The Association of Matrix Metalloproteinase Gene Polymorphisms and Periodontitis: An Overview

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Periodontitis is a multifactorial inflammatory disease, pathogenic bacteria being the primary etiological agents. The host response and the severity of clinical manifestation are determined by genetic and environmental factors. There is some evidence that the individual response to environmental variations in the immune response in periodontitis is associated with genetic factors. Matrix metalloproteinases (MMPs) are a family of proteolytic enzymes located in the extracellular matrix. Their primary function is the breakdown of connective tissue components. Their role in the oral cavity is very vital. In this literature review, we summarized the contemporary knowledge on the function of MMPs in oral cavity and periodontal disease.

Keywords: Extracellular matrix, gene polymorphism, gingival crevicular fluid, matrix metalloproteinases, periodontitis

INTRODUCTION

Periodontitis is a chronic inflammatory disease that caused an irreversible damage to the periodontal attachment and the alveolar bone. As disease progresses, it may lead teeth loss.[1] Periodontitis can be divided into two forms: chronic periodontitis (CP) and aggressive periodontitis (AgP) based on several criteria as in American Academy of Periodontology (AAP) classification in 1999.[2] It is estimated that periodontitis prevalence (in both forms) can reach up to 72% of middle-aged US population[3] and at 89% of Indian population.[4] This difference in prevalence between the two populations can be explained by disease nature and other factors.[3,4]

Host response considered as a modulating factor; only 8% of tea workers in Sri Lanka who never involved in oral hygiene program developed severe periodontitis and 81% of them had moderate periodontitis. The explanation of such difference in severity and how the human body reacts to is not fully understood.[1] Host response involves many contributing factors such as systemic condition, smoker status, genetic basis, and other factor directly or indirectly affecting...
the host. Genetic factors were evident in studies and they found 50% of periodontitis accounted for genetics factors that lead researchers to investigate the genetic polymorphism by either genome-wide associations (GWAS) or single-nucleotide polymorphisms (SNPs) to detect gene mutations and allelic variants leading to abnormal function of proteins.[4,5]

Matrix metalloproteinase (MMP) enzymes are thought as host-derived proteinases. They play an essential part in the embryonic development, morphogenesis, tissue repair, and pathological behavior during connective tissue destruction and play dissimilar role in oral environments in periodontitis. They could be used as a biomarker in gingival crevicular fluid (GCF). MMPs are zinc-dependent zymogens. Their primary function is related to degradation, chemokine’s inactivation, cell proliferation, angiogenesis, and apoptosis.[3-4]

Our aim in this literature review was to look into the genetic polymorphism in MMPs on periodontitis patient.

**SEARCH METHODOLOGY**

Using PubMed, Google Scholar, Embase, and MEDLINE databases for the key words “matrix metalloproteinases, polymorphism, periodontal disease, periodontitis, chronic periodontitis and aggressive periodontitis” we retrieved all clinical trials and systemic reviews. Only human studies that were written in English were included. Inappropriate articles by title and meta-analyses were omitted. Further exclusion by reading the abstract led to the most appropriate articles to our topic.

**MATRIX METALLOPROTEINASE STRUCTURE, HISTOLOGY CLASSIFICATION, AND FUNCTION**

MMPs are family of 24 enzymes; they have similar structure in approximately 40% of time. They are zinc-dependent endopeptidase and usually secreted in an inactive form, except the membrane-associated MMPs (MT-MMPs). The primary structure of one MMP can be divided into three main segments: N-terminal peptide, the catalytic segment (lined with a hinge to the), and C-terminal domain.[6] In all secreted MMPs (except MMP-7 and MMP-26), the catalytic domain is followed by a C-terminal hemopexin-like domain contributing to substrate and tissue inhibitor of metalloproteinase (TIMP) binding, proteolytic activity, and membrane activation. In the MT-MMPs, the C-terminal domain attaches the molecule to the plasma membrane. A type 2 transmembrane MMPs (MMP-23) has cysteine array and immunoglobulin-like domains instead of the conserved hemopexin-like domain.[5]

