# Matrix metalloproteinases in periodontics: A review

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## Abstract
Matrix metalloproteinases (MMPs) constitute of different zinc containing enzymes which break down specific extracellular matrix components destroying matrix equilibrium and structural integrity. MMPs have multiple different actions in tissues. MMPs are mainly produced by multiple host cells like fibroblasts, inflammatory cells, epithelial cells. Balance between the production of MMPs and its inhibitors are essential to maintain the normal physiologic structure of host tissues. Overproduction of MMPs might lead to pathological conditions. Though MMPs are secreted less in quantity, it can be an useful biomarker for the detection and to know progression of periodontal diseases.

**Keywords:** Matrix metalloproteinases, Extracellular Matrix, Periodontal Disease, Biomarker.

## Introduction
Tissue remodelling depends of the formation as well as breakdown of extracellular matrix (ECM). The matrix metalloproteinases (MMPs) play a major role in the process for maintaining the integrity of connective tissue. In 1962, Jerome Gross & Charles Lapiere[1] discovered collagenases, present in a wide variety of vertebrates, invertebrates and plants.In 1966, Fullmer et al[2] described human gingival collagenase. A group of zinc and calcium dependent protein digesting enzymes are collectively named as Matrix metalloproteinases. It can degrade extracellular matrix, basement membrane and also can act on inerleukins (IL) and other cytokines, growth factors and chemokines.[3] Metal ions are crucial in its function. Chelating agents such as EDTA can inhibits its action as it can easily binds with metal ions.

**Sources of MMP:** Matrix metalloproteinases can be secreted by different host cells and bacteria as follows:

**a. Fibroblasts:** Collagenases are produced by both resident gingival and periodontal ligament fibroblasts. MMP-1 (collagenase-1), MMP-13 (collagenase-13), MMP-2 (gelatinase A), MMP-3 (stromelysin-1), and MT1-MMP (MMP-14) are mainly produced by fibroblasts.

**b. Inflammatory Cells:** Though neutrophils and macrophages produce matrix metalloproteinases, collagenase and gelatinase in periodontitis are mostly produced by neutrophils.[4] The major MMPs in neutrophils are MMP-8 (collagenase-2) and MMP-9 (gelatinase B).

**c. Epithelial Cells:** In 1998, Uitto et al.[5] reported that the periodontal pocket epithelial cells can produce matrix metalloproteinase-13 (collagenase-3). Gelatinase A (MMP-2) are also secreted by inflamed pocket epithelium and has a important role in epithelial cell migration. Gelatinase B (MMP-9) and matrilysin (MMP-7) are also epithelial type MMPs.

**d. Bacteria:** Few microorganisms such as Porphyromonas gingivalis and Actinobacillus actinomycetemcomitans are capable of producing bacterial collagenases.[6] In 2000,Travis & Protempa described the role of bacterial enzymes in ECM destruction.[7] The role of bacterial MMPs are not quite evident.

**Role of matrix metalloproteinases in periodontal disease**

In past days researchers thought microbes are only the main causative factor for the diseases. Recent studies are aimed to search the host response against the microbes. Surprisingly, many host factors are found to be responsible for disease initiation and progression as well. Matrix metalloproteinase (MMP) is one of them.

Periodontitis is characterized as the loss of periodontal attachment which is due to extensive breakdown of collagen fibers. The role of matrix metalloproteinases in pathological tissue destruction is established. In periodontal diseases, matrix metalloproteinases play important roles in the degradation of the extracellular matrix, basement membrane and protective serpins as well as in the modification of cytokine action and activation of osteoclasts. Matrix metalloproteinase-3 (stromelysin) first degrades proteoglycans and fibronectin which coats collagen fibrils. Then the collagen fibers are exposed which is degraded by collagenase into fragments. Many cross-sectional studies reported the presence of MMPs in periodontal diseases and also positive correlations.[8,9]

**Regulation of MMP**

The function of MMPs can be regulated by four ways:

1. **Transcriptional regulation of MMP expression:** MMPs are secreted at a low rate in normal tissues but increases on demand. Subcellular granules of neutrophils stores MMP-8 and MMP-9and releases rapidly called selective degranulation, and MMP-7 storage in secretory epithelial cells in exocrine glands is an exception to this inductive *de novo* production.[10] MMP expression is regulated at the transcriptional level by many growth factors and cytokines, oncogenes, hormones. The AP-1 transcription factor complexes are stimulated by extracellular stimulus to bind into the AP-1 binding site in the MMP gene that results in stimulation for MMP secretion.
2. **By Precursor Activation:** MMPs are mostly secreted in non-active form. The activation from non active form to active form is required for the enzyme function. This requires the interaction between cysteine residue and zinc ion. During activation, the opening of the Cys-Zn2+ bond allows Zn2+ to react with H2O to maintain the stabilized open form of MMP, after which it still needs to pass through several structural changes to become fully active.
3. **Substrate Specificity:** A certain level of regulation of MMP activity is encoded at the level of the substrate. Although enzymes have somewhat overlapping substrate specificities, there are also notable differences, particularly with respect to the cleavage of the collagens.
4. **Inhibition:** Inhibitors of MMPs has an important role in preventing its overproduction and avoiding the tissue destruction that might lead to pathological condition. Thus the development of MMP inhibitors has a key therapeutic role.

Inhibition may take place:

a. By interaction with an active Zn2+-site
b. By cleaving the active enzyme
c. By binding it to a non-active complex form.
d. To influence the MMP levels it is also possible to down-regulate MMPs at the transcriptional level.

Endogenous inhibitors are tissue inhibitors of metalloproteinases (TIMPs) and Serum α2-macroglobulin and exogenous (synthetic) inhibitors are Zn2+- and Ca2+-chelating agents (EDTA and 1,10 phenanthroline), Phosphorus containing peptides(Phosphonamidate and phosphinate analogs of tripeptides), Sulfur based inhibitors(mercaptan derivatives), Hydroxamic acid derivatives, Bisphosphonate, Tetracyclines.

**MMP as biomarker**

Literature states that chronic periodontits has a typical intermittent nature in its disease process. There is an active phase and a remission phase too. With clinical evaluation it would be a revolutionary to find a specific biomarker to diagnose the current status of periodontitis. The biomarker should be available and easily collected from gingival crevicular fluid (GCF) and cost effective. Matrix metalloproteinase has important role in connective tissue degradation and the overproduction of it would indicate active disease process. Though the enzyme is found very less in quantity in GCF, it can act as a biomarker. More advance research on it is required to establish the effectiveness of MMPs as a potent biomarker.

## Conclusion

Overproduction of MMPs leads to many tissue destructive pathological conditions. In normal physiologic condition, host cells maintain the balance in production of MMPs and its inhibitors. This balance is essential to keep harmony. As MMP is responsible factor for tissue destruction it might have some diagnostic value too. Further research is necessary to establish its predictive value in periodontal diseases. Highly sensitive tests are required and tests should be cost effective as well that can be useful for all the clinicians. Early diagnosis definitely will improve the prognosis of periodontal diseases and that will be beneficial for the patients.

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