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An investigation of the relationship between rheumatological diseases and soluble receptor for advanced glycation end products

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Abstract. – OBJECTIVE: Soluble receptor for advanced glycation end products (sRAGE) is one of the forms of RAGE. It is a trap receptor that has a role in inhibiting pro-inflammatory processes that will occur with the combination of RAGE and its ligands. Our study aims to examine the level of sRAGE in rheumatological inflammatory diseases and its relationship with these diseases.

PATIENTS AND METHODS: A total of 60 patients with Behçet's disease (BD), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and 22 healthy control individuals were included in the study. Comorbidity status, sRAGE levels, disease activity scores, demographic and laboratory data of the patients were recorded. Serum sRAGE levels in these diseases and healthy controls were determined by Enzyme-Linked Immunosorbent Assay (ELISA) kit spectrophotometrically.

RESULTS: Serum sRAGE levels in the patient groups were significantly higher when compared to the healthy control group ($p < 0.001$ for all). On the other hand, when the patient groups were compared with each other in terms of sRAGE levels, there was no significant difference ($p > 0.05$ for all). The serum sRAGE levels were not correlated with C-reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR), and disease activity scores ($p > 0.05$ for all).

CONCLUSIONS: Serum sRAGE levels increased in BD and in other inflammatory rheumatological diseases. However, this increase does not directly correlate with inflammatory markers and disease activity scores. These results suggest that serum sRAGE level may not be used as a biomarker for disease activity in BD and in other rheumatological diseases.

Key Words:
sRAGE, Behçet's disease, Rheumatological diseases, Inflammation.

Introduction

The receptor for advanced glycation end products (RAGE) – first isolated from the human lung[1] – is a signal transduction molecule that recognizes several signaling molecules. RAGE serves as a receptor for advanced glycation end products (AGEs) and is involved in pro-inflammatory processes, although their exact function is yet to be clarified. RAGE is expressed in numerous tissues and when it interacts with AGEs, inflammation and oxidation occur[2]. Due to its involvement in Alzheimer's and cardiovascular diseases, which are associated with aging, it has been suggested that RAGE plays an important role in physiological aging as well[3,4].

RAGE has several soluble forms and one of them is soluble RAGE (sRAGE), which is released from pericytes and endothelial cells. It functions as a decoy receptor for a number of RAGE ligands, including AGEs. Thus, sRAGE has an inhibitory effect on the pro-inflammatory processes mediated by RAGE and its ligands[5,6].

Rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) are defined as chronic inflammatory rheumatological diseases with unspecified etiologies. RA is a progressive disease that symmetrically damages the joints by causing inflammation[7]. It has been found that increased serum AGE levels in patients with RA are associated with the severity of the disease[8]. On the other hand, sRAGE applications have been shown to have anti-inflammatory effects on the experimental models[9]. The role of the RAGE pathway has also been investigated in SLE with immunological abnormalities. It has been stated that sRAGE levels are a potential biomarker and a future therapeutic target in SLE patients[10,11].

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The clinical prognosis of BD includes recurrent oral aphtha, genital ulcers, and chronic uveitis, characterized by systemic vasculitis that may involve veins of all diameters[12,13]. Although the expression of RAGE is minimized or absent in normal tissues, it increases during inflammation or cancer. This makes RAGE an ideal target in the development of treatment strategies for chronic inflammatory diseases. In this context, changes in the sRAGE levels in case of chronic inflammatory diseases and their association with inflammatory processes have been of great research interest. However, there is no study investigating the role of the RAGE pathway in the pathophysiology of BD. The present study aimed to investigate the changes in the sRAGE levels in chronic rheumatological diseases, including BD, RA, and SLE, and to study the association of this change with inflammation.

Patients and Methods

Patients

The study included patients with BD (n = 20), RA (n = 20), SLE (n = 20), and healthy controls (n = 22) who presented to the rheumatology clinic from March 1, 2020, to May 1, 2020 (Figure 1). The participants' comorbidity status, sRAGE levels, disease activity scores, demographic and laboratory data were recorded. The International Study Group criteria were used for the diagnosis of patients with BD[14], and the disease activity was determined by the Behcet's Disease Current Activity Form (BDCAF)[15]. The classification criteria of the 2010 American College of Rheumatology/European League Against Rheumatism was used for the purpose of diagnosing patients with RA[16], in whom the 28-joints Disease Activity Score (DAS28) was used to assess the disease activity[17]. Lastly, the revised classification criteria of the American College of Rheumatology were used for the diagnosis of patients with SLE[18], and the SLE Disease Activity Index 2000 (SLEDAI-2K) was used to measure disease activity[19]. The exclusion criteria of the study included pregnant women, individuals aged below 18 years and individuals with other chronic inflammatory diseases.

