

Evaluation of Calprotectin Levels in First-Degree Relatives of Patients with Ulcerative Colitis

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Abstract: Recent studies have shown the diagnostic value of fecal as well as serum calprotectin in predicting the severity and activity of inflammatory bowel disease. Given the strong familial and inherited predisposition to inflammatory bowel disease, it is assumed that changes in calprotectin levels are also influenced by familial predispositions. Therefore, the present study aimed to evaluate the level of fecal calprotectin in patients and their first-degree relatives in order to determine the relationship between changes in this marker and its possible familial orientation. The study participants were the first-degree relatives ($n = 100$) of the patients ($n = 33$) with the definitive diagnosis of ulcerative colitis who referred to Rasoul-e-Akram hospital in 2018 and 2019. The fecal value of calprotectin was assessed using the ELISA method in both patients and the relatives. Fecal calprotectin level in patients was estimated to be $232.09 \pm 44.16 \mu\text{g/g}$. Fecal calprotectin level in the parents was $86.06 \pm 12.66 \mu\text{g/g}$, in siblings was $58.02 \pm 7.24 \mu\text{g/g}$ and in the patient's children was $47.40 \pm 4.77 \mu\text{g/g}$. Fecal calprotectin levels were not affected by baseline indices such as gender, age, or BMI (either in patients or their relatives) and therefore these baseline factors had no effect on fecal calprotectin levels. Although fecal calprotectin levels are significantly longer in patients with ulcerative colitis than in healthy controls, the higher level of this marker among first-degree relatives of patients than healthy individuals also indicates the inherited tendency of changes in this marker in terms of high risk of disease in first-degree relatives of patients. These changes in fecal calprotectin levels will be independent of gender, age, and BMI

Keywords: Evaluation, Calprotectin Levels, Ulcerative Colitis

1. Introduction

Ulcerative colitis is a type of inflammatory bowel disease that has a prevalence of 63.6 per 100,000 people and is usually mild to moderate in more than 80% of patients [1]. The incidence of this disease is about 6 per 100,000 people [2], which varies in different geographical areas. About 1.4 million people in the United States and 2.2 million in Europe suffer from this disease, and various risk factors such as smoking and appendectomy have been suggested as factors that increase the risk of ulcerative colitis [3]. Of course, it should be noted that the risk factors for ulcerative colitis in Iran are similar to those risk factors that have already been reported in other countries [4]. Ulcerative colitis is mostly mild; but in severe cases, it can

cause stress and anxiety [5]. This is so important that in some areas, despite treatment, 17% of patients with severe disease die [6] shows the importance of determining the severity of the disease in order to carry out proper treatment planning so that we can reduce morbidity and mortality and the overall burden of the disease. The most important issue in patients with this disease is the severity of gastrointestinal inflammation due to the recurrence and remission periods of the disease, and in this regard, some leukocyte markers such as calprotectin released by neutrophils in the gastrointestinal tract, both in the blood and feces are helpful [7]. Calprotectin is a calcium binding protein that is found mainly in neutrophils and to a lesser extent in monocytes and reactive macrophages [8]. It belongs to a subgroup of proteins that is associated with acute/chronic

inflammatory disorders and a number of malignancies [8, 9].

This inflammatory marker can be used as a non-invasive measurable indicator of gastrointestinal inflammation in patients with ulcerative colitis, and at the same time it can be used to monitor the therapeutic results and follow-up of patients. In this regard, the sensitivity of this marker ranged between 94 and 100% based on the underlying conditions of the patients [10-12]. Due to the genetic characteristics of ulcerative colitis, there is a possibility of involvement in first-degree relatives of these patients [13] and thus the earlier diagnosis of disease in relatives, the better prognosis of disease in the relatives of the patients can be expected. Additionally, Due to its non-invasiveness and high sensitivity of calprotectin, this marker can be a good candidate for screening in close asymptomatic relatives of patients with ulcerative colitis. Accordingly, and considering the importance of the matter, in this study we decided to investigate the level of calprotectin in first-degree relatives of patients with ulcerative colitis.

