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The Role of Faecal Calprotectin in the Evaluation of Disease Activity in Spondyloarthritis Patients: A Cross-sectional Study

Spondiloartrit Hastalarında Hastalık Aktivitesinin Değerlendirilmesinde Fekal Kalprotektinin Yeri: Bir Kesitsel Çalışma

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ABSTRACT

Aim: Spondyloarthritis (SpA) is a group of chronic, inflammatory diseases characterized by involvement of the axial and peripheral joints, as well as extra-articular manifestations. It is important to assess disease activity (DA) for treatment and follow-up. Although there are commonly used scoring systems, they may lack sensitivity and specificity in determining DA. One potential biomarker for DA is calprotectin, a calcium-binding protein released from monocytes and macrophages during inflammation. Faecal calprotectin (fCal) is frequently used in the diagnosis and follow-up of inflammatory bowel diseases. Significant intestinal inflammation has also been shown in active SpA. The aim of this study was to test the utility of fCal as a marker of DA.

Materials and Methods: The study included patients with ankylosing spondylitis and psoriatic arthritis, admitted to our hospital between October 2019 and February 2020. Patients with gastrointestinal symptoms were excluded. Demographic data, DA scores, and laboratory test results were obtained from patient records. The correlation between fCal levels and DA parameters was analysed.

Results: fCal levels were correlated with the erythrocyte sedimentation rate (ESR) but not with C-reactive protein levels. Among the DA scores, only the AS Disease Activity Score (ASDAS)-ESR was found to be correlated. Non-steroid users and cigarette smokers exhibited lower levels of fCal.

Conclusion: fCal levels were found to be associated with ESR but not with C-reactive protein levels. fCal is only correlated with ASDAS-ESR, and lower fCal levels were observed in those using non-steroidal drugs and smokers.

Keywords: Ankylosing spondylitis, biomarker, fecal calprotectin, inflammatory bowel disease, spondyloarthritis

ÖZ

Amaç: Spondiloartritler (SpA), aksiyal ve periferik eklem tutulumu ve ekstra-artiküler bulgularla seyreden kronik, enflamatuvar bir hastalık grubudur. Hastalık aktivitesinin (HA) değerlendirilmesi tedavi ve izlem açısından önemlidir. Güncel pratikte HA'yı değerlendirmede kullanılan çeşitli klinik ölçekler ve laboratuvar testleri mevcuttur. Ancak bu laboratuvar belirteçlerinin HA'yı belirlemedeki duyarlılık ve özgüllükleri istenilen seviyede değildir. Kalprotektin, enflamasyon halinde monosit, makrofajlardan salınan kalsiyum bağlayıcı bir proteindir. Enflamatuvar bağırsak hastalıklarının tanı ve takibinde sıkça kullanılmaya başlanan bir biyobelirtecidir. SpA'da de ciddi oranda bağırsak enflamasyonu gösterilmiştir. Bu çalışmada fekal kalprotektinin (FK) HA belirteci olarak SpA'de kullanılabilirliğinin test edilmesi amaçlamıştır.

Gereç ve Yöntem: Ekim 2019-Şubat 2020 tarihi arasında Ege Üniversitesi Tıp Fakültesi Hastanesi Romatoloji polikliniğine başvuran ankilozan spondilit (AS) ve psoriatik artritli (PsA) hastalar dahil edildi. Enflamatuvar bağırsak hastalığı olan ya da gastrointestinal semptomları olanlar dahil edilmedi. Demografik veriler, hastalığa ilişkin bilgiler, HA skorları ve laboratuvar tetkikleri hasta kayıtlarından elde olundu. Tüm olgularda FK testi çalışıldı. Ardından FK düzeyleri ile hastalık aktivite parametreleri arasındaki korelasyon incelendi.

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Bulgular: FK seviyesi, eritrosit sedimantasyon hızı (ESH) ile ilişkiliyken C-reaktif protein düzeyleri ile ilişkili bulunmadı. HA ölçeklerindense yalnızca ankilozan spondilit hastalık aktivite skoru (ASDAS)-ESH ile ilişkili bulundu. Non-steroid ve sigara kullananlarda FK düzeyi daha düşük saptandı.

