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Relationship between fecal calprotectin level and disease activity in patients with hidradenitis suppurativa

Emel Eşer[1] | Burhan Engin[1] | Pelin Yüksel[2] | Bekir Sami Kocazeybek[3] | Zekayi Kutlubay[1] | Server Serdaroğlu[1] | Özge Aşkın[1]

[1]Department of Dermatology, Cerrahpaşa Medical Faculty, Istanbul University, Istanbul, Turkey

[2]Department of Pharmaceutical Microbiology, Faculty of Pharmacy, Bezmi Alem Vakif University, Istanbul, Turkey

[3]Department of Microbiology, Cerrahpaşa Medical Faculty, Istanbul University, Istanbul, Turkey

Correspondence
Emel Eşer, Department of Dermatology and Venereology, Istanbul University, Cerrahpaşa Medical Facuty, Koca Mustafa Paşa Mahallesi, Cerrahpaşa Caddesi No:53, 34096, Fatih/İstanbul, Turkey.
Email: dremeleser@gmail.com

Abstract

Background: Hidradenitis suppurativa is a chronic, inflammatory, recurrent disease with recurrent abscesses, and sinus tract formation leading to scarring. Calprotectin has immunomodulatory, antimicrobial, and antiproliferative properties and is a calcium-binding protein primarily found in the neutrophil cytoplasm. In recent years, a significant relationship between the activity of various diseases and the level of calprotectin has led to the conclusion that there may be a similar relationship in hidradenitis suppurativa.

Objective: To determine the relationship between disease activity and fecal calprotectin levels in patients with hidradenitis suppurativa.

Methods: Fifty patients with hidradenitis suppurativa (case group) who present to the Dermatology and Venerology Department between December 6, 2017, and April 6, 2018, and 36 healthy volunteers (control group) were enrolled in our study. Fecal calprotectin levels we requantitatively calculated using enzyme-linked immunosorbent assay.

Results: In patients with active hidradenitis suppurativa, the level of stool calprotectin was higher than that of patientsin remission, and this difference was statistically significant ($p < .001$). There was no statistically significant correlation between disease stage and fecal calprotectin levels in patients with hidradenitis suppurativa ($p = .14$). Age, sex, smoking and alcohol use, anti-TNF-α treatment, and fecal calprotectin levels were not significantly correlated. In our study, fecal calprotectin levels in patients with active hidradenitis suppurativa were higher than inpatients in remission ($p < .001$).

Conclusion: Fecal calprotectin can beused as a marker of disease activity in hidradenitis suppurativa.

KEYWORDS

calprotectin, disease activity, hidradenitis suppurativa

1 | INTRODUCTION

Hidradenitis suppurativa is a chronic, inflammatory, recurrent disease with recurrent abscesses, sinus tract formation, and scars (Kurek et al., 2012; Zouboulis et al., 2015). Follicular obstruction plays a major role in pathogenesis of hidradenitis suppurativa (acne ınversa) (Wollina, Koch, Heing, Kittner, & Nowak, 2013). Markers indicating inflammation are extremely important in assessing the activity of the disease because there are recurrences in the clinical course of the disease. In the diagnosis and follow-up of inflammatory

diseases, many biochemical parameters can be examined in various body samples.

Calprotectin has been shown to be a sensitive, objective, and noninvasive marker of inflammation in many studies. Calprotectin is a calcium-binding protein with immunomodulatory, antimicrobial, and antiproliferative properties, and is found predominantly in the neutrophil cytoplasm. Some authors have evaluated fecal calprotectin as "intestinal erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)" (Van Rheenen, Van de Vijver, & Fidler, 2010). In diseases such as rheumatoid arthritis, systemic vasculitis, Still disease, Sjogren's syndrome, polymyalgia rheumatic, and ankylosing spondylitis, calprotectin levels are associated with disease activity, such as ESR and CRP. In recent years, a significant relationship between the activity of various diseases and the level of calprotectin has led to the conclusion that there may be a similar relationship in hidradenitis suppurativa. In our study, disease activity and fecal calprotectin levels were investigated in patients with hidradenitis suppurativa.

