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Araştırma Makalesi / Original Article

İNFLAMATUAR BAĞIRSAK HASTALARINDA SERUM RESOLVİN D1 VE E1 DÜZEYLERİNİN DEĞERLENDİRİLMESİ

EVALUATION OF SERUM RESOLVIN D1 AND E1 LEVELS IN PATIENTS WITH INFLAMMATORY BOWEL DISEASES

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ÖZET

Giriş: Resolvin molekülleri, inflamatuar barsak hastalıklarında (İBH) anti-İnflamatuar aktiviteye sahiptir. Çalışmamızda serum resolvin D1 (RvD1) ve resolvin E1 (RvE1) düzeylerinin İBH'da klinik ve laboratuvar özellikler ile korelasyon gösterip göstermediğini değerlendirilmesi planlanmıştır.

Yöntemler: Bu vaka-kontrol çalışmasına İBH''lı 62 hasta [32 ülseratif kolit (ÜK), 30 Crohn hastalığı (CH) bulunan vaka] ve 28 sağlıklı kontrol dahil edildi. ÜK hastalarının klinik ve endoskopik özellikleri Mayo Klinik Skorlama (MKS) sistemine göre CH vakalarının klinik aktivitesi ise Crohn Hastalık Aktivite İndeksine (CHAİ) göre kaydedildi. Serum RvD1 ve RvE1 ölçümü için insan RvD1 ve RvE1 enzim bağımlı immunosorbent testi (ELISA) kitleri kullanılmıştır.

Bulgular: Serum RvD1 konsantrasyonları ÜK ve CH'da sağlıklı kontrollere göre anlamlı olarak düşük bulundu [182,69 (118,24-450,80) ng/L ve 342,07 (203,57-989,04) ng/L ve 353,65 (216,14-1125,40) ng/L, sırasıyla, *p= 0.002*]. RvD1 ve RvE1 konsantrasyonları, klinik olarak remisyon fazında olan ÜK hastalarında aktivasyon fazında olanlara göre daha yüksekti [602,18 (176,13-1181,60) ng/L ve 170,37 (113,21-216,21) ng/L, *p=0,005*-302,10 (122,18-527,37) ng/L ve 74,17 (67,38-122,66) ng/L, sırasıyla, *p=0,004*]. RvD1 değerleri inaktif endoskopik bulgusu olan ÜK'li hastalarda aktif hastalığı olanlara göre daha yüksekti [426,11 (175,94-891,03) ng/L ve 169,62(109,97-202,80) ng/L, sırasıyla *p=0,009*]. ROC (receiver operating characteristic curve) analizi serum RvD1 ve RvE1 düzeylerinin, ÜK'de artan Mayo klinik skorları yönünden tanısal değerinin bulunduğunu göstermiştir (AUC=0.809, 95% CI: 0.630-0.988, *p<0.001* ve AUC=0.814, 95%CI: 0.637-0.991, sırasıyla, *p<0.001*).

Sonuç: Azalmış serum RvD1 değerleri, ÜK hastalığının teşhisi ve hastalık aktivitesinin değerlendirilmesinde yardımcı bir biyobelirteç olarak kullanılabilir.

Anahtar Kelimeler: Ülseratif kolit, resolvin D1, biyobelirteç.

ABSTRACT

Introduction: Resolvin molecules have anti-inflammatory activity in inflammatory bowel diseases (IBDs). We aimed to evaluate whether serum resolvin D1 (RvD1) and resolvin E1 (RvE1) values can correlate to clinical and laboratory traits of IBDs.

Methods: This case-control study included 62 patients with IBDs (32 ulcerative colitis (UC) patients, 30 Crohn's disease (CD) patients) and 28 healthy controls. The Mayo Clinical scoring system (MCS) was used for the clinical and endoscopic features for UC, and the Crohn's disease activity index was used to assess the disease activity in CD patients. Human RvD1 and RvE1 kits were used for the serum enzyme-linked immunosorbent assay.

