Gluten Sensitivity Aftershock! Is a Low-FODMAP Diet the Next Big Thing?

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Looking Beyond Gluten

Over the past decade, gluten avoidance has become the most popular dietary trend in the United States, with over 100 million Americans consuming gluten-free products, most of whom do not have celiac disease.

In fact, the term *non-celiac gluten sensitivity* (NCGS) was minted to describe individuals who manifest a clinical disorder related to ingestion of gluten. NCGS is characterized by a series of self-reported gastrointestinal (GI) symptoms similar to those with irritable bowel syndrome (IBS): abdominal pain, gas and bloating, nausea, diarrhea, or constipation. While data seemed to convincingly support a role for gluten in causing many of these GI symptoms, recent studies have suggested that there is more to the story. It may be incorrect to attribute any clinical response to the presence or absence of gluten, as differences in the content of other dietary components (eg, wheat proteins, poorly absorbed carbohydrates) may also be responsible. This was clearly shown by Biesiekierski and colleagues in a double-blind crossover study of persons with self-reported NCGS who were feeling well on a gluten-free diet. These patients improved further on a diet in which FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) were eliminated. GI symptoms consistently and significantly improved for all participants during the phase of reduced intake of FODMAPs. When these patients were re-challenged by reintroduction of gluten into the otherwise low-FODMAP diet, they did not experience a specific or dose-dependent relapse.

Possible Explanations for FODMAP Sensitivity

It has long been recognized that patients with IBS may experience sudden or worsening abdominal pain and bloating after ingesting certain foods, including historically recognized "culprits" like milk and other dairy products, legumes, and select fruits. The hypothesized mechanisms have included immune and mast cell activation, mechanoreceptor stimulation, and chemosensory activation. The most recently cited triggers are short-chain carbohydrates collectively known as FODMAPs. A low-FODMAP diet has been reported to induce a clinical response in 50%-80% of patients with IBS, with specific improvement in bloating, flatulence, diarrhea, and global symptoms.

Components of FODMAPs are nearly ubiquitous and include fructose (found in stone fruits and sweeteners), lactose (dairy products), fructans (wheat-based products), galacto-oligosaccharides (legumes), and polyols such as xylitol and mannitol (fruits and artificial sweeteners). These highly fermentable carbohydrates are poorly absorbed from the small intestine and thus enter the colon, where they osmotically increase luminal water volume, induce gas and short-chain fatty acid production through fermentation by colonic bacteria, and increase intestinal motility. This leads to luminal distension, bloating, and diarrhea. FODMAPs may also affect the gut microbiota, gut immune function, and the gut mucosal barrier—factors that might also be involved in generating GI symptoms in patients with visceral hypersensitivity.

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Gibson and coworkers thus proposed that reduction in the dietary intake of these indigestible or slowly absorbed, short-chain carbohydrates would minimize bloating and stretching of the intestinal wall, thereby decreasing bowel contractions and pain. This broad reduction approach differed from previous dietary strategies in which one or two specific species of carbohydrates (eg, lactose, fructose, or sorbitol) were restricted.

The early success has allowed the FODMAP diet to become a popular option, and resources that describe the FODMAPs composition of various foods are readily available. These known "gas-producing foods" are being avoided by patients plagued by excessive flatulence and bloating. This may indeed be a viable management option, but restriction may have important unintended consequences, as FODMAPs variably exert important physiologic effects: increasing stool bulk, enhancing calcium absorption, modulating immune function, decreasing serum cholesterol levels, and stimulating the growth of certain microbial groups such as *Bifidobacteria* (a prebiotic effect). In addition, bacterial fermentation of FODMAPs results in the production of short-chain fatty acids that exert a trophic effect on colonocyte metabolism.

Does the Evidence Support Efficacy?

In reviewing the spate of studies extolling the benefits of a low-FODMAP diet in patients with IBS, there is a noticeable lack of uniformity. The studies suffer from varying definitions of clinical response, inclusion of patients without clearly stratifying them by Rome criteria–based IBS subtypes, disparity in the symptom questionnaires

employed, low sample sizes, short diet durations, and variable rigor in diet restriction and implementation (eg, some provide all the food, others a dietitian-led educational approach). Feeding studies are difficult to "blind" if the diet components are included as whole foods. It is unclear as to whether there is a dose-dependent response to FODMAPs reduction: greater outcome with better adherence. With such broad restriction, it is also unclear as to which prohibited food component was responsible for the favorable response in any individual patient.

With these caveats in mind, there are several key studies that demonstrate the reported effect of FODMAPs restriction on patients with IBS.

