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Gastrointestinal motility disorders in inflammatory bowel diseases

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from the esophagus to the anorectum, and which will be extensively covered in this review. It is conceivable that at least part of this derangement is strictly related to inflammatory cytokine trafficking and neuromuscular changes; however, given the high prevalence of functional gastrointestinal disorders in the general population, this overlap might also be serendipitous. However, it is worth noting that literature data on this topic are relatively scarce, sometimes quite outdated, and mostly focused on the interplay between irritable bowel syndrome and inflammatory bowel disease. Nevertheless, both researchers and clinicians must be aware that symptoms related to gastrointestinal motility disorders may be highly prevalent in both active and inactive inflammatory bowel disease, correlate with greater psychological comorbidity and poorer quality of life, and may negatively influence the therapeutic approaches.

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Abstract

The relationship between motility and inflammatory gastrointestinal disorders is at the same time complex and intriguing since these conditions might share some genetic, environmental, immunological and microbial predisposing factors. In addition, significant symptom overlapping may occur, muddling the waters within the clinical context. Although on one hand this represents a challenge for the clinician for a potential under- or over-treatment and diagnostic delay, on the other hand it possibly represents an opportunity for the researcher to better disclose the intimate relationship between chronic (often low-grade) inflammation, motor disorders and deranged sensory function. The best example is probably represented by Crohn's disease and ulcerative colitis. In fact, a number of gastrointestinal motor disorders have been described in association with these diseases, disorders which span

Key words: Crohn's disease; Gastrointestinal motility disorders; Gut; Inflammatory bowel diseases; Perception; Ulcerative colitis

Core tip: Gastrointestinal motor disorders are not infrequently associated with inflammatory bowel disease and may represent a confounding factor, especially when inflammation has subsided or the clinical picture is in remission. Since these entities may involve all the segments of the gastrointestinal tract, it is important that clinicians and researchers be aware of this potential overlap, since lack of knowledge may lead to mistreatment or overtreatment. However, literature data on this topic are relatively scarce and are extensively covered in this review.

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INTRODUCTION

Inflammatory bowel diseases (IBD), mainly represented by Crohn's disease (CD) and ulcerative colitis (UC), are emerging pathological conditions whose epidemiological rising is thought to be related to the westernization of lifestyle and industrialization^[1]. The genesis of IBD is quite complex and numerous pathophysiological factors are now recognized to be involved in the predisposition, triggering, progression and outcome of these conditions^[2].

Interestingly, several of these factors are the same thought to be responsible for the genesis of (at least some of) gastrointestinal motor abnormalities, disorders that are classified among the so-called functional gastrointestinal disorders^[3], *i.e.*, those pathological entities in which no known structural (pathological or radiological) abnormalities, infectious or metabolic causes are present^[4]. However, in recent years it has become evident that, at least for some of these entities, the pathophysiological mechanisms, defined as "idiopathic" until now, can actually be reconducted to some form (sometimes very subtle) of low grade inflammation. This is, for instance, the case of esophageal achalasia^[5,6], functional dyspepsia^[7,8], irritable bowel syndrome (IBS)^[9] and chronic constipation^[10,11], where the presence of limited number of inflammatory cells infiltrating the mucosa and/or the myenteric plexus has been reported. On the other hand, the recent description of enteric nervous system (ENS) abnormalities in IBD patients (mainly represented by myenteric plexitis)^[12,13] may justify alterations of the normal motor function and visceral reflexes of the gut.

Thus, as we will see below, the co-existence of IBD and gastrointestinal motor disorders may somewhat represent more than a serendipitous occasion and it is likely that motility and/or perception abnormalities play a role in the clinical pictures of IBD, sometimes complicating the physician's assessment and the patient's lifestyle. To what extent these motor abnormalities provoke or correlate with gastrointestinal symptoms reported by IBD patients during remission is rather unknown. However, despite potential limitations, the majority of studies report a greater frequency of "IBS-like" symptoms in quiescent IBD compared to the background population^[14].

GENERAL CONSIDERATIONS

The relationship between gastrointestinal motility disorders and IBD is a quite complex one and not well elucidated yet since multiple variables appear to play a role. For instance, IBS-like symptoms are frequently found in patients with IBD considered to be in clinical remission and it is very difficult to distinguish these symptoms as due to IBS or to persisting occult inflammation^[15]. More-

over, symptoms related to motility/functional gastrointestinal disorders are highly prevalent in both active and inactive IBD and correlate with greater psychological comorbidity and poorer quality of life^[16,17]. Some data also suggest that intercurrent infectious gastroenteritis may increase IBD risk in IBS patients^[18]. However, as can be seen from the literature evidence, most data on the relationship of functional gastrointestinal disorders/IBD is actually focused on the relationship of IBS/IBD and the other gastrointestinal motor abnormalities are relatively neglected. The following paragraphs will take into consideration these relationships for each segment of the gastrointestinal tract (Table 1).

