Journal of Clinical Periodontology
Official Journal of The European Federation of Periodontology
Founded by the British, Dutch, French, German, Scandinavian, and Swiss Societies of Periodontology

J Clin Periodontol 2008; 35: 1027–1031 doi: 10.1111/j.1600-051X.2008.01329.x

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Matrix metalloproteinase-8 concentration in shallow crevices associated with the extent of periodontal disease

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Passoja A, Ylipalosaari M, Tervonen T, Raunio T, Knuuttila M. Matrix metalloproteinase-8 concentration in shallow crevices associated with the extent of periodontal disease. J Clin Periodontol 2008; 35: 1027–1031. doi: 10.1111/j.1600-051X.2008.01329.x.

Abstract

Objective: The aim of this study was to analyse the association between matrix metalloproteinase-8 (MMP-8) concentration in shallow, mostly non-bleeding gingival crevices, and the extent of periodontal disease.

Material and Methods: Plaque, bleeding on probing (BOP), probing pocket depth (PPD) and attachment level (AL) were assessed clinically in 48 patients with chronic periodontitis. MMP-8 concentrations in gingival crevicular fluid (GCF) from four shallow (PPD $\leqslant$ 3 mm), and four diseased sites and in serum, were measured by enzyme-linked immunosorbent assay.

Results: The mean concentration of MMP-8 in GCF from shallow crevices was 11.8 $\pm$ 12.8 ng/ml and from diseased sites was 150.1 $\pm$ 91.8 ng/ml. In subjects with moderate to high plaque scores, a statistically significant association was found between MMP-8 concentration from shallow crevices and the extent of AL $\geqslant$ 4 mm ($p = 0.028$) and AL $\geqslant$ 6 mm ($p < 0.001$).

Conclusion: The above association between MMP-8 concentration in shallow crevices and attachment loss provides a new aspect to future studies of MMP-8 as a prognostic marker for periodontal disease.

Key words: gingival crevicular fluid; MMP-8; periodontal disease; shallow crevices

Accepted for publication 30 August 2008

Matrix metalloproteinases (MMPs) form the most important family of proteinases that participate in the normal turnover of periodontal tissues and they are also responsible for the degradation of most matrix proteins during periodontal diseases (Uitto et al. 2003, Sorsa et al. 2004). MMP-8 is mainly secreted by polymorphonuclear leucocytes, but also from other cells such as oral epithelial cells, plasma cells and fibroblasts (Sorsa et al. 1992, Van Lint & Libert 2006). MMP-8 is expressed in a latent, non-active form and it is activated by a so-called cystein switch (Sorsa et al. 2004). There is in vitro evidence that reactive oxygen species and other proteolytic enzymes such as cathepsin G, MMP-3 and MMP-10 activate proMMP-8 (Uitto et al. 2003, Beklen et al. 2006). Liu et al. (2006) have reported that smoking modulates the expression of MMP-8 in periodontal tissues, MMP-8 expression being significantly higher in the periodontal tissue of smokers than non-smokers.

Several studies strongly indicate that the amount and activity of MMP-8 are highly increased in gingival crevicular fluid (GCF) of diseased periodontal pockets in chronic periodontitis patients. The increased amount and activity of MMP-8 correlates with the severity of periodontal disease (Lee et al. 1995, Kinane et al. 2003, Uitto et al. 2003). Periodontal treatment such as scaling and root planing has been documented to decrease MMP-8 levels and activity markedly (Kinane et al. 2003). Periodontal pockets or sites with poor response to treatment have been documented to have persistently elevated MMP-8 levels (Mäntylä et al. 2006). The levels of MMP-8 were significantly higher in GCF when *Prevotella intermedia*, *Tannerella forsythia* and *Treponema denticola* were present (Söder

Conflict of interest and source of funding statement

The authors declare that they have no conflict of interests.
No external funding.

et al. 2006). Great variation occurs in the levels of MMP-8 in healthy and periodontally treated sites, as indicated in the earlier studies (Chen et al. 2000, Mäntylä et al. 2003).