Results: RvD1 concentrations were significantly lower in UC and CD patients compared to the control group [182.69 (118.24-450.80) ng/L and 342.07 (203.57-989.04) ng/L vs. 353.65 (216.14-1125.40) ng/L respectively, *p=0.002*]. RvD1 and RvE1 concentrations were higher in UC patients who were in the clinically remission phase than the patients in the activation phase [602.18 (176.13-1181.60) ng/L and 170.37 (113.21-216.21) ng/L, *p=0.005* vs. 302.10 (122.18-527.37) ng/L and 74.17 (67.38-122.66) ng/L, *p=0.004*, respectively]. RvD1 values were higher in UC patients who had inactive endoscopic findings than the patients having active disease [426.11(175.94-891.03 ng/L and 169.62(109.97-202.80) ng/L, *p=0.009,* respectively]. The ROC (receiver operating characteristic curve) analysis revealed RvD1 and RvE1 levels had considerable diagnostic significances for the increased MCS in UC (*AUC=0.809, 95%CI: 0.630-0.988, p<0.001 vs AUC=0.814, 95%CI: 0.637-0.991, p<0.001).*

Conclusion: Decreased serum RvD1 values might be used as an auxiliary biomarker for the diagnosis and the activity of UC.

Keywords: Ulcerative colitis, resolvin D1, biomarker.

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INTRODUCTION

Ongoing chronic inflammation caused by enteric microbiota as a result of the sustained immune response is a mainstay of the pathogenesis in inflammatory bowel diseases (IBDs). Current medical treatments focus on the inhibition of immune activation (1).

In humans, acute inflammation is a normal protective response when host cells are repeatedly affected by injury or by microbial pathogens. The resolution process makes acute inflammation unnoticeable and self-limited without progressing to the chronic phase (2). The failure of resolution leads to chronic inflammation and tissue damage. Termination of the neutrophil infiltration and phagocytosis of the apoptotic neutrophils and cellular debris by macrophages are the two key events in the resolution process (3).

The resolution process is mainly directed by biochemical molecules and specialized pro-resolving mediators (SPMs) (2, 4). In the acute phase of the inflammation, prostaglandins and leukotrienes are synthesized from arachidonic acid. They recruit neutrophils and increase vascular permeability. Simultaneously, SPMs, which include resolvins, are synthesized from lipids by the effect of neutrophils and macrophages (5).

Resolvins are lipid-structured resolution molecules synthesized from omega-3 polyunsaturated fatty acids (PUFA). They exert anti-inflammatory activity. D-series resolvins (resolvin D1-5) are synthesized from docosahexaenoic acid (DHA) while E-series resolvins (resolvin E1-3) are synthesized from eicosapentaenoic acid (EPA) (3). The therapeutic role of the replacement of omega-3 PUFA and SPMs in chronic inflammatory diseases has also been pronounced (2, 6).

Dysfunctions in the resolution of inflammation are thought to be associated with the pathogenesis of autoimmune and inflammatory diseases such as systemic lupus erythematosus, type 1 diabetes, rheumatoid arthritis, multiple sclerosis, and IBDs (3, 7, 8). The measurement of SPMs in urine, serums, and stools has been proposed as a marker associated with the activation of IBDs (9). With regards to irritable bowel syndrome (IBS)-induced inflammation in the gut, serum levels of RvD1 were reported to be lower in patients with constipation-dominant IBS than in healthy controls (10).

Resolvin D1 and E1 are the most investigated SPMs (11-15). In terms of clinical and laboratory features of IBDs, there is currently a scarcity of data regarding serum RvD1 and RvE1 levels. This study aimed to evaluate whether serum RvD1 and RvE1 levels of patients with IBDs could serve as diagnostic and prognostic markers correlating to the clinical, biochemical and endoscopic representation of the diseases.

METHODS

Subjects

Thirty-two patients with ulcerative colitis (UC), 30 patients with Crohn's disease (CD) and 28 healthy controls admitted to the gastroenterology department of our institute between December 2021 and June 2022 were included in the study. The Local Ethics Committee approved the study (12.04.2022/E-46059653-020). Written informed consent was obtained from all participants.

