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REVIEW ARTICLE

Diet as a therapeutic tool in chronic gastrointestinal disorders: Lessons from the FODMAP journey

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Abstract

Background and Aim: Diet is a powerful tool in the management of gastrointestinal disorders, but developing diet therapies is fraught with challenge. This review discusses key lessons from the FODMAP diet journey.
Methods: Published literature and clinical experience were reviewed.
Results: Key to designing a varied, nutritionally adequate low-FODMAP diet was our accurate and comprehensive database of FODMAP composition, made universally accessible via our user-friendly, digital application. Our discovery that FODMAPs coexist with gluten in cereal products and subsequent gluten/fructan challenge studies in nonceliac gluten-sensitive populations highlighted issues of collinearity in the nutrient composition of food and confirmation bias in the interpretation of dietary studies. Despite numerous challenges in designing, funding, and executing dietary randomized controlled trials, efficacy of the low-FODMAP diet has been repeatedly demonstrated, and confirmed by real-world experience, giving this therapy credibility in the eyes of clinicians and researchers. Furthermore, real-world application of this diet saw the evolution of a safe and effective three-phased approach. Specialist dietitians must deliver this diet to optimize outcomes as they can target and tailor the therapy and to mitigate the key risks of compromising nutritional adequacy and precipitating disordered eating behaviors, skills outside the gastroenterologist's standard tool kit. While concurrent probiotics are ineffective, specific fiber supplements may improve short-term and long-term outcomes.
Conclusions: The FODMAP diet is highly effective, but optimal outcomes are contingent on the involvement of a gastroenterological dietitian who can assess, educate, and monitor patients and manage risks associated with implementation of this restrictive diet.

Introduction

In the management of chronic intestinal disorders, diet has proven a powerful management tool. For celiac disease, this first became evident in the 1930s when Dicke's insightful observations prompted the conclusion that avoiding wheat transformed the once dismal outcomes of children with this condition.[1] Now, the gluten-free diet is the only proven therapy for celiac disease, for both the induction and maintenance of small intestinal healing. Likewise, in active Crohn's disease, clinical observations by Voitk *et al*. in 1973 that an elemental diet induced remission in patients awaiting surgery led to enteral nutrition becoming a first-line therapy in pediatric (and to a lesser extent adult) patients.[2] Finally, in irritable bowel syndrome (IBS), the low Fermentable Oligo-, Di- and Mono-saccharides And Polyol (FODMAP) diet, emerged following decades of observation that in high doses, slowly absorbed and indigestible sugars and oligosaccharides induced acute IBS-like symptoms.[3] While restricting individual sugars had limited success in ameliorating gut symptoms, the collective reduction of these sugars—designated FODMAPs (Fig. 1)—had additive and beneficial effects on gut symptoms in three out of four patients with IBS.[4] Mounting evidence has replicated these findings, and the FODMAP diet has since gained traction as effective therapy in real-world clinical practice.[5]

Overview of challenges associated with developing a diet therapy

Diet therapies that provide new concepts, particularly if they challenge long-held beliefs, meet with a wall of criticism, driven by strong, preconceived belief systems regarding the role of diet to treat disease. Everyone eats, thus biases in this area are universal. Gastroenterologists are no different in that their belief systems are shaped by their upbringing, their life experiences, their clinical practice, and often the idea that good health should follow from what is considered a healthy diet. These beliefs are likely accurate in conditions in which disease prevention and treatment are the same, such as application of a low glycemic index diet to prevent and treat diabetes, but contradictory in other diseases, such as use

Figure 1 Examples of foods high in FODMAPs. Examples of the predominant FODMAP content, in terms of fructans, galacto-oligosaccharides (GOS), fructose (in excess of glucose), lactose, sorbitol, and mannitol, are shown for some of those foods.

