treatment response, enabling personalized treatment planning. Studies have demonstrated that baseline levels of certain inflammatory mediators and genetic polymorphisms are associated with treatment outcomes following non-surgical and surgical periodontal therapy [72]. Additionally, changes in biomarker levels during treatment may provide early indication of therapeutic efficacy, allowing for timely modification of treatment approaches [73].

The relationship between periodontal disease and systemic conditions has been well-established, with bidirectional associations observed with diabetes, cardiovascular disease, and adverse pregnancy outcomes [74]. Biomarkers may help identify periodontal patients at increased risk for systemic complications, enabling integrated care approaches. For instance, elevated levels of C-reactive protein (CRP) and IL-6 in periodontal patients may indicate increased systemic inflammatory burden and cardiovascular risk [75]. Similarly, specific microbial and host response profiles may identify diabetic patients at higher risk for periodontal complications [76].

The prognostic utility of biomarkers is enhanced by multi-marker approaches and longitudinal monitoring. Combining biomarkers from different categories (e.g., inflammatory mediators, microbial markers, genetic factors) can provide a more comprehensive assessment of disease risk and progression [77]. Furthermore, serial biomarker measurements over time may offer dynamic assessment of disease activity and treatment response, enabling proactive management strategies [78].

Despite these promising developments, challenges remain in implementing biomarker-based prognostic tools in clinical practice. These include the need for standardized protocols, validation in diverse populations, establishment of clinically relevant thresholds, and development of cost-effective testing strategies [79]. Future research should focus on addressing these challenges and translating prognostic biomarker discoveries into clinically useful tools for personalized periodontal care.

Discussion

The emerging biomarkers in periodontal disease discussed in this review represent a significant advancement in our ability to diagnose, monitor, and predict the course of periodontal conditions. The evidence suggests that these biomarkers, particularly when used in combination, offer considerable promise for enhancing early detection, differentiating between disease phenotypes, monitoring treatment response, and predicting disease progression [80].

One of the key insights from this review is the shift from single-marker approaches to multi-marker panels and omics-based technologies. The complex and multifactorial nature of periodontal disease necessitates comprehensive biomarker profiles that reflect various aspects of pathogenesis, including microbial challenge, host response, tissue

degradation, and bone remodeling [81]. Multi-marker approaches have consistently demonstrated superior diagnostic and prognostic accuracy compared to single biomarkers, highlighting the importance of integrating multiple biological parameters for a more complete assessment of periodontal status [82].

Saliva has emerged as a particularly promising biological sample for periodontal biomarker detection, offering advantages of non-invasive collection, ease of sampling, and comprehensive reflection of both local and systemic conditions [83]. The development of point-of-care salivary diagnostic devices could revolutionize periodontal practice by enabling chairside assessment of disease activity and treatment response [84]. However, challenges remain regarding standardization of collection and processing protocols, establishment of reference ranges, and validation in diverse populations [85].

The integration of omics technologies has significantly expanded our understanding of periodontal disease pathogenesis and biomarker discovery. Proteomics, metabolomics, transcriptomics, and microbiome analyses have revealed complex molecular signatures associated with periodontal health and disease [86]. These approaches have identified numerous novel biomarkers and provided insights into disease mechanisms that were not apparent from single-marker studies [87]. However, the complexity and cost of omics technologies present challenges for clinical implementation, and further research is needed to translate these discoveries into clinically useful tools [88].

Despite the considerable progress in periodontal biomarker research, several gaps in the literature remain apparent. First, there is a need for large-scale longitudinal studies to validate the prognostic utility of emerging biomarkers. Most current studies are cross-sectional or have limited follow-up periods, restricting our ability to determine the true predictive value of biomarkers for disease progression and treatment outcomes [89]. Second, there is a lack of standardization in biomarker measurement protocols, making it difficult to compare results across studies and establish clinically relevant thresholds [90]. Third, the influence of various confounding factors, such as systemic conditions, medications, smoking, and genetic background, on biomarker profiles requires further investigation [91].

The clinical implications of emerging biomarkers in periodontal disease are substantial. Biomarker-based approaches could enable earlier intervention, personalized treatment planning, and more precise monitoring of disease activity and treatment response [92]. This could lead to improved treatment outcomes, reduced healthcare costs, and enhanced patient quality of life [93]. Furthermore, the integration of periodontal biomarkers with systemic health assessments could facilitate more comprehensive care approaches, particularly for patients with diabetes, cardiovascular disease, and other conditions associated with periodontal inflammation [94].

From a research perspective, the identification of novel biomarkers and the elucidation of their roles in periodontal disease pathogenesis provide valuable insights into disease mechanisms and potential therapeutic targets [95]. This knowledge could inform the development of novel treatment strategies targeting specific molecular pathways involved in periodontal tissue destruction [96]. Additionally, biomarker research could contribute to the reclassification of periodontal disease based on molecular profiles rather than purely clinical parameters, leading to more precise disease categorization and personalized treatment approaches [97].

Conclusion

The field of periodontal biomarker research has evolved significantly, moving beyond traditional clinical parameters to embrace molecular approaches that offer deeper insights into disease processes. Emerging biomarkers, including host-derived inflammatory mediators, tissue breakdown products, microbial signatures, genetic

markers, and omics-based profiles, demonstrate considerable promise for enhancing the diagnosis and prognosis of periodontal disease. Multi-marker approaches appear to offer superior accuracy compared to single biomarkers, reflecting the complex and multifactorial nature of periodontal pathogenesis.

Saliva has emerged as a particularly promising biological sample for biomarker detection, offering advantages of non-invasive collection and comprehensive reflection of both local and systemic conditions. The development of point-of-care salivary diagnostic devices could revolutionize periodontal practice by enabling chairside assessment of disease activity and treatment response.

Despite these advances, challenges remain regarding standardization, validation, and clinical implementation of biomarker-based approaches. Large-scale longitudinal studies are needed to establish the prognostic utility of emerging biomarkers, while standardized protocols and clinically relevant thresholds must be developed to facilitate translation into routine practice.

Future research should focus on integrating multi-marker approaches with traditional clinical assessment, developing cost-effective point-of-care testing devices, and exploring the potential of artificial intelligence and machine learning for biomarker data analysis. Additionally, the relationship between periodontal biomarkers and systemic health outcomes warrants further investigation to enable more comprehensive care approaches.

The integration of novel biomarkers into periodontal practice has the potential to transform patient care, enabling earlier intervention, personalized treatment planning, and more precise monitoring of disease activity and treatment response. This biomarker-based approach represents a significant step toward precision periodontics, where interventions are tailored to individual risk profiles and disease activity, ultimately improving treatment outcomes and patient quality of life.

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