Irritable Bowel Syndrome: The Role of Food in Pathogenesis and Management

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Abstract: Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder that affects approximately 10% to 20% of the general adult population in Europe and the Americas and is characterized by abdominal pain and altered bowel habits in the absence of reliable biomarkers. The pathophysiology of IBS is poorly understood and is currently thought to represent a complex interplay among the gut microbiota, low-grade inflammation, impaired mucosal barrier function, visceral hypersensitivity, gut motility, and alterations in the gut-brain axis. In any individual patient, 1 or more of these factors may interact to generate symptoms. Although up to 50% of patients report postprandial exacerbation of symptoms, few studies have critically assessed the role of diet in IBS. Furthermore, although many patients with IBS adopt any one of a host of dietary changes in an attempt to alleviate their symptoms, there has been, up until recently, little scientific basis for any dietary recommendation in IBS. This review discusses the contribution of diet to the pathophysiology and symptoms of IBS.

Irritable bowel syndrome (IBS) is a common yet poorly understood functional gastrointestinal (GI) disorder that has been estimated to affect between 10% and 20% of the general adult population in Europe and the Americas.[1,2] The cardinal clinical features are recurrent/episodic abdominal pain in association with an altered bowel habit; bloating and distension are common additional complaints. By definition, IBS has no identifiable organic cause, and no reliable diagnostic biomarker has been identified; thus, the diagnosis rests on clinical features alone. To provide uniformity and reproducibility in the clinical definition of IBS, the Rome criteria have been developed and are currently in their third iteration.[2] Given the varied symptomatology of this disorder, and in an attempt to establish coherent clinical and pathophysiologic populations, patients with IBS have been subtyped according to their predominant stool pattern. Four IBS subtypes have been identified: constipation-predominant IBS (IBS-C), diarrhea-predominant
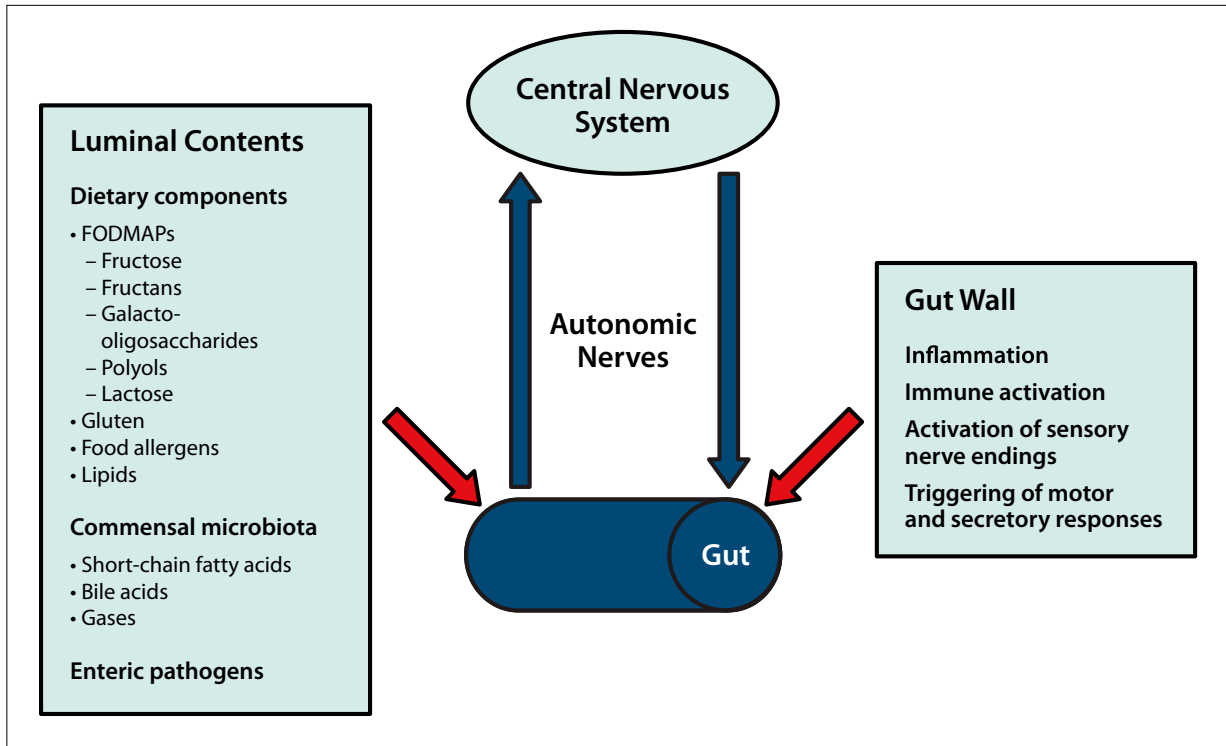
Figure. Potential interactions between diet and the host in irritable bowel syndrome. Input from the central nervous system, mediated by the autonomic nerves (and/or hormonally), may influence gut function and lead to an exaggerated response to food ingestion. Stress may exaggerate these effects, which may be further exacerbated by gut hypersensitivity. Food allergens may generate immune/inflammatory responses. Several food components or their metabolites may directly or indirectly impact symptoms. Interactions between the commensal microbiota and food may lead to the generation of short-chain fatty acids, bile acids, and gases that cause symptoms. Changes in the microbiota, whether gross with the introduction of pathogens or more subtle, will lead to inflammatory responses or immune activation in the gut wall and trigger sensory, motor, and secretory responses.

