Cumhuriyet Dental Journal

Volume 17 Issue 3

doi:10.7126/cdj.58140.5000004490

available at http://dergipark.ulakbim.gov.tr/cumudj/

RESEARCH ARTICLE

Comparative analysis of the potential effect of phase I therapy on gingival crevicular fluid myeloperoxidase levels in non-diabetic and diabetic patients with periodontitis

Hakan Özdemir, DDS, PhD,[a] Hakan Develioğlu, DDS, PhD,[a] Nermin Yamalık, DDS, PhD,[b] Hüseyin Aydın, DDS, PhD,[c] Kaya Eren, DDS, PhD,[d]

[a]*Department of Periodontology, Faculty of Dentistry, Osmangazi University, Eskişehir, Turkey*
[b]*Department of Periodontology, Faculty of Dentistry, Hacettepe University, Ankara, Turkey*
[c]*Department of Biochemistry, Faculty of Medicine, Cumhuriyet University, Sivas, Turkey*
[d]*Department of Periodontology, Faculty of Dentistry, Gazi University, Ankara, Turkey*

ARTICLE INFO

Article history:
Received 01 February 2014
Accepted 18 February 2014

Keywords:
Diabetes mellitus
Myeloperoxidase
Cronic periodontitis
Gingival crevicular fluid

ABSTRACT

Objectives: To evaluate the effect of periodontal therapy on clinical parameters as well as on myeloperoxidase (MPO) activity in the gingival crevicular fluid (GCF) of patients with type 2 diabetes mellitus and of systemically healthy individuals.

Materials and Methods: 24 type 2 DM patients subjects, and 21 systemically healthy individuals, both groups with chronic periodontitis, and systemically and periodontally healthy individuals were enrolled. Periodontal clinical parameters, namely periodontal probing depth (PD), plaque index (PI), gingival index (GI), clinical attachment level (CAL), and gingival bleeding time index (GBI), as well as GCF MPO activity, were assessed before and 3 months after non-surgical periodontal therapy. GCF enzyme activity was spectrophotometrically analyzed. Possible correlation between clinical periodontal status and MPO activity was also evaluated.

Results: Despite the relatively stable clinical measures and GCF MPO content in the periodontally-healthy subjects, the clinical periodontal status improved, as significant reductions were observed in all of the clinical parameters in periodontitis patients with and without diabetes ($p<0.05$). GCF MPO activity presented with significant reductions in both of the periodontally-diseased groups after phase I treatment ($p<0.05$), however it could not reach to the level of periodontal health ($p<0.05$).

Conclusions: Periodontal inflammation is likely to play the major role in the higher MPO activity observed at diseased sites, while diabetes mellitus do not seem to further increase the production of this enzyme. Periodontal treatment can provide successful improvement in clinical periodontal parameters and reduction in enzyme profile of GCF in diabetics.

Corresponding author at: Hakan OZDEMIR, Department of Periodontology, Faculty of Dentistry, Osmangazi University, Eskişehir, Turkey. Tel.: 02222393750, Fax.: 02222391273, E-mail: hozdemir52@hotmail.com

INTRODUCTION

Periodontitis is an infection caused by bacteria on tooth surface in the periodontal pockets and is characterized by the loss of supporting tissues of the tooth.[19] It is well-demonstrated that host-derived proteolytic enzymes play an important role during this process.[6] A wide array of enzymes are available in the GCF and previous studies generally provided evidence regarding the involvement of such enzymes in periodontal destruction.[30]

Myeloperoxidase (MPO) is one of the host enzymes stored in the azurophilic granules of polymorphonuclear neutrophiles, which exhibit an increased activity at periodontitis sites and decreased levels after periodontal treatment. Such characteristics support the role for MPO in destructive periodontal diseases.[2,27]

Further, MPO is widely accepted as a promising marker for periodontal inflammation as MPO-derived oxidants are shown to contribute to tissue damage during inflammation[4] through catalyzing the formation of a number of reactive oxidant species[2,4] and can generate nitrating capacity for lipids and proteins.

