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Review Article

Role of Matrix Metalloproteinase-8 (MMP-8) in the Diagnosis of Dental Diseases: A Review

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Abstract

Matrix Metalloproteinase-8 (MMP-8), a neutrophil-derived collagenase, has emerged as a promising biomarker for diagnosing periodontal and peri-implant diseases. Its elevated levels in oral fluids correlate with active connective tissue breakdown and disease progression. This review synthesizes recent evidence on the biological functions of MMP-8, its diagnostic applications, assay techniques, limitations and future clinical potential.

Keywords: MMP-8; Aactive MMP-8 (aMMP-8); Periodontal Disease; Peri-Implantitis; Biomarker; Oral Fluids

Introduction

Periodontal disease remains a leading cause of tooth loss worldwide, driven by chronic inflammation and host-mediated tissue destruction. Traditional clinical indicators, such as probing depth and radiographic bone loss, are retrospective and provide limited insight into current disease activity [1]. In this context, biomarkers like MMP-8 have gained prominence for their potential to detect active periodontal tissue degradation and enhance diagnostic accuracy [2].

Biological Role of MMP-8

Matrix metalloproteinases are zinc-dependent proteolytic enzymes involved in Extracellular Matrix (ECM) remodelling. Among them, MMP-8 (neutrophil collagenase) is primarily released from neutrophils in response to bacterial challenge and inflammatory signalling. MMP-8 efficiently degrades type I collagen, the predominant structural protein in periodontal connective tissues, compelling its relevance to periodontal breakdown. Active MMP-8 (aMMP-8) rather than total enzyme levels reflects ongoing collagenolytic activity in disease states.

Matrix metalloproteinase-8 (MMP-8) mediates excessive degradation of the extracellular matrix during periodontal inflammation leading to tissue destruction. In response to periodontal pathogens, activated neutrophils, fibroblasts and other host cells release increased levels of MMP-8, which is further upregulated by pro-inflammatory cytokines such as interleukin-1β and tumour necrosis factor-α [3]. Once activated from its latent pro-enzyme form by bacterial proteases, reactive oxygen species or other matrix metalloproteinases, MMP-8 preferentially degrades type I collagen, the principal structural component of gingival connective tissue and the periodontal ligament. In periodontal disease, the normal balance between MMP-8 and its endogenous inhibitors, namely Tissue Inhibitors of Metalloproteinases (TIMPs), is disrupted, resulting in uncontrolled collagen breakdown. This progressive degradation of collagen fibers leads to loss of periodontal attachment, increased pocket depth and destabilization of the supporting tissues of the tooth, while also indirectly promoting alveolar bone resorption through enhanced inflammatory signalling.

MMP-8 levels in Periodontal Disease

Elevated *in-vivo* levels of MMP-8 in Gingival Crevicular Fluid (GCF) and saliva are associated with periodontitis severity and clinical measures such as probing pocket depth, attachment loss and bleeding indices. Recent meta-analytic evidence indicates robust diagnostic performance of MMP-8 in detecting periodontal disease, with pooled sensitivity around 0.83 and specificity near 0.77 across diverse diagnostic assays and sample types. GCF has superior diagnostic accuracy compared to saliva or mouth rinse samples for this purpose [4].

In periodontal health, MMP-8 is present in very low concentrations in Gingival Crevicular Fluid (GCF) and saliva [5]. It is mostly in the latent (inactive) form and its activity is tightly regulated by Tissue Inhibitors of Metalloproteinases (TIMPs). This balance between MMP-8 and TIMPs maintains normal tissue remodelling without connective-tissue breakdown.

In gingivitis, inflammatory changes lead to increased neutrophil migration into the gingival tissues. As a result, total MMP-8 levels are moderately elevated, but the majority remains in the inactive form. Since gingivitis does not involve irreversible connective-tissue destruction, the increase in active MMP-8 (aMMP-8) is limited. This explains why gingivitis is a reversible condition despite inflammation.

Periodontitis is characterized by a marked increase in both total and active MMP-8 levels in GCF and saliva. Periodontopathogenic bacteria stimulate neutrophils, macrophages and fibroblasts to release large amounts of latent MMP-8, which is subsequently activated by bacterial proteases, reactive oxygen species and other MMPs.

Elevated aMMP-8 levels correlate strongly with clinical parameters such as increased probing pocket depth, clinical attachment loss and radiographic bone loss. High MMP-8 levels indicate ongoing collagen degradation and active disease progression, rather MMP-8 levels show site-specific variation, with significantly higher concentrations at deep periodontal pockets, bleeding sites and actively progressing lesions. Clinically healthy sites in the same patient will exhibit comparatively lower levels, highlighting the value of MMP-8 as a marker of local disease activity rather than past tissue damage [6].

Clinical Significance of measuring MMP-8

Successful periodontal treatment, including scaling and root planing or surgical therapy, results in a significant reduction in MMP-8 levels, particularly aMMP-8. Persistent elevation after therapy may indicate residual inflammation or risk of disease recurrence.

