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Serum-soluble receptor for advanced glycation end-products values might have diagnostic and prognostic significances in ulcerative colitis

İrfan Küçük[1], Ersin Tural[2], Yusuf Yazgan[1], Başak Çakır Güney[3], İdris Yıldırım[1], Tuğba Akbaş Şimşek[1], Musa Salmanoğlu[3]

[1]Department of Gastroenterology, Sultan 2. Abdulhamid Han Training and Research Hospital, University of Health Sciences, İstanbul, Turkey
[2]Department of Pediatrics, Sultan 2. Abdulhamid Han Training and Research Hospital, University of Health Sciences, İstanbul,Turkey
[3]Department of Internal Medicine, Sultan 2. Abdulhamid Han Training and Research Hospital, University of Health Sciences, İstanbul, Turkey

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ABSTRACT

Aims: There is evidence of anti-inflammatory qualities associated with a soluble receptor for advanced glycation end products (sRAGE). We aimed to evaluate whether serum sRAGE levels of patients with inflammatory bowel diseases (IBDs) could serve as a biomarker by utilizing several clinical and laboratory models of disease activity for these individuals.

Methods: This case-control study included 77 ulcerative colitis (UC) patients (51 males and 26 females), 49 Crohn's disease (CD) patients (33 males and 16 females) and 54 healthy controls (38 males and 16 females). In UC, the UC Mayo Clinical Scoring system (MCS) was used for the clinical and endoscopic features. The histological activity index (HAI) of UC patients was determined by Truelove and Richards method. The Crohn's disease activity index (CDAI) was utilized for CD patients.

Results: In comparison to the control group, the median sRAGE concentrations in UC patients were significantly lower. [911.17 ng/L (322.91-1682.19 vs 1420.96 ng/L (816.68-2320.08), respectively, p=0.008)]. The patients with CD did not significantly differ from the other groups. The MCS and HAI values of UC patients negatively correlated to the serum sRAGE values (rho=-0,610, p<0.001 vs rho=-0,742 respectively, p<0.001). CD patients in remission had higher sRAGE values than patients having active disease [1720.42 ng/L (1005.68-2414.41) vs. 923.36 ng/L (601.61-1361.22 respectively, p=0.002]. CD patients under treatment had higher sRAGE values than patients without any treatment [1361.22 ng/L (821.26-1944.2) vs. 879.38 ng/L (601.61-1239.41) respectively, p=0.033]

Conclusion: Serum sRAGE might be an auxiliary biomarker for the clinical and laboratory traits of UC.

Keywords: Ulcerative colitis, receptor, advanced glycation end-products

INTRODUCTION

The term "receptor for advanced glycation endproducts" (RAGE) was initially utilized to describe a receptor for advanced glycation endproducts (AGE), and to date several other ligands including S100/calgranulins, calprotectins and advanced oxidation protein end products (AOPPs) have been identified.[1] RAGE is a cell-surface member of the immunoglobulin superfamily and ligands binding the extracellular domain of RAGE lead to nuclear factor kappa B (NFκB) activation via intracellular signaling.[2] Pro-inflammatory cytokines like tumor necrosis factor alpha (TNF-α) are released and active matrix metallopeptidase-9, which cleaves membrane-bound RAGE, and soluble RAGE (sRAGE) is released into circulation.[3]

In circulation, sRAGE has been reported to play a protective anti-inflammatory role by acting as a decoy receptor. sRAGE binds to membrane-bound RAGE ligands and prevents them interacting with cell membranes. It antagonizes the pathological effects mediated by RAGE.[4] In addition to several diseases including diabetes, cancer and rheumatic diseases, sRAGE and its ligands were implicated in inflammatory bowel diseases (IBDs).[3-9] Another innate immune system pattern-recognition receptor that is crucial to the development of chronic inflammatory diseases like IBDs is RAGE.[10,11] Previous studies about sRAGE in IBDs revealed debatable results and limited data exist about the role of sRAGE.[7-12] RAGE pathway has also been declared as a therapeutic target for IBDs.[13-16]

Corresponding Author: Başak Çakır Güney, dr.bskckr@gmail.com

The role of sRAGE with different disease activity models in IBDs has yet to be elucidated. In accordance with this, our goal was to determine whether serum sRAGE levels of IBD patients could serve as a biomarker by using the different clinical and endoscopic disease activity assessment models with the histological activity in UC patients according to Truelove Richards method.[17]

METHODS

The study was carried out with the permission of Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Scientific Researches Ethics Committee (Date: 17.11.2021, Decision No: 235-211084517). The study protocol complies with the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) as reflected in a priori approval by the institution's human research committee. Written informed consent was obtained from all participants.

