

Diagnosis and management of functional symptoms in inflammatory bowel disease in remission

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Abstract

Inflammatory bowel disease (IBD) patients in remission may suffer from gastrointestinal symptoms that resemble irritable bowel syndrome (IBS). Knowledge on this issue has increased considerably in the last decade, and it is our intention to review and summarize

it in the present work. We describe a problematic that comprises physiopathological uncertainties, diagnostic difficulties, as IBS-like symptoms are very similar to those produced by an inflammatory flare, and the necessity of appropriate management of these patients, who, although in remission, have impaired quality of life. Ultimately, from almost a philosophical point of view, the presence of IBS-like symptoms in IBD patients in remission supposes a challenge to the traditional functional-organic dichotomy, suggesting the need for a change of paradigm.

Key words: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Irritable bowel syndrome; Functional gastrointestinal disease

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Core tip: Many inflammatory bowel disease patients in remission suffer from ongoing gastrointestinal symptoms that resemble those of irritable bowel syndrome and that hinder their quality of life. We review the pathogenesis of these symptoms, their prevalence and the best management strategies.

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INTRODUCTION

More than thirty years ago, in 1983, it was first reported that a significant proportion of patients with inflammatory bowel disease (IBD) with normal

mucosa in endoscopic examination nevertheless suffered from gastrointestinal symptoms allegedly of functional origin^[1]. Almost twenty years passed until the next significant investigation addressing this issue was published, in 2002 by Simrén *et al.*^[2]. From that year on, an important number of studies have been published providing a more profound knowledge about functional symptoms in IBD in remission. It is our objective in the present work to review this knowledge.

Within functional digestive disorders, we will focus on irritable bowel syndrome (IBS) because its symptoms (abdominal pain, diarrhea, constipation, fecal incontinence) resemble those of flare-up of IBD. Differential diagnosis between IBD flare and IBS-like symptoms is a diagnostic challenge with critical consequences. Immunomodulators could be prescribed unnecessarily or ongoing inflammation managed inadequately with, for example, antispasmodics, delaying initiation of proper treatment when not resulting in adverse events.

Some authors have explored the prevalence of IBS symptoms in active IBD^[3-5]. We consider, as many others, that it is very difficult to discriminate reliably symptoms attributable to IBD from those secondary to a functional disorder in that setting, so we will not explore this aspect further.

Increasing knowledge about the occurrence of IBS symptoms in IBD patients with no macroscopic inflammation, has led to the definition of so-called "IBD-IBS". This concept, together with further awareness of links between the two entities, challenges the traditional functional-organic dichotomy and leads to the elaboration of a broader biopsychosocial model of disease that should allow a better understanding of patients' medical condition that the classical dogma fails to achieve^[6-8].

We have structured the review following a question-and-answer scheme with intent to reproduce what comes into mind of the physician in the outpatient clinic. Key conclusions in each section are presented.

HOW DO I KNOW THAT IBD IS IN REMISSION?

To confidently define remission non-invasively we should use not only clinical indexes but also C-reactive protein (CRP) and fecal calprotectin. Radiological procedures could be of help in unclear cases. Endoscopy would still be necessary to confirm remission in many cases.

The definition of remission in IBD is not straightforward, as it is a broad concept that includes several aspects: (1) clinical remission (absence of symptoms); (2) endoscopic remission (mucosal healing); and (3) deep remission (no symptoms and mucosal healing).

To enhance the optimal diagnosis of remission several indices are available to monitor IBD inflammatory

activity, such as the Crohn's Disease Activity Index (CDAI) or the Harvey-Bradshaw index for Crohn's disease (CD), or the Mayo score for ulcerative colitis (UC). They are a composite of objective items (such as analytical determinations), objective items self-reported by the patient (such as number of stools per day) and purely subjective items such as pain intensity or degree of wellbeing. Although valuable in monitoring disease progression and activity^[9] and therefore widely used in clinical trials, these indices do not correlate perfectly with endoscopic/histological activity or analytical parameters, probably because they all include subjective items^[10-12]. Sub-analyses of some recent clinical trials show that up to 18% of randomized patients, all with scores in the range of active disease as defined in the inclusion criteria, actually had no evidence of endoscopic inflammation^[13]. Lahiff *et al.*^[10] measured CDAI in 44 CD patients and in 47 IBS patients, and noticed that 62% of IBS patients had a score higher than 150 (the usual threshold for inclusion in IBD clinical trials) and that mean scores were higher in IBS patients (183 points vs 157, $P < 0.05$). More intense pain and worse perception of general wellbeing were the main contributors to the final score in IBS. Authors conclude that remission cannot be determined solely on clinical indices, as their subjective components makes it impossible to separate functional from inflammatory symptoms^[10,14].

