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Effect of Periodontal Treatment on the Crevicular Level of High-mobility Group Box 1 and Soluble Triggering Receptor Expressed on Myeloid Cells 1 in Patients with Chronic Periodontitis

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ABSTRACT

The present study aimed to compare the levels of high-mobility group box 1(HMGB1) and soluble triggering receptor expressed on myeloid cells (sTREM1) in the gingival crevicular fluid (GCF).

This cross-sectional cohort trial investigated two groups of 22 eligible chronic periodontitis and 22 periodontally healthy individuals (student volunteers) both before and after the periodontal treatment. GCF was collected from the deepest pockets with clinical attachment loss≥3 mm. Both groups received oral hygiene instructions, and scaling and root planning were performed in the test group.

Enzyme-linked immunosorbent assay kit (ELISA) was used to measure the levels of HMGB1 and sTREM1 in GCF samples collected before and 1 month after non-surgical periodontal treatment.

The results showed that HMGB1 levels were significantly higher in the chronic periodontitis patients than those of the healthy individuals before treatment ($p<0.02$) and decreased significantly after periodontal treatment, which reduced gingival inflammation. Furthermore, the levels of sTREM1 marker were significantly higher in periodontitis patients before ($p<0.001$) and 1 month after treatment than in healthy individuals ($p<0.003$) although its crevicular levels decreased after periodontal therapy in periodontitis group.

The higher levels of sTREM1 and HMGB1 cytokines in GCF of periodontitis patients and the significant decrease after the introduction of the periodontal treatment underlines the importance of HMGB1 and sTREM1 in pathogenesis of periodontitis.

Keywords: Chronic periodontitis; Gingival crevicular fluid; HMGB1 protein; TREM1 protein

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INTRODUCTION

Periodontal diseases have been proven to be a major cause of tooth loss all over the world. Even though the microbial products in plaque biofilm have been known to be the main risk factor for destruction of tooth supporting tissues, the host immune factors play a pivotal role in progression or remission of periodontitis.[1] In the last few years, there has been a growing interest in finding sensitive diagnostic biomarkers that could alarm the initiation of periodontal disease prior to any irreparable damage. Undivided attention has been recently paid to the level of inflammatory markers in gingival crevicular fluid (GCF) as a non-invasive approach for diagnosis of periodontal diseases.[2] High mobility group box 1 (HMGB1) and soluble triggering receptor expressed on myeloid cells (sTREM1) are rather fresh terms with effects under evaluation. HMGB1 is a non-histone nuclear protein that binds to DNA and is found in the majority of eukaryotic cells. It is both actively released from macrophages and monocytes, stimulated by lipopolysaccharides or TNF-α and is passively released from necrotic and injured cells.[3]

As a delayed cytokine-like inflammatory mediator, HMGB1 is released at the end of inflammatory activities and its level significantly increases in food poisoning conditions.[4] The inflammatory nature of periodontal diseases appears to increase HMGB1in value, yet further studies are required in this regard.

TREM1 is a newly identified extracellular receptor on neutrophils and a subset of monocytes. It has a regulatory effect on the innate immune responses, leading to amplified production of pro-inflammatory cytokines.[5] The enhanced expression of TREM-1 has been illustrated in a series of both infectious inflammatory diseases such as sepsis[6,7] and pneumonia[8] and non- infectious diseases like rheumatoid arthritis.[9] It has been recently reported that TREM-1 expression and secretion in soluble form becomes up-regulated once human neutrophils[10] and monocytes[11] have been exposed to porphyromonas gingivalis (a putative periodontal pathogen).

As a limited number of studies have been investigated the role of HMGB1 and sTREM1 in periodontal pathogenesis, further research on identifying the destructive activities of these cytokines is needed. In our previous study, the concentrations of HMGB1 and sTREM1were found to be higher in periodontitis patients.[12] Since, it is well established that non-surgical periodontal therapy (scaling/root planning and plaque control) reduces gingival inflammation. In the present study, we evaluated the effect of periodontal therapy on the crevicular level of these two biomarkers to determine their potential significance in the activity of the periodontal disease. In order to do so, the study compared the levels of HMGB1 and sTREM1 in the gingival crevicular fluid of healthy subjects and the patients with chronic periodontitis before and after periodontal treatment.