It is well-demonstrated that MPO is a significant GCF component that is involved in the pathogenesis of inflammatory periodontal diseases.[27] Many studies are available demonstrating the close association of this enzyme with the clinical and microbial signs of periodontal disease[27,30] and increased GCF MPO levels at periodontally-diseased sites.[27] The increased amount of MPO activity at diseased sites from patients with chronic and aggressive periodontitis[30] and decreased MPO activity after successful periodontal treatment[14] further confirm the role of MPO in destructive periodontal diseases. MPO is also suggested as a good indicator of neutrophil activity at failed peri-implant sites.[1]

Diabetes mellitus (DM) is a disease with two types described[15] as insulin dependent diabetes mellitus (IDDM) and non insulin dependent diabetes mellitus (NIDDM), and this disease is regarded as a risk factor for periodontal disease.[11] Many studies are available about the interrelated nature of DM and periodontal disorders11. While DM may ease the progression of periodontal disease,[3] control of oral infection may help in the metabolic control of DM.[9] Periodontal disease is three times more prevalent in individuals with type 2 diabetes mellitus (T2D)[1] and is recognized as the ''sixth complication of diabetes.[2] Most studies report a more generalized and severe periodontal breakdown in patients with DM with poor plaque control.[18,21] Enzymatic studies in DM with periodontal disease patients have shown higher enzyme levels in GCF.[7]

Quantitative and qualitative analysis of GCF samples, as well as clinical parameters, are accepted methods for the evaluation of clinical periodontal status and early and destructive stages of inflammatory response. Moreover, it is useful for a better understanding of the pathogenesis of periodontal diseases. The aim of the present study is to comparatively analyze GCF MPO activity in chronic periodontitis patients with and without diabetes and determine the possible impact of non-surgical periodontal therapy on the MPO profile of GCF. Furthermore, consideration of the validity of GCF MPO activity in reflecting the actual clinical periodontal status was also aimed.

MATERIALS- METHODS

Criteria for inclusion and experimental groups

A total of 65 individuals were included in the study. All of the participants were selected from among those who were

referred to Department of Periodontology, Faculty of Dentistry, Cumhuriyet University, Sivas, Turkey. Special care was taken to ensure that the participants had no history of antibiotics, anti-inflammatory drugs and/or periodontal treatment within the past 6 months, and no history of any systemic disease except for NIDDM (type 2 dibetes mellitus). All participants were non-smokers. Participants were analyzed within the following three categories: I) Chronic periodontitis with NIDDM patients (n=24), II. Systemically healthy subjects with chronic periodontitis (n=21), III. Systemically and periodontally healthy individuals to serve as the control group (n=20). Patients with NIDDM were diagnosed in the Faculty of Medicine and were under medical control. The patients with diabetes were good control of diabetes and, the mean Haemoglobin A1c (HgA1c) values were between 6.5% and 8.0 %.[31] Individuals with chronic periodontitis were diagnosed after clinical and radiographical examinations based on the presence of clinical attachment loss, probing depth, and an alveolar bone loss. The study was designed according to the Helsinki Declaration and approved by the Ethical Committee of Faculty of Dentistry, Cumhuriyet University. A signed informed consent was also obtained from all of participants before all examinations, sampling or periodontal care.

Determination of clinical periodontal status

For determination of the clinical the periodontal status, probing depth (PD) and attachment level (AL) were measured using a Goldman Fox Williams probe, and gingival index (GI)[14], plaque index (PI)[22] and gingival bleeding time index (GBTI)[16] scores were recorded. All measurements were performed at baseline by the same clinician who was a periodontologist and repeated 3 months after periodontal treatment.

Sampling of gingival crevicular fluid

The maxillary four incisor teeth were selected as the sampling site in order to avoid any saliva contamination. Sampling site was isolated with cotton rolls and was gently dried with air spray. The supragingival plaque was also removed. GCF samples were obtained from the selected pockets (4-6 mm). To minimize the risk of mechanical trauma, standardized paper strips (Periopaper, Oraflow, Plainview, NY, USA) were gently inserted 1 mm into the pocket/crevice for 30 seconds as described by Rudin et al.[20] Samples contaminated by the saliva or blood were excluded. Thus, four strips were taken from each patient. Volume quantification was made using an electronic device, Periotron (Periotron 8000, Oraflow, Plainview, NY, USA). Paper strips were immediately placed into Eppendorf tubes, which were stored at –70°C until the assay was performed. GCF sampling was performed at baseline and repeated 3 months after periodontal treatment.

Periodontal treatment

After the clinical index records and GCF sampling, phase I periodontal treatment was performed containing oral hygiene instructions, scaling, and root planning for all patients. Only oral hygiene instructions were provided and no medication or mouth rinses were recommended.

Determination of myeloperoxidase activity

MPO activity was detected using the kinetic spectrophotometric analysis according to the method of Suziki et al.,[24] using 220 mM phosphate buffer (pH 5.4) containing 1.6 mM synthetic tetramethyl benzidine (TMB), 0.5% hexadecylmethyl ammonium bromide (HETAB), 1mM H2O2, and 0.1 ml GCF. After adding H2O2, at 37°C

temperature, the oxidation of TMB started and records were taken using a spectrophotometry. The absorbance change per minute was observed. One unit of MPO activity was defined as the amount of enzyme producing one absorbance change per unit under the analysis properties. GCF MPO content was expressed both as total MPO activity and MPO concentration.