FODMAPs, fermentable oligo-, di-, and monosaccharides and polyols.

IBS (IBS-D), mixed IBS (IBS-M), and unsubtyped IBS. Although any given patient may move from 1 type to another over a life span, the populations located at the ends of the spectrum do appear to be different.[3]

The pathophysiology of IBS is unknown, and it is unlikely that a single unifying factor will explain it. IBS currently is seen as representing the outcome of a complex interplay between the gut-brain axis. A number of peripheral and central abnormalities have been described. Peripheral abnormalities range from gut dysmotility, visceral hypersensitivity, low-grade mucosal inflammation, and impaired epithelial barrier function to alterations in the composition of the intestinal microbiota. Central abnormalities range from aberrant central nervous system representation of gut events and aberrant stress responses to disturbances along the hypothalamic-pituitary-adrenal axis.[4-7] How these interact and their relative primacy in a given subject or IBS subgroup is unclear.

Although diet has traditionally been assigned a relatively minor role in the pathogenesis of IBS, 50% of patients with IBS report postprandial exacerbations of symptoms either as a direct or deferred reaction.[8-10] Indeed, diet along with stress and the menstrual cycle are, by far, the most common precipitating or exacerbating factors in IBS.[11] Although few studies have been conducted on the role of diet in IBS, recent research has suggested that an allergy or hypersensitivity to certain foods may prompt the onset of and/or increase the severity of symptoms through immune activation. Alternately, research also suggests that intolerance to poorly absorbed carbohydrates, such as fructose, lactose, sorbitol, and other sugar alcohols, is a major problem in IBS.[12]

Despite the widespread advocacy of allergy testing in IBS, the role of food allergy remains disputed. Although the use of a diet low in fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs) has shown promise in symptom control and has been widely advocated, its precise place in IBS treatment remains to be defined.[13]

The patient with IBS is currently prey to a wide range of competing and often conflicting dietary recommendations. This review will attempt to critically appraise the current status of the understanding of food in IBS pathophysiology (Figure) and management.

Food Ingestion and Symptoms in Irritable Bowel Syndrome

Before discussing the potential roles of food allergy and intolerance in IBS, the potential role of the physiologic response to food must be addressed. All physiologic processes in the gut, including motility, secretion, and blood flow, respond to food intake, or the anticipation thereof, to maximize digestion and absorption. Both neural (in particular, the vagus nerve) and hormonal elements contribute to these responses. Signals along the gut-brain axis may initiate, perpetuate, or modulate the food response. Other factors, including mucosal immune responses and even the gut microbiota, may participate in this bidirectional interaction.[14-16]

The central nervous system communicates with the enteric nervous system via the sympathetic and parasympathetic branches of the autonomic nervous system. The anticipation and/or ingestion of food stimulates the autonomic nervous system, leading to such well-described physiologic responses as the cephalic phase of gastric acid secretion, receptive relaxation of musculature in the upper GI tract, and the gastrocolonic response. Given the frequent localization of IBS pain to the left lower quadrant and of the prominence of postprandial urges to defecate, the gastrocolonic response was an early target of investigation in IBS. Not only were patients with IBS shown to exhibit an exaggerated gastrocolonic response, but exaggerated responses to food ingestion were also demonstrated in the small intestine and even the gallbladder.[17-20] It is interesting, therefore, that alterations in the autonomic nervous system have been reported in patients with IBS, the most consistent findings being increased sympathetic nervous system activity.[21-23] Changes in parasympathetic nervous system activity have been less consistent, and, although responses have varied, decreased parasympathetic responses have been observed more frequently in patients with IBS compared with healthy controls.[21-23]

