Irritable Bowel Syndrome on Inflammatory Bowel Disease in Deep Remission: No Relation with Remission Deepening and Inflammation

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ABSTRACT

Background: *The aim of the study was to establish the frequency of irritable bowel syndrome (IBS) in patients with inflammatory bowel disease (IBD) in clinical, endoscopic, and histologic remission and in relation to both the depth of remission and inflammation markers.*

Methods: *Patients with ulcerative colitis (UC) and with Crohn's disease (CD) in clinical remission for at least 6 months were enrolled in the study. All of the patients underwent colonoscopy, and biopsy specimens were taken to evaluate endoscopic and histopathologic remission. Patients were evaluated according to Rome III criteria for IBS. Fecal calprotectin level and blood samples for C-reactive protein (CRP), sedimentation rate, and fibrinogen levels were studied.*

Results: *IBS frequency was 20.9% in UC cases and 28.9% in CD cases in clinical remission. Rates with and without endoscopic remission in UC (20.5% vs. 22.2%, P = .727) and CD (25% vs. 33.3%, P = .837, respectively) were not different. Similarly, rates with and without histopathologic remission in UC (15.7% vs. 26.6%, P = .723), and CD (21.4% vs. 33.3%, P = .999) were not statistically different. Also, it was not related to inflammation markers.*

Conclusion: *IBS frequency among IBD patients with remission was in a substantial rate; these rates kept up with the process of deep remission and even complete mucosal healing and were irrelevant to inflammation.*

Keywords: *Inflammatory bowel diseases, remission, irritable bowel syndrome, inflammation*

INTRODUCTION

Inflammatory bowel disease (IBD) is a group of chronic inflammatory disorders that can affect any part of the gastrointestinal tract and is characterized by a course of flare-ups and remissions. The progression and prognosis of the disease has changed greatly with the discovery of steroids in the 1950s, immunosuppressants in the 1970s, and biologics in recent years. Although these treatment methods prevent serious complications and improve the quality of life, there is not enough evidence that they change the natural course of these diseases. Now the goal of IBD treatment is complete mucosal healing. It is known that when this goal is achieved, the need for hospitalization, the need for surgery, and the risk of developing malignant complications decrease.[1-3] Although the clinical and laboratory findings of IBD improve during remission, chronic abdominal pain and changes in the frequency and the viscosity of stool are frequently observed. Studies revealed that abdominal pain occurs in 20-50% of IBD patients even when clinical and/or endoscopic remission is achieved.[4,5] Inflammation, obstruction, psychological, psychosocial, neurobiological, and genetic factors play a role in the etiopathogenesis of abdominal pain in IBD patients. Among the causes of abdominal pain in IBD patients, irritable bowel syndrome (IBS), a functional bowel disease, may also be identified.[6-13] IBS is a chronic disorder, the etiopathogenesis of which involves biological, psychological, and social factors. Clinical manifestation of IBS includes chronic or recurrent abdominal pain or discomfort, changes in the habits and frequency of defecation, alleviation of abdominal pain by defecation, and swelling. The Rome criteria are used for diagnosis.[14,15] The frequency of IBS in the normal population is approximately 12%.[16] But, IBS occurs 2-3 folds higher among IBD patients than it occurs in the normal population.[17] Many IBD patients in remission suffer from ongoing gastrointestinal symptoms that resemble those of IBS and that hinder their quality of life.

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It was first shown by Isgar in 1983 that a significant portion of IBD patients with normal mucosa at endoscopic examination had functional gastrointestinal disturbing symptoms.[18] Since then, studies on the subject are still ongoing. It is not clear why IBS develops after remission in IBD. Some studies have shown low grade inflammation in IBS.[19-28] While these results brings the nature of remission into question whether it reflects a real remission, it also suggests that IBS-like symptoms can still be present in true deep remission. IBD patients in clinical remission may not yet be in endoscopic and histopathologic remission and the presenting symptoms during remission may manifest as IBS by chance or as low-grade inflammation that could not be detected clinically, and this dilemma needs to be resolved. Therefore, we aimed to investigate the incidence of IBS in IBD patients in clinical remission and its relationship with subsequent deepening endoscopic and histological remission and in deep remission. Also, the second aim was to evaluate the relation between the existence of IBS and both mucosal and systemic inflammation markers.