So far, there is no analysis in which MMP-8 collected from shallow crevices is related to the severity of periodontitis. We analysed the association between the extent of periodontal disease and MMP-8 concentration in GCF from shallow, mostly non-bleeding crevices in subjects with moderate to severe periodontitis. According to our hypothesis, the MMP-8 level in shallow crevices is associated with the extent of periodontal disease on patient level.

Material and Methods

Subjects

A total of 48 patients (32 females and 16 males) with moderate to severe chronic periodontitis, originally referred to periodontal specialist therapy, volunteered to participate. The mean age (± SD) of the subjects was 44.6 (± 11.5) years (range 22–75 years) (Table 1).

All the subjects were examined by the same periodontal specialist (T. R.) at the Specialist Dental Health Care Unit, City of Oulu. The informed consent of all the subjects was obtained and the study protocol was accepted by the Ethical Committee of the Faculty of Medicine, University of Oulu, Finland. Subjects needing prophylactic antibiotic medication in association with periodontal probing as well as those with rheumatoid arthritis, diabetes mellitus and asthma, and those with immunosuppressive medication or antibiotics during the past four months were excluded from the study. Smoking history was obtained by interviewing the subjects in association with the clinical examination and the subjects were categorized as non-smokers and smokers. There were 20 non-smokers and 28 smokers (Table 1).

Clinical examination

Clinical measurements were made on four surfaces (mesiobuccal, midbuccal, distobuccal and midlingual) of each tooth, excluding third molars. After drying with air, the presence of visible plaque was assessed according to scores 2 and 3 of the Silness & Löe (1964) plaque index. A ball-pointed periodontal probe with 2 mm graduations was used to measure probing pocket depth (PPD) from the gingival margin to the base of the crevice/pocket. The presence/absence of bleeding 20–30 s after probing [bleeding on probing (BOP)] and the periodontal attachment level (AL) from the cemento-enamel junction to the base of the crevice/pocket were registered.

Table 1. Characteristics of the subjects

Parameter	All subjects ($n = 48$)	Group A ($n = 30$)	Group B ($n = 21$)
Age			
Mean (± SD)	44.6 ± 11.5	47.8 ± 11.7	49.8 ± 12.3
Range	22–75	27–75	29–75
Gender			
Females	32	20	15
Males	16	10	6
Smoking habits			
Non-smoker	20	14	11
Smoker	28	16	10
Periodontal parameters*			
Plaque	24.7 ± 19.7	21.1 ± 20.4	23.4 ± 22.4
BOP	78.7 ± 19.1	70.9 ± 19.2	72.0 ± 16.3
PPD ⩾ 4 mm	45.7 ± 20.3	37.8 ± 18.4	37.7 ± 17.9
PPD ⩾ 6 mm	12.2 ± 14.9	9.6 ± 12.7	10.1 ± 12.8
AL ⩾ 4 mm	40.3 ± 25.4	34.8 ± 22.8	35.9 ± 24.1
AL ⩾ 6 mm	13.3 ± 15.4	10.8 ± 12.3	11.8 ± 13.6
MMP-8 concentration (ng/ml)			
Shallow crevices: mean ± SD	11.8 ± 12.8	11.4 ± 12.6	12.4 ± 14.3
Range	0.8–55.0		
Diseased sites: mean ± SD	150.1 ± 91.8	150.1 ± 97.4	149.0 ± 95.9
Range	5.5–320.0		
Serum: mean ± SD	7.6 ± 4.6	7.6 ± 4.9	7.8 ± 5.6
Range	0.1–27.0		

The subjects in Group A presented 0–1 sites (out of the four sampled sites) with bleeding on probing (BOP) and the subjects in Group B presented no bleeding in the sampled sites.

*Individual percentages of affected sites.

PPD, probing pocket depth; AL, attachment level; MMP-8, matrix metalloproteinase-8.

