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# GCF LEVELS OF sRAGE AND MCP-1 IN TYPE-2 DIABETIC PATIENTS WITH PERIODONTITIS: A PRELIMINARY REPORT

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## ABSTRACT

Background and Aim: Diabetes mellitus-related chronic complications can affect multiple organs, including the macrovascular and microvascular systems, as well as the periodontium. Advanced glycation end products (AGE), its receptor (RAGE) and soluble receptor (sRAGE) interaction is critically involved in the pathobiology of both diseases. Monocyte chemoattractant protein-1 (MCP-1) is an essential chemokine responsible for the recruitment of monocytes to inflammatory lesions in the vasculature, an initial step of atherosclerosis. This study aimed to compare the levels of MCP-1 and sRAGE in the gingival crevicular fluid (GCF) of periodontitis patients with type 2 diabetes and those without, hypothesizing that these levels may vary based on diabetic status

Materials and Methods: Nine patients with periodontitis and diabetes (DP), 12 periodontitis (P) patients without diabetes, 12 systemically and periodontally healthy subjects (HC) were enrolled in this case-control study. Clinical periodontal parameters and HbA1c values were evaluated. Gingival crevicular fluid samples were analysed for sRAGE and MCP-1 by an enzyme-linked immunosorbent assay. The significance of differences were assessed with Kruskall-Wallis test. Pairwise comparisons were made with Dunn test.

Results: sRAGE and MCP-1 levels were significantly higher in periodontitis group than healthy controls ($p<0.05$). There was no difference between DP and P groups ($p>0.05$). Positive correlation was detected between sRAGE and MCP-1 levels in disease groups ($p=0.000$, $r=0.976$ for DP group; $p=0.000$, $r=0.982$ for P group respectively).

Conclusion: MCP-1 and sRAGE may have a functional role in the diabetic-periodontal pathogenesis. Further studies must be carried out to understand the contribution of sRAGE and MCP-1 in periodontal inflammation with or without diabetes.

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**Keywords:** GCF, Periodontitis, sRAGE, MCP-1, Type 2 Diabetes

## INTRODUCTION

Periodontitis is a chronic inflammatory disease associated with dysbiotic plaque bacteria that results in destruction of the tooth's supporting tissues. The persistent stimulation of the host immune cells by periodontopathogens triggers a chronic inflammatory response, which in turn leads to bone resorption The cytokine-mediated pathways play an important role in the periodontal inflammation. These pathways give direction to the protective or destructive nature of the immune-inflammatory response that related to periodontal tissue destruction. Many host inflammatory and immune mediators have been identified in gingival crevicular fluid (GCF) both in healthy and diseased periodontal conditions.[1] Monocyte chemoattractant protein-1 (MCP-1) is an essential chemokine with chemotactic monocytes, macrophages, and T lymphocytes involved in chronic inflammatory diseases such as atherosclerosis, rheumatoid arthritis, osteoarthritis, and periodontitis.[2] MCP-1 is expressed by leukocytes, keratinocytes, vascular endothelial cells and mononuclear phagocytes in inflamed gingiva.[3] It has been showed that GCF levels of MCP-1 were higher in (formerly) generalized aggressive and chronic periodontitis compared to healthy group.[4, 5] Hanazawa et al.[6] detected the marked MCP-1 gene expression in gingival tissues from all adult periodontal patients tested, but not at all in those from healthy subjects.

Diabetes mellitus (DM) has long been considered to be one of the systemic conditions that influences the relative risk for periodontal diseases.[7] Studies have suggested a bidirectional relationship between glycaemic control and periodontitis. Changes in the microbial-host interactions in the periodontium of diabetic patients are numerous, including alterations in host defenses such as impaired function of polymorphonuclear leukocytes, including a reduced chemotactic response.[8] Another consequence of hyperglycemia is the irreversible formation and accumulation of advanced glycation end products (AGEs) in the tissues. Advanced glycation end products (AGEs) were described as one of the causes of the development and progression of diabetes-related complications.[9] AGEs are a complex group of oxidant compounds formed by the nonenzymatic glycation of proteins, lipids, and nucleic acids. AGEs accumulate organs with advancing age and poor glycemic control.[10] AGEs are biologically active and may initiate a range of cellular response including stimulation of monocyte chemotaxis, osteoclast induced bone resorption, proliferation of vascular smooth muscle cells, aggregation of platelets, and stimulation of secretion of inflammatory cytokines, collagenase and several growth factors.[11]