Sonuç: FK seviyesi, ESH ile ilişkili bulunurken C-reaktif protein düzeyleri ile ilişki göstermemiştir. FK, sadece ASDAS-ESH ile ilişkilidir ve non-steroid ilaçlar ve sigara kullananlarda FK düzeyinin daha düşük olduğu gözlemlenmiştir.

Anahtar Kelimeler: Ankilozan spondilit, biyobelirteç, fekal kalprotektin, enflamatuvar bağırsak hastalığı, spondiloartrit

INTRODUCTION

The definition of spondyloarthritis (SpA) refers to a group of chronic inflammatory rheumatologic diseases with common clinical features and genetic risk factors, all of which may involve axial or peripheral joints characterized by new bone formation[1]. The diseases considered as forms of SpA include ankylosing spondylitis (AS), non-radiographic axial SpA (nr-axSpA), peripheral SpA, psoriatic arthritis (PsA), arthritis associated with inflammatory bowel disease (IBD), reactive arthritis (formerly known as Reiter syndrome) and childhood-onset SpA[2,3]. Although AS and IBD are distinct diseases, there is clinical and genetic evidence supporting an overlapping pathogenic relationship[4]. There are studies showing that 5-10% of AS patients have concomitant IBD and that 25-50% of asymptomatic AS patients may have macroscopic and 50-60% may have microscopic intestinal inflammation[5,6]. PsA is also associated with extra-articular symptoms including inflammatory bowel disease, but these symptoms are rarer than in AS[7]. The prevalence of IBD associated with PsA is reported to be 3.3%[8]. Compared to patients with psoriasis and irritable bowel disease, patients with PsA have been shown to have more lymphocytic cell infiltration in the duodenal epithelium and villi[9].

Calprotectin is a proinflammatory protein produced mainly by neutrophils, monocytes and macrophages in a calcium-dependent manner in response to damage at the site of inflammation[10]. Calprotectin can be detected in various tissues and body fluids such as blood, mucosal epithelium, synovium and feces[11,12]. Faecal calprotectin (fCal) levels have been shown to increase in IBD patients as a direct result of increased neutrophil migration across the inflamed mucosa in the intestinal lumen[12]. Moreover, in individuals with IBD, fCal levels correlate with the endoscopic and histologic grade of intestinal inflammation and are used in the diagnosis and monitoring of the disease[13]. Due to its proinflammatory properties, calprotectin levels have also been studied in rheumatologic diseases[14]. Serum calprotectin levels have been shown to predict relapse in rheumatoid arthritis, PsA and anti-neutrophil cytoplasmic antibody-associated vasculitis[14,15]. In SpA, there are many publications supporting that both serum and fCal are significantly increased and correlated with disease activity[14,16,17].

This study aimed to test the usability of fCal levels as a marker of disease activity in SpA. With this aim, fCal levels were measured in SpA patients and the correlation of these levels with disease activity scales in use was examined.

MATERIAL AND METHODS

Patient Selection

Our single-center, cross-sectional study was conducted in consecutive patients admitted to the Internal Medicine-Rheumatology outpatient clinics of Ege University Faculty of Medicine Hospital between October 2019 and February 2020. Patients who met the diagnosis of AS[18] according to the criteria of the Assessment of Spondyloarthritis International Society and PsA[19] according to the Classification of Psoriatic Arthritis Study Group, were ≥18 years old and gave written informed consent to participate were included in our study. Patients with gastrointestinal symptoms (diarrhea, abdominal pain, bloody-mucous stools), IBD in themselves or their families, malignancy or active infection were excluded. The approval for the study was received from the Ege University Faculty of Medicine Clinical Research Ethics Committee (decision no: 04.09.2019_19-9T/60, date: 04.09.2019). The study was performed in accordance with the principles of the Declaration of Helsinki.