Subjects

The study included 77 patients with ulcerative colitis (UC), 49 patients with Crohn's disease (CD) and 44 healthy controls, admitted to the gastroenterology department of our institute between December 2021 and November 2022.

Participants with any clinical conditions that could change the serum sRAGE level such as sepsis, uncontrolled diabetes and hypertension, hyperlipidemia, any malignancies, severe organ failure (heart failure, chronic renal disease, chronic obstructive lung disease, coronary artery disease) autoimmune and/or chronic inflammatory diseases, and those who had contra-indications for colonoscopy were excluded from the study. The healthy control group included participants whose colonoscopy results were normal. The disease duration, medications for IBDs, co-morbidities, and medications in all groups were recorded. Biochemical tests were performed just before the colonoscopy procedure.

Assessment of the Clinical and Endoscopic Activities

The Mayo Clinical score (MCS) was applied for the patients with UC and was scored between 0-12.[18]

Scores of ≤2 were classified as clinical remission whereas scores of >2 indicated an activation. The Crohn's disease activity index (CDAI) was used to assess the disease activity in the patients with CD.[19]

The disease extent of the patients with IBDs was defined in agreement with the Montreal classification.[20] In UC, proctitis and left-sided colitis were recorded as localized disease, whereas extensive localization and pancolitis were recorded as extensive disease. The Mayo endoscopic activity scoring (MES) index was used for the endoscopic activation of UC; normal mucosa and mild disease were recorded as endoscopic remission, whereas moderate and severe disease were recorded as active disease.[18]

Measurement of Serum sRAGE

After centrifugation of the venous blood samples at 5000×g for 10 minutes at 30°C, the supernatant serum was stored at (–) 80°C until analysis. The human RAGE Enzyme-Linked Immunosorbent Assay (ELISA) Bioassay Technology Laboratory Kit (Cat. No. E0031Hu, Lot:20221011) was used (Intra-Assay: CV<8 %, Inter-Assay:CV<10 %) with a microplate reader (Biotech Epoch 2 Microplate ELISA Reader, USA).

Histopathologic Evaluation in UC

The same pathologist who was blind to the participants evaluated the formalin-fixed paraffin-embedded H&E-stained colonic biopsies of the UC patients and performed grading through a scale similar to that developed by Truelove and Richards method. Active inflammation, chronic inflammation and crypt distortion were the components of the scale. The histopathologic activity index (HAI) was defined as the sum of the scores of these components.[17]

Statistical Analysis

Statistical analyses were conducted utilizing SPSS 15.0. Descriptive statistics were provided as proportions for categorical variables and as medians with inter-quartile ranges for continuous variables. Comparisons for continuous variables were carried out using the Mann-Whitney U test and the Kruskal-Wallis test, while the chi-square test was used for categorical variables. Spearman's correlation analysis was employed to investigate for associations between the parameters. Receiver Operating Characteristics (ROC) analysis was conducted by free-online tool 21. The confidence level for statistical significance was set at 0.95 ($p<0.05$).

RESULTS

In total, 77 UC patients (51 males and 26 females), 49 CD patients (33 males and 16 females) and 54 healthy controls (38 males and 16 females) participated in the study. Demographic, clinical and laboratory characteristics of the participants are presented in Table 1. The groups were similar with respect to age and gender.

The median sRAGE concentrations were significantly lower in UC patients compared to the control group (911.17 ng/L vs 1420.96 ng/L, p=0.008). sRAGE concentrations were not statistically significant between the patients with CD and healthy controls, UC and CD groups (Table 1).