Statistical analysis

Data obtained were analyzed by the statistical computer program SPSS. Inter-group differences were analyzed using two-way analysis. Impact of periodontal treatment on clinical periodontal status and GCF MPO profile was evaluated by variance analysis in repeated measurements, Benforroni test, and paired sample t-test. Correlation analysis was used for the determination of the possible relationship between MPO total activity/concentration and clinical parameters (sampling sites). Statistical significance was considered for $p<0.05$.

RESULTS

The mean age was 45.13±3.88 for the diabetes group, 43.81±3.36 for the chronic periodontitis group, and 44.55±5.66 for the control group, and the differences in age were found statistically insignificant ($p>0.05$). A relatively even distribution of female and male participants was also observed.

Clinical findings

The mean values for clinical parameters are given in Table 1. There was a statistically significant reduction in all clinical parameters between baseline and 3rd month clinical index values in diabetics with periodontitis and chronic periodontitis ($p<0.05$). However, no significant difference was observed in the control groups ($p>0.05$). At baseline, clinical parameters were found to be higher in both of the diseased groups when compared to control group ($p<0.05$). However, the difference between the two diseased groups was not significant ($p>0.05$). When the clinical measurements were repeated at the 3rd month, no significant difference among the groups were noticed for any of the clinical parameters ($p>0.05$).

Laboratory findings

The mean total MPO levels of three groups at baseline and 3rd month were summarized in Table 2. At baseline, total MPO activity was higher in the two periodontally-diseased groups when compared to the control group ($p<0.05$). However, difference between diabetics (1.02 U/site) and non-diabetics (0.81 U/site) was not significant ($p>0.05$). In both patients groups of diabetics with periodontal disease and individuals with chronic periodontitis, a significant reduction was noticed in total MPO levels following non-surgical periodontal treatment ($p<0.05$). On the other hand, total MPO activity presented with a stability between baseline (0.06 U/site) and 3rd month (0.05 U/site) in the control group ($p>0.05$). Despite a similar reduction at the third month after periodontal treatment, GCF MPO levels in diabetics (0.19 U/site) and chronic periodontitis patients (0.20 U/site) did not still reach to the level of periodontal health (0.05 U/site) ($p<0.05$). Similar results were obtained when GCF MPO content was expressed as concentration. Periodontal treatment resulted in significant reductions in MPO concentration in periodontally-diseased diabetics and non-diabetics ($p<0.05$). However, at the 3rd month, MPO

concentration in diabetics (0.38 U/μl) and chronic periodontitis patients (0.40 U/μl) was still higher than periodontal health group (0.14 U/μl) ($p<0.05$; Table 3).

Correlations between the MPO activity and clinical parameters

Baseline total MPO activity levels and clinical parameters are summarized in Table 4.

Table 1. The mean value SD of clinical parameters among the groups at baseline and 3rd month.

	Baseline	3rd month	p value
DCP (n=24)			
Gingival index	2.34±0.64	0.60±0.23	p=0.0000
Plaque index	2.29±0.42	0.62±0.16	p=0.0000
GBTI	3.07±0.52	0.79±0.35	p=0.0000
Probing depth (mm)	4.96±0.32	1.93±0.27	p=0.0000
Attachment level (mm)	6.65±0.19	5.13±0.20	p=0.027
CP (n=21)			
Gingival index	2.19±0.43	0.60±0.23	p=0.0000
Plaque index	2.36±0.36	0.57±0.16	p=0.0000
GBTI	3.45±0.41	0.79±0.35	p=0.0000
Probing depth (mm)	4.98±0.16	1.89±0.36	p=0.0000
Attachment level (mm)	6.58±0.17	5.15±0.17	p=0.025
HI (controls n=20)			
Gingival index	0.59±0.14	0.54±0.24	p=0.176
Plaque index	0.63±0.18	0.57±0.10	p=0.054
GBTI	0.07±0.04	0.05±0.03	p=0.052
Probing depth (mm)	1.82±0.25	1.68±0.19	p=0.065

Table 2. The mean value of total MPO (U) activity levels among the groups.

