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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (4): Irritable bowel syndrome

# Irritable bowel syndrome: Emerging paradigm in pathophysiology

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## Abstract

Irritable bowel syndrome (IBS) is one of the most common gastrointestinal disorders, characterized by abdominal pain, bloating, and changes in bowel habits. These symptoms cannot be explained by structural abnormalities and there is no specific laboratory test or biomarker for IBS. Therefore, IBS is classified as a functional disorder with diagnosis dependent on the history taking about manifested symptoms and careful physical examination. Although a great deal of research has been carried out in this area, the pathophysiology of IBS is complex and not completely understood. Multiple factors are thought to contribute to the symptoms in IBS patients; altered gastrointestinal motility, visceral hypersensitivity, and the brain-gut interaction are important classical concepts in IBS pathophysiology. New areas of research in this arena include inflammation, postinfectious low-grade inflammation, genetic and immunologic factors, an altered microbiota, dietary factors, and enteroendocrine cells. These emerging studies have not shown consistent results, provoking controversy in the IBS field. However, certain lines of evidence suggest that these mechanisms are important at least a subset of IBS patients, confirming that IBS symptoms cannot be explained by a single etiological mechanism. Therefore, it is important to keep in mind that IBS requires a more holistic approach to determining effective treatment and understanding the underlying mechanisms.



**Key words:** Pathophysiology; Irritable bowel syndrome; Inflammation; Immunologic; Genetics; Microbiota; Diet; Enteroendocrine cell

**Core tip:** In recent years, several novel mechanisms of irritable bowel syndrome (IBS) that likely relate to previously established IBS theories have been identified. Inflammation and postinfectious low-grade inflammation are emerging areas requiring clarification with regard to IBS pathophysiology. Immunological and genetic predisposition along with altered microbiota are critical in IBS development, while several dietary factors and enteroendocrine cells may also play roles in this syndrome. However, none of these accounts for the full repertoire of IBS symptoms, and the pathophysiology of this condition is not fully understood.

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## INTRODUCTION

Irritable bowel syndrome is a functional gastrointestinal disorder that manifests symptoms of recurrent abdominal pain associated with changes in bowel habit without

organic abnormalities[1], and its prevalence ranges from 5% to 15%[2]. According to the Rome Ⅲ Diagnostic Criteria, irritable bowel syndrome (IBS) is defined as a syndrome with recurrent abdominal pain or discomfort occurring at least 3 d per month over a 3-mo span. It is associated with two or more of the following characteristics: (1) improvement with defecation; (2) change in stool frequency with onset; and (3) change in stool form with onset[3]. Many studies in IBS pathophysiology over the past decades have focused on colonic dysmotility, visceral hypersensitivity, and the brain-gut interaction. Recently, however, other mechanisms have been actively studied, including inflammation[4], post-infectious low-grade inflammation[5], immunologic factors[6], altered microbiota[7], dietary factors[8] and enteroendocrine cells[9]. However, evidence regarding their roles in IBS remains controversial. Recently, the definition of IBS has been challenged by growing evidence of organic abnormalities in patients who satisfy the Rome criteria for IBS[10,11]. Due to these new paradigms, IBS may no longer classify as an absolute functional disorder. In this article, we briefly summarize the classical concepts and follow with a discussion of the recent research pertaining to the new models of IBS pathophysiology. Better understanding of these emerging paradigms will aid the diagnosis and management of IBS.