of fiber-free liquid diets (exclusive enteral nutrition) to induce remission in Crohn's disease. Such belief systems may impose barriers to the fair assessment of grant applications and publications and may impart confirmation bias in the interpretation of clinical studies. Examples of the latter are presented later. Most medical and gastroenterological training has limited teaching regarding food composition and gastrointestinal physiology related to food. The greatest challenge in working up a diet therapy is producing quality evidence for efficacy. Designing a double-blind randomized controlled trial (RCT) of a diet therapy has multiple areas of controversy and difficulty, particularly masking of the study food or diet, controlling for confounders, the choice of the comparator or placebo diet, and the assessment of adherence to the diets, as discussed in detail elsewhere.[6] One consequence of these problems is the absence of high-level evidence for most diet therapies (as is expected from pharmaceutical trials). Elimination and rechallenge studies are fraught with placebo and nocebo effects, together with collinearity of various components in food. Longer term RCTs are almost impossible to design when assessing the sustained efficacy of a therapeutic diet. Translating dietary effects to humans from observations in experimental animals is prone to many problems, including the dose and form of food components, the nature of the control diet, and differences in gastrointestinal tract physiology. Funding is also a problem in that a diet cannot be patented, thus the same type and level of investment into drug therapies cannot be achieved. Finally, there are many concepts in dietetics and nutrition that are steeped in tradition, but may be quite inaccurate and misleading. With such an overview of the issues, the journey that our group has taken in defining and assessing the FODMAP diet has taught us many lessons, some of which are outlined in the following.

Lesson #1: Dietary manipulation of food components requires knowledge of food content

One of the earliest lessons was that, in order to design a therapeutic diet that specifically restricted FODMAP intake, accurate data regarding the FODMAP composition of food were required. This observation led to the establishment of an extensive and ongoing program to measure the FODMAP content of foods (e.g. fruits, vegetables, legumes, cereals, and dairy) using validated methodology (including high performance liquid chromatography and enzymatic methods) and adhering to strict standard operating procedures dictated by Food Standards Australia New Zealand. Having also learnt that food processing can alter FODMAP content, we tested a wide array of processed foods and established a food certification program to enable food manufacturers to certify that their specific products are low in FODMAPs. Cut-off values that define whether a serve of food is low in FODMAPs were developed after many years of observation and clinical evaluation.[7] To enable patients, dietitians and clinicians to access this large and growing database of FODMAP food composition, the team developed the Monash FODMAP diet App,[8] which uses a traffic light system to indicate if foods are low, moderate, or high in FODMAPs (Fig. 2). This App represents the only comprehensive FODMAP database in the world, thus is highly successful and forms the backbone for all FODMAP diet management. Income