Overall, MMP-8 levels increase progressively from health to gingivitis and are highest in periodontitis. Unlike traditional methods that only reveal past destruction, aMMP-8 acts as a real-time indicator of current collagenolytic activity (specifically collagen type I) and predicts future disease progression [7]. Measurement of aMMP-8 in GCF or saliva provides a biochemical indicator of active periodontal tissue destruction and serves as a useful adjunct to conventional clinical diagnosis.

Diagnostic Applications of MMP-8

Periodontal Disease

Elevated levels of active MMP-8 (aMMP-8) therefore indicate current disease activity, rather than past tissue damage. Conventional diagnostic methods such as probing depth, clinical attachment level and radiographs provide information on previous tissue destruction. In contrast, increased aMMP-8 levels in Gingival Crevicular Fluid (GCF) and saliva reflect active collagen degradation and ongoing disease progression. Thus, MMP-8 serves as a real-time marker of active periodontitis, helping to identify sites with continuing tissue breakdown.

aMMP-8 (collagenase-2) is the primary collagenolytic protease involved in the degradation of periodontal tissues. It provides higher diagnostic sensitivity and specificity for periodontitis than total MMP-8 (tMMP-8) [8]. MMP-8 levels increase in the early stages of periodontal disease, sometimes before significant clinical attachment loss becomes evident. This makes MMP-8 useful for early diagnosis and for identifying individuals or sites at high risk of disease progression. Elevated baseline MMP-8 levels are associated with a greater likelihood of future attachment loss. A progressive increase in MMP-8 levels is observed from periodontal health to gingivitis and is highest in periodontitis. Gingivitis typically shows moderate increases in total MMP-8, whereas periodontitis is characterized by high levels of active MMP-8. This allows MMP-8 measurement to help distinguish

between reversible gingival inflammation and irreversible periodontal destruction. Thus, elevated aMMP-8 levels in oral fluids reflect the active, rather than stable, phase of disease as observed from the difference between periodontitis from gingivitis [8].

Because MMP-8 levels in GCF are site-specific, they can be used to identify actively diseased periodontal sites within the same mouth [9]. This supports targeted, site-specific periodontal therapy and improves diagnostic precision. Following successful periodontal therapy, MMP-8 levels especially aMMP-8 show a significant reduction, correlating with clinical improvement. Persistently elevated levels may indicate residual disease or risk of recurrence. Hence, MMP-8 is valuable for monitoring treatment outcomes.

Multiple systematic reviews and meta-analyses published in 2024 and 2025 have confirmed that salivary and GCF MMP-8 levels are significantly higher in individuals with periodontitis or gingivitis compared with healthy controls and correlate with clinical periodontal parameters [10].

Chairside point-of-care (POC) tests detecting aMMP-8 in mouth rinse and GCF (e.g., PerioSafe®) provide rapid, non-invasive assessments and show potential for early detection of active disease before invasive clinical signs become apparent [11].

Peri-Implant Diseases

Peri-implant mucositis and peri-implantitis are initiated by bacterial biofilm accumulation on implant surfaces. This triggers an inflammatory response characterized by neutrophil infiltration and release of latent MMP-8 into the peri-implant sulcus. Activation of MMP-8 by bacterial proteases and inflammatory mediators leads to connective-tissue degradation. Elevated levels of active MMP-8 (aMMP-8) therefore indicate ongoing peri-implant tissue destruction, rather than past damage.

In peri-implant health, MMP-8 levels in Peri-Implant Sulcular Fluid (PISF) and saliva are low and predominantly inactive. In peri-implant mucositis, MMP-8 levels show a moderate increase, reflecting soft-tissue inflammation without bone loss. In peri-implantitis, there is a marked elevation of aMMP-8, corresponding to active collagen breakdown and peri-implant bone loss. This progressive increase allows MMP-8 to serve as a biochemical discriminator between health, mucositis and peri-implantitis [12].

Elevated aMMP-8 levels can be detected before radiographic bone loss becomes evident, enabling early diagnosis of peri-implantitis and timely intervention to prevent implant failure.

MMP-8 levels in PISF are site-specific, allowing identification of actively inflamed or progressing peri-implant sites [13]. This helps clinicians distinguish localized peri-implantitis from generalized inflammation and plan targeted therapy. Successful peri-implant therapy, including mechanical debridement, antimicrobial treatment or surgical intervention, results in a reduction of MMP-8 levels. Persistent elevation of aMMP-8 after treatment may indicate incomplete resolution of inflammation or risk of disease recurrence. Thus, MMP-8 is useful for monitoring treatment outcomes and long-term implant maintenance.

Meta-analysis of studies comparing MMP-8 levels in Peri-Implant Crevicular Fluid (PICF) reveals significantly elevated MMP-8 levels in peri-implantitis cases compared to healthy implants, indicating its association with peri-implant disease processes. However, further diagnostic accuracy research is required for definitive clinical validation [14].

