

Low FODMAP in 2017: Lessons learned from clinical trials and mechanistic studies

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Abstract

Given the prevalence of irritable bowel syndrome (IBS) and the suboptimal response to most therapeutic approaches, there has been increasing interest in and adoption of dietary treatment strategies, such as the low Fermentable Oligo-, Di-, & Mono-Saccharides and Polyols (FODMAP) diet. FODMAPs are a diverse group of carbohydrates that exert effects in the gastrointestinal tract not only via fermentation but likely via alterations in the microbiota, metabolome, permeability, and intestinal immunity as well. Clinical evidence for efficacy of this diet is mounting, but there are significant questions regarding short- and long-term safety and effects on the microbiota and nutrition that remain unanswered. This review article interprets the recent findings reported in this issue of *Neurogastroenterology and Motility* and summarizes the mechanistic and clinical efficacy data of the low FODMAP diet in IBS patients to date.

KEYWORDS

diet, fermentation, irritable bowel syndrome, microbiota

1 | INTRODUCTION

Irritable bowel syndrome (IBS) is a prevalent condition that leads to considerable morbidity and disability.¹ Despite this, healthcare expenditures for the treatment of organic diseases consume a disproportionate portion of the healthcare pie and leave little for so-called “quality of life” disorders like IBS. In addition, the heterogeneity inherent to the phenotype and pathogenesis of IBS has created significant challenges in drug therapy development for this chronic disease, and the absolute therapeutic gain from traditional therapies has been marginal, typically ranging from 7% to 15%.² As a consequence, providers and IBS patients are increasingly being forced to find solutions for their symptoms that do not involve prescription medications. When one considers that two-thirds of IBS patients associate their symptoms with eating a meal,^{3,4} the importance of finding effective, evidence-based dietary solutions becomes obvious. Furthermore, IBS patients are demanding more “natural,” accessible, cost-effective, and safe options to treat their disease. Unfortunately, traditional dietary advice for IBS patients, such as regulating fiber intake or fat content, is not evidence-based and often has proven ineffective.^{5–8} Thus, the low FODMAP (Fermentable Oligo-, Di-, & Mono-Saccharides and Polyols) diet has been gaining popularity for the treatment of this condition. This review

article interprets the recent findings of Hustoft et al.⁹ reported in this issue of *Neurogastroenterology and Motility* and summarizes the mechanistic and clinical efficacy data of the low FODMAP diet in IBS patients to date.

2 | MECHANISTIC INSIGHTS

FODMAPs are a diverse group of poorly absorbed carbohydrates thought to contribute to gastrointestinal symptoms, likely via multiple pathways (Figure 1). Conventional thinking has focused on the cumulative effects of consuming excessive amounts of all FODMAPs. Undigested, non-absorbed FODMAPs create an osmotic load and are then fermented by small intestinal and colonic bacteria. This leads to the production of short chain fatty acids and gases (hydrogen, methane, carbon dioxide), which can trigger symptoms particularly in patients who have underlying abnormalities in gut motility and visceral sensation.^{10,11} Collectively, these effects can exert primary and secondary effects on motility, visceral sensation, and the gut microbiota that may result in symptoms of cramping, bloating, distention, and flatulence in a subset of IBS patients.^{12–14} However, recent work suggests that the various FODMAPs exert different effects

along the GI tract parts of the GI tract. Using functional magnetic resonance imaging (fMRI), investigators from the UK showed differential effects of fructose and fructans in the small intestine and colon in healthy volunteers and IBS patients.^{15,16} After fructose and inulin (a fructan) challenges, healthy controls had significantly lower symptom scores after either fructose or inulin consumption than patients with IBS, despite similar fMRI parameters and breath hydrogen responses.¹⁶ Fructose led to increased small-bowel water content in both IBS patients and controls (potentially accelerating small-bowel transit and peristalsis as well) whereas inulin increased colonic volume and gas via fermentation by resident bacteria. This indicates that colonic hypersensitivity, rather than greater gas production or distension, drives FODMAP-related symptoms in some IBS patients.