Sites for GCF collection, sampling of GCF and MMP-8 laboratory analysis

The selection of four healthy and four diseased sites for GCF collection was based on visual inspection for clinical signs of inflammation, including colour change and swelling. In the present analysis of 48 subjects, the shallow crevices include sites with PPD ⩽ 3 mm, 67% of the sampled sites presented no BOP. In subgroup A subjects ($n = 30$), one site at most out of the four shallow sites selected for sampling presented BOP, and in subgroup B ($n = 21$), there was no BOP in the selected shallow sites (Table 1). All the diseased sites were BOP and 90% were PPD ⩾ 4 mm in depth.

The area of GCF collection was isolated, supragingival plaque removed and a Periopaper (IDE Interstate, Amityville, NJ, USA) was placed at the orifice of the crevice/pocket for 30 s. After that the strips were placed into 50 μl of 0.9% phosphate-buffered saline. After 1 h in ice, the GCF samples were centrifuged at 9,220 *g* for 15 min. and stored at − 70°C until analysed. Before the analysis, the GCF samples collected from four shallow sites were pooled together and also the samples from diseased sites were pooled together. The total levels of MMP-8 in GCF were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) (Quantikine®; R&D Systems Inc., Minneapolis, MN, USA) according to the manufacturers instructions.

Data analysis

The severity of periodontal disease was expressed as the extent (percentages) of affected sites per subject. Two different threshold values were used for PPD and AL (⩾ 4 mm and ⩾ 6 mm). Associations between MMP-8 concentration in GCF from both shallow crevices and clinically diseased sites, and the extent of periodontal disease were analysed using Pearson's correlation test. Regression analysis was used to study more detailed associations between MMP-8 concentration and the extent of AL ⩾ 4 mm and AL ⩾ 6 mm. In addition to smoking

and individual plaque scores, interaction terms between MMP-8 concentration and both smoking and plaque scores were included in the regression model to study possible confounding/modifying effects. The subjects were stratified by plaque scores and separate regression models were constructed for those with no/minimal amount of plaque and for those with moderate to high amount. Three different cut-off points of the percentage of sites with plaque were used: the lowest *versus* the three highest quartiles (cut-off point 12.5%), the lowest *versus* the two highest tertiles (cut-off point 15.0%) and the median (cut-off point 20.0%).

Results

The periodontal health status of the subjects was poor, as indicated by the high frequency of deepened periodontal pockets with PPD ⩾ 4 mm (45.7%) (Table 1). Advanced periodontal disease measured as PPD ⩾ 6 mm and AL ⩾ 6 mm was found in 12.2% and 13.3% of the sites, respectively. The mean concentration of MMP-8 in sites with shallow crevices of all subjects was 11.8 ng/ml (range 0.8–55.0 ng/ml), in diseased sites 150.1 ng/ml (range 5.5–320.0 ng/ml) and in serum 7.6 ng/ml (range 0.1–27.0 ng/ml). Serum concentrations of MMP-8 did not correlate with the extent of periodontal disease. MMP-8 concentrations in sites with shallow crevices were significantly higher in smokers compared with non-smokers (15.3 *versus* 7.0 ng/ml, respectively, $p = 0.026$).

Unadjusted associations between MMP-8 concentrations from shallow crevices and the extent of both attachment loss categories were highly significant, whereas no association was found between the MMP-8 levels of diseased sites and the extent of attachment loss (Table 2). The associations between the extent of periodontal pocketing and MMP-8 levels were slightly weaker. Also, using more strict criteria for patient selection, e.g. out of the four sampled sites, only one bleeding site at most (Group A) or no bleeding sites (Group B), even more significant correlations were found between the extent of periodontal disease and MMP-8 concentrations (correlation coafficients 0.4 or higher, Table 3).

