*Review Article*

# Potentials of Salivary Matrix Metalloproteinase 9 to Discriminate Periodontal health and disease

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**Abstract:** Periodontitis is a chronic inflammatory disease resulted from aggravated immune response to a dysbiotic subgingival microbiota of a susceptible host. Consequences of periodontitis are not only limited to the devastating effect on the oral cavity but extends to affect general health of the individual and also exerts economic burdens on the health systems worldwide. Despite these serious outcomes of periodontitis; however, they are avoidable by early diagnosis with proper preventive measures or non-invasive interventions at earlier stages of the disease. Clinically, diagnosis of periodontitis could be overlooked due to certain limitations of the conventional diagnostic methods such as periodontal charting and radiographs. Utilization of readily available biomarkers in the oral biofluids represents a potential opportunity to overcome these issues. This topic received great attention in the last decades and one of these biomarkers is matrix metalloproteinase 9 which is highlighted in this review as one of the candidates that can be used for diagnosis of periodontal diseases.

**Keywords:** *matrix metalloproteinases, periodontal disease, periodontitis, diagnosis.*

## Introduction

Periodontitis is a multi-factorial chronic inflammatory disease characterized by destructive events to the supporting structures of the teeth. At the terminal stages of this disease, tooth loss is inevitable result with subsequent deterioration in function, esthetic, and quality of life [1, 2]. The main etiological factor responsible for the initiation and progression of periodontitis is the dysbiotic biofilm leading to chain immune-inflammatory reactions which are further modified by genetic and environmental risk factors [3]. Periodontitis is one of the most prevalent chronic disease affecting humankind. Statistics indicate that periodontitis of different severities affect up to 50% of the populations worldwide [4]. This is associated with negative outcomes on different aspects of individual's oral and systemic health and also exerting an economic burden in developed and developing countries [2].

Shifting of subgingival microbiota from symbiotic to dysbiotic biofilm is the keystone factor for triggering an intense immune response and inflammatory reaction responsible for the development and progression of periodontitis [5, 6]. Periodontitis-associated destructive events are characterized by upregulation of pro- and inflammatory cytokines and proteolytic enzymes responsible for damaging the periodontal tissues. For instance, MMP responsible for extracellular matrix remodeling during health; however, when their levels exceed the normal concentrations is an alarming sign of progressive periodontitis [7, 8]. In addition, during health state, lytic action of MMPs is normally regulated and neutralized by the tissue inhibitors of matrix metalloproteinases (TIMP) [9]. On contrary, during periodontitis, available TIMP in the tissue is not enough to counteract excessively-produced MMPs [10].

One of the main issues related to periodontitis is its early diagnosis by the general practitioners. This is related to certain drawbacks of the conventional diagnostic methods especially when the disease is in its early stages. Over last decades, many researchers investigated the diagnostic potential of many biomarkers available in oral biofluids to use them as surrogates for diagnosis and prediction of periodontal diseases. This review aimed to highlight available evidence about the diagnostic power of matrix metalloproteinase (MMP)-9 to differentiate periodontal health and disease.

**Diagnosis of periodontal disease, dilemma of periodontal parameters**

Towards the end of 2017, joint workshops of American Academy of Periodontology and European Federation of Periodontology led to the announcement of the latest classification system for periodontal diseases and conditions. This novel scheme differs greatly from the older classification system issued in 1999 [11].

Although many issues related to the older system were solved by the new one, issues related to the conventional diagnostic methods still exist. Among these problems is that clinical parameters measurements are highly dependent on the operator's skills and experience. In addition, recording of periodontal parameters could be affected by periodontal probe dimensions, force of application, and direction of the probe [12-14]. Furthermore, full-mouth periodontal charting is a time-consuming and equally tedious process for the operator and the patient. Moreover, radiographs are 2-dimensional images of 3-dimensional objects in which certain structures could be obscured or dimensionally distorted [12-14]. However, despite these limitations, periapical radiograph is indispensable tool to detect interproximal bone loss particularly in early stages of periodontitis which is potentially missed during periodontal probing. Indeed, correct diagnosis is essential step for tailoring solid treatment plan and predicting progression of periodontitis [15, 16].

