World Journal of Gastroenterology

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World J Gastroenterol 2020 July 14; 26(26): 3712-3719

DOI: 10.3748/wjg.v26.i26.3712

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

OPINION REVIEW

Functional gastrointestinal disorders in inflammatory bowel disease: Time for a paradigm shift?

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Author contributions: Vasant DH and Ford AC both reviewed the literature; Vasant DH wrote the paper; Ford AC reviewed and helped write the paper, and provided important intellectual input.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Manuscript source: Invited manuscript

Received: March 28, 2020
Peer-review started: March 28, 2020
First decision: April 18, 2020

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Abstract

Recent advances in biological therapies have revolutionalised and redefined treatment targets in inflammatory bowel disease (IBD). There is now a stronger emphasis on achieving the more stringent therapeutic goals of mucosal and histological healing, rather than clinical remission alone. Consequently, the treatment of refractory "functional" gastrointestinal symptoms, often attributed as the aftermath of previous inflammation, has recently become more prominent in quiescent disease. With further expected advances in anti-inflammatory treatments on the horizon, the burden of such symptoms in quiescent disease, which have been relatively neglected, is set to become an even bigger problem. In this article, we highlight the current state of research and understanding in this field, including recent developments and clinical practice guidelines on the diagnosis and management of functional gastrointestinal symptoms, such as irritable bowel syndrome and functional anorectal and pelvic floor disorders, in patients with quiescent IBD. These disorders are not only highly prevalent in these patients, they are often misdiagnosed, and are difficult to treat, with very few evidence-based therapies. Moreover, they are associated with substantial impairment in quality-of-life, considerable morbidity, and psychological distress. There is therefore an urgent need for a change in emphasis towards earlier recognition, positive diagnosis, and targeted treatment for patients with ongoing functional gastrointestinal symptoms in the absence of active IBD. This article also highlights the need for further research to develop much needed evidence-based

Revised: April 23, 2020
Accepted: July 1, 2020
Article in press: July 1, 2020
Published online: July 14, 2020

P-Reviewer: Chiba T, Lipták P
S-Editor: Ma YJ
L-Editor: A
E-Editor: Ma YJ

therapies.

Key words: Irritable bowel syndrome; Inflammatory bowel disease; Functional gastrointestinal disorders; Faecal incontinence; Pelvic floor dyssynergia

Core tip: Functional gastrointestinal symptoms, in the absence of inflammation, affect around one-third of inflammatory bowel disease (IBD) patients in remission, causing significant psychological distress and impairment of quality of life. As IBD therapies continue to advance, functional gastrointestinal symptoms, as a consequence of previous inflammation, are set to become a bigger problem. Here, we review the current evidence base, highlight a recently proposed diagnostic algorithm, and discuss empirical treatment guidance for functional gastrointestinal symptoms in quiescent IBD. We also discuss future considerations and areas of unmet need to stimulate further research.

Citation: Vasant DH, Ford AC. Functional gastrointestinal disorders in inflammatory bowel disease: Time for a paradigm shift? *World J Gastroenterol* 2020; 26(26): 3712-3719
URL: https://www.wjgnet.com/1007-9327/full/v26/i26/3712.htm
DOI: https://dx.doi.org/10.3748/wjg.v26.i26.3712

INTRODUCTION

Recent advances in medical therapies for both ulcerative colitis (UC) and Crohn's disease (CD) have improved the frequency and depth of remission in patients with inflammatory bowel disease (IBD)[1]. With the current availability of biological agents targeting multiple disease mechanisms including anti-tumour necrosis factor-α, anti-integrin, and anti-interleukin 12/23 drugs, as well as janus kinase inhibitors, the goals of IBD treatment have changed dramatically in recent years. Moreover, the introduction of several, more cost-effective, biosimilar drugs, have also improved access to some biological agents[2].

As a result of these developments, complete mucosal and histological healing, which appears to lead to improved outcomes for patients[3-5], has become a realistic therapeutic target. Consequently, clinical remission is no longer the recommended standard of care, and a more aggressive, "treat to target approach" , has been advocated[6-8]. This change in emphasis, together with the use of biochemical and endoscopic measures of subclinical inflammation to assess disease activity, has led to increasing awareness of a group of patients with IBD who have refractory gastrointestinal symptoms, in the absence of objective inflammation[9]. Indeed, recent data have shown that there is often a poor correlation between symptoms and mucosal inflammation in IBD[10]. Although the potential for co-existence of "functional" gastrointestinal symptoms in a proportion of patients with quiescent IBD was first described over 30 years ago[11], this group of patients has received minimal attention in the medical literature until relatively recently.

The pathophysiology of functional gastrointestinal disturbances in quiescent IBD is likely to be multifactorial, with numerous experimental studies demonstrating post-inflammatory changes in gut motility[12-17], permeability[18,19], impaired colorectal function (abnormal colonic tone, rectal compliance and impaired anal sphincter function)[14], and visceral hypersensitivity[20-23]. With further progress in controlling inflammation successfully in patients with IBD anticipated, it is likely that there will be an even higher burden of refractory functional symptoms in IBD clinics in the future. However, despite overlap of functional symptoms being common in patients with IBD, there are limited evidence-based treatment options. This article discusses recent developments in this field, to highlight areas of unmet need, and suggest future directions and treatment paradigms.