Because of stronger and more consistent associations between MMP-8 concentration and AL measurements, especially AL ⩾ 6 mm (Tables 2 and 3), AL was used as the outcome variable in further analyses. In a separate model, the interaction term between MMP-8 concentration and the individual plaqe score was statistically significant and, therefore, further analyses were performed after stratifying the subjects by the individual plaque scores. In subjects with moderate to high amount of plaque (> 12.5% of sites per subject), a statistically significant association was found between MMP-8 concentration from shallow crevices and the extent of sites with both AL ⩾ 4 mm ($p = 0.028$) and AL ⩾ 6 mm ($p < 0.001$) (Table 4). In subjects with no or only minimal amount of plaque, no such associations were found. Analyses using the two other cut-off points (15.0% and 20.0%) yielded consistent results. As the interaction term between MMP-8 concentration and smoking was not statistically significant, no separate models were constructed for smokers and non-smokers.

Table 2. Correlations between the extent of periodontal disease (% of sites per subject) and MMP-8 concentration in GCF from shallow and diseased sites of all subjects ($n = 48$)

MMP-8 concentration (ng/ml)	BOP	PPD ⩾ 4 mm	PPD ⩾ 6 mm	AL ⩾ 4 mm	AL ⩾ 6 mm
Shallow crevices	0.275	0.368	0.259	0.435	0.588
	$p = 0.058$	$p = 0.010$	$p = 0.075$	$p = 0.002$	$p = 0.000$
Diseased sites	0.153	0.171	0.256	− 0.045	− 0.066
	$p = 0.299$	$p = 0.244$	$p = 0.079$	$p = 0.760$	$p = 0.658$

BOP, bleeding on probing; PPD, probing pocket depth; AL, attachment level; GCF, gingival crevicular fluid; MMP-8, matrix metalloproteinase-8.

Table 3. Correlations between the extent of periodontal disease (% of sites per subjects) and MMP-8 concentration in shallow crevices in Groups A and B

MMP-8 concentration (ng/ml)	PPD ⩾ 4 mm	AL ⩾ 4 mm	AL ⩾ 6 mm
Group A	0.417	0.464	0.521
	$p = 0.022$	$p = 0.010$	$p = 0.003$
Group B	0.392	0.456	0.539
	$p = 0.079$	$p = 0.038$	$p = 0.012$

PPD, probing pocket depth; AL, attachment level; MMP-8, matrix metalloproteinase-8.
A: Subjects with no more than one bleeding site out of the four sampled sites.
B: Subjects with no bleeding in the four sampled sites.

Table 4. Smoking adjusted associations between MMP-8 (ng/ml) in GCF from shallow crevices and extent of AL ⩾ 4 mm and AL ⩾ 6 mm in subjects with low (⩽ 12.5%, $n = 12$) and high (> 12.5%, $n = 36$) individual plaque scores

	β	95% CI for β	p-value
Low plaque scores			
AL ⩾ 4 mm			
MMP-8 concentration	1.4	− 1.7–4.6	0.323
Smoking	− 0.03	− 28.0–28.0	0.998
AL ⩾ 6 mm			
MMP-8 concentration	1.0	− 0.1–2.2	0.068
Smoking	6.3	− 3.9–16.5	0.193
High plaque scores			
AL ⩾ 4 mm			
MMP-8 concentration	0.7	0.1–1.3	0.028
Smoking	− 14.3	− 32.5–3.9	0.119
AL ⩾ 6 mm			
MMP-8 concentration	0.7	0.4–1.1	< 0.001
Smoking	− 0.5	− 11.1–10.2	0.930

AL, attachment level, mean percentage of affected sites per subjects; MMP-8, matrix metalloproteinase-8.
Smoking, non-smokers *versus* smokers.

Discussion

The main finding of our study was that a statistically significant association exists

between the extent of attachment loss and MMP-8 concentration in shallow crevices of subjects with moderate to high plaque scores. No such association could be found in subjects with no or only minimal amount of plaque. Nor could we found any significant association between MMP-8 concentration in GCF collected from diseased sites and periodontal health status. Because of the cross-sectional setting of the present study, no definite conclusion of a causal relationship between MMP-8 concentration in shallow crevices and advanced periodontal destruction can be drawn. It cannot, however, be fully excluded that the significant association between MMP-8 concentration and loss of attachment, a long-term measure of periodontal tissue destruction, could be indicative of higher susceptibility to periodontal disease. One limitation of our study is that we did not include a periodontally healthy control group to study the variation of MMP-8 secretion.

