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REVIEW ARTICLE

Salivary and inflammatory biomarkers in periodontitis: Current evidence and clinical applications

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Abstract

Periodontitis is a chronic inflammatory disease that leads to progressive destruction of the tooth-supporting tissues, while conventional clinical parameters mainly reflect past tissue damage and provide limited information on current disease activity. This review aims to critically summarize current evidence on salivary and inflammatory biomarkers associated with the onset, progression, and monitoring of periodontitis, with particular emphasis on their clinical applicability and current limitations in periodontal practice. A narrative review of the literature was conducted using PubMed, Scopus, and Web of Science databases. Priority was given to systematic reviews, meta-analyses, longitudinal clinical studies, and clinically relevant human studies published in English that addressed salivary inflammatory biomarkers in relation to periodontal disease activity, diagnosis, progression, and treatment monitoring. Evidence indicates that salivary cytokines, chemokines, matrix metalloproteinases, acute-phase proteins, and oxidative stress markers are associated with periodontal inflammation and tissue destruction. Among these, IL-1β, IL-6, TNF-α, and MMP-8 show the strongest associations with disease activity and treatment response. Although salivary biomarkers demonstrate strong biological associations with periodontal inflammation, heterogeneity among studies and lack of standardized diagnostic thresholds currently limit their routine chairside implementation. Further well-designed longitudinal studies are required to facilitate clinical translation.

Keywords: Periodontitis; Saliva; Inflammatory biomarkers; Cytokines; Matrix metalloproteinases

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1. Introduction

Periodontitis is a chronic multifactorial inflammatory disease affecting the supporting structures of the teeth and represents one of the leading causes of tooth loss worldwide.[1] According to current classification systems, periodontitis is characterized by progressive destruction of periodontal tissues driven by a dysregulated host immune response to a dysbiotic oral biofilm.[2,3] Although microbial challenge is essential for disease initiation, the severity and progression of periodontitis are largely determined by host-related inflammatory and immune mechanisms.[4]

The complex interaction between periodontal pathogens and the host immune system results in sustained inflammation, connective tissue degradation, and alveolar bone resorption.[4,5] Pro-inflammatory mediators, including cytokines and proteolytic enzymes, play a pivotal role in amplifying tissue destruction and perpetuating disease activity.[6,7] Understanding these biological processes is fundamental for identifying adjunctive biomarkers that reflect current disease activity rather than cumulative tissue damage.

Conventional diagnostic methods, such as probing pocket depth, clinical attachment loss, and radiographic assessment of bone loss, remain the cornerstone of periodontal diagnosis.[3] However, these clinical parameters primarily provide retrospective information and are limited in their ability to identify early disease activity or predict future progression.[8] Consequently, there is increasing interest in adjunctive diagnostic approaches that offer real-time insight into the biological activity of periodontal disease.

Biomarkers related to inflammation, immune response, and tissue degradation have emerged as promising tools for the diagnosis, prognosis, and monitoring of periodontitis.[9,10] Among the biological fluids investigated, saliva has attracted considerable attention due to its non-invasive collection, ease of sampling, and potential to reflect both local periodontal inflammation and systemic inflammatory status.[11-13] Salivary biomarkers are derived from multiple sources, including gingival crevicular fluid, periodontal tissues, immune cells, and salivary glands, making saliva a valuable medium for periodontal diagnostics.

Accumulating evidence suggests that salivary inflammatory mediators, such as cytokines, chemokines, matrix metalloproteinases (MMPs), and acute-phase proteins, are associated with the presence, severity, and progression of periodontal disease.[14-16] Moreover, advances in high-sensitivity analytical techniques and point-of-care diagnostic technologies have further enhanced the clinical potential of saliva-based biomarker assessment.[17,18]

Periodontal pathogenesis involves a highly structured dysbiotic biofilm that interacts with host immune cells, leading to activation of neutrophils, macrophages, and T-lymphocyte subsets and subsequent release of inflammatory mediators and tissue-degrading enzymes.[19-22] Host–microbe interactions mediated by cytokines such as interleukin-1 and tumor necrosis factor further amplify connective tissue destruction and alveolar bone loss.[23,24] In addition, MMPs and oxidative stress pathways contribute significantly to extracellular matrix breakdown and periodontal tissue damage.[25,26] The chronic inflammatory burden associated with periodontitis has also been linked to systemic conditions, particularly cardiovascular diseases, supporting the concept of a bidirectional oral–systemic relationship.[27,28]

The aim of this review is to critically summarize current evidence on salivary and inflammatory biomarkers associated with the onset, progression, and monitoring of periodontitis. Emphasis is placed on their biological relevance, clinical applicability, and limitations, as well as future perspectives for integrating biomarker-based approaches into personalized periodontal care and routine clinical practice.