Participants with any clinical conditions that could change serum RvD1 and RvE1 levels such as sepsis, any malignancies, severe organ failure, acute or chronic infections, autoimmune and/or chronic inflammatory diseases, gut resection, and those who had contraindications for colonoscopy were excluded from the study. The healthy control group included participants who underwent a colonoscopy for indications other than IBDs and whose colonoscopy results were normal.

The disease duration, family history (IBD in 1st degree relatives), medications for IBDs, comorbidities, previous surgical operations and medications in all study groups were recorded. Complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and other biochemical tests were performed before the colonoscopy procedure.

Assessment of Clinical and Endoscopic Activity in Patients

The Mayo Clinical score (MCS) was applied for the UC patients and was scored between 0-12 (16). 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 CD patients and scores of <150 were noted as clinical remission whereas scores of ≥150 were noted as activation (17).

The disease extent (DE) of the patients with IBDs was defined in agreement with the Montreal classification (18). In UC, the DE was classified as remission, proctitis, left-sided colitis or pancolitis. For the localization of UC, proctitis and left-sided colitis were recorded as localized disease and pancolitis as extensive disease. The localization of CD was classified as remission ileal, colonic or ileocolonic disease (18).

The Mayo endoscopic activity sub scoring (MEAS) index was used for the endoscopic activation of UC and was classified as remission (0), mild (1), moderate (2) or severe (3) colitis. Scores of (0) and (1) were recorded as endoscopic remission whereas (2) and (3) were recorded as activation (16).

Resolvin D1 and Resolvin E1 Measurements

Venous blood samples were drawn for the routine biochemical tests and the serum for RvD1 and RvE1 was separated after centrifugation of the sample at 5000×*g* for 10 minutes at 30 °C. The supernatant serum was stored at (−80) °C for 6-9 months until the analyses were conducted. For the measurements of RvD1 and RvE1 using serum Enzyme-Linked Immunosorbent Assay (ELISA), the commercially available Human Resolvin D1 ELISA Kit (Bioassay Technology Laboratory, Cat. No. E 7450 Hu, Lot: 202206001) and Human Resolvin E1 ELISA Kit (Bioassay Technology Laboratory, Cat. No. E 7078 Hu, Lot:

202206001) were used according to the instructions of the manufacturer (Intra-Assay: CV<8 %, Inter-Assay: CV<10 %) using a microplate reader (Biotech Epoch 2 Microplate ELISA Reader, USA).

Statistical analysis

Statistical analyses were performed using the SPSS 15.0 and MedicReS AI Smart Biostatistics Software version 21.3 software programs. Descriptive statistics were presented as counts and percentages for categorical variables, whereas the mean and standard deviation or median values with extremes were used for the continuous variables. The Mann-Whitney U and Kruskal-Wallis tests were used for the comparison of continuous variables. Spearman's Rho correlation analysis was conducted for evaluating associations between parameters. The receiver operating characteristics (ROC) curve analysis and binomial diagnostic accuracy were performed for parameters that showed significant differences between groups. The confidence level for statistical significance was defined as 0.95 (p<0.05).

RESULTS

Thirty-two patients with UC (24 males and 8 females, with a median age of 36 (27.5-43.00) years), 30 patients with CD (22 males and 8 females, with a median age of 30 (25-44.25) years) and 28 healthy controls (21 males and 7 females, with a median age of 31.50 (28.00-45.00) years) 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. Males dominated all participant groups. The median CRP and ESR concentrations in the patient groups were significantly higher than the control group (p<0.001, p<0.001). The WBC and neutrophil counts were not different between the groups.

The median RvD1 concentrations were significantly lower in the patients with UC and CD compared to the control group (182.69 ng/L and 342.07 vs. 353.65 ng/L respectively, *p=0.002*). Although the median RvE1 concentrations were lower in the patients with IBDs than the control group, the results were not statistically significant (82.47 ng/L and 106.89 ng/L vs 110.60 ng/L, respectively, *p=0.505*) (Table 1).

Serum RvD1 concentrations were higher in the UC patients who were in remission than those that had a clinically active disease (602.18 ng/L vs. 170.37, *p=0.005*). The serum RvE1 concentrations were also higher in the UC patients who were in remission than the patients with clinically active disease (302.10 ng/L and 74.17 ng/L, respectively, *p=0.004*). Serum RvD1 values were higher in UC patients who had inactive endoscopic findings than the patients having active endoscopic findings (426.11 ng/L and 169.62 ng/L, *p=0.009,* respectively) (Table 2).