A number of hormones play an integral part in the gut's responses to food.[16] Enteric endocrine cells populating the gut, which secrete an array of hormones, such as motilin, gastrin, cholecystokinin (CCK), and peptide YY, respond to the anticipation and/or arrival of food or the products of digestion and, thereafter, modulate the fate of gut contents in either a paracrine or endocrine manner. Secretion of these hormones can be altered in IBS. Motilin is secreted in the interdigestive period and released on distension of the duodenum and stimulates gastric motility. Although altered motilin levels have been observed in IBS, results have been conflicting, with studies variably demonstrating increased, decreased, and similar levels of motilin in comparison with healthy controls.[24-26]

Ghrelin, thought to play a major role in satiety, also stimulates motility. Interestingly, higher circulating ghrelin levels have been described in patients with IBS and could contribute to associations between food ingestion, dysmotility, and IBS symptoms in some affected persons.[27,28] CCK release is stimulated by the arrival of fat and protein into the proximal gut and delays gastric emptying, increases gut motility, and enhances rectal hypersensitivity.[29] Both fasting and postprandial levels of CCK are elevated in IBS, and an exaggerated response or hypersensitivity to CCK can cause symptoms of constipation, bloating, or abdominal pain.[19,24,29]

Serotonin transporter polymorphism genes have been associated with IBS. Serotonin, a neurotransmitter and paracrine-signaling molecule secreted primarily from enterochromaffin (EC) cells, accounts for approximately 80% of total body serotonin secretion. Increased EC cells, elevated postprandial serotonin levels, and decreased serotonin reuptake due to decreased affinity for the reuptake transporter protein have been reported in different IBS subtypes, with EC cell increase being observed in postinfectious IBS and postprandial elevation of serotonin as well as decreased uptake observed in IBS-D.[30-32] Serotonin stimulates receptors responsible for peristalsis and secretion in the GI tract and acts to promote communication along the gut and on the gut-brain axis. The postprandial diarrhea and urgency commonly reported by patients with IBS-D may be due to an exaggerated serotonin response, leading to increased peristalsis and secretions.[30]

Stress and Psychologic Factors

Psychologic disorders (eg, anxiety and depression) are frequent comorbidities in IBS, and stress has been associated with exacerbations of IBS symptoms.[33-36] Furthermore, a feature of IBS is an exaggerated stress response.[5] Many patients report eschewing social events to avoid embarrassment due to postprandial exacerbation of symptoms (eg, flatulence and distension) and lack of access to toilet facilities, leading to social isolation.[37]

Corticotrophin-releasing hormone (CRH) mediates the stress response of the gut-brain axis and has been shown to increase colonic motility and promote inflammation via increased intestinal permeability in patients with IBS.[38] Other effects of CRH on the gut that may contribute to IBS symptoms include an alteration of the gut microbiota, altered secretions, visceral sensitivity, and mucosal blood flow.[39] CRH antagonists can reduce pain in patients with IBS, further underlining the possible role of CRH in the pathophysiology of IBS.[40]

Dietary Perceptions of Patients with Irritable Bowel Syndrome

Many patients with IBS associate 1 or more foods with the onset of symptoms, and two-thirds of patients report

Table 1. Dietary Surveys of Patients with Irritable Bowel Syndrome

Study	Dietary Survey	Results
Simrén et al[43]	Patients with IBS (n=330) graded their perceived symptoms against a list of 35 foods.	63% attribute their GI symptoms to foods, especially carbohydrates and fats.
Monsbakken et al[41]	Patients with IBS (n=84) completed a survey based on symptoms related to food, foods limited or avoided, and adequacy of diet.	62% limited or excluded food from their diet. 12% had an inadequate diet.
Ostgaard et al[47]	Patients with IBS (n=36) and patients with IBS given dietary guidance (n=43) completed FFQs detailing intakes of macro- and micronutrients and providing information on meal patterns.	Patients had significantly lower intakes of certain food groups due to self-restriction compared with patients with IBS given dietary advice by a healthcare professional.
Williams et al[44]	Patients with IBS (n=104) completed an FFQ, and their dietary intake was compared with UK DRVs.	Patients have an adequate intake of nutrients when compared with DRVs.
Hayes et al[46]	Patients with IBS (n=135) completed a dietary survey on their perceptions of the role of diet in their symptoms and whether they restrict their diet based on this.	90% attributed their symptoms to certain foods, with 9.6% restricting milk products, 7.4% restricting fruit, and 5.2% restricting vegetables. Only a small percentage of patients sought professional dietary guidance.