## CLASSICAL CONCEPTS IN THE PATHOPHYSIOLOGY OF IBS

### *Gastrointestinal dysmotility*

Gastrointestinal dysmotility is recognized as one of the primary pathophysiological mechanisms in IBS, but it does not fully correlate with symptomatic bowel disturbances. Colonic motor activity in healthy subjects mainly consists of non-propagating and sporadic contractions and progression of intestinal contents by propagating movements termed high-amplitude propagated contractions (HAPCs)[12-14]. The frequent occurrence of HAPCs in IBS patients may explain the frequent bowel movements that cause diarrhea in diarrhea-predominant IBS (D-IBS)[15,16], whereas HAPCs are rarer in patients with constipation-predominant IBS (C-IBS)[17]. Colonic transit is generally accelerated in D-IBS and delayed in C-IBS according to several studies; however, reports on the relationship between colonic motility and IBS subtypes are inconsistent[18]. In one survey, 70% of C-IBS and 50% of D-IBS patients noted the feeling of incomplete evacuation[19]. In contrast, more recent data provided evidence that pelvic floor dyssynergia (PFD) causes symptoms characteristic of non-diarrhea predominant IBS (non-D IBS), including straining, incomplete evacuation, blockage, digitation, and anal pain, suggesting that anorectal function tests should be considered in patients with non-D IBS and PFD symptoms[20].

### *Visceral hypersensitivity*

According to the classical concepts, IBS is caused by visceral hypersensitivity resulting in abdominal pain or discomfort and gastrointestinal motor disorder, which lead to alterations in defecation patterns; *i.e.*, diarrhea or constipation. Numerous studies have demonstrated the link between IBS and increased intestinal sensitivity[21]. Rectal hypersensitivity was proposed as a marker for IBS, and rectal sensory thresholds measured by rectal barostat testing were lower in IBS patients compared to healthy controls after rectal distention[22]. Most research so far has focused on colonic sensitivity[23,24] but hypersensitivity has also been observed in the esophagus[25], stomach[26] and small intestine[27] with IBS. Many studies have shown visceral sensitivity in IBS to correlate with stress[28] and food intake[29]. Colorectal sensitivity is attenuated in IBS patients after intake of a meal[30,31], and the visceral stimulus is significantly higher during stress in IBS patients than in healthy controls[32,33]. Therefore, visceral hypersensitivity is considered to be the conglomeration of peripheral and central processes[34], and its determinants are considered to be a combination of intrinsic and environmental factors.

### *Brain-gut interaction*

Alterations in the brain-gut axis are a new concept in IBS pathophysiology. Environmental, cognitive, and emotional states can affect intestinal sensory perception[35,36]. Corticotropin-releasing hormone (CRH) is a major mediator of stress responses in the brain-gut axis, affecting the functions of both the brain and the gut[37,38]. Intravenous administration of CRH exacerbated colonic motility[39], while peripheral administration of a CRH antagonist blocked the stress-induced increase in colonic motility, visceral perception, and negative mood[40]. Several studies have demonstrated brain-gut interactions using brain imaging. For example, Hamaguchi *et al*[41] showed that distention of the descending colon activated portions of the brain that are highly related to pain recognition and emotion. Mayer *et al*[42] reported that IBS patients exhibit increased activation of brain regions that potentially correspond to the perception of rectal distension. Finally, Mertz *et al*[43] showed differences in activation of brain regions in response to a painful rectal stimulus in IBS patients compared to controls.

## INFLAMMATION

Recent evidence supports a role for inflammation in IBS pathophysiology and generation of IBS symptoms in a subset of patients. Chadwick *et al*[44] performed studies of colonoscopic biopsy specimens from patients meeting the Rome criteria for clinical diagnosis of IBS. Immunohistological assessment showed an increased number of activated immunocompetent cells, including T-lymphocytes, neutrophils, and mast cells in the intestinal mucosa, suggesting a role for the mucosal immune system in pathogenesis. Subsequent studies demonstrated an increased frequency of several surrogate markers for inflammation in IBS patients, the most con-

