Research Article (Araştırma Makalesi)

Soluble Receptor Level of Advanced Glycation (sRAGE) Products in Serum in Patients with Systemic Lupus Erythematosus

Sistemik Lupus Eritematozuslu Hastalarda Serumda Gelişmiş Glikasyon Ürünlerinin Çözünür Reseptörü (SRAGE) Seviyesi

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Özet

Amaç: Sistemik Lupus Eritematozus (SLE) nükleer otoantijenlere karşı antikor oluşumu ile karakterize otoimmün bir hastalıktır. İleri Glikasyon Reseptörü (RAGE) nötrofiller, makrofajlar ve T hücreleri gibi birçok bağışıklık sistemi hücresi tarafından üretilir ve birçok ligand sınıfı ile etkileşime girer. Bu sonuçlar ışığında, RAGE'nin çözünebilir formu olan sRAGE seviyesi hastalık aktivitesi ile ilişkili olabilir. Bu bilgiler ışığında, plazma sRAGE düzeyleri ile SLE arasında bir ilişki olup olmadığını değerlendirmeyi amaçladık.

Gereç ve Yöntemler: SLE tanısı konmuş on sekiz hasta (E/K: 1/17) ve herhangi bir hastalık tanısı olmayan yirmi bir hasta (E/K: 2/19) kontrol grubu olarak çalışmaya dahil edildi. Bu hastalarda plazma sRAGE düzeyi ELIZA (enzyme-linked immunosorbent assay) kiti (BioVendor Research and Diagnostic Products) kullanılarak ELIZA yöntemi ile ölçüldü. Elde edilen veriler gruplar arasında karşılaştırıldı.

Bulgular: Ortalama plazma sRAGE düzeyi SLE hastalarında sağlıklı kontrol hastalarına göre daha düşüktü ancak istatistiksel olarak anlamlı değildi (p=0.966). Çalışmamızda SLE'li hastalarda SLEDAI ve sRAGE düzeyleri arasında pozitif bir korelasyon bulundu (r=0.628, p=0.005). SLE'li hastalar arasında anlamlı bir korelasyon bulunmamasına rağmen, aktif SLE olarak sınıflandırılan on dört hasta ile kontrol grubu arasında sRAGE düzeyleri pozitif korelasyon göstermiştir.

Sonuç: Çalışmamızda, SLE'li hastalarda plazma sRAGE düzeylerinin sağlıklı kontrollere göre daha düşük olduğunu, ancak aktif SLE'li hastalarda plazma sRAGE düzeylerinin inaktif SLE'li hastalardaki plazma sRAGE düzeylerinden daha yüksek olduğunu bulduk. SLE'li hastalarda sRAGE düzeylerindeki azalmanın bu çözünür reseptörün tükenmesi ile açıklanabileceğini varsaydık. Çalışmamız, SLE'li hastalarda kan sRAGE düzeylerinin sağlıklı kontrollere göre daha yüksek olduğunu gösteren benzer bir başka çalışmadan farklıydı. Kan sRAGE düzeyleri, aktif hastalık sırasında, sakin SLE hastalarına kıyasla önemli ölçüde artmıştır.

Anahtar kelimeler: Sistemik Lupus Eritematozus, sRAGE, Hastalık Aktivitesi

Abstract

Objective: Systemic Lupus Erythematosus (SLE) is an autoimmune disease characterized by antibody formation against nuclear autoantigens. A receptor for Advanced Glycation (RAGE) is produced by many immune system cells, such as neutrophils, macrophages, and T cells, and interacts with many classes of ligands. In light of these results, the level of sRAGE, the soluble form of RAGE, may be associated with disease activity. In light of this information, we aimed to evaluate whether there is a relationship between plasma sRAGE levels and SLE.

Materials and Methods: Eighteen patients diagnosed with SLE (M/F: 1/17) and twenty-one patients without any disease diagnosis (M/F: 2/19) were included as the control group. In these patients, plasma sRAGE level was measured by ELIZA method using an ELIZA (enzyme-linked immunosorbent assay) kit (BioVendor Research and Diagnostic Products). The data obtained were compared between the groups.

Results: The mean plasma sRAGE level was lower in patients with SLE than in healthy control patients but not statistically significant (p=0.966). Our study found a positive correlation between SLEDAI and sRAGE levels in patients with SLE (r=0.628, p=0.005). Although no significant correlation was found between patients with SLE, sRAGE levels were positively correlated between fourteen patients classified as active SLE and the control group.