ESOPHAGUS

Although relatively uncommon (about 5%-8% in both adults and children^[19,20]), esophageal involvement has become increasingly recognized in IBD, especially in patients with CD^[21], even in the absence of specific symptoms as patients more frequently undergo upper endoscopic evaluations^[22]. The clinical manifestations are usually due to the mucosal and/or transmural involvement by the inflammatory process. One report showed an achalasia-like motility disorder in a patient with dysphagia and CD, with the esophageal dysmotility being due to the extensive inflammatory/fibrotic process^[23]. To date, no specific clinical or manometric investigations have been carried out in IBD patients, except a small group of UC patients undergoing esophageal manometry as a pathological control group^[24] in whom no abnormalities were found compared with normal controls.

It is worth noting that gastro-esophageal reflux symptoms are more frequent in patients with active IBD compared with those with quiescent disease^[25] and are associated with a reduced quality of life and increasing likelihood of anxiety and depression compared to controls^[26].

STOMACH

Upper gastrointestinal involvement in IBD patients may be found in about 15%-20% of patients^[27,28]. However, subtle microscopical abnormalities of the stomach and duodenum may be also present in patients with IBD and might explain some upper gastrointestinal symptoms^[29]. However, to date, only a few studies have investigated gastric motor function in patients with IBD. An earlier study with barium meal (a suboptimal method to evaluate gastric motor activity) on three patients with gastric involvement showed loss of normal gastric motility^[30]. A subsequent scintigraphic study on pediatric patients showed that gastric emptying was normal in UC patients and delayed in about 30% of children with CD^[31]. This delay was more prominent in malnourished children^[32]. The scintigraphic findings of normal gastric emptying in UC adults have been confirmed by other authors^[33]. Gastric emptying after intestinal resection in adults with CD proved to be within normal limits and the authors

Table 1 Summary of motor abnormalities and gastrointestinal symptoms in inflammatory bowel diseases patients in each segment of the gastrointestinal tract

Segment	Motor changes	Symptoms	Ref.
Esophagus	Aspecific, achalasia-like (rare)	Gastroesophageal reflux	[18,19,24,25]
Stomach	Delayed emptying	Not reported (?)	[30,31,34,35]
Biliary tree	Possible reduction of cyclic contractions of gallbladder due to deranged phase III and motilin peaks	Symptoms related to gallstones	[41,42]
Small bowel	Large amplitude, rapidly propagated waves in small bowel of UC after proctocolectomy	IBS-like symptoms	[49,57-60]
	Reduced small bowel contractions, increased incidence single and clustered propagated contractions in CD		[63,64]
Colon	Decreased contractility in UC with accelerated transit.	Diarrhea	[75-77]
	Reduced tone after meals		[80]
	Increased propulsive activity		[81]
Anorectum	Low anal pressure, poor rectal distensibility, reduced compliance, enhanced perception	Incontinence, urgency	[84-88] [90-93] [94,95]

UC: Ulcerative colitis; CD: Crohn's disease.

concluded that the diarrhea observed in these subjects should not be attributed to rapid gastric emptying^[34]. In a scintigraphic study on gastric emptying in adult patients with non-obstructive CD and no upper gastrointestinal involvement, we showed that, compared with healthy volunteers, no overall significant differences were found; however, subgroup analysis revealed that symptomatic patients and those with colonic involvement had a significantly delayed gastric emptying compared to controls. Such a difference was also observed between symptomatic and asymptomatic patients^[35]. Another scintigraphic study investigated the occurrence and putative pathophysiological mechanisms of gastric motor disorders in a small group of adult IBD patients and concluded that disturbances of gastric emptying are most pronounced in CD and might partly be caused by excessive CCK release^[36].