2. Materials and Methods

In this descriptive cross-sectional study, the aim was to evaluate the level of calprotectin in first-degree relatives of patients with ulcerative colitis. The study participants were the first-degree relatives of the patients with the definitive diagnosis of ulcerative colitis who referred to Rasoul-e-Akram hospital in 2018 and 2019. Exclusion criterion was individuals' dissatisfaction with sampling for calprotectin or history of inflammatory disorders or using anticoagulants. The baseline characteristics including demographics (gender and age) were medical history were collected by interviewing the patients and their relatives. The body mass index was determined by weight in kilograms divided by the square of the height in meters. The fecal value of calprotectin was assessed using the ELISA method in both patients and the relatives.

Descriptive analysis was used to describe the data, including mean \pm standard deviation (SD) for quantitative variables and frequency (percentage) for categorical variables. Chi square test, independent t test and Mann-Whitney U test were used for comparison of variables. The association between the quantitative indices was tested by the Pearson's or Spearman's test. For the statistical analysis, the statistical software IBM SPSS Statistics for Windows version 22.0 (IBM Corp. Released 2013, Armonk, New York) was used. P values <0.05 were considered statistically significant.

3. Results

In the present study, a total of 33 patients with ulcerative colitis and 100 relatives of their degree were included in the study. The mean age of men and women was 42.84 ± 16.77 years and 40.46 ± 13.97 years, respectively with no significant difference ($p = 0.40$). The mean age of parents, siblings and children was 56.38 ± 13.47 years, 35.52 ± 5.75 years and 27.48 ± 4.99 years, respectively. Also, the mean BMI in men and women was

25.89 ± 2.58 kg/m² and 27.07 ± 2.61 kg/m², respectively, which was significantly higher in women ($P = 0.027$).

The mean level of fecal calprotectin concentration in patients was 232.09 ± 44.16 μ g/g. Also, fecal calprotectin levels in male and female patients were 236.00 ± 46.35 μ g/g and 228.18 ± 41.95 μ g/g, respectively, which showed no difference between the two sexes ($P = 0.378$). As shown in Table 1, the level of fecal calprotectin was independent to baseline parameters of gender, age, and BMI of patients. There was no significant correlation of patients' fecal calprotectin levels with baseline variables including age ($r = 0.004$, $P = 0.969$) and BMI ($r = -0.071$, $P = 0.485$). The mean level of fecal calprotectin concentration in patients was significantly higher than their parents' fecal calprotectin (232.09 ± 44.16 μ g/g and 86.06 ± 12.66 μ g/g, $P < 0.001$). The mean level of fecal calprotectin in patients' relatives was estimated to be 63.8 ± 18.57 μ g/g. The mean level of fecal calprotectin in patients was significantly higher than in their brothers and sisters (232.9 ± 44.16 μ g/g versus 58.02 ± 7.24 μ g/g, $p < 0.001$). The mean level of fecal calprotectin in patients was also significantly higher than in their children (232.9 ± 44.16 μ g/g and 47.40 ± 4.77 μ g/g, respectively, $P < 0.001$). Based on Tokay analysis of ANOVA test, fecal calprotectin levels were higher in patients than parents, and in parents high than siblings and children of patients studied. As shown in Table 2, in parents, siblings, and offspring, the value of calprotectin did not depend to their age and BMI.

Table 1. Fecal calprotectin levels in patients based on underlying characteristics.

Characteristics	Fecal calprotectin level (μ g/g)	P value
Total	232.09 \pm 44.16	
Gender		0.378
Male	236.00 \pm 46.35	
Female	228.18 \pm 41.95	
Age		0.701
<40 years	233.64 \pm 44.57	
>40 year	230.21 \pm 44.08	
Body mass index, kg/m ²		0.257
<25kg/m ²	239.43 \pm 36.37	
>25kg/m ²	228.64 \pm 47.24	

Table 2. Fecal calprotectin levels in patients based on underlying characteristics.