Systemic levels of several proinflammatory markers are increased in type 2 DM subjects, thereby amplifying a chronic inflammatory disease state.[12, 13] Receptor of AGEs (RAGE) is a multiligand, signal transduction receptor which forms a central part of the cell surface binding site for AGEs.[14] In recent studies, AGE and it's receptor RAGE are found to be responsible for type 2 diabetic complications.[8, 11-15] Katz et al.[16] demonstrated expression of RAGE in the gingival tissues of patients with chronic periodontitis by immunohistochemistry and reported significant increase in mRNA for RAGE in the diabetic gingiva. Moreover, it was shown that blockage of RAGE by administration of soluble receptor for advanced glycation end prducts (sRAGE) supressed periodontal bone loss in diabetic mice.[17] sRAGE is the extracellular ligand-binding domain of RAGE. It could act as a competitive inhibitor of RAGE and it may have a protective effect on alveolar bone loss.[17] It was reported that it prevents cell-bound RAGE signalling. Engagement of RAGE with AGEs stimulates MCP-1 expression in various types of cells.[18, 19] Nakamura et al.[11] investigated 86 serum samples of type 2 diabetic subjects and reported significant correlation of MCP-1 levels with AGEs and soluble RAGE (sRAGE). The sRAGE-MCP-1 axis may be an important pathway of tissue destruction in diabetes associated periodontitis. Moreover the knowledge about the human sRAGE in GCF is still limited.[20] Thus the hypothesis of the present study is sRAGE and MCP-1 levels in GCF may differ according to the presence of periodontal disease and/or diabetes.

Therefore the basic aim of the present study was to evaluate the MCP-1 and sRAGE in GCF of chronic periodontitis patients with and without type 2 diabetes.

## MATERIALS AND METHODS

Thirty three adult patients referred to the Department of Periodontology at Hacettepe University were included in the study. Patients were divided into 3 groups: 1) Nine periodontitis patients with type 2 diabetes (DP), 2) 12 systemically healthy periodontitis patients (P), 3) 12 systemically and periodontally healthy control individuals (HC). The HC group consisted of individuals with no periodontal disease history and no clinical signs of inflammation. The diagnosis of periodontitis was made according to the 2017 World Workshop on the Classification

of Periodontal and Periimplant diseases and conditions.[21] According to this, stage I and II periodontitis patients were included in the study.

Informed consent was obtained from all subjects and study was performed in accordance with the Declaration of Helsinki with the approval of Hacettepe University Ethic Boards and Commissions (Approval number: FON 09/3-39). All subjects were non-smokers and had at least 20 teeth. None of the subjects used antibiotics, anti-inflammatory medications and did not received periodontal therapy within 3 months prior to the study. Subjects with active infectious diseases such as hepatitis, HIV infection and tuberculosis or chronically treated with medications (phenytoin, cyclosporine-A or calcium channel blockers), as well as females who were lactating or pregnant were excluded. Probing depth (PD), clinical attachment level (CAL), plaque index (PI),[22] gingival index (GI),[22] and bleeding on probing (BOP) were recorded for all subjects at baseline. For the diabetic subjects glycated hemoglobin (HbA1c) values were recorded.

Maxillary anterior teeth were selected for GCF sampling, in order to eliminate the possibility of contamination with saliva. GCF samples were collected from 6 maxillary anterior sites per patient. Teeth were isolated with cotton rolls and gently dried with air. A standard paper strip (Perio-paper, IDE Interstate, Amityville, NY, USA) was inserted into the sulcus to the depth of 1-2 mm for 30s. Results were recorded and reported as total amounts. A calibrated Periotron 8000 (Oroflow, Inc, NY, USA) was used to determine the GCF volume. Strips contaminated by blood were excluded. After collection of the gingival fluid, the strips were immediately placed in sterile Eppendorf tubes containing 10 mM $NaH_2PO_4$ and 150 mM NaCl, pH 7.2, followed by mixing and centrifugation at 800 g. The GCF samples were stored at -80 C until subsequent analysis.

GCF samples were analysed for sRAGE and MCP-1, using commercially available enzyme-linked immunosorbent Assays (ELISA, Oroflow Inc.). Analyses were performed according to the manufacturer's protocol. Results were calculated using the standard curves created in each assay. The total amount of cytokines in GCF was determined in picograms (pg).

### *Statistical analysis*

The clinical parameters were expressed as mean ± standart deviation and analysed by the ANOVA test. Because the data were not normally distributed, sRAGE and MCP-1 levels in GCF were expressed as medians (minimum-maximum) and the significance of differences were assessed with Kruskall-Wallis test. The $p$ value of <0.05 was considered to be statistically significant. Pairwise comparisons were made with Dunn test. Correlations were investigated using Spearman's test.

## RESULTS

Demographic variables of the groups were given in Table 1. The healthy group was significantly younger compared to the disease groups (p=0.001). Mean HbA1c value of the diabetic patients was 7.21 (min 5.9, max 8.5).