Eswaran and colleagues compared the efficacy of a low-FODMAP diet versus a diet based on the traditional modified National Institute for Health and Care Excellence (mNICE) guidelines for patients with IBS and diarrhea (IBS-D). The mNICE is a multifaceted approach that prescribes a high fluid intake, alcohol and caffeine restriction, and limited fiber intake. Over half (52%) of the low-FODMAP diet group versus 41% of the mNICE group reported adequate relief of their symptoms. Compared with baseline scores, the low-FODMAP diet led to a greater reduction in abdominal pain, bloating, consistency, frequency, and urgency than the mNICE diet.

In a separate study, this group compared the effects of the low-FODMAP diet with the traditional dietary recommendations on health-related quality of life (QOL), anxiety and depression, work productivity, and sleep quality in patients with IBS-D. After 4 weeks, a significantly higher proportion of patients in the low-FODMAP diet group had a meaningful clinical response, based on an increased IBS-QOL score, than subjects in the mNICE group (52% vs 21%). Of note, anxiety scores and activity impairment were significantly reduced in those adhering to the low-FODMAP diet compared with the mNICE diet.

Several other studies have achieved a similar outcome. In one prospective study, the efficacy of the low-FODMAP diet was durable over a follow-up period of approximately 16 months in 90 consecutively treated patients with IBS. A somewhat lower response rate was reported by Böhn and coworkers who compared the effects of a diet low in FODMAPs with traditional dietary advice. Patients with IBS were randomly assigned to either a diet low in FODMAPs or a dietary approach frequently recommended for patients with IBS (a regular meal pattern; avoidance of large meals; and reduced intake of fat, insoluble fibers, caffeine, and gas-producing foods, such as beans, cabbage, and onions). The severity of IBS symptoms was reduced in both groups during the intervention, without a significant difference between the groups. At the end of the 4-week diet period, 50% of the patients in the low-FODMAP diet group had reductions from baseline in the IBS Symptom Severity Score (IBS-SSS) of >50, the minimal change considered to be clinically relevant, compared with 46% of patients in the traditional IBS diet group.

Quality of the Data

Krogsgaard and colleagues systematically analyzed the quality of published trials on the symptomatic effects of the low-FODMAP diet for patients with IBS. Nine randomized controlled trials (RCTs) were eligible (542 patients). The authors found a high risk for bias in these RCTs; an absence of diets studied in a randomized,

controlled setting for more than 6 weeks; and a lack of trials that examined the effect of reintroduction. They commented that the symptomatic effects reported in the trials could possibly be driven primarily by a placebo response.

A meta-analysis by Marsh and colleagues supported the efficacy of a low-FODMAP diet in the treatment of functional gastrointestinal symptoms. They suggest further research ensuring that studies include dietary adherence, include a greater number of patients, and assess the long-term adherence to a low-FODMAP diet.

In addition to the RCTs assessing a low-FODMAP diet, a published real-world experience with the low-FODMAP diet reported that approximately 70% of patients with IBS respond. This is significant because the monitored feeding studies do not reflect real-world conditions, where people must make their own food choices, with variable rigor and adherence.

Which Patients Benefit?

While dietary intervention may be effective in reducing symptom severity in patients with IBS, not all patients respond. This raises the question as to which factors govern the response—and can we predict the response?

Certain subgroups of patients with IBS have an altered gut microbiota composition which can be further altered by variations in dietary composition. Thus, gut microbiome biomarkers may be associated with the efficacy of a low-FODMAP diet. Several investigators have noted that diets that differ in their FODMAPs content alter the colonic luminal microenvironment; therefore, the fecal bacterial profile of patients with IBS may predict responsiveness to a diet low in FODMAPs.

McIntosh and coworkers compared the effects of low- and high-FODMAP diets on the metabolome and the microbiome of patients with IBS. The IBS-SSS was reduced in the group receiving a low-FODMAP diet but not in those ingesting a high-FODMAP diet. The profile of urine metabolites also differed significantly. Of specific importance, histamine, an important pathophysiologic mediator and a measure of immune activation, was reduced eightfold in the low-FODMAP diet group; histamine is known to excite enteric cholinergic neurons and stabilization of mast cells, and histamine antagonists have been reported to improve IBS symptoms. In addition, the high-FODMAP diet decreased the relative abundance of bacteria involved in gas consumption, which could worsen symptoms.

Bennet and colleagues also determined that diets differing in FODMAPs content favorably affect gut bacteria and that the resultant bacterial profiles could predict intervention responses. Responders to the low-FODMAP dietary intervention were discriminated from nonresponders before and after intervention by their fecal bacterial profiles. Bacterial abundance tended to be higher in nonresponders to the low-FODMAP diet compared with responders. A low-FODMAP diet was associated with reduced *Bifidobacterium* and *Actinobacteria* in patients, correlating with lactose consumption.