DRVs, dietary reference values; FFQs, food frequency questionnaires; GI, gastrointestinal; IBS, irritable bowel syndrome.

restricting their diet, often instigating dietary changes themselves or turning to alternative sources for dietary advice (Table 1).[41,42] Foods most often implicated are wheat, milk, fructose, caffeine, certain meats, fatty foods, alcohol, spices, dairy products, and grains (Table 1).[43-46] However, there are insufficient published data on the dietary practices of patients with IBS, and studies examining relationships between particular foods and IBS symptoms are particularly lacking. Although there is evidence that patients with IBS restrict their diets, the extent of the avoidance of nutritionally important food groups is hard to pinpoint based on available data.[47]

Food Allergy and Intolerance

Food allergy, traditionally denoted by an activation of immunoglobulin (Ig) E-mediated antibodies to a food protein, has not been linked convincingly to IBS pathogenesis, although patients with IBS have been shown to have a higher incidence of atopy.[48-50] Others have suggested a role for IgG-mediated immune reactions. Two studies have demonstrated that when patients with IBS were given an exclusion diet to avoid foods that were shown to promote elevated IgG antibodies, a significant decline in symptoms and a corresponding improvement in rectal function were reported.[51,52] A recent 12-week study, which excluded specific IgG-associated foods, resulted in significant declines in abdominal pain, distension, and diarrhea in patients with IBS-D compared with a healthy control group.[53] However, doubt remains about the role of IgG in IBS. Zuo and colleagues found no significant relationship between IgG antibodies and symptom intensity,[54] and studies demonstrating positive results have been criticized on the basis of study populations.[55]

Further studies on the relevance of IgG antibodies to IBS symptoms are required to legitimize a tentative link.

Whereas food allergy can be explained as a specific immune reaction to consumption of a certain food, food intolerance is a nonimmune-mediated adverse reaction. For example, whereas a person allergic to cow milk protein may have an immune reaction after consumption of products containing cow milk, persons with lactose intolerance have reduced levels or an absence of lactase.[56]

Carbohydrate Intolerance in Irritable Bowel Syndrome

Although it is known that acute exposure to sugars, such as lactose, fructose, and sorbitol, can provoke abdominal cramps, diarrhea, bloating, and flatulence in persons who lack tolerance, the impact of chronic exposure to these molecules in the pathophysiology of chronic, recurrent IBS is less clear. It has recently been suggested that a more generalized intolerance to certain carbohydrates may be more relevant to IBS.

FODMAPs
The FODMAP theory, which was introduced in the early 2000s, proposes that specific nondigested or poorly digested carbohydrates contribute to common IBS symptoms and induce alterations in gut motility and secretion.[57] The prominent role of FODMAPs has been attributed to their diminutive size, high osmotic activity, and the speed at which these carbohydrates are fermented by colonic bacteria.[58] Symptoms associated with a high-FODMAP diet include pain, bloating, distension, flatulence, and diarrhea. Luminal distension by unabsorbed or fermented FODMAPs could be seen as the basis for many of the symptoms of IBS.

Solids, liquids, and gases have been suggested to play a part in distension of the distal, small, and proximal large bowels. Solids contribute through the ingestion of dietary fiber, which increases the volume of bacteria, and through osmotic effects. Liquid volumes are influenced by osmotic loads in both the small and large bowels and the absorptive capacity of the colon. Increased gas production by colonic bacteria can lead to distension in the large bowel.

Low-FODMAP diets have been shown to reduce GI symptoms compared with high-FODMAP diets and unrestricted diets and also when compared with National Institute for Health and Clinical Excellence (NICE) standard dietary advice.[58-62] One study that compared a low-FODMAP diet to NICE standard dietary advice in patients with IBS reported significantly greater satisfaction with symptom response in patients with a low-FODMAP diet (76%) compared with NICE standard dietary advice (54%),[60] which consists of avoiding resistant starch, limiting sugar-free foods, limiting fruit to 3 portions per day, and controlling insoluble fiber intake depending on symptoms (ie, increase intake gradually in constipation, and limit intake in diarrhea).[39]

The low-FODMAP diet also was associated with significantly lower scores for bloating, flatulence, and abdominal pain, as evidenced in a recent study of patients with nonceliac gluten sensitivity.[63]

Fructose, Fructans, and Galacto-Oligosaccharides

Fructose is a monosaccharide usually ingested either as free fructose, enzymatically extracted from the disaccharide sucrose, or polymerized as fructans. Common dietary sources of fructose include apples, pears, and honey. Transport mechanisms, via the GLUT-5 or GLUT-2 transporter, can be saturated by high doses of fructose. Tolerance threshold levels are difficult to estimate, but an upper threshold for absorption is apparent even in healthy populations.[64] Fructose malabsorption can be diagnosed by a hydrogen breath test, although debate surrounds its accuracy.[65] Absorption of fructose also depends on whether it is transported alone or with glucose. Fructose is better absorbed with equal or higher levels of glucose, which results in less undesirable symptoms.[66] It is likely that sorbitol has an additive effect to fructose, such that symptoms are further exacerbated.[67] Fructose that reaches the colon unabsorbed provides a prebiotic substrate for some resident bacteria, increasing the production of short-chain fatty acids (SCFAs) and gases, including hydrogen, which may result in excessive flatulence, bloating, and loose stools.[68]

