

Food: The Forgotten Factor in the Irritable Bowel Syndrome

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KEYWORDS

• Carbohydrate • Lactose • Fructose • FODMAP
• Gluten • Lipid • Diet

Between 7% and 20% of adults experience symptoms compatible with the irritable bowel syndrome (IBS), a disorder defined by the presence of recurring episodes of abdominal pain in association with altered bowel habits and no evidence of a structural or easily identifiable biochemical abnormality that might explain these symptoms.^{1,2} Several factors have been suggested as playing a role in the pathogenesis of IBS, including disturbed motility, the brain-gut axis, genetic factors, impaired gut barrier function, immunologic dysregulation, the gut microbiome, and psychosocial factors. More recently, there has been increasing attention on the role of food in IBS. Patients have long associated their IBS symptoms with the ingestion of certain foods, combinations of foods, or a meal itself. More than 60% of IBS patients report worsening of symptoms after meals, 28% of these within 15 minutes after eating and 93% within 3 hours.¹ Unfortunately, the lack of empiric data proving a causal link or consistently documenting symptom improvement has caused health care providers to view dietary interventions with skepticism. Furthermore, even to this day, gastroenterologists and primary care providers receive virtually no structured training in dietary interventions for IBS. This lack of enthusiasm for dietary counseling has increasingly caused providers to be misaligned with their patients who are increasingly seeking more holistic solutions for their IBS symptoms. Out of desperation, many providers recommend or passively stand by as their patients empirically attempt various dietary manipulations, such as the elimination of fatty foods, fruits, gluten, or milk/dairy products or modifying dietary fiber content. This haphazard approach not surprisingly leads to inconsistent results, which can be frustrating to both patients and providers.

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Several disorders and diseases can masquerade as or exacerbate the symptoms of IBS. For example, few clinicians would dispute that celiac disease and lactose intolerance are important considerations in patients presenting with IBS symptoms. These two well-defined disorders likely represent the tip of the iceberg, however, pertaining to the role of food in IBS. This article reviews the literature supporting a causal link between food and the symptoms of IBS as well as the evidence supporting dietary intervention as a means of treating IBS.

THE SCOPE OF THE PROBLEM

Adverse reactions to food are acknowledged by 5% to 45% of the general population,³⁻⁵ and GI complaints are predominant in approximately one-third to one-half of those affected.^{1,6} Offending foods are often referred to as trigger foods, dietary triggers, or culprit foods,⁷ sometimes leading to a nutritionally inadequate diet.³ Although food intolerance is a common perception among the general population, it can be demonstrated in only a relatively small proportion of the population when double-blind food elimination and challenge studies are employed. In a population study of food intolerance of 20,000 patients, 20.4% complained of food intolerance. Of the 93 subjects who entered the double-blind, placebo-controlled food challenge, 11.4%–27.4% had a positive reaction, with estimated prevalence of reactions to the 8 foods tested varying from 1.4% to 1.8% depending on the method of testing used. Women perceived food intolerance more frequently and showed a higher rate of positive results to food challenge.

Among individuals with IBS,^{3,5,8-12} 20% to 67% complain of subjective food intolerance, which is more prevalent than similar reports in matched controls.^{5,9,13} One population-based study reported a prevalence rate of perceived food intolerance of greater than 50% among subjects with IBS, a rate that was 2-fold greater than that reported by those without IBS.⁵ Another found that patients in a GI clinic with a final diagnosis of a functional disorder were four times more likely to report food allergies (FAs) or adverse reaction to food.¹³ The likelihood of a patient's symptoms being functional increased even further if adverse reactions to both drugs and foods were reported. Such complaints seem to correlate with female gender and anxiety level in those with functional GI disorders.¹⁴

Many patients suffering from IBS report an association of symptoms with specific foods. Although the foods that induce symptoms may be specific, the associated symptoms are often nonspecific and consistent with functional disorders, such as IBS. Many patients identify specific trigger foods (most commonly dairy, fructose, wheat products, and caffeine), but there is little evidence that IBS patients with food-related complaints are suffering from a true FA.¹⁵ Although there are undoubtedly some patients with IBS symptoms who suffer from an FA, the proportion of the total population of IBS sufferers with a true FA is small.¹⁶⁻²¹ Alternatively, there is likely to be substantial overlap between food intolerances/sensitivities and IBS, because these syndromes often have similar clinical presentations.

It is not uncommon for IBS patients to experiment with their diet or limit their diet before seeking medical attention.³ The foodstuffs most commonly implicated are wheat, corn, dairy products, coffee, tea, and citrus fruits. In a 2005 population-based sample comparing dietary consumption of specific food items and nutrients between individuals with IBS or dyspeptic symptoms and those without symptoms, no differences were seen in the consumption of frequently suspected culprit foods.²² In a survey of more than 1200 individuals with IBS, 63% were interested in knowing which foods to avoid. The lifestyle changes they had made or considered for treatment

of IBS included small meals (69%); avoiding fatty foods (64%); higher fiber intake (58%); and avoiding milk products (54%), carbohydrates (43%), caffeine (41%), alcohol (27%), and high-protein foods, such as meats (21%).²³

HOW DOES FOOD CAUSE IBS SYMPTOMS?

Food processing is the primary function of the gastrointestinal (GI) tract, and food ingestion, through mechanosensation and nutrient sensing, causes major changes in GI sensorimotor and secretory function, which may contribute to symptom generation in IBS. On ingestion of nutrients, the proximal stomach relaxes and upper GI motility switches from interdigestive to fed state motility, characterized by phasic contractions in the antrum and the small bowel.²⁴ In addition, food ingestion stimulates gastric and pancreatic secretion and is associated with the release of several anorexigenic hormones, such as cholecystokinin (CCK) and glucagon-like peptide-1 (GLP-1).^{24,25} Hence, food can influence symptom generation from the GI tract by stimulation of mechano- or chemoreceptors, activation of motor reflexes pathways, by altered secretion, and by (colonic) fermentation.