According to all this, additional tools are needed to establish a reliable diagnosis of remission in IBD^[15]: (1) Endoscopic examination of the intestinal mucosa is the gold standard to determine inflammatory activity and the most reliable test to define remission. However, endoscopy is invasive and uncomfortable, not devoid of side effects. Moreover, there are no clear or widely accepted criteria of endoscopic remission. On top of that, small bowel inflammatory activity can be very difficult to evaluate, even though the availability of the endoscopic capsule has increased in recent years; (2) Radiological imaging in IBD has lately experienced great advances. Ultrasound, computerized tomography (CT) and magnetic resonance imaging (MRI) are no longer used solely to rule out complications such as abscesses or perforation. They all play an increasing role in assessing the extent of disease, presence of active inflammation, transmural involvement and even response to treatment, all of which are especially true for MRI^[16]; (3) CRP is the best serum marker of inflammatory activity in IBD, and reliably predicts treatment response^[17,18]. It is therefore widely used in clinical practice. CRP is however an unspecific acute phase reactant, and up to 25% of patients with inflammatory activity will have normal levels^[19,20]; and (4) Determination of fecal markers of neutrophilic activity in intestinal mucosa is a simple tool that reliably predicts the presence of significant mucosal inflammation^[21,22]. Calprotectin is the most used

marker and has excellent diagnostic performance. In a meta-analysis the area under the receiver operating characteristic (ROC) curve was 0.97, with an optimal cut-off value of 50 mcg/g that yielded 93% sensitivity and 94% specificity in discriminating IBD from IBS^[22]. Further on, calprotectin levels correlate very well with endoscopic activity^[23-27], predict occurrence of a flare^[28] and are capable of predicting response to treatment^[27,29-31]. However, calprotectin also rises in other situations, such as with non-steroidal anti-inflammatory drugs (NSAIDs) use, and we lack a cut-off point that defines remission reliably^[32]. As we describe in detail later, measurement of fecal calprotectin in IBD patients in remission could determine if the presence of symptoms is due to true functional syndromes or to ongoing inflammation^[5,33-35].

ARE ALL PATIENTS IN REMISSION SUSCEPTIBLE TO SUFFERING IBS-LIKE SYMPTOMS?

Some IBD patients have risk factors for developing conditions such as bile salt diarrhea that can mimic IBS-like symptoms.

IBD patients in remission with previous intestinal surgery, stenosis or stomas are at risk of developing small intestine bacterial overgrowth (SIBO), sub-occlusive crisis or bile acid malabsorption. These three conditions cause symptoms that resemble IBS. Many authors exclude such patients when considering IBD-IBS prevalence, but others do not (Table 1). None have systematically carried out tests to rule out such conditions before definitive diagnosis, such as breath tests, enteroclysis, or a SeHCAT [tauroselcholic (75 selenium) acid] test respectively. Before establishing a purely functional nature of symptoms, it seems reasonable to consider such tests in IBD patients at risk of suffering these conditions or to carry out an empirical therapeutic trial for example with non-absorbable antibiotics or cholestyramine^[36-38].

WHICH CRITERIA ARE VALID TO DIAGNOSE FUNCTIONAL SYMPTOMS IN IBD PATIENTS?

In absence of better alternatives, Rome III criteria can be used to diagnose IBS in IBD patients in remission.

Irritable bowel syndrome is defined by the presence of abdominal pain or discomfort associated with changes in stool frequency or consistency. To date there is no biomarker available that can reliably confirm or exclude it. It is therefore a clinical diagnosis based on exclusion of organic disease in the presence of alarm symptoms (weight loss, anemia, gastrointestinal bleeding, *etc.*) and fulfillment of predefined criteria. Currently Rome III criteria

are without a doubt the most used to define IBS in epidemiological studies, clinical trials and everyday practice (Table 2)^[39-41].

There are no consensus definitions for diagnosis of IBS-like symptoms in quiescent IBD. In general, investigators have used diagnostic criteria that were validated in non-IBD patients (Table 1). In 2005 Barratt *et al.*^[42] observed that several symptoms were more frequent when their etiology was functional and not inflammatory (exclusively daytime symptoms, bloating, excess gas, fatigue). They elaborated the St Mark's Diary Score, a tool to diagnose IBS-like symptoms in quiescent IBD. However, this score has not been validated externally to date.