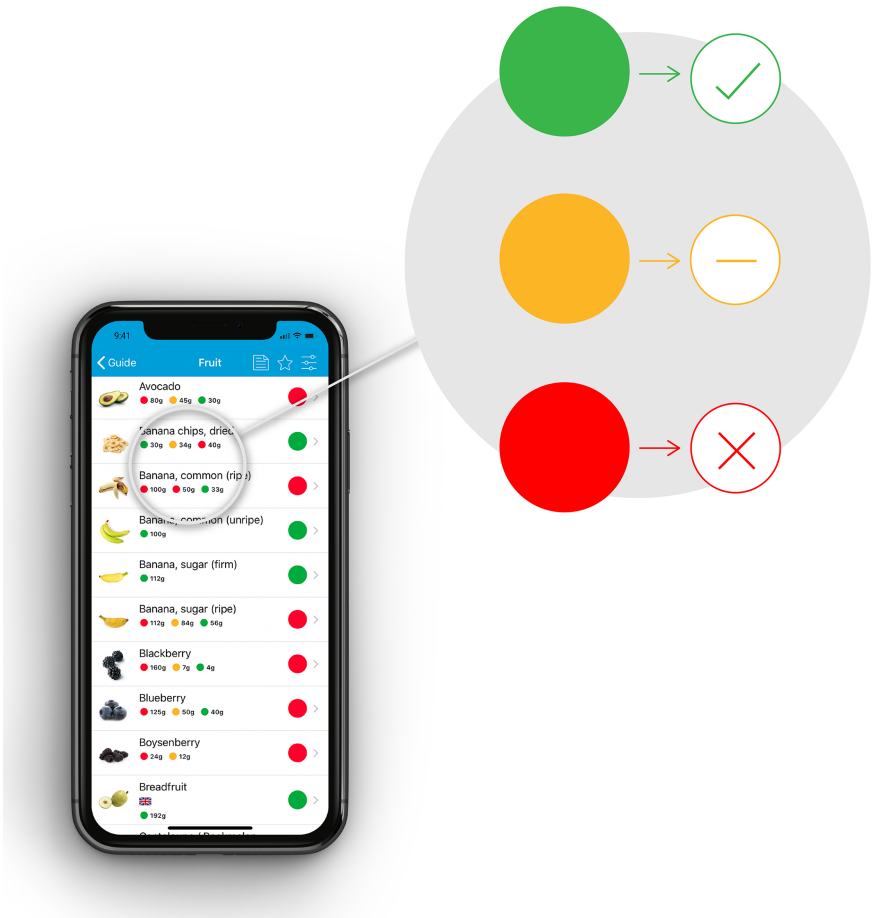

Figure 2 The traffic light system for the FODMAP content of typical serves of individual foods in the Monash University FODMAP Diet App. 'Green' foods are low in FODMAPs and should be well tolerated. "Amber" foods are moderate in FODMAPs and should be limited. "Red" foods are high in FODMAPs and should be avoided.

from App sales is reinvested in the FODMAP food analysis program and the development of other tools to facilitate implementation of the diet—a sustainable model that overcame difficulties sourcing ongoing external funding.

Lesson #2: Be aware of confirmation bias

An unanticipated finding from assessing the FODMAP content of food was that FODMAPs and gluten coexist in breads and cereals, whereby high-FODMAP cereals were typically gluten-containing and gluten-free cereals were very low in FODMAPs. At the time of this observation, the phenomenon of nonceliac gluten sensitivity (NCGS) was gaining popularity. This condition is basically characterized by the amelioration of gut symptoms on a gluten-free diet and symptoms recurrence upon gluten challenge (although a more detailed definition was developed in a consensus meeting[9]). However, we hypothesized that, because wheat was used to challenge gluten in the early studies,[10] it was the fructans triggering symptoms, not the gluten per se. The securement of FODMAP-depleted gluten enabled a small pilot, blinded parallel-group rechallenge study in patients with self-reported NCGS.[11] This study yielded two important findings. First, that nocebo effects were high, which was not surprising given patients knew they could be given gluten. Secondly, there was a small and statistically significant difference in the symptom severity between patients receiving gluten *versus* placebo. These learnings prompted a more tightly designed and better powered rechallenge study to more definitively determine whether gluten was inciting symptoms. Potential confounders were minimized, especially by controlling for FODMAPs and by providing all food, in a well-powered double-blinded cross-over design using different doses of gluten in 34 patients.[12] Four key observations were made. First, at baseline, many patients had moderate symptoms despite strict adherence to a gluten-free diet. Secondly, all patients experienced a reduction in symptom severity during the run-in period when placed on a low-FODMAP diet (in addition to being gluten-free). Thirdly, nocebo responses were again relatively high. Finally and most importantly, only three subjects had gluten-specific responses, but these were not present when a further blinded rechallenge was performed.[12] The unequivocal conclusion was that gluten was not the trigger in this patient group. This study prompted much outrage, and more than 10 blinded cross-over rechallenge studies have been subsequently performed in patients fulfilling NCGS criteria. Nearly all had similar results.[13–15] A multiple cross-over study performed in Norway pointed to fructans as the trigger and not gluten.[15]

The reason for describing these studies is that the authors of some of the studies interpreted the results as evidence for the presence of gluten sensitivity. Patients who developed more severe symptoms after ingesting food in the gluten arm compared with placebo were considered to have NCGS, but those who developed more severe symptoms associated with placebo were regarded as

nocebo responses.[16–19] If such interpretation is valid, they were also describing "nonceliac placebo-sensitivity."[20] While issues with nocebo responses render demonstration of gluten-specificity of responses challenging in studies of such cross-over design, many conclusions reached are examples of confirmation bias,[21] presumably because the authors passionately believed that gluten was the demon. The power of preconceived beliefs was obviously very strong and would appear to remain so.