2. Saliva as a diagnostic medium

Saliva has emerged as a valuable biological fluid for disease diagnostics due to its non-invasive collection, ease of handling, and cost-effectiveness.[29] It contains a complex mixture of locally and systemically derived components, including enzymes, cytokines, antibodies, hormones, microbial products, metabolites, and nucleic acids, reflecting both oral and systemic physiological and pathological processes.[30,31]

In periodontal disease, saliva mirrors the inflammatory status of periodontal tissues and the host–microbial interactions occurring within the oral cavity. Inflammatory mediators and tissue degradation products originating from periodontal lesions enter saliva primarily through gingival crevicular fluid, epithelial transudation, and local glandular secretion.[32] Consequently, alterations in salivary biomarker profiles have been shown to correlate with periodontal disease presence, severity, and progression.[33]

Compared with serum and gingival crevicular fluid, saliva offers several practical advantages for clinical and research applications. Its collection does not require invasive procedures, specialized equipment, or extensive training, allowing for repeated sampling and facilitating large-scale screening and longitudinal monitoring.[34] These characteristics make saliva particularly attractive for chairside diagnostics and personalized periodontal care.

Despite its advantages, several limitations must be considered when interpreting salivary biomarker data. Salivary composition is influenced by multiple factors, including circadian rhythm, flow rate, age, smoking status, systemic conditions, medication use, and oral hygiene practices.[35] In addition, variability in sampling protocols, storage conditions, and analytical methods may affect biomarker stability and reproducibility across studies.[36]

Recent advances in analytical technologies have significantly enhanced the diagnostic potential of saliva. High-sensitivity immunoassays, proteomic and

metabolomic approaches, and microfluidic point-of-care platforms have enabled the detection of low-abundance biomarkers with improved accuracy and clinical feasibility.[37,38] These technological developments support the integration of saliva-based diagnostics into routine periodontal practice, bridging the gap between research and clinical application.

Overall, saliva represents a promising diagnostic medium for assessing inflammatory biomarkers associated with the evolution of periodontitis. Standardization of collection and analysis protocols, along with validation in well-designed clinical studies, remains essential for the successful translation of salivary biomarker research into everyday periodontal care.[39]

3. Classification of biomarkers in periodontal diagnostics

Periodontal biomarker research encompasses a broad spectrum of molecular and technological approaches that extend beyond traditional inflammatory mediators. Biomarkers associated with periodontal disease can be classified into several categories according to their biological origin, analytical methodology, and potential clinical application. This classification is important for understanding both the current maturity of available biomarkers and the existing gaps that still limit their routine implementation in periodontal practice.[9,10,14,40]

Proteomic biomarkers currently represent the most extensively investigated category in periodontal diagnostics. These include inflammatory cytokines, chemokines, MMPs, acute-phase proteins, and enzymes involved in connective tissue degradation and host immune response. Among them, interleukin-1 beta (IL-1β), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and matrix metalloproteinase-8 (MMP-8) demonstrate the strongest evidence regarding their association with periodontal inflammation, tissue destruction, and treatment response. Most available evidence supporting these biomarkers derives from observational studies, longitudinal clinical studies, and systematic reviews, while several point-of-care applications are currently under investigation or early clinical implementation.[14-18,40-45]

Genomic biomarkers constitute another important category and include genetic polymorphisms associated with host susceptibility to periodontal disease. Variations in genes encoding inflammatory mediators, particularly interleukin-1 gene polymorphisms, have been associated with increased risk and severity of periodontitis. However, genomic biomarkers mainly provide information regarding disease susceptibility rather than current inflammatory activity and therefore remain primarily predictive rather than diagnostic tools. In addition, considerable inter-individual and ethnic variability currently limits their clinical applicability.[24,46]

Metabolomic biomarkers represent an emerging field focused on the analysis of metabolites and metabolic pathways associated with periodontal inflammation and tissue breakdown. Salivary metabolites related to oxidative stress, lipid peroxidation, and microbial metabolism have demonstrated promising associations with periodontal disease activity. Nevertheless, metabolomic approaches remain largely exploratory due to limited standardization, methodological heterogeneity, and insufficient longitudinal validation.[40,47-50]

Microbiological biomarkers are based on the detection of periodontal pathogens and microbial dysbiosis associated with disease progression. The presence of specific pathogens, including Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola, has been strongly associated with periodontitis. However, microbial biomarkers alone may not adequately reflect disease activity, as host inflammatory response plays a major role in tissue destruction and clinical progression.[5,19,40]

