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Matrix Metalloproteinases (MMPs) As Diagnostic and Prognostic Tool - A Systematic Review

Dr. Suhani Goel

Periodontist

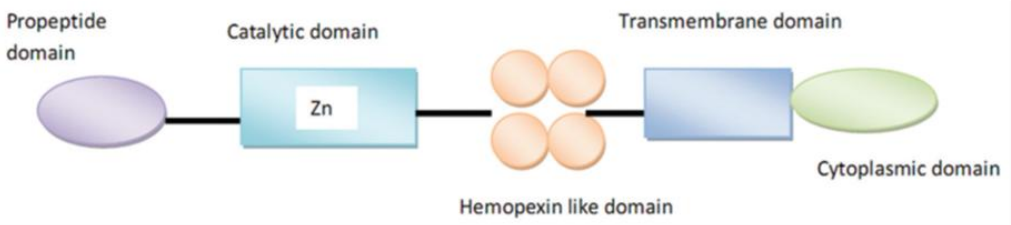
Abstract: ***Background: Periodontitis is a microbiological disease which is identified by the immune mediated degradation of periodontal supporting tissues and tooth loss. Matrix metalloproteinases (MMPs) are key proteases involved in destructive periodontal diseases resulting in degradation of extracellular matrix and basement membrane (BM) components. Method: Literature was searched systematically and studies were identified based on the-PICO (Glossary of evidence based terms 2007). A total of 10 studies were included in this systematic review. Result: This systematic review evaluated published RCTs on association of periodontal disease and levels of circulating MMPs along with the change in MMPs levels post periodontal therapy (NSPT). Conclusion: MMP levels decreases postoperatively in Gingival Crevicular Fluid (GCF) in Chronic Periodontitis patients.***

Keywords: periodontitis, matrix metalloproteinases, immunity, inflammation, Gingival Crevicular Fluid

1. Introduction

Microbial invasion plays a major part in initiation and maintenance of inflammatory process in periodontal diseases. Matrix metalloproteinases (MMPs) (also called matrixins) are a large family of calcium dependent zinc-containing endopeptidases, which are responsible for tissue remodeling and degradation of extracellular matrix including collagen,elastin,gelatin,matrix glycoprotein and proteoglycans.(1)

MMPs family basically have three basic, distinctive domains: Amino-terminal propeptide,a catalytic domain(for proteolytic activity), carboxyl terminal hemopexin-like domain(cleave triple helical interstitial collagens).(2)



To date, in humans, the MMP family comprises 26 members.

MMPs can be divided into six subgroups: Collagenases, stromelysins, gelatinases or type IV collagenases, matrilysins, metalloelastase, and membrane type metalloproteinase. (3)

Table 1: Classification of MMPs

COLLAGENSES	MMP-1,MMP-8,MMP-13
GELATINASES	MMP-2,MMP-9
STROMELYSINS	MMP-3,MMP-10,MMP-11,MMP-12
MATRILYSINS	MMP-7,MMP-26
MT-MMPs (MEMBRANE TYPE)	MMP-14,MMP-15,MMP-16,MMP-17,MMP-24,MMP-25
OTHER MMPs	MMP-18,MMP-19,MMP-20

MMPs are responsible for degradation of collagen fibres and their high activity is seen in gingival crevicular fluid of inflammatory conditions like periodontitis. Thus, MMP could act as diagnostic and prognostic makers.

Research question:
Can analysis and variation of MMPs prove their efficacy as reliable diagnostic and prognostic tools?

2. Methodology

This systematic review was based on PRISMA (Preferred Reporting Items For Systematic Reviews and Meta Analyses)

Search strategy:
Literature was searched systematically and studies were identified based on the-
PICO (Glossary of evidence based terms 2007).

3. Discussion

This systematic review evaluated association of periodontal disease and levels of circulating MMPs along with the change in MMPs levels post periodontal therapy (NSPT)

The following MMPs were assessed in GCF pre and post periodontal therapy in Chronic Periodontitis patients.

MMP-1
MMP-1 or interstitial collagenase is an important regulator of connective tissue remodeling and is present in high concentrations in inflamed gingival regions especially in periodontal diseases.[4]

Ghodpage PS et al 2013 (7) showed significant reduction in MMP-1 levels from baseline (9.98ng/ml) to (3.13ng/ml) after NSPT.