Most investigators agree that the stomach does not meaningfully detect the nutrient or caloric composition of a meal and that mechanical distention by the meal is the major gastric sensory signal upon food intake.²⁶ Tension-sensitive mechanoreceptors in the stomach are involved in detecting the ingested nutrient volume and in triggering relaxation of the proximal stomach, which enables storage of the meal without a rise in intragastric pressure.^{27,28} Probably through similar mechanisms, the volume of the meal in the stomach is a trigger for the initial phase of the gastrocolonic reflex, a meal-induced increase in tone, and phasic contractility of the colon.^{29,30} The early (gastric) phase of colonic contractile activity in response food intake is mediated by activation of gastric mechanoreceptors and can be reproduced by distention of a gastric balloon, and suppressed by atropine. A later (intestinal) phase depends on duodenal delivery of nutrients.²⁹

Passage of nutrients to the small intestine activates a different set of neural and hormonal responses.²⁴ The small intestine is well equipped to sense the presence of nutrients and their composition. Specialized receptors on enteroendocrine cells detect the presence of specific food constituents, pH, and osmolarity of small intestinal contents, and through altered release of peptides and other signaling molecules, neural and hormonal pathways are activated that may influence GI sensorimotor function and afferent signaling. In general, the presence of nutrients, gastric acid, or hyperosmolar fluids in the duodenum activates neurohormonal pathways that slow further delivery of gastric contents to the small intestine through inhibition of gastric tonic and phasic contractions and through closure of the pylorus.^{24,31} For instance, lipids in the duodenum activate long-chain free fatty acid receptors GPR120 and possibly GPR40 and release CCK from I-cells.³² CCK is a potent enhancer of colonic motility and of GI motility and has been implicated in the intestinal phase of the gastrocolonic reflex, based on observations in a dog model.³³ The gastrocolonic reflex is exaggerated in IBS patients as a group, and this reflex has been implicated in the early postprandial increase in IBS symptoms that is present in the majority of patients.^{34,35} In humans, however, the colonic response to food ingestion was not inhibited by the CCK-A receptor antagonist loxiglumide.³⁴ Recent studies have shown an exaggerated increase in rectal sensitivity to distention after ingestion of a meal in IBS.^{35,36} Because lipids were the strongest stimulus in these studies, it has been suggested that CCK might be involved, and exogenously administered CCK was shown to enhance rectal sensitivity in health.^{36,37}

Intestinal nutrient sensing is extensive, and several nutrient-related components have the ability to activate afferent pathways, alter GI reflex activity, or change the release of GI peptides. The presence of glucose in the lumen induces release of GLP-1 and serotonin, among other gut hormones, from enteroendocrine cells, through the sodium-glucose cotransporters, SGLT1 and SGLT3.³⁸ These peptides may alter visceral sensorimotor function and could contribute to food-induced symptom aggravation.^{9,39} More recently, it has been shown that the small intestine also expresses the T1R and T2R G-protein-coupled taste receptors families.⁴⁰ Taste receptors interact with specific G α subunits, including α -gustducin, a taste-specific signaling protein. Because immunohistochemical studies have shown expression of α -gustducin in several types of enteroendocrine cells, it has been hypothesized that activation of taste receptor signaling molecules may alter the release of GI peptides, such as PYY, GLP1, or CCK.⁴⁰ In turn, these hormones may alter endocrine secretions and appetite, but they may also affect motor behavior and sensory signaling, thereby contributing to changes in symptoms induced by ingestion of a meal.³⁹ Finally, the gut also expresses members of the superfamily of transient receptor potential cation channels on enteroendocrine cells and afferent nerves.⁴¹ These may sense aspects of luminal contents, such as acidity, or the presence of food components, such as menthol or capsaicin, which may alter GI sensorimotor function through activation of neural or humoral pathways.⁴¹ The presence of taste receptors and transient receptor potential channels and their coupling to release of functionally relevant GI signaling molecules or activation of neural pathways could potentially help explain some of the intolerances to specific foods or tastes that IBS patients report and which cannot be explained by food allergies.^{9,39}

The physical properties of nutrients may also contribute to meal-related symptom aggravation, without involvement of sensing of nutrient composition. Nonabsorbable components of ingested food may also contribute to symptom generation and perception in IBS, either through changes in motility and transit that they induce or through fermentation by bacterial flora in the colon. Osmotically active substances in the small intestine, such as nonabsorbable sugars, attract fluids and this may lead to increased intestinal contractility, accelerated colonic transit, increased flatulence, and diarrhea.^{42–44} It is conceivable that such responses may be aggravated in IBS patients, where small intestinal transit and water content may already differ from health.⁴⁵ Fiber, especially insoluble, may promote bacterial fermentation in the large intestine and symptoms of bloating and distention.⁴⁶ Because the colonic flora may differ in IBS from health, these processes could potentially be altered in IBS, but additional studies are needed.⁴⁷

In summary, food can influence symptom generation from the GI tract through many pathways. These include activation of mechanoreceptors by the volume and physical properties of the meal and activation of chemoreceptor-activated pathways through a multitude of nutrient-sensing mechanisms. Nonabsorbable components may influence GI function and sensations through osmotic actions and colonic fermentation. There is emerging evidence of some altered nutrient-related GI functions in IBS, which include an exaggerated gastrocolonic reflex, enhanced sensitization to rectal distention after lipid ingestion, and changes in colonic bacterial flora that may be relevant for fermentation of nonabsorbable remnants. Detailed studies investigating potentially altered nutrient sensing in IBS are still lacking.