Enzyme-Linked Immunosorbent Assay (ELISA)

A commercially available human sRAGE ELISA Kit (#E0031Hu, Bioassay Technology Laboratory, Shanghai, China) was used to determine the sRAGE levels in the serum obtained from the patients with BD, RA, SLE, and healthy controls. The ELISA reaction was performed according to the manufacturer's protocol. Following the reaction, the absorbance values were measured with a spectrophotometric plate reader by comparing each sample to the standard curve, and consequently, the serum sRAGE concentrations were determined.

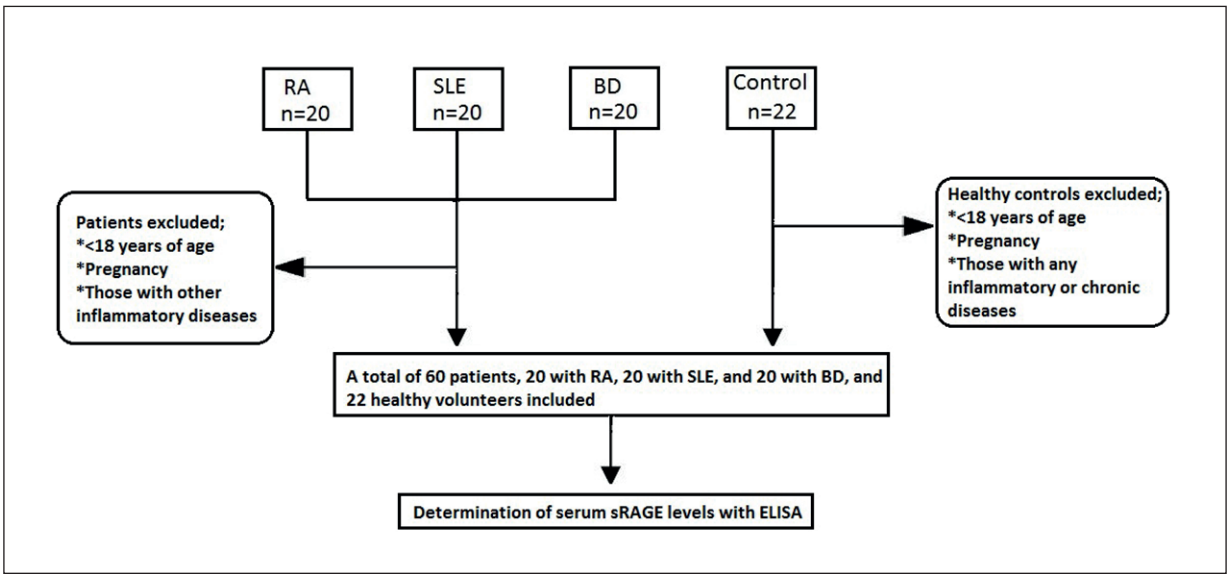

Figure 1. Patient flow diagram. BD: Behcet's disease, RA: Rheumatoid arthritis, SLE: Systemic lupus erythematosus.

Table I. Demographic and laboratory data of the study groups.

	BD	RA	SLE	Healthy control	*p*-value
Gender (female/male)	10/10	14/6	18/2	12/10	0.032
Age (year)	38.65 ± 10.61	54.90 ± 12.49	48.35 ± 14.15	42.00 ± 8.16	< 0.001
Atherosclerosis (n)	3	2	2	-	0.357
Diabetes mellitus (n)	2	2	2	-	0.499
Hypertension (n)	3	6	8	-	0.008
Smoking (n)	6	5	5	-	0.058
CRP (mg/L)	5.62 ± 7.52	19.77 ± 47.09	6.45 ± 7.72	5.59 ± 2.13	0.171
ESR (mm/h)	29.80 ± 17.70	46.00 ± 27.31	35.95 ± 18.32	14.68 ± 5.31	< 0.001
sRAGE (ng/mL)	11.60 ± 5.47	14.03 ± 4.86	11.10 ± 6.68	4.44 ± 2.89	< 0.001

BD: Behcet's disease, RA: Rheumatoid arthritis, SLE: Systemic lupus erythematosus, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, sRAGE: Soluble receptor for advanced glycation end products.