HOW MANY IBD PATIENTS IN REMISSION HAVE IBS-LIKE SYMPTOMS?

IBD-IBS prevalence data are very variable due to heterogeneity in remission definition, diagnostic criteria and exclusion criteria. Pooling prevalences of the most homogeneous studies shows that about a third of quiescent IBD patients will suffer from IBS-like symptoms.

From 1983 until 2014 a total of 19 studies have measured the prevalence of IBS-like symptoms in IBD^[1-5,33-35,42-52]. Two of these publications refer to the same IBD cohort^[34,49], leaving 18 prevalence estimations. Two studies explore IBS symptoms in IBD patients regardless their inflammatory activity status^[42,47]. The 16 remaining studies are summarized in Table 1. Three studies report IBS-like prevalences in both active and quiescent IBD^[3-5]; from these studies we have extracted only data referring to IBD in remission. There are 10 cross-sectional studies, one prospective study (patients are followed systematically and in each visit they are assessed for presence of IBS-like symptoms) and 5 are case-control studies in which IBS-like symptoms prevalence in IBD patients is compared to IBS prevalence in non-IBD patients. Fourteen studies use the Rome criteria for IBS diagnosis (6 Rome II, 6 Rome III, one both and another Rome II and Manning criteria), one uses Manning criteria only^[1,53] and the last one uses a validated gastrointestinal symptom questionnaire^[2].

The range of reported prevalences is quite wide (11%-64%), also in CD (12%-68%) and in UC (9%-60%) separately. Pooled prevalence is 30.9%, 38.1% in CD and 27.8% in UC (Table 1). These differences in prevalence were not attributable to type of diagnostic criteria used, as a meta-analysis by Halpin *et al.*^[54] that analyzed the studies published up to 2012 concludes. Possible alternative explanations are the small sample size of many of the studies, the variability in diagnostic criteria used to define IBD remission, the variability of exclusion criteria, and the absence of controls in most of them.

Table 1 Summary of studies that have determined prevalence of irritable bowel syndrome-like symptoms in quiescent inflammatory bowel disease

