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Relationship between familial mediterranean fever and soluble receptor for advanced glycation end products

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Abstract

Familial Mediterranean fever (FMF) is the most common hereditary autoinflammatory disease worldwide and is characterized by recurrent fever and serositis. Serum soluble receptor for advanced glycation end products (sRAGE) is an isoform of RAGE and sRAGE acts as a trap receptor for ligands and blocks the RAGE–ligand axis. This study aimed to examine the change in sRAGE levels in FMF and to investigate its relationship with inflammation. This study included patients with FMF (n=20) and healthy controls (n=22). Morbidity status, sRAGE levels, demographic and laboratory data were recorded. Pregnant women, individuals aged <18 years, and those with other chronic inflammatory diseases were excluded. Statistical Package for Social Sciences (SPSS) Version 22.0 was used to conduct all statistical analyses and all data are expressed as mean and standard deviation (SD). The serum sRAGE levels were 12.21±6.70 ng/mL and 4.44±2.89 ng/mL in the patient and control groups, respectively. Accordingly, the sRAGE levels of patients with FMF were significantly higher ($p<0.001$). Comorbidities had no effect on the sRAGE levels of the patient group and no correlation was found between the sRAGE and inflammatory biomarkers. sRAGE levels are elevated in FMF but does not seem to be a promising candidate as a biomarker for FMF.

Keywords: Familial Mediterranean fever, soluble receptor for advanced glycation end products, inflammation

Introduction

Familial Mediterranean fever (FMF) is the most common hereditary autoinflammatory disease worldwide [1,2]. Although cases have been reported from around the world, the disease is given this name as it more commonly occurs in Mediterranean- and Middle Eastern-origin communities [3]. FMF is characterized by recurrent fever and serositis. Severe pain attacks are observed to occur in the abdomen, chest, and joints due to inflammation in the serosal membranes in these regions. FMF episodes, which usually begin in childhood, can last up to 72 hours, and patients often show self-recovery [4]. Nonspecific findings can accompany these episodes. Specific and unique skin findings for FMF, such as erysipelas-like erythema, can also be observed [5].

Pyrin protein has a very important role in the pathogenesis of FMF. Pyrin comprises 781 amino acids and it is encoded by the Mediterranean fever (MEFV) gene located on the short arm of the 16th chromosome [6]. Although the exact function of pyrin secreted from white blood cells is not clearly understood, it is known to have an anti-inflammatory effect. Pyrin exerts this effect by binding to various proteins and inhibiting interleukin (IL)-1β, which results in a very strong pyrogenic effect [7,8]. Mutations in MEFV results in impaired pyrin function, which in turn activates IL-1β and initiates a severe inflammatory process.

Serum soluble receptor for advanced glycation end products (sRAGE) is an isoform of receptor for advanced glycation end products (RAGE) with a molecular weight of approximately 45 kDa. Normally, intracellular signal transmission occurs, and the inflammatory process begins as a result of the interactions between RAGE and several types of ligands in the membrane [9]. But sRAGE acts as a trap receptor for ligands and blocks the RAGE–ligand axis. Thus, sRAGE shows an indirect anti-inflammatory effect [10].

Understanding the mechanisms underlying FMF pathophysiology will guide in its diagnosis and effective treatment. Keeping this in mind, this study aimed to examine the change in sRAGE levels in FMF and to investigate its relationship with inflammation.

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Materials and Methods

Patients

This study included patients with FMF (n=20) and healthy controls (n=22). Morbidity status, sRAGE levels, demographic and laboratory data were recorded. The Tel-Hashomer diagnostic criterion [11] was used to diagnose FMF, and the scoring system developed by Pras et al. [12] was used to determine disease severity. Pregnant women, individuals aged <18 years, and those with other chronic inflammatory diseases were excluded.

Enzyme-Linked Immunosorbent Assay

A commercially available human sRAGE enzyme-linked immunosorbent assay (ELISA) Kit (#E0031Hu, Bioassay Technology Laboratory, China) was used to measure the sRAGE levels in the serum samples obtained from the patients and controls. ELISA was performed according to the manufacturer's protocol. Absorbance values were measured using a spectrophotometric plate reader and comparing each sample value to the standard curve; subsequently, serum sRAGE levels were determined.

Statistical analysis

Statistical Package for Social Sciences (SPSS) Version 22.0 was used to conduct all statistical analyses and all data are expressed as mean and standard deviation (SD). The Chi-square test was used to determine the differences in the categorical variables between the groups. The Kolmogorov–Smirnov test was used to check whether the data conformed to normal distribution, and the Student's t-test was used to compare the normally distributed variables between the groups. Further, Pearson's correlation analysis was performed. A P value of <0.05 was considered statistically significant in all analyses.

Ethical approval

The study protocol was approved by the local ethics committee (Ethics approval no: OMU-KAEK 2022/53).

Results

Study included 20 patients with FMF and a mean age of 31.85±9.01 years and 22 healthy controls with a mean age of 42.00±8.16 years. Four patients with FMF were experiencing an attack during laboratory analysis. Demographic and laboratory data of the patient and controls groups and the comorbidity status of the patient group are presented in Table 1.

The serum sRAGE levels were 12.21±6.70 ng/mL and 4.44±2.89 ng/mL in the patient and control groups, respectively. Accordingly, the sRAGE levels of patients with FMF were significantly higher (p<0.001) (Figure 1). There was also a significant difference between the groups in terms of age, sex, and ESR (p<0.05). After adjusting for age and sex, sRAGE levels in the FMF patients were still significantly higher compared with those of the control group (p<0.001).

Comorbidities had no effect on the sRAGE levels of the patient group. The patient group's PRAS score was 7.60±2.30. No correlation was found between the sRAGE and both ESR (r=0.099, p=0.68) and CRP (r=0.127, p=0.603). In addition, no difference was found between the serum sRAGE of patients experiencing an attack and those who were not.