According to their cleavage capability, they can be classified into six groups: collagenases, gelatinases, matrilysins, stromelysin membrane-associated MMPs, and MMPs with no group designation. Classification with numbers MMP-1 to MMP-28 is used for designation. MMPs can cleave the major and minor components of the extracellular matrix (ECM), with few exceptions such as MMP-11 and MMP-23. MMPs have the ability to lysis ECM components as well as acting as an activator for important biological molecules. The mode of action of dissimilar types of MMPs is greatly dependent on the group, which they belong to. For example, the Collagenases (MMP-1, MMP-8, and MMP-13) can degrade the interstitial collagen (types I, II, and III). The Gelatinases include MMP-2 and MMP-9, and have a broader function as they primarily cleave collagen type IV in basal membranes, but they can also denatured collagen types V, VII, X, XIV, elastin, fibronectin, and aggrecan.[5,6]

On the contrary, Stromelysins can cleave the non-collagenous ECM such as fibronectin, proteoglycans, laminin, and glycoproteins. The collagen degradation of the cell membrane is chiefly the function of MT-MMPs. The macrophage elastase and other MMPs, mainly MMP-12, can cleave elastin, laminin, fibronectin, emalogenin, entactin, collagen, basal membrane, chondroitin sulfate, and others.[7]

**MATRIX METALLOPROTEINASE ROLE IN ORAL ENVIRONMENT**

MMPs are fundamental in both physiological and pathological events in oral cavity. They have been isolated from specimens of GCF, enamel, saliva as well as periodontal tissues. MMPs are involved in various events like enamel formation, cell migration, tissue remodeling, wound healing, and organogenesis. Several studies showed that MMPs have a concrete role in the remodeling of the organic matrix of dentin and bone during oral tissue formation and repair.[8,9]

MMPs have a variety of roles in physiological events like immune response, inflammation and ECM remodeling. Their production, activation, and inhibition are all tightly regulated in health; it is only when uncontrolled dysregulation of MMPs occurs, that destructive actions ensue.[7,4]

**Role in enamel and dentine formation**

In enamel, MMP-20 is a tooth-specific MMP and known as enamelysin, which is expressed by ameloblast and odontoblast. It plays a significant function in enamel and dentine formation. In the case of mutations of MMP-20, defective enamel will be formed as seen in amelogenesis imperfecta. Also, MMP-2, MMP-9,
MMP-8, and MMP-14 produced by odontoblasts have a regulation role during dentine formation and after mineralization of the dentine, the inactive forms of MMPs will be trapped within the calcified dentine.[10]  

Role in dental caries
Different hypotheses about how MMPs have a role in caries were proposed. One of which reported that excessive bacterial acids rise acidic pH, which in turn activates MMPs to digest the dentin matrix. It was also reported that the breakdown of the Small Integrin-binding Ligand N-linked Glycoproteins (SIBLINGs) by the caries may enhance the release of MMPs and their activation, which subsequently leads to caries. Therefore, MMP inhibition may provide treatment pathway to stop caries progression in dentin.[11]  

Role in adhesive restorations
In adhesive restoration, the weakest layer is a hybrid layer located at interface between restoration and tooth structure and becomes weaker at dentin due to humid nature of dentine. As a result of acidity of caries and acid etching, both had ability to degradation of dental collagen that leads to an abundant release of MMP (MMP-2 and MMP-9) as protective measures, but in the case of adhesive restoration the released MMP will potentially degrade the exposed collagen fiber within hybrid layer and that will have affect a negative effect on strength of bond at hybrid layer and by applying MMPs inhibitors such as chlorohexidine digluconate the strength of bond at hybrid layer increases.[10-12]  