Recent advances have also introduced digital and artificial intelligence (AI)-assisted analytical approaches into periodontal research. Machine learning algorithms and computational analysis of complex biomarker panels may improve diagnostic precision and support individualized risk assessment. These approaches enable the integration of clinical, molecular, microbiological, and imaging data into predictive models that may facilitate personalized periodontal care in the future. Despite their considerable potential, digital biomarker approaches remain in early stages of clinical validation.[40,51,52]

Overall, proteomic inflammatory biomarkers currently demonstrate the highest level of clinical maturity, while genomic, metabolomic, microbiological, and digital biomarkers continue to evolve as complementary approaches within precision periodontology. Further standardization, multicenter validation studies, and integration of multi-biomarker panels are required before widespread routine clinical implementation can be achieved.[40,43-45,50-56]

The classification of major biomarker categories and their current clinical maturity is summarized in Table 1.

4. Inflammatory biomarkers in saliva

Inflammatory biomarkers play a central role in the pathogenesis and progression of periodontitis and have therefore been extensively investigated as potential diagnostic and prognostic indicators.[57] Saliva contains a

Table 1. Classification of biomarkers in periodontitis and their current clinical maturity

Biomarker category	Examples	Main clinical relevance	Current evidence level	Clinical maturity	Main limitations
Proteomic biomarkers[14-18,41,42]	IL-1β, IL-6, TNF-α, MMP-8	Reflect inflammatory activity and tissue destruction	Strong observational and longitudinal evidence	Moderate–high	Lack of standardized thresholds
Genomic biomarkers[24,46]	IL-1 gene polymorphisms	Assess host susceptibility and disease risk	Moderate	Low–moderate	Ethnic variability and limited predictive value
Metabolomic biomarkers[47-49]	Oxidative stress metabolites, lipid peroxidation products	Reflect metabolic and oxidative changes	Emerging	Low	Limited standardization and validation
Microbiological biomarkers[5,19]	Porphyromonas gingivalis, Tannerella forsythia	Identify dysbiosis and periodontal pathogens	Moderate	Moderate	Limited ability to reflect disease activity alone
Imaging biomarkers[3,8]	Radiographic bone loss assessment	Evaluate structural periodontal destruction	Established	High	Mainly retrospective assessment
Digital/AI-assisted biomarkers[40,51,52]	Machine learning-integrated biomarker panels	Support predictive diagnostics and personalized care	Emerging	Low	Lack of large-scale validation

Abbreviations: AI: Artificial intelligence; IL: Interleukin; MMP: Matrix metalloproteinase; TNF-α: Tumor necrosis factor alpha.

broad spectrum of inflammatory mediators originating from periodontal tissues, gingival crevicular fluid, immune cells, and salivary glands, reflecting the local inflammatory burden associated with periodontal disease.[58]

4.1. Cytokines and chemokines

Pro-inflammatory cytokines are among the most widely studied salivary biomarkers in periodontitis. IL-1β is a key mediator of periodontal tissue destruction, promoting osteoclast activation, MMP expression, and connective tissue breakdown.[59] Elevated salivary IL-1β levels have been consistently associated with disease severity and active periodontal inflammation, supporting its role as a marker of ongoing disease activity.[60]

Interleukin-6 is a multifunctional cytokine involved in both local and systemic inflammatory responses. Increased salivary concentrations of IL-6 have been reported in patients with periodontitis and correlate with clinical parameters such as probing pocket depth and clinical attachment loss.[61] TNF-α further amplifies inflammatory signaling and bone resorption and has been detected at higher levels in saliva from individuals with moderate to severe periodontitis.[62]

Chemokines, particularly interleukin-8, play a critical role in neutrophil recruitment and activation within periodontal tissues. Alterations in salivary chemokine profiles may reflect active inflammatory processes and have been proposed as indicators of disease progression and inflammatory burden.[63]

4.2. Matrix metalloproteinases

Matrix metalloproteinases are proteolytic enzymes responsible for the degradation of extracellular matrix components and are directly involved in periodontal connective tissue destruction. Among them, MMP-8 and MMP-9 have received particular attention as salivary biomarkers due to their strong association with collagen degradation and inflammatory cell infiltration.[41]

Elevated salivary levels of MMP-8 have been consistently linked to active periodontal tissue breakdown and disease progression, making it one of the most promising biomarkers for assessing current disease activity.[64] MMP-9, which participates in extracellular matrix remodeling and leukocyte migration, has also been shown to increase in advanced stages of periodontitis and may complement MMP-8 in multi-biomarker diagnostic panels.[65]