Table 1. Demographic, clinical and laboratory characteristics of the study population

	UC Patients n=77	CD Patients n=49	Control Group n=54	p
Gender, n (%)				
Female	26 (33.8)	16 (32.7)	16 (33.3)	0.992
Male	51 (66.2)	33 (67.3)	38 (66.6)	
Age (years), median (IQR)	37 (25.50-51.5)	37 (25.5-48)	37 (29-48.25)	0.942
CRP (mg/L), median (IQR)	12.09 (3.36-40.50)	11.48 (2.68-31.62)	2.73 (0.88-4.77)	<0.0011
ESR (mm/h), median (IQR)	35 (13-70)	30 (13.5-50)	9 (3-17.25)	<0.0012
Leucocyte ($\times10^3$/µl), median (IQR)	8.01 (6.48-10.58)	8.59 (7.01-11.23)	7.70 (6.33-9.10)	0.122
Neutrophils ($\times10^3$/µl), median (IQR)	5.08 (3.80-6.97)	6.18 (4.53-8.69)	4.64 (3.76-5.96)	0.0063
Serum sRAGE (ng/L), median (IQR)	911.17 (322.91-1682.19)	1182.32 (759.1-1848.93)	1420.96 (816.68-2320.08)	0.0104
Disease duration (years), median (IQR)	2 (0.5-6)	1.5 (0-4.5)		
Location of UC , n (%)				
Remission	4 (5.2)			
Limited disease	43 (55.8)			
Extensive colitis	30 (39)			
Location of CD , n (%)				
Remission	1 (2)			
Ileal	32 (8.2)			
Colonic	4 (65.3)			
Ileocolonic	12 (24.5)			
Mayo Endoscopic Score of UC, n (%)				
Remission (0)	5 (6.5)			
Mild (1)	25 (32.5)			
Moderate (2)	29 (37.7)			
Severe (3)	18 (23.4)			
Treatments, n (%)				
No treatment	26 (33.8)	18 (36.7)		
Only Mesalamine	31 (40.2)	3 (6.1)		
Only Azathioprine	1 (1.2)	2 (4)		
Only BA	2 (2.5)	2 (4)		
Mesalamine± steroids ± azathioprine ±BA	17 (22)	24 (48.9)		
Mayo Clinical Score of UC, median (IQR)				
Remission (score ≤ 2), n (%)	16 (20.8)			
Activation (score>2), n (%)	61 (79.2)			
Histological Acitivity Index in UC, median (IQR)	6 (3-7)			
Crohn's Diaease Acitivity Index				
Remission (score <150), n (%)	20 (40.8)			
Activation (score≥150), n (%)	29 (59.2)			

Abbreviations: CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IQR: Inter quartile range; sRAGE: soluble receptor for advanced glycation end products, UC: Ulcerative colitis; CD: Crohn's disease; IBD: Inflammatory bowel disease, BA:Biological agents
Footnotes: 1Tukey HSD: Significant difference in comparison of UC vs controls, UC vs CD (p=<0.001, p<0.001); 2Tukey HSD: Significant difference in comparison of UC vs controls, CD vs controls (p<0.001, p<0.001); 3Tukey HSD: Significant difference in comparison of CD vs controls (p=0.004); 4Tukey HSD: Significant difference in comparison of UC vs controls (p=0.008).

Serum sRAGE concentrations were higher in UC patients in remission compared to patients with clinically active disease (2168,27 ng/L vs. 761,51 ng/L respectively, p<0.001) (Table 2). There was no statistically significant difference with respect to treatment status in UC patients. UC patients with limited disease and those who were in remission also had higher sRAGE values (Table 2). The MCS and HAI values of UC patients negatively correlated to the serum sRAGE values (rho=-0,6, p<0.001 vs rho=-0,742 respectively, p<0.001). Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), leucocyte, and neutrophil values were inversely correlated to serum sRAGE values (Table 3).

CD patients who were in remission had higher serum sRAGE values than the patients having clinically active disease (1720.42 ng/L vs. 923.36 ng/L respectively, p=0.002). CD patients who were under treatment had higher serum sRAGE values than the patients without any treatment (1361.22 ng/L vs. 879.38 ng/L respectively, p=0.033) (Table 2). The CDAI, CRP and ESR values inversely correlated to serum sRAGE concentrations (Table 3).

Table 2. Serum sRAGE values in clinical and endoscopic features of the patients with IBDs