Apart from fermentation effects, FODMAPs may also generate symptoms via immune activation. Given that wheat products contain high FODMAP content, predominantly fructans and galacto-oligosaccharides (GOS), studies focusing on non-celiac wheat sensitivity (NCWS) may be potentially extrapolated to IBS patients.^{17,18} Possible mechanisms for NCWS (and thus a response to a low FODMAP diet) include increased intestinal permeability of tight junctions or stimulation of lamina propria macrophages leading to pro-inflammatory cytokines.^{19,20} Histamine, a signaling molecule known to underlie IBS symptoms, may also be affected by the low FODMAP diet. McIntosh et al.²¹ compared urinary metabolomic profiles of 40 IBS patients after 21 days of a low- or high-FODMAP diet. Following dietary intervention there was a significant separation in urinary metabolomic profiles of patients with IBS in the two diet groups. In the low FODMAP diet group, urinary histamine level decreased significantly after the intervention ($P < .05$) compared to the high-FODMAP group. The authors postulate that degranulation of mast cells may occur due to direct signaling from short chain fatty acids (SCFAs) or from intestinal distension via fermentation, thereby modulating IBS symptoms.

Key Points

- There are likely multiple mechanisms by which FODMAPs exert their effects along the GI tract.
- A low FODMAP diet is likely helpful in treating IBS symptoms, but the evidence is not entirely supportive of this approach.
- The low FODMAP diet has potential limitations, including effects on the intestinal microbiota and metabolome.

3 | EVIDENCE OF CLINICAL BENEFIT

There is a growing body of evidence to support the efficacy of the low FODMAP diet in patients with IBS symptoms.^{22–26} The first study demonstrating a link between dietary FODMAPs and symptoms comes from Shepherd and Gibson's 2008 Australian work during which IBS patients were more likely to experience gastrointestinal symptoms after blinded consumption of escalating doses of fructose or fructans than after glucose.²³ This approach was novel because until this time, dietary strategies focused on the elimination of a single carbohydrate type (ie, lactose, sorbitol, fructose) rather than entire groups of carbohydrates. Subsequent retrospective and randomized studies of dietary FODMAP restriction have reported symptomatic improvement in 52%–76% of IBS patients.^{11,24,27–29} Many studies involving diet for IBS suffer from placebo effect, limited duration, lack of rigorous endpoints, lack of randomization/blinding, and limited dietary assessment to confirm adherence.

The results of randomized controlled trials for the low FODMAP diet in IBS patients have not been uniformly positive, especially when compared with active interventions in a more "real world" setting where food was not supplied to subjects.^{30,31} Bohn et al.³¹

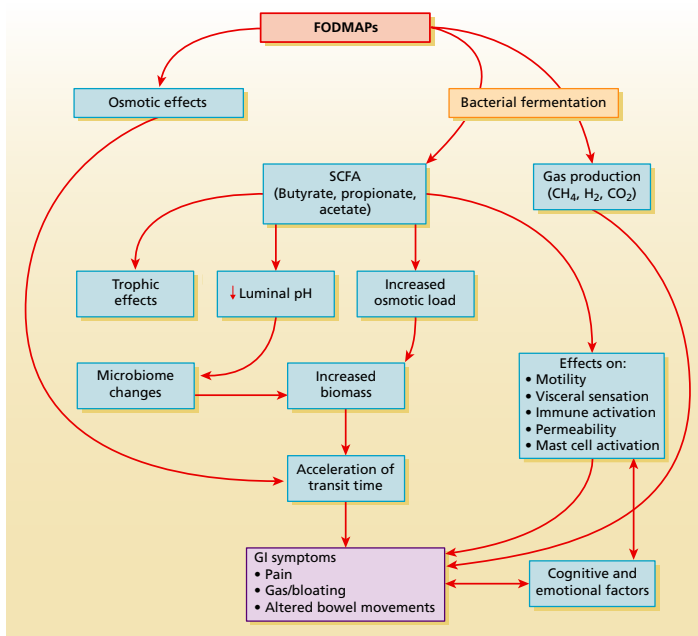


FIGURE 1 Mechanisms by which Fermentable Oligo-, Di-, & Mono-Saccharides and Polyols may cause Gastrointestinal symptoms. Adapted from Spencer M, et al. Current treatment Options in Gastroenterology. 2014; 12:424-440