MATERIALS AND METHODS

Participants

The study design was approved by the Ethics Committee of Tehran University of Medical Sciences (No. 93-02-70-25304). 44 participants [22 students with healthy periodontium (HP) and 22 patients suffering chronic periodontitis (CP)] were enrolled in this cross-sectional cohort study. The patients were selected from those referred to the Department of Periodontology, Faculty of Dentistry, Tehran University of Medical Sciences. The diagnosis of periodontal status was made according to the classification proposed by American Academy of Periodontology.[13]

Inclusion Criteria

The following criteria were set as the requisites for the participants:

-No use of any medications during the last 6 months
-No record of smoking tobacco or using drugs
-No systemic disorders (diabetes mellitus, cancer, immune system disorders, metabolic diseases of bone, and diseases affecting the wound healing potential)
-No pregnancy or breast-feeding
-No history of periodontal treatment during the last 1 year
-No sign of gingival inflammation, no bone loss, and no clinical attachment level (CAL≤3mm) for HP group.
-Clinical sign of gingival inflammation, CAL≥3mm, probing depth (PD) ≥ 5mm, and bone loss in more than 30% of teeth for CP group.

Clinical measurements

After signing an informed consent form, all participants were examined for probing depth (PD), clinical attachment level, bleeding on probing (BOP)

and plaque index (PI) to determine the periodontal status of them. They were selected after the clinical examinations and radiographic evaluations. Based on the following protocol, the indices were recorded and the gingival crevicular fluid samples were collected from one pocket ≥5 mm. The selected sites were isolated by cotton rolls, and supra gingival plaque was removed by a rubber cup. Then, Periostrips (Periopaper, Oraflow Inc., USA) were placed in the tooth cervix and held in place for 30 seconds.[14] The Periostrips were placed in microtubes. A total of 300 µL of PBS was added to each microtube. The samples were centrifuged at 10000 rpm for 30 minutes. Then, the samples were stored at -70°C until the tests were carried out. After collection of all samples, the gingival crevicular fluid samples were defrosted and specific enzyme-linked immunosorbent assay kits were used to determine the levels of HMGB1 (BlueGene, Biotech, Shanghai, China) and sTREM1 (DuoSet, R&D Systems, Abingdon, UK).

Next, the subjects with chronic periodontitis were instructed in oral hygiene and received phase I periodontal therapy by one single operator. The treatments consisted of scaling by an ultrasonic scaler, followed by polishing in two stages. The patients were followed on a weekly basis for 1 month and their oral hygiene status was controlled. After a month, the gingival crevicular fluid samples were collected from the same areas and tested.

As with the CP group, the samples in healthy group, were collected from the area with a probing pocket depth of <3 mm.

PD values were analyzed along with the evaluation of the clinical outcome of periodontal treatment.

Statistical Analysis

SPSS Statistical software was used for data analysis (SPSS Package; PC version 21, SPSS, Chicago, IL, USA). Data were checked for normal distribution using Kolmogrov Smirnov test. Regarding normal distribution, T-test was used to evaluate the clinical parameters and the levels of HMGB1 and sTREM1 between groups. Repeated-measures ANOVA was used to test statistically significant changes in the levels of these markers before and after periodontal therapy. The analyses performed at $p<0.05$ level of significance. Correlation between cytokines levels and clinical parameters were obtained using Pearson correlation test at $p<0.05$ significant level.

RESULTS

44 patients, 21 males and 23 females were enrolled in this study. The demographic and periodontal parameters of the study subjects are summarized in Table 1. All the periodontal parameters were significantly higher in periodontitis group ($p<0.05$) and in CP group after phase I periodontal therapy all of these indices improved ($p<0.05$).

Mean values of GCF concentration of HMGB1 and sTREM1 of two study groups, before and after non-surgical periodontal therapy were listed in Table 2.

GCF level of HMGB1 in chronic periodontitis group was higher (Student's T test, $p<0.02$) than healthy subjects and decreased statistically after periodontal therapy (ANOVA test, $p<0.04$). The groups

Table 1. Demographic and clinical characteristics of patients in healthy periodontium and chronic periodontitis groups

	CP patients (n=22)	HP patients (n=22)
Gender	13 male/ 9 female	8 male/ 14 female
Age (years)	45.4±1.9	23.3 ±2.1
BOP (% sites)	72 %	0%
Plaque Index (% sites)	88%	17%
PD (mm; mean ±SD)		
pretreatment	6.45±0.31	2.2±0.36
post treatment	5.33±0.89	1.72±0.56

BOP: bleeding on probing, PD: probing depth, CP: chronic periodontitis, HP: healthy periodontium, SD: standard deviation

Table 2. Changes in crevicular concentrations of HMGB1 and sTREM1 before and after treatment, in /and between both groups

	HMGB1 (Mean ± SD)		sTREM1 (Mean ± SD)	
	Pretreatment	**Post treatment**	**Pretreatment**	**Post treatment**
CP patients (ng/ml)	1.68±0.33[a,c]	1.41±0.28[b,c]	1.79 ±0.24[d,f]	**1.47±0.21[e,f]**
HP patients (ng/ml)	1.43±0.32 [a]	1.26±0.31 [b]	1.52 ±0.25 [d]	**1.28±0.18 [e]**