Lesson #3: Demonstrating efficacy of the low-FODMAP diet

Replacing high-FODMAP foods with low-FODMAP foods over 4–6 weeks appeared to be of considerable benefit to the majority of patients with IBS in our own clinical experience, and such observations were published in a nonrandomized study.[22] However, for acceptance that this did not represent placebo effect only, RCTs were required. A high-quality way of demonstrating efficacy of a diet is via a feeding study (to optimize adherence and control for dietary confounding factors) and compare with a typical diet in a blinded, randomized protocol. Indeed, such a study showed clear separation of symptoms between the low-FODMAP and typical Australian dietary arms, and that about 72% of patients responded.[23] Following this, there were RCTs with various comparator diets, for example, from Canada (*vs* a high-FODMAP diet),[24] from the United States (*vs* a modified NICE diet),[25] and from the United Kingdom (*vs* a well-validated placebo diet).[26] All demonstrated benefit of the low-FODMAP over the comparator diet. In contrast, a study from Sweden showed no benefit compared with their standard diet, although responses in both were only about 50% and FODMAP-rich foods were restricted on both diets.[27] Actual FODMAP intake (excluding lactose, which is unlikely to be a FODMAP in a Swedish population due to the very low prevalence of hypolactasia) was low before the intervention and differed minimally between the arms.[27] Thus, rather than being a negative study, it may have shown that efficacy is less likely when the increment of change in FODMAP intake is minimal. Meta-analysis of comparative trials (there are now 14 published)[28,29] and real-world experience have supported the efficacy of the low-FODMAP diet. However, conducting tightly controlled dietary feeding studies is not easy, and criticisms regarding blinding, power, and potential bias[30] are easy to direct at dietary studies,[30] even though some of these may be inaccurate in fact.[31] As such, the use of a low-FODMAP diet for patients with IBS has been rated on GRADE criteria (designed for assessment of drug trials) as "weak recommendation and very low quality of evidence." While this rating is hard to avoid with dietary studies, all RCTs should aim for the best possible quality. Nevertheless, the FODMAP diet has gained credibility among dietitians and the medical fraternity and is now recommended guidelines for management of IBS in many countries including Canada, the United States, the United Kingdom, and Korea.[32–35]

Lesson #4: Allowing diets to evolve over time

When a new drug is released onto the market, it is supported by efficacy data from RCTs for its target disease group. However, in real-world practice, indications and recommendations on how to use the drug are modified over time. Similarly, the FODMAP diet has evolved into a three-phase diet based on good dietetic principles (i.e. to achieve a minimally restrictive, nutritionally adequate diet for the long term) and confirmed in clinical experience[5,36] (Fig. 3). Thus, the initial "low-FODMAP diet" (that was subjected to RCTs) is the first of three phases and used to determine whether IBS symptoms are sensitive to FODMAPs. Phases 2 and 3 of the diet were formally described drawing on experience that told us that individuals vary in the amount and type of FODMAPs that they tolerate, that the physiological effects of FODMAPs vary, and that many patients maintain adequate IBS symptom control over time, even as they liberalize their diet and restrict a smaller range of high-FODMAP foods (e.g. onions, garlic, and breads).[37] In Phase 2, the low-FODMAP diet is continued, but the patient completes a series of food challenges using foods high in only one FODMAP. For example, milk can be used for a lactose challenge, because milk is high in lactose, but does not contain any other FODMAPs. Challenging each FODMAP separately is important as tolerance to each may vary. In Phase 3, the aim is