The clinical relevance of salivary MMPs is further supported by the development of chairside diagnostic tests capable of detecting active forms of these enzymes, facilitating rapid assessment of periodontal disease status and response to therapy.[42]

4.3. Diagnostic performance and analytical considerations

Several salivary biomarkers have demonstrated promising diagnostic performance in distinguishing periodontal health from disease, although substantial heterogeneity exists among published studies. Among currently investigated biomarkers, matrix metalloproteinase-8 (MMP-8), particularly its activated form (active matrix metalloproteinase-8 [aMMP-8]), has shown some of the most consistent associations with active periodontal tissue destruction and disease progression.

Systematic reviews and meta-analyses have reported that salivary and oral fluid aMMP-8 assays may achieve sensitivity values ranging approximately from 75% to 85% and specificity values ranging from 70% to 80% for the detection of active periodontal inflammation and tissue breakdown. Nevertheless, reported diagnostic accuracy varies considerably depending on study design, disease classification criteria, assay methodology, and patient population characteristics. Consequently, these values should be interpreted cautiously and should not yet be considered universally standardized diagnostic thresholds.[43-45] These findings further support the potential utility of aMMP-8 as one of the most clinically advanced salivary biomarkers currently available for periodontal diagnostics.

Inflammatory cytokines such as IL-1β and IL-6 have also demonstrated significant associations with periodontal disease severity and treatment response. However, the diagnostic reproducibility of cytokine-based assays remains affected by biological variability, differences in saliva collection protocols, and inter-laboratory methodological heterogeneity. Similar limitations apply to oxidative stress markers and metabolomic biomarkers, which currently remain primarily investigational rather than fully validated clinical diagnostic tools.[40,60,61]

Analytical validity represents another major challenge in salivary biomarker diagnostics. Variability in assay sensitivity, sample processing, storage conditions, and laboratory calibration may substantially affect biomarker quantification and reproducibility across studies. Although enzyme-linked immunosorbent assays, multiplex immunoassays, and point-of-care technologies have significantly improved biomarker detection capabilities, universal standardization has not yet been achieved.[35,36,39]

Importantly, most currently available biomarkers should still be considered promising or emerging biomarkers rather than definitive, standalone diagnostic tools. Current evidence increasingly supports the use of combined multi-biomarker panels integrating inflammatory mediators, proteolytic enzymes, microbial profiles, and clinical parameters in order to improve diagnostic precision and prognostic reliability.[40,50]

The diagnostic performance and current clinical applicability of selected salivary biomarkers are summarized in Table 2.

Table 2. Diagnostic performance and clinical applicability of selected salivary biomarkers in periodontitis

Biomarker	Approximate sensitivity	Approximate specificity	Main clinical relevance	Supporting evidence	Current clinical applicability
aMMP-8[41-45,64]	75–85%	70–80%	Detection of active periodontal tissue destruction	Systematic reviews, meta-analyses, PoC studies	Most clinically mature salivary biomarker
IL-1β[59,60,66]	70–80%	65–75%	Reflects active inflammatory burden	Observational and longitudinal studies	Promising adjunctive biomarker
IL-6[51,61]	65–75%	60–70%	Associated with disease severity and treatment response	Clinical observational studies	Potential monitoring biomarker
TNF-α[23,62,66]	60–75%	60–70%	Associated with inflammatory activity and bone resorption	Cross-sectional studies	Primarily investigational
CRP[67,68]	Variable	Variable	Reflects systemic inflammatory burden	Systematic reviews	Limited periodontal specificity
Oxidative stress markers[47-49]	Variable	Variable	Reflect oxidative tissue injury	Exploratory metabolomic studies	Emerging biomarkers

Notes: Diagnostic values represent approximate ranges reported across heterogeneous studies and should not be interpreted as universally standardized diagnostic thresholds.

Abbreviations: aMMP-8: Active matrix metalloproteinase-8; CRP: C-reactive protein; IL: Interleukin; MMP: Matrix metalloproteinase; PoC: Point-of-care; TNF-α: Tumor necrosis factor alpha.