Groups	T MPO (site) (Baseline)	T MPO (U/site) (3rd month)	p value
DCP (n=24)	1.02±0.69	0.19±0.05	p<0.05
CP (n=21)	0.81±0.43	0.20±0.04	p<0.05
HI (n=20)	0.06±0.05	0.05±0.04	p>0.05

At baseline, total MPO levels presented correlations with all of the clinical parameters, except for AL, in both the diabetics with periodontitis. There were positive and strong correlations with PI, GI and PD ($p<0.05$), and positive and weak correlations with GBTI scores ($r=0.416$, $p<0.05$). Similar correlations were also observed for the chronic periodontitis group, as there was a positive and strong correlation with PI, GI and PD ($p<0.05$), positive and weak correlation with GBTI scores, and no correlation with AL ($p>0.05$) in both groups. Control group also revealed significant correlations between total MPO levels and the clinical parameters, being a positive and strong for PD, and positive and weak for the rest ($p<0.05$). In all of the groups, positive and weak correlations were observed between total MPO activity and all clinical measures at the 3rd month ($p<0.05$), while no correlations were observed between MPO concentration and clinical measures in any group and at any time interval ($p>0.05$).

DISCUSSION

In clinical medicine, after analysis of most body fluids, data are frequently presented as concentration; however, due to several unique features of GCF such as relatively small volume, difficulties in volume standardization, risk of evaporation and contamination, principles of body fluids may not be totally applicable to GCF.[13,30] Previous GCF-related studies[13,25,30] are available demonstrating a discrepancy between 'concentration' and 'total activity' modes of data presentation, more significant correlations between clinical parameters and total activity expression, and suggesting total activity as a more appropriate mode of data presentation for certain GCF components. With specific reference to MPO, the similarity of both modes of data presentation for MPO was also previously reported.[30] In the present study with both modes of data presentation, the reduction in MPO activity was obvious. However, since no correlation of MPO concentration with the clinical parameters was observed,[8] findings of the present study may support the suggestion that total activity mode of data presentation might better reflect the clinical periodontal status than when expressed as concentration.[2,23,30]

The correlation between clinical periodontal status and enzymatic profile of GCF may present discrepancies between studies.[23] While significant correlations between GCF MPO activities can be observed in some studies,[2,12] others may lack such correlations.[23] Findings of the present study confirm the interrelated nature of GCF MPO profile and the clinical periodontal status, as significant correlations were observed between total MPO activity and clinical parameters recorded. Eley et al.[5] reported that the correlation between clinical parameters and GCF enzyme were better for total enzyme activity than the concentration mode of data presentation. The reason for some GCF constituents not to show any correlation with the clinical parameters was

Table 3. The mean value of MPO concentration among the groups.

Groups	Baseline (U/µl)	3rd month (U/µl)	p value
DCP (n=24)	1.45±0.64	0.38±0.10	p<0.05
CP (n=21)	1.31±0.62	0.40±0.07	p<0.05
HI (n=20)	0.23±0.11	0.14±0.06	p>0.05

Table 4. Correlation between the total MPO activity levels/concentration and clinical parameters.

Groups	Total MPO Activity		MPO Concentration	
	Baseline r	3rd month r	Baseline r	3rd month r
DCP (n=24)				
PI	0.674*	0.404	0.074	0.100
GI	0.626*	0.310	0.026	0.010
GBTI	0.416	0.403	0.046	0.053
PD (mm)	0.686*	0.366	0.086	0.066
AL (mm)	0.286	0.201	0.056	0.050
CP (n=21)				
PI	0.610*	0.387	0.110	0.087
GI	0.612	0.287	0.082	0.077
GBTI	0.429	0.303	0.119	0.103
PD (mm)	0.645*	0.354	0.105	0.094
AL (mm)	0.235	0.157	0.095	0.107
HI (n=20)				
PI	0.437	0.360	0.087	–0.060
GI	0.346	0.245	0.106	0.085
GBTI	0.431	0.452	0.121	0.102
PD (mm)	0.612*	0.463	0.102	0.083
AL (mm)	-		-	-

*p<0.05 strong - positive correlation

interpreted as the possibility of changes in the GCF profile to precede the apparent clinical changes related to periodontal pathologies.[5] The interrelated nature of GCF MPO activity with the recorded clinical parameters may suggest the potential of MPO to reflect the actual periodontal status. Further, higher MPO activity at diseased sites might be interpreted as a sign of the intensity of PMNs migration at a given site, as MPO is suggested to serve as an index of PMNs migration.[30] The extent of MPO activity detected at healthy sites is likely to be related to the subclinical

inflammatory status and the constant flow of PMNs to sulcus.[18]