MATERIALS AND METHODS

Study Population

In this study, patients with ulcerative colitis (UC) and with Crohn's disease (CD) in clinical remission at least 6 months, during their follow-up and control visits to Gastroenterology Outpatient Clinic of our University Hospital, were enrolled during the period between June 2015 and October 2017. The study was conducted in compliance with a written approval by the local ethics committee. A written informed consent form, including the aims and scope of the study, was prepared for the study groups.

Exclusion Criteria

Under 18 years of age, patients with history of bowel surgery, active steroid and non-steroidal antiinflammatory drug use, presence of active disease, pregnancy, celiac disease, colon cancer, and obesity were excluded. Abdominal ultrasonography was performed on all patients to exclude other organic pathologies that could cause abdominal pain; obstructive, vascular-ischemic, and pancreatobiliary pathologies were evaluated by means of computerized tomography or MRI; acid-peptic diseases were excluded by performing upper GIS endoscopy.

Clinical remission was defined as Crohn's Disease Activity Index (CDAI) <150 for Crohn's Disease, whereas Truelove-Witts Activity Index "mild" and Simple Clinical Colitis Activity Index <2 were defined for UC.

For all cases included in the study, complete medical history and physical examination were done. Demographic characteristics, type of disease, duration of disease, disease involvement, and treatment received, duration of remission, smoking history, family history, extraintestinal symptoms, and comorbidities were questioned and recorded in a structured data form. For IBS, a questionnaire based on Rome III criteria was applied. Colonoscopies were performed based on the consent of the patients; endoscopic evaluations of remission were performed according to the Mayo score in UC patients and according to Crohn's disease Endoscopic Index of Severity in CD patients, and histopathologic remission evaluations were done on the basis of multiple biopsies taken from both the site of the former disease detected bowel wall and an undetected site . Endoscopic remission was identified by Mayo score = 0 for UC and by Crohn's Disease Endoscopic Index of Severity (CDEIS) $\leq$3 for CD. Histopathologic remission was evaluated by Goebes score in UC patients.[29] GS < 2.0 was accepted as remission. For CD, D'Haens score = 0 was accepted as remission.[30]

Fecal specimens for calprotectin, blood samples for serum C-reactive protein (CRP), fibrinogen levels, and sedimentation rate determinations were obtained. For calprotectin concentration in the samples, the lower detection limit was 10 µg/g and the upper detection limit was 1800 µg/g.

Statistical Analyses

According to the statistical analysis of the data obtained from the study, categorical data were summarized in numbers and percent, and continuous data in mean ± standard deviation or in median (percentiles) depending on the type of distribution of the data. For correlation analyses of the categorical variables, Pearson chi-square and likelihood ratio test statistics were preferred among other cross-tabulation statistics. For quantitative variables, based on the type of data distribution, Mann–Whitney *U* test, a non-parametric test, was used for comparison of the 2 groups. Multiple comparisons of groups were performed using analysis of variance (ANOVA). For the variables showing variations, post hoc Scheffe and Dunnett's multiple comparison test were used to detect the differences in the groups.

- Shapiro–Wilk test results for normality control were interpreted. Variants are not compatible with normal distribution. The non-parametric statistical method (Mann–Whitney) was used in group comparisons because the data did not show normal distribution.

- When summarizing the data, the median and 25-5% were given.
- The differences between the groups in terms of age were evaluated by parametric Student's *t*-test.
- Mean ± standard deviation (min–max) values were given as summary statistics.
- Homogeneous distribution control of the disease groups in terms of gender was evaluated with chi-square statistics.
- *P* values were interpreted to 95% CI (α = 0.05).

RESULTS

In the study, 43 cases with UC (male/female: 25/18 (58.1%/41.9%), mean age: 49.32 ± 11.85 years), and 38 cases with CD (male/female: 19/19 (50%/50%), mean age: 46.84 ± 12.33 years) were evaluated. Data were homogeneous in terms of age (*P* = .359) and gender (*P* = .610).