	n	%	sRAGE (ng/L)			p
			Median	IQR		
Ulcerative Colitis						
Treatment						
No treatment	26	33.80	1142.59	632.8	1908.19	0.097
Under treatment	51	66.20	862.93	245.35	1518.43	
Mayo clinical scoring						
Remission (score ≤ 2)	16	20.80	2168.27	1174.34	4158	<0.0013
Activation (score >2)	61	79.20	761.51	245.35	1185.07	
Disease extension						
Remission	4	5.20	4857.63	3968	5360.37	<0.0013
Limited	43	55.80	1115.02	626.78	1825.34	
Extensive	30	39.00	492.62	151.57	938.2	
Mayo endoscopic activity						
Remission	30	39.00	1466.27	911.17	5156.34	<0.0013
Activation	47	61.00	755.82	177.56	2260.8	
Crohn's disease						
Treatment						
No treatment	18	36.70	879.38	601.61	1239.41	0.0331
Under treatment	31	63.30	1361.22	821.26	1944.2	
Crohn's disease activity index						
Remission (score<150)	20	40.80	1720.42	1005.68	2414.41	0.0022
Activation (score≥150)	29	59.20	923.36	601.61	1361.22	
Location of CD						
Remission	1	2.00	3942.89	3942.89	3942.89	0.261
Ileal	32	65.30	1090.4	759.1	1608.63	
Colonic	4	8.20	1482.74	1073.12	1943.47	
Ileocolonic	12	24.50	1181.36	631.68	1711.01	

Abbreviations: sRAGE: soluble receptor for advanced glycation end products; IQR: Inter quartile range; UC: Ulcerative colitis; CD: Crohn's disease; IBDs: Inflammatory bowel diseases. Footnotes: 1Statistically significant at the confidence level of 0.95; 2Statistically significant at the confidence level of 0.99; 3Statistically significant at the confidence level lower than 0.999

Table 3. Correlations between the serum sRAGE values and the clinical, laboratory variables of the patients with IBDs

Serum sRAGE (ng/L)	rho	p
Ulcerative Colitis		
CRP (mg/L)	-0.715	<0.0013
ESR (mm/h)	-0.486	<0.0013
Leucocyte (×10³/µl)	-0.371	0.0012
Neutrophil (×10³/µl)	-0,409	<0.0013
Mayo clinical scoring	-0.610	<0.0013
Histological activity index	-0.742	<0.0013
Crohn Disease, (n=49)		
CRP (mg/L)	-0.552	<0.0013
ESR (mm/h)	-0.425	0.0021
Leucocyte (×10³/µl)	-0.188	0.197
Neutrophil (×10³/µl)	-0.176	0.226
Crohn's disease activity index	-0.509	<0.0013

Abbreviations: sRAGE: soluble receptor for advanced glycation end products; IBDs: Inflammatory bowel diseases, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate. Footnotes: 1Statistically significant at the confidence level of 0.99; 2Statistically significant at the confidence level of 0.999; 3Statistically significant at the confidence level lower than 0.999

Receiver operating characteristics (ROC) analysis demonstrated that sRAGE levels possessed diagnostic utility in forecasting remission in patients with Crohn's disease (CD) and ulcerative colitis (UC), with area under the curve (AUC) values of 0.764 and 0.858, respectively (p<0.001 for both) (see Figure 1 and Figure 2). The determined cut-off levels for sRAGE values, predicting clinical remission in patients with CD and UC, were 1587.64 and 1012.29, respectively.

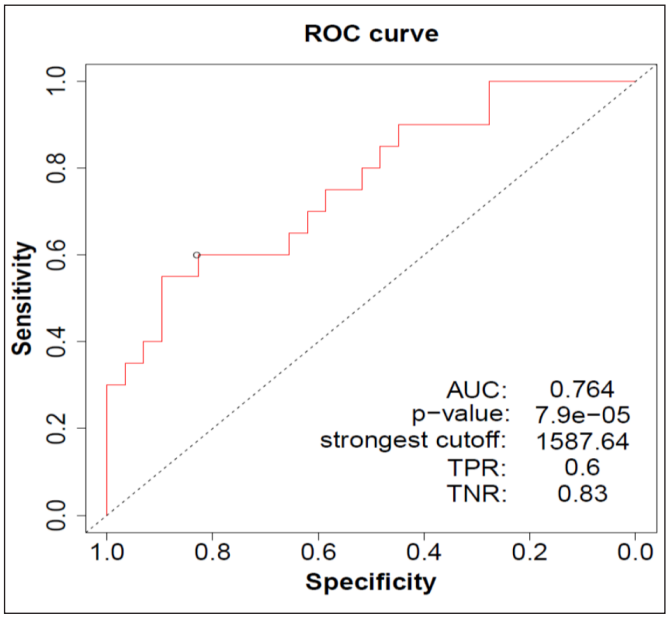

Figure 1. Diagnostic value of sRAGE levels to predict remission in patients with Crohn disease.