Fructans are oligo- or disaccharides composed of a long chain of fructose and ending in a glucose molecule. They are found mainly in wheat, rye, barley, and onions. Fructans include fructo-oligosaccharides (FOS), which

are molecules with a chain length of less than 10 units, and inulins, which contain longer chains. Galacto-oligosaccharides (GOS) are present in the diet as raffinose, comprising a fructose, glucose, and galactose molecule, and stachyose, which is raffinose with an extra galactose molecule; legumes are major dietary sources of GOS. FOS and GOS are classified as sources of dietary fiber and are increasingly being added to common foods for their prebiotic effect. They are usually well tolerated by healthy persons, although not digestible, and are fermented in the colon by the gut microbiota, stimulating growth of the resident microbiota (eg, Bifidobacteria). GOS have been shown to improve pain, bloating, and constipation in patients with IBS, but long-chain fructans have been associated with worsening pain, bloating, and diarrhea and have also evoked GI symptoms in healthy subjects.[69-71]

Polyols

Polyols are sugar alcohols and are plentiful in the Western diet as sorbitol and other sweeteners, such as mannitol, xylitol, maltitol, and isomalt. They are absorbed by passive diffusion, at a rate that varies by molecule intestinal permeability, which differs depending on intestinal location and the presence or absence of disease. Some polyols are too large to diffuse through intercellular spaces and remain unabsorbed, exerting an osmotic effect leading to flatulence, abdominal pain, and osmotic diarrhea. Water volume movement also can contribute. For example, volumes have been seen to decrease after ingestion of mannitol and increase following a mixed liquid and solid meal.[72]

Lactose

The FODMAP concept can be extended to include lactose in patients who do not have a normal absorptive capacity for this sugar.[73] Lactose is a disaccharide hydrolyzed by the enzyme lactase. A reduction in or lack of this enzyme can cause unabsorbed lactose to pass into the colon. Bacterial fermentation then produces SCFAs and gases, leading to flatulence, diarrhea, bloating, and nausea. Lactose malabsorption can be defined as the existence of unabsorbed lactose in the colon due to the partial hydrolysis of lactose, whereas lactose intolerance indicates the presence of GI symptoms due to unabsorbed lactose. Although the studies that have been carried out were not blinded or controlled, there appears to be consistent evidence that GI symptoms improve when milk is removed from the diet.[74-76]

The symptoms of lactose maldigestion (malabsorption and intolerance) are similar to IBS and include flatulence, bloating, abdominal pain, and diarrhea. The contribution of lactose maldigestion to IBS depends on the prevalence of lactose maldigestion in the population studied and may also be influenced by the immigrant population.[77]

Testing for Allergy and Intolerance in Irritable Bowel Syndrome

Because many patients with IBS perceive food as a primary contributor to their symptoms and find conventional medical therapies unsatisfactory, there has been an increase in the popularity of food intolerance testing, allergy testing, and alternative remedies.

Surveys have shown that 27% of patients with IBS turn to alternative remedies to alleviate symptoms, and 65% find homeopathy to be an acceptable treatment,[78,79] although such approaches may not prove effective when studied in randomized, controlled trials.[80] Food intolerance tests are widely available and offer blood testing for IgG levels against a range of foods. Both the American Academy of Allergy and Clinical Immunology and the Task Force of the European Academy of Allergy and Clinical Immunology agree that the clinical utility of IgG testing is, as of yet, unsubstantiated and could lead to dietary restrictions that increase the risk of nutritional inadequacies in patients who test positive.[81,82]

Gluten and Irritable Bowel Syndrome

Celiac disease is defined as an immune reaction to gluten characterized by immunologic changes and structural abnormalities in the bowel, resulting in GI symptoms and/or dysfunction. Some of the symptoms that commonly occur in patients with celiac disease, such as abdominal pain, bloating, and diarrhea, are similar to those that typify IBS.[83] Given this overlap in symptomatology and the fact that celiac disease is thought to have a prevalence of approximately 1% in many developed and developing nations where wheat ingestion is common, it should come as no surprise that diagnostic confusion may arise. Indeed, the prevalence rate of celiac disease among the IBS populations has ranged from as low as 0.4% to as high as 11%, and some investigators have suggested that a diagnosis of celiac disease is 4 times more likely in a patient with IBS than a control subject.[84-86] Many factors conspire to muddy the waters here: the accuracy of diagnostic tests for celiac disease, the extent to which celiac disease has been sought in a given population, symptom overlap, and the likelihood of coincident concurrence of 2 common disorders. Human leukocyte antigen (HLA) types linked to celiac disease, such as HLA-DQ2 and HLA-DQ8, have been identified among nonceliac gluten-sensitive patients with IBS.[87,88] Immunologic markers of celiac disease in serum are typically negative among patients with IBS who respond to a gluten-free diet but have been detected in duodenal fluid from such patients.[89]