sistent finding being an increased number of mast cells in the gastrointestinal (GI) tracts of IBS patients[4,45-47]. Mast cells are associated with wound healing, defense against pathogens, and hypersensitivity in GI mucosa. They degranulate to release inflammatory and immune mediators, which cause the recruitment of other inflammatory cells into the GI mucosa. Several studies have indicated that increased mast cells in IBS patients may correlate with certain symptoms of IBS, such as bloating and abdominal pain[46,48]. Another finding is the presence of activated T-lymphocytes in mucosal biopsy specimens from IBS patients[4,46,49]. Several studies have demonstrated an increase in the infiltration of lymphocytes in the myenteric plexus of patients compared to healthy controls[46,47,50]. Furthermore, patients with IBS have more activated T-cells in their colonic biopsies and blood samples[51]. T lymphocytes are involved in adaptive immunity and have multiple functions, such as the activation of B lymphocytes and macrophages and the destruction of infected host cells[52]. In addition, enhanced expression of proinflammatory cytokines in peripheral blood mononuclear cells[53] and serum[54] may confer a predisposition to immune activation in patients with IBS. In the following section, we will review the data supporting the role of inflammatory and proinflammatory cytokines in IBS.

IBS-like symptoms seen in ulcerative colitis (UC) patients during the remission phase appear to involve inflammation[55-57]. It is assumed that chronic inflammation in the colon during the remission phase, associated with altered sensory and motor functioning, can lead to IBS-like symptoms[58,59]. Fecal calprotectin was significantly higher in IBD patients displaying IBS-like symptoms than those lacking IBS-like symptoms, indicating the presence of occult inflammation in the former[55]. One group reported elevated levels of beta-defensin 2 peptides (HBD-2) in fecal fluid derived from IBS patients[60]. HBD-2 is an antimicrobial peptide recently implicated in the pathogenesis of inflammatory bowel disease[61]. These results suggest an activation of the mucosal innate defense system toward a proinflammatory response in IBS patients without macroscopic signs of inflammation.

There is also evidence of microscopic inflammation in IBS. In our previous study, conducted in 42 IBS patients diagnosed by the Rome Ⅱ criteria, the microscopic findings of mucosal hyperplasia, lymphocyte aggregation, and increased eosinophil counts were more frequently observed in the IBS group than the control group. Microscopic colitis does not appear to be associated with IBS symptoms[62]. A study in Malaysia also identified microscopic inflammations in D-IBS subjects that did not meet the criteria for classical microscopic colitis. In this study, the most common pathological findings were mixed chronic and acute inflammatory cells, lymphocytes, plasma cells and neutrophils[63]. IBS onset following an episode of gastroenteritis [post-infectious IBS (PI-IBS) is indicative of a role for inflammation in the pathogenesis of IBS (discussed below)]. Although large amount of research focusing on inflammation in the pathophysiology of IBS, as discussed in this section, this concept should be studied further to develop a potential future therapy for IBS.

## POST-INFECTIOUS LOW-GRADE INFLAMMATION

Recently, numerous studies indicated that bacteriologically confirmed gastroenteritis is critical in the pathogenesis of IBS[5,64,65]. Also called post-infectious IBS (PI-IBS), first proposed by Stewart[66] in 1950, this is a case where IBS symptoms emerge in a patient - who has not previously met the Rome criteria for IBS - following an infectious illness characterized by two or more of the following: fever, vomiting, diarrhea, or a positive bacterial stool culture[67]. Most patients with infectious gastroenteritis recover in a few days, but approximately 10% of patients experience persistent symptoms (*e.g.*, abdominal pain or diarrhea) that progress to IBS[64]. In the meta-analysis by Thabane *et al*[65], the odds of developing IBS increased six- to seven-fold in patients with an episode of acute gastroenteritis. The mechanisms of PI-IBS are still not clear, yet studies have indicated that inflammation[68], genetic polymorphisms in genes associated with immune responses to infectious pathogens[69], and immune functioning[70] may contribute to the occurrence of PI-IBS.

Low-grade inflammation is recognized as the main pathophysiology of PI-IBS. El-Salhy *et al*[71] reported that rectal biopsy specimens taken from patient after *Campylobacter* gastroenteritis showed increases in leucocytes, lymphocytes, mast cells and endocrine cells. Another study reported that 3 mo post-gastroenteritis, patients who had PI-IBS continued to increase their chronic inflammatory cell counts, while those in healthy controls returned to normal levels[72]. Furthermore, several studies demonstrated that intestinal mast cell infiltration and activation following an infection often resulted in mucosal inflammation and the development of PI-IBS[5,73]. Such findings support a relationship between mucosal inflammation and PI-IBS. Development of IBS following non-GI infection has also been reported[74], and other recent study found that viral and bacterial enteritis outbreaks can lead to PI-IBS in a considerable proportion of patients (13%)[75].