UC involvement sites of the patients were E1 in 9 patients (20.9%), E2 in 21 patients (48.9%), and E3 in 13 patients (30.3%). CD involvement sites were L1 in 15 patients (39.5%), L2 in 6 (15.8%) and L3 in 17 patients (44.7%). CD type were B1 in 31 patients (81.6%), B2 in 1 patient (2.6%), B3 in 1 patient (2.6%), B1+B3 in 2 patients (5.3%), and B1+B2 in 3 patients (7.9%).

The mean disease duration of UC patients was 78 ± 11 months. Average disease duration in CD was 76 ± 28 months. The duration of remission was an average of 26 ± 8.2 months in UC and 19 ± 11 months in CD.

IBS frequency in UC and CD in clinical remission are 20.9 and 28.9%, respectively. Rates with and without endoscopic remission in UC were 20.5% versus 22.2% (*P* = .727) and in CD were 25% versus 33.3% (*P* = .837), respectively. Rates with and without histopathologic remission in UC were 15.7% versus 26.6% (*P* = .723) and in CD were 21.4% versus 33.3% (*P* = .999). Endoscopic and histopathologic remission rates and association with IBS in patients with clinical remission are shown in Figure 1. Frequency of IBS did not differ statistically according to the remission pattern in both diseases (Figures 1-3). In both diseases, there were patients in clinical remission who did not undergo endoscopic remission and histopathological remission. There was no endoscopic remission in 20.9% (9/43) of UC patients and 47.3% (18/38) of CD patients; no histopathologic remission was observed in 44% (15/34) of UC patients and 30% (6/20) of CD patients.

There was no statistically significant relationship between the site of involvement and the frequency of IBS in patients with UC (*P* = .726). Also in CD patients, there was no statistically significant relationship between the site of involvement and the frequency of IBS (*P* = .321). There was no difference in terms of disease duration and clinical remission duration (*P* = .643). There was no statistically significant difference in the relationship between smoking and IBS frequency in patients with UC (*P* = .163) and CD (*P* = .371) in remission.

The relationship between inflammation markers and IBS in patients in remission is shown in Tables 1 and 2.

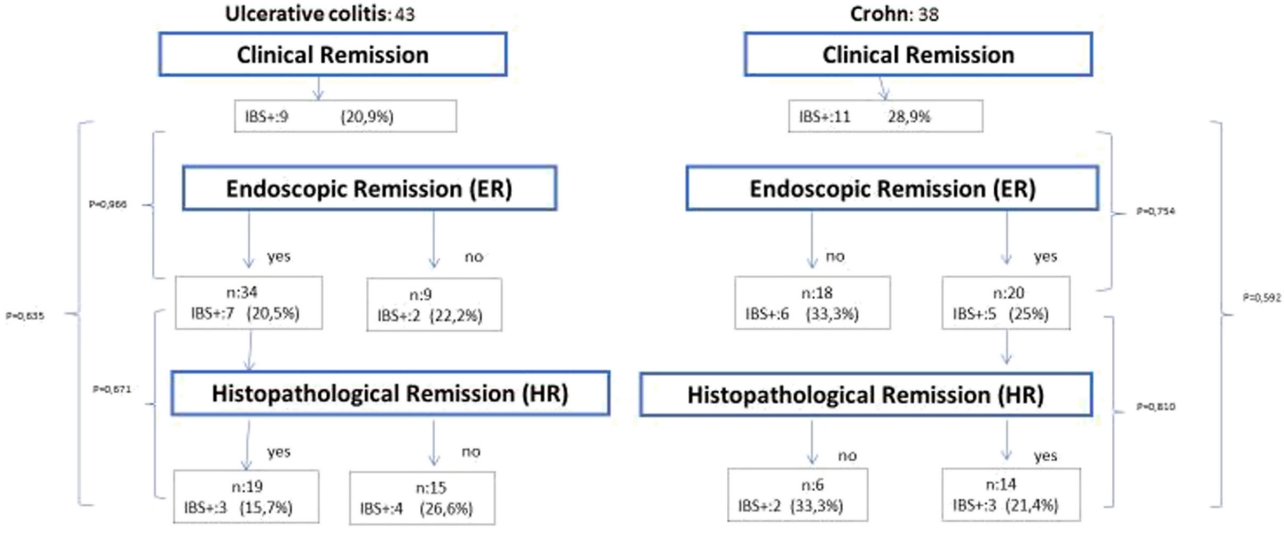

Figure 1. The relationship between IBS and depth of remission in ulcerative colitis and Crohn's disease.