Gulay et al in 2002(14)showed that MMP-1 levels significantly decreased after phase I periodontal therapy from baseline (1.58+0.74mg/site) to (1.02+0.33mg/site) after 6 weeks post treatment.(NSPT).
The above two studies 7, 14 thus indicate that MMP-1 levels in GCF could act as reliable and prognostic indicators.

MMP-3
Stromelysin‑1 (MMP‑3) is effective at degrading proteoglycans and fibronectin.(15)

Pawar et al 2015(5)showed significant reduction in GCF levels of MMP-3 (4.49±1.15ng/ml to 3.20±0.31ng/ml) after phase 1 periodontal therapy.

Reddy et al 2013(8) evaluated MMP-3 levels in GCF increases with progression of periodontal disease (7.490+1.963ng/ml) and decreases significantly after treatment(NSPT) (2.129+1.101ng/ml).

Tuter G et al (12) showed that GCF MMP-3 levels decreased significantly after phase I periodontal therapy pre- av:9.0 (4.12–33.55)ng/ml and post- av:5.5 (1.65–10.87)ng/ml.

MMP-8
MMP-8 (collagenase-2) plays a central role in the turnover and degradation of periodontal tissues. (15)

According to Skurska et al (6) MMP-8 levels in GCF decreased significantly after phase I periodontal therapy (from 89.85 ± 45.24ml to 42.18 ± 38.19ml) at both 3 and 6 months post treatment (NSPT followed by antibiotic amoxicillin or PDT)

Konopka L et al 2012(9) showed that (NSPT) resulted in a significant decrease in the amount MMP-8 levels in the GCF (from 18.6 ± 6.4ng/ml to 7.3 ± 3.3ng/ml)

According to Macaccini AM et al (10) higher levels of MMP-8 levels were detected in the GCF samples of CP patients(0.43+0.35)compared with the controls.3 months after non-surgical periodontal therapy(NSPT), the MMP-8 levels decreased significantly (0.42+0.27) only in the CP group.

Sorsa T et al 2010(11) showed that MMP-8 levels in GCF reduced after treatment (NSPT) but was not statistically significant(15.9+13.4 ng/ml to 10.5+4.6 ng/ml)

According to Kinane DF et al (13)MMP-8 levels reduced after initial treatment (NSPT) but this difference was not statistically significant.(33.8+37.8 ng/ul to 16.0+24.5 ng/ul).

MMP-9
MMP-9 is 84 kDa enzyme mainly secreted by polymorphonuclear leukocytes. According to Skurska et al 2015(6) Compared to baseline, the MMP-9 levels showed a significant reduction at 3 and 6 months.(from 106.65ml to 33.05ml)(NSPT followed by antibiotic amoxicillin and metronidazole)

According to Marcaccini AM et al(12)higher MMP-9 levels in chronic periodontitis group(0.36+0.6) and reduction after treatment.(0.1+0.3).(NSPT)

MMP-13
MMP-13 or collagenase-3 plays a vital role in periodontal tissue destruction.Alsoplays a role in osteoclast activation and enhanced collagen affinity.

According to Pawar et al 2015 (7) GCF MMP-3 and -13 levels decreased significantly after phase 1 periodontal therapy. (NSPT) (from 1513.8±2380.6ng/ml to 1243.3±2014.2ng/ml).

Based on evaluation of published data, MMP-1, 3, 8, 9 and 13 of GCF was assessed in patients of chronic periodontitis at baseline and post phase I therapy.

All these above mentioned metalloproteinases levels (MMP-1, 3, 8, 9 and 13) revealed a statistically significant decrease in GCF levels post phase I therapy.

Based on these 10 studies it can be concluded that MMP evaluation of GCF may act as an effective and efficient diagnostic and prognostic tool.

4. Conclusion

Periodontitis is a chronic inflammatory disease characterized by interaction between periodontopathic bacteria and the host inflammatory response resulting in release of pro-inflammatory cytokines leading to the destruction of periodontal tissues and alveolar bone. Inflammatory destruction of periodontal attachment apparatus is the hallmark of periodontal disease ultimately resulting in tooth loss.