Table 1. Clinical and demographic characteristics of the study population.

Demographic Characteristics	UC Patients n=32	CD Patients n=30	Control Group n=28	p value
Gender, n (%)				
Female	8 (25)	8 (26.66)	7 (25)	0.986
Male	24 (75)	22 (73.33)	21(75)	
Age (years), median (IQR)	36 (27.5-43.00)	30 (25-44.25)	31.50 (28.00-45.00)	0.997
CRP (mg/L), median (IQR)	13.57 (3.63-32.19)	14.78 (1.83-31.72)	1.60 (0.67-4.63)	<0.001[2]
ESR (mm/h), median (IQR)	33.00 (13.25-50.50)	31.00 (14.75-49.50)	4.00 (2.25-12.50)	<0.001[3]
WBC (x10^3/µL), median (IQR)	8.19 (6.56-11.59)	8.37 (6.81-10.69)	7.88 (6.22-10.34)	0.676
Neutrophils (x10^3/µL), median (IQR)	5.84 (3.84-7.25)	5.78 (4.01-8.02)	4.56 (3.73-6.36)	0.229
Serum Resolvin-D1 (ng/L), median (IQR)	182.69 (118.24-450.80)	342.07 (203.57-989.04)	353.65 (216.14-1125.40)	0.002[1]
Serum Resolvin-E1 (ng/L), median (IQR)	82.47 (68.90-329.55)	106.89 (64.67-299.48)	110.60 (82.52-385.11)	0.504
Disease duration(years), median (IQR)	1.00 (0.00-4.00)	2.75 (0.50-7.50)		
Location of UC , n (%)				
Remission	2 (6.25)			
Limited disease	21 (65.62)			
Extensive colitis	9 (28.12)			
Location of CD , n (%)				
Remission		1 (3.33)		
Ileal		19 (63.33)		
Colonic		3 (10)		
Ileocolonic		7 (23.33)		
Mayo Endoscopic Subscore of UC, n(%)				
0 (Inactive disease)	3 (9.37)			
1 (Mild)	10 (31.25)			
2 (Moderate)	13 (40.62)			
3 (Severe)	6 (18.75)			
Treatments of the patients , n (%)				
No treatment	12 (37.5)	13 (43.3)		
5-ASA	20 (62.5)	11 (36.6)		
Steroids	1 (3.33)	9 (30)		
Azothioprin	4 (12.5)	9 (30)		
Anti-TNF alpha	1 (3.33)	5 (16.6)		
IBD in first degree relatives,n (%)	6 (10.24)			
Mayo Clinical Score of UC , median (IQR)	5.50 (2.00-8.00)			
Remission (score ≤ 2), n (%)	10 (31.25)			
Activation (score>2), n (%)	46 (68.75)			
Crohn's Diaease Acitivity Index				
Remission (score <150), n (%)	11 (36.66)			
Activation (score≥150), n (%)	19 (63.33)			

Abbreviations: CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; WBC: White blood cells; UC: Ulcerative colitis; CD: Crohn's disease; 5-ASA: 5-aminosalycilate; TNF: Tumor necrosis factor; IBD: Inflammatory bowel disease

Footnotes:

[1]Tukey HSD: Significant difference in comparison of UC vs controls, UC vs CD (p=0.002, p=0.004); [2]Tukey HSD: Significant difference in comparison of UC vs controls, CD vs controls (p<0.001, p=0.001); [3]Tukey HSD: Significant difference in comparison of UC vs controls, CD vs controls (p<0.001, p<0.001); [4]Tukey HSD: Significant difference in comparison of UC vs controls, CD vs controls, UC vs CD (p=0.010, p<0.001, p=0.048).

Table 2. Serum resolvin-D1 and E1 levels in different demographic and clinical features of the patients with inflammatory bowel diseases.