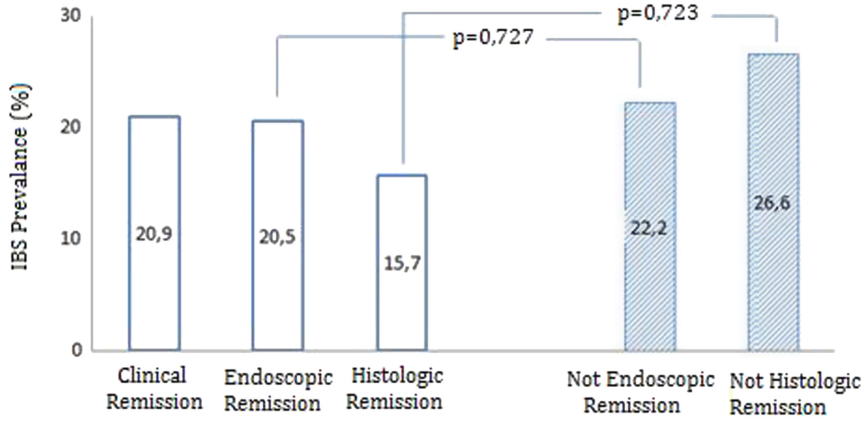

Figure 2. The relationship between IBS in endoscopic and histologic remission and non-remission in ulcerative colitis patients.

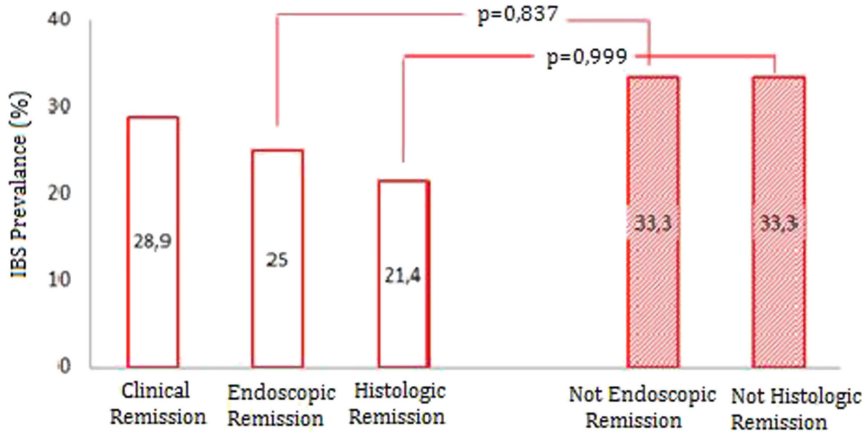

Figure 3. Relationship between IBS in endoscopic and histologic remission and non-remission in Crohn's patients.

There was a difference in sedimentation value only in UC patients in clinical (4 mm/h vs. 13 mm/h, *P* = .004) and endoscopic remission (10 mm/h vs. 4 mm/h, *P* = .021). There was no difference in CD. There was no correlation between the remission pattern and the frequency of IBS in terms of serum CRP, fecal calprotectin, and fibrinogen levels in both disease groups.