Chumpitazi and colleagues determined the efficacy of a low-FODMAP diet in children with IBS, and whether gut microbial composition and/or metabolic capacity

are associated with the outcome.Compared with baseline, children had fewer episodes of abdominal pain during the low-FODMAP diet and more daily episodes during the traditional diet. Responders were enriched at baseline in taxa with a known greater saccharolytic metabolic capacity (eg, *Bacteroides*, *Ruminococcaceae*, and *Faecalibacterium prausnitzii*).

Hustoft and coworkers also reported that in patients with diarrhea-predominant or mixed IBS, a blinded low-FODMAP diet improved the IBS-SSS and microbiome profile.

In addition, Staudacher and colleagues performed a randomized, placebo-controlled study to determine the effects of a low-FODMAP diet on symptoms and the fecal microbiota in patients with IBS.A higher proportion of patients eating the low-FODMAP diet had adequate symptom relief (57%) compared with the sham diet group (38%). The abundance of *Bifidobacterium* species was lower in fecal samples from patients on the low-FODMAP diet. It is unclear whether the changes noted were due to the collective FODMAPs restriction or removal of a single component, such as lactose.

In summary, diets differing in FODMAPs content have marked effects on gut microbiota composition. A low-FODMAP diet was associated with higher fecal pH (7.37 vs 7.16), greater microbial diversity, and reduced total bacterial abundance compared with the traditional diet. These prebiotic effects may benefit colonic health. This raises the question of whether a prebiotic supplementation would enhance the beneficial effect. Wilson and colleagues randomly assigned patients with IBS to three different interventions, noting significant differences between symptom relief at week 4 between controls (30%), those on a low-FODMAP diet alone (50%), and those on a low-FODMAP diet plus the prebiotic B-galacto-oligosaccharide(67%). The low-FODMAP diet plus the prebiotic group had markedly improved individual IBS symptoms. Furthermore, the investigators observed significant differences in fecal *Bifidobacteria* content between the low-FODMAP diet plus the prebiotic and sham groups.

One Size Will Not Fit All

In my opinion, a low-FODMAP diet is one more tool to add to our armamentarium for the management of patients with IBS. However, the reception of this recommendation by our patients will be variable. On the plus side, a dietary approach has intuitive appeal, and many patients have already identified a correlation of symptoms with certain foods. Yet, the long-term effectiveness is unknown, and stringent restriction of FODMAPs may bring unintended consequences, such as inadequate nutrient intake and adverse effects from altered gut microbiota. For example, it is well recognized that adhering to a gluten-free diet puts one at risk for reduced intake of fiber, iron, zinc, calcium, folate, other B-group vitamins, and natural antioxidants. In addition, although dietary interventions are considered low-risk, the long-term effects of the rapid and marked alterations in the colonic microbiome are unknown.

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In a recent review of IBS, Ford and colleagues recommended, as an initial approach to affected persons, increased exercise and stress reduction, as well as dietary modifications. They suggested a slow increase in the content of dietary soluble fiber if the patient has IBS with constipation, or instituting a low-FODMAP diet temporarily if the patient has IBS with diarrhea or the mixed subtype of IBS.

When implementing a low-FODMAP diet, it is important to first inform patients and their families about what is not known about the role of dietary components in exacerbating or alleviating the symptoms of IBS. Then, in view of the highly restrictive nature of the diet, patients may be advised to use a "selective restriction" approach, which may be best accomplished with a registered dietician.

There are no scientifically validated guidelines, but during the induction phase, all FODMAP groups are restricted. It may be effective to individualize the recommended dietary strategy by eliminating certain components of the FODMAPs class, wheat products, and/or gluten sequentially.

After 4-6 weeks, consider reducing the level of restriction with a step-wise reintroduction of the restricted foods, focusing on specific FODMAP groups. Patients will need to pay attention to food labels in search of FODMAP content.

Next Steps

Our hope is that future clinical trials will determine which component of the spectrum of FODMAPs may be responsible for the symptoms in a given patient.

Dissecting the list of restricted foods into component parts will help to determine whether a less restrictive dietary approach could be effective for that specific patient. Identification of specific dietary triggers for each individual patient will allow a more personalized, and possibly more effective, strategy for the management of IBS symptoms.

Emerging data regarding the individual "intolerance or sensitivity" profile of patients with IBS will allow a rational basis for a restricted diet, whether that involves gluten, wheat, FODMAPs, or any other substance—instead of riding the crest of the latest dietary wave.