4.4. Acute-phase proteins and systemic inflammatory markers

Acute-phase proteins, such as C-reactive protein (CRP), have traditionally been used as systemic inflammatory markers but have also been detected in saliva. Elevated salivary CRP levels have been associated with periodontal disease severity and may reflect both local periodontal inflammation and systemic inflammatory burden.[67]

The presence of acute-phase proteins in saliva underscores the potential link between periodontitis and systemic inflammatory conditions and highlights the value of salivary biomarkers in assessing the broader health implications of periodontal disease.[68]

4.5. Oxidative stress–related biomarkers

Oxidative stress represents an important mechanism contributing to periodontal tissue damage. Activated immune cells generate reactive oxygen species that induce lipid peroxidation, protein modification, and DNA damage within periodontal tissues.[47] Salivary biomarkers related to oxidative stress, including lipid peroxidation products and measures of total antioxidant capacity, have been shown to be altered in patients with periodontitis.[48]

Increased oxidative stress markers and reduced antioxidant capacity in saliva are associated with disease severity and progression, suggesting that these parameters may complement inflammatory cytokines and proteolytic enzymes in comprehensive biomarker panels.[49]

However, current evidence remains heterogeneous, with considerable variability in study design, sample size, and biomarker quantification methods, which limits direct comparison across studies and reduces the strength of clinical recommendations.

The main salivary and inflammatory biomarkers associated with periodontal inflammation, tissue destruction, and disease evolution are summarized in Table 3.

Table 3. Salivary and inflammatory biomarkers associated with periodontitis

Biomarker category	Biomarker	Biological relevance in periodontitis	Clinical significance	Key references
Pro-inflammatory cytokines	IL-1β	Promotes osteoclast activation, MMP expression, connective tissue breakdown	Strong association with disease activity and severity; potential marker of active inflammation	23,59,60
	IL-6	Regulates local and systemic inflammatory responses; enhances bone resorption	Correlates with probing depth and attachment loss; reflects inflammatory burden	24,61
	TNF-α	Amplifies inflammatory cascades and alveolar bone resorption	Associated with moderate–severe periodontitis and disease progression	24,62
Chemokines	IL-8	Neutrophil recruitment and activation at periodontal sites	Reflects active inflammatory cell infiltration	63
MMPs	MMP-8	Collagen degradation; key mediator of periodontal tissue destruction	Strong marker of active disease and treatment response; chairside tests available	41,42,64
	MMP-9	Extracellular matrix remodeling and leukocyte migration	Associated with advanced disease; complementary to MMP-8 in panels	65
Acute-phase proteins	CRP	Systemic inflammatory marker linked to periodontal inflammation	Reflects local and systemic inflammatory burden	67,68
Oxidative stress markers	Lipid peroxidation products	Indicators of oxidative tissue damage	Associated with disease severity and progression	47,48
	Total antioxidant capacity	Reflects host defense against oxidative stress	Reduced levels linked to active periodontitis	48,49
Multi-biomarker panels	Combined cytokines, MMPs, oxidative markers	Capture the multifactorial nature of the disease	Improved diagnostic and prognostic accuracy	51,69-71

Abbreviations: CRP: C-reactive protein; IL: Interleukin; MMP: Matrix metalloproteinase; TNF-α: Tumor necrosis factor alpha.

5. Clinical applications of salivary biomarkers in periodontal practice

The dynamic nature of periodontitis requires diagnostic tools capable of reflecting ongoing biological activity rather than cumulative tissue damage. In this context, biomarkers offer significant advantages over conventional clinical parameters by providing real-time insight into inflammatory activity, tissue destruction, and host response.[72]

5.1. Early disease detection

Early stages of periodontitis are often clinically silent or difficult to differentiate from gingivitis using traditional diagnostic criteria. Salivary inflammatory biomarkers have demonstrated potential in identifying subclinical inflammatory changes before irreversible periodontal tissue destruction occurs.[73] Elevated salivary levels of cytokines such as IL-1β, IL-6, and TNF-α have been reported in individuals with early periodontal inflammation, supporting their use as early indicators of disease initiation.[74]

Matrix metalloproteinases, particularly MMP-8, have been proposed as markers of active collagen degradation and early connective tissue breakdown. Increased salivary MMP-8 levels may therefore identify individuals at higher risk for disease progression and support timely preventive or therapeutic interventions.[75]

5.2. Disease progression

As periodontitis advances, sustained inflammatory activity and proteolytic tissue destruction lead to distinct changes in biomarker profiles. Increased salivary concentrations of pro-inflammatory cytokines, chemokines, and MMPs have been consistently correlated with clinical indicators of disease severity, including probing pocket depth, clinical attachment loss, and alveolar bone resorption.[69,70]

Evidence from longitudinal studies suggests that single biomarkers may be insufficient to fully capture disease complexity. Instead, combined biomarker panels incorporating inflammatory mediators, proteolytic enzymes, and oxidative stress markers may offer improved diagnostic accuracy and prognostic value for assessing disease progression.[71]