Role in gingival crevicular fluid and saliva
GCF and saliva contain different types of MMPs. Most likely the cell origin of MMPs in GCF and saliva are the polymorphonuclear (PMN) leucocytes. Many observations confirmed that PMN leucocytes are the chief contributors of MMP in GCF. For example, early research showed metabolites in GCF originated from plasma, and PMN leucocytes. Also, it was shown that GCF contains α-2M, albumin, and immunoglobulins that are present at high concentrations, produced by PMN leucocytes and carried to the GCF via different carriers (CL, Mr 92K GL, elastase, and myeloperoxidase.[13,14]  

Role in periodontal disease
It is known that periodontitis (chronic or aggressive) is one of the dental pathologies where genetic component and phenotypic alterations contribute to overall disease progression and severity. Periodontal disease is a long-lasting chronic inflammation and tissue destruction, which lead into pocket formation and bone loss. Destruction process is predominantly related to bacterial challenge that can lead to overexpression of defense mechanism such as MMPs and other mediators. They are formed by infiltrating neutrophils, macrophages, and resident cells of periodontium. Moreover, there is a significant bank of evidence implicating the pivotal role of MMPs in periodontal tissue destruction in disease. Several MMPs, such as MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, and MMP-9, have been found in higher proportion on GCF and saliva samples obtained from periodontitis patients and evident for direct correlation with severity and progress of periodontal disease by high expression of MMP or imbalance of tissue inhibitor of MMPs. Among them, MMP-8 has shown in many laboratories and chair side studies to be elevated in disease and appears as a promising biomarker.[13-15]

Apart from MMP-8, MMP-13 and MMP-14, by virtue of pro-MMP-9 effects, have been observed to be involved periodontal tissue destruction by coordinated effects with other proteinases of the family. Activated MMPs are in turn able to stimulate production of other signaling molecules such as cytokines and chemokines further cementing its role in regulating periodontitis progression.[10] It was found that treatment of periodontitis with scaling and root planning (SRP) reduced level of different MMPs (MMP-1, MMP-2, MMP-3, MMP-8, MMP-9, MMP-12, and MMP-13).[16,17]  

It was also found that nonsurgical therapy with antibiotics as well reduced the levels of MMP-8. Phase 1 therapy, wherein elimination/control of etiological factors is carried out, has been found to reduce levels of MMPs and increased ratio of TIMPs. Interestingly, by detection MMP-8 and MMP-1 from GCF could be useful biomarkers to distinguish between different types of periodontitis also for mentoring of the disease during maintenance phase.[6,17]  

Matrix Metalloproteinase and Polymorphism
Any genetic polymorphisms that influence MMP expression or their activity can also affect predisposition to periodontitis. Several polymorphisms have been detected in promoter regions of several MMPs. There are potential areas susceptible to polymorphism in the MMP structure, mainly MMP-2-753C/T, MMP-3-1171A5/A6, MMP-8-799C/T, MMP-9-1562C/T, and MMP-12-357Asn/Ser.[5,7-9]  

In MMP-1, gene alteration occurs at the allele 1607 on chromosome; there have been four cohort studies: one with mixed races, one on China mainly for Asians, one on Turkish population, and one in Brazilian race. Two
showed an association with CP, one showed probable link to CP or AgP, and one showed a limited role. In MMP-2, allele alteration occurs at 753C/T location. Relation with periodontal disease has been investigated in one Caucasian race, one Chinese, and one Turkish with a limited role in all of them. The Asian cohort showed an association with AgP found in TIMP-2-418GC gene polymorphism. No association was observed between GAgP and polymorphism MMP-3-1171 A5/A6. No effect on AgP and CP in Japanese population. MMP SNPs were not associated with susceptibility to periodontitis. Association was observed between AgP and MMP-1 2G/2G, MMP-3 5A/5A, MMP-9 C/C. Association was observed between MMP3 and CP disease progression. We found four publications studied the effect on periodontitis development: three via peripheral blood samples and one by gingival fluid assessments. Three showed association with periodontal disease and one showed that both SNPs on −799C/T and +17C/G in the MMP-8 gene were not associated with periodontitis. MMP-9 gene alteration at 1562 C/T is one of the most investigated polymorphisms. We found 10 studies investigating MMP-9 alone or with other MMP effect on periodontal disease. Four on Caucasian race, two on mixed races, three on Asians, and one on India. Most of these were performed using the polymerase chain reaction analyzing DNA from either blood or oral samples. Six showed strong or probable association with periodontitis,