BILIARY TREE

Although the hepatobiliary tree is frequently affected in patients with IBD^[37], its motor function has been scarcely investigated in these subjects and only a few data are available in the literature. An ultrasound study carried out in a small group of IBD patients during continuous enteral nutrition revealed that gallbladder contractility and responsiveness to intravenous cholecystokinin are preserved in such instances^[38]. Another ultrasound study reported that after ileo-cecal resection, fasting gallbladder volume is decreased, whereas postprandial gallbladder motility is normal^[39]. Cholecystectomy specimens from patients with IBD did not show significant histopathological differences compared to controls^[40]. Nevertheless, gallstone prevalence is increased in CD patients; site and duration of disease and previous intestinal resections are considered as risk factors, even although data are conflicting^[41]. In 25 asymptomatic, uncomplicated CD patients we found a significant derangement of phase III of migrating motor complex in terms of occurrence, cycling and origination from the antro-duodenal region. Moreover, no clear peaking of motilin before phase III

was found^[42]. Therefore, we hypothesized that in some patients with CD, a reduction of cyclic phasic contractions of gallbladder occurs because of a decreased incidence of motilin peaks and phases III of the migrating motor complex in the antro-duodenal area. Thus, the lack of periodic stirring of bile contained in the gallbladder may lead to supersaturation and stone formation^[43].

SMALL BOWEL

The small bowel represents the main anatomic site of involvement for patients with CD, even although the terminal ileum may be rarely involved in UC^[44]. *In vitro* studies showed that inflammation impairs the contractile responses of human small intestine^[45] and this may be observed even with minimal inflammatory responses^[46].

Thus, IBD patients may complain of symptoms not only related to the active phases of their disease, but also to low grade inflammation that produces symptoms correlated to autonomic dysfunction and abnormalities of the motor activity or of visceral sensations^[47]. These symptoms are associated with lower quality of life and higher healthcare utilization in IBD patients and may herald a cohort at risk for worse outcomes^[48] since they may be present even in patients with quiescent disease, in whom the quality of life may be severely impaired by this association^[49,50]. In addition, in these patients a potential overtreatment with drug-related toxicity might occur. On the above grounds, it is therefore not surprising that a substantial number of IBD patients experience IBS-type symptoms (abdominal pain and discomfort, diarrhea, constipation)^[14], symptoms that often originate from low-grade inflammation causing abnormal motility and perception, especially (but not only) in the small intestine^[51]. These patients exhibit similar pathophysiological features to people diagnosed with IBS in the general community^[52-54], suggesting that the conditions are not mutually exclusive, may coexist in a considerable number of IBD patients^[55], and that clinical indexes may be insufficient to discriminate between the two conditions^[56].

Fortunately, the availability of fecal markers of inflammation may be quite useful in this setting^[57]. However, it should be kept in mind that a certain number of IBD patients with normal fecal calprotectin levels experience IBS-type symptoms and exhibit similar features to people diagnosed with IBS in the general community, suggesting that the conditions are not mutually exclusive and may co-exist in a considerable number of IBD patients^[55].

Concerning objective measurements, it is worth noting that, notwithstanding the frequent involvement, the small bowel motor function (due to the relatively invasive manometric techniques needing deep intestinal intubation and prolonged periods of recordings) has been scarcely investigated in IBD.

UC

The few available studies have been conducted on the small bowel of patients after proctocolectomy and ileal pouch-anal anastomosis. In a manometric study on eight such patients, the authors concluded that jejunoileal motility is not greatly altered by this kind of surgery. However, the appearance of large amplitude, rapidly propagating waves in the proximal jejunum after operation may be a response to increased storage within and distention of the distal bowel^[58]. Subsequently, similar findings (also by electromyographic assessment) have been reported by other authors^[59,61]. Interestingly, the defunctionalized ileum in these patients is able to regain at least some of its motor function after a brief period of meal stimulation^[62].

CD

In a study conducted on nine patients with partial mechanical obstruction due to CD, jejunal manometry showed that after the meal the most striking finding was the regular occurrence of clustered contractions. The associated periods of quiescent motor activity may account for the unexpectedly reduced postprandial frequency and motility index in obstructed patients compared with normal subjects^[63]. Another manometric study, carried out in CD patients without any sign of occlusion receiving total parenteral nutrition for acute exacerbation of the disease, showed that after correction of nutritional status and clinical improvement, jejunal motility is almost normal in most patients, although some abnormalities (mainly affecting the interdigestive motor complexes) may be documented in a few subjects^[64]. In a manometric study on fasting and postprandial gastroduodenal motor activity carried out in 35 patients with inactive CD^[65], we observed abnormal motility aspects in 74% of these patients and concluded that most patients with inactive, uncomplicated CD display marked gastrointestinal motor disorders, characterized either by reduced incidence of small bowel contractions and increased incidence of single or clustered propagated contractions.