5.3. Treatment monitoring

Salivary biomarkers have also been extensively investigated as tools for monitoring the response to periodontal therapy. Successful non-surgical and surgical periodontal treatment has been associated with significant reductions in salivary levels of inflammatory cytokines and MMPs, reflecting decreased inflammatory burden and reduced tissue breakdown.[76]

The ability to assess treatment response through non-invasive salivary testing supports a more personalized approach to periodontal care. Biomarker-based monitoring may help identify non-responders, guide supportive periodontal therapy, and optimize long-term disease management strategies.[4]

Overall, the integration of salivary and inflammatory biomarkers into periodontal diagnostics offers promising opportunities for improving early detection, risk assessment, and treatment monitoring across different stages of periodontitis. Nevertheless, further validation through well-designed longitudinal clinical studies is necessary to establish standardized biomarker thresholds and confirm clinical reliability.[17]

Despite promising findings, the clinical translation of salivary biomarkers remains limited due to the lack of standardized diagnostic thresholds, variability among populations, and insufficient validation in large-scale longitudinal studies.

The potential clinical utility of selected salivary biomarkers in daily periodontal practice, along with their current limitations, is summarized in Table 4. The level of evidence for each biomarker is based on the consistency and quality of available clinical studies.

5.4. Clinical translation and point-of-care diagnostics

Although most salivary biomarkers remain primarily investigational, recent advances in point-of-care technologies have accelerated the potential clinical translation of selected biomarkers into routine periodontal practice. Among currently available candidates, aMMP-8 represents the most clinically mature salivary biomarker and has demonstrated promising applicability in chairside diagnostics.[42-45]

Rapid oral fluid aMMP-8 tests have been developed to facilitate real-time assessment of active periodontal tissue destruction and inflammatory burden directly in the dental setting. These assays offer several practical advantages, including non-invasive sampling, rapid turnaround time, and the possibility of repeated monitoring during supportive periodontal therapy. Clinical studies suggest that aMMP-8 point-of-care testing may support early disease detection, identification of active periodontal breakdown, and monitoring of treatment response.[42,43,75]

Despite these promising developments, several limitations continue to restrict widespread implementation. Considerable variability exists regarding sampling protocols, assay methodologies, diagnostic thresholds, and

Table 4. Potential clinical utility of selected salivary biomarkers in periodontal practice

Biomarker	Reflects	Possible clinical use	Current limitation	Level of Evidence
IL-1β[59,60,66,74]	Active inflammation	Adjunctive indicator of active periodontal breakdown	No standardized cut-off values	Moderate
IL-6[51,61,69]	Inflammatory burden	Monitoring response to periodontal therapy	Inter-individual variability	Moderate
TNF-α[23,62,69]	Disease severity	Risk stratification in moderate–severe cases	Limited chairside validation	Low–moderate
MMP-8[41-45,64,75]	Collagen degradation	Chairside detection of active tissue destruction	Cost and assay variability	Moderate–high
CRP[67,68,70]	Systemic inflammatory burden	Screening in patients with systemic comorbidities	Non-specific marker	Low

Abbreviations: CRP: C-reactive protein; IL: Interleukin; MMP: Matrix metalloproteinase; TNF-α: Tumor necrosis factor alpha.

interpretation criteria across studies. Furthermore, most currently available salivary biomarker assays have not yet been universally integrated into international periodontal diagnostic guidelines.[17,40]

Economic considerations also represent an important barrier to routine implementation. The cost of advanced laboratory assays, proprietary point-of-care devices, and maintenance of specialized diagnostic equipment may limit accessibility, particularly in general dental practice and low-resource healthcare settings. In addition, reimbursement policies and cost-effectiveness analyses remain insufficiently established in many healthcare systems. Nevertheless, ongoing technological advances and increasing commercialization of point-of-care platforms may progressively improve affordability and accessibility in routine periodontal practice.

Current evidence increasingly supports the concept that future periodontal diagnostics will likely rely on integrated multi-biomarker platforms rather than isolated biomarkers alone. Combining salivary inflammatory mediators, microbial profiles, host-response markers, and digital risk assessment tools may improve diagnostic precision and facilitate personalized periodontal management strategies.[40,51,52]

Overall, although salivary biomarker-based diagnostics have not yet achieved universal routine clinical implementation, ongoing technological advances and growing translational evidence suggest that selected biomarkers, particularly aMMP-8, may soon become valuable adjunctive tools in periodontal diagnostics and monitoring.