When studying MMP-8 concentration in GCF, possible contamination by MMP-8 in saliva or blood should be taken into consideration. We discarded the blood-containing strips and isolated the sample sites carefully from saliva. In addition, a vast majority of the samples from healthy sites were collected from the upper front area and contamination by saliva could thus be avoided. Another possibility is that periodontal inflammation causes systemic elevation of MMP-8 in serum, which is then reflected in higher levels of MMP-8 in GCF. However, we analysed the concentration of MMP-8 in serum and it was not dependent on the extent of the periodontal disease. Consequently, the above issues may not be seen as sources of error in our study. Different MMP-8 antibodies have been used in previously published studies of MMP-8 expression in periodontal disease (Kinane et al. 2003, Liu et al. 2006, Söder et al. 2006). Based on the fact that we used a commercially available ELISA assay measuring both active and latent forms of MMP-8, it is the total concentration of MMP-8 in shallow crevices that can be seen as indicative of increased periodontal tissue destruction. We did not test whether similar results would have been obtained using other MMP-8 antibodies.

The role of gene polymorphism in relation to MMP expression is unclear (Astolfi et al. 2006, Chen et al. 2007) and so far, there are no published reports about MMP-8 gene polymorphism in periodontal disease. However, there are studies concerning several cytokine gene polymorphisms associated with an increased risk of periodontal disease. Increased production of a given cytokine is associated with carriage of a risk genotype. Previously, the risk of having periodontal disease has been related to carriage of rare alleles of single cytokine and reseptor molecule genes such as IL-1, TNF-α, IL-6 and CD-14 (Taylor et al. 2004, Loos et al. 2005, Shapira et al. 2005, Takashiba & Naruishi 2006, Tervonen et al. 2007, Yoshie et al. 2007). It can be that some or several of these cytokines are for their part modulating MMP-8 expression. At least IL-1β is known to induce gene expression of MMP-8 in gingival fibroblasts in vitro (Abe et al. 2001). We found significantly higher MMP-8 levels in smokers when compared with non-smokers, which is in line with the results of Liu et al. (2006). Mäntylä et al. (2006) found a controversial result when analysing MMP-8 concentrations from GCF and also found that non-smokers responded better to conventional periodontal therapy and maintained treatment results better. We used smoking as a covariate in a regression model. Association between MMP-8 concentration and the extent of attachment loss remained significant even after smoking was considered. Although smoking is generally considered an effect modifier (Hymann et al. 2002, Ylöstalo & Knuuttila 2006), we could not find interaction between smoking and MMP-8 concentration in GCF from shallow crevices in the present subjects. Plaque, on the other hand, turned out to be an effect modifier and therefore the associotion between MMP-8 concentration and attachment loss were analysed after stratifying the subjects by plaque scores.

In short, the MMP-8 levels in GCF from shallow gingival crevices associated with the extent of AL $\geqslant$ 4 mm and AL $\geqslant$ 6 mm. Future follow-up studies are needed to investigate MMP-8 in healthy sites as a prognostic marker for periodontal disease.

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Clinical Relevance

Scientific rationale for the study: It is well known that MMP-8 concentrations are significantly increased in GCF collected from diseased periodontal sites. We studied the association between MMP-8 and periodontitis with a new perspective; MMP-8 concentrations in shallow, mostly non-bleeding gingival crevices, in relation to the extent of periodontal disease.

Principal findings: In the presence of moderate and high levels of plaque, GCF concentration of MMP-8 in shallow crevices was associated with the extent of periodontal disease at the subject level.

Practical implications: Increased MMP-8 concentration in shallow crevices may be a marker of increased periodontal destruction.