Ref.	Type	Sample size (CD/UC)	Criteria used to define IBD remission	Exclusions (IBD characteristics or previous surgery)	Criteria used to define IBS	IBD-IBS prevalence <i>n</i> (%)
Isgar <i>et al</i> ^[11]	Case-control	98 (0/98) 98 non-IBD controls	Endoscopic remission, steroid-free	Not further specified	Manning	UC: 33 (33.7)
Simrén <i>et al</i> ^[2]	Cross-sectional	83 (40/43)	CD: Physician global assessment, endoscopic/radiological remission and normal inflammatory markers (Hb, ESR, CRP, platelets, albumin) UC: Endoscopic remission, no blood nor mucus, normal CRP	Stenotic CD CD patients with > 2 surgeries Significant comorbidities	Gastrointestinal symptom questionnaire validated	37 (44.6) CD: 23 (57) UC: 14 (33)
Zaman <i>et al</i> ^[43]	Cross-sectional	55 (30/25)	Stable symptoms, no changes in medication for 3 mo	Not available	Rome II	35 (63.6) CD: 20 (66.7) UC: 15 (60)
Minderhoud <i>et al</i> ^[44]	Case-control	107 (34/73) 66 non-IBD controls	CD: CDAI < 150 UC: CAIUC < 10	Significant comorbidities	Manning Rome II	Manning: 33 (30.8) CD: 8 (23.5) UC: 25 (34.2) Rome II : 37 (34.6) CD: 14 (41.7) UC: 23 (31.5)
Farrokhyar <i>et al</i> ^[45]	Cross-sectional	149 (105/44)	No changes/addition of medication nor change dosage in the last year	Not further specified	Rome II	31 (20.8) CD: 27 (26) UC: 4 (9.1)
Ansari <i>et al</i> ^[46]	Case-control	50 (0/50) 100 non-IBD controls	Mayo score ≤ 2 (bleeding score = 0, endoscopic score 0-1)	Not further specified	Rome II	UC: 23 (46)
Keohane <i>et al</i> ^[33]	Cross-sectional	106 (62/44)	CD: CDAI < 150 UC: UCAI ≤ 3 For both: physician's global assessment, CRP < 10 mg/L, no use of steroids or biological agents in previous 6 mo	Not further specified	Rome II	54 (50.9) CD: 37 (59.7) UC: 17 (38.6)
Piche <i>et al</i> ^[48]	Cross-sectional	92 (92/0)	CDAI < 150 for > 6 mo, endoscopic/radiologic remission (CDEIS < 6), normal inflammatory markers (CRP, Hb, ESR, platelets, albumin)	Stenosis CD patients with previous surgery Recent corticoid use	Rome III	CD: 42 (45.7)
Barratt <i>et al</i> ^[5]	Case-control	276 (110/166) 348 non-IBD controls	CD: HBI < 5 UC: SCCAI < 5	Not further specified	Rome II	31 (11.2) CD: 14 (12) UC: 17 (9)
Bryant <i>et al</i> ^[4]	Cross-sectional	93 (47/43) ¹	Physician's global assessment using inflammatory markers, histological and endoscopic activity and clinical data	Not further specified	Rome III	12 (12.9) (no CD/UC differentiation)
Jelsness-Jørgensen <i>et al</i> ^[49]	Cross-sectional	89 (28/61)	CD: SCDAI < 4 UC: SCCAI < 3 No current steroid treatment	Not further specified	Rome II Rome III	Rome II : 21 (23.6) CD: 6 (21.4) UC: 15 (24.6) Rome III: 30 (33.7) CD: 8 (28.6) UC: 22 (36.1)
Kim <i>et al</i> ^[50]	Cross-sectional	226 (107/119)	No changes on therapy in last year, normal limits of CRP, hemoglobin, no blood or mucus in stools for UC	CD with stenotic/penetrating phenotype Previous surgery	Rome III	82 (36.3) CD: 50 (46.7) UC: 32 (26.9)
Berrill <i>et al</i> ^[5]	Cross-sectional	97 (40/57)	CD: HBI < 5, CRP < 10 mg/L UC: SCCAI < 3, CRP < 10 mg/L	Ileostomy, colostomy or total colectomy	Rome III	31 (32) CD: 13 (32.5) UC: 18 (31.6)
Jonefjäll <i>et al</i> ^[35]	Pro-spective	94 (0/94)	Mayo ≤ 2 (endoscopic < 1) No relapse during 3 mo before inclusion	Significant comorbidities	Rome II	UC: 25 (27)
Vivinus-Nébot <i>et al</i> ^[51]	Cross-sectional	49 (31/18)	CD: CDAI < 150, CDEIS ≤ 4 UC: UCAI ≤ 3, Mayo = 0 For both: physician's global assessment, CRP < 10 mg/L, no use of steroids over the last year	Stenotic or complicated CD Significant comorbidities	Rome III	18 (36.7) CD: 11 (35.4) UC: 7 (38)
Fukuba <i>et al</i> ^[52]	Case control	172 (0/172) 330 non-IBD controls	CAI ≤ 4, CRP < 5 mg/L	Colectomy	Rome III	UC: 46 (26.7)

Total	-	1836 (726/1107) ¹	-	-	Total: 567 (30.9) CD: 259 (38.1) ² UC: 296 (27.8) ²
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¹In the original article the numbers given by the authors do not add up to the total of patients and they do not specify if the rest correspond to undetermined colitis; ²For the pooled prevalences in CD and UC, patients from study of Bryant et al have not been included as they do not state a differentiated IBS-IBD prevalence for CD and UC respectively. CD: Crohn's disease; UC: Ulcerative colitis; IBD: Inflammatory bowel disease; IBS: Irritable bowel disease; CRP: C reactive protein; Hb: Haemoglobin; ESR: Erythrocyte sedimentation rate; CDAI: Crohn's disease activity index; CAIUC: Clinical activity index for ulcerative colitis; UCAI: Ulcerative colitis activity index; CDEIS: Crohn's disease endoscopic index of severity; HBI: Harvey-Bradshaw index; SCCAI: Simple clinical colitis activity index; SCDAI: Simple Crohn's disease activity index; CAI: Colitis activity index.

Table 2 Irritable bowel syndrome Rome III criteria

Recurrent abdominal pain or discomfort at least 3 d per month in the last 3 mo (with onset at least 6 mo prior to diagnosis) associated with two or more of the following Relieved with defecation Onset associated with a change in frequency of stools Onset associated with a change in form (appearance) of stools

Adapted from Longstreth *et al*^[40].