Several lines of evidence indicate that inflammation and immune cells play roles in the intestinal neuroendocrine system, which controls GI sensory-motor function[76]. Dunlop *et al*[77] identified an association between PI-IBS and the persistence of mucosal abnormalities, enterochromaffin cell (EC) hyperplasia, and increased mucosal permeability, including intestinal inflammation. Increased permeability facilitates transfer of antigens through the intestinal mucosa, which leads to inflammatory cascades characterized by increased immune cell numbers. Serotonin secretion from EC cells, which regulates the gut immune system, can be attenuated by the secretory products of immune cells[78,79].

There are reports of increased levels of the proinflammatory cytokines in plasma levels of PI-IBS patient[54] and significantly greater IL-1β mRNA expression in the rectal mucosa of patients with IBS symptoms following acute gastroenteritis, but not in asymptomatic control subjects[73,80]. Flagellin antibodies were observed more frequently in patients with PI-IBS, indicating that immune activation in response to luminal triggers plays a role in the development of IBS[81,82]. Flagellins are primary triggers of innate and adaptive immunity, thus driving pathogen-induced acute inflammation[83]. These observations suggest that inflammatory responses to infection, rather than the infective pathogen itself, are an important predisposition to the occurrence of PI-IBS.

## IMMUNOLOGIC AND GENETIC FACTORS

More recent data indicate an influence of genetics on the development of IBS. A survey of twins in Norway showed that the concordance for IBS in monozygotic twins was significantly higher than in dizygotic twins, providing robust evidence for the involvement of genetic factors in the etiology of IBS[84]. To date over 60 candidate genes have been reported as positively associated with IBS[85]. It should be noted that many of these studies had conflicting results; nevertheless, similar surrogate markers are being examined. Discrepancies may be due to differences in IBS subtypes of the study subjects, or in the processes by which the studies recruited their control groups, or in the laboratory methodologies used. However, it is noteworthy that many of these cases demonstrated genetics as a potential etiological factor. The representative genetic factors for IBS pathophysiology associate with inflammation, neurotransmitters, and bile acid synthesis.

### *Inflammation*

Transient mucosal inflammation is crucial for the manifestation of IBS, despite the original definition of this syndrome that implies the lack of signs of active inflammation[86]. According to the evidence, subsets of IBS patients share genetic susceptibility loci for inflammation. The relatively well-studied IBS gene is *TNFSF15*, which has been confirmed in genome-wide association studies to mediate mucosal inflammation in IBD[87]. In Crohn's disease, TNFSF15 is up-regulated with intestinal inflammation and functions in nuclear factor κB activation, potentiation of IL-2 signaling, and secretion of interferon gamma by T lymphocytes[88]. Three cohort studies performed in the United Kingdom[69], Sweden and the United States[89], and England[90] identified a significant association between TNFSF15 and IBS. Belmonte *et al*[91] provided further evidence for altered intestinal immune activation. Increased toll-like receptor (TLR) expression has previously been observed in IBD[92]. In this study, the expression of TLR2 and TLR4 differed significantly among the IBS subtypes. The increased TLR expression in mixed-type IBS patients provoked intracellular signaling pathways that resulted in increased expression of the mucosal proinflammatory cytokines IL-1 and IL-8[91]. Villani *et al*[93] suggested genetic risk factors for the development of PI-IBS based on a 2300-patient cohort in Walkerton, Ontario. They found that TLR9, IL-6, and CDH1 variants persisted as independent risk factors for PI-IBS. Similarly, Brint *et al*[94] reported elevated levels of TLR4 and TLR5 level in PI-IBS patients, supporting the involvement of the innate immune system leading to an inflammatory response.