compared the low FODMAP diet to standard dietary advice and found that about half of each group improved with the intervention, with no significant difference between the two groups after 4 weeks. Each group received dietitian counseling, and all IBS subtypes were included. Similar improvements in each group were noted for most individual symptoms as well (bloating, abdominal pain). Our group recently completed the first US comparative effectiveness trial comparing the low FODMAP diet vs usual dietary recommendations in IBS patients with diarrhea (IBS-D) using a similar study design in 92 patients.³⁰ There was no significant difference between the interventions for the primary endpoint of adequate relief (52% with a low FODMAP diet vs 41% with usual dietary recommendations). However, a significantly greater proportion in low FODMAP diet group than the usual dietary recommendation group experienced improvement in abdominal pain and bloating, two of the most bothersome complaints associated with IBS. In addition, significant improvements were seen in stool consistency, stool frequency, and urgency compared to usual dietary recommendations for IBS. Significant improvements in quality of life measures, as well as anxiety were seen in the low FODMAP diet compared to usual dietary recommendations for IBS.³² The primary endpoints were negative in both trials that utilized an active comparator and dietitian-directed dietary interventions, highlighting some of the limitations of the low FODMAP diet in the clinical setting (see below). However, the results for the secondary endpoints differed, likely explained by intrinsic differences in genetics, microbiome, diet, and cultural issues between the study populations, in addition to variation in dietary advice and IBS subtype.

4 | DIET LIMITATIONS

Although the popularity of this dietary approach has progressively increased worldwide, the low FODMAP diet has a number of important shortcomings. This approach, while clinically effective, is highly restrictive and may be confusing to administer, leading to potential problems with adherence. Another issue is that the full elimination phase is *not* intended to be continued indefinitely; if a patient improves during the full elimination phase, providing tailored dietary counseling to re-introduce FODMAP containing food groups to arrive at each individual's version of the low FODMAP diet is recommended. The duration of the full low FODMAP diet has potential long-term implications considering that fermentable carbohydrates such as FODMAPs provide substrates for "healthy" GI bacteria. Indeed, several studies comparing the effects of a low FODMAP diet to a habitual diet demonstrated a reduction in the proportion and concentration of *Bifidobacteria*.^{9,24} Another study did not demonstrate a decrease in *Bifidobacteria*, but did show a decrease in total bacteria abundance,³³ the consequences of which have not been well characterized. In addition to changing the microbiota, fermentation creates by-products such as SCFAs, including butyrate, providing nutrients and other benefits for the colonic mucosa and playing a critical role in the luminal microenvironment (Figure 1).³⁴ Thus, while the low FODMAP diet may improve GI symptoms, long-term avoidance of FODMAPs may have potentially harmful effects on colon health. Studies investigating the effects of the low FODMAP diet on the colon

metabolome are conflicting. Halmos et al. found no change in SFCA concentration between the low FODMAP diet and a habitual Australian diet,³³ while others have observed a decrease in SCFA compared to a habitual diet.⁹

In this issue, Hustoft et al.⁹ report the results of a crossover study designed to investigate the importance of fructo-oligosaccharides (FOS) in symptom generation in IBS patients. After 3 weeks of a low FODMAP diet, 20 patients with non-constipated IBS received either 10 days of FOS or placebo supplements, followed by a washout period of 3 weeks, followed by another 10-day cross-over period. The authors analyzed inflammatory cytokines throughout the study, and SCFAs and gut microbiota composition were analyzed as well. Most patients had severe IBS symptoms as measured by IBS-SSS. Interestingly, all patients improved with the low FODMAP diet (defined as reduction in at least 50 points IBS-SSS) and all patients completed the trial. When the FOS supplement was introduced, significantly fewer subjects reported control of IBS symptoms compared to placebo, with no order effect observed (80% vs 30%). There was a large inter-subject variability in the responses to FODMAP provocation (FOS vs placebo) as compared to FODMAP reduction. Levels of IL-6 and IL-8 (but not TNF- α) both decreased significantly after 3 weeks of a low FODMAP diet, with a median reduction of 0.065 pg/mL and of 2.95 pg/mL, respectively. Cytokine levels did not change in response to FOS supplementation, however. *F.prausnitzii*, *Actinobacteria*, and *Bifidobacterium* abundance were significantly altered in both dietary interventions (decreased in low FODMAP diet, increased again with FOS supplementation). Levels of total SCFAs and n-butyric acid both decreased significantly following a low FODMAP diet as compared to baseline, but SCFA levels were otherwise not significantly altered when comparing values from samples obtained at baseline, following a low FODMAP diet, and after FOS supplementation.