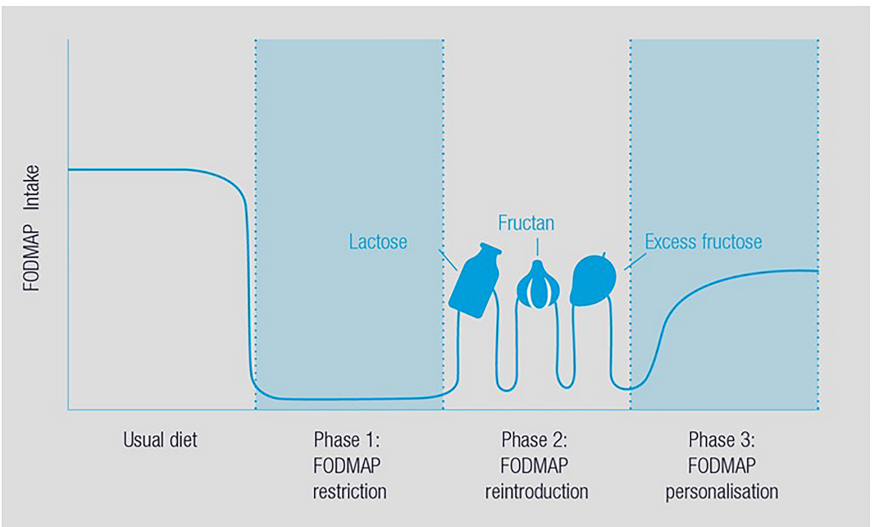

Figure 3 The three-phased FODMAP program. Phase 1 involves avoidance of high-FODMAP foods and replacement with low-FODMAP foods in the same food groups. If there is response to such restriction over 2–6 weeks, Phase 2 is commenced in which a food containing single FODMAPs is challenged in a dose-dependent manner to gage tolerance, followed one-by-one with foods containing other FODMAP types. With the learnings from this reintroduction, a personalized FODMAP diet can be utilized in the long term. Total FODMAP restriction may be very limited, but the patient is able to adjust according the sensitivity of the gut. Episodes of high-FODMAP intake are avoided.

to relax dietary restrictions, expand the diet and establish a "personalized FODMAP diet" for the long term. Foods that are well tolerated are included the diet, while poorly tolerated foods are restricted, but only to a level needed to maintain symptom relief. Over time, the level of FODMAP restriction can be titrated to manage symptom flares and/or fluctuating IBS symptoms.

This evolution in the dietary strategy provided patients with ongoing satisfaction with symptom relief and a less restrictive long-term diet. Unfortunately, however, Phase 3 has not been studied in a randomized way, but prospective observational studies have confirmed ongoing effectiveness of the dietary approach.[38–43]

Lesson #5: A specialist dietitian is integral to optimally delivering a therapeutic diet

There are numerous successful examples of dietitian-led delivery of the FODMAP diet[22,23,44–47] and clinical guidelines now endorse this model, including recommendations from the British Society of Gastroenterology 2021,[35] the American College of Gastroenterology 2021,[32] the British Dietetic Association 2016,[48] and the NICE Guidelines 2015.[49]

Despite this, dietitians are either not available or not funded in many parts of the world. However, for several reasons, the active involvement of a dietitian is key to optimizing outcomes (Fig. 4). First, dietitians are trained in the art of nutritional assessment and can identify nutritional risks when applying a restrictive diet. Secondly, dietitians can assess eating behaviors and identify disordered eating and/or eating disorders. Disordered eating refers to irregular or maladaptive eating behaviors or habits that may have nutritional and psychosocial implications, while eating disorders are characterized by severe and persistent disturbance in eating behaviors, together with clinically significant medical and/or psychosocial consequences. Specific conditions include anorexia nervosa (driven by an intense fear of gaining weight); avoidant restrictive food intake disorder (in which inability to meet appropriate nutritional and/or energy needs is driven by poor appetite, picky eating and, particularly in patients with IBS, concern about symptom induction by eating food); and orthorexia nervosa (characterized by a preoccupation with healthy eating driven by the individual's belief system as to what is healthy/unhealthy). Determining the actual prevalence of these conditions in patients with IBS is complicated, because more than 60% of patients modify their diet in an effort to control symptoms and validated screening tools are lacking. Nonetheless, concerning eating behaviors are common (possibly affecting up to 44%)[50] and, disturbingly, there appears to be little awareness of disordered eating behaviors and their importance in dietary management among gastroenterologists.[51] While little is known about the risk of precipitating eating disorders by initiating a FODMAP diet, restrictive diets are contraindicated in patients with a history of disordered eating behaviors, particularly without adequate psychological support. Thirdly, upon assessing eating behaviors and screening for nutritional risks, the dietitian can advise on the wisdom of dietary management and, if suitable, recommend the best FODMAP strategy to apply (refer further). Fourthly, a dietitian can ensure that a low-FODMAP diet is carefully planned to ensure that nutritional adequacy is maintained. This is important, because without careful planning the diet can compromise intake of a range of