FOOD ALLERGY VERSUS FOOD INTOLERANCE

Up to 25% of the general US population believes they have an FA.⁴⁸ True FA, however, occurs in approximately 4% to 8% of children and 1% to 4% of adults in the United

States. Although controversial, there are data to suggest that the prevalence of FA is increasing.^{49–53} Few children retain their FA into adulthood, which accounts for the decrease in prevalence between children and adults. Many studies demonstrate that 50% to 90% of presumed food allergies are not actually allergies but rather a food intolerance (some adverse reaction to food) or food aversion (refusal to eat a food because it is potentially hazardous, socially inappropriate, or distasteful).

True FA is an immunologically mediated, adverse reaction that occurs reproducibly after a susceptible individual ingests a specific food. Although nonfood allergies can be diagnosed by well-defined criteria, the diagnosis of FA is far more difficult. This is particularly true for the clinical spectrum of food-related allergic manifestations that occur in the digestive tract, because many symptoms, such as oral/throat itching, nausea, vomiting, abdominal pain, diarrhea, and constipation, are vague and can be mistaken for other conditions. The best-established food reactions are IgE-mediated (considered type I hypersensitivity) and non-IgE-mediated reactions (including type III hypersensitivity [IgG or IgM immune complex reactions] and type IV hypersensitivity [delayed-type or cell-mediated reactions]). (See **Table 1** for a classification of pathophysiologic reactions to foods.)

The best-established mechanism in FA is due to the development of IgE antibodies against the offending food (most commonly cow milk, eggs, peanuts, tree nuts, seafood, and shellfish). The diagnosis of an IgE-mediated FA is made by a carefully taken case history, supported by the demonstration of IgE sensitization either by skin prick tests or in vitro tests, and confirmed by positive food challenge. If the reaction is not IgE mediated (as in some children with cow milk allergy), however, these tests are often unrevealing. A helper T cells type 2 cytokine pattern is prevalent in allergic individuals at the site of the gut-associated lymphoid and mucosal system. Because individuals can develop immunologic sensitization (as evidenced by the presence of allergen-specific IgE) to food allergens without having clinical symptoms on exposure to those foods, an IgE-mediated FA requires both the presence of sensitization and the development of specific signs and symptoms on exposure to that food. Sensitization alone is not sufficient to define FA.⁵⁴ The formation of IgE antibodies on antigen exposure may not necessarily induce clinical manifestations and vice versa (the

Table 1
Pathophysiologic classification of adverse reactions to food

	Immunopathology	Disorder
Allergic	IgE dependent (acute onset)	Urticaria/angioedema
		Oral-allergy syndrome (pollen-food related)
	IgE antibody associated/cell mediated (delayed onset/ chronic)	Asthma, rhinitis
		Anaphylaxis
Nonimmunologic	Cell mediated (delayed onset/ chronic)	Atopic dermatitis
		Eosinophilic gastroenteropathies
	Toxic	Dietary protein enterocolitis
		Dietary protein proctitis
	Pharmacologic	Celiac disease
		Infection/food poisoning
	Metabolic	Caffeine, histamine, tyramine, monosodium glutamate
		Galactosemia, alcohol intolerance, lactose intolerance

quiescence of atopic disease does not necessarily correlate with a decrease in antibodies). Clinicians, however, may use the detection of these antibodies to identify potential offending antigens, the clinical significance of which can only be confirmed by reproduction of symptoms after oral food challenge. Furthermore, the absence of such antibodies helps exclude the presence of IgE-mediated FA. A double-blind placebo-controlled food challenge is the gold standard for establishing the presence of FA. Reproduction of GI symptoms with a single-blind or open food challenge is suggestive but subject to a higher likelihood of placebo response.

The spectrum of food allergies also includes delayed-onset or cell-mediated diseases, such as eosinophilic GI diseases (esophagitis, gastroenteritis, and colitis), food protein-induced enterocolitis syndromes (occurring in young children), and food-induced atopic dermatitis. These may be T-cell or IgE mediated. Two specific presentations that also fall within the FA category are the pollen food syndrome and the latex-FA syndrome, which both present with cutaneous and GI complaints and may include bronchospasm and anaphylaxis.

Food intolerances are non-immune-mediated adverse reactions to food and may be due to factors within foods, such as pharmacologic agents (histamine, sulfites, and caffeine), enzyme deficiency of the host (lactase deficiency), host-specific metabolic disorders (galactosemia and alcohol intolerance), or idiosyncratic responses induced by an unknown mechanism. To date, there has been no widely accepted definition put forth by an internationally sanctioned organization. Symptoms may cover a wide spectrum, but are usually minor complaints, such as headaches. Pharmacologic reactions to food and food additives may be caused by vasoactive amines (dopamine, histamine, serotonin, phenylethylamine, and tryamine) in selected foods, and food additives, such as sulfites, tartrazine, and monosodium glutamate. Symptoms of this type of reaction usually manifest outside of the GI tract in the form of headache, asthma, and urticaria.

FOOD ALLERGY AND FOOD INTOLERANCE IN IBS

Many studies have tried to examine the prevalence of FA in patients with GI symptoms. In one study of patients with IBS and inflammatory bowel disease (IBD), 32% complained of adverse reactions to food as a cause of their GI symptoms.⁸ FA was suspected, however, according to several criteria in only 14% and could be confirmed by endoscopic allergen provocation and/or elimination diet and rechallenge in only 3.2% of patients. Similar results were reported by Dainese and colleagues¹⁰ who found no difference in the frequency of positive skin prick tests in IBS patients when comparing those with and without self-reported adverse reactions to food. Similarly, there was little consistency between the specific foods reported to cause intolerance and those resulting from the tests (11 of 80 patients, 13.7%).