Characteristics Related to the Disease

Bath ankylosing spondylitis disease activity index (BASDAI) was used as a tool to assess disease activity in patients with AS[20]. In addition, the ankylosing spondylitis disease activity score (ASDAS), which was thought to reflect inflammatory processes better than the BASDAI and which was created by integrating [C-reactive protein (CRP)] or [erythrocyte sedimentation rate (ESR)] into some parameters of the BASDAI (questions two, three and six of the scale), was also used[21,22]. According to the BASDI scale, those with BASDI<4 were classified as inactive and those with BASDI≥4 as active disease. According to ASDAS, ASDAS<1.3=inactive disease; 1.3≤ASDAS<2.1=low activity; 2.1≤ASDAS<3.5=high activity; ASDAS≥3.5=very high activity disease[23]. (ESR, mm/hour) and (CRP, mg/L) levels, which are commonly used to measure disease activity in clinical practice, were obtained from the records of the patient file, from the notes of the visit of the period when the stool sample was taken.

Bath ankylosing spondylitis disease functional index was used as a chronicity score indicating the level of functional limitation[24]. Demographic data (age, gender, disease duration, current treatment, smoking) were also obtained from outpatient follow-up files.

Laboratory Methods

Fecal Calprotectin Measurement

Participants were asked to give their stool samples during their hospital visits and to bring them to the laboratory without waiting. fCal in stool samples was analyzed by lateral flow method in Ege University Medical Faculty Clinical Biochemistry Laboratory (CalFast® XT Eurospital Diagnostic, Italy). The measurement range was 50-1005 mg/kg and a cut-off value of 70 mg/kg was used. Values <70 mg/kg were considered negative and values above 70 mg/kg were considered positive (for statistical evaluation, results given as <50 and ≥1005 mg/kg in laboratory results were recorded as 49 and 1006 mg/kg, respectively).

Statistical Analysis

In summarizing the data obtained from the study, mean ± standard deviation or median, minimum and maximum values were presented in tables depending on the distribution for continuous (numerical) variables. Categorical variables were summarized as number and percentage. Normality of numerical variables was evaluated by the Shapiro-Wilk, Kolmogorov-Smirnov and Anderson-Darling tests. To compare the differences of categorical variables between groups, the Pearson's chi-square test was used in 2x2 tables with an expected number of observations of five or more, and the Fisher's exact test was used when the expected number of observations was less than five. In comparing numerical variables between two independent groups, the Mann-Whitney U test was applied when numerical variables did not show normal distribution. The correlation of fCal, disease activity scores and acute phase reactants was evaluated by the Spearman's correlation analysis. IBM® SPSS® version 25.0 software was used for statistical analysis. In the analyses, the limit of statistical significance was accepted as $p<0.05$.

RESULTS

A total of 100 patients, including 88 (88%) diagnosed with AS and 12 (12%) with PsA, were included in the study. 62% of the patients were male. The mean age was 44±11.06 (19-67) years and the median disease duration was 9 (10-35) years. Extra-articular involvement was anterior uveitis in 13 cases and 39 patients were active smokers. The distribution of disease characteristics laboratory and disease activity scale scores according to all groups and diagnoses is summarized in Table 1. The median fCal level in the entire group was 72.5 mg/kg (49-1006) and its positivity (>70mh/kg) was 51%.

While 79 (79%) of the patients included in the study were using non-steroidal anti-inflammatory drugs (NSAIDs), 73 (73%) patients were using conventional synthetic disease modifying anti-rheumatic drugs (sulfasalazine 32 patients, methotrexate 32 patients, leflunomide 9 patients) and 38 (38%) patients were using anti-TNF agents. Corticosteroid use was present in only 3 (3%) patients.

When we examine the distribution of the patients according to activity scores, 28% of the patients were active according to BASDAI, 56% according to ASDAS-CRP, and 44% had high and very high disease activity according to ASDAS-ESR. The distribution of patients according to disease activity scales is summarized in Figure 1.