Statistical Analysis

SPSS Version 22.0 (IBM Corp, Armonk, NY, USA) was used for all the statistical analyses of the study and the data were expressed in the form of standard deviation. The Chi-square test was used to investigate the difference in the intergroup categorical data. Tukey's test was used as a post-hoc test for the binary comparison of the groups. The linear data were assessed using the one-way variance analysis. The correlation analysis of the data was performed by the Pearson's test. $p<0.05$ was considered as statistically significant.

Ethics Committee Approval

The study protocol was approved by the Local Ethics Committee (Ethics Approval No. OMU-KAEK 2021/517), and informed consent forms were obtained from all the patients and healthy volunteers.

Results

The study included 20 patients who met the inclusion criteria for each disease group and 22 healthy volunteers. The mean age of the patients included in the BD, RA, and SLE groups, and the healthy controls group was 38.65 ± 10.61 years, 54.90 ± 12.49 years, 48.35 ± 14.15 years and 42.00 ± 8.16 years, respectively. The demographic information, comorbidity status, and laboratory data pertaining to the three patients and healthy control groups are presented in Table I. The serum sRAGE levels were significantly higher in the patient groups than the healthy control groups ($p < 0.001$ for all, Figure 2). Even after adjusting for age and hypertension (HT), there was a significant difference in the sRAGE levels among all the groups ($p < 0.001$). However, no significant difference in the sRAGE levels was observed when patient groups were compared with each other ($p > 0.05$ for all).

The disease activity scores were as follows: the BDCAF score for patients with BD was 4.7 ± 2.9, DAS28 score for patients with RA was 5.31 ± 1.8, and SLEDAI score for patients with SLE was 7.8 ± 6.2. No statistical correlation between the serum sRAGE levels and the C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and disease activity scores for the patients with BD ($r = 0.022$, $p = 0.928$; $r = 0.277$, $p = 0.238$; $r = -0.050$, $p = 0.760$; respectively), RA ($r = -0.163$, $p = 0.492$; $r = -0.387$, $p = 0.092$; $r = -0.016$, $p = 0.921$; respectively), and SLE ($r = 0.194$, $p = 0.411$; $r = 0.426$, $p = 0.061$; $r = 0.057$, $p = 0.728$; respectively) were observed.

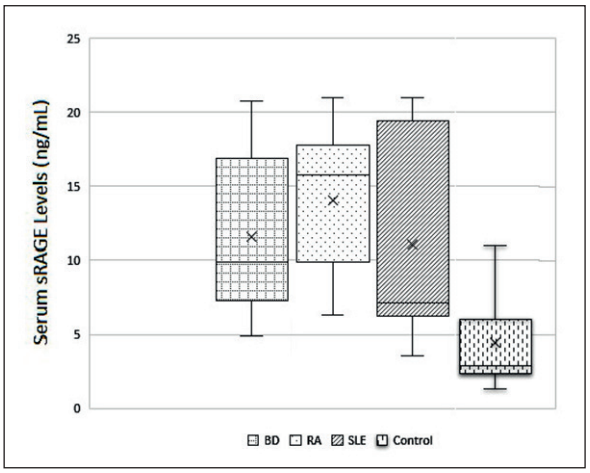

Figure 2. The box-plot graphic showing the serum sRAGE levels of Behcet's disease (BD) patients, Rheumatoid arthritis (RA) patients, Systemic lupus erythematosus (SLE) patients, and healthy controls. ***$p < 0.001$ *vs.* control group.

No significant difference in terms of smoking ($p = 0.910$), HT ($p = 0.210$), atherosclerosis ($p = 0.850$), and diabetes mellitus (DM) ($p = 1.000$) on intergroup comparison based on the frequency of comorbidity was observed.

Discussion

The serum sRAGE levels in the patients with rheumatological inflammatory diseases (BD, RA, and SLE). The serum sRAGE levels were higher in all the disease groups than the healthy control group. No significant difference in the sRAGE levels was observed among the compared disease groups. Furthermore, when the patients with active and without active diseases were compared with each other, no significant difference was seen in the sRAGE levels.