The full mouth periodontal scores of study groups are shown in Table 2. The PD and PI values were similar between groups. GI and BOP values were statistically lower in healthy control group than periodontitis with diabetes (DP) and periodontitis group without diabetes (P) (p<0.05). CAL values were highest in DP group but reached significance only with HC group (p<0.05). Total amounts were greater in DP and P group than HC group for both sRAGE and MCP-1 but statistical significance was detected between P-HC groups (p<0.05) (Table 3). In periodontitis groups significant correlations were detected between sRAGE and MCP-1 levels (p=<0.001, r=0.976 for DP group; p=<0.001 r=0.982 for P group respectively).

## DISCUSSION

In the present study the total amounts of sRAGE and MCP-1 in GCF of periodontitis patients with or without type 2 diabetes were evaluated. sRAGE was identified in the GCF of both diabetic and non-diabetic subjects, and the total amount of sRAGE was higher in the periodontitis groups compared to healthy controls. sRAGE was studied in many chronic diseases in serum samples.[23] Present literature points out the function of this molecule as a therapeutic target related to complications of diabetes.[24] The results of this study contribute to the knowledge on sRAGE, which has very limited data in the current literature related to diabetes and periodontitis. Singhal et al.[20] reported an opposite result to the present study. They found the highest level of sRAGE in periodontally healthy and non-diabetic group and lowest in diabetic periodontitis group. They postulated that the synthesis of sRAGE can be inhibited directly by hyperglycemia or by increased levels of cytokine and/or hyperglycemia-induced AGEs.[20] The studies examining sRAGE levels in periodontitis is limited.[20, 25, 26] Detzen et al.[26] found significantly lower levels of sRAGE

Table 1. Demographic variables of the study groups

| Study Parameters | DP (n=9) n (%) | P (n=12) n (%) | HC (n=12) n (%) | p |
|---|---|---|---|---|
| Sex | | | | |
| Male | 5 (31.2) | 6 (37.5) | 5 (31.3) | 0.941[a] |
| Female | 4 (23.5) | 6 (35.3) | 7 (41.2) | |
| | ± S.d. | ± S.d. | ± S.d. | |
| Age | 52.87 ± 10.45 | 51.54 ± 9.72 | 35.0±9.77 | 0.000[b] |

p<0,05; a=Chi-square Test; b=Anova Anaysis HC: normoglycemic and periodontally healthy group, DP: Type 2 diabetic subjects with periodontitis group, P: Periodontitis without diabetes.

Table 2. Clinical periodontal parameters of the study groups.

| Parameters | DP group (n=9) | P group (n=12) | HC group (n=12) | $P^a$ | $P^b$ | $P^c$ | $P^d$ |
|---|---|---|---|---|---|---|---|
| **PD** | | | | | | | |
| Full mouth | 2.47±0.23 | 2.36±0.32 | 1.89±0.10 | | | | 0.99 |
| Sampled site | 2.40±0.92 | 1.98±0.74 | 1.73±0.42 | 0.51 | 0.11 | 0.20 | |
| **CAL** | | | | | | | |
| Full mouth | 3.17±0.24 | 2.64±0.35 | 1.95±0.10 | 0.09 | 0.001 | 0.50 | |
| Sampled site | 2.43±0.91 | 1.98±0.74 | 1.73±0.42 | 0.51 | 0.11 | 0.07 | |
| **GI** | | | | | | | |
| Full mouth | 0.97±0.14 | 1.19±0.15 | 0.33±0.05 | < 0.001 | 0.0013 | 0.80 | |
| Sampled site | 1.31±0.54 | 0.91±0.55 | 0.03±0.04 | < 0.001 | 0.001 | 0.66 | |
| **BOP (%)** | | | | | | | |
| Full mouth | 70.75±10.44 | 78.83±7.23 | 26.41±5.95 | <0.001 | 0.001 | 0.50 | |
| Sampled site | 87.50±23.15 | 69.45±40.1 | 3.33±4.92 | <0.001 | 0.001 | 0.92 | |
| **PI** | | | | | | | |
| Full mouth | 0.63±0.17 | 0.62±0.16 | 0.31±0.04 | | | | 0.120 |
| Sampled site | 0.57±0.55 | 0.57±0.49 | 0.05±0.14 | <0.001 | 0.02 | 0.50 | |

p<0.05; $p^a$=HC-P; $p^b$: HC-DP; $p^c$: DP-P $p^d$: p value according to ANOVA.
HC: normoglycemic and periodontally healthy group, DP: Type 2 diabetic subjects with periodontitis group, P: Periodontitis without diabetes.
PD: probing depth, CAL: clinical atachment level, GI:gingival index, BOP: bleeding on probing, PI: Plaque index

Total amounts of sRAGE and MCP-1 in GCF of study groups.