Table 1. Distribution of age, disease duration, disease assessment scores, acute phase responses and fecal calprotectin levels in all groups and diagnostic subtypes

	All group	AS	PsA
[§]Age (year)	44 (11.06)	44 (10.84)	44 (13.09)
[†]Disease duration (year)	9 (10-35)	8 (0.1-35)	11.5 (1-26)
[†]fCal level (mg/kg)	72.5 (49-1006)	76.5 (49-1006)	49 (49-470)
fCal positivity (%)	51	52.2	41.6
[†]BASDAI	2.29 (0-8.9)	2.25 (0-7.2)	2.36 (0-8.9)
BASFI	1.75 (0-8)	1.75 (0-8)	1.61 (0-7.29)
[§]ASDAS-CRP	2.24 (0.96)	2.22 (0.91)	2.40 (1.31)
[§]ASDAS-ESR	2.11 (0.98)	2.07 (0.94)	2.38 (1.25)
[†]CRP (mg/L)	5.06 (0.3-50)	5.78 (0.3-46.30)	4.54 (1.51-50)
[†]ESR (mm/h)	13 (1-91)	13 (1-91)	11.5 (3-89)

[§]Mean (SD), [†]median (min-max), BASDAI: Bath ankylosing spondylitis disease activity index, fCal: Faecal calprotectin, BASFI: Bath ankylosing spondylitis functional index, ASDAS: Ankylosing spondylitis disease activity score, CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate, AS: Ankylosing spondylitis, PsA: Psoriatic arthritis

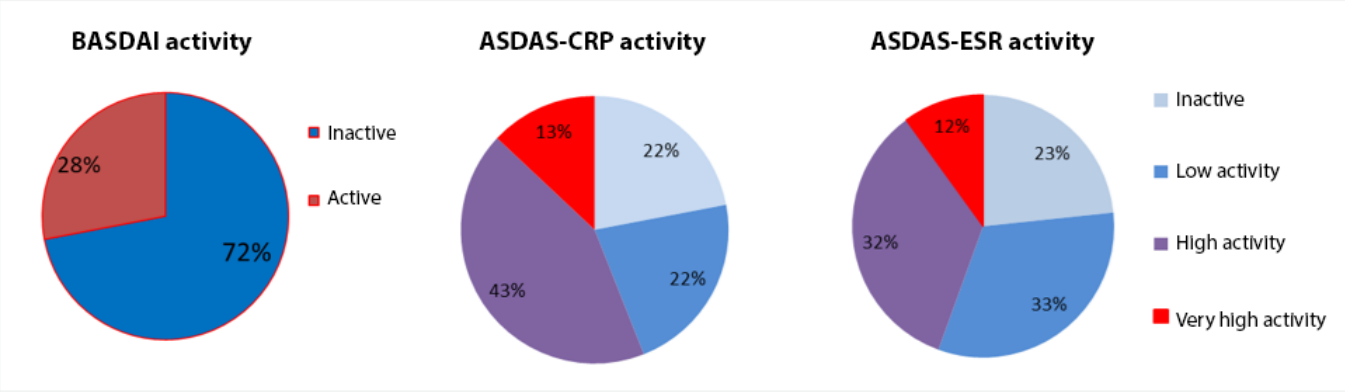

Figure 1. Distribution of disease activity according to BASDAI, ASDAS-ESR and ASDAS-CRP

BASDAI: Bath ankylosing spondylitis disease activity index, ASDAS: Ankylosing spondylitis disease activity score, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

Correlation of Fecal Calprotectin with Disease Activity

While fCal levels showed a significant correlation with ESR, which is one of the laboratory parameters (r=0.289, p=0.003), it did not show a significant correlation with CRP levels (p=0.403). Among the composite disease activity indices, only ASDAS-ESR was found to have a significant relationship with fCal levels (r=0.218, p=0.029). No statistically significant relationship was found between fCal levels and BASDAI and ASDAS-CRP scores (p=0.420, p=0.361, respectively). It could not be evaluated whether the fCal and ESR, fCal and ASDAS-ESR relationships found in the whole group continued in the subgroups (AS and PsA) because the distribution of patients in the subgroups was unbalanced (88AS, 12 PsA) and the number was not sufficient, especially in the PsA group.