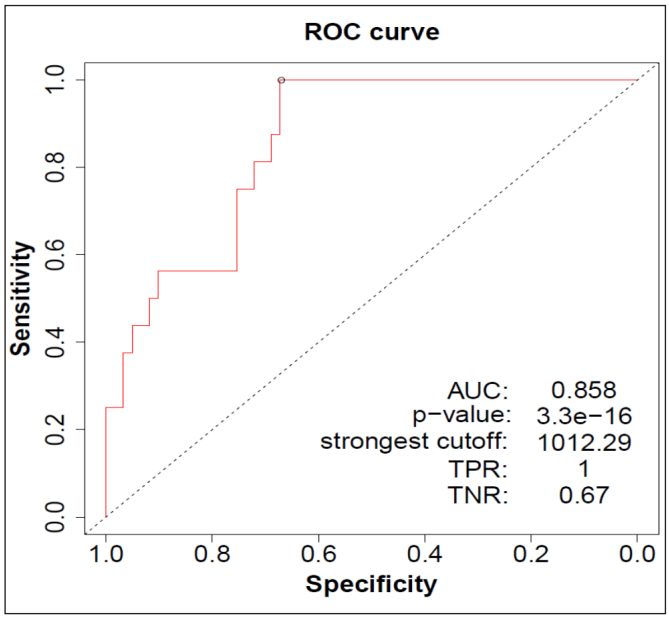

Figure 2. Diagnostic value of sRAGE levels to predict remission in ulcerative colitis patients.

DISCUSSION

Pathogenicity-related molecular pathways focusing on the diagnosis and the treatment of chronic inflammatory diseases, including IBDs, are gaining interest.[3] The patients with IBDs may undergo invasive endoscopic procedures which can cause discomfort. The clinical, endoscopic and biochemical findings can be inconsistent with each other in IBDs.[21] Searching for the ideal biomarkers correlating to all disease activity parameters, like fecal calprotectin (Fcp), is an important concern in IBDs.[22-24]

Acute inflammation is a normal protective response when host cells are repeatedly affected by injury or by microbial pathogens, and normally it is terminated silently for homeostasis. Host cells are programmed to end the noxious pro-inflammatory stimuli while the inflammatory process goes on. With this regard, some molecular pathways are defined like pro-resolving molecules and RAGE is another pathway for the control of inflammatory process.[3,25] Due to the inconsistent results according to the literature, the diagnostic and prognostic value of sRAGE in clinical settings remains controversial.[3]

Lower serum sRAGE concentrations were reported in UC patients than in the control group and the difference was statistically significant in our study. Although serum sRAGE concentrations in CD patients were lower than the control group, it was not statistically significant. Regarding the anti-inflammatory effect of sRAGE, it might be probable that the decreased sRAGE levels in patients with IBDs may increase inflammatory tendencies in addition to the other pathogenic mechanisms.

We think that lower sRAGE values in UC patients compared with the healthy controls are more likely to be due to the consuming of sRAGE with RAGE ligands because of ongoing pro-inflammatory stimuli.[8] Lower sRAGE values in the patients with IBDs than in the healthy controls were also reported in previous studies.[7,8] However, a prior study additionally identified that UC patients had greater sRAGE values than the control group (but not CD patients).[9]

Meijer et al.[7] reported lower sRAGE values in UC patients, but there was no statistically significant difference between the patients with CD and the control group. In this study, UC clinical activity was obtained by the 'Simple Clinical Colitis Activity Index' (SCCAI); the Rachmilewitz index was applied in the colonoscopy.[7,26,27]. There were inverse correlations between the serum sRAGE, endoscopic activity and the SCCAI. These results are consistent with our study in which the MCS and the MES indexes were used for UC. Despite the different methods of disease activation, these findings highlight the diagnostic and prognostic significance of lower serum sRAGE values for UC. Along with CRP, leucocyte, neutrophil and ESR values were also inversely correlated to serum sRAGE concentrations in the current study.

Meijer et al.[7] did not report statistically significant differences between the sRAGE values of CD patients and the controls. They applied the Harvey Bradshaw index (HBI) for the clinical activity of CD and mucosal scores were investigated through the 'Simple Endoscopic Score for CD'.[28,29] HBI scores correlated with the endoscopic disease activity scores in CD patients, as did CRP. In contrast, there was no correlation between sRAGE concentrations and endoscopic activity, and HBI scores.