Relative	R coefficient	P value
Parents		
Age	-0.005	0.950
Body mass index	-0.146	0.148
Siblings		
Age	0.172	0.088
Body mass index	0.184	0.066
Offspring		
Age	-0.189	0.144
Body mass index	-0.091	0.389

4. Discussion

Recent studies have shown the diagnostic value of fecal and serum calprotectin levels in predicting the severity and activity of inflammatory bowel disease, and in this regard,

even the diagnostic value of this marker has exceeded other inflammatory indicators associated with the disease. Given the strong familial and inherited predisposition to inflammatory bowel disease, it is assumed that changes in calprotectin levels are also influenced by familial predispositions. Therefore, the present study aimed to evaluate the level of fecal calprotectin in patients and their first-degree relatives in order to determine the relationship between changes in this marker and its possible familial orientation. In the present study, firstly, the level of fecal calprotectin in patients was estimated to be 232.09 ± 44.16 $\mu\text{g/g}$, which was completely consistent with few similar studies in this regard. In a study by Montalto *et al* [14], the level of fecal calprotectin in patients with ulcerative colitis was estimated to be about $256 \mu\text{g/g}$, which was consistent with our study. In the study of Thjodleifsson *et al* [15], the level of fecal calprotectin in patients with Crohn's disease was 47 mg/l , which will be about $240 \mu\text{g/g}$ with the conversion of the corresponding unit, which was again in the range of the number obtained in our study. But in some studies, in other societies, the number obtained was far beyond our scope. In the study of Xiang *et al* [16], the level of fecal calprotectin in patients with active ulcerative colitis was estimated to be $402.16 \mu\text{g/g}$. But what can be seen in almost all studies is a significant increase in fecal calprotectin levels in patients with IBD compared to healthy controls.

As the second finding of the study; the increase in fecal calprotectin level in patients with ulcerative colitis in first-degree relatives of patients was also beyond normal, but still had a significant distance from the level of this marker in patients. In this regard, the level of fecal calprotectin in the patient's parents was 86.06 ± 12.66 , in siblings was $58.02 \pm 7.24 \mu\text{g/g}$, in the patient's children was $47.40 \pm 4.77 \mu\text{g/g}$ and in the patient's spouse was $50.32 \pm 47/37 \mu\text{g/g}$. In this regard, it is necessary to mention a few important points. First, the trend of changes in fecal calprotectin levels in first-degree relatives (a decreasing trend in order to reduce the relationship with the patient) can indicate a significant relationship between increasing fecal calprotectin levels and its familial tendency. In other words, it can be expected that the level of fecal calprotectin in the patient's parents will be much higher than the patient's spouse, which is the same result. Secondly, in the present study, due to ethical considerations, it was not possible to sample healthy controls, but compared to the results of previous studies, the level of fecal calprotectin in the relatives of our patients was higher than the normal level of this marker in other Studies have been beyond. In the studies, the level of fecal calprotectin in the studies was estimated between 31.6 to $35.9 \mu\text{g/g}$. Therefore, the evidence obtained indicates the effect of family relationship of the patient with the patient with fecal calprotectin levels. In the present study, we also found that the level of fecal calprotectin is not affected by underlying indicators such as gender, age or BMI (both in patients and their relatives) and therefore these underlying factors will not affect the level of fecal calprotectin.

5. Conclusion

As a final conclusion, although fecal calprotectin levels are significantly longer in patients with ulcerative colitis than in healthy controls, the higher level of this marker among first-degree relatives of patients than healthy individuals also indicate the inherited tendency of changes in this marker in terms of high risk of disease in first-degree relatives of patients. These changes in fecal calprotectin levels will be independent of gender, age, and BMI.

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