			Resolvin-D1 (ng/L)		Resolvin-E1 (ng/L)	
		n	Median (IQR)	p	Median (IQR)	p
Crohn's disease						
Gender	Male	22	342.07 (208.19-958.68)	0.801	139.09 (82.19-324.94)	0.063
	Female	8	595.28 (193.84-1189.72)		64.34 (55.31-231.56)	
Treatment	No treatment	13	254.01 (196.84-402.21)	0.035[1]	125.47 (71.42-302.98)	0.711
	Under treatment	17	953.73 (206.65-1177.40)		92.34 (58.88-339.99)	
IBD in 1st degree relatives	Negative	24	370.57 (205.11-1020.07)	0.432	101.59 (62.40-303.51)	0.705
	Positive	6	274.43 (153.44-645.68)		182.40 (77.92-307.30)	
Crohn's disease activity index	Remission (score <150)	11	640.36 (254.01-1098.37)	0.200	105.00 (67.41-284.16)	0.966
	Activation (score≥150)	19	316.27 (192.12-936.54)		125.47 (56.50-309.96)	
Location of CD	Remission	1	640.36	0.589	98.18	0.204
	Ileal	19	392.09 (203.57-1152.76)		85.59 (56.50-283.60)	
	Colonic	3	272.13		319.50	
	Ileocolonic	7	254.01 (143.11-973.52)		108.78 (67.41-341.24)	
Ulcerative Colitis						
Gender	Male	24	182.69 (132.11-450.80)	0.749	92.59 (71.01-329.55)	0.428
	Female	8	176.51 (109.82-497.68)		71.30 (63.18-428.29)	
Treatment	No treatment	12	163.76 (116.09-202.61)	0.116	73.72 (61.92-137.85)	0.209
	Under treatment	20	222.00 (135.41-787.14)		92.59 (73.13-372.76)	
IBD in 1st degree relatives	Negative	24	182.69 (118.24-532.09)	0.881	76.70 (68.90-203.26)	0.334
	Positive	8	188.81 (129.79-410.30)		245.36 (70.10-515.10)	
Mayo Clinical Scoring	Remission (score ≤ 2)	10	602.18 (176.13-1181.60)	0.005[2]	302.10 (122.18-527.37)	0.004[2]
	Activation (score >2)	22	170.37 (113.21-216.21)		74.17 (67.38-122.66)	
MEAI	Remission (score 0,1)	13	426.11(175.94-891.03)	0.009[2]	138.03(71.07-430.30)	0.323
	Activation (score 2,3)	19	169.62(109.97-202.80)		75.20(68.53-125.26)	
Location of UC	Remission	2	287.52	0.275	309.35	0.178
	Limited	21	187.57 (163.01-773.20)		86.75 (69.81-452.77)	
	Extensive	9	150.97 (112.13-229.24)		75.20 (63.66-110.11)	

Abbreviations: IQR: Inter quartile range; UC: Ulcerative colitis; CD: Crohn's disease; IBD: Inflammatory bowel disease, MEAI: Mayo endoscopic activity index
Footnotes: [1]Statistically significant at the confidence level of 0.95; [2]Statistically significant at the confidence level of 0.99.

In the UC patients, there was a positive correlation between the serum RvD1 and RvE1 concentrations. The MCS of UC negatively correlated to the serum RvD1 and RvE1 concentrations (rho=-0.61, *p<0.001 and* rho= -0.49*, p=0.005,* respectively*)*. The neutrophils, WBCs, ESR and CRP values also negatively correlated to the serum RvD1 concentrations in the UC patients (Table 3).

In terms of localization of the disease, family history of IBDs, treatment status and serum resolvins, correlation analyses did not reveal any significant results for either disease. The difference between the serum RvD1 concentrations of the CD patients who were not undergoing treatment and those undergoing treatment was statistically significant (254.01 ng/L vs. 953.73 ng/L, *p=0.035*, respectively) (Table 2). In the CD patients, the disease duration positively correlated to the serum RvD1 values and the age of the patients negatively correlated to the serum RvE1 values (Table 3).