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Studies Evaluated	Type of MMPS	Clinical Parameters Evaluated	Procedure	Inference
Pawar et al (5), 2015	MMP-3 MMP-13	PI,GI,PD, CAL	MMP-3 Baseline-4.49±1.15ng/ml 6 weeks-3.20±0.31ng/ml MMP-13- Baseline-1513.8±2380.6ng/ml 6 weeks-1243.3±2014.2ng/ml	GCF levels of MMP-3 and MMP-13 were significantly lower in the healthy group than both the pre- and post-treatment CP group. GCF MMP-3 and -13 levels decreased significantly after phase 1 periodontal therapy
Skurska et al(6),2015	MMP-8 MMP-9	PI,GI,PPD, CAL	(SRP and antibiotic therapy) MMP-8 Baseline-42.18 ± 38.19ml 3 months-81.10 ± 50.99ml 6 months-89.85 ± 45.24ml MMP-9 Baseline-172.26 ± 106.65ml 3 months-68.36 ± 66.88ml 6 months-58.2 ± 33.05ml (SRP and PDT) MMP-8 Baseline-61.30 ± 63.43ml 3 months-35.81 ± 41.94 6 months-30.32 ± 29.77ml MMP-9 Baseline-352.92 ± 73.72ml 3 months-199.55 ± 169.39ml 6 months199.55 ± 169.39ml	MMP-8 In the AB group-statistically significant decrease of MMP-8 GCF level at both 3 and 6 months post treatment. In PDT group-decrease of MMP-8 GCF level but the change was not statistically significant. MMP-9 Compared to baseline, the MMP-9 levels showed, inboth groups, a decrease at 3 and 6 months.

Ghodpage PS et al(7) 2014	MMP-1	PI,GI,CAL,PPD, PBI	Baseline(BT)- 3.98ng/ml After 6 weeks(AT) 3.13ng/ml	All of the clinical parameters were significantly reduced after treatment. MMP-1 levels also significantly decreased afrer treatment.
Reddy et al(8),2013	MMP-3	GI,PD,CAL	Baseline-7.490+1.963ng/ml After 8 weeks 2.129+1.101ng/ml	MMP-3 levels in GCF increases with progression of periodontal disease and decreases after treatment.
Konopka Ł et al(9),2012	MMP-8	PI,GI,PPD, CAL	Baseline- 18.6 ± 6.4ng/ml After 1 week- 11.0 ± 6.6ng/ml After 4 week- 7.3 ± 3.3ng/ml	.Scaling and root planning resulted in a significant decrease in the amount MMP-8 levels in GCF.
Marcaccini AM et al (10)	MMP-8 MMP-9	PI,GI,PPD, CAL	MMP-8 Baseline- 0.43+0.35 After 3 months- 0.42+0.27 MMP-9 Baseline-0.36+0.6 After 3 months-0.1+0.3	MMP-8 and MMP-9 At baseline, higher levels of MMP-8 and MMP-9 were detected in the GCF samples of CP patients. 3 months after non-surgical periodontal therapy, the MMP-8 and MMP-9 levels decreased significantly.
Sorsa T et al (11), 2010	MMP-8	PPD,CAL	MMP-8 Baseline – 15.9+13.4 ng/ml After 1 month- 10.5+4.6 ng/ml	GCF MMP-8 levels reduced after treatment. Change of GCF MMP-8 levels after treatment analysed by Amersham ELISA were not statistically significant.
Tuter G et al (12) 2005	MMP-3	PPD,GI,PI, CAL	Baseline 9.0 (4.12–33.55)ng/ml After 6 weeks 5.5 (1.65–10.87)ng/ml	GCF MMP-3 level decreased significantly after phase I periodontal therapy.
Kinane DF et al (13), 2003	MMP-8	MGI,BOP CAL,PPD,PI	Baseline- 33.8+37.8 ng/ul 6-8 weeks- 23.5+33.0 ng/ul After 3 months 16.0+24.5 ng/ul	MMP-8 levels reduced significantly from baseline to 3 months after non-surgical periodontal therapy.
Gulay T et al (14) 2002	MMP-1	PPD,GI,PI, CAL	Baseline- 1.58+0.74mg/ste After 6 weeks 1.02+0.33mg/site	A statistical significant difference was observed in the levels of MMP-1 before and after treatment. Thus,levels of MMP-1 in GCF decreased after phase I periodontal therapy