TABLE 1 Demographic characteristics of patients and controls

	Stage			
	Early stage	Higher stage	Controls	Total
Gender[a]				
Female	16	9	22	47
Male	8	17	14	39
Cigarette[a]				
No smoker	8	4	19	31
Smoker	16	22	17	55
Alcohol[a]				
No alcohol	18	22	29	69
Drinking alcohol	6	4	7	17
Age[b]				
Mean ± SD	31.28 ± 9.91	37.46 ± 11.88	38.88	
Minimum	17	18	17	
Maximum	48	57	68	
BMI[a]				
Mean ± SD	27.38 ± 5.21	29.41 ± 5.49	25.9	
Minimum	18.73	16.33	17.2	
Maximum	38.75	40.58	29.4	

[a]Chi squared.
[b]Mann–Whitney *U*.

2 | MATERIALS AND METHODS

Patients admitted to the Skin and Venereal Diseases Polyclinic between December 6, 2017, and April 6, 2018 who had been diagnosed with new hidradenitis suppurativa clinically or had previously been diagnosed as having hidradenitis suppurativa and had come to at least one checkup between these dates were evaluated. This is a case–control study in hidradenitis suppurativa. The demographic characteristics of all patients included in the study, such as sex, height, weight, body mass index (BMI), additional disease, smoking and alcohol use, history of drugs used for hidradenitis suppurativa, disease duration, disease stage, and background and family information, were interrogated and recorded on the follow-up forms. Those who use at least one standard alcoholic drink (a bottle of beer, a small glass of whiskey or wine) per week were identified as alcohol users.

Patients were evaluated at three stages according to the Hurley stage. Stage 1 patients were accepted as early stage, Stage 2 and 3 patients were regarded as being advanced stage. Patients with inflammatory bowel disease (IBD) such as ulcerative colitis and Crohn's disease in addition to hidradenitis suppurativa were not included in the study. Patients with hidradenitis suppurativa with abscesses, smooth fistulas, erythematous, painful, sensitive papules/nodules/plaques, and other lesions suggesting inflammation were accepted as having active disease. Patients with lesions with no clinical signs of inflammation, remission, or that did not belong to the inflammatory milium-like scars were included in the non-active group. The duration of treatment for antitumor necrosis factor (TNF), the patient receiving the least 3 months, the maximum 1 year. Nine of 50 patients received anti TNF treatment for 3-12 months.

2.1 | Collection and storage of samples

All patients participating in the study and the volunteers in the control group provided fecal samples for evaluation of calprotectin levels. The samples were stored in refrigerator for a maximum of 72 hours at +4°C and were then studied using enzyme-linked immunosorbent assay (ELISA), each with an individual calprotectin tube.

2.2 | Measurement of calprotectin levels

The ELISA kit (Fecal Calprotectin ELISA Kit, FARMASINA, 2017, Turkey) consisted of 96 wells. The ELISA wash fluid was diluted prior

TABLE 2 The relationship between stage of disease and fecal calprotectin level

Calprotectin level					
	Number of patients	Mean (SD)	Minimum	Maximum	*p*[a]
Stage					
Early stage	24	21.61 ± 48.21	3.52	219.23	.14
Higher stage	26	284.20 ± 1,109.64	1.89	5,655.00	

[a]Mann–Whitney *U*.

TABLE 3 Relationship between disease activity and fecal calprotectin level

Calprotectin level					
	Number of patients	Mean (SD)	Minimum	Maximum	p^a
Activity					
Active	25	7.15 ± 4.72	1.89	22.10	<.001
Not active	25	309.17 ± 1,128.34	5.55	5,655.00	

[a]Mann–Whitney *U*.

TABLE 4 Relation of the calprotectin and receiving anti-TNF-α treatment

Calprotectin level					
	Number of patients	Mean (SD)	Minimum	Maximum	p^a
Anti-TNF-α					
Receiving treatment	9	25.36	85.65	4.74	.255
Without treatment	41	187.31	5,655.00	1.89	

[a]Mann–Whitney *U*.

to application. A total of three controls and seven standards were used. In the remaining 86 wells, the fecal samples of the study group and control group were examined.

2.3 | Statistical methods

Descriptive (e.g., mean, median) evaluations of all variables included in the study were calculated. Descriptive statistics are mean (X̄), standard deviation (SD), and minimum and maximum values for continuous data; categorical data are presented together with numeric (*n*) values and percent (%) ratios. The Mann–Whitney test was performed. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, Ver.21) program. In statistical decisions, $p < .05$ was accepted as a sign of significant difference.