HMGB1: high-mobility group box 1, sTREM1: soluble triggering receptor expressed on myeloid cells, SD: Standard deviation, CP: Chronic periodontitis, HP: Healthy periodontium

a) $p<0.02$ (HMGB1: CP-pre vs HP-pre)

b) $p= 0.094$ (HMGB1: CP-post vs HP -post)

c) $p= 0.016$ (HMGB1: CP-pre vs CP-post)

d) $p= 0.001$ (sTREM1: CP-pre vs HP -pre)

e) $p= 0.003$ (sTREM1: CP-post vs HP -post)

f) $p= 0.0001$ (sTREM1: CP-pre vs CP-post)

Table 3. Correlation between HMGB1 and sTREM1 levels in gingival crevicular fluid with clinical parameters before and after treatment

		Probing Depth		Plaque Index
		Before therapy	**After therapy**	
HMGB1	Correlation	0.263	0.294	0.182
	p-value	0.085	0.053	0.238
sTREM1	Correlation	0.415	0.379	0.379
	p-value	0.005*	0.011*	0.003*

HMGB1: high-mobility group box 1, sTREM1: soluble triggering receptor expressed on myeloid cells

*correlation is significant at 0.05 level

did not significantly differ in HMGB1 levels, after phase I periodontal treatment, in spite of slightly higher levels in patients with periodontitis.

The baseline ($p<0.005$) and post treatment ($p<0.005$) levels of sTREM1 were significantly higher in the CP patients compared to the healthy subjects. Based on the results of ANOVA, periodontal non-surgical therapy significantly reduced the sTREM1 levels in periodontitis patients ($p<0.0001$). The correlation between GCF levels of the cytokines and clinical parameters were evaluated and summarized in Table 3. The concentration of sTREM1 was positively correlated with PI and PD ($p<0.05$). Furthermore, a positive significant correlation was observed between crevicular levels of sTREM1 and HMGB1, ($p=0.001$).

DISCUSSION

The main objective of this paper was to evaluate the effect of non-surgical periodontal therapy on the GCF levels of HMGB1 and sTREM1 in periodontally healthy participants and patients with chronic periodontitis. As the body of literature indicates, it has been the first study investigating the effect of non-surgical periodontal therapy on GCF levels of HMGB1 and sTREM1 in two CP and HP groups. HMGB1, an inducer of pro-inflammatory cytokines, has been suggested to be an important mediator in destructive processes of periodontitis.[12,15] As reported earlier, GCF had a potential diagnostic value to identify the activity of periodontal diseases or the treatment outcomes.[2,15]

Accordingly, the results of the study showed that at baseline, GCF levels of HMGB1 in CP group were significantly higher than HP group and they significantly decreased subsequent to non-surgical treatment in both groups. Despite the significant decrease after treatment, the HMGB1 levels remained significantly higher in patients with chronic periodontitis compared to healthy participants.

HMGB1 stimulated periodontal ligament cells to secrete IL-6 and IL-1 through receptors such as RAGE, toll-like receptors (TLR)2 and TLR4.[16] In addition, there was an increase in levels of extracellular HMGB1 in the salivary glands of patients with Sjögren's syndrome. Under the inflammatory conditions of salivary glands, HMBG1 formed a pro-inflammatory cycle in association with TNF-α and IL-1β for the induction of chronic properties.[17] Anti-HMGB1 antibody had the capacity to protect mice against chronic diseases of lungs, decrease injuries, and limit the release pro-inflammatory factors such as IL-1β and TNF-α.[18]

Various cells such as neutrophils, macrophages,[19] and gingival epithelial cells[20] could release HMGB-1. It was shown that exposure of human monocyes to extracellular HMGB-1 provoked cytokine synthesis like IL-1α, IL-1ß, TNF, IL-6, IL-8, but not IL-10 or IL-12.[21] The reason why HMGB1 has attracted much attention in the domain of periodontitis is the important role it played in progression of inflammatory conditions such as septic shock, rheumatoid arthritis, and atherosclerotic lesions.[7,9,21]

Recently released papers have all suggested the aggregation of HMGB1 in gingival tissues of patients with chronic periodontitis and synthesis of pro-inflammatory factors in such tissues. Although the results obtained in indicated the presence of HMGB1 in GCF of patients with periodontitis,[20] there was no comparison made with GCF of healthy participants. In addition, immunohistochemical studies have shown that HMGB1 is mainly expressed in the nucleus of the gingival epithelial cells of healthy tissues, but it was transferred from the nucleus to the cytoplasm of gingival cells in chronic periodontitis. This translocation might be regulated by inflammatory mediators like TNF-α.[20]