Previous studies are available regarding the analysis of MPO in periodontal diseases.[18,23,29,30] Yamalık et al.[30] reported MPO activity to be lower at periodontally healthy sites than diseased sites. Över et al.[18] also revealed an increased GCF MPO activity with periodontal destruction. Similar results were obtained in the studies of Wolff et al.[29] and Smith et al.[23] Further, as an indicator of leukocyte migration, presence/absence of MPO in either GCF or peri-implant sulcus fluid (PISF samples) is suggested to be a relatively better marker of clinical periodontal or peri-implant health and inflammatory status when compared to nitrite level.[25] Higher GCF MPO production at periodontally diseased sites observed in the present study are generally in line with all these previous studies that underline MPO as an ingredient of GCF and as a specific enzyme related to the pathogenesis of periodontal diseases.[25,27,30] Polymorphonuclear leukocytes that accu mulate at sites of gingival inflammation release various products, including MPO, as a result of the bacteria-host interaction. Thus, increased GCF MPO at periodontally-diseased sites is attributed to the increase in gingival inflammation as a result of leukocytes entering the gingival sulcular area.[2]

As far as presence/absence of MPO activity at individual sites were concerned, it was observed that 33 of 260 sites lacked detectable amount of MPO, and nearly half of them (n=15) were the sites designated as periodontally healthy. As MPO is related to PMNs and the inflammatory status, absence of MPO at periodontally healthy sites may be expected. However, further studies are needed to analyze the absence of MPO at periodontally-diseased sites and in particular the possibility of MPO being related to active/passive phase of the disease.

Smith et al.[23] reported reduced GI values after periodontal treatment, while Westfelt et al.[28] particularly reported reduced plaque amount after the periodontal treatment in diabetic patients. Clinical parameters improved with periodontal treatment in the present study. Our results confirm the impact of initial periodontal care on the clinical periodontal status of patients with and without diabetes.[1,15] Regarding the probing depth and attachment level, no difference was noticed between the two diseased groups,[21] which is in line with the previous studies which revealed similar probing depths[17,21] and attachment levels[28] in diabetics and non diabetics. However, there are also studies that show more attachment loss in patients with diabetes.[21] In addition to improved clinical periodontal status, MPO levels at diseased sites were reported to be reduced after the periodontal treatment.[23] The decrease in MPO levels observed in the present study after non-surgical periodontal treatment generally supports this finding. Further, this finding is also in line with the previous studies that report a decrease in GCF enzymatic profile after periodontal treatment.[8,13] Reduction in the bacterial load after mechanical care, and the subsequent reduction in inflammation is likely to lead to less MPO production at the previously diseased sites. Despite the significant reduction in diabetics and chronic periodontitis patients, the MPO content of GCF from periodontally-diseased sites were still higher than the sites with clinical health, indicating the limitations of phase 1 treatment at sites with considerable amount of periodontal destruction, and thus the need for further periodontal treatment, such as surgical treatment.

It has been well-demonstrated that there is a strong correlation between diabetes and periodontal disease and diabetes can affect the periodontal tissues negatively[9] Many studies are available

which demonstrate a relationship between neutrophil defects and periodontal disease,[30] while neutrophil function is well-determined to be impaired in diabetic patients.[26] As an enzyme particularly related to PMNs, the present study was conducted in order to analyze MPO activity in diabetics with periodontitis. Although the baseline total MPO activity levels in type II diabetes with chronic periodontitis was higher than levels in chronic periodontitis, this difference did not reach to a significant level. Thus, it may be speculated that the chemotactic factors within the periodontal pocket is essential for the PMN migration, and their presence result in a similar extent of migration and a subsequent MPO activity. As far as diabetic patients under good metabolic control were concerned, diabetes mellitus did not seem to have a further impact on GCF MPO profile. Thus, we agree that a good metabolic control might positively affect periodontal healing.[10] However; the limited number of participants in the present study also needs to be taken into account when interpreting these results. Further studies concerning a larger group of diabetic patients with both good and poor metabolic control presenting with and without periodontal diseases may increase our understanding of the role of MPO in response to periodontal inflammation and the contribution of metabolic control of diabetes to host response involved in destructive periodontal disorders.

Based on the limitations of the present study, it can still be suggested that GCF MPO profile primarily depends on the presence/extent of periodontal inflammation rather than having diabetes mellitus. Periodontal treatment can provide successful improvement in clinical periodontal parameters and reduction in enzyme profile of GCF in both diabetics and non-diabetics.

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How to cite this article: Hakan Özdemir, Hakan Develioğlu, Nermin Yamalık, Hüseyin Aydın, Kaya Eren. Comparative analysis of the potential effect of phase I therapy on gingival crevicular fluid myeloperoxidase levels in non-diabetic and diabetic patients with periodontitis. Cumhuriyet Dent J 2014;17(3):256-266.