2.4 | Financial resource

The financial source of the work was provided by the researcher.

2.5 | Ethics committee approval

The study was approved by the Ethics Committee of Istanbul University Cerrahpaşa Medical Faculty (ethics committee approval number: 83045809-604.01.02).

3 | RESULTS

Fifty patients with hidradenitis suppurativa were included in the study. Of these 25 (50%) had active inflammatory lesions. The remaining 25 (50%) of patients comprised those without remnants of any inflammatory lesions. According to the Hurley stage, 24 (48%) patients were Stage 1 (early stage) and 26 were Stage 2–3 (advanced stage). In addition to 50 patients with hidradenitis suppurativa, a control group of 36 healthy volunteers was included to work for statistical comparison. Nine (18%) patients were receiving anti-TNF treatment (all Stages 2 and 3). Information with demographic characteristics is shown in Table 1.

The fecal calprotectin levels of the patients were compared with the disease stage. The relationship between the disease stage and the level of stool-raised calprotectin is shown in Table 2. There was no statistically significant correlation between disease progression and fecal calprotectin levels in patients with hidradenitis suppurativa ($p = .14$).

When the relationship between disease activity and calprotectin levels was assessed, in patients with active hidradenitis suppurativa disease, the level of calprotectin in stool was higher than in those without disease activity, and this difference was statistically significant ($p < .001$). The relationship between fecal calprotectin level and disease activity in patients with hidradenitis suppurativa is shown in Table 3.

Patients receiving anti-TNF-α therapy were independently evaluated to assess the effect of this treatment on the level of calprotectin. A total of nine patients, all in advanced stage (Stage 2 or 3), received anti-TNF-α therapy. The relationship between fecal calprotectin levels and the use of anti-TNF-α drugs in patients with hidradenitis suppurativa is shown in Table 4. There was no significant difference in fecal calprotectin levels between patients using anti-TNF-α and those who did not ($p = .255$).

4 | DISCUSSION

Calprotectin measurements were obtained either from feces or from serum material in various disease settings, and therefore were representative of different stages and clinical implementations. It has been reported that calprotectin measurements were correlated with

different types of malignancies and their staging. In colorectal carcinoma, it was reported that T3 or T4 stages of disease were associated with higher levels of fecal calprotectin levels in comparison with the T1 or T3 disease (Lehmann et al., 2014). In endometrial carcinoma, increased plasma calprotectin values were reported to be indicative of high International Federation of Gynecology and Obstetrics scores and poor survival rates (Ni Bhriain et al., 2009). Nevertheless, it is reported that calprotectin levels are higher in patients with endometrial carcinoma, in comparison with those diagnosed as having invasive carcinoma of the ovary, borderline carcinoma of the ovary, or benign ovarian tumors (Ni Bhriain et al., 2009).

In a study performed by Alempijevic et al. in 2004, patients with hepatic cirrhosis were evaluated and the association between calprotectin levels and the stages of the disease was investigated. This study used Child–Pugh scoring and the Model for End-stage Liver Disease to stage hepatic disease. There was no significant correlation between calprotectin levels and the disease stage (Alempijevic et al., 2014). In another study with 137 patients with primary sclerosing cholangitis, calprotectin was measured from the bile and the severity of the disease was scored using Mayo Risk Score (MRS). This study reported that biliary calprotectin measurements were correlated with noted MRS (Voigtlander et al., 2014). In our study, patients with hidradenitis suppurativa were evaluated in three different stages according to the Hurley staging system. Stage 1 patients have early stage disease, and Stage 2 and 3 patients have advanced stage disease. Statistical analysis revealed no significant association between fecal calprotectin values and disease stage. It is important to note here that Hurley staging is not correlated with disease activity in contrast with most other staging tools. Despite an important number of studies underlying the association between fecal calprotectin levels and disease stage, we found no such correlation. This may be due to the fact that Hurley staging is incapable of evaluating disease activity (Zouboulis et al., 2017). Although there is no correlation between Hurley staging and fecal calprotectin or inflammation, disease activity might provide a better insight into the inflammatory status.