Conclusions: In our study, we found that plasma sRAGE levels in patients with SLE were lower than in healthy controls, but plasma sRAGE levels in patients with active SLE were higher than plasma sRAGE levels in patients with inactive SLE. We hypothesized that reduced sRAGE levels in patients with SLE could be explained by the depletion of this soluble receptor. Our study differed from another similar study showing that blood sRAGE levels were higher in patients with SLE than in healthy controls. Blood sRAGE levels were significantly increased during active disease compared with patients with quiescent SLE.

Keywords: Systemic Lupus Erythematosus, sRAGE, Disease Activity

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INTRODUCTION

Many organs are affected by the chronic autoimmune illness known as systemic lupus erythematosus (SLE). Although the source of the disease is unknown, genetic and environmental factors have been implicated as well as several antibodies directed against self-components (1). RAGE, a member of the immunoglobulin superfamily, is a multi-ligand receptor for advanced glycation end products. Many immune cells, such as macrophages, neutrophils, and T cells, generate RAGE, which interacts with various kinds of ligands (2). At the moment, S100/calgranulin family members, advanced glycation end products (AGEs), and high mobility group box-1 (HMGB1) interact with known RAGE ligands.

Studies have identified HMG-1 as a damage-associated molecule (DAMP) (3). This nuclear protein promotes the inflammatory response while contributing to chromatin shape and transcriptional control (4). Extracellular HMGB1 interacts with toll-like receptors 2 and 4 and RAGE on cell surfaces (TLR-2 and TLR-4). Type 1 interferon (IFN), which is crucial in the pathophysiology of SLE, is created as a result of this interaction. This is vital to the development of SLE's pathogenesis (5,6). After RAGE interacts with macrophages and activates them with HMGB1, the resulting production of tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6) occurs. It has been asserted that HMGB1 is required for RAGE's involvement in all of these pathophysiologic processes (7,8). High blood HMGB1 levels have been linked in certain studies to an increase in lupus activity (9).

A process in which non-enzymatic glycosylation attaches to circulating substances including lipids, proteins, or nucleic acids results in the formation of the class of ligands known as AGEs. During this time, oxidative damage and hyperglycemia are factors. Renal failure and diabetic mellitus (DM) have both been linked to AGE buildup (10). Increased AGE levels were observed to positively correlate with endothelial RAGE levels in studies, and RAGE immunoreactivities are brought on by increasing AGE levels (11,12). Studies have found that a rise in AGE is accompanied by an increase in MMP (particularly MMP-9) in macrophages (13). When MMP levels rise, sRAGE and esRAGE plasma levels rise as well. Patients with SLE have also been observed to have higher AGE levels (14). The RAGE-AGE pathway is thought to be involved in the development of many disorders because AGEs regulate RAGE induction (15).

Only vertebrates express the approximately twenty calcium-binding protein family receptors that make up the S100 protein family, which function as receptors for advanced glycation end products (16). This protein family functions as DAMP-like HMGB1 and aids intracellular signaling. S100s are produced by many bodily cells during inflammation, making them a useful indicator of disease activity (17). Several investigations have discovered a correlation between the S100 subclass proteins S100A8 (calgranulin A) and S100A9 (calgranulin B), and the activity of the SLE illness (18,19).

The enzyme matrix metalloproteinase (MMP) transforms the RAGE receptor into the cytosolic and transmembrane fragmented forms of the receptor, respectively (20). RAGE interacts with HMGB1, AGE, and S100 as its plasma-soluble form, or sRAGE. Some ligands that promote inflammation are caught by sRAGE. Combining sRAGE-HMG1, sRAGE-AGE, and sRAGE-S100 stops these ligands from interacting with RAGE, which inhibits the pro-inflammatory pathway (21). Furthermore, sRAGE binds to RAGE and prevents it from dimerizing. As a result, decreasing serum sRAGE levels cause RAGE signaling and inflammation-stimulating RAGE. Several chronic inflammatory disorders, including rheumatoid arthritis (RA), primary Sjögren's syndrome, and multiple sclerosis (MS), have been linked to low serum sRAGE levels (22).

According to all these pathophysiologic pathways, the pathophysiology of systemic lupus erythematosus may be significantly influenced by sRAGE. Serum sRAGE levels in SLE patients have been the subject of several investigations up to this point, with mixed findings being reported (23,24). On the other hand, research using animal models has produced promising findings about the therapeutic potential of sRAGE (25,26). These investigations imply that it could be a potential therapeutic target for inflammatory illnesses with a chronic course. Hence, to ascertain if disease activity, and clinical, and laboratory factors are linked with sRAGE, we examined plasma sRAGE levels in this investigation.