DISCUSSION

Although IBD is a chronic autoinflammatory disease of unknown etiology, there have been important developments especially in the field of treatment in recent years. Despite all the advances, IBD may continue to cause discomfort with various problems even after remission. Abdominal pain occurs in 20-50% of the IBD patients in whom clinical and/or endoscopic remission is achieved.[4,5] IBS after remission is one of the causes of abdominal pain. However, it is not clear why IBS-like symptoms develop after remission in IBD. Is it because of an ongoing low-grade inflammation, impaired intestinal motility and increased sensitivity, microbiota changes, or psychic factors?[6,19,28,31,32] If the continuation of mucosal disease and inflammation is one among the factors of post-remission IBS etiology, it is rational to expect the frequency of IBS to decrease when remission deepens and endoscopic and histological recovery occurs. In our study, we evaluated the frequency of IBS in patients with clinical remission followed by endoscopic and histological remission and whether there is a difference with the depth of remission. In our study, 20.9% of UC patients and 28.9% of CD had symptoms consistent with IBS after clinical remission. The frequency of IBS is 20.5% and 25% in UC and CD in the case of endoscopic remission, respectively; this frequency was 15.7% and 21.4%, respectively, in the case of histological remission, and there was no statistical difference (Figures 1-3). Among these groups, IBS frequency was highest in CD group that was not in histopathologic remission but did not reach

Table 1. The Relationship Between Inflammation Markers and IBS in Patients with Remission in UC

	Ulcerative Colitis								
	Clinical Remission			Endoscopic Remission			Histopathological Remission		
	IBS+	IBS–	*P*	IBS+	IBS–	*P*	IBS+	IBS–	*P*
CRP (mg/L)	2.00 (0.80-4.90)	1.97 (0.78-2.98)	.492	1.10 (0.70-2.10)	1.10 (0.70-2.10)	.881	2.00 (0.18-4.20)	1.26 (0.45-2.33)	.911
Sedimentation rate	13.00 (8.00-17.50)	4.00 (2.00-9.25)	.004	10.00 (600-.15.00)	4.00 (2.00-9.00)	.021	10.00 (6.00-20.00)	2.50 (2.00-9.75)	.081
Fibrinogen (mg/dl)	285.00 (252.50-354.50)	265.50 (236.50-322.00)	.238	262.00 (250.00-330.00)	264.00 (235.00-296.00)	.431	285.00 (250.00-330.00)	242.50 (233.25-289.75)	.180
Fecal Calprotectin (µg/ml)	142.95 (51.55-1392.07)	7.56 (43.77-306.89)	.387	76.33 (41.71-218.84)	62.75 (31.81-142.48)	.624	41.71 (19.90-142.95)	44.28 (29.13-90.23)	.655

*Median [%25-%75]

Table 2. The Relationship Between Inflammation Markers and IBS in Patients with Remission in CD

	Crohn Disease								
	Clinical Remission			Endoscopic Remission			Histopathological Remission		
	IBS+	IBS–	*P*	IBS+	IBS–	*P*	IBS+	IBS–	*P*
CRP (mg/L)	2.40 (0.30-6.60)	2.80 (1.80-5.00)	.595	2.40 (0.30-4.35)	2.80 (1.80-4.00)	.726	0.30 (0.30-3.50)	2.80 (2.30-4.60)	.118
Sedimentation rate	7.00 (3.00-15.00)	11.00 (6.00-16.00)	.439	5.00 (2.50-14.00)	11.00 (5.00-15.00)	.313	3.00 (2.00-7.00)	12.00 (5.00-15.00)	.119
Fibrinogen (mg/dL)	300.00 (232.00-318.00)	289.00 (247.00-398.00)	.747	232.00 (199.50-383.00)	252.00 (235.00-339.00)	.407	232.00 (184.00-318.00)	252.00 (234.00-339.00)	.243
Fecal Calprotectin (µg/mL)	306.00 (33.24-1142.08)	105.31 (33.72-383.30)	.267	118.99 (25.85-724.16)	38.30 (25.14-78.59)	.238	306.23 (28.47-1142.08)	33.72 (22.30-78.59)	.139

*Median [25-75%].

the level of significance. Another important point is that clinical remission is not compatible with endoscopic and histological remission. In our study, among UC patients in clinical remission, 20.9% of the cases had no endoscopic remission and 55.8% had no histological remission. As a result, deep remission rate was only 44% in the UC group. In the CD group, these rates were 47.3% and 63%, respectively, and deep remission rate was 36.8%. These results also show us that although they are valuable in evaluating disease activity and progression, clinical activity indexes are insufficient in evaluating endoscopic and mucosal healing. The limited correlation between CDAI and inflammation has also been demonstrated by Saverymuttu et al.[33] Disease activity indices show a poor correlation to abdominal pain. Similarly, no correlation has been established between disease activity indices and endoscopic healing.[34-37] In our study IBS symptoms did not increase in the presence of endoscopic and histologic disease activity.

