Irritable Bowel Syndrome-Like Symptoms in Ulcerative Colitis Patients in Clinical Remission: Association with Residual Colonic Inflammation

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Keywords

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Abstract

Ulcerative colitis (UC) patients in clinical remission often experience irritable bowel syndrome (IBS)-like symptoms. The prevalence rate of UC patients meeting the definition of IBS, such as shown by the Rome criteria, is significantly higher in those without ongoing clinical activity as compared to healthy controls. Several studies have investigated residual low-grade inflammation found in colonic mucosa of quiescent UC patients and its association with development of IBS-like symptoms. In these patients, residual colonic inflammation was evaluated using endoscopy and histology findings, as well as fecal calprotectin level and shown to not be simply associated with the presence of IBS-like symptoms in UC patients in clinical remission. However, these results are limited by the low number of related investigations conduct-

ed. Additional appropriately designed studies are necessary to confirm the relationship of low-grade colonic inflammation with IBS-like symptoms associated with UC.

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Introduction

Irritable bowel syndrome (IBS), a functional disorder of the intestines, is characterized by abdominal pain and discomfort, along with alterations of bowel habits [1–5]. On the contrary, ulcerative colitis (UC), a major form of inflammatory bowel disease (IBD), is a chronic immune- and inflammation-mediated intestinal disorder characterized by clinical symptoms, including bloody stool, diarrhea, and fever. Organic intestinal lesions are not usually found in IBS patients, thus the IBS disease entity is recognized to be fundamentally different from IBD. However, recent studies have revealed that etiological factors, such as genetic background, history of infectious gastroenteritis, impaired gut barrier function, and psychological stress,

overlap between IBS and IBD [6–14]. Moreover, overlaps have also been observed between these diseases with regard to clinical symptoms [15]. Notably, IBS-like symptoms are often found in UC patients who have no evidence of the ongoing clinical disease activity [6, 8, 16]. Numerous studies have demonstrated possible mechanisms related to the development of IBS-like symptoms in quiescent UC patients [14–18]. In this review article, we focus on the degree of residual low-grade colonic inflammation in UC patients in clinical remission who were evaluated by endoscopy and histological findings, as well as fecal calprotectin (FC) level and discuss their association with the development of IBS-like symptoms.

Prevalence of IBS in General Population

A number of epidemiological studies have reported the prevalence of IBS in a variety of populations in various countries [4, 14, 19, 20]. In an evaluation presented by Manning, prevalence based on Rome I or Rome II criteria ranged from 2.3 to 22% [21–24]. Furthermore, we recently reported that the prevalence of IBS in subjects who underwent general medical check-ups was 4.8% (Rome III criteria) [25]. On the contrary, a Japanese study conducted by Miwa [26] revealed that the prevalence of IBS was 13.1% (Rome III criteria). Although such heterogeneity may be dependent on the enrolled population, as well as sample size and the criteria used for diagnosis, the prevalence of IBS in the general population based on numerous previous studies is estimated to be approximately 10%.

Prevalence of IBS-Like Symptoms in UC Patients in Remission

Successful treatment of UC patients with anti-inflammatory and immunomodulatory drugs leads to the induction of remission. However, even after remission has been induced, as assessed by validated clinical scores, some patients have frequent abdominal symptoms, such as pain and discomfort with altered bowel habits, which are widely recognized as “IBS-like symptoms.”

Several previous studies enrolled patients without ongoing disease activity (clinical remission) and investigated the prevalence of symptoms meeting the criteria for IBS. Halpin and Ford [27] presented results of a systematic review and meta-analysis regarding the prevalence of IBS-like symptoms in UC patients in remission. They ex-

amined 3,045 articles, and analyzed data obtained from 6 cross-sectional and 4 case-control studies selected from those that identified and reported IBS-like symptoms in examined patients, and reported a pooled prevalence of 31.0%, which was significantly higher than that of the control cases in those studies (7.5%). However, the remission criteria used in those studies varied, as some focused only on clinical symptoms as remission criteria [28–33], while others defined remission in their UC patients by evaluating both clinical and endoscopic findings [34–36]. Since residual colonic inflammation is often found in UC patients with clinical evidence of remission, it is possible that achievement of endoscopic remission (mucosal healing; MH) in addition to the absence of ongoing clinical symptoms may reduce the development of IBS-like symptoms. Previous studies have reported that the prevalence of IBS-like symptoms is associated with the degree of MH assessed by endoscopic and histological examination findings, and FC level.