The aforementioned drawbacks of the clinical diagnostic methods necessities the seek for alternative, time-saving, cost-effective, and accurate diagnostic methods. Salivary biomarkers are readily available and can be collected non-invasively could be the solution for reliable and quick screening of the patients using chairside techniques.

**Matrix Metalloproteinase 9 as a diagnostic tool for periodontal disease**

The MMP9 is one of the key proteolytic enzymes responsible for degrading collagen and gelatin in the extracellular matrix proteins during periodontal health and disease [17, 18]. Type IV collagen is the main target of MMP9, thereby, the action of this enzyme leads to disintegration of the basal membrane [19]. In addition, MMP9 is also responsible for attracting osteoclasts to the site of bone

resorption [20, 21, 22]. Indeed, these actions are more obvious during periodontitis when the concentrations of MMP9 increased beyond neutralizing action of TIMP [23].

The fact that MMP9 alongside other inflammatory mediators/cytokines are significantly increased during periodontal disease as compared to health attracted the interest of investigators to use them as diagnostic biomarkers. Available literature proposed that salivary MMP9 exhibits high accuracy to discriminate periodontal health from disease [24-27].

Search of literature showed limited number of publications which investigated MMP9, in different oral biofluids including saliva, as a diagnostic tool for periodontal disease (Table 1). However, all these studies were observational and were conducted on a limited sample size. In addition, impact of real-life situations such as smoking and systemic diseases were not considered and their effect on the diagnostic potential of MMP9 still not clear.

**Table 1:** The diagnostic accuracy of salivary matrix metalloproteinase 9 as a biomarker for periodontal diseases.

| Reference | Study population | Sample | Conclusions |
|---|---|---|---|
| **Bostanci et al., 2021** [28] | Periodontitis, gingivitis, and healthy periodontium (n=127) | WUS | Combination of MMP9 with other biomarkers demonstrated high accuracy (up to 100%) to differentiate health from disease. |
| **Kim et al., 2020** [29] | Periodontitis and healthy periodontium (n=137) | WUS | MMP9 showed an accuracy of 82% to differentiate periodontitis from healthy periodntium |
| **Kim et al., 2020** [30] | Periodontitis and healthy periodontium (n=149) | WUS | Salivary S100A8 and MMP9 showed high diagnostic/prognostic value for periodontitis. |
| **Alassiri et al., 2018** [31] | Periodontitis, periimplantitis, healthy periodontium (n=80) | Oral rinse, PISF, GCF | The tests are valid to differentiate periodontal and peri-implant health from disease |

Whole unstimulated saliva (WUS), peri-implant sulcular fluid (PISF), gingival crevicular fluid (GCF)

## Conclusions

Available studies showed encouraging and promising results for using MMP9 to differentiate periodontal health from disease. However, the level of evidence cannot support the use of this enzyme as a diagnostic chairside tool as further controlled studies with higher standards are required before translating the results into clinical practice.

**Conflict of interest:** None.

## References

1. Kinane DF, Stathopoulou PG and Papapanou PN. Periodontal diseases. Nat Rev Dis Primers. 2017;3:17038.

2. Botelho J, Machado V, Leira Y, Proença L, Chambrone L and Mendes JJ. Economic burden of periodontitis in the United States and Europe: An updated estimation. J Periodontol. 2022;93:373-379.

3. Kornman KS. Mapping the pathogenesis of periodontitis: a new look. J Periodontol. 2008;79:1560-8.

4. Nazir M, Al-Ansari A, Al-Khalifa K, Alhareky M, Gaffar B and Almas K. Global Prevalence of Periodontal Disease and Lack of Its Surveillance. ScientificWorldJournal. 2020;2020:2146160.

5. Darveau RP. Periodontitis: a polymicrobial disruption of host homeostasis. Nat Rev Microbiol. 2010;8:481-90.

6. Offenbacher S. Periodontal diseases: pathogenesis. Ann Periodontol. 1996;1:821-78.

7. Weng H, Yan Y, Jin YH, Meng XY, Mo YY and Zeng XT. Matrix metalloproteinase gene polymorphisms and periodontitis susceptibility: a meta-analysis involving 6,162 individuals. Sci Rep. 2016;6:24812.