In addition, the effects of medications and smoking on fCal levels were also reviewed as possible confounding factors. fCal positivity was detected at a significantly lower rate in patients using NSAIDs than in those not using NSAIDs (45.57% vs. 71.42%, respectively; p=0.035). However, when the relationship between NSAID use alone and fCal positivity was evaluated, no statistically significant relationship was detected (p=0.310). No significant relationship was detected when the use of drugs in the other treatment group [sulfasalazine, methotrexate, leflunomide, anti tumor necrosis factor (TNF)] and fCal were tested. fCal positivity was found to be significantly lower in active smokers than in non-smokers (38.46% vs. 59.02%, respectively; p=0.045).

DISCUSSION

In this study, the relationship between fCal levels and disease activity in SpA patients was examined. According to the data obtained, the median fCal level was 72.5 mg/kg (49-1006) and 51% of the results were positive. In the literature, fCal positivity in SpA patients is reported in a wide range, between 38% and 72% (B16,25-27). As expected, this may be due to differences in the methods, kits and limit values used to measure fCal levels, racial characteristics that vary depending on the geographical region where the study was conducted, or differences in the patients' nutritional habits and intestinal microbiota. In this regard, since the study conducted by Ercalik et al.[28] was conducted in our country, it can be assumed that it was conducted in patient populations with similar genetic characteristics and even similar environmental and nutritional habits in terms of region. However, in this study, fCal positivity in AS patients is given as 11.3%, which seems to be quite low compared to our results. Considering that the patient age (44±11.06 in our study versus 43.90±13.42 in the other study) and the use of biological agents (38% in our study versus 40% in the other study) were similar in both studies, it may be possible to suggest that the main reason for the difference is the use of NSAIDs. Likewise, 79% of the patients in our study used NSAIDs, while this rate was 33% in the study by Ercalik et al.[28] NSAIDs are the first and most frequently used drug group in the treatment of SpA. NSAIDs have been shown to increase intestinal permeability and inflammation in healthy individuals[30]. However, the results regarding the relationship between NSAIDs and fCal positivity are contradictory[25-27,31,32]. It has been reported that fCal levels are higher in patients who regularly use NSAIDs[26] and that a 3-week drug interruption causes a decrease in fCal levels[31]. On the contrary, there are also studies suggesting that NSAID use does not affect the level of fCal[25,27,32]. In our study, we found that fCal positivity was more frequent in NSAID users (fCal was positive in 45.6% of NSAID users and 71.4% of non-NSAID users, p=0.035). Of course, these different results in the literature may be due to

differences in other drugs used concomitantly with NSAIDs and differences in patient cohorts depending on the inclusion/exclusion criteria. In this context, we think that more detailed and prospective studies are needed to examine the relationship between NSAID use and fCal levels.

Another drug group frequently used in the treatment of SpA is biological agents, especially TNF alpha inhibitors[29]. There are some studies showing that fCal levels may decrease with the use of TNFα inhibitors[26,33], but there are also studies in which this was not observed[25,27]. Although we could not show a significant relationship between the use of TNFα inhibitors and the level of fCal in our study, it is not possible to comment on this issue since the number of patients was not sufficient.

In the previous literature, it has been shown that there is a correlation between fCal level and CRP and/or ESR, and therefore, it has been suggested that fCal may be an auxiliary laboratory parameter for disease activity[26,34,35]. In our study, a significant correlation was observed between fCal levels and ESR (r=0.289, p=0.003), supporting that fCal may be related to inflammatory processes. However, in contrast to ESR, we did not detect a significant correlation with CRP in our study (p=0.403). This suggests that fCal may be more strongly associated with certain inflammatory markers, but may not be equally associated with all biomarkers. Unlike ESR, CRP is a protein produced by the liver and is not affected by age, gender, erythrocyte count and serum protein levels[36]. Therefore, the fact that the level of fCal is correlated with ESR while it is not correlated with CRP may be due to the fact that the level of fCal increases as a result of chronic subclinical intestinal inflammation rather than disease activity. The fact that CRP increases more rapidly in acute inflammation and decreases more rapidly when inflammation subsides is also supportive of this.

