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The value of fecal calprotectin as a marker of intestinal inflammation in patients with ulcerative colitis

İbrahim Koral ÖNAL[1], Yavuz BEYAZIT[1], Burçin ŞENER[2], Burak SAVUK[1], Diğdem ÖZER ETİK[1], Abdurrahim SAYILIR[1], Erkin ÖZTAŞ[1], Serkan TORUN[1], Yasemin ÖZDERİN ÖZİN[1], Bilge TUNÇ DEMİREL[1], Aysel ÜLKER[1], Ülkü DAĞLI[1]

Department of [1]Gastroenterology, Yüksek İhtisas Teaching and Research Hospital, Ankara
Department of [2]Microbiology, Hacettepe University, School of Medicine, Ankara

Background/aims: *To assess intestinal inflammation, simple, inexpensive and objective tools are desirable in inflammatory bowel disease. This study aimed to evaluate fecal calprotectin as a marker of active disease in ulcerative colitis.* ***Materials and Methods:*** *Sixty patients with a diagnosis of ulcerative colitis and 20 controls were recruited into the study. The disease activity of ulcerative colitis was determined by modified Truelove-Witts criteria and Rachmilewitz endoscopic index. The enzyme-linked immunosorbent assay was used to measure the concentrations of fecal calprotectin. C-reactive protein, erythrocyte sedimentation rate and hemogram were also measured, and inflammatory markers were compared with fecal calprotectin in determining disease activity.* ***Results:*** *Fecal calprotectin concentration in the patients with active ulcerative colitis (n=30) was significantly higher than that in the inactive ulcerative colitis group (n=30) and in the controls (n=20) (95% confidence interval: 232.5 (0.75-625) vs 11.7 (0.2-625), 7.5 (0.5-512) mg/L, p<0.001). There was no significant difference between the patients with inactive ulcerative colitis and controls (p>0.05). The calprotectin concentration was greater in the patients with a more severe clinical index, higher endoscopic activity (>4), elevated C-reactive protein, leukocytosis, and extensive colitis (p<0.05). The areas under the curve of the receiver operating characteristics were 0.817, 0.809, 0.532, and 0.507 for C-reactive protein, fecal calprotectin, leukocyte count, and erythrocyte sedimentation rate, respectively. There was a significant correlation between the fecal calprotectin concentration and the endoscopic activity in ulcerative colitis (r = 0.548, p<0.001).* ***Conclusions:*** *Fecal calprotectin is a useful marker in the diagnosis of active disease and evaluation of clinical and endoscopic activity in ulcerative colitis.*

Key words: Fecal calprotectin, ulcerative colitis, biological marker, fecal marker

İntestinal inflamasyonun bir belirteci olarak fekal kalprotektin'in ülseratif kolitli hastalardaki değeri

Amaç: *İnflamatuvar barsak hastalığında, intestinal inflamasyonun basit, ucuz ve objektif yollarla saptanması istenen bir durumdur. Bu çalışmanın amacı ülseratif kolitte aktif hastalık belirteci olarak fekal kalprotektin düzeylerini değerlendirmektir.* ***Gereç ve Yöntem:*** *Çalışmaya 60 ülseratif kolitli hasta ve 20 sağlıklı kontrol dahil edildi. Ülseratif kolit hastalık aktivitesi modifiye Truelove-Witts kriteri ve Rachmilewitz endoskopik indeksine göre ölçüldü. Fekal kalprotektin konsantrasyonu ölüçümünde ELİSA yöntemi kullanıldı. C-reaktif protein, eritrosit sedimantasyon hızı ve hemogram ölçümleri de yapıldı ve hastalık aktivitesinin saptanması açısından fekal kalprotektin ile bu inflamatuvar belirteçler karşılaştırıldı.* ***Bulgular:*** *Aktif ülseratif kolitli hastalarda (n=30) saptanan fekal kalprotektin konsantrasyonu, inaktif ülseratif kolitli hastalar (n=30) ve kontrol grubuna (n=20) göre anlamlı oranda yüksekti (%95 güven aralığında sırasıyla; 232.5 (0.75-625), 11.7 (0.2-625) ve 7.5 (0.5-512) mg/L, P < 0.001). İnaktif ülseratif kolitli hastalar ve kontrol grubu arasında fark saptanmadı (P > 0.05). Kalprotektin konsantrasyonu, daha ciddi klinik indeksi, yüksek endoskopik aktivitesi (>4), artmış C-reaktif proteini, lökositozu ve ekstensif koliti olan hastalarda daha yüksekti (P < 0.05). Eğri altındaki alan, C-reaktif protein, fekal kalprotektin, lökosit sayımı ve eritrosit sedimantasyon hızı için sırasıyla 0.817, 0.809, 0.532 ve 0.507 olarak bulundu. Fekal kalprotektin konsantrasyonu ile endoskopik aktivite arasında anlamlı ilişki saptandı (r = 0.548, P < 0.001).* ***Sonuç:*** *Fekal kalprotektin, ülseratif kolitli hastalarda aktif hastalık tanısı ve klinik ve endoskopik aktivitenin değerlendirilmesinde yararlı bir belirteçtir.*