### Table 1: Studies related to MMP-1-1607

| MMP type       | Author            | Year | Periodontitis | Cases | Controls | Sample type | Country | Race   | Outcome                                                                 |
|----------------|-------------------|------|---------------|-------|----------|-------------|---------|--------|--------------------------------------------------------------------------|
| MMP-1-1607     | Cao et al. [4]    | 2005 | AgP           | 40    | 52       | Blood       | China   | Asian  | May be associated with AgP in Chinese population.                          |
|                | de Souza et al. [8] | 2003 | CP            | 50    | 37       | Oral swab   | Brazil  | Mixed  | Associated with the severe CP.                                            |
|                | Repeke et al. [5] | 2009 | CP            | 178   | 190      | Oral swab   | Brazil  | Brazilian | Had a limited role in periodontitis.                                      |
|                | Pirhan et al. [7] | 2008 | CP            | 102   | 98       | Blood sample and GCF | Turkey  | Turkish | Associated with severe CP.                                                |
|                | Holla et al. [9]  | 2004 | CP            | 133   | 196      | Blood       | Czech   | Caucasian | Significantly increased frequency in CP.                                    |

MMP = matrix metalloproteinase, AgP = aggressive periodontitis, CP = chronic periodontitis, GCF = gingival crevicular fluid

| MMP type       | Author            | Year | Periodontitis | Cases | Controls | Sample type | Country | Race   | Outcome                                                                 |
|----------------|-------------------|------|---------------|-------|----------|-------------|---------|--------|--------------------------------------------------------------------------|
| MMP-2-753C/T   | Chen et al. [9]   | 2007 | AgP           | 79    | 128      | Oral swab   | China   | Chinese | Association with AgP found in TIMP-2-418GC gene polymorphism.             |
|                | Gurkan [12]       | 2007 | AgP           | 92    | 157      | Blood sample | Turkey  | Turkish | No association was observed between GAgP and polymorphism.                 |
| MMP-3-1171 A5/A6 | Itagaki et al. [10] | 2004 | AgP           | 37    | 142      | Blood sample | Japan   | Asian  | No effect on AgP and CP in Japanese population.                            |
|                | Astolfi et al. [11] | 2006 | CP            | 114   | 109      | Oral swab   | Brazil  | Mixed  | MMP SNPs were not associated with susceptibility to periodontitis.        |
|                | Loo et al. [13]   | 2011 | CP            | 280   | 250      | Blood sample | China   | Asian  | Association was observed between CP and MMP-1 2G/2G, MMP-3 5A/5A, MMP-9 C/C |
|                | Letra et al. [14] | 2012 | CP            | 99    | 302      | Saliva & gingival biopsy | Brazil  | Mixed  | Association was observed between MMP3 and CP disease progression.        |

MMP = matrix metalloproteinase, AgP = aggressive periodontitis, CP = chronic periodontitis, SNP = single-nucleotide polymorphism, GAgP = generalized aggressive periodontitis
and four showed no true association. Identifying different polymorphism leading to periodontitis may help to build new therapeutics or diagnostic tool. We summarized the most frequent polymorphism in the structure of different MMPs published as potential causes for periodontitis in Tables 1–3.\textsuperscript{[18-22]}