Several studies identified specific genetic polymorphisms in proinflammatory cytokines, which have an influence on GI functions, motility, epithelial permeability, and visceral sensation[95-97]. TNF-alpha is produced by monocyte-derived activated macrophages, and this cytokine plays on important role in chronic inflammatory states such as IBD[98]. According to a study in the Netherlands, increased TNF-alpha levels were significantly more prevalent in IBS patients compared to healthy controls, while no such association was found for polymorphisms in the *IL-10* gene[6], an anti-inflammatory cytokine involved in the regulation of immune and inflammatory responses. Several studies identified that certain IBS patients may be genetically predisposed to decreased production of IL-10 and subsequent development of low-grade inflammatory manifestations of IBS[99]. In a study done in Mexico, the high IL-10 producer genotype is less prevalent in IBS patients than healthy controls[86]. However, in the abovementioned Netherlands study, *IL-10* genotypes were similarly distributed among patients with IBD compared to healthy controls[6]. In contrast, in Japanese subjects, the frequency of the IL-10 genotype was significantly higher in IBS-D and UC than that in controls[100]. Although IL-10 might be associated with susceptibility to IBS development, many important questions remain regarding this relationship.

### *Neurotransmitters and cytokines*

Among the single genetic polymorphisms associated with IBS, the role of the serotonin transporter (*SERT*) gene polymorphism (*SLC6A4*) has been relatively well explored in IBS. This polymorphism varys according to geographical region and ethnic population. In a meta-analysis, a genetic polymorphism in the gene region responsible for *SERT* activity was not associated with IBS[101]. However, subsequent studies reported inconsistent results. Kumar *et al*[102] did show that a *SLC6A4* polymorphism was significantly associated with IBS, and Wang *et al*[103] found that different *SERT* genotypes could influence *SLC6A4* promoter efficiency and *SERT* mRNA and protein expression in the colonic mucosa.

G proteins are expressed in all human cells and play a crucial role in signal transduction, particularly ligand-receptor interactions. The G protein is encoded by the *GNbeta3* gene. Although, *GNbeta3* polymorphisms have been linked to functional dyspepsia, such association was not observed with IBS[104,105]. However, Saito *et al*[106] reported a significant interaction between the *GNbeta3*

polymorphism and infection during IBS development, suggesting that IBS is a complex genetic disorder with both a genetic and environmental component for expression of symptoms.

Neuropeptide S (NPS) is a bioactive 20 amino acid peptide that selectively binds and activates the neuropeptide S receptor (NPSR1). NPSR1 induces the production of several neuropeptides, including cholecystokinin, vasoactive intestinal peptide, peptide YY, and somatostatin. NPSR1 variants are associated with gastrointestinal motor and sensory functions that are relevant to IBS[107].

The endocannabinoid system, involved in motility[108], sensation[109], secretion[110,111] and inflammatory[112,113] functions in the gastrointestinal tract, has been proposed as a mechanism in the development of IBS. The endocannabinoid anandamide is inactivated by the fatty acid amide hydrolase (FAAH), and single nucleotide polymorphisms (SNPs) in the *FAAH* gene (*C385A*) have been associated with accelerated colonic transit time in D-IBS[108].

### Genetic variation in bile acid synthesis

Genetic variation in the genes controlling bile acid synthesis may contribute to abnormal bowel pattern and symptoms in IBS. Bile acid malabsorption stimulates colonic motility and secretion and has been associated with D-IBS[114]. Hepatic bile acid synthesis is partially controlled by feedback inhibition *via* the fibroblast growth factor 19 (FGF19); FGF19 binds to the FGF receptor 4 and the co-receptor Klotho-beta (KLB), leading to suppression of the rate-limiting enzyme in bile acid synthesis[115]. Wong *et al*[116] reported that a SNP in the *KLB* gene (rs17618244), is associated with accelerated colonic transit in IBS-D. A previous study suggested that the G protein-coupled bile acid receptor 1 (GpBAR1/TGR5) is expressed in myenteric, cholinergic, nitrergic neurons in the colon and in the proximal small intestine, indicating that bile acids may alter intestinal and colonic motility[117]. Camilleri *et al*[118] demonstrated that variations in TGR5 might contribute to altered SBT and colonic transit in D-IBS patients.