The importance of early recognition and a positive diagnosis of functional overlap

Functional gastrointestinal disorders (FGIDs), are the most common disorders seen by gastroenterologists[24], affecting around 35% of the general population[25]. Based on their putative pathophysiology, these disorders have recently been re-defined as disorders

of gut-brain interaction, and there is now an increased emphasis on making a positive diagnosis of the majority of these conditions, using symptom-based criteria, in the absence of red flag symptoms[26,27]. In the general population, functional bowel disorders are the most common of these disorders of gut-brain interaction, affecting almost 30% of people[25] and, interestingly, these conditions have a similar, or even higher, prevalence in the IBD clinic[9,11]. Indeed, pooled prevalence data from a 2012 meta-analysis suggested a prevalence of symptoms compatible with irritable bowel syndrome (IBS) of 35% in quiescent IBD, with a higher prevalence in CD compared with UC[28].

The majority of studies included in this meta-analysis pre-dated the availability of faecal calprotectin (FC) as a non-invasive biochemical marker of gut inflammation and therefore reported the frequency of IBS-type symptoms in patients in clinical remission. However, even in subsequent studies that have used markers of biochemical remission, such as FC, mucosal remission, or histological remission the proportion of patients with IBD reporting these symptoms remains in the region of 25% to 30%[29-31]. Importantly, and consistently, these functional bowel symptoms in IBD are associated with significant psychological distress, and impair quality of life to a similar extent to that seen in patients with IBD with confirmed active gastrointestinal inflammation[29,32-37]. Similarly, although even less well studied, functional anorectal disorders[38] including evacuatory disorders[39] and faecal incontinence[40,41], are often reported in patients with quiescent disease[32]. In the absence of active inflammation, escalation of IBD therapy, including potentially inappropriate use of corticosteroids or immunosuppressive drugs is likely to be futile[42], leading to further patient dissatisfaction, costly, and carries the risk of serious adverse effects[43-47]. This underlines the importance of early recognition of functional gastrointestinal symptoms in patients with IBD.

Unlike the diagnosis of FGIDs in a non-IBD population, the diagnosis of overlapping FGIDs in IBD first requires some investigation, in order to exclude active inflammation. As recommended in a recently proposed diagnostic algorithm, a stepwise approach using biochemical tests including FC, followed by endoscopy and biopsies, or cross sectional imaging, should be followed[48]. Although not the focus of the current paper, it is also important to consider and, where appropriate, exclude treatable mimics of FGIDs, such as bile acid diarrhoea, small intestinal bacterial overgrowth, or pancreatic insufficiency, particularly where there are risk factors such as ileal disease or a history of predisposing surgical intervention[49].

Following the exclusion of active inflammation and important potential mimics, careful consideration should be given to the likely mechanism of symptoms, based upon the predominant clinical features, and recognising that there are likely to be several perturbations contributing to the pathophysiology. In addition to the traditional IBD-focused clinical history, particularly in the absence of active inflammation and structural pathology, screening questions for positive diagnostic features of FGIDs and risk factors for pelvic floor dysfunction are important[38]. These include IBS symptoms (abdominal pain, bloating, and altered bowel habit or stool form), obstructive defaecatory symptoms, including incomplete emptying, straining, features of overflow diarrhoea or impaction, and rectal digitation. The latter is an important clinical feature, which appears to be predictive of response to pelvic floor biofeedback[50,51]. Faecal incontinence should also be specifically screened, for as it has been shown to be highly prevalent in patients with IBD[52], but may be underreported due to embarrassment on the part of patients[53]. This approach will help identify those in whom pelvic floor and anorectal physiology investigations are appropriate.

Current strategies for management of functional gastrointestinal disorders in IBD

One of the most important steps in managing overlapping FGIDs in this context is optimising the patient-provider relationship, providing clear, understandable explanations, and a positive diagnosis. This is likely to improve acceptance of the diagnosis, engagement with treatment, and also helps manage expectations, all of which are important in achieving a positive clinical outcome.

As highlighted in a recent expert review[48], there are very few randomised controlled trials or prospective studies on the management of functional gastrointestinal symptoms in IBD. Current practice is therefore largely empirical, and often based upon the central tenets of IBS management using dietary, pharmacological, or psychological approaches (Table 1). One of the interventions with some evidence in clinical trials, as well as in a blinded re-challenge study in quiescent IBD, is a diet low in fermentable oligo-, di-, or mono-saccharides, and polyols (FODMAPs)[54-56]. Further evidence for the low FODMAP diet in patients with quiescent IBD and co-existent functional gastrointestinal symptoms comes from recent

Table 1 Therapies empirically used to treat functional gastrointestinal symptoms in inflammatory bowel disease requiring validation in future clinical trials