The prevalence of IBS-like symptoms is increased in patients with allergic symptoms, such as rhinitis and asthma, when compared with nonallergic patients.⁵⁵⁻⁵⁷ Another study showed that patients with asthma have an increased prevalence of IBS relative to patients with other pulmonary disorders and healthy subjects.⁵⁸ Minor histologic abnormalities in the GI tract of patients with atopic diseases have been documented.⁵⁹⁻⁶² Likewise, the presence of atopic conditions is increased in patients with diarrhea-predominant IBS.^{17,63} This higher prevalence of allergic symptoms in unselected gastroenterology patients and the higher prevalence of IBS-like symptoms in allergic patients both suggest that atopic disease and GI complaints may be associated, independently of whether or not patients suspect food hypersensitivity as the main cause of their symptoms.^{55,57}

Some authors have posited that patients with atopic diseases have impaired gut barrier function as indicated by increased intestinal permeability.^{64–66} The potential association between atopic disease, mild intestinal mucosal inflammation, and IBS symptoms in patients with self-reported food hypersensitivity was recently explored by Lillestol and colleagues.⁶⁷ Symptoms, skin prick tests, serum markers of allergy, and intestinal permeability were recorded in 71 adult patients with self-reported FH. Patients with self-reported food hypersensitivity had a high prevalence of IBS and atopic disease (93% and 61%, respectively). Atopic patients had increased intestinal permeability and density of IgE-bearing cells compared with nonatopic patients, but GI symptoms did not differ between groups. Some investigators have suggested atopic IBS as a new subgroup of IBS, with the intestinal mucosal mast cell as a possible pivotal pathophysiologic factor.⁵⁷ For further discussion on the link between immune response and functional bowel disease, readers are directed to a recent comprehensive review.⁶⁸

Elevated levels of both food-specific serum IgE and IgG4 antibodies have been associated with food hypersensitivity-induced atopic conditions also, although the significance of elevated IgG4 antibody has been questioned. There is emerging evidence that these antibodies are pathophysiologically relevant in IBS.^{20,69} Zar and colleagues²⁰ tested 108 IBS patients with IgG4 titers, skin prick tests, and IgE titers and compared with controls. Of 16 common food articles, there were significantly higher titers in the IBS group to wheat, soy, beef, pork, and lamb compared with controls but no difference in IgE titers or skin prick tests. No correlation was seen between the pattern of elevated IgG4 antibody titers and patient symptoms (ie, no difference among IBS subtypes).

The identification of patients with FH and IBS symptoms can be challenging, and a newer application of the basophil activation assay has been used in attempt to further characterize these patients. A recent report by Carroccio and colleagues⁷⁰ evaluated the prevalence of food hypersensitivity to milk or wheat and the performance of this *in vitro* basophil activation assay for FH in patients with IBS symptoms. This test has previously been applied to allergy diagnoses, but the investigators used this technique to identify FH in a group of IBS patients. One hundred and twenty patients with IBS based on Rome II criteria completed questionnaires addressing their symptoms and any possible self-perceived FH. Patients underwent a 4-week diet that strictly eliminated milk, wheat, egg, tomato, and chocolate. Responders subsequently underwent a series of double-blind, placebo-controlled, 2-week oral food challenges with milk and wheat. Ultimately, 24 (20%) of the IBS patients had a positive food challenge to milk and/or wheat (16% both, 3% milk, and 2% wheat) and were diagnosed with FH. Patients with FH developed symptoms after a median of 3 days of food challenge and 50% had to discontinue the food challenge because of recurrent symptoms. The FH patients tended to carry a longer diagnosis of IBS and showed a higher frequency of self-perceived food intolerance. Still, the majority of patients with self-perceived food intolerance had a negative response to double-blind food challenge. A small subset of patients who denied a relationship between food and their symptoms had a positive response to double-blind food challenge. The *in vitro* basophil activation assay was more often abnormal than were the serum measurements of total IgE and serum food-specific IgE. Using double-blind food challenge as a gold standard, specificity of the *in vitro* basophil activation assay was 86% in the IBS subjects with no false-positive results identified in the healthy controls. There was a high frequency of false-positive results when patients with other chronic intestinal inflammatory diseases were tested. More work is needed to validate the accuracy of the basophil activation assay used in this study.

Useful information on the role of foods in GI immunoallergic reactions could come from the colonoscopic allergen provocation test developed by Bischoff and colleagues.⁷¹ Briefly, during colonoscopy, specific food allergens were found to trigger mucosal weal and flare reactions in 54 of 70 (77%) patients with abdominal symptoms suspected of being food related, whereas no reaction was observed in healthy volunteers. The clinical relevance of these findings, however, requires further study.

ELIMINATION DIETS

Many investigators have investigated dietary manipulation as a potential treatment strategy for patients with IBS. In 1982, Jones and colleagues¹² were among the first to demonstrate symptom improvement after an elimination diet in two-thirds of their IBS patients. Based on such results, they and others hypothesized that food intolerance was the major factor underlying the pathogenesis of IBS and that a therapy based on a diet that excluded certain foods could be effective in IBS patients.¹¹ Subsequent studies, however, failed to conclusively confirm this hypothesis, with some groups demonstrating food hypersensitivity in only IBS patients with associated atopic disease or IBS-D and still others finding little benefit from exclusion diets.^{72–74} Overall, response rates to exclusion diets have ranged from 15% to 71%,^{11,12,18,72–75} with dairy products, wheat, and eggs the most commonly implicated food items. Foods high in salicylates or amines may also be problematic for IBS patients.

The reasons that underlie the widely variable response rates with exclusion diets are unknown but may include the lack of standardized protocols among the studies, varying inclusion/exclusion criteria, and inconsistent definitions of food intolerance and positive food challenge. Furthermore, a placebo diet is difficult to incorporate in clinical trials and the high placebo response in such trials necessitates large sample sizes to achieve appropriate power. Well-designed studies are needed to evaluate the role of exclusion diets in patients with IBS symptoms.