## ALTERED INTESTINAL MICROBIOTA

The intestinal microbiota has recently been assumed to be an important predisposition factor for IBS. The most convincing evidence is that IBS can develop in predisposed persons who have experienced gastroenteritis. Other evidence indicates that bacteria may contribute to the pathophysiology of IBS, since luminal- and mucosa-associated microbiota can influence their host *via* immunomicrobial interactions[119]. In addition, small intestinal bacterial overgrowth (SIBO) has been implicated in a subset of IBS patients.

Earlier studies found that the intestinal microbiota in IBS patients differs from that in healthy individuals, with a decrease in the *Bifidobacterium* spp. population and an increase in the *Enterobacter* population being the most consistent findings[120,121]. In a study using real-time PCR assays, results included significantly lower counts of *Lactobacilli* in D-IBS than C-IBS specimens, lower counts of *Bifidobacterium* spp. in D-IBS than the other groups, and significantly higher counts of *Veillonella* spp. counts in the C-IBS group than healthy controls[122]. High-throughput analysis of 16S ribosomal RNA gene cloning and sequencing identified that the fecal microbiota is considerably altered in IBS, as IBS patients have lower *Lactobacillus* and *Bifidobacterium* spp. counts than healthy subjects[123]. Subsequent molecular studies confirmed that IBS patients have fecal microbiota differing from normal subjects[124-126]. Results regarding the intestinal microbiota in IBS are difficult to interpret due to the heterogeneity of the conditions and the observation that alterations of the intestinal microbiota may not be consistent across each subtype of IBS. Furthermore, the precise role of the luminal *vs* the mucosal-associated microbiota in IBS remains uncertain. Nevertheless, previous evidence consistently showed differences in the bacterial composition of feces between IBS and normal controls. Changes in the intestinal flora might result in the proliferation of species that produce more gas[127,128] during the development of IBS symptoms that bring about gas-induced distension. The direct effects of bacterial production on colonic contractility[129], intestinal myoelectrical activity[130], and pain response[131,132] have been identified in several *in vitro* studies. Also, a role for the microbiota in the induction of IBS symptoms is supported by the findings that probiotics improve flatulence and abdominal distension[133,134] and that rifaximin provides significant improvements in IBS symptoms, including bloating, abdominal pain, and loose or watery stools[135].

A growing body of research implicates SIBO in the symptoms of IBS, but this issue remains under debate. SIBO proved to be more prevalent in patients with IBS patients[136-138], and its eradication with antibiotics relieved the symptoms of IBS[139-142]. The presence of SIBO might be associated with abnormalities in small intestinal motor function. Pimentel *et al*[143] found that patients with IBS and SIBO experience few, if any, phase Ⅲ events during short-term manometric measurements compared to controls. In contrast, Posserud *et al*[144] performed intestinal manometry and culturing of intestinal aspirates taken from IBS and control groups, found that IBS subjects have fewer Major Migrating Complex phase Ⅲ events compared to patients without SIBO. However, there were no differences in other motility parameters, and no correlation between bacterial numbers and the pattern of IBS symptoms was detected. SIBO is typically diagnosed *via* indirect methods, such as positive early glucose or lactulose breath tests, and the accuracy of these methods is arguable. These diagnostic limitations have resulted in wide range of reports for SIBO prevalence (10% to 84%) in patients with IBS[145,146]. Regardless, slightly elevated intestinal bacterial numbers are inarguably more prevalent in IBS patients, and so further studies of this area are required.