Anahtar kelimeler: Fekal kalprotektin, ülseratif kolit, biyolojik belirteç, fekal belirteç

Address for correspondence: Erkin ÖZTAŞ
Department of Gastroenterology, Yüksek İhtisas Teaching and Research Hospital, Kızılay Street: No: 2 Ankara, Turkey
Phone: + 90 312 306 13 34 • Fax: + 90 312 312 41 20
E-mail: droztaserkin@gmail.com

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INTRODUCTION

Assessment of intestinal inflammation in inflammatory bowel diseases (IBDs) remains a difficult challenge. Endoscopy with biopsy sampling, as the most reliable method, is an invasive diagnostic tool. Several markers including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), acid glycoprotein (AGP), and platelet count have been used for the determination of disease activity in ulcerative colitis (UC) (1-7), but none of them is specific for gut inflammation. Clinical indices of disease activity, such as the ulcerative colitis activity index (UCAI) and Truelove-Witts criteria reflect the patient's well-being and quality of life rather than the degree of mucosal inflammation.

A prominent feature of mucosal histology in patients with active IBD is infiltration by neutrophil granulocytes (8). Calprotectin is a major protein of neutrophils and macrophages and it accounts for about 60% of the cytosol of these cells (9). This protein can resist metabolic degradation caused by intestinal bacteria, and it is relatively stable in stools for up to one week at room temperature (10). Several studies have shown that elevated fecal calprotectin (FC) levels correlate with intestinal inflammation, both in adults and children (11-12), and monitoring of FC level has the ability to predict relapse in IBD (13,14).

The aim of the present study was to reveal the role of FC in determining disease activity in UC by looking at relationships among FC, peripheral blood neutrophils, CRP, modified Truelove-Witts activity index, and endoscopic mucosal appearance defined by Rachmilewitz (15,16).

MATERIALS AND METHODS

Sixty patients with UC (age: 49.7±10.7 years) were enrolled in the study, including 21 patients with proctitis, 33 with left-sided colitis, and 9 with extensive colitis. Laboratory parameters included hemoglobin (Hb) (ranges: 14–18 g/dl for men, 12–16 g/dl for women), white blood cell count (WBC) (range: 4,000–10,000/mm^3), neutrophil count (range: 1,800-6400/mm^3), platelet count (range: 150,000–450,000/mm^3), ESR (range: 0-20 mm/hr), and CRP (0-7.44 mg/dl). Rectosigmoidoscopy was performed in all patients. The patients' disease activities were assessed according to the modified Truelove-Witts Severity Index and Rachmilewitz endoscopic index (15,16). The patients with inactive UC had been in clinical remission for at least one year. The control group consisted of 20 subjects (age: 50.8±11.9 years) with no confirmed abnormality in the upper or lower digestive tract. The study was approved by the Local Ethics Committee (report no: B.10.4.ISM.4.06.00.15).

The stool samples of the patients were collected in plastic containers and stored at -70°C until the time of measurement. The stool samples were thawed and 100 mg of the sample measured by the use of a stool sample preparation kit (Roche Diagnostics, Manheim, Germany) was suspended in 5 ml extraction buffer. Following homogenization, the supernatant was diluted to 1:50 and the calprotectin level was analyzed quantitatively by enzyme-linked immunosorbent assay (ELISA) using PhiCal Calprotectin ELISA kit (Immundiagnostik AG, Bensheim, Germany). The results were read as absorbance values obtained at 450 nm. To obtain the calprotectin concentration in stool samples, the estimated value from the standard curves was multiplied by the dilution factor (2500) and the results were expressed as mg/L.