The frequency of IBS in İBD was studied first by Isgar et al.[18] and the frequency of IBS was found as 33% in 98 UC patients in clinical remission. This rate is higher than the prevalence of IBS in the general population. The frequency of IBS has been reported as 10-20% in the West.[38] In a meta-analysis by Halpin et al.,[11] IBS frequency in patients in clinical remission was found to be 25-46% and terminal ileum surgery that causes bacterial overgrowth in small intestines and malabsorption of bile acid was considered one of the causes responsible for higher frequency of IBS symptoms in CD than in UC. After the first study on the subject, various studies were carried out. However, Teruel et al.[13] showed how heterogeneous the studies were in their review in which they evaluated the studies on the subject from 1983 to 2014. They evaluated 18 studies investigating the prevalence of IBS-like symptoms in IBD. The range of prevalence reported is quite wide (11-64%) in CD (12%-68%) and in UC (9-60%) separately. Pooled prevalence is 30.9%: 38.1% in CD and 27.8% in UC. As this review shows, the recruitment criteria, remission assessment criteria, and IBS diagnostic criteria were quite heterogeneous. Fourteen studies use the Rome criteria for IBS diagnosis (6 Rome II, 6 Rome III, 1 both, and 1 Rome II and Manning criteria), 1 uses only Manning criteria,[18,39] and the last one uses a validated gastrointestinal symptom questionnaire.[25]

With respect to the definitions of remission, there are few coincidences between the different studies, ranging from simple clinical assessment[6,40] to a well-defined combination of IBD activity indexes and CRP quantification.[8,10,41,42]

While active IBD patients were included in some of the studies,[12,41,43] those with silent disease were included in some.[41,43] Two studies explored IBS symptoms in IBD patients regardless of their inflammatory activity status.[44,45] While active IBD patients were included in some of the studies,[12,41,43] those with silent disease were included in some.[41,43] Strikingly only 7 studies include endoscopic evaluation to define remission.[10,12,18,25,42,46,47] Of those, some allow a low grade of inflammation and only 4 use endoscopic indexes.[10,42,46,47] There are 10 cross-sectional studies and 1 prospective study (patients are followed systematically and in each visit they are assessed for the presence of IBS-like symptoms), and 5 are case-control studies in which IBS-like symptoms are prevalent in IBD patients as compared to IBS prevalence in non-IBD patients.

The prevalence variability seems greater in those studies without endoscopic criteria in remission definition (11.2-63.6%) than in those with defined endoscopic criteria (12.9-46%). In the 5 studies that included only patients with normal-appearing mucosa, variability persisted (range 12.9-45.7%).

Regarding variability in exclusion criteria, it is interesting to focus on the 6 studies that exclude patients with previous abdominal surgery (mainly in CD cohorts) to reduce confusion and bias.[10,25,41,42,48,49] In these studies, which include a total of 719 patients (310 CD and 409 UC), the prevalence range is narrower but still considerable and still greater in CD: range, 32-44.6% for all patients, 35.4-57% in CD, and 26.7-38% in UC.

The duration of disease, type, and localization of the disease, age, gender, smoking, and psychic factors were examined in IBD patients who developed IBS following clinical remission. Studies analyzing these factors did not find a significant association with the prevalence of functional symptoms.[8,10,25,41] In our study, we showed that factors such as disease duration, type, localization, age, gender, and smoking have no effect on the development of IBS symptoms after remission. In our study, patients who had undergone a surgical operation were excluded.