With respect to definitions of remission there are few coincidences between the different studies, ranging from simple clinical assessment^[43,45] to a well-defined combination of IBD activity indexes and CRP quantification^[5,33,48,51]. Strikingly only 7 studies include endoscopic evaluation to define remission^[1,2,4,35,46,48,51]. Of those, some allow a low grade of inflammation^[1,46] and only four use endoscopic indexes^[35,46,48,51]. The prevalence variability seems greater in those studies without endoscopic criteria in remission definition (11.2%-63.6%) than in those with (12.9%-46%). In the five 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 six studies that exclude patients with previous abdominal surgery (mainly in CD cohorts) to reduce confusion and bias (see previous sections)^[2,5,48,50-52]. In these studies, which include a total of 719 patients (310 CD, 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.

All five case-control studies reported a higher prevalence of IBS-like symptoms in IBD patients in remission than in non-IBD controls. The meta-analysis by Halpin *et al*^[54] calculated for IBD as a whole an OR of 4.39 (95%CI: 2.24-8.61). In the study by Fukuba *et al*^[52], not included in the meta-analysis, the numbers were similar for UC (OR = 7.17; 95%CI: 3.94-13.0).

Some studies have investigated if there are any variables associated with the occurrence of IBS-like symptoms. Although the conclusions are hampered by small sample size of many of them, these are the main results: (1) Gender: two studies report that women have a higher risk of suffering IBS-like symptoms while in remission, as happens in conventional IBS^[4,5];

another study reports a higher risk in men^[46]; (2) Age: leaving aside the study by Farrokhyar *et al*^[45] that reported a higher risk for patients over 40 years of age (OR = 3.2) most studies have failed to show an association between age and risk of suffering IBS-like symptoms while in remission; (3) Extension and/or location of IBD: two studies analyzed this variable and did not find a significant association with the prevalence of functional symptoms^[5,33]; (4) IBD duration: only analyzed in one study with a small sample size, no significant association was found^[2]; and (5) Previous surgery: analyzed only in three studies, pooled prevalence of functional symptoms was higher in operated patients (60% vs 32.4%)^[2,30,41].

IF THEY ARE IN REMISSION, WHY DO THEY HAVE SYMPTOMS?

Several pathogenic mechanisms can explain the occurrence of IBD-IBS beyond a merely random effect. Dysmotility, visceral hypersensitivity and increased mucosal permeability are the best studied ones.

Several studies have investigated why some IBD patients in remission remain asymptomatic while others experience ongoing symptoms of functional origin. We summarize the different explanations that have been considered.

It is just a random effect

IBS is one of the most frequent gastrointestinal diseases worldwide, with a prevalence that ranges from 10% to 15% of the general population^[55-58]. A similar prevalence in quiescent IBD patients would be expected. However, as we have described in the previous section, prevalence of IBD-IBS is more than double^[54]. It is therefore obvious that there must be further reasons other than merely chance that explain the occurrence of IBS symptoms in IBD.

Inflammation persists

Microscopic inflammation in normal-appearing mucosa could persist after resolution of an acute flare and justify persistence of symptoms in spite of mucosal healing^[59,60].

In 2010 Keohane *et al*^[33] analyzed 106 IBD patients in remission, all with normal CRP levels, and found significantly higher fecal calprotectin levels in patients

with functional symptoms than in asymptomatic patients (414.7 mg/kg vs 174.9 mg/kg in CD patients, 591.1 mg/kg vs 229.8 mg/kg in UC). They concluded against a real overlap between IBD and IBS, as persistence of symptoms would be provoked by inflammation persistence ("IBD is IBS unless proven otherwise"). It should be highlighted however, that they did not perform endoscopy systematically, so active inflammation could not be ruled out completely. Along the same lines, the work of Vivinus-Nébot *et al.*^[51] reported that symptomatic patients had higher levels of tumor necrotic factor alpha (TNF- α), as well as a trend towards a higher amount of intraepithelial lymphocytes and eosinophils. These studies imply that these patients could theoretically be candidates for IBD treatment escalation, a hypothesis neither proven nor tested to date.

Against this perspective several publications appeared in the following years reporting a considerable proportion of symptomatic patients with normal levels of fecal calprotectin^[5,35,61], which means that there must be additional pathogenic factors and that treatment escalation in these patients should be considered very carefully, if at all.

IBD induces dysmotility

Several studies have detected similar colonic motility patterns in quiescent IBD than those described in IBS (higher number of low-amplitude propagated contractions)^[62-64]. Subtle changes in antroduodenal motility in quiescent CD have also been described^[65]. These alterations in intestinal motility could be related to autonomic nerve system dysfunction that has been described in IBD patients in remission^[66-69].