Parametric data are presented as mean±SD, range, and median values, or as indicated otherwise. For categorical variables, percentages were provided. Categorical variables were compared with the X^2 test. A Kolmogorov–Smirnov test was used to evaluate whether FC values followed a normal (Gaussian) distribution. The Mann-Whitney test and unpaired t test were used to assess differences in the laboratory parameters between the groups, and Spearman's correlation was used to analyze the correlation between the parameters. All the p values were two tailed; p values <0.05 were considered statistically significant. The receiver operating characteristics (ROC) (sensitivity and specificity) were assessed by the curve analysis as described by Henderson (17).

RESULTS

There was a significant difference in the calprotectin concentration between the patients with active UC and the patients with inactive UC ($p<0.01$) (Table 1, Figure 1). The calprotectin concentration was greater in the patients with inactive UC than in the controls, but the difference was not significant ($p>0.05$) (Table 1, Figure 1). The patients with active UC had higher levels of CRP, ESR and leukocyte count than the patients with inactive UC and the controls, but the only significant difference was observed in CRP (Table 1). There was no significant difference between the patients

with inactive UC and the controls regarding these parameters (p>0.05) (Table 1). The calprotectin concentration was greater in the patients with a more severe clinical index, a high index of endoscopic activity (EAI), elevated CRP, leukocytosis, and extensive colitis (p<0.05) (Table 2). As shown in Table 3, the concentrations of FC and CRP were significantly correlated with active disease and

Table 1. The clinical and demographic characteristics of the patients with ulcerative colitis and the controls

	Control (n=20)	Inactive UC (n=30)	Active UC (n=30)	P*
Age (years)†	50.8±11.9	50.6±10.3	48.7±11.2	> 0.05
Male/Female (n)	10/10	21/9	23/7	> 0.05
Duration of disease† (year)	-	6.8±4.9	5.4±3.1	> 0.05
Duration of remission† (year)	-	4±2.9	-	> 0.05
Extent of involvement (%)				
Extensive colitis		1 (3.3)	5 (16.7)	
Left-sided colitis	-	16 (53.3)	17 (56.7)	> 0.05
Proctosigmoiditis		13 (43.3)	8 (26.7)	
Therapy (%)				
Mesalazine		30 (100)	25 (83.3)	< 0.05
Mesalazine-Steroid	-	-	3 (10)	
Mesalazine-Steroid-AZA		-	2 (6.7)	
Fecal calprotectin (mg/L)‡	7.5 (0.5-512)	11.7 (0.2-625)	232.5 (0.75-625)	< 0.001
Leukocyte count (/mm^3)†	6592±1547	7239±1540	7498±1804	> 0.05
CRP (mg/dl)‡	3.4 (2-5)	3.4 (0.3-11.5)	11.9 (1.3-34)	< 0.001
ESR (mm/hr)†	12±5	15.3±8.8	19.3±16.1	> 0.05
Thrombocyte count (/mm^3)†	329500±100608	264566±76473	279843±78993	> 0.05

† Mean±SD; ‡ Median (Min-Max); UC: Ulcerative colitis. AZA: Azathioprine. CRP: C-reactive protein. ESR: Erythrocyte sedimentation rate. *Statistically significant if p<0.05.

Table 2. Concentrations of fecal calprotectin and various markers for disease activity in the patients with ulcerative colitis

	Fecal Calprotectin (mg/L)†	P*
Modified Truelove-Witts Class		
Mild (n=22)	332 (0.75-625)	1
Moderate (n=8)	428.7 (6-625)	
Severe	-	
EAI ≥4	232.5 (0.75-625)	< 0.001
EAI <4	11.7 (0.2-625)	
Patients with elevated CRP (>7.44 mg/dl)	332 (8.5-625)	< 0.001
Patients with normal CRP	23.3 (0.2-625)	
Patients with elevated ESR (> 20 mm/hr)	137.2 (0.2-625)	0.119
Patients with normal ESR	51.3 (0.5-625)	
Patients with leukocytosis (> 10^4/mm^3)	285 (73.7-625)	0.008
Patients without leukocytosis	43.6 (0.2-625)	
Patients with neutrophilia (>6400/mm^3)	232.5 (3.1-625)	0.161
Patients without neutrophilia	83 (0.2-625)	
Patients with thrombocytosis (>450,000/mm^3)	51.2 (1.6-285)	0.818
Patients without thrombocytosis	62.3 (0.2-625)	
Extent of involvement		
Extensive colitis	625 (175-625)	
Left-sided colitis	93.2 (0.2-625)	0.012
Proctosigmoiditis	14 (0.5-625)	