## DIETARY FACTORS

Although the "response to food" is not included in the diagnostic criteria for IBS, most patients claim their symptoms are triggered by certain foods, which are then avoided to alleviate symptoms[147,148]. Many researchers have focused on the role of diet in IBS in recent years. Also, guidance on diet management for patients with IBS has been revealed as improving their quality of life and symptoms[149,150]. The sensory component of the gastro-colonic reflex following nutrient intake is exaggerated in IBS patients[30], and IBS patients with intraluminal lipids exhibited impaired intestinal gas clearance because of an upregulated reflex inhibition in small bowel transit[151]. One study demonstrated that postprandial GI disorders in IBS patients might be associated with cellular immune function along the neuroendocrine-immune axis[152]. Furthermore, altered autonomic responses after a meal might cause exacerbated postprandial symptoms in IBS patients[153].

### *Food allergy and intolerance*

Many IBS patients report that their symptoms are associated with specific foods; thus, the possibility of food allergies causing IBS symptoms has been proposed. Food allergy/hypersensitivity is defined as an allergic response in susceptible individuals following ingestion of a specific food (*e.g.*, cow's milk, peanuts, soybeans)[154,155]. However, there is little evidence that food allergies play a role in IBS. Several studies have reported that fructose-sorbitol malabsorption frequently occurs in IBS patients, but the results were similar in healthy volunteers; further, the response to a low lactose diet was disappointingly low in IBS patients experiencing lactose malabsorption, indicating a lack of obvious association between food allergy and IBS[156,157]. Several lines of evidence indicate that an altered immune response and inflammation may be involved in food hypersensitivity in IBS patients. There are reports of IgG-mediated food hypersensitivity and improved IBS symptoms when patients are placed on elimination diets[158-160]. Carroccio *et al*[161,162] demonstrated in IBS patients with food hypersensitivity an activation of serum basophils after stimulation with food antigens and increased levels of fecal eosinophil cationic proteins and tryptases. However, further investigations are necessary to validate the accuracy of the methods used in these studies before any claims can be made.

Food intolerances are defined as non-toxic and non-immune-mediated adverse reactions to food or to the presence of pharmacological agents within food, including histamines, sulfates, monosodium glutamate, serotonin, norepinephrine and tyramine[163]. Food intolerance is a possible factor underlying the pathogenesis of IBS, according to the finding that symptoms improved with an elimination diet[164]. However, subsequent studies showed little benefit from these diets[165,166]. Although specific food intolerances in IBS have been explored through patient questionnaires[167,168], the role of food intolerance in IBS remains questionable due to the lack of a reliable methodology and well-designed trials. Well-designed studies with standardized protocols are thus necessary.

### *Poorly absorbed nutrients*

A recently proposed mechanism by which dietary factors might contribute to IBS symptoms suggests that poor absorption of nutrients influence GI function and sensation through osmotic actions and colonic fermentation[163]. Short-chain carbohydrates, such as fructose and dietary starch, are poorly absorbed, causing a number of ingested carbohydrates to enter the distal small bowel and colon. Consequently, these provide substrates for short-chain fatty acid (SCFA) generation by bacterial fermentation and increase the osmotic pressure[169]. The short-chain carbohydrates called Fermentable Oligo-saccharides, Di-saccharides, Mono-saccharides And Polyols (FODMAPs) contribute to IBS; however, IBS symptoms in such cases are triggered by luminal distension that induces abdominal pain, bloating, flatus, and altered bowel habits[170]. A number of studies suggesting effects of dietary manipulation, particularly elimination of FODMAPs, further support the importance of poor nutrient absorption in the development of IBS symptoms[171,172]. In addition, fecal SCFA were increased in D-IBS[173]. SCFA stimulate colonic transit and motility *via* intraluminal release of 5-hydroxytryptamine (5-HT)[174] and high-amplitude propagated colonic contractions[175], according to *in vivo* studies.