MATERIALS AND METHODS

The study's participants were twenty-one healthy controls and eighteen SLE patients. Age, sex, and the length of time since the sickness first manifested itself were among the patients' socio-demographic variables that were noted.

sRAGE measurement of plasma An automated ELISA reader (Thermo Scientific, Finland), a computer application, and a commercial ELISA kit (BioVendor Research and Diagnostic Products) were used to measure the levels of human sRAGE serum (Skanlt for Multiscan FC 2.5.1). The range of analysis was 1-3200 pg/mL, and the sensitivity was 19.2 pg/mL. 5.3% within the study and 8.8% between studies for CV. The outcomes were expressed in ng/mL.

Clinical measures, illness duration, therapeutic regimens, standard laboratory test outcomes, antibody findings, and SLE Disease Activity (SLEDAI) ratings were noted. Individuals under the age of 18, those with rheumatologic conditions other than SLE, and those with long-term conditions including diabetes mellitus and hypertension that may have an impact on sRAGE levels were also disqualified. Patients having a history of drinking alcohol or smoking cigarettes were excluded.

Statistical Analysis

The data analysis tool utilized was IBM SPSS version 22. The Shapiro-Wilk test was used to assess the data's appropriateness for a normal distribution of the variables. Using independent samples t-tests, two-group comparisons of the variables with a normal distribution were carried out. The Mann-Whitney U test was applied for variables that could not be distributed normally. The Pearson test was used to examine the association between the variables. The distributional link between categorical variables was analyzed using the Chi-square test. We utilized frequency (n), ratio (%), mean, standard deviation, and median min-max as statistical metrics. The threshold for statistical significance was set at 0.05.

RESULTS

The study included 18 SLE patients (M/F: 1/17) and 21 patients (M/F: 2/19) as the control group. Four patients were considered inactive in the SLE group, and 14 were considered active SLE according to SLEDAI criteria. The mean age (years, mean ± SD) of the patients diagnosed with SLE was "39.7 ± 11.0," and the mean age of the healthy control group was "40.9 ± 7.8". The patients with SLE mean disease duration (months, mean ± SD) was "49.9 ± 40.6". Height (mean ± SD cm), weight (mean ± SD kg), and BMI (mean ± SD kg/m2) were "163.2 ± 10", "68.5 ± 12", "26.9 ± 2.3" and "165.2 ± 8", "67.5 ± 9", "27 ± 3" in patients with SLE and control group, respectively. Five patients with SLE were diagnosed with malar rash, three with neurologic problems, eight with arthritis, four with lupus nephritis, three with vasculitis, and three with serositis.

The mean plasma sRAGE level in patients with SLE (949.8 ± 397.0 pg/mL) was lower than in healthy control patients (954.9 ± 341.9 pg/mL) but not statistically significant (p=0.966). Plasma sRAGE levels in patients with active SLE (1527.5 ± 327.2 pg/mL) were higher than sRAGE levels in patients with inactive SLE (784.8 ± 223.4 pg/mL) and statistically significant (p<0.01). There was a positive correlation between SLEDAI and sRAGE levels in patients with SLE (r=0.628, p=0.005).

To investigate the possible effects of different treatment modalities on plasma sRAGE levels in patients with SLE, we compared plasma sRAGE levels in treated and untreated patients. The treatment received by the patients is summarized in **Table 1**. The mean plasma sRAGE level of 1 patient who received no treatment was "1172 pg/mL", the mean plasma sRAGE level of patients receiving monotherapy was "936.81 ± 405.3 pg/mL," and the mean plasma sRAGE level of the healthy control group was "954.9 ± 341.9 pg/mL". The mean plasma sRAGE level of SLE patients treated with polytherapy was "915.3 ± 442.4 pg/mL". There was no statistically significant difference between the three groups (p=0.581, p=0.617, p=0.451).

Table 1. Treatment in patients with SLE

Treatment	Patıents Wıth SLE
Without treatment Monotherapy [n(%)]	1 (5.6%)
Monotherapy [n(%)]	5 (27.8%)
Polypharmacy [n(%)]	12 (66.7%)
Steroid [n(%)]	15 (83.4%)
Cyclophosphamide [n(%)]	5 (27.8%)
Hydroxychloroquine [n(%)]	3 (16.7%)
Mycophenolate mofetil [n(%)]	5 (27.8%)
Azathioprine [n(%)]	7 (38.9%)
Methotrexate [n(%)]	4 (22.3%)
Rituximab [n(%)]	2 (11.1%)
Intravenous immunoglobulin (IVIG) [n(%)]	2 (11.1%)

In our study, photosensitivity, oral ulcer, malar rash, discoid rash, acute skin lupus, chronic skin lupus, avascular necrosis, arthritis, nephritis, vasculitis, serositis, myositis, Raynaud's findings were considered as clinical features of SLE. A positive correlation was found between plasma sRAGE level and malar rash, one of the clinical findings of patients with SLE (r=0.49, p=0.39).