SPECIFIC DIETS

Fiber Supplements

Although increasing dietary fiber continues to be a standard recommendation for patients with IBS, the efficacy of fiber for IBS is more nuanced than appreciated by most clinicians. A recent systematic review and meta-analysis, which evaluated the efficacy of fiber as a treatment for IBS, included 12 trials and 591 patients.⁷⁶ Included studies compared various forms of fiber with placebo or, in one study, a low-fiber diet. Two of the studies included only IBS-C patients and another had 49% IBS-C patients. Overall, 52% patients assigned to fiber had persistent symptoms or no improvement in symptoms after treatment compared with 57% assigned to placebo or a low-fiber diet (relative risk [RR] 0.87; 95% CI, 0.76 to 1.00; $P = .05$). There was no statistically significant heterogeneity detected between studies ($I^2 = 14.2\%$, $P = .31$). The number needed to treat (NNT) with fiber to prevent one patient with persistent symptoms was 11 (95% CI, 5 to 100). There was no evidence of funnel plot asymmetry, suggesting no publication bias. Only 7 of the 12 studies, however, scored 4 or more on the Jadad scale. When only these 7 higher-quality studies were included in the analysis, the borderline treatment benefit for fiber was no longer evident (RR of persistent symptoms 0.90; 95% CI, 0.75 to 1.08).

The data suggest that not all types of fiber supplementation are created equally, at least not as pertaining to the treatment of IBS. In 5 studies (221 patients) that compared insoluble bran with placebo or a low-fiber diet, bran failed to improve overall

IBS symptoms (RR of persistent or unimproved symptoms 1.02; 95% CI, 0.82 to 1.27).⁷⁶ In one study that evaluated bran in IBS patients, 55% of patients were actually made worse by bran whereas only 10% found it helpful.⁷⁷ All symptoms of IBS were exacerbated by bran, with bowel disturbance most often adversely affected, followed by abdominal distension and pain. Alternatively, 6 studies (321 patients) evaluated soluble ispaghula/psyllium versus placebo. Ispaghula was effective at improving overall IBS symptoms (RR of persistent or unimproved symptoms 0.78; 95% CI, 0.63 to 0.96). The NNT with ispaghula to prevent one patient from experiencing persistent symptoms was 6 (CI, 3 to 50). There was no evidence of funnel plot asymmetry and 5 of 6 studies scored 4 or more on the Jadad scale. A recent comparative effectiveness trial evaluated the relative efficacy of psyllium, 10 g (n = 85); bran, 10 g (n = 97); or rice flour (placebo) (n = 93), twice daily (mixed with food, preferably yogurt) for 12 weeks.⁷⁸ At 1 month, 57% of patients taking psyllium experienced adequate symptom relief for 2 of 4 weeks of treatment compared with 40% with bran (NNT = 6; 95% CI, 4–104) and 35% with placebo (NNT = 5; 95% CI, 3–15). Although psyllium yielded significant benefits after the second month, treatment benefits were no longer significant after 3 months. Bran offered significant benefits only after 3 months of treatment. More than 60% of subjects randomized to psyllium or bran reported moderate adverse events, the most common of which were constipation and diarrhea.

When fiber is recommended, use of a soluble supplement, such as ispaghula or psyllium, is best supported by the available evidence. Fiber should be started at a nominal dose and slowly titrated up over the course of weeks to a target dose of 20 to 30 g of total dietary fiber per day. Even when used judiciously, fiber can exacerbate problems with abdominal distension, flatulence, constipation, and diarrhea.^{11,76–79}

Gluten Restriction

Celiac disease is an immune-mediated disease that occurs as a consequence of exposure to gluten, a storage protein in wheat, barley, and rye. In patients with celiac disease, dietary gluten induces an abnormal mucosal immune response in genetically susceptible individuals associated with the markers HLA-DQ2 and HLA-DQ8. Patients with classic celiac disease suffer a variety of GI symptoms, such as bloating, abdominal pain, and diarrhea, and have villous atrophy on small bowel mucosal biopsies.⁸⁰ Patients with celiac disease typically experience rapid clinical and more gradual histologic improvements on a gluten-free diet.⁸¹ Recent literature from around the world suggests that approximately 4% of patients with IBS symptoms actually have celiac disease.⁸² Studies from the United States suggest that a smaller proportion, approximately 1%, of patients with typical IBS symptoms turn out to have biopsy-proved celiac disease.^{83,84} There are data to suggest that a larger proportion of patients with IBS symptoms, although not meeting criteria for the diagnosis of celiac disease, are gluten sensitive.^{85,86} Gluten sensitivity is a term used to refer to a heterogeneous group of conditions in which gluten leads to some adverse clinical, serologic, or histologic reaction, which improves with dietary gluten restriction. Such patients often experience GI symptoms that can be clinically indistinguishable from patients with celiac disease or IBS.^{87–89}

Gluten sensitivity encompasses a broad array of disorders ranging from latent celiac disease to FA/hypersensitivity to simple intolerance. There is some acceptance that persistent low-grade inflammation may be present in a subset of patients with IBS, and multiple driving factors have been proposed, including small bowel bacterial overgrowth, postinfectious causes, and immune-mediated responses to specific dietary constituents, such as gluten.^{90–94} Several proposed mechanisms for gluten sensitivity

without celiac disease exist, including increasing intestinal permeability of tight junctions or stimulating lamina propria macrophages and leading to a proinflammatory cytokine milieu.⁸⁶ Nonceliac disease subjects who are +HLA-DQ2 may possess innate cells in a state of heightened activation compared with subjects who are DQ2-.