IBD induces hypersensitivity

Several experiments with rectal balloon distension showed initially that IBD patients in remission had higher visceral pain thresholds (*i.e.*, tolerance to pain was higher) than IBS patients^[70,71]. Cerebral activity induced by peripheral stimuli in quiescent CU patients resembled more that of healthy population than the one of IBS patients^[72]. IBD patients would therefore have reduced visceral sensitivity, which could be interpreted as an adaptive response in the context of chronic-recurrent inflammation.

However, when visceral sensitivity in IBD patients in remission has been studied based on the presence or absence of functional symptoms, findings have been different. A study in pediatric IBD patients in remission with residual abdominal pain observed that they presented rectal pain thresholds lower than those of healthy volunteers and similar to those of patients with functional digestive diseases^[73]. Further on, two studies measured in rectosigmoid junction biopsies the density of nerve fibers that presented the transient potential vanilloid receptor type 1 (TRPV1), implicated

in nociception and in IBS visceral hypersensitivity^[74,75]. They observed that in symptomatic IBD patients in remission the density was significantly higher than in healthy controls and in asymptomatic IBD patients. Additionally, the number of TRPV1 fibers was proportional to pain intensity referred by the patient. IBD-IBS patients would therefore have hypersensitivity induced by up-regulation of TRPV1, which could in turn be mediated by central generated stimuli. Mast cells, which participate in the generation of abdominal pain in IBS^[76,77], have also been involved in pain generation in IBS-IBD^[78]. At the molecular level, it has been described additionally an up-regulation of serotonin synthesis, a well-known mediator in visceral motility and sensitivity^[79].

IBD induces mucosal permeability increment

In IBS, intestinal permeability is constantly increased and is proportional to symptom intensity^[51,80]. This phenomenon would increase mucosal exposure to endoluminal antigens that could in turn induce inflammatory, sensitive or motor responses responsible for patients' symptoms. In IBD in remission similar findings have been reported: Permeability is higher than that of healthy volunteers and is even higher in symptomatic patients^[51,81]. The permeability increment has been also related to the risk of suffering a relapse^[82,83].

Microbiota disturbance plays a role

Composition of the gut flora is disturbed in both IBS and IBD, although it is not really established whether it is a cause or a consequence of the physiological alterations that characterize such entities or of the treatments patients receive^[84-86]. No studies have explored flora composition in IBD-IBS patients or compared it with asymptomatic IBD patients in remission.

Similarities with post-infectious IBS

After acute gastroenteritis odds of developing IBS are increased 6-7 fold^[87,88]. This post-infectious IBS (PI-IBS) is conceptually very similar to IBS in quiescent IBD, as both would be caused by post-inflammatory mechanisms. Although dysmotility and hypersensitivity do not seem to explain the development of symptoms after the infection^[89], mast cells and increased intestinal permeability have been involved as in IBD-IBS^[7,90].

Psychological stress: Pivotal role as well?

Specific role of psychological distress in pathogenesis of IBS symptoms in quiescent IBD remains to our knowledge uninvestigated. Evidence from its implication in IBS pathogenesis (both PI-IBS and conventional IBS)^[89,91] and in IBD flare induction^[92] makes it highly possible, in our opinion, that an important link exists with IBS-IBD.

Table 3 Studies that explore quality of life and anxiety in inflammatory bowel disease patients in remission with irritable bowel syndrome-like symptoms