8. Romanos GE and Bernimoulin JP. [Collagen as a basic element of the periodontium: immunohistochemical aspects in the human and animal. 1. Gingiva and alveolar bone]. Parodontol. 1990;1:363-75.

9. Murphy G. Tissue inhibitors of metalloproteinases. Genome Biol. 2011;12:233.

10. Checchi V, Maravic T, Bellini P, Generali L, Consolo U, Breschi L and Mazzoni A. The Role of Matrix Metalloproteinases in Periodontal Disease. Int J Environ Res Public Health. 2020;17.

11. Caton JG, Armitage G, Berglundh T, Chapple ILC, Jepsen S, Kornman KS, Mealey BL, Papapanou PN, Sanz M and Tonetti MS. A new classification scheme for periodontal and peri-implant diseases and conditions - Introduction and key changes from the 1999 classification. J Periodontol. 2018;89 Suppl 1:S1-s8.

12. Slots J. Periodontitis: facts, fallacies and the future. Periodontol 2000. 2017;75:7-23.

13. Andrade R, Espinoza M, Gómez EM, Espinoza JR and Cruz E. Intra- and inter-examiner reproducibility of manual probing depth. Braz Oral Res. 2012;26:57-63.

14. Lafzi A, Mohammadi AS, Eskandari A and Pourkhamneh S. Assessment of Intra- and Inter-examiner Reproducibility of Probing Depth Measurements with a Manual Periodontal Probe. J Dent Res Dent Clin Dent Prospects. 2007;1:19-25.

15. Papapanou PN, Sanz M, Buduneli N, Dietrich T, Feres M, Fine DH, Flemmig TF, Garcia R, Giannobile WV, Graziani F, Greenwell H, Herrera D, Kao RT, Kebschull M, Kinane DF, Kirkwood KL, Kocher T, Kornman KS, Kumar PS, Loos BG, Machtei E, Meng H, Mombelli A, Needleman I, Offenbacher S, Seymour GJ, Teles R and Tonetti MS. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Periodontol. 2018;89 Suppl 1:S173-s182.

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16. Shaddox LM and Walker CB. Treating chronic periodontitis: current status, challenges, and future directions. Clin Cosmet Investig Dent. 2010;2:79-91.

17. Kim HD, Sukhbaatar M, Shin M, Ahn YB and Yoo WS. Validation of periodontitis screening model using sociodemographic, systemic, and molecular information in a Korean population. J Periodontol. 2014;85:1676-83.

18. Chen Q, Jin M, Yang F, Zhu J, Xiao Q and Zhang L. Matrix metalloproteinases: inflammatory regulators of cell behaviors in vascular formation and remodeling. Mediators Inflamm. 2013;2013:928315.

19. Jotwani R, Eswaran SV, Moonga S and Cutler CW. MMP-9/TIMP-1 imbalance induced in human dendritic cells by Porphyromonas gingivalis. FEMS Immunol Med Microbiol. 2010;58:314-21.

20. Xie R, Kuijpers-Jagtman AM and Maltha JC. Osteoclast differentiation and recruitment during early stages of experimental tooth movement in rats. Eur J Oral Sci. 2009;117:43-50.

21. Somerville RP, Oblander SA and Apte SS. Matrix metalloproteinases: old dogs with new tricks. Genome Biol. 2003;4:216.

22. Delaissé JM, Andersen TL, Engsig MT, Henriksen K, Troen T and Blavier L. Matrix metalloproteinases (MMP) and cathepsin K contribute differently to osteoclastic activities. Microsc Res Tech. 2003;61:504-13.

23. Şurlin P, Oprea B, Solomon SM, Popa SG, Moţa M, Mateescu GO, Rauten AM, Popescu DM, Dragomir LP, Puiu I, Bogdan M and Popescu MR. Matrix metalloproteinase -7, -8, -9 and -13 in gingival tissue of patients with type 1 diabetes and periodontitis. Rom J Morphol Embryol. 2014;55:1137-41.