Table 1. Demographic and laboratory data of the study groups

	Healthy control	FMF	p
Gender (female/male)	12/10	17/3	0.033
Age (year)	42.00±8.16	31.85±9.01	<0.001
Atherosclerosis (n)	-	-	-
Diabetes mellitus (n)	-	1	0.288
Hypertansion (n)	-	1	0.288
Smoking (n)	-	4	0.027
ESR (mm/h)	11.18±3.06	34.00±23.90	<0.001
CRP (mg/L)	6.95±1.09	14.10±21.91	0.173
sRAGE (ng/mL)	4.44±2.89	12.21±6.70	**<0.001**

FMF; Familial Mediterranean fever, ESR; Erythrocyte sedimentation rate, CRP; C-reactive protein, sRAGE; Soluble receptor for advanced glycation end products

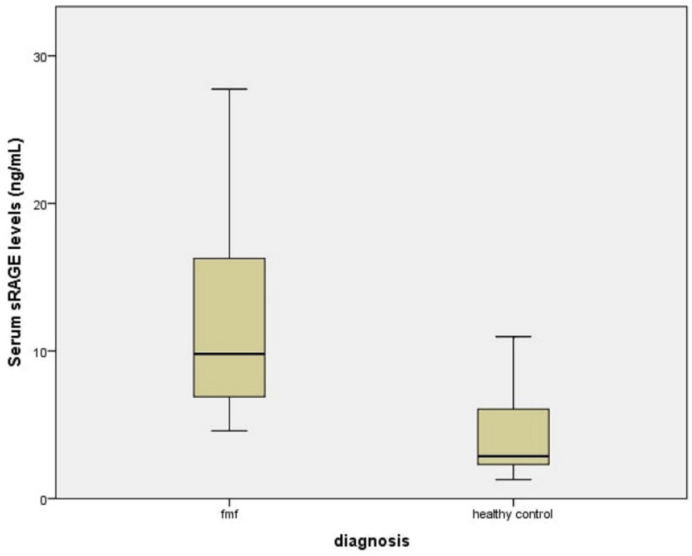

Figure 1. Serum sRAGE levels of FMF patients and healthy controls

Discussion

The RAGE pathway is normally involved in the clearance of the end products of metabolic pathways. In the present study, the potential role of this RAGE pathway in the physiopathology of FMF was investigated. Serum samples from patients with FMF and healthy controls were obtained and the sRAGE levels were compared between the two groups. We found that the sRAGE levels were significantly higher in FMF patients than in the controls. Further, the sRAGE levels of patients in the attack and non-attack periods were compared and no significant difference was found. In addition, no correlation was found between the sRAGE levels and inflammatory markers in the patient group. This is the first study to investigate the relationship between sRAGE levels and FMF disease.

Previous studies have investigated the RAGE pathway for non-FMF inflammatory rheumatic diseases. In a study including 31 female patients with systemic lupus erythematosus (SLE) and 26 healthy volunteers, Nowak et al. examined the levels of sRAGE and AGEs, which are ligands that bind to RAGE and accelerate inflammation. Compared with the control group, serum AGE levels

were increased in SLE patients whereas sRAGE levels decreased [13]. In a study involving 60 patients with rheumatoid arthritis, the sRAGE levels were higher in FMF patients than in the controls [14]. In another study involving 52 patients with adult onset still disease and 36 patients with SLE, patients showed higher levels of AGEs and lower levels of sRAGE than the control group [15]. Therefore, contradictory results have been obtained in the literature in terms of sRAGE levels. There may be several factors responsible for this, including age, comorbidities, and medications used, all of which are considered to have an effect on sRAGE levels, as well as the number of active patients. In the present study, sRAGE were significantly higher in patients with FMF than in healthy controls with no correlation with inflammatory biomarkers.

sRAGE circulates in the blood and binds to circulating RAGE ligands and sequesters them through the kidneys. Thus, in a sense, it competes with membrane-bound RAGE and blocks the activation of inflammatory pathways [16]. From this perspective, sRAGE levels should increase in inflammatory diseases and show a correlation with inflammatory markers. However, sRAGE levels were found to be low in many disorders, such as hypertension, myocardial infarction, Alzheimer's, and vascular dementia [17-19]. In contrast, elevated sRAGE levels were reported in diabetes mellitus, which is similar to the results of the present study [20]. In a study conducted on patients with SLE, it was reported that sRAGE levels were also affected by the treatment duration. Accordingly, it was determined that sRAGE levels decreased in patients who received treatment for <1 month and increased in patients who received treatment for >1 month compared with healthy controls [21]. The results of these studies suggest that sRAGE pathophysiology is complex and that factors other than those previously thought may also influence sRAGE levels.

Study limitations

There are certain limitations of this study. Although the level of sRAGE in patients with FMF is a matter of interest, this was a cross-sectional study and had limited ability to demonstrate every stage of inflammation. In addition, measurements should be taken more frequently to demonstrate changes in sRAGE levels with respect to the treatment options and treatment duration. Furthermore, more factors that could affect sRAGE levels, such as kidney function tests and medical treatment, need to be recorded.

Conclusion

In conclusion, sRAGE levels are elevated in FMF. However, this increase does not show a direct correlation with inflammatory biomarkers and disease activity score. In addition, contradictory results regarding sRAGE levels have been obtained in various studies. Taken together, sRAGE does not seem to be a promising candidate as a biomarker for FMF. Further studies are needed to identify the factors affecting sRAGE levels and the possible role of sRAGE in the pathogenesis of inflammation.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
The study protocol was approved by the local ethics committee (Ethics approval no: OMU-KAEK 2022/53).

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