Treatment	Gastrointestinal symptom(s) targeted
Low FODMAPs diet	Bloating, visceral pain, diarrhoea
Anti-motility agents (*e.g.*, loperamide, ondansetron)	Exaggerated gastro-colic reflex, faecal urgency, diarrhoea, faecal incontinence
Laxatives and pro-motility agents (*e.g.*, prucalopride, linaclotide)	Slow colonic transit, constipation
Antispasmodics	Visceral pain, bloating
Gut-brain neuromodulators (*e.g.*, antidepressants)	Visceral pain, faecal urgency, diarrhoea
Probiotics	Bloating, altered bowel habit
Pelvic floor biofeedback	Evacuatory dysfunction, faecal urgency, faecal incontinence
Psychological interventions (*e.g.*, hypnotherapy, cognitive behavioural therapy)	Visceral pain, bloating, altered bowel habit, non-colonic symptoms

FODMAPs: Fermentable oligo-, di-, or mono-saccharides, and polyols.

trial data demonstrating a significantly greater improvement in gastrointestinal symptom scores and significantly higher rates of symptom relief after 4 wk of a low FODMAP diet, compared with a sham exclusion diet[57].

Unfortunately, there remains very little evidence for the efficacy of specific pharmacological therapies in this patient group. Current approaches include the use of laxatives, prokinetics, such as prucalopride in those with chronic constipation (often those with distal colonic disease or proctitis), antispasmodics, anti-diarrhoeal drugs, such as loperamide, or central neuromodulators, such as antidepressants[48]. Although the latter class of drugs are one of the mainstays for the treatment of abdominal symptoms in IBS[58], to date there has been only one randomised controlled trial in CD, which did not show any benefit of fluoxetine in preventing relapse of disease activity in patients with quiescent disease[59]. In another retrospective study, using tricyclic antidepressants, the authors demonstrated moderate improvement of residual symptoms despite "optimal" medical therapy, particularly in those with UC[60]. Despite the fact that certain probiotics appear beneficial in the induction and maintenance of UC in particular[61], their efficacy in patients with overlapping FGIDs and quiescent disease has not been evaluated specifically, and should be assessed in future clinical studies.

In patients with anorectal dysfunction, or pelvic floor dyssynergia confirmed on anorectal physiology, targeted pelvic floor physiotherapy and biofeedback therapy appear to be of benefit in several small uncontrolled studies[39,62-64], underlining the importance of screening for these conditions in the IBD clinic. Several psychological interventions have been shown to be of benefit in patients with IBS, including gut-directed hypnotherapy[65] and cognitive behavioural therapy (CBT)[58]. Although these interventions may also benefit some patients with IBD, there have been few studies to date, most of which have not been conducted in patients with co-existent functional gastrointestinal symptoms[66]. Although the long-term benefits are unclear, CBT may have a short-term role in improving depression and quality of life in patients with IBD, and hypnotherapy has been shown to be of benefit in only two small studies[66,67].

CONCLUSION

Co-existent FGIDs are common in IBD, and are often under recognised and difficult to treat. Clinicians specialising in IBD are likely to soon become victims of their own success; as treatments targeting inflammation continue to improve they are likely to see more functional gastrointestinal symptoms, as a consequence of prior inflammation, in their clinics. There is therefore the need for a paradigm shift in the approach to some patients with IBD. Previously, in the absence of active inflammation as a cause for their symptoms, patients were often given reassurance that their disease was quiescent, but little else in the way of explanation as to why they were experiencing these symptoms, or how they should be managed. With improvements in our understanding of FGIDs in quiescent IBD, it is essential that clinicians have a

positive, structured, approach to managing these patients. The recent American Gastroenterological Association clinical practice update and diagnostic algorithm has helped raise awareness of these issues, and provided some much needed recommendations as to how to approach this group of patients[48]. There remains, however, an urgent need for evidence-based therapies, as most of the pharmacological treatment of these symptoms is empirical, and extrapolated from the IBS literature. At present, the key to successful management of FGIDs in IBD is recognition, early diagnosis, clear communication, avoidance of inappropriate escalation of IBD-related medications, and a careful and holistic clinical assessment to select appropriate patients for a low-FODMAP diet, and pelvic floor and physiology investigations. The latter, in the appropriate setting, may lead to targeted interventions such as biofeedback, which can improve symptoms as well as quality of life.

Future research should focus on developing specific evidence-based treatments for quiescent symptoms in IBD, based on the results of well-designed clinical trials. A forthcoming randomised study in the United Kingdom, funded by the National Institute for Health Research, has been designed to study the effectiveness of both dietary and pharmacological interventions in this setting. The study, a multi-arm multi-stage trial of a low FODMAP diet, amitriptyline, ondansetron, or loperamide, will include almost 500 patients with UC with ongoing diarrhoea, despite a FC < 250 mcg/g[68]. It is anticipated that this trial will provide much needed evidence as to how best to manage this group of patients. In addition to identifying effective medical therapies, there is also a need to develop a better evidence-base for psychological and behavioural therapies, as well as pelvic floor interventions, with larger clinical trials in patients with quiescent IBD. An improved understanding of the mechanism of pelvic floor dysfunction in quiescent disease as a prelude to potential neuromodulatory therapies is also required.

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