DISCUSSION

In this research, we discovered that plasma sRAGE levels in SLE patients were lower than in healthy controls, but that plasma sRAGE levels in SLE patients who were actively ill were greater than those who were inactively ill. Previous research has demonstrated that a variety of immune systems, including neutrophils, T cells, and macrophages, release RAGE (2). According to our study, patients with active SLE had higher levels of sRAGE than those with inactive SLE. With an increase in immune cells, sRAGE synthesis rises during active illness. The consumption of HMGB1, AGE, and S100 ligands, which occur with the enhanced pro-inflammatory response by interacting with sRAGE, may be the cause of the decreased sRAGE level in active SLE patients compared to the healthy control group. This finding from our investigation could offer a little hint as to how sRAGE functions in the pathophysiology of SLE. Moreover, this finding implies that sRAGE has a role in the pathogenesis of SLE. According to certain research, SLE patients have higher levels of HMGB1, an essential ligand, which causes sRAGE to bind and become depleted throughout the inflammatory process (27,28). The pathophysiologic process we described in our study and the findings are supported by this research. Further research should clarify if alternative splicing and proteinases are also involved in controlling sRAGE levels in SLE patients.

Our findings were different from those of another investigation that revealed blood sRAGE levels to be greater in SLE patients compared to healthy controls. Comparing individuals with quiescent SLE to those with active illness, blood sRAGE levels were considerably higher (29). The results may be influenced by pharmaceutical usage, which is one explanation for this disparity. The limited sample size of this study might potentially bring on the disparity.

In contrast to the study by C.Y.Ma et al, we did not find a relationship between sRAGE levels and age or duration of the disease (28). This finding implies that the relationship between sRAGE and disease activity is complete and irrespective of illness duration. The pathophysiologic mechanism previously indicated is supported by this finding. Once more, we discovered a connection between sRAGE and malar rash. We did not discover a connection between sRAGE and the involvement of other organs. This finding demonstrates that there is an association between sRAGE and disease severity irrespective of organ involvement as all patients with malar rash belonged to the group of individuals with active SLE. According to Tan et al., serum sRAGE levels are correlated with how severe nephropathy is in type 2 diabetic individuals (30). No correlation between organ involvement and severity was found in our investigation. Research has revealed that patients with poor renal function may have a rise in serum sRAGE (31,32). This outcome may be different in people with type 2 diabetic nephropathy due to lower glomerular filtration rate rather than organ involvement. Patients with lupus nephritis in our study did not have lower GFR; instead, they had proteinuria. As a result, we were unable to find a connection between nephritis and sRAGE. This research indicates that sRAGE may reflect disease activity irrespective of organ involvement.

The generation of autoantibodies is a crucial aspect of SLE. Nevertheless, our investigation did not see an association between autoantibodies and sRAGE levels in SLE. In one investigation, sRAGE levels were equivalent between ANA-negative and ANA-positive SLE patients. Moreover, in a second investigation, plasma sRAGE levels in individuals with anti-dsDNA anti-Sm positivity were not significantly different from those with negative results (28,33). Our findings demonstrated that sRAGE level was not related to the generation of autoantibodies. No correlation between any antibody and sRAGE was found in our investigation. According to this finding, sRAGE may be linked to disease activity without regard to organ involvement or autoantibody positivity. The pathophysiologic mechanism will be further clarified by more research.

In conclusion, the RAGE pathway may play a role in the pathogenesis of SLE, as indicated by low plasma sRAGE levels in SLE. This study suggests that there may be an inverse relationship between sRAGE levels and disease severity in SLE. This suggests that sRAGE has a role in the pathophysiology of SLE. Age, gender, organ involvement, and autoantibody positivity did not seem to have any effect on the association with sRAGE. It is currently unclear how sRAGE levels change as the disease and its treatment progresses. With more patients, it will be easier to understand the relationships between sRAGE and clinical features of SLE.

Conflict of Interest: The author(s) declared no potential conflicts of interest concerning this article's research, authorship, and/or publication. Written informed consent was obtained from all patients for publication.

Ethical Approval: Our study was approved by Kahramanmaraş Sütçü İmam University Medical Ethics Committee with the decision dated 21.3.2018 and numbered 2018/06. The study is done in accordence with Helsinki principles.

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