The ROC curve analysis revealed serum RvD1 and RvE1 levels had a considerable diagnostic significance for the increased disease activity in UC (Figures 1 and 2). Positive levels of serum RvD1 and RvE1 values (cut-off >288.48 ng/L and >125.6 ng/L, respectively) highlighted the increased MCS in UC (AUC=0.809, 95%CI: 0.630-0.988, *p<0.001* vs AUC=0.814, 95%CI: 0.637-0.991*, p<0.001*) (Table 4).

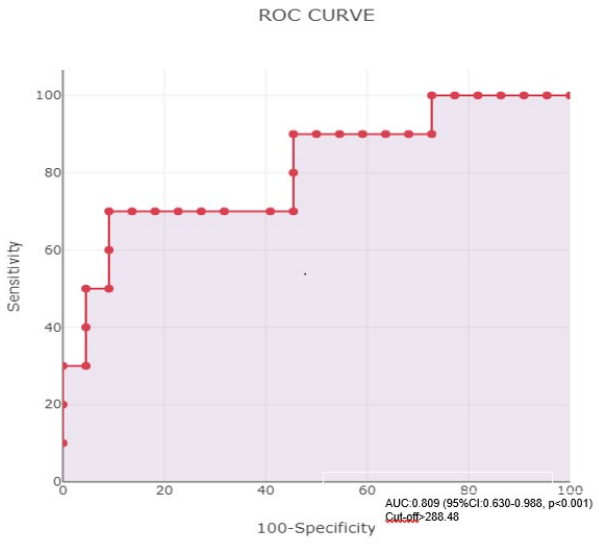

Figure 1. ROC curve analyses of the predictive values of serum Resolvin D1 concentrations for the Mayo clinical scoring of ulcerative colitis

Table 3. Correlations between the clinical and laboratory variables and serum resolvins in the patients with inflammatory bowel diseases

	Serum Resolvin-D1		Serum Resolvin-E1	
	rho	p	rho	p
Crohn Disease, (n=30)				
Age (years)	-0.02	0.922	-0.37	0.043[1]
Disease duration (years)	0.40	0.027[1]	-0.12	0.522
CDAI	-0.34	0.063	0.02	0.918
Resolvin-D1 (ng/L)			-0.06	0.753
Resolvin-E1 (ng/L)	-0.06	0.753		
CRP (mg/L)	-0.69	.000	0.16	0.412
ESR (mm/h)	-0.73	.000	0.17	0.359
WBC (x10^3/µL)	-0.20	.278	0.09	0.618
Neutrophil (x103/µL)	-0.15	.428	-0.11	0.569
Ulcerative colitis, (n=32)				
Age (years)	-0.16	0.395	-0.08	0.685
Disease duration (years)	0.12	0.507	0.12	0.526
Resolvin-D1 (ng/L)			0.45	0.010[2]
Resolvin-E1 (ng/L)	0.45	0.010[2]		
MCS	-0.61	<0.001[3]	-0.49	0.005[2]
CRP (mg/L)	-0.75	<0.001[3]	-0.71	<0.001[3]
ESR (mm/h)	-0.56	0.001[3]	-0.50	0.004[2]
WBC (x10^3/µL)	-0.59	<0.001[3]	-0.53	0.002[2]
Neutrophil (x10^3/µL)	-0.58	0.001[3]	-0.46	0.009[2]

Abbreviations: CDAI: Crohn's disease activity index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; WBC: White blood cells; MCS: Mayo clinical score
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

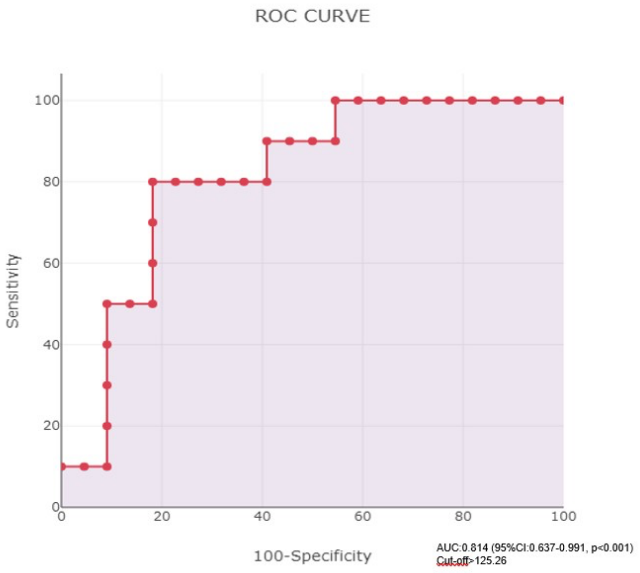

Figure 2. ROC curve analyses of the predictive values of serum Resolvin E1 concentrations for the Mayo clinical scoring of ulcerative colitis