Endoscopic Findings

Isgar et al. [34] and Simrén et al. [35] included endoscopic findings in their criteria for determining remission of UC, though these definitions were not sufficiently validated. We found several studies including our own that discussed endoscopic findings in association with IBS-like symptoms in UC patients (Table 1). In these studies, Rome II or III criteria were used for the diagnosis of IBS-like symptoms, while endoscopic remission was defined by Mayo (MES ≤ 1) or Matts (Matts grade ≤ 2) endoscopic score. Ansari et al. [36] used MES ≤ 1 to define endoscopic remission and found that the prevalence of IBS-like symptoms in such patients was 46%, which was relatively higher as compared to previous studies of UC patients in clinical remission. We previously investigated the influence of endoscopic remission (Matts grade ≤ 2) on prevalence of IBS-like symptoms in 172 UC patients in clinical remission (clinical activity index, CAI < 4) [25]. However, the difference between clinical and endoscopic remission was not significant (26.7 vs. 25.6%). Furthermore, a more recent study revealed that the prevalence of IBS-like symptoms in UC patients in endoscopic remission (MES ≤ 1) was 26.6%, which was similar to that in previous studies of such patients [37].

Although Matts grade ≤ 2 and MES ≤ 1 are widely recognized for defining endoscopic remission, mild mucosal activity remains in the colonic mucosa of patients diagnosed as Matts grade 2 or MES 1. In this regard, the prev-

Table 1. Prevalence of IBS-like symptoms in UC patients in endoscopic remission

Author (ref.)	Country	Criteria [#]	Criteria [†]	Endoscopic remission ^{\$}	IBS-like symptoms, <i>n</i> (%)
Ansari et al. [36]	Iran	Rome II	MES* ≤1	50	23 (46.0)
Fukuba et al. [25]	Japan	Rome III	Matts grade ≤2	39	10 (25.6)
			Matts grade =1	13	2 (15.4)
Jonefjäll et al. [38]	Sweden	Rome III	MES ≤1**	132	24 (18.2)
Henriksen et al. [37]	Norway	Rome III	MES ≤1	165	44 (26.6)
			MES =0	118	30 (27.1)

[#] Criteria for diagnosis of IBS-like symptoms.

[†] Criteria for diagnosis of endoscopic remission.

^{\$} Number of patients in endoscopic remission.

** Remission criteria included fecal calprotectin <200 (μg/g).
MES, mayo endoscopic subscore.

Table 2. Prevalence of IBS-like symptoms in association with fecal calprotectin levels

Author (ref.)	Country	UC patients*	Criteria**	Fecal calprotectin (μg/g)		<i>p</i> value
				IBS-positive (N [‡])	IBS-negative (N [‡])	
Keohane et al. [31]	Ireland	<i>n</i> = 44	Rome II	591.1 [#] (17)	229.8 [#] (27)	<0.01
Jelsness-Jørgensen et al. [46]	Norway	<i>n</i> = 61	Rome III	347.7 [#] (15)	189.3 [#] (46)	ns
Jonefjäll et al. [38]	Sweden	<i>n</i> = 132	Rome III	18 ^{\$} (24)	31 ^{\$} (108)	ns
Hoekman et al. [47]	Netherlands	<i>n</i> = 74	Rome III	51 ^{\$} (33)	77 ^{\$} (41)	ns
Henriksen et al. [37]	Norway	<i>n</i> = 260	Rome III	297 [#] (71)	197 [#] (189)	ns

* Number of UC patients in clinical remission.

** Criteria for diagnosis of IBS-like symptoms.

[‡] Number of patients with or without IBS-like symptoms.

[#] Mean.

^{\$} Median.

absence of IBS-like symptoms may be decreased in patients with complete endoscopic remission, defined as Matts grade 1 and MES 0 [38]. In our previous study, when endoscopic remission was strictly defined as Matts grade 1, the prevalence of IBS-like symptoms decreased from 25.6 to 15.4% (Table 1) [25]. In contrast, a more recent study did not find a difference in regard to the prevalence of IBS-like symptoms between patients classified as MES 0 (25.4%) and MES ≤1 (26.6%; Table 1) [37]. Therefore, it is unclear whether endoscopic evidence of remission is directly associated with the prevalence of IBS-like symptoms in UC patients in clinical remission. In fact, the number of studies of this issue is still quite limited and further investigations are necessary.

Fecal Calprotectin Level

Calprotectin is a calcium- and zinc-binding protein that is released mainly by neutrophils. Since infiltration of neutrophils during intestinal inflammation results in the release of calprotectin in stools, termed FC, its level is well correlated to mucosal activity in UC patients [39–43]. In particular, FC level is considered to be an effective surrogate marker for evaluating mucosal healing in UC patients in clinical remission [44, 45].