Assay Techniques and Sampling Considerations

Accurate assessment of MMP-8 in oral disease depends on both appropriate sampling and reliable assay techniques [15]. MMP-8 can be measured with Enzyme-Linked Immunosorbent Assays (ELISA), time-resolved Immunofluorometric Assays (IFMA) and lateral-flow immunoassay POC tests. IFMA often shows higher sensitivity and specificity compared to ELISA and POC tests. While GCF sampling offers high site-specific diagnostic accuracy, mouthrinse and salivary samples allow for a rapid, non-invasive evaluation of the entire mouth GCF sampling remains a preferred diagnostic fluid due to its proximity to periodontal tissues and higher correlation with local disease activity [16]. aMMP-8 Point-Of-Care Tests (POCT), such as mouthrinse or GCF-based lateral flow tests, provide rapid results (within 5-15 minutes). These tests are valuable for screening, grading (e.g., distinguishing Stage IV), monitoring treatment outcomes and identifying patients at risk of future periodontal breakdown. While GCF sampling offers high site-specific diagnostic accuracy, mouthrinse and salivary samples allow for a rapid, non-invasive

evaluation of the entire mouth. A threshold of 20 ng/mL is often used to differentiate active periodontal breakdown (≥ 20 ng/mL) from health/low-risk conditions (< 20 ng/mL) (Table 1,2) [17].

Sample Type	Source	Main Use	Advantages	Limitations	Common Assays Used
Gingival Crevicular Fluid (GCF)	Periodontal sulcus	Diagnosis of active periodontitis (site-specific)	• Reflects local disease activity • Site-specific • High diagnostic value	• Small volume • Technique-sensitive • Risk of blood contamination	ELISA, IFMA, Western blot, Chairside aMMP-8 test
Peri-Implant Sulcular Fluid (PISF)	Implant sulcus	Diagnosis of peri-implant mucositis and peri-implantitis	• Site-specific • Early detection of peri-implantitis	• Very small volume • Technique-sensitive	ELISA, IFMA, Chairside aMMP-8 test
Saliva	Whole oral cavity	Screening and risk assessment	• Non-invasive • Easy collection • Suitable for chairside tests	• Not site-specific • Influenced by flow rate and systemic inflammation	ELISA, Chairside aMMP-8 test
Serum / Plasma	Systemic circulation	Research, systemic association studies	• Reflects systemic inflammation	• Low specificity for oral disease • Invasive	ELISA, IFMA

Table 1: Sampling methods vs assay techniques for MMP-8.

Assay Technique	Form Detected	Application	Advantages	Limitations
ELISA	Total MMP-8 / aMMP-8	Research and reference diagnostic method	• High sensitivity and specificity • Quantitative	• Time-consuming • Requires laboratory
Immunofluorometric Assay (IFMA)	Mainly aMMP-8	Research and validation studies	• Very high sensitivity • Differentiates active vs latent forms	• Expensive • Limited availability
Western Blot	Pro- and active MMP-8	Confirmatory research	• High specificity • Molecular identification	• Semi-quantitative • Labor-intensive
Zymography	Enzymatic activity	Experimental studies	• Measures functional activity	• Not quantitative • Technically demanding
Chairside / Point-of-Care Tests	Active MMP-8	Clinical screening and monitoring	• Rapid • Non-invasive • Chairside use	• Semi-quantitative • Variable cut-off values

Table 2: Assay techniques for MMP-8.

Integrative Clinical Insights

Emerging evidence indicates that MMP-8 levels are influenced by systemic conditions such as diabetes, where elevated salivary MMP-8 correlates with periodontal severity. This highlights the complex interplay between systemic health and periodontal inflammation and strengthens the rationale for biomarkers in risk stratification and precision dentistry [18]. Salivary biomarker profiling, including MMP-8, interleukins and other inflammatory mediators, is increasingly recognized as a non-invasive diagnostic approach with potential applications beyond oral disease to systemic inflammatory conditions [19].

Limitations and Challenges

Despite promising results, several challenges limit clinical adoption of MMP-8 diagnostics:

- Biological variability due to smoking, systemic conditions and genetic factors

- Lack of standardized thresholds across different assays and populations
- POC tests currently supplement rather than replace conventional diagnostics

Integration of biomarker data with clinical and radiographic findings is essential for robust diagnosis.

Future Perspectives

Future research should emphasize longitudinal cohort studies, standardized assay protocols and multi-biomarker panels combining MMP-8 with other markers for enhanced sensitivity and specificity. Development of digital diagnostics and machine learning integration represents a frontier for precision oral health risk prediction.

Conclusion

MMP-8, particularly its active form, is a clinically relevant biomarker for diagnosing and monitoring periodontal and peri-implant diseases. Its elevation in oral fluids precedes overt clinical destruction, offering a promising avenue for early detection, risk stratification and personalized disease management.

Conflict of Interest

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Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore, was exempt.

Informed Consent Statement

Informed consent was taken for this study.

Authors' Contributions

All authors contributed equally to this paper.

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