Table 3: Studies related to \textit{MMP-8-799C/T} and \textit{MMP-9-1562C/T}

| MMP type          | Author            | Year | Periodontitis | Cases | Controls | Sample type         | Country   | Race     | Outcome                                                                 |
|-------------------|-------------------|------|---------------|-------|----------|----------------------|-----------|----------|-------------------------------------------------------------------------|
| \textit{MMP-8-799C/T} | Chou \textit{et al.}\textsuperscript{[15]} | 2011 | CP            | 361   | 106      | Blood sample         | Taiwan    | Asian    | \textit{MMP-8} found to be associated with the risks of CP            |
|                   | Chou \textit{et al.}\textsuperscript{[15]} | 2011 | AgP           | 96    | 106      | Blood sample         | Taiwan    | Asian    | \textit{MMP-8} found to be associated with the risks of AgP           |
|                   | Holla \textit{et al.}\textsuperscript{[9]} | 2012 | CP            | 341   | 278      | Gingival sample      | Czech     | Caucasian | No differences between CP and controls in the \textit{MMP-8-799C/T} polymorphisms |
|                   | Emingil \textit{et al.}\textsuperscript{[17]} | 2014 | AgP           | 100   | 167      | Blood sample         | Turkey    | Caucasian | \textit{MMP-8-799C/T} polymorphisms might be associated with AgP, particularly in male |
| \textit{MMP-9-1562C/T} | de Souza \textit{et al.}\textsuperscript{[6]} | 2005 | CP            | 100   | 100      | DNA of oral mucosa   | Brazil    | Mixed    | Polymorphism is not associated with CP.                               |
|                   | Holla \textit{et al.}\textsuperscript{[9]} | 2006 | CP            | 169   | 135      | PCR                  | Czech     | Caucasian | Polymorphisms not associated CP in Czech population.                   |
|                   | Keles \textit{et al.}\textsuperscript{[19]} | 2006 | CP            | 70    | 70       | Blood sample         | Turkey    | Caucasian | Polymorphism is associated with severe CP.                              |
|                   | Chen \textit{et al.}\textsuperscript{[9]} | 2007 | AgP           | 79    | 128      | PCR                  | China     | Asian    | Only association with AgP found in TIMP-2-418GC gene polymorphism      |
|                   | Gurkan \textsuperscript{[12]} | 2007 | AgP           | 112   | 157      | PCR                  | Turkey    | Caucasian | \textit{MMP-9} could be associated with a reduced risk for AgP          |
|                   | Isaza-Guzmán \textit{et al.}\textsuperscript{[19]} | 2011 | CP            | 69    | 54       | Saliva               | Colombia  | Mixed    | \textit{MMP-9} was not linked to periodontal clinical status           |
|                   | Li \textit{et al.}\textsuperscript{[20]} | 2012 | CP            | 122   | 532      | PCR                  | China     | Asian    | \textit{MMP-9-1562} SNPs found to be associated with increased susceptibility to CP |
|                   | Hadi \textit{et al.}\textsuperscript{[21]} | 2017 | CP            | 50    | 50       | Blood sample         | Indonesia | Asian    | Polymorphism is significantly associated with periodontitis.          |
|                   | Rai \textit{et al.}\textsuperscript{[22]} | 2010 | AgP and CP    | 148   | 121      | Blood sample         | India     | Indian   | \textit{MMP-9} was found to associated with Increased risk to AgP and CP |

\textit{MMP} = matrix metalloproteinase, \textit{AgP} = aggressive periodontitis, \textit{CP} = chronic periodontitis, \textit{DNA} = deoxyribonucleic acid, \textit{PCR} = polymerase chain reaction, \textit{SNP} = single-nucleotide polymorphism
CONCLUSION
We performed this literature review to better understand their mechanism of active and function within the oral cavity, as well, to identify the gap in literature. Genetic polymorphism studies have shown variances depending on geographical location, ethnicity of population, and type of periodontal disease. So while it may be difficult to draw a definitive conclusion, what we can observe is that MMPs are the primal gateways for irreversible periodontal tissue destruction and polymorphisms in specific promoter regions can influence the disease susceptibility. Further corroborative evidence can help in developing genetic therapeutic targets in future for better control or prevention of disease. Locally we were not able to find any published research from Saudi Arabia or including a Saudi population.

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Conflicts of interest
There are no conflicts of interest.

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