24. Kc S, Wang XZ and Gallagher JE. Diagnostic sensitivity and specificity of host-derived salivary biomarkers in periodontal disease amongst adults: Systematic review. J Clin Periodontol. 2020;47:289-308.

25. de Morais EF, Pinheiro JC, Leite RB, Santos PPA, Barboza CAG and Freitas RA. Matrix metalloproteinase-8 levels in periodontal disease patients: A systematic review. J Periodontal Res. 2018;53:156-163.

26. Victor DJ, Subramanian S, Gnana PP and Kolagani SP. Assessment of Matrix Metalloproteinases-8 and -9 in Gingival Crevicular Fluid of Smokers and Non-smokers with Chronic Periodontitis Using ELISA. J Int Oral Health. 2014;6:67-71.

27. Saglam M, Kantarci A, Dundar N and Hakki SS. Clinical and biochemical effects of diode laser as an adjunct to nonsurgical treatment of chronic periodontitis: a randomized, controlled clinical trial. Lasers Med Sci. 2014;29:37-46.

28. Bostanci N, Mitsakakis K, Afacan B, Bao K, Johannsen B, Baumgartner D, Müller L, Kotolová H, Emingil G and Karpíšek M. Validation and verification of predictive salivary biomarkers for oral health. Sci Rep. 2021;11:6406.

29. Kim H-D, Lee C-S, Cho H-J, Jeon S, Choi Y-N, Kim S, Kim D, Jin Lee H, Vu H, Jeong H-J and Kim B. Diagnostic ability of salivary matrix metalloproteinase-9 lateral flow test point-of-care test for periodontitis. J Clin Periodontol. 2020;47:1354-1361.

30. Kim. HD, Kim S, Jeon S, Kim SJ, Cho HJ and Choi YN. Diagnostic and Prognostic ability of salivary MMP-9 and S100A8 for periodontitis. J Clin Periodontol. 2020;47:1191-1200.

31. Alassiri S, Parnanen P, Rathnayake N, Johannsen G, Heikkinen AM, Lazzara R, van der Schoor P, van der Schoor JG, Tervahartiala T, Gieselmann D and Sorsa T. The Ability of Quantitative, Specific, and Sensitive Point-of-Care/Chair-Side Oral Fluid Immunotests for aMMP-8 to Detect Periodontal and Peri-Implant Diseases. Dis Markers. 2018;2018:1306396.

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**إمكانات استخدام Matrix Metalloproteinase 9 اللعابية للتمييز بين صحة اللثة وأمراضها**
**أحمد رمزي عطرجي**

**المستخلص**
التهاب دواعم السن هو مرض التهابي مزمن ينتج عن تفاقم الاستجابة المناعية لميكروبات تحت اللثة لمضيف حساس. لا تقتصر عواقب التهاب دواعم السن على التأثير المدمر على تجويف الفم فحسب ، بل تمتد لتؤثر على الصحة العامة للفرد وأيضًا تفرض أعباء اقتصادية على النظم الصحية في جميع أنحاء العالم. على الرغم من هذه النتائج الخطيرة لالتهاب دواعم السن ؛ ومع ذلك ، يمكن تجنبها عن طريق التشخيص المبكر مع التدابير الوقائية المناسبة أو التدخلات غير الغازية في مراحل مبكرة من المرض. سريريًا ، يمكن ان يهمل تشخيص التهاب دواعم السن بسبب بعض العيوب المرتبطة بطرق التشخيص التقليدية مثل مخططات اللثة والتصوير الشعاعي. يمثل استخدام المؤشرات الحيوية المتاحة بسهولة في السوائل الحيوية الفموية فرصة محتملة للتغلب على هذه المشكلات. حظي هذا الموضوع باهتمام كبير في العقود الماضية وأحد هذه المؤشرات الحيوية هو **matrix metalloproteinase 9** والتي تم تسليط الضوء عليها في هذه المراجعة كأحد المرشحين الذين يمكن استخدامها لتشخيص أمراض اللثة.

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