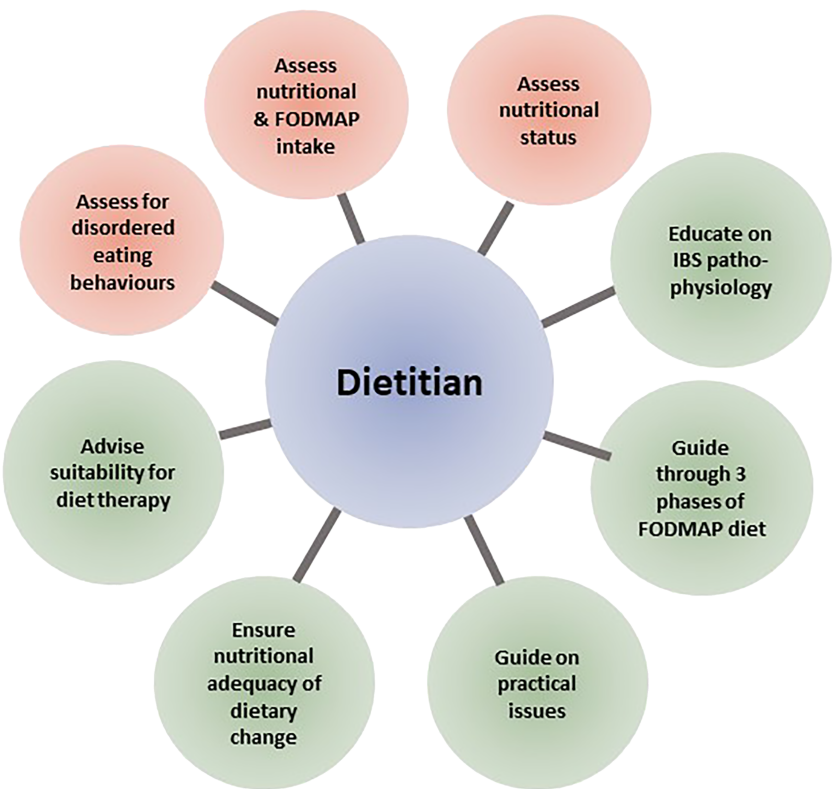

Figure 4 The multiple roles of a dietitian in the assessment of a patient with irritable bowel syndrome (IBS), the provision of advice regarding the suitability for and recommended dietary approach, and the delivery of education on IBS, teaching and monitoring of the dietary approach with an eye to ensuring nutritional adequacy and practicality.

micronutrients, including calcium, fiber, B vitamins, and iron.[52] It is unclear whether the same can be achieved if the diet is self-taught or delivered by nondietitians, but certainly medical practitioners have neither the training nor the time to achieve such goals. Fifthly, dietitians can guide patients through Phases 2 and 3 of the diet, ensuring that specific dietary triggers are identified in a systematic manner and that a minimally restrictive diet is implemented long term. Dietitians are key in these latter phases of the diet, with research confirming that patients do better when a FODMAP diet is followed under the guidance of a dietitian, particularly in Phases 2 and 3.[53] Effective long-term symptom control by restricting a small number of very high-FODMAP foods can be achieved with less need for extra dietary or pharmacological support than observed in those not taught by dietitians.[53] Finally, many practical aspects of dietary management, such as reading food labels and modifying recipes, are not likely to be imparted by the patient's doctor.