Ref.	Sample size (CD/UC)	Questionnaires used	Results
Simrén <i>et al</i> ^[2]	83 (40/43) 37 IBD-IBS (23/14)	GSRS HADS STAI PGWB	Higher anxiety and depression scores in IBD-IBS (worst in CD)
Minderhoud <i>et al</i> ^[44]	107 (34/73) 37 IBD-IBS (14/23)	IBDQ	Lower QoL scores in IBD-IBS
Farrokhyar <i>et al</i> ^[45]	149 (105/44) 31 IBD-IBS (27/4)	sIBDQ EQ-5D	Occurrence of any FGID taken in count (not only IBS-like) Lower QoL scores in CD patients with FGID Difference not significant for UC
Ansari <i>et al</i> ^[46]	50 (0/50) IBD-IBS: 23 (0/23)	SF-36	Lower QoL scores in IBD-IBS than in asymptomatic and similar to patients in flare
Keohane <i>et al</i> ^[33]	106 (62/44) 54 IBD-IBS (37/17)	IBSQ HADS	QoL scores only significantly lower in UC-IBS Levels of anxiety and depression only significantly higher in UC-IBS
Piche <i>et al</i> ^[48]	92 (92/0) 42 IBD-IBS (42/0)	French-validated IBS severity scoring system Likert scales FIS Short BDI	Higher severity, impact, depression and fatigue scores in CD-IBS No significant differences in anxiety level
Barratt <i>et al</i> ^[3]	276 (110/166) 31 IBD-IBS (14/17)	SF-36 HADS	No differentiation between IBD patients in remission or in active phase Lower QoL scores and higher anxiety, depression scores in IBD-IBS
Bryant <i>et al</i> ^[4]	93 (47/43) 12 IBD-IBS (no CD/UC differentiation)	sIBDQ HADS BDQ-6	Occurrence of any FGID taken in count (not only IBS-like) Lower QoL scores and higher anxiety and depression scores in IBD patients with any FGID Lowest scores in IBS-like symptoms
Jelsness-Jørgensen <i>et al</i> ^[49]	89(28/61) 30 IBD-IBS (8/22)	FQ RFIPC	More fatigue scores in IBD-IBS (worst in UC) More concerns in UC-IBD (difference non significant for CD)
Kim <i>et al</i> ^[50]	226 (107/119) 82 IBD-IBS (50/32)	EQ-5D HADS	Occurrence of any FGID taken in count (not only IBS-like) Lower QoL scores and higher anxiety and depression scores in UC-IBS (difference non-significant for CD)
Berrill <i>et al</i> ^[5]	97 (40/57) 31 IBD-IBS (13/18)	HADS	No differentiation between IBD patients in remission or in active phase Higher anxiety and depression scores in IBD-IBS
Jonefjäll <i>et al</i> ^[35]	94 (0/94) 25 IBD-IBS (0/25)	HADS SF-36	Lower QoL scores and higher anxiety scores in UC-IBS (difference in depression score non-significant)
Vivinus-Nébot <i>et al</i> ^[51]	49 (31/18) 18 IBD-IBS (11/7)	French-validated IBS severity scoring system	Higher severity and impact scores in IBD-IBS

IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn’s disease; GSRS: Gastrointestinal symptom rating scale; HADS: Hospital anxiety and depression scale; STAI: Spielberger state trait anxiety inventory; PGWB: Psychological general well-being index; IBSQ: Inflammatory bowel disease questionnaire; QoL: Quality of life; sIBDQ: Inflammatory bowel disease questionnaire; EQ-5D: EuroQOL-5D; FGID: Functional gastrointestinal disorders; FIS: Fatigue impact scale; BDI: Becks depression inventory; BDQ-6: Bowel disease questionnaire-6; FQ: Fatigue questionnaire; RFIPC: Rating form of inflammatory bowel disease patients concerns.

I HAVE ACHIEVED REMISSION IN MY PATIENT. WHY SHOULD I CONTINUE TO BE CONCERNED?

In spite of being in remission, IBD-IBS patients have an impaired quality of life, and deserve attention and care.

IBD patients in general have a worse quality of life (QoL) than controls, mostly related to disease activity^[93-95]. Even though quiescent IBD patients with IBS-like symptoms are not at risk of suffering direct complications of IBD such as perforations, abscesses or toxic megacolon, their symptoms can be very intense and significantly reduce their QoL, maybe as much as an actual flare does. In Table 3 we summarize all studies that have analyzed the effect of IBS-like symptom occurrence in different QoL scores and in

anxiety and depression scales^[2-5,33,35,44-46,48-51]. Although they are quite heterogeneous, all of them consistently show that IBD patients in remission who have IBS-like symptoms have a worse QoL and a greater probability of suffering from depression or anxiety than those who remain asymptomatic.

HOW DO WE TREAT FUNCTIONAL SYMPTOMS IN IBD PATIENTS IN REMISSION?

Evidence in IBD-IBS treatment is very poor to date. It is reasonable to apply usual IBS treatment strategies (diet modification, antispasmodics, antidepressants, probiotics, *etc.*) in the meantime.

The literature addressing this question is very scarce and of little quality, mostly based on experts’

recommendations^[8,38,96,97]. It seems very reasonable to follow a step-up approach to avoid over-medication in patients who very probably are already on immunosuppressive maintenance drugs.