When the patients were evaluated by disease activity instead of Hurley stages, it was reported that patients with active hidradenitis suppurativa had higher levels of fecal calprotectin in comparison with those with lower disease activity. There is a lack of published studies evaluating the association between disease activity and calprotectin measurements in patients with hidradenitis suppurativa; however, similar studies have been conducted in patients with other inflammatory conditions. When considered as a predictor of inflammation, it is reasonable to expect that fecal calprotectin could be used in patients with hidradenitis suppurativa in order to evaluate disease activity.

A number of studies were performed in order to evaluate the association of disease activity and calprotectin levels in patients with rheumatologic diseases. A study compared fecal calprotectin levels of 51 patients with ankylosing spondylitis and 43 healthy controls (Duran et al., 2016). This study concluded that the fecal calprotectin levels in patients with ankylosing spondylitis were higher whereas serum calprotectin measurements were not statistically different in comparison to those measured for healthy controls (p = .233).

Fecal calprotectin values have long been used in order to evaluate disease activity in patients with gastrointestinal symptoms particularly IBD. In a study, colonoscope examinations were performed for 44 patients with Behçet's disease and 25 of them revealed ulcerations. Patients with colonoscopically proven ulcers had significantly higher levels of fecal calprotectin in comparison with the other patients with Behçet's disease (Kim et al., 2017). Studies with patients with ulcerative colitis showed that fecal calprotectin might be a good indicator of mucosal improvement (Yamaguchi et al., 2016). Nevertheless, fecal calprotectin measurements give physicians a clue as to whether gastrointestinal disease is of inflammatory origin. The use of calprotectin values provides an alternative to colonoscope examinations.

The impact of anti-TNF-α therapy on calprotectin levels was evaluated in various disease settings, particularly in IBD. It has been suggested that fecal calprotectin could be a good indicator of remission in patients with Crohn's disease using anti-TNF-α (Boschetti et al., 2015). A study evaluated the role of fecal calprotectin measurements in 72 patients with IBD using anti-TNF-α (20 patients with ulcerative colitis and 52 with Crohn's disease) and reported that the benefit of this marker was better pronounced while predicting if an endoscopically reported lesion would be permanent, rather than predicting clinical remission (Tursi, Elisei, Picchio, Giorgetti, & Brandimarte, 2015). A study by Molander et al. published in 2012 concluded that fecal calprotectin measures were of predictive value in mucosal improvement of patients with IBD using anti-TNF-α (Molender et al., 2012). In our study, nine patients among those with advanced stage disease were on anti-TNF-α therapy. Fecal calprotectin values were not significantly different between patients on anti-TNF-α and the other patients (p = .255). On the other hand, it is difficult to conclude if the calprotectin levels were associated with anti-TNF-α, because the sample was too small. Besides since the initial fecal calprotectin levels of our patients prior to anti-TNF-α, it was not possible to compare the initial and final calprotectin levels.

It is possible to measure calprotectin levels both in feces and serum. In our study, we measured fecal calprotectin levels. There are, on the other hand, numerous studies that preferred to measure calprotectin in serum. In one of those, 33 patients with polymyalgia rheumatica and 10 patients with temporal arteritis were followed for 3 years and it was reported that calprotectin levels were correlated with levels of acute phase reactants, particularly the ESR. Furthermore, it has been shown that calprotectin levels dropped following systemic prednisolone therapy (Brun, Madland, Gran, & Myklebust, 2005). In a study performed in 2011 by Aochi et al., calprotectin was measured in the sera of patients with psoriasis vulgaris, pustular psoriasis, psoriatic arthritis, atopic dermatitis, and healthy controls. Serum calprotectin levels were higher in patients with psoriatic arthritis and pustular psoriasis in comparison with healthy controls. Moreover, it was emphasized that the serum calprotectin levels were not associated with body surface area (Aochi et al., 2011).

Several biochemical parameters are measured in numerous tissues and materials during the diagnosis and follow-up of inflammatory diseases. Recently, it has been reported in various studies that calprotectin is a sensitive, objective, and noninvasive biomarker. In

some of these studies, calprotectin levels were found to be correlated with disease activity in various disease settings. According to our data, we suggest that fecal calprotectin measurement is of predictive importance while evaluating disease activity, although it is not directly associated with disease staging in hidradenitis suppurativa.

CONFLICT OF INTEREST

None declared for all the authors.

ORCID

Emel Eşer https://orcid.org/0000-0001-7333-3998

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