To the best of our knowledge, this is the first study to investigate the sRAGE levels in patients with BD. Despite distinct elevation in the sRAGE levels observed in this study in patients with BD, the increase was not associated with CRP, ESR, and disease activity. It is notable that although the sRAGE levels were elevated in BD and other inflammatory diseases in this study, there was no statistical correlation with inflammatory markers. The fact that sRAGE levels are not correlated with inflammatory markers in BD does not mean that sRAGE does not play a role in the pathophysiology of the disease. It is stated that the task of sRAGE is to ensure the clearance of the end products formed as a result of the inflammation[20].

Previous studies[9,21] have shown that sRAGE treatment has anti-inflammatory effects on experimental models. There are also results in human studies that support the anti-inflammatory effects of sRAGE. One study claimed that individuals with high levels of circulating sRAGE have a slower rate of carotid artery disease progression, and potential anti-inflammatory effects of sRAGE[22]. In another study by Kehribar et al[23] on patients with COVID-19, the sRAGE levels were observed to have increased in asymptomatic patients, whereas it decreased in patients with significant lung involvement. These results indicate that although the serum sRAGE levels tend to increase in several inflammatory diseases, clear pathophysiological understanding underlying this increase is yet to be established. In addition, the increase in sRAGE level in BD indicates that the sRAGE pathway contributes to the pathophysiology of BD. It also suggests that sRAGE applications have an anti-inflammatory potential in BD.

The AGEs levels, including pentosidine in the serum and synovial fluid, increase in direct proportion to the inflammatory markers, CRP and ESR in patients with RA. Consequently, it was suggested that AGEs are associated with the local oxidative stress in the joints through nonenzymatic pathways[8]. A previous study[24] investigated the serum sRAGE levels in patients diagnosed with RA and noninflammatory joint disease and healthy controls. It was observed that the sRAGE levels were distinctively lower in patients with RA than the other two groups. Nakhjavani et al[25] found in a study of 60 patients diagnosed with RA that the sRAGE levels were higher than the healthy control group; moreover, the sRAGE levels were positively correlated with CRP, ESR, and disease activity. Similarly, in the present study, the sRAGE levels were significantly higher in patients with RA than the healthy control group. On the other hand, no association between the sRAGE and CRP, ESR, and disease activity was observed. Factors such as HT, DM, body mass index (BMI), medications, and smoking are considered to affect the serum sRAGE levels and might account for the differences between the two studies. In addition, the difference in the number of active patients might have led to the aforementioned variance in the results of the two studies.

Varying results have been reported in studies that have investigated the sRAGE levels in patients with SLE as well. Yu et al[11] found that the sRAGE levels were lower in patients with active SLE. Wang et al[26] found a negative correlation between arterial stiffness and sRAGE levels in female patients with SLE. Contrary to the above-mentioned studies, Nienhuis et al[27] found that the sRAGE levels in patients with SLE were significantly higher than in the control group. Similarly, the sRAGE levels were higher in the present study and not associated with disease activity. In Ma et al[28], the varying results reported in patients with SLE were explained in terms of treatment duration. The patients with SLE who received treatment for less than 1 month had lower levels of sRAGE than the healthy group, and the sRAGE levels were higher in the patients with SLE who received treatment for more than a month than the healthy group. In the light of the above-mentioned studies, it was suggested that several factors influence sRAGE levels, including the duration of the treatment.

Limitations

The present study has certain limitations. Although the sRAGE levels were investigated in three different inflammatory diseases, the study's ability to show the inflammatory relationship was limited as it was a cross-sectional study. As one limitation of this study, the way how sRAGE levels change in response to the treatment could have been demonstrated through more frequent measures. In addition, medications that may possibly affect the sRAGE levels, kidney function tests, and BMI records could have been maintained.

Conclusions

In conclusion, the serum sRAGE levels are elevated in BD and other inflammatory rheumatological diseases. However, this increase was not observed to have direct correlation with the inflammatory markers and disease activity scores. These results further suggest that the serum sRAGE levels cannot be used as a biomarker for inflammatory rheumatological diseases. Further studies are required to investigate the possible role of AGE-RAGE axis signaling pathways and sRAGE in the pathogenesis of diseases.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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