LARGE BOWEL

Since this viscus is the most frequently affected target in UC, it is not surprising that (also due to its relatively easier

access), concerning motility and perception, the researchers' interest has focused more on the colon than on the other hollow viscera. Indeed, there is wide experimental evidence that inflammation may affect the motor^[66-69] and perceptive^[70-72] function of the large bowel. Interestingly, these effects are observed after resolution of the inflammatory phenomena^[73] and might be related to the fact that, at least for a subset of patients, a complete mucosal healing is not (or never) reached^[74] and a persistent sub-clinical inflammation associated with increased colonic paracellular permeability may be associated with the presence of IBS-like symptoms^[75]. It is also worth noting that the role of inflammation is not limited to the mucosa and muscular components of the bowel wall, but also involves the neuroenteric circuitries (*i.e.*, the ENS)^[12,13,76].

Early manometric studies carried out in the rectosigmoid area revealed decreased colonic contractility in patients with UC^[77,78] and correlated this decrease with the presence of diarrhea^[79], findings also confirmed by myoelectric techniques^[80]. Subsequently, the simultaneous assessment of motility and transit in UC patients carried out by a combined manometric/scintigraphic approach confirmed that the reduced colonic motor activity is also present in more proximal segments and that these patients have increased propagated activity of the colon that may speed the transit of contents^[81]. Moreover, it has been demonstrated by studies conducted with the barostat that UC patients display reduced tone of the descending colon following meals^[82]. More recent studies evaluating 24 h manometric recordings of colonic motility in patients with UC showed that, compared to controls, patients with moderately active disease have increased propulsive activity (of both high and low amplitude), a mechanism likely to be responsible for the diarrhea^[83]. This mechanism may be related to the distension of the large bowel^[84] due to accumulation of fluids and inflammatory materials. Interestingly, the increased number of high-amplitude propagated contractions reduces in UC patients in remission, whereas the low-amplitude propulsive activity remains higher compared to controls, possibly contributing to the persistence of abdominal symptoms in a subgroup of patients^[85].

ANORECTUM

CD

Anorectal manometric variables and rectal sensation have been reported to be abnormal in CD patients, even in those with only microscopic involvement^[86-89]. In particular, low pressures due to anal involvement are strongly correlated with fecal incontinence^[90]. Other authors, however, were unable to correlate urgency with anorectal variables or sensation^[91]. It is worth noting that poor rectal distensibility may predict a worse outcome of ileorectal anastomosis^[92].

UC

The frequency and urgency of defecation and the fecal incontinence in these patients may be due to a hyper-

sensitive, hyperactive and poorly compliant rectum^[93-95]. In patients with active disease, no abnormalities of the sphincter functions are present, whereas perception to stimuli appears altered compared to controls^[96,97].

Postoperative conditions

Anorectal manometry can predict the early outcome after closure of a diverting ileostomy in patients with ileorectal anastomosis since it has been shown that the number of bowel movements after surgery strongly correlated with the anal pressure and the neorectal compliance^[98]. This technique also helped to elucidate better the effects of surgery; in fact, prolonged manometric examination showed that the internal anal sphincter is damaged in the course of mucosal proctectomy and endoanal anastomosis, whereas after restorative proctocolectomy with stapled, end-to-end anastomosis a normal function of the internal sphincter is preserved^[99]. Of note, it has been shown that preservation of the rectoanal inhibitory reflex correlated with a decrease in the incidence of nocturnal soiling after confectioning of a double-stapled ileoanal reservoir^[100]. Thus, several authors have relied on functional assessment to tailor the surgical reconstructive approach in UC patients^[101-105].

CONCLUSION

Although relatively frequent, the co-presence of gastrointestinal motility abnormalities in IBD patients is still relatively unexplored. In fact, looking at the literature data, it is evident that only a few studies are available and most of the more recent literature is focused on the relationship of IBS/IBD^[106]. Thus, information on this topic is still scarce, especially concerning the upper gut. In addition, no controlled data are available regarding the response to treatment of motility changes and/or functional symptoms in IBD.

Moreover, little information is available on whether these motor abnormalities may influence delivery of drugs within the gut in IBD patients since most studies on this topic have been carried out in healthy volunteers. However, some patient data suggest that an increased gastrointestinal transit might impair absorption of several mesalazine formulations^[107]. An accelerated transit might also modify the release of budesonide or multi matrix formulation compounds, but data are lacking^[108]. Finally, some literature data suggest that abnormalities of rectal wall motility might increase mesalazine absorption in IBD patients with ileorectal anastomosis compared to controls^[109].

Hopefully, with the rising interest in the role of low grade inflammation as an important pathophysiological factor in the genesis of several gastrointestinal disorders^[110], more information will be available on the role of neuroimmune interactions leading to symptoms that may complicate the clinical picture in patients with IBD, especially when the major flares of disease are resolved.

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