It has been argued that some patients with positive celiac antibody tests and evidence of genetic predisposition (+HLA-DQ2 or -DQ8) but only subtle abnormalities or entirely normal small bowel histology eventually develop villous atrophy and, thus, belong to the spectrum of celiac disease.^{86,95} Wahnschaffe and colleagues⁸⁷ described a group of patients reporting IBS-D symptoms with +HLA-DQ2, minimal immunopathologic changes on duodenal biopsies (increased intraepithelial lymphocytes [IELs]), elevated celiac disease-associated antibodies in duodenal aspirate, and increased IgA deposition in the intestinal villi. Such IBS-D patients experienced significant reductions in symptoms with a gluten-free diet. Subsequent studies have shown a high likelihood of response to GFD in patients with GI symptoms, abnormal celiac disease antibody testing and genetic markers DQ2/DQ8, but normal or minimal small intestinal mucosal lesions.^{87,95-97} In a follow-up study, Wahnschaffe and colleagues enrolled 41 patients with IBS-D, +HLA-DQ2/DQ8, and positive IgA and IgG antibodies to tissue transglutaminase and/or gliadin. GI symptoms and antibody levels were followed after 6 months of a gluten-free diet.⁸⁵ In IBS-D patients, celiac disease-associated serum IgG antibodies (37%) and HLA-DQ2 expression (39%) were significantly more frequent than in a control group of IBD patients (18% and 23%, respectively). After 6 months of a gluten-free diet, stool frequency and GI symptom score returned to normal values in 60% of IBS-D patients who were positive and in 12% who were negative for HLA-DQ2 and celiac disease-associated serum IgG ($P<.05$). The investigators concluded that celiac disease-associated serum IgG and HLA-DQ2 expression may identify a subset of IBS-D patients who respond to a gluten-free diet.

It is also important to emphasize that the finding of increased IELs on small bowel biopsy is not specific for celiac disease. A variety of other conditions, including *Helicobacter pylori* infection, small intestinal bacterial overgrowth, IBS, diabetes mellitus, microscopic colitis, and the use of various medications, have been associated with this histologic finding.⁹⁸ Thus, in the absence of abnormal celiac antibodies or HLA-DQ2/8, other causes for duodenal lymphocytosis should be sought. That being said, the proportion of IBS patients with the isolated finding of increased IELs on small bowel biopsy who respond to a gluten-free diet remains to be clearly defined. Similarly, the proportion of IBS patients with isolated abnormal celiac antibody test results who will improve on a gluten-free diet is also unknown. **Table 2** may serve as a useful

Table 2 Proposed management of patients with IBS symptoms and testing for celiac disease				
Symptom	LD	HLA-DQ2/8	Serology	Treatment
IBS	+	+	+	Trial of GFD
IBS	+	–	–	Consider other cause
IBS	–	+	+	GFD or follow
IBS	–	–	–	Treat IBS

Abbreviations: GFD, gluten-free diet; LD, lymphocytic duodenosis.
Data from Verdu EF, Armstrong D, Murray JA. Between celiac disease and irritable bowel syndrome: the “no man’s land” of gluten sensitivity. *Am J Gastroenterol* 2009;104(6):1587–94.

guide for identifying patients who may benefit from a trial of a gluten-free diet, depending on their symptoms, biopsies, genotype, and serologies.

Sugar/Carbohydrate Restriction

Carbohydrate malabsorption is a potential cause of symptoms in patients with IBS. Of the various sugars that have been suggested as playing a role in IBS, lactose has been most extensively studied. Lactose is a disaccharide that is cleaved to its constituent monosaccharides, glucose and galactose, by the intestinal brush border enzyme lactase. In the face of lactase deficiency, lactose is presented to colonic bacteria, leading to fermentation and the production of short chain fatty acids as well as various gases, including hydrogen, methane, and/or carbon dioxide.⁹⁹ Lactose malabsorption does not universally lead to symptoms in persons with lactase deficiency.^{100,101} When individuals with lactose malabsorption develop GI symptoms, such as abdominal cramping, bloating, flatulence, and diarrhea, they are said to suffer with lactose intolerance. Many patients who associate their GI symptoms with the ingestion of dairy products have no evidence of lactose malabsorption.¹⁰² On the basis of data from 7 studies using lactose hydrogen breath testing, a recent systematic review found that more than a third of IBS patients have lactose malabsorption and that lactose intolerance is more common in IBS patients than controls.¹⁰³ From a pragmatic standpoint, this should not be surprising because the clinical consequences of lactose malabsorption are likely to be exaggerated in patients with IBS who often have underlying abnormalities in motility and visceral sensation. Patients who are thought to have lactose intolerance are typically treated with a lactose-restricted diet. Data from largely uncontrolled studies suggest that 40% to 85% of IBS patients with lactose malabsorption improve on a lactose-restricted diet.^{39,104,105} A recent systematic review found that there were insufficient data to support the efficacy of lactose-reduced solutions, milk with reduced lactose content, probiotics, or incremental lactose administration in the hopes of inducing colonic adaptation for lactose intolerance.¹⁰⁶

Fructose is another sugar that has been implicated as a potential trigger for symptoms in patients with IBS. Fructose is naturally found in honey, fruits, and table sugar. In the modern Western diet, one of the largest sources of fructose is high-fructose corn syrup, which is the primary sweetener in soft drinks and many prepared foods. The human intestine does not have a specific enzyme for digestion or transport of fructose; absorption of fructose primarily relies on facilitation by glucose transporters (GLUT 5 and GLUT 2), which can be overwhelmed after the ingestion of large amounts of fructose.^{107–109} Fructose absorption is much more efficient in the presence of glucose; in fact, fructose malabsorption (FM) is more likely to occur when fructose is taken alone as opposed to in combination with glucose. This provides an explanation for why most persons tolerate high-fructose corn syrup, which contains near equimolar amounts of fructose and glucose. Delivery of the free fructose to the lumen of the distal small intestine and proximal large bowel may exert an osmotic effect and result in more luminal water, increasing the liquidity of intestinal contents and increasing transit. Malabsorbed fructose and nonabsorbed fructans (long chains of fructose molecules) are, like malabsorbed lactose, fermented by colonic bacteria, leading to the development of GI symptoms in some individuals.¹⁰⁸