6. Limitations and challenges

Despite the growing body of evidence supporting the use of salivary and inflammatory biomarkers in periodontitis, several limitations and challenges currently hinder their routine clinical application. Most available studies are cross-sectional or include relatively small cohorts. In addition, differences in study design, patient selection, periodontal case definitions, and analytical methods[77] complicate direct comparisons and limit the generalizability of findings.

Salivary biomarker levels are influenced by a wide range of biological and behavioral factors, such as age, sex, smoking status, systemic diseases, medication use, and oral hygiene practices.[78] In addition, circadian variations and differences in salivary flow rate may further affect biomarker concentrations, introducing additional sources of variability that must be carefully controlled in both research and clinical settings.[79]

Smoking represents one of the most important confounding factors affecting salivary biomarker interpretation in periodontal disease. Tobacco exposure may alter inflammatory cytokine expression, oxidative stress pathways, immune cell function, and salivary flow characteristics, potentially masking active inflammatory responses despite ongoing periodontal tissue destruction. Smokers have been shown to exhibit altered concentrations of inflammatory mediators, including interleukins, TNF-α, and oxidative stress-related biomarkers, which may complicate direct comparison with non-smoker populations. Similar confounding effects may also occur in patients with systemic inflammatory diseases, diabetes mellitus, cardiovascular disorders, and other chronic conditions associated with dysregulated immune responses. These factors further emphasize the need for individualized interpretation and standardized biomarker assessment protocols in periodontal diagnostics.[35,78,79] These observations highlight the importance of considering smoking status when interpreting salivary biomarker profiles in both clinical and research settings.

Methodological issues related to saliva collection, processing, and analysis also represent significant challenges. Variations in sampling protocols (stimulated versus unstimulated saliva), storage conditions, and assay sensitivity can affect biomarker stability and measurement accuracy.[80] The lack of standardized protocols across studies remains a major barrier to the validation and clinical translation of salivary biomarkers.

Another critical limitation is the absence of universally accepted diagnostic thresholds for most salivary inflammatory biomarkers. Although numerous biomarkers have demonstrated significant associations with periodontal disease activity and severity, their clinical interpretation remains challenging without clearly defined cut-off values.[81] Moreover, single biomarkers are unlikely to adequately capture the complex and multifactorial nature of periodontal disease.

Inter-individual variability in host immune response further complicates biomarker-based diagnostics. Genetic susceptibility, environmental exposures, and microbial diversity may result in distinct biomarker profiles among patients with similar clinical presentations.[46] These factors highlight the need for multi-biomarker panels and personalized diagnostic approaches rather than reliance on isolated markers.

Addressing these limitations requires well-designed, large-scale longitudinal studies, standardized methodologies, and rigorous validation of biomarker panels in diverse populations. Only through such efforts can salivary and inflammatory biomarkers be reliably integrated into routine periodontal diagnostics and clinical decision-making.[82] Nevertheless, recent advances in biomarker research have begun to address several of these limitations, providing new insights into the diagnostic and prognostic potential of salivary biomarkers.

7. Recent evidence and emerging perspectives (2020–2025)

Recent advances in periodontal research have further strengthened the role of salivary and inflammatory biomarkers in the diagnosis and monitoring of periodontitis. A growing body of recent high-quality evidence supports the integration of biomarker-based approaches into clinical practice, particularly in the context of personalized and precision dentistry.

A recent systematic review and meta-analysis demonstrated that combinations of molecular biomarkers in oral fluids provide high diagnostic accuracy for periodontitis, outperforming single-marker approaches and highlighting the importance of multi-biomarker panels in clinical decision-making.[40]

In addition, longitudinal evidence has provided important insights into the dynamic behavior of biomarkers during disease progression and treatment. Changes in salivary and serum inflammatory mediators over time have been shown to correlate with periodontal disease activity and response to therapy, reinforcing their role as tools for disease monitoring and prognostic assessment.[51]

Recent systematic reviews and clinical studies have further confirmed the central role of key inflammatory mediators, including IL-1β, TNF-α, and MMPs, particularly MMP-8, as promising indicators of periodontal inflammation and tissue destruction.[43-45,66]

Moreover, advances in salivary diagnostics highlight the added value of integrating host-response biomarkers with microbial and immunological components, including salivary immunoglobulins and microbiome-derived markers, which provide a more comprehensive understanding of periodontal disease pathophysiology.[53,54]

Emerging evidence also supports the application of salivary biomarker-based screening tools in clinical and community settings, facilitating early detection of periodontal disease and improving preventive strategies.[55]

Despite these promising developments, important challenges remain, including variability in biomarker expression, lack of standardized diagnostic thresholds, and heterogeneity among study populations. Further large-scale and longitudinal studies are required to validate biomarker panels and support their routine clinical implementation. Collectively, these developments highlight the transition from exploratory biomarker research to clinically applicable diagnostic strategies, paving the way for future innovations in periodontal care.