This manuscript from Norway addresses several unanswered questions about the low FODMAP diet. Because of its cross-over design and lack of worsening symptoms with the maltodextrin placebo, it is clear that a placebo response is not entirely responsible for the effect of the diet. In addition, although IBS symptoms significantly worsened in response to FOS, the severity was not comparable to the symptom level observed at baseline. This lends weight to the belief that while individual FODMAP restriction may be partially beneficial, collective FODMAP restriction (at least in this patient population) may be required to achieve maximum symptom response. There was however a larger inter-subject variability in response to the two supplements, supporting the view that each patient's threshold/FODMAP sensitivity is specific and may be individualized.

Based on this and other studies,^{21,24,33} it seems clear that the low FODMAP diet has effects on the microbiota and metabolome, decreasing SCFAs and bacteria thought to promote GI health. The fact that the abundance of several bacteria (*F.prausnitzii*, *Actinobacteria*, and *Bifidobacterium*) rebounded after 10 days of FOS supplementation is reassuring, that the effect of dietary change is temporary. However after FOS supplementation, both cytokine levels and SCFA levels were unchanged. Reasons for this are not clear—perhaps 10 days of FOS supplementation is not of sufficient duration, or that alternate FODMAPs are driving those changes.

5 | UNANSWERED QUESTIONS

The efficacy of a low FODMAP diet for IBS is becoming increasingly obvious but several areas remain to be clarified: (i) the mechanism(s) by which FODMAP restriction improves symptoms, (ii) long-term effects/safety in terms of gut microbiota and potential nutritional deficiencies, (iii) standardization of a reintroduction protocol, (iv) whether or not complete exclusion of all FODMAPs is necessary for full clinical benefit, and (v) improving patient selection to enrich symptom response. These questions are linked, and as we determine the mechanism(s) by which FODMAP exclusion alleviates IBS symptoms, the answers to the remaining questions will become more apparent.

If an IBS patient improves with the full elimination of dietary FODMAPs, a reintroduction phase begins to determine an individual patient's FODMAP intolerances. Given both the concerns about long-term effects of the low FODMAP diet on the microbiota and overall nutrition, as well as the restrictive nature of the diet, the full low FODMAP diet is not meant to serve as a long-term solution for patients with IBS. The current means by which FODMAP reintroduction is conducted varies dramatically from center to center and is driven by the biases and clinical experiences of providers rather than evidence. It is a poorly defined trial-and-error process which is clearly suboptimal and may expose patients to prolonged or even unnecessary suffering as they try to identify their personal FODMAP triggers. There are currently little scientifically rigorous data to allow an evidence-based approach to FODMAP reintroduction and consequently, there is no widely accepted protocol for this process. This leaves providers to develop their own non-evidence based protocols to address the complexities surrounding (i) specific foods used to challenge patients, (ii) FODMAP dose, and (iii) duration of exposure. Generating a structured reintroduction protocol for clinical practice would serve as a construct for clinicians worldwide to guide dietitians and patients during this process. In addition, further investigative efforts should be made to determine if the observed changes in the microbiota mitigated by the low FODMAP diet remain once certain FODMAPs are re-introduced to tolerance.

One could image a future where it may then be possible to construct a less restrictive version of the low FODMAP diet, which offers similar clinical benefits to most IBS patients. Determining a less restrictive version of the low FODMAP diet could improve adherence, create wider appeal, and ease the financial and logistic burden for this dietary approach. Facebook, Netflix, and Google currently curate user content based on our demographics, past purchases, and search histories. There is no reason then that we as clinicians cannot grasp the tools to do the same for our patients: to curate their care based on their preferences, symptoms, and biomarker data including stool and metabolomic profiles.

CONFLICT OF INTERESTS

The author has no competing interests.

AUTHOR CONTRIBUTION

SE wrote the entire manuscript.

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