Unlike this study, we used CDAI for the clinical activity of CD, as although HBI is a simplified scoring system of CDAI, results may be inconsistent due to the methodological differences. The CDAI scores inversely correlated to the sRAGE values. The patients in the remission phases had higher sRAGE values. As a limitation, we did not include any endoscopic activity indices for CD patients. As in the study of Meijer et al.[7] we also did not report any correlation to CD localization but we noted negative correlations between CRP, ESR and sRAGE concentrations. Larger sample-sized cohorts may reveal significant correlations in terms of the relationship between the disease extension, endoscopic activity, and the other specialties of the patients with CD and serum sRAGE values.

Ciccocioppo et al.[8] evaluated the levels of serum sRAGE, S100A12 - which is a RAGE ligand belonging to the S100 protein family - CRP and Fcp (S100A8/A9) in the IBD patients. They also consisted of patients with irritable

bowel syndrome as the control group. CDAI for CD patients and the 'Ulcerative Colitis Endoscopic Index of Severity' for UC patients were applied for the clinical activity.[26] The HAI were evaluated according to the 'Global Histologic Disease Activity Score' for CD and the 'Geboes Grading System' for UC.[8,30,31] When splitting the data amongst the groups, significantly lower levels of sRAGE were observed in UC patients than the other groups, whilst no significant difference between CD patients and controls appeared evident. These results were also consistent with our study. Serum S100A12 values were not different between the groups and Fcp was higher in patients with IBDs. An inverse correlation was found in terms of the serum levels of sRAGE with both clinical and endoscopic activity indexes either in CD or in UC. With regard to the HAI, no correlation was reported for UC, but an inverse correlation was noted between serum sRAGE values and the HAI of CD patients. There was an inverse correlation between sRAGE values and Fcp.[8]

Calprotectin is a RAGE ligand and Fcp is recognized to be a strong indicator of inflammation in IBD.[22,32] Testing Fcp is not an easy procedure and it is expensive. FCp was found to be related to both active disease and mucosal healing in evaluating the disease activity of UC but the threshold value was not accurately determined.[22,33] Thus, it could be valuable to evaluate the correlations between Fcp and serum sRAGE values. As a limitation of our study, we did not measure Fcp values in IBDs patients. Although sRAGE concentrations were not statistically significant between the patients with CD and healthy controls, UC and CD groups, we think that larger sample-sized cohorts of the patients with CD can reveal significant results. If it could be proven in future studies, as an inexpensive and easily applicable test, sRAGE might be used as a valuable marker for IBDs.

The patients with UC who were in remission according to the clinical and laboratory results, and those with limited disease in the colonoscopy had higher sRAGE values and an inverse correlation was reported between the HAI of UC and sRAGE. This was a valuable result because mucosal healing is the best therapeutic goal and an indicator for the activity of patients with IBDs.[14]

The patients with CD who were under treatment had higher sRAGE values, and inverse correlations between the disease activity of IBDs and serum-lower sRAGE values in the patients without any treatment might be ascribed to the consuming of sRAGE to prevent increased pro-inflammatory activation. It may partly be due to the disturbances in the innate immune system in IBDs because RAGE pathway is also a pattern-recognition receptor.[10,11]

Opposite results between sRAGE values and disease presentation, and laboratory features in different populations may be due to methodological differences, including the ELISA kits utilized, and also variations in the control groups. Treatment modalities might also affect the results.[7-9]

For IBDs, RAGE pathway was also declared as a therapeutic target.[13] Today, current medical treatments for IBDs focus on the inhibition of immune activation but they cannot achieve complete remission.[23] Topical delivery of sRAGE into the gut mucosa might be an adjunctive treatment modality.

The major limitation of the current study was the small number of the study population as it was a single-centered trial. Larger cohorts might reveal significant results for the diagnostic accuracy of serum sRAGE in IBDs. Comparing Fcp values with serum sRAGE concentrations could be more valuable for the assessment of diagnostic and prognostic accuracy of serum sRAGE.

CONCLUSION

Diagnostic strategies with the possibility of therapeutic interventions can be developed by identifying new, practical and objective biochemical markers in IBDs. Serum sRAGE can be a valuable biomarker for the clinical and laboratory traits of UC. Further studies are required to delineate the diagnostic and therapeutic accuracy of sRAGE in IBDs.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Scientific Researches Ethics Committee (Date: 17.11.2021, Decision No: 235-211084517).

Informed Consent: Written informed consent was obtained from all participants.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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