† Median (Min-Max); UC: Ulcerative colitis. CRP: C-reactive protein. ESR: Erythrocyte sedimentation rate. EAI: Endoscopic activity index. *Statistically significant if p<0.05.

clinical and endoscopic activity index in UC ($p<0.05$). Only FC showed a significant correlation with the extent of involvement (Table 3). The correlation coefficients between active UC and the concentrations of FC, CRP, ESR, and leukocyte count were 0.540, 0.578, 0.04, and 0.041, respectively (Table 3). The ROC curves for FC (the area under the curve, AUC, 0.809±0.057; $p<0.001$), for CRP (AUC, 0.817±0.059; $p<0.001$), for ESR (AUC, 0.507±0.079; $p>0.05$), and for leukocyte count (AUC, 0.532±0.077; $p>0.05$) are shown in Figure 2. For differentiation of active UC from inactive UC, specificity was highest for CRP and sensitivity was highest for FC (Table 4).

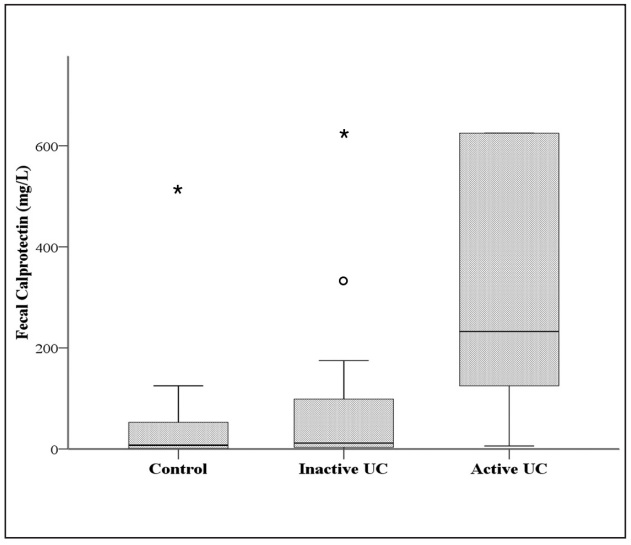

Figure 1. Concentrations of fecal calprotectin in the patients with ulcerative colitis (UC) and the controls. Inactive UC vs the control, $p>0.05$; active UC vs inactive UC, $p>0.05$.

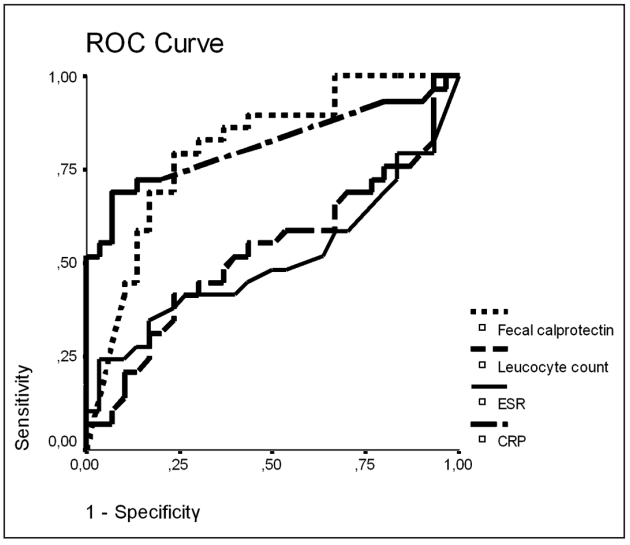

Figure 2. The ROC curve analysis on the abilities of calprotectin, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and leukocyte count to distinguish between active and inactive ulcerative colitis.

Table 3. The Spearman's correlation coefficients for the relation between fecal calprotectin values and various markers for disease activity in patients with ulcerative colitis

	Active UC	Modified Truelove-Witts Class	EAI	Extent of involvement
Fecal calprotectin (mg/L)	0.540*	0.543*	0.548*	0.333*
CRP (mg/dl)	0.578*	0.543*	0.555*	0.124
ESR (mm/hr)	0.04	0.32*	0.188	0.102
Leukocyte count (/mm^3)	0.041	0.087	0.032	0.187
Neutrophil count (/mm^3)	0.179	0.223	0.179	0.093
Thrombocyte count (/mm^3)	0.097	0.081	0.204	0.231

UC: Ulcerative colitis. CRP: C-reactive protein. ESR: Erythrocyte sedimentation rate. EAI: Endoscopic activity index.*Statistically significant ($p<0.05$).