The literature suggests that the prevalence of FM is similar between healthy volunteers and patients with functional disorders, but there is some literature to suggest that FM is associated with the development of GI symptoms in a subset of individuals.^{107,108,110,111} In a study by Shepherd and Gibson,¹¹² nearly 30% of IBS patients were unable to tolerate a large load of fructose or fructans, and no such

problem occurred in non-IBS patients with or without FM. This reinforces the notion that in IBS patients, any form of carbohydrate malabsorption is likely to result in the development of symptoms. Restricting dietary intake of fructose may lead to symptomatic benefits in patients with IBS, but high-quality evidence is lacking. In particular, the methodology and clinical value of the fructose hydrogen breath test has been questioned.¹⁰⁹

Acknowledging the limitations of the fructose hydrogen breath test, the prevalence of a positive result has been reported to be 11% to 70% in healthy individuals¹⁰⁸ and 40% to 80% in individuals with functional gastrointestinal disorders, such as IBS. As both natural and processed dietary sources of fructose usually contain glucose, including high-fructose corn syrup, breath testing with pure fructose may not reflect fructose ingestion under normal circumstances. Fructose breath testing alone may overestimate the true prevalence of FM in controls and IBS. When breath testing was performed with both fructose alone and with high-fructose corn syrup in IBS patients and healthy controls, FM was more prevalent with fructose alone than with high-fructose corn syrup, but this did not vary significantly between healthy patients and those with IBS.¹¹⁰

Other symptoms linked with FM, in particular mood disorders and depression, have also been improved with dietary restriction of fructose.¹¹³

In patients with functional abdominal bloating and evidence of fructose or lactose malabsorption, 67% of patients who were educated in dietary restriction had 50% symptom resolution.¹¹⁴ The specificity of this response is questioned by the fact that only patients with positive HBTs were offered the fructose-restricted diet.

The concepts put forth in the preceding paragraphs addressing lactose and fructose malabsorption/intolerance can almost certainly be extended to any of a number of other carbohydrates when ingested in sufficient quantities. The excessive ingestion of sorbitol or mannitol can result in a similar spectrum of GI symptoms as lactose malabsorption or FM and can exacerbate the symptoms of IBS. A recent prospective, randomized, controlled pilot study tested the hypothesis that a very low carbohydrate diet might provide benefit to the symptoms of IBS. Austin and colleagues¹¹⁵ reported that 10 of 13 patients with IBS (77%) experienced adequate relief for 4 of 4 weeks of a very low carbohydrate diet. Another study of 239 individuals with either IBS or nonspecific functional bowel complaints showed an improvement in symptoms after elimination of some combination of sorbitol, lactose, or fructose for 1 month.¹¹⁶ Also, a very low carbohydrate diet based on animal sources of fat and protein is associated with an increased all-cause, cardiovascular, and cancer-related mortality compared with a very low carbohydrate diet based on plant sources of fat and protein.¹¹⁷

FODMAP Restriction

An extension of the concept of sugar/carbohydrate restriction as a treatment for IBS is offered by the restricted Fermentable Oligo-, Di-, and Mono-saccharides And Polyols (FODMAP) diet. FODMAPs represent a family of poorly absorbed, short-chain carbohydrates, which are highly fermentable in the presence of gut bacteria. Taking into consideration comments regarding gluten sensitivity as well as sugar/carbohydrate malabsorption (discussed previously), the major FODMAPs in the Western diet include fructose, linear or branched fructose polymers called fructans, and lactose. **Table 3** provides information regarding the FODMAP food groups and examples of specific foods within each group. Fermentation of these substrates results in gas production and an increased fluid load with secondary luminal distension and resultant peristalsis involving the distal small bowel and proximal colon.

Table 3
Foods rich in FODMAPs by category

FODMAP	Fructose	Polyols	Lactose	Fructans and Galactans
High FODMAP food sources	Apples, pears, watermelon, honey, fruit juices, dried fruits, high-fructose corn syrup	Sugar alcohols (sorbitol, maltitol, mannitol, xylitol, and isomalt), stone fruits, avocado, mushrooms, cauliflower	Milk (cow, goat, sheep), yogurt, soft cheeses (ricotta, cottage)	Wheat, rye, garlic, onions, artichokes, asparagus, inulin, soy, leeks, legumes, lentils, cabbage, Brussels sprouts, broccoli
Alternative lower FODMAP food sources	Citrus, berries, bananas, grapes, honeydew, cantaloupe, kiwifruit	Sweeteners, such as sugar, glucose, other artificial sweeteners not ending in “-ol” (sucralose, aspartame)	Lactose-free dairy products, rice milk, hard cheeses	Starches, such as rice, corn, potato, quinoa. Vegetables, such as winter squash, lettuce, spinach, cucumbers, bell peppers, green beans, tomato, eggplant

All nonprocessed meats are generally low in FODMAPs.

It is not difficult to imagine how these physiologic events could lead to the development of symptoms, such as bloating, distension, abdominal pain/cramping, or diarrhea, in particular in patients with underlying IBS.¹¹⁸ The effect of dietary FODMAP content on the production of hydrogen and methane gases and the induction of functional symptoms was recently studied by Ong and colleagues,¹¹⁹ who performed a randomized, single-blind, crossover trial in 15 healthy controls and 15 patients with IBS by Rome III criteria. Each group consumed a high or low FODMAP diet for 2 days. Higher levels of breath hydrogen excretion were seen with the high-FODMAP diet in both healthy volunteers and IBS patients. Breath hydrogen but not methane levels were higher in the IBS patients than controls. The investigators concluded that dietary FODMAPs were associated with prolonged hydrogen production and led to a greater degree of GI symptoms in IBS patients than controls. In addition to simply reducing exposure to fermentable substrates, it is also conceivable that elimination of dietary FODMAPs might alter the gut microbiome through prebiotic effects, reduce or change the products of fermentation, improve intestinal barrier function, or affect function of smooth muscle or the enteric nervous system.^{120,121} The effects of FODMAPs on fecal fluid content were recently elucidated.¹²² Twelve patients with ileostomies were evaluated to understand the effect of dietary FODMAPs on the nature and volume of ileal effluent and to document perceived changes in ileostomy output. Patients ingested either a high or low FODMAP diet during 4-day periods during this randomized, crossover, single-blind study. Compared to the low FODMAP diet, ileostomy output volume with the high-FODMAP diet was increased by 20% whereas water content and dry weight increased by 20% and 24%, respectively. Participants also perceived effluent consistency as thicker with the low FODMAP diet compared with the high-FODMAP diet. Furthermore, rats fed FODMAPs have been shown to develop more severe colitis after infection with *Salmonella* species.¹²³ This is a particularly interesting observation given the mounting evidence to suggest that IBS can occur after an acute gastroenteritis and that one of the most potent predictors of postinfectious IBS is the duration and severity of the index gastroenteritis.¹²⁴