DISCUSSION

The pathogenesis of IBDs is heterogeneous and it has not been fully elucidated. Immune dysregulation is believed to have a major pathogenic role (1). Growing evidence exists about the pathogenesis of chronic inflammatory diseases. The resolution of the acute inflammation aims to terminate the inflammatory process without tissue damage and the resolution process starts during the initial phases of acute inflammation (2, 3). It is mediated by SPMs, which include lipoxins, resolvins, protectins and marezins (5).

Resolvins promote the termination of neutrophil infiltration, the clearance of apoptotic cells by macrophages, tissue remodeling and homeostasis, and this process is called as efferocytic clearance (2, 3). Prostaglandin D2 and E2 are known to promote the generation of resolvins via neutrophils and macrophages (3).

Resolvins and other SPMs are thought to prevent the chronicity of acute inflammation and it has been suggested for a long time that SPMs take part in the pathogenesis of IBDs (9, 19, 20, 21). Resolvin D1, a member of the SPM family, exerts anti-inflammatory, antioxidant, anti-fibrosis, anti-apoptotic, and anti-tumor effects. It is known to be the

Table 4. Diagnostic value of serum Resolvin D1 and E1concentrations in ulcerative colitis.

	Sensitivity	Specificity	LR(+)	LR(-)	LR(+)/LR(-)
Resolvin D1 (>288.48) for predicting MCS of UC[1]	0.700	0.905	7.700	0.333	23.340
Resolvin E1 (>125.26) for predicting MCS of UC[1]	0.800	0.905	4.400	0.244	18.000

Abbreviations: MCS: Mayo clinical scoring, UC: ulcerative colitis.
Footnotes: [1]Statistically significant at the confidence level lower than 0.99

most potent resolving molecule (22). In the experimental models, RvD1 has been reported to have a protective role for small intestinal inflammation and it also has an anti-tumor potential in colitis-associated cancer (21, 23). RvE1 was also found to dampen tissue damage (24, 25).

This study aimed to evaluate the serum RvD1 and RvE1 concentrations in the clinical and laboratory presentation of IBDs**.** According to the literature, this research is the first study that evaluates both serum RvD1 and RvE1 concentrations in the adult IBDs population. The most important finding in this study was the lower serum RvD1 values in the UC and CD patients compared to the healthy controls. The mean serum RvD1 concentration was the lowest in the UC patients.

In a recent study, Kikut et al. (26) evaluated the serum SPMs including the serum RvD1 and RvE1 values using the liquid chromatography method in the pediatric and adolescent population with IBDs. The study included 34 CD (mean age of 13.76±2.69 years) and 30 UC (mean age of 14.15±3.31 years) patients but no healthy controls. Similar to this study's results, lower concentrations of RvD1 were detected in the UC patients than in the CD patients. Although lower serum RvD1 values were found in clinically active UC patients in the current study, Kikut et al. (26) did not find such a relation in their study group, which may be partly due to the different study population and the measurement methods of serum RvD1 in these studies.

Negative correlations were found between the routine laboratory determinants of inflammation and the serum RvD1 values in patients with UC in this study. The WBC and neutrophil values were not different in the groups but the CRP and ESR values, as expected, were higher in the patients. Similar leukocyte values in the groups can be partly due to the medications used by the patients with IBDs. The aforementioned information highlights that resolvin activation is mediated by neutrophils and macrophages at the onset of inflammation (2,3).