In our study, we also evaluated the relationship between clinical, endoscopic, and histological findings as well as local and systemic inflammation markers to evaluate the relationship between the incidence of post-remission IBS

with depth of remission and complete mucosal healing. For this, CRP, fecal calprotectin, sedimentation rate, and blood fibrinogen levels were calculated. CRP is the best serum marker for inflammatory activity in IBD and reliably predicts treatment response.[50,51] Determination of fecal markers of neutrophilic activity in intestinal mucosa is a simple tool that reliably predicts the presence of significant mucosal inflammation.[52,53] Fecal calprotectin is the most used parameter in IBD patients in remission which can determine if the presence of symptoms is due to true functional syndromes or to ongoing inflammation.[8,41,46,54]

In our study, fecal calprotectin, CRP, and fibrinogen levels did not show a statistical difference between the data obtained from cases with or without IBS symptoms based on endoscopic and histological healing. Only sedimentation rate had a statistical difference between patients with and without IBS symptoms in endoscopic and histological remission in the UC group. However, in many studies, significance of fecal calprotectin and CRP are superior to fibrinogen and sedimentation with respect to endoscopic remission in UC and CD; CRP, fibrinogen, and sedimentation are weaker than calprotectin in identifying histopathologic remission.[55-60]

Similar to our results, Berril et al.[41] in their study which excluded patients with surgery, have not found a significant difference between the fecal calprotectin levels of the cases of IBD in clinical remission with or without IBS symptoms (IBS+: 111; IBS–: 50 µg/g). Berrill et al. have concluded that IBS symptoms that occur in IBD have similar characteristics of IBS diagnosed in the general population, and these 2 diseases can occur concomitantly. In another study by Keohane et al.,[8] fecal calprotectin levels of the cases of CD and UC in clinical remission in the presence of IBS symptoms were found to be highly elevated and statistically significant. In conclusion, the increase in the levels of fecal calprotectin was interpreted to be associated with ongoing disease activity and clinically manifested itself with the occurrence of IBS symptoms. But, in this study, there were only patients with clinical remission. Endoscopic and histological remission states were unknown, and patients who had undergone surgery were also included in the study. As a result, in our study, no significant relation was detected between inflammation markers and IBS symptoms in IBD patients in remission. This led us away from the view that subclinical inflammation is involved in the pathogenesis of IBS and demonstrated that IBS may occur as it occurs in the general population and can be coexistent with IBD.

Most recently, Henriksen et al. showed in the Inflammatory Bowel South-Eastern Norway (IBSEN) study that IBS-like symptoms in UC are common in patients in deep remission as in inflammation.[61] In their evaluation of 260 UC patients 20 years after their initial diagnosis, IBS symptoms according to Rome III criteria were recorded. The patients underwent colonoscopy with biopsies and/or the level of fecal calprotectin was analyzed. The overall prevalence of IBS-like symptoms was 27% in patients who had no signs of inflammation in colonic biopsies (deep remission). No difference in prevalence of IBS-like symptoms was found between patients with ongoing inflammation and patients in deep remission.

In conclusion, post-remission IBS was quite common in IBD patients, and even in those with deep remission, the frequency of IBS remained high and was not associated with inflammation markers. This suggests that the possible causes of IBS development after remission in IBD patients may be multiple including alone or together, bile acid malabsorption, lactose intolerance, bacterial overgrowth, microbiota alteration, post-IBD motility disorder or visceral hypersensitivity, and the psychosocial conditions of the cases.

Ethics Committee Approval: The study was conducted in compliance with a written approval by the local ethics committee.

Informed Consent: A written informed consent form, including the aims and scope of the study, was prepared for the study groups.

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Author Contributions: Concept – O.S., B.B.; Design – O.S., B.B.; Supervision – O.S., E.Ü.; Resource – O.S., B.B.; Materials – O.S., B.B., E.Ü., E.A.; Data Collection and/or Processing – B.B., H.D.C.; Analysis and/or Interpretation – O.S., E.Ü., E.A., H.D.C.; Literature Search – O.S.; Writing – O.S.; Critical Reviews – O.S.

Conflict of Interest: The authors have no conflict of interest to declare.

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