Table 4. Specificity and sensitivity for fecal calprotectin, C-reactive protein, erythrocyte sedimentation rate, and leukocyte count for differentiation of active ulcerative colitis from inactive disease

Marker	Cut-off	Sensitivity (%)	Specificity (%)
Fecal calprotectin (mg/L)	99.5	79.3	76.7
CRP (mg/dl)	3.9	73.3	86.7
ESR (mm/hr)	19.5	43.3	83.3
Leukocyte count (/mm^3)	6950	56.7	46.7

CRP: C-reactive protein. ESR: Erythrocyte sedimentation rate.

DISCUSSION

In the present study, we evaluated FC as a surrogate marker of disease activity in UC. Our results showed that FC was a sensitive and reliable indicator of active disease in patients with UC. FC was also correlated with the degree of clinical activity as well as endoscopic severity. FC was the only parameter that was associated with the more extensive involvement in UC.

The neutrophils are the main sources of reactive oxygen derivatives, active lipids, inflammatory cytokines, and proteases. The presence of calprotectin in feces is directly proportional to neutrophil migration toward the intestinal tract (18). The FC excretion of indium-labeled autologous granulocytes has been suggested as the gold standard test in assessing bowel inflammation in IBD. However, it involves an exposure to radiation and prolonged fecal collection (19). On the other hand, FC measurement is a simple, harmless and noninvasive method. Our results agree with the previous studies that found that FC was a good marker for differentiation of active UC from inactive UC (11-14). Furthermore, FC was as effective as CRP and superior to ESR and leukocytosis as a discriminating parameter. FC, as well as CRP, was significantly correlated with clinical activity, and this finding was consistent with the literature (11,20). The correlation was stronger than the one between ESR and disease activity. These differences may result from the fact that FC is a local and direct marker of intestinal inflammation, whereas ESR and leukocytosis are systemic and indirect indicators of gastrointestinal disease.

Our data revealed a significant association between FC and endoscopic activity. Endoscopic findings have been shown to correlate with FC levels in patients with IBD (20,21). FC concentrations also correlate with histological findings, such that it was proposed to be a more sensitive indicator than endoscopy in evaluating IBD activity (22). It is known that most of the IBD patients in clinical remission have residual inflammation in the colonic mucosa, and some of these develop symptomatic relapse over time (14,23,24). A study showed that FC was useful in predicting impending clinical relapse –especially during the following three months- in IBD (25). The authors also suggested that normalized FC level may be used as a marker for treatment response in patients with IBD (25). However, it was reported that FC may better reflect disease activity in UC than in Crohn's disease (26).

In our study, it was observed that for differentiation of active UC from inactive UC, sensitivity was highest for FC, and the cut-off value was determined to be 99.5 mg/L (Table 4). An optimal calprotectin cut-off point for predicting active IBD is not well defined. As the unit of FC, some studies used µg/g (13,25), whereas others preferred mg/L (20). Another reason may be that the cut-off value differs accordingly to the specific assay used, and direct comparisons would only be valid if the same assay was being used. Furthermore, different cut-off values are suggested for different patient categories, higher for patients with known inflammatory conditions while lower for screening purposes (18). Regarding its sensitivity and specificity and the absence of a universally accepted cut-off value, FC is not a gold standard test but rather an adjunctive method. All clinicians must be careful, since a false-negative FC test would lead to delayed treatment and continuation of symptoms, whereas a false-positive test would lead to an unnecessarily invasive endoscopy with possible complications from colonic perforation.

A large number of neutrophils infiltrate the mucosa in many infective diseases, such that FC is elevated in a number of organic gastrointestinal disorders (27,28). Therefore, FC could not be used as a marker to differentiate between UC and infective colitis. It has been suggested that FC has a good diagnostic precision for separating organic and functional intestinal diseases (29,31). However, we did not observe a significant difference between the patients with inactive UC and the controls in our series. We think that this subject necessitates further studies involving a more homogeneous and well-defined group of patients. FC cannot take the place of an endoscopic examination in the diagnosis of organic disease.

In conclusion, FC is a useful marker in the diagnosis of active disease and evaluation of clinical and endoscopic activity in UC. It can be used as an adjunct to endoscopic examination in clinical practice.

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