| | DP group (n=9) | P group (n=12) | HC group (n=12) | P |
|---|---|---|---|---|
| sRAGE (pg) median (min-max) | 52.48 (8.83-95.50) | 49.91* (1.91-172.87) | 12.45 (6.56-49.12) | 0.010* |
| MCP-1 (pg) median (min-max) | 41.51 (6.27-93.83) | 37.60* (1.34-146.45) | 10.31 (5.32-38.35) | 0.016* |

*= considered significant according to HC
HC: normoglycemic and periodontally healthy group, DP: Type 2 diabetic subjects with periodontitis group, P: Periodontitis without diabetes.

in the serum of patients with periodontitis compared to periodontally healthy controls.[26] Kim et al.[25] while not statistically significant, also observed a trend towards lower sRAGE levels in patients with periodontitis.[25] The present study is the only one, apart from the study by Singhal et al.[20] that examined sRAGE using GCF samples, allowing a direct comparison. In the previous report, patients had HbA1c values below 7%, whereas in the current study, considering that most patients had uncontrolled diabetes, we believe this difference may have influenced the results.

sRAGE has been described as a "sponge" for AGEs and may have protective functions, as it lacks the $NH_2$-terminus and cannot activate NF-kB signaling.[27] The lower levels of circulating sRAGE were reported to be associated with risk of diabetes and coronary heart disease.[27] Serum levels of sRAGE are reduced in some chronic inflammatory diseases like rheumatic arthritis, Alzheimer's disease coronary artery diseases.[23] On the other hand, there are studies that have reported elevated levels of sRAGE compared to healthy controls in type 1,[28] type 2 diabetes [29] and impaired renal function[30] similar to the present study results. Thus Prasad et al.[31] have suggested to use AGEs/sRAGE ratio rather than total circulating level. The difference of the present study results and the previous one may be interpreted better in the light of this data. We observed difference between periodontitis and healthy groups and diabetic groups in our recent study regarding this ratio (unpublished data). Thus, the role of sRAGE in periodontitis should be examined in future studies with larger groups. The small sample size was a limitation of the present study as mentioned the same in an earlier report [20] (Observed power analysis for sRAGE was calculated as 0.812). Because of the sample size, the statistically significant difference in diabetic periodontitis group may not be detected. Another limitation of the study is that the samples were obtained from the shallow pockets of the periodontitis patients and the patients were localized periodontitis. However the analysis of shallow pockets of the periodontitis patients suggests that monitoring of sRAGE and MCP-1 may be useful in predicting disease risk. Additionally, the inclusion of a periodontally healthy diabetes group could have contributed to a better evaluation of the results.

The present study results represents that sRAGE and MCP-1 has an association with periodontal inflammation Regardless of diabetic status, sRAGE and MCP-1 levels were found to be higher in periodontitis patients compared to healthy individuals.Additionally, they are positively correlated with each other (p=000).

Enhanced expression of MCP-1 in periodontally diseased tissues was demonstrated in the literature in systemically healthy subjects.[4-6] [32-34] In the present study we have demonstrated similar results, in both chronic periodontitis groups with or without diabetes, GCF levels of MCP-1 were higher according to healthy controls. Monocyte chemotactic activity of crevicular fluid of adult periodontal patients was reported to increase with severity of the disease.[6] MCP-1 is an important chemokine to the cells of monocyte/macrophage lineage. Thus MCP-1 may play an important role in amplification of inflammatory signals and disease progression. Besides its local effects in GCF, MCP-1 plays an important role in early phase of atherosclerosis by monocyte recruitment to vessel Wall.[35, 36] Elevations in serum MCP-1 levels of diabetic patients (high risk patients for atherosclerosis) were reported.[37]

In the present study we have reported the GCF MCP-1 levels in diabetic situation. Nakamura et al. concluded that circulating levels of AGEs and sRAGE are independent determinants of serum MCP-1 levels in patients with type 2 diabetes.[11] Our present observations suggest the AGEs-RAGE system may be mainly involved in the elevation

of MCP-1 and/or they enhance each other's effects in periodontitis. Thus in diabetic patients, periodontal disease control should be suggested because these interactions may lead atherosclerotic cascade. This patient group may benefit from supression of periodontal inflammation.

## CONCLUSION

MCP-1 and sRAGE may have a functional role in periodontal inflammation, and disease risk. Further studies with larger groups must be carried out to understand the contribution of sRAGE and MCP-1 in periodontal inflammation with or without diabetes.

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The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

## CONFLICT OF INTEREST

Yağmur Deniz Yıldırım declares that he has no conflict of interest. Esra Ercan declares that he has no conflict of interest. Güliz N. Güncü declares that he has no conflict of interest. Ezel Berker declares that he has no conflict of interest.

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## ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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