Interestingly, colonic transit was increased in patients with IBS-D among those expressing HLA-DQ8 or both HLA-DQ8 and HLA-DQ2.[87] Nevertheless, celiac disease can be readily defined on the basis of serology, small intestinal histology, and mucosal immunopathology.

Based on clinical observations and other evidence, the concept of nonceliac gluten disorders—although described as a no-man's land between celiac disease and IBS[90]—has begun to gain traction among gastroenterologists and clinical investigators. A consensus group has recently attempted to tackle the definition of celiac disease and related entities, which have remained largely unchanged since the 1970s.[91] This group recommends that the term "gluten intolerance" should not be used because symptoms may not be due to gluten itself but to other properties of wheat. The group proposes instead that the term "gluten-related disorders" be used to encompass all conditions related to gluten (including celiac disease).

As for the patient with IBS symptoms who does not have celiac disease but claims to be gluten-intolerant, the consensus group recommends that the term "nonceliac gluten sensitivity" be used and defines this condition as "one or more of a variety of immunologic, morphologic, or symptomatic manifestations that are precipitated by ingestion of gluten in people in whom [celiac disease] has been excluded."[91]

Some evidence suggests that a gluten-free diet reduces diarrhea in patients with IBS-D, and patients with abdominal pain and bloating also reported resolution of symptoms after 6 months of a gluten-free diet.[88] A double-blind placebo-controlled trial in nonceliac patients with IBS adhering to a gluten-free diet described similar results on gluten rechallenge. A significantly higher percentage of patients (68%) who blindly ingested gluten reported inadequate control of symptoms compared with 40% of patients who blindly ingested placebo (gluten-free).[92] The beneficial effects of gluten restriction on symptoms have been shown to be significant even within a week. A pathophysiologic basis for gluten effects in these subjects was revealed by Vazquez-Roque and colleagues who randomized 45 subjects with IBS-D to either a gluten-containing or a gluten-free diet and found that the gluten-containing diet induced more bowel movements, increased small intestinal permeability, altered tight-junctional biology, and enhanced systemic immune responses, especially among subjects who possessed the haplotypes that are associated with celiac disease.[93]

Can response to a gluten-free diet be predicted in one or another patient with IBS? Studies of serum antibody levels and HLA-typing as well as small intestinal histology and immunopathology have not provided consistent results.[88,89,92,93] Augmented levels of mucosal serotonin in the small bowel also have been linked to celiac disease,[94] and serotonin excess may exacerbate dyspepsia.[95] Wheat contains high levels of fructans, so it is plausible that improvement in symptoms on a low-FODMAP diet may indeed be due

to a gluten-free diet; however, in a very recent double-blind crossover study, Biesiekierski and colleagues found that, when tested on low-FODMAP and gluten-free diets, only 8% of symptom improvement observed could be attributed to gluten exclusion alone, with the majority of the benefit related to the reduction/exclusion of FODMAPs.[63]

Lipids in Irritable Bowel Syndrome

Reflecting the complexity of its digestion and assimilation, fat is a powerful stimulant of many GI functions. Although problems with fatty foods have been implicated in patients with IBS in a number of surveys,[43-46] studies that attempted to define the fat content of diets of patients with IBS have had conflicting conclusions.[44,96-98] The physiologic response to lipids in health and in functional disorders, including IBS, was recently reviewed in detail by Feinle-Bisset and Azpiroz, who concluded that, although laboratory studies have consistently demonstrated enhanced responses of a number of gut functions to lipids, there have been few attempts to translate this into clinical benefit for patients with IBS or to investigate relationships between specific dietary lipids and symptoms.[99] For example, there have been few attempts made to modify dietary fat intake in IBS, and, with the exception of one study that demonstrated a symptomatic response to pancrealipase,[100] attempts to enhance lipid assimilation in IBS are notable for their absence. In IBS, the gastrocolonic motor response to lipid ingestion is exaggerated, rectal hypersensitivity is accentuated, and gas transit through the gut is delayed in response to duodenal lipid infusion.[101] These effects could contribute to cramps, urgency, diarrhea, pain, bloating, and pain. It is interesting to note that, in IBS, the small intestine and even the gallbladder share in this hyperresponsiveness to high-fat meals or CCK released by such meals.[102]

Food, Gut Microbiota, and Inflammation

The gut microbiota plays a pivotal role in gut homeostasis in health and in the pathogenesis of a number of intestinal and extraintestinal diseases. It includes a diverse population of approximately 10^{14} bacterial cells, 10 times more than the total number of human cells.[103] The functions of the gut microbiota include protection of the host from enteropathogens, development of the host immune system, participation in host metabolism, and contribution to nutrition.