There is a growing body of evidence to support the efficacy of the FODMAP diet in patients with IBS symptoms. Small, early studies reporting promising results with the FODMAP diet in patients with IBS were met with skepticism. Critics were quick to discount the positive results as placebo response or dismiss the diet as impractical.^{112,114} Two recent studies provide support for the use of the FODMAP diet in patients with GI symptoms. In a telephone survey study of 72 patients with inflammatory bowel disease (IBD) from Australia, the vast majority of patients were able to reduce FODMAP intake moderately if not completely. Those who adhered to the diet enjoyed impressive improvements (defined as an improvement of at least 5 points on a 21-point balanced scale) in overall abdominal symptoms, pain, bloating, flatulence, and diarrhea at a mean follow-up of 17 months (25th–75th percentiles = 7–26 months). This retrospective study did not report on potential confounders, including disease activity or concurrent medical therapies for IBD. Underscoring some of the practical issues around this diet, when patients were asked about ease of implementing and palatability of the FODMAP diet, they assigned scores of 3 and 2 out of 10, respectively.¹²⁵

A recent randomized, double-blind, quadruple-arm, crossover, placebo-controlled, rechallenge trial in IBS patients and a positive fructose hydrogen breath test result attempted to isolate whether or not the benefits of the FODMAP diet were attributable to exclusion of fructose, fructans or both.¹²⁶ All 25 IBS patients included had previously responded to a low FODMAP diet and all 3 subtypes of IBS (diarrhea,

constipation, and mixed bowel pattern) were included. After 10 days on a low FODMAP diet, patients were challenged with prepared drinks containing escalating doses of fructose, fructans, fructose/fructan mix, or glucose. Symptoms were assessed daily by 100-mm visual analog scales. Dose-dependent increases in abdominal symptoms, abdominal pain, wind, and bloating were seen with fructose, fructans, and the fructose/fructan mixture arms. Symptom scores were significantly greater for these groups compared with the glucose group. The fructose-fructan mix caused greater symptom severity than did fructose alone. These results suggest that exclusion of both fructose and fructans is likely to be crucial to the benefits of a low FODMAP diet.

The low FODMAP diet differs from most other elimination diets in that no initial attempts are made to identify specific culprit foods. Rather, the FODMAP approach uses a more empiric strategy of initially eliminating or at least significantly reducing all of the most likely culprit foods. In persons who respond to the full elimination phase, specific FODMAP food groups are sequentially reintroduced, allowing determination of the particular foods that the patient cannot tolerate. Given the complexity of the diet, the time necessary to obtain an adequate dietary history, the time needed to explain the intervention, and the need for ongoing dietary counseling, the authors' group believes that the FODMAP diet is best undertaken with the assistance of a trained dietician. For details regarding the practical implementation of the FODMAP diet, readers are directed elsewhere.^{112,127} On introducing this diet to a clinical practice, it is natural for providers to initially presume that the complexity of the diet guarantees patient noncompliance. The authors and other investigators have found that IBS patients often desire a more holistic approach to their care. They often are interested in learning about dietary interventions, particularly when symptom onset is related to eating a meal. In support of this statement, a recent survey conducted in more than 1200 IBS patients found that more than 60% of respondents wanted to learn about which foods to avoid.²³ In addition, many IBS patients with meal-related symptoms have tried a variety of dietary restrictions and, often, are already on a highly restricted diet by the time they see a specialist. Unfortunately, haphazard attempts at dietary exclusion are often unsuccessful and potentially dangerous. Such IBS patients have proved that they are highly motivated for dietary interventions and many of them actually express relief when provided with a construct that specifically addresses the foods that they can eat and those that they should avoid.

CONCLUDING COMMENTS

Many of the therapeutic options commonly used for IBS have proved unsatisfactory both to patients and providers, likely due to the inherent complexity and heterogeneity of the disorder. In a subset of patients, diet seems to play a role in the development of symptoms. Many patients are now demanding a more holistic approach to their care. Although dietary interventions may be the low-hanging fruit for such patients, their success is highly dependent on the presence of a motivated patient and caregiver. Despite the fact that gastroenterologists spend more time with their patients than most clinicians,¹²⁸ the time required for a complete dietary assessment and overhaul is beyond the capability/resources of even the most dedicated physician. Thus, access to a dietician with expertise and experience with GI disorders, such as IBS, improves the chance of a successful outcome after dietary interventions. Practical considerations aside, dietary intervention as a therapeutic option for IBS is promising. Some of the many questions for future studies include (1) How do individual foods and combinations of foods affect the microbiome, neuroendocrine, and immune function,

motility, and sensation of the GI tract? (2) Which subgroups of patients are more or less likely to respond to which type of dietary intervention? (3) What are the most practical ways in which to introduce dietary interventions into clinical practice? (4) Are dietary interventions cost-effective when compared with medical therapies for IBS? (5) Might incremental benefits be derived by combining dietary interventions with medical therapies? Only by answering such questions will we be able to fill in the many blanks that remain in the evolving story of dietary interventions for IBS.

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