Limited data also suggest that changes in intestinal microbiota may be relevant for fermentation of non-absorbable nutrients[169]. Tana *et al*[176] showed that an altered GI microbiota contributes to the higher levels of SCFA and abdominal symptoms in IBS. In addition, many studies have explored the effect of dietary fiber on IBS symptoms. Although dietary fiber has commonly been a standard recommendation for patients with IBS[177], some evidence suggests that it may aggravate symptoms of IBS, such as flatulence, bloating and abdominal pain[76,127,128]. In a recent meta-analysis, patients administered fiber in their diets had persistent or unimproved symptoms compared to control groups that ingested placeboes or lower fiber diets[177]. Some investigators suggest that insoluble fiber intake does not significantly improve IBS symptoms, whereas soluble fiber intake can effectively improve overall IBS symptoms[178,179]. These results suggest that not all types of fiber are equally influential on IBS.

### *Gluten intolerance*

Patients with celiac disease (CD) often experience IBS-like symptoms[180,181]. Therefore, it has been proposed that IBS patients should be routinely examined for CD[163,181]. Certain evidence suggests that dietary gluten intolerance also occurs in patients with IBS, and those whose symptoms improve with such diets may have a genetic susceptibility to gluten[182,183]. However, two groups of investigators recently published contrasting

results. Vazquez-Roque *et al*[184] conducted randomized controlled trials in D-IBS patients consuming gluten-free diets *vs* gluten-containing diets. The group consuming gluten showed increased stool frequency, small intestinal permeability, and reduced mRNA expression of tight-junction proteins in bowel mucosa compared to the patients consuming the gluten-free diet. However, Biesiekierski *et al*[185] reported that gluten might be not be a specific trigger of GI symptoms in IBS patients, as most patients' symptoms were not exacerbated with gluten exposure; there was no evidence of specific or dose-dependent effects of gluten in the expression of serum and fecal markers of intestinal inflammation/injury and immune activation. Further studies are being conducted to determine the role of gluten intolerance in IBS.

## ENTEROENDOCRINE CELLS

Abnormalities in neuroendocrine peptides and amines derived from enteroendocrine cells can cause disturbances in digestion, GI motility and sensation in IBS patients[76,186]. These abnormalities are stimulated by gut luminal content, contributing to the development of symptoms in IBS[187]. Enteroendocrine cells release various bioactive substances, including gastrin, secretin, stomatostatin, cholecystokinin, chromogranins and serotonin[79]. Enterochromaffin cells, which are scattered throughout the GI mucosa, are the dominant type of enteroendocrine cells; they synthesize, store, and release serotonin in response to luminal stimuli[187]. Serotonin affects motility, sensation, and secretion in the gut through the activation of receptors present on enteric nerves and sensory afferents[188]. Studies demonstrated an increase in the release of serotonin in patients with D-IBS[189,190] and PI-IBS[191], while impaired release was found in patients with C-IBS[191,192]. The increased release of 5-HT triggered by luminal stimuli activates immune cells supporting the role of 5-HT in gut inflammation[79].

In addition to serotonin, enteroendocrine cells release chromogranin and secretogranin, which can influence several GI functions, such as immune modulation and inflammation[79]. El-Salhy *et al*[193-195] showed that decreased density of chromogranin A (CgA)-containing cells was found in duodenum, terminal ileum and colonic mucosa of IBS patients. Whereas, other studies demonstrated that serum CgA levels increase in IBS patients[196,197]. Recently, Ohman *et al*[9] showed that IBS patients with rapid colonic transit have higher levels of fecal CgA, secretogranin (Sg) Ⅱ, and SgⅢ, but lower levels of chromogranin B, compared to healthy subjects. Based on the data, granins could serve as useful biomarkers of IBS; however, the role of granins in IBS has not been revealed.

## CONCLUSION

There is abundant evidence supporting the claim that IBS should no longer be considered an absolute idiopathic functional disease. In recent years, attention has been directed towards the role of inflammation, gut microbiota, immunity, genetics, dietary factors, and enteroendocrine cells. As a result, IBS is regarded as a multifactorial condition that affects individuals differentially. Understanding these mechanisms will be useful for the development of a more specific, individualized treatment strategy and for the clinical management of IBD patients.

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