The severity of inflammation is found to be associated with the quantity of the neutrophils and the neutrophilic infiltration of the crypts results in cryptitis and crypt abscesses, which are the pathognomonic histopathologic features in IBDs (1). The precise role of neutrophils in IBDs remains controversial (27). The inability of neutrophils to produce sufficient SPMs molecules including resolvins, may result in low levels of serum resolvin concentrations. Besides the many other factors in the pathogenesis of IBDs, insufficient production of resolvins may be the reason for chronic inflammation in the gut.

Although the WBC and neutrophil values were not different in the groups in the study, higher acute phase reactants but lower resolvin concentrations may be a clue for the incapability of resolvin activation in IBDs. In addition, lower resolvin concentrations might be more valuable than neutrophilic activation in IBD pathogenesis.

Karatay et al. (10) investigated the role of circulating RvD1 in patients with constipation dominant irritable bowel syndrome (IBS-C) regarding subclinical inflammation encountered in the gut. They reported lower serum RvD1 concentrations in IBS-C patients than in the control group. RvD1 levels were also found to be the lowest in patients having more severe abdominal pain, which was ascribed to an RvD1 deficiency that led to subclinical mucosal inflammation. These results might indicate the protective role of RvD1 against chronic inflammation in the gut.

Serum RvE1 concentrations were also lower in patients with IBD than in the control group in this study but the results were not statistically significant. Kikut et al. (26) observed statistically significant lower concentrations of RvE1 in the CD group relative to UC in the younger IBDs population. When they compared the acute phases of both diseases, they noted significantly higher serum RvE1 concentrations in the acute phase of UC. Since the ages of the CD patients were inversely correlated to the serum RvE1 values in this study's analyses, patient age might have affected the serum RvE1 values, which provides an explanation to the conflicting results in both studies. It is thought that larger sample-sized cohorts might reveal significant results about serum RvE1 in patients with IBDs.

On the other hand, positive correlations were observed between serum RvD1 and serum RvE1 values both in UC and CD in this study. These results might explain the simultaneous activation of these molecules in the resolution processes of IBDs.

In a previous study, serum RvE1 concentrations between UC patients and healthy controls were evaluated. Although the serum RvE1 values were found to be higher in the UC patients compared to the control group, the difference was not statistically significant. In the UC patients, serum RvE1 levels were also not significantly different in the activation and remission phases (25).

In light of the current data, there are conflicting results about serum RvE1 concentrations and IBDs, but further investigations are needed for confirmation**.** It is thought that low serum RvD1 values might be an auxiliary marker for the diagnosis and the activity of UC.

Despite treatment, IBDs have relapsing and remitting courses. Alterations of resolvins in gut mucosa may partly be responsible for these episodes. Replacement of SPMs has been proposed as a new treatment modality in chronic inflammatory diseases and immunoresolvent therapy is a term that defines the replacement of resolvins in chronic inflammatory diseases (11-15). A strong body of evidence exists about the therapeutic utility of SPMs. Lenabasum is a composition of ajulemic acid and it is an orally active drug that stimulates SPMs. Fish oil contains abundant DHA and EPA and it has also been declared to have therapeutic efficacy (3).

Today, current medical treatments for IBDs focus on the inhibition of immune activation but they cannot achieve complete remission (1). The European Crohn's and Colitis Organization (ECCO) guidelines state that the treatment of IBDs should not only control the symptoms but should also prevent the underlying cause of the disease (28). Mucosal healing is the best therapeutic goal for IBDs (29). It is hoped that the topical delivery of resolvins into the gut mucosa might be an adjunctive treatment modality that may accomplish the best therapeutic goal in IBDs.

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 show the relationship between the disease extension, endoscopic activity, and the other specialties of IBDs and resolvins. An assessment of RvD1 and RvE1 activity in tissue samples, in addition to the serum values, could reveal precise information in IBDs. We also think that comparison of fecal calprotectin values with serum resolvin concentrations could be more valuable for the assessment of diagnostic and prognostic accuracy of serum resolvins.

Diagnostic strategies with the possibility of therapeutic interventions can be developed by identifying new practical and objective biochemical markers in IBDs. In conclusion, serum RvD1 can be a valuable biomarker for UC with respect to lower serum RvD1 values. The current study about the serum RvD1 and RvE1 values in IBDs should be taken into consideration as preliminary and a first step of future research.

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

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