Changes in the gut microbiota have been well documented in relation to the use of antimicrobials and the ingestion of probiotics during episodes of gastroenteritis and in relation to a number of chronic diseases. In recent years, advances in molecular techniques used to characterize the gut microbiota have resulted in a deeper understanding of this field.[104] Alteration of the composition of the gut

microbiota (dysbiosis) and, especially, interactions between bacteria and components of the diet or the products of digestion may play a role in the pathogenesis and symptomatology of IBS. Flatulence, for example, may be a consequence of a reduction in methanogenic bacteria or, alternately, it may result from an increase in the numbers of gas-producing organisms, leading to the liberation of gases as a by-product of bacterial fermentation.

As discussed, undigested carbohydrates into the colon will provide more substrate for fermentation as well as act as a prebiotic. Local changes in gas production in conjunction with enhanced sensitivity to gas distension may contribute to bloating in IBS.[105]

Studies in patients with IBS have shown alterations in the microbiota, such as an increased ratio of Firmicutes to Bacteroidetes and a reduction in *Lactobacillus* or *Bifidobacterium* species.[7] Symptoms may be attributed to the properties of these bacteria. For example, increased numbers of Firmicutes may cause abdominal pain, as they secrete large amounts of proteases, which have been shown to stimulate sensory afferents in the gut.[106-108] Both *Lactobacillus* and *Bifidobacterium* species have anti-inflammatory effects in the gut; their depletion could contribute to low-grade inflammation.[109,110]

Species-specific alterations in the microbiota are observed in different IBS subtypes; for example, the methanogen *Methanobrevibacter smithii* has been associated with IBS-C and methane has been associated with slow intestinal transit.[111,112] In comparison to IBS-C and IBS-M, the abundance of *Faecalibacterium* species, which produce butyrate,[113] was found to be reduced in IBS-D,[7] and butyrate enemas have been shown to decrease rectal pain perception in healthy controls.[114] In inflammatory bowel disease, *Faecalibacterium* species confer anti-inflammatory effects by blocking NK-κ β activation and interleukin (IL)-8 production.[115] Changes in the microbiota also have been linked to altered bile acid metabolism and stool formation in IBS.[116]

Because the GI tract contains the largest mass of lymphoid tissue in the body, it is therefore not surprising that systemic and mucosal immune system activation has been illustrated in IBS.[5] Observed mucosal changes include mast cell and T-lymphocyte activation and altered gene expression resulting in functional alterations of the host mucosal immune response to microbial pathogens.[117] Proinflammatory cytokine levels (eg, IL-6, IL-8, tumor necrosis factor-α, and IL-1β) are elevated in the systemic circulation of patients with IBS compared with controls.[5] Alterations in the gut microbiota can influence these inflammatory changes, as evidenced by studies in germ-free animals.[118,119] That dietary factors might influence these immunologic phenomena in IBS is illustrated by the impact of probiotic supplementation.

Probiotics have shown promise in the management of IBS; however, results of studies have been inconsistent due to, in large part, differences in strain and species studied, duration of therapy, and trial design. Of relevance is that *Bifidobacterium infantis* 35624 was shown to result in alleviation of symptoms in patients with IBS in 2 clinical trials[110,120] and also has been shown to exert potent anti-inflammatory effects.[121] A detailed discussion of the role of probiotics in IBS is beyond the scope of this article and has been reviewed elsewhere.[122-124]

Animal studies have shown that alterations in diet result in changes to the microbiota.[125] Few human studies have examined interactions between diet and the gut microbiota. To emphasize the importance of diet in modifying the microbiota, Claesson and colleagues were recently able to define striking correlations between diet, gut microbial composition, and clinical status in the elderly.[126] Thus, they were able to define subgroups with distinct microbiota signatures based on place of residence (eg, home, day care, nursing home, or hospital). Free-living community dwellers demonstrated a more diverse diet and also a more diverse composition of their gut microbiota.[126]