8. Future perspectives

Advances in molecular biology, omics technologies, and diagnostic platforms are expected to significantly enhance the clinical applicability of salivary biomarkers in periodontology. High-throughput proteomic, transcriptomic, and metabolomic approaches have expanded the spectrum of detectable biomarkers and improved understanding of the complex biological pathways involved in periodontal disease progression.[56]

A major future direction lies in the development of multi-biomarker panels rather than reliance on single markers. Combining inflammatory cytokines, MMPs, oxidative stress indicators, and microbial signatures may improve diagnostic accuracy and potentially enhance discrimination between health, gingivitis, and different stages of periodontitis.[50] Such integrated approaches

better reflect the multifactorial and dynamic nature of periodontal disease.

Technological innovations in point-of-care diagnostics are also expected to facilitate the translation of salivary biomarker research into routine clinical practice. Microfluidic devices, lab-on-a-chip systems, and chairside immunoassays allow rapid, sensitive, and cost-effective detection of biomarkers directly in the dental setting.[52] These tools may support real-time assessment of disease activity, risk stratification, and monitoring of treatment response.

Personalized periodontal medicine represents another promising area of future development. Biomarker-based diagnostics could enable individualized risk assessment, tailored treatment planning, and customized maintenance protocols based on each patient's biological profile.[83] Integration of salivary biomarker data with clinical parameters, imaging findings, and digital health records may further enhance precision in periodontal care.

In addition, growing evidence linking periodontitis with systemic inflammatory conditions underscores the potential role of salivary biomarkers in broader medical screening and interdisciplinary care.[84] Saliva-based diagnostics may therefore contribute not only to improved periodontal outcomes but also to early identification of patients at increased risk for systemic diseases associated with chronic inflammation.

Future research should prioritize large-scale, longitudinal clinical studies to validate the predictive value of salivary and inflammatory biomarkers and establish standardized protocols and diagnostic thresholds.[85] Such efforts are essential for ensuring reproducibility, clinical reliability, and widespread adoption of biomarker-based diagnostics in periodontology.

8.1. Artificial intelligence and digital biomarker integration

Recent advances in AI, machine learning, and computational biology are expected to significantly influence the future development of salivary biomarker-based diagnostics in periodontology. The growing complexity of biomarker research, particularly the integration of inflammatory mediators, proteomic profiles, microbial signatures, and clinical variables, has created increasing interest in AI-assisted analytical approaches capable of handling large multidimensional datasets.[40,52]

Machine learning algorithms may facilitate the identification of complex biomarker patterns associated with periodontal disease activity, progression, and treatment response. Such approaches could improve diagnostic precision, support risk stratification, and enhance individualized periodontal management. In addition, AI-assisted models may contribute to the development of predictive diagnostic systems capable of identifying patients at increased risk for rapid disease progression before substantial tissue destruction becomes clinically evident.[51,52]

Digital biomarker integration may also support the combination of salivary biomarker data with radiographic findings, periodontal clinical parameters, electronic health records, and systemic health indicators. This multidimensional approach aligns with the principles of precision and personalized dentistry and may improve clinical decision-making in the future.[52,83,84]

Despite these promising perspectives, several important limitations remain. AI-based diagnostic models require large-scale standardized datasets, external validation, and robust methodological transparency before routine clinical implementation can be achieved. Ethical considerations, data privacy concerns, and algorithm reproducibility also represent important challenges requiring further investigation.

Nevertheless, the integration of AI with salivary biomarker analysis represents a rapidly evolving and potentially important future direction in periodontal diagnostics and may contribute substantially to the transition toward precision periodontal medicine.

9. Conclusion

Salivary and inflammatory biomarkers provide insight into the biological mechanisms underlying periodontal initiation and progression and may complement conventional clinical and radiographic parameters by reflecting current inflammatory activity. The non-invasive nature of saliva collection and its ability to capture both local and systemic inflammatory signals make it an attractive medium for adjunctive periodontal diagnostics.

However, substantial biological variability, methodological heterogeneity, and the lack of standardized diagnostic thresholds currently limit routine chairside implementation. Before widespread clinical integration can be achieved, multicenter longitudinal validation studies, harmonized analytical protocols, and the development of clinically applicable multi-biomarker diagnostic algorithms are required. With appropriate validation and standardization, salivary biomarker assessment has the potential to contribute to more individualized and biologically driven periodontal care.

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