Similar to acute phase responses, the results of studies examining the correlation of fCal with composite disease activity scales also contain contradictions. Contrary to studies showing that fCal level and BASDAI were correlated[25,34], we did not find a correlation between fCal and BASDAI. Similarly, we did not find a correlation between fCal and ASDAS-CRP, another composite disease activity scale. Similar to our data, Simioni J et al.[27] also failed to show a significant relationship between fCal level and CRP and ASDAS-CRP, although many studies support the opposite[16,25,26]. On the other hand, we found a significant association between fCal level and only ASDAS-ESR among the disease activity scores. We think that the reason why fCal was associated with ASDAS-ESR while it was not associated with ASDAS-CRP was the indirect effect of ESR and CRP, which we used to calculate these scores.

Finally, when the relationship between smoking and inflammation is considered, it is known that smoking may have both proinflammatory and anti-inflammatory activity. Previous studies have demonstrated that disease activity increases with smoking in autoimmune diseases such as systemic lupus, Crohn's disease and Graves' disease[37-39]. In contrast, active smoking has been shown to reduce oral aphthae in Behçet's disease (BD) and to be inversely associated with disease activity in ulcerative colitis (UC)[40,41]. In this study, similar to patients with BD and UC, we found a negative correlation between active smoking and fCal positivity (p=0.045). It is known that intestinal BD and inflammatory bowel diseases show similar characteristics in terms of genetic background, pathogenesis, clinical features and response to anti-TNF therapies[42]. Therefore, our finding of a relationship between smoking and fCal level may be due to the fact that intestinal inflammation in SpA shows similar pathogenetic features with inflammatory bowel diseases and thus with BD.

Study Limitations

The most important limitation of our study is that its cross-sectional nature limits the evaluation of the effects of fCal levels on long-term disease progression. In addition, the fact that it was conducted in a single center covering a specific geographical region limits the generalizability of the findings to different populations and ethnic groups. Other limitations include the lack of a control group, the lack of scoring systems such as PsARC, which is more specific for PsA activity, and the lack of restrictions on the use of NSAIDs before stool sampling. These limitations should be taken into consideration when interpreting the results of our study and guiding future research. On the other hand, the inclusion of PsA patients, the exclusion of patients with The gastrointestina symptoms and concomitant IBD, and the comparison of different disease activity indices can be considered as strengths of the study. Our findings may serve as a basis for deepening and expanding research in this field.

CONCLUSION

The results of this study support the use of fCal levels in SpA patients as a potential biomarker for a more sensitive and specific assessment of disease activity as an indicator of inflammation. This may contribute to more effective management of treatment plans, especially given its significant correlation with ESR. However, the finding that fCal was not correlated with CRP suggests that this biomarker may not be a universal indicator for all patients and should be evaluated on a patient-by-patient basis. Larger and longer-term studies are needed to confirm the findings and integrate fCal into clinical practice. In particular, studies examining how fCal levels change under different treatment strategies and how they affect disease progression would be useful.

Ethics

Ethics Committee Approval: The approval for the study was received from the Ege University Faculty of Medicine Clinical Research Ethics Committee (decision no: 04.09.2019_19-9T/60, date: 04.09.2019). The study was performed in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Written informed consent to participate were included in our study.

Authorship Contributions

Concept: E.S., B.B., F.Y.Z., Design: E.S., B.B., F.Y.Z., Data Collection or Processing: E.S., N.G.U., F.Y.Z., Analysis or Interpretation: E.S., N.G.U., F.Y.Z., Literature Search: E.S., B.B., N.G.U., Writing: E.S., F.Y.Z.

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