Given the fact that alterations in the microbiota are seen in IBS, it stands to reason that diet could be a contributor to microbial populations in affected persons and, thereby, a contributor of IBS. Staudacher and colleagues recently demonstrated the direct effect of fermentable carbohydrate restriction on the gut microbiota of patients with IBS. Significantly lower levels of Bifidobacteria were found in patients with IBS following a low-FODMAP diet than in those on a nonrestricted diet.[59] Given that IBS symptoms improved with reduced Bifidobacteria composition and that Bifidobacteria supplementation has successfully alleviated IBS symptoms, an apparently contradictory relationship exists between gut bacteria strains and IBS symptoms that prompts further research.[59,110]

Postinfectious Irritable Bowel Syndrome

Ingestion of enteropathogens (eg, *Campylobacter* and *Salmonella* species) due to contaminated food and water can cause acute gastroenteritis. Although the majority of patients improve and return to normal bowel habits, IBS develops in some with an incidence that varies from 3.6% to 36.2%, compared with 0.3% to 10.2% in controls.[127-130] Overall, there is a 7-fold increased risk for the development of postinfectious IBS. Risk factors include longer duration of illness, severe diarrhea, prolonged fever, younger age, and psychologic comorbidities (including anxiety and depression).[127,131-134] Pathophysiologic changes in patients with postinfectious IBS include increased EC cells in the rectal mucosa, increased intraepithelial lymphocytes, and increased postprandial

serotonin levels.[32,130] Animal studies have shown that rats fed *Campylobacter jejuni* with subsequent clearance of the organism demonstrate increased intraepithelial lymphocytes, bacterial overgrowth, and altered stool form.[135] This supports the evidence that IBS is mediated via low-grade inflammation.

Dietary Management of Irritable Bowel Syndrome Symptoms

Traditional dietary advice for the prevention of IBS symptoms has been to adopt a high-fiber diet; however, as no discernible difference in symptoms has been found in human studies comparing high-fiber intake with low-fiber intake, the role of fiber in symptom prevention remains moot.[136] A recent review and meta-analysis of treatments available for IBS concluded that soluble fiber supplementation, such as ispaghula, was likely to be beneficial in alleviating common IBS symptoms and constipation, in particular, but that insoluble fibers, such as bran, did not replicate these benefits compared with a placebo, albeit the latter did not cause symptom exacerbation either.[137] The evidence is not definitive, however, and further studies are needed to demonstrate convincing results.[138] Two issues need to be stressed in relation to fiber: its nature (ie, soluble or insoluble) and the manner in which it is prescribed. Although sudden increases in fiber intake could well provoke symptoms, whereas much more gradual increments may be better tolerated, these assumptions have not been formally tested.

Despite the lack of solid evidence for many dietary recommendations in IBS,[139] the issue must be addressed in clinical practice because patients are convinced that specific foods exacerbate symptoms. The British Dietetic Association and NICE guidelines recommend that dietary and lifestyle advice should be routinely provided to patients with IBS, as detailed in Table 2.[140]

The lack of adequately powered and well-designed randomized, controlled trials pertaining to dietary intervention in IBS somewhat dilutes the recommendations that have, for the most part, been based more on common sense and anecdote than science. More recent attempts to formally test approaches such as low-FODMAP and gluten-free diets may provide more clear-cut guidance. Embarking on low-FODMAP and gluten-free diets without the supervision of a qualified dietician is not to be recommended, however. Low-FODMAP and gluten-free diets are complex, restrictive, and, for some, financially burdensome. At the very least, an attempt should be made between the gastroenterologist and dietician to assess the patient's nutritional status and document relationships between certain foods and symptoms before diet restrictions are prescribed.

Table 2. Treatment Modalities for Irritable Bowel Syndrome

First-Line Treatment
• Establishment of a regular eating pattern and a healthy eating lifestyle
• High intake of noncaffeinated, noncarbonated, alcohol-free fluids throughout the day
• Dietary assessment of the impact of milk and lactose, dietary fiber, and fatty foods

Second-Line Treatment

• Symptom-specific dietary interventions
  – Addition of linseed products
  – Addition of probiotics

• Low-FODMAP diet

Third-Line Treatment
• Elimination diets, which are used for 3 to 4 months, including the food reintroduction phase

FODMAP, fermentable oligo-, di-, and monosaccharide and polyol.

Summary

Many external and internal factors may contribute to the etiology of IBS. The role of food in the pathogenesis of IBS remains ill defined, and the effects of food ingestion on the gut-brain axis, immune system, gut microbiota, and digestive process are still under investigation. Increasingly, though, dietary manipulations are being recommended in the management of IBS, often on the basis of little evidence or bogus science. Some approaches, such as the low-FODMAP diet, gluten restriction, and probiotic supplementation, have been subjected to more rigorous assessment and show considerable promise. However, more fundamental studies on the effect of diet on the pathogenesis of IBS, as well as attempts to select patients who will respond best to a given dietary intervention, are needed.

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