Diet interventions

Some authors recommend elaborating a diary to detect foods and beverages that provoke symptoms and eliminate them whenever feasible^[97]. This is not easy as noxious effects can be accumulative (*i.e.*, symptoms may appear after eating them for several days and not immediately) and dose-dependent (*i.e.*, small amounts could be well tolerated)^[96]. IBS literature is rich in food lists that have been involved in symptom triggering, and most include lactose, caffeine, fat-rich foods, deep fried foods, chewing gums, alcohol and sorbitol^[98,99]. In recent years efforts are being made in order to establish a more systematic and more evidence-based approach to diet management in IBS. Diets with low quantities of fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) reduce symptoms in well-designed clinical trials^[100]. This strategy could be useful in IBD-IBS patients, but remains unproven^[101].

Fiber supplementation

Hallert *et al.*^[102] carried out a small, placebo-controlled trial of ispaghula husk in ulcerative colitis patients in endoscopic remission who complained of several gastrointestinal symptoms. Although not defined by the authors as IBS, the symptoms they describe were those typically present in it (pain, diarrhea, urgency, constipation, bloating, *etc.*). Ispaghula was more effective than placebo in improving those symptoms so fiber supplementation could be beneficial. In contrast, other authors recommend fiber reduction based on the fact that fiber, especially the insoluble subtype, can exacerbate symptoms in IBS (mainly bloating and flatulence)^[103-105].

Antispasmodics and antidiarrheals

Antispasmodics as a group are useful in IBS management and have a favorable safety profile^[105,106]. They could be used in quiescent IBD patients with IBS-like symptoms, although no specific trials have been published to explore their efficacy. The theoretical risk exists of inducing toxic megacolon if IBD is active^[103,107].

Loperamide has no clearly proven efficacy in treating IBS but can nevertheless be useful to manage diarrhea^[105,106]. It has to be used with caution if at all during a flare, as it could induce a toxic megacolon^[108,109]. A placebo-controlled trial in CD patients with chronic diarrhea showed benefits of loperamide in alleviating symptoms, so its judicious use could offer satisfactory relief in patients in remission with ongoing diarrhea^[103,110].

Antidepressants

Antidepressants as a group, both tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRI), are effective in providing global symptom relief in IBS^[105,106]. Besides their neuro-modulatory action they could exert an anti-inflammatory effect, as shown in animal models^[111]. Most publications^[112] referring to use of antidepressants in IBD are case reports that globally suggest a beneficial effect of these drugs not only in psychological symptoms but also in somatic ones. A more recent retrospective study has shown that IBD patients with concurrent depression who were under high dose antidepressant regimens had fewer disease flares and had less need of steroids^[113]. Iskandar *et al.*^[114] have published the only original work to date that addresses specifically the potential utility of antidepressants in IBD-IBS. In their retrospective cohort study they compared the efficacy of low dose TCAs in 81 IBD patients in remission or with mild disease who complained of ongoing gastrointestinal symptoms, with that registered in a cohort of IBS patients. At least moderate improvement was achieved in 59.3% of IBD patients (higher in UC patients), similar to the proportion obtained in IBS. Data on other antidepressants such as SSRI in IBD are lacking.

Any other options?

No other treatments have been explored in IBD-IBS, but there are several fields very interesting for future research. Involvement of gut flora in both IBS and IBD (see above), efficacy of non-absorbable antibiotic rifaximin and of probiotics in IBS^[105,106], and promising results of probiotics in UC^[115] suggest that intestinal microbiome modulation could be useful in IBD-IBS treatment. Hypersensitivity and central nervous system involvement make psychological therapies, also tested in IBS^[105,106], an additional interesting option to be evaluated in the future.

CONCLUSION

IBD patients in remission suffer quite frequently from symptoms that resemble IBS. So-called IBD-IBS is probably secondary to several factors, including post-inflammatory dysmotility and hypersensitivity, mast cell activation and increased epithelial permeability. Even though these patients are in remission their quality of life can be as low as during an acute flare, so an effort should be undertaken to recognize and treat this condition as satisfactorily as possible. Evidence on best management options of these patients is almost nonexistent. It seems reasonable to use the same drugs that have proven efficacy in IBS, such as antispasmodics and antidepressants, while we wait for future prospective trials.

Concurrence of IBS and IBD, existence of post-

infectious IBS and the common pathogenic mechanisms between both entities, teach us that the classic functional-organic dichotomy is very probably obsolete. The old schema would be substituted by a unifying biopsychosocial model according to which we should not limit our therapeutic efforts to resolving inflammation but rather extend our scope to treatment of any symptoms patients report that impair their QoL and psychological well-being.

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