Several groups have investigated the correlation between the prevalence of IBS-like symptoms and FC level in UC patients in clinical remission (Table 2). In a previous study reported by Keohane et al. [31], IBS-like symp-

toms were detected in 38.6% of UC patients in remission (Rome II criteria) and were significantly associated with an increased level of FC. In a recent study reported by Jonefjäll et al. [38], who defined remission criteria based on endoscopic findings (MES $\leq$ 1) and FC level (<200 μ g/g), the prevalence of IBS-like symptoms was relatively low (18.2%) (Table 1). This latter finding suggests that a lower level of FC, in addition to endoscopic remission, may be associated with a reduced rate for the prevalence of IBS-like symptoms.

On the contrary, recently published studies that used Rome III criteria did not find a correlation between FC level and prevalence of IBS-like symptoms, though average or mean FC levels varied among them (Table 2) [31, 37, 38, 46, 47]. In our recent study, we also did not find a significant increase in the level of FC in UC patients with IBS-like symptoms in clinical remission (data not shown). Thus far, the results of studies related to this issue remain controversial, and possibly dependent on the study population and sample size, as well as remission criteria used for defining UC and IBS-like symptoms.

Histological Findings

Histological changes such as infiltration of various inflammatory cells without endoscopic evidence of inflammation have been found in certain populations of IBS patients. These findings have been primarily observed in patients with post-infectious IBS (PI-IBS), which is defined as a type of IBS that develops in previously asymptomatic individuals following an episode of acute gastroenteritis caused by bacterial or viral infection [4–7]. PI-IBS is found in approximately 10–20% of patients diagnosed with IBS [4, 14, 48]. Previous studies of affected patients have reported a variety of immune cells, including T cells (CD3⁺, CD4⁺, CD8⁺ cells), macrophages, B cells, and mast cells, infiltrating the mucosa of the small and large intestines without endoscopic inflammation. In addition, increased levels of interleukin-1 β and interferon- γ have been found in rectal and colonic biopsy tissues in patients with PI-IBS [4, 14, 49–52]. Taken together, these findings suggest that histological evidence of intestinal inflammation in the absence of endoscopic activity may have a relationship with the pathogenesis of IBS.

On the contrary, residual low-grade histological inflammation is often found in the colonic mucosa of UC patients even after they show clinical and endoscopic re-

mission [53], which might be associated with the development of IBS-like symptoms. Recently, Henriksen et al. [37] investigated the influence of histological inflammation on the prevalence of IBS-like symptoms in UC patients with endoscopic evidence of remission and lower FC levels. They did not find reduced frequency of IBS-like symptoms in these cases, even when histological inflammation was not revealed in colonic biopsy findings. The study was the first to report the influence of histological inflammation on IBS-like symptoms in UC patients in remission. In patients with PI-IBS, various factors related to systemic immune activation, in addition to histological inflammation, have been reported. In this regard, the pathogenesis of IBS symptoms in PI-IBS patient may differ from that in UC patients in remission, though low-grade histological inflammation is observed in association with both disease entities.

Relapse of UC with or without IBS-Like Symptoms

In a recent investigation, we reviewed the records of UC patients in clinical remission who had been enrolled in our previous study to determine the period without relapse in association with IBS-like symptoms. In the clinical remission group with IBS-like symptoms, the mean relapse-free period was shorter as compared to that of patients in the group without such symptoms, suggesting that the presence of IBS-like symptoms is predictive of UC relapse [54]. However, endoscopic activity (Matts grade) was significantly higher in the group of patients with IBS-like symptoms. Therefore, we speculate that residual inflammation in colonic mucosa might have an influence on UC relapse. Nevertheless, this is the only study presented that investigated this issue and further investigations to confirm the influence of IBS-like symptoms on relapse of UC are needed.

Conclusion

Our findings indicate that the degree of residual low-grade colonic inflammation, as evaluated by endoscopy and histology findings, as well as FC level, is not correlated with the prevalence rate of IBS-like symptoms in all cases. Although IBS-like symptoms in certain patients may be predominantly affected by low-grade colonic inflammation, such a population has not been clearly shown, possibly because of the limited number of appropriate studies. On the contrary, apart from colonic in-

flammation, the pathogenesis of IBS has been reported to be associated with a variety of factors, including genetics, visceral hypersensitivity, increased gut permeability, microbiota dysbiosis, immune activation, and abnormal serotonin metabolism. Overlaps between colonic inflammation and those factors might have an influence on the presence of IBS-like symptoms in quiescent UC patients. Additional studies are necessary to more fully understand

the pathogenesis of IBS-like symptoms in UC patients in remission, ultimately leading to the development of new therapeutic options.

Disclosure Statement

The authors have no financial or other conflicts of interest to declare in relation to the contents of this article.

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