Luo et al (2011) evaluated the expression of HMGB1 in gingival tissues, GCF, and peri-implant crevicular fluid in patients with periodontitis and peri-implantitis. Authors reported up regulation of HMGB1 in the gingival tissues and peri-implant crevicular fluid of these patients which was associated with an increase in the concentration of IL-1β, IL-6 and IL-8 cytokines. They suggested HMGB1 as an important diagnostic marker in the treatment of chronic periodontitis and peri-implantitis.[15]

Based on the results of the present study, HMGB1 concentrations and probing depth in patients with periodontitis were higher than healthy participants both before and after phase I periodontal treatment, indicating the fact that it might be possible to determine HMGB1 levels in GCF to identify the participants susceptible to periodontitis and treat them at early stages of the disease. The results of previous studies suggest that constant release of HMGB1 could be at least considered as a partially important signaling agent for the widespread destruction of the periodontium.

Along with HMGB1, this study was focused on the crevicular levels of sTREM1, as another inflammatory mediator. The concentration of this cytokine in patients with periodontitis was significantly higher than that in healthy participants at baseline. In spite of a significant decrease in the sTREM1 values after treatment, it was again higher in patients with chronic periodontitis compared to healthy participants.

During the infection process, TREM1 is up regulated at monocyte and neutrophil levels. After being activated by an unknown ligand, TREM1 activates interactions mediated by TLR, resulting in the up regulation of the synthesis of pro-inflammatory cytokines such as IL-1α and TNF-α and chemokines such as IL-8.[22]

Subsequently, TREM1 and TLR combine to increase inflammatory reactions, synthesis of cytokines, immediate degranulation of neutrophils, and phagocytic respiratory burst.[23] The soluble form of TREM1is also released into body fluids after being flowed by metalloproteinases.[24] sTREM1 is released by myeloid cells such as macrophages, monocytes and neutrophils, but it might be released from epithelial cells, too. Recently TREM1 has also been identified at keratinocyte levels.[5] Some studies have shown an increase in the sTREM1 concentrations in different biologic fluids in conditions like sepsis, pneumonia, septic arthritis, and uterine infections.[25] Despite previous observations, the role of sTREM1 has not been exactly elucidated in the mechanism of inflammation. Some studies have shown that up regulation of sTREM1 was mediated by bacteria and

therefore, sTREM1 could be considered a specific marker for infection in many pathologic conditions.

Some bacterial species such as *Pseudomonas aeroginosa* and *Staphylococcus aureus* increase the expression of TREM1 at cellular level. Recently, the ability of *Porphyromononas gingivalis* to increase the gene expression of TREM1 in myelomonocytic cell line was confirmed.[10,11]

Three clinical studies indicated the higher crevicular level of sTREM1 in periodontitis affected sites.[12,26,27] Bisson et al. observed that the GCF levels of sTREM1in chronic periodontitis sites were 14 times higher compared to healthy participants. Multivariate analysis revealed that concentration of sTREM1was positively correlated with pocket depth and smoking status of the participants.[26] In present study, positive correlation was found between plaque score, pocket depth and sTREM1 levels. Accordingly, it could be suggested that sTREM1 levels in GCF is associated with the severity of periodontal disease. In the study by Belibasakis et al. it was shown that the total amounts of sTREM1in chronic and aggressive periodontitis were 3.6 and 4.4 folds of healthy participants and correlated with the levels of red complex bacteria.[27] Furthermore, an increase in salivary and serum levels of sTREM1 was found in patients with periodontitis compared to healthy subjects.[28]

Given the cross-sectional nature of the present study, despite the higher levels of sTREM1 and HMGB1, a cause-and-effect relationship could not be established between the biomarker levels and periodontitis. It is not clear if the release of sTREM1 and HMGB1 in GCF has a role in the incidence of periodontal disease or it has a protective role against bacterial infections. However, an increase in the concentration of these cytokines might have a predictive value in periodontal diagnosis.

Since higher levels of these immunomodulators have been shown in systemic diseases, further clinical trials could be done to assess the possible correlation between serum and crevicular levels of these markers. Such studies could introduce GCF analysis as a promising minimally invasive method for diagnosis of systemic diseases.

Based on the higher values of HMGB 1 and sTREM1 in periodontitis affected sites and meaningful decrease after periodontal treatments, the results underline the importance of HMGB1 and sTREM1 in the pathogenesis of periodontitis. It might be worth suggesting these cytokines to be further investigated in clinical trials with larger sample size to determine their values as diagnostic markers of the periodontal disease.

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