

Do MMPs in the Oral Fluid Act as a Noninvasive Biomarker for Diabetes Mellitus-associated Periodontal Diseases?

Kaviyarasi Renu¹, Veeraraghavan Vishnu Priya², Abilash Valsala Gopalakrishnan³

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Diabetes mellitus is found to be the most essential chronic disease, caused mainly due to insulin production deficiency or its resistance to an act of it. Deficiency in insulin production mediates alteration of metabolism; it leads to hyperglycemia and further influences systemic abnormalities.¹ In periodontal diseases, the most important type is chronic periodontitis. This is due to the inflammation which was initially activated by gingival bacteria which supports the tissue in the periodontal region.² Periodontal disease causes an imbalance between the pathogen present in the periodontal region and the response to the immune system in the host.³ This further disturbs the tissues which surround the tooth and finally leads to tooth loss. Diabetes mellitus has more risk of periodontitis enhancement.⁴ The increased glycemic level in diabetes mellitus increases the periodontitis severity.⁵ Diabetes and periodontitis are interconnected diseases; hyperglycemia in diabetes causes periodontal eradication *via* dysregulated response to the inflammation, which leads to enhancement of immune reaction.⁶ On the other hand, periodontitis increases the glucose level which further contributes to the impact of the diabetic condition.⁷ Matrix metalloproteinases (MMPs) have an important role in the physiological mechanism and process of pathogenesis and acts on the extracellular matrix remodeling and its proteolytic degradation.⁸ The synthesis of MMPs is by enzymes inactive forms, which are produced by cysteine residues bonds with the zinc ions. MMPs are involved in the process of proliferation of cells, adhesion, and migration of cells; factors involved in growth; signaling events, and the process of chemo healing. It is highly needed for inflammatory reaction and wound healing.⁹ There are different types of MMPs were found depending on the specificity of the substrate and homologies of its structure. Some of them are: MMP-1, -13, and -8 belong to the collagenase; MMP-9 and -2 belong to gelatinase; MMP-11, -10, -11 belong to stromelysin; MMP-25, -23, -24, -14, -16, -15, -17 belong to membrane-type MMPs and MMP-7 belong to matrilysin and MMP-12 belongs to metalloelastase.¹⁰ Diabetes doesn't cause periodontitis but it increases the destruction of periodontal tissue in an irreversible form. They have elevated the production of collagen, changes in the synthesis of glycosaminoglycans and collagen levels, and alteration in the production of cytokines. This contributes to the MMPs formation.¹¹ The periodontal tissue degradation is essentially mediated by the enzymes which are released during inflammation, especially MMPs.¹² There are a few MMPs that are involved in periodontal diseases and diabetes, which we will discuss further. The establishment of MMP-14 is linked with low TIMP-2 levels, which activates pro-MMP-2. There is an increased level of MMP-14 is observed in the gingival tissues in periodontal-associated diabetes.¹⁰ In the oral fluid, there is

^{1,2}Centre of Molecular Medicine and Diagnostics (COMManD), Department of Biochemistry, Saveetha Dental College and Hospital, Saveetha Institute of Medical and Technical Sciences (Deemed to be University), Chennai, Tamil Nadu, India

³Department of Biomedical Sciences, School of Biosciences and Technology, Vellore Institute of Technology (VIT), Vellore, Tamil Nadu, India

Corresponding Author: Kaviyarasi Renu, Centre of Molecular Medicine and Diagnostics (COMManD), Department of Biochemistry, Saveetha Dental College and Hospital, Saveetha Institute of Medical and Technical Sciences (Deemed to be University), Chennai, Tamil Nadu, India, Phone: +91 8124849023, e-mail: kaviyarasirenu.92@gmail.com

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an elevation of collagenase-2 or MMP-8 is observed in diabetes-associated periodontal patients. This contributes to the major risk factor for periodontitis in diabetic patients.¹³ Diabetes increases the MMP-8 level in periodontal subjects which shows that it acts as a biomarker for diabetes-associated periodontal diseases.¹⁴ In gingival tissue, there is an increased MMP-8 level and MMP-9 level in diabetic chronic periodontic subjects. These augmented level of MMP-8 and -9 leads to an impaired process of healing in chronic periodontic-associated diabetic patients.¹⁵ In contrast to this, there is a study that shows that there are no significant alterations in the level of the MMP-8 and -9 in diabetes-associated periodontal diseases. This is due to its study limitation such as the lack of studies in a long time follow-up to determine this biomarker in diabetes-associated periodontal diseases.¹⁶ There is an elevated expression of the gingival MMP-2 and MMP-9 by TNF- α activation, which contributes to the inflammation in diabetes-associated periodontal diseases.¹⁷ In the diabetes-associated periodontal diseases show there is an augmented expression of gingival MMP-7, activated by hyperglycemia *via* reactive oxygen species. On the other hand, its suppression impairs the gingival transmigration of neutrophils.¹⁸ There is an elevated expression of MMP-9 in diabetes mellitus associated with chronic periodontitis which is due to hyperglycemia, it contributes to elevated inflammation which detaches proinflammatory cytokines and further causes periodontal tissue degradation.¹⁹ There are different MMPs determined in periodontal disease alone or diabetes alone, exploring the link between different types of MMPs in periodontal-

associated diabetes needs to be elucidated in the future. In conclusion, the oral fluid such as gingival or saliva, the presence of MMPs contributes to the development of the non-invasive diagnosis of diabetes-associated periodontal diseases.

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