Thus, the dietitian forms an integral part of patient management via their unique ability to undertake nutritional assessments, to mitigate the risks of dietary manipulation,[50] to optimally deliver dietary instruction,[53] and to monitor patients and troubleshoot when dietary issues arise.

Lesson #6: Therapeutic diets carry risks that must be considered

Like all interventions, the balance of risks and benefits must be weighed before prescribing therapeutic diets. However, there is limited awareness among clinicians and patients of the key risks of restrictive diets. This may be the exacerbation or precipitation of disordered eating behaviors/eating disorders and nutritional problems,[50,51] but also the common false belief that diet always has a better safety profile than pharmacological agents. It is for this reason that expert commentaries recommend that diet therapies be included in the multidisciplinary management of IBS, led by dietitians and psychologists.[50,51,54,55] Clinicians should also consider the psychosocial implications of therapeutic diets, including social isolation, perceived difficulties with travel and eating out, and the additional cost of specialty food items.[56] Finally, attention should be paid to the use of language to avoid demonizing specific foods[50] and to avoid linear thinking about the pathogenesis of symptoms (i.e. all related to food).

Thus, targeting the FODMAP diet to suitable patients is essential. Prerequisites include the presence of functional gut symptoms (this is not a diet for "good health"), adequate patient motivation to modify food choice, and a sufficiently high baseline FODMAP intake such that a low-FODMAP diet can impart symptomatic relief. While other predictive markers of response to this diet have been proposed, none so far have gained traction due to a lack of evidence of reliability. For example, breath hydrogen testing for fructose or sorbitol malabsorption are poor predictors of response[57] and, while the analysis of feces for the spectra of microbiota[58,59] or volatile organic compounds[60] have shown promise, neither are ready for clinical application. There are numerous contraindications to restrictive diets, including the presence of undernutrition and disordered eating patterns, young age due to the importance of growth and psychosocial development in children,[61,62] adherence to other dietary restrictions, the presence of other nutritionally demanding conditions (e.g. inflammatory bowel disease or pregnancy), and reduced capacity to apply dietary change (e.g. elderly patients). The involvement of a skilled dietitian and/or psychologist assists in targeting this therapy and allows the trial of alternative approaches such as "FODMAP gentle,"[5] although this approach has not been formally evaluated for efficacy.

Lesson #7: Safety of the diet in the long term

Interestingly, of all possible adverse effects of a FODMAP diet, the main concern of many has related to the effects of FODMAP restriction on the microbiota. This concern is based upon two observations. First, the relative abundance of fecal Bifidobacteria spp. reduces when FODMAPs are restricted in some studies,[26,46,63–65] but not in others.[66] Ingestion of fructans and GOS may selectively increase the density of Bifidobacteria in the colon,[67] an effect that is described as "prebiotic," given the putative health benefits of Bifidobacteria. Secondly, in the pivotal feeding study that established the efficacy of the low-FODMAP diet,[23] the relative density of bacterial groups important in the production and/or delivery of butyrate to the colonic epithelium was consistently and markedly lower compared with the control (typical Australian) diet.[63] This suggested that reducing dietary FODMAP intake might induce a dysbiosis. However, the findings associated with the low-FODMAP arm were similar to those when the same patients were consuming their habitual diet (prior to the intervention). Thus, we have postulated that the higher density of such butyrate-delivering bacteria was due to the composition of the control diet. In fact, the fructan and GOS intake in the control arm was greater than that in the habitual diet of the patients. Hence, the differences between the microbial populations observed reflected selective stimulation of those bacterial groups by the control diet and not suppression by reduction of FODMAP intake.[63] Indeed, a recent detailed and carefully controlled metagenomic analysis of fecal microbiota before, during and after strict FODMAP restriction in 41 patients with IBS demonstrated that the low-FODMAP diet was associated with durable correction of dysbiosis in patients with IBS.[66] Importantly, data to date indicate that low-FODMAP-induced changes in microbiota reverse with the personalized diet.[38,43]

Lesson #8: Value-adding to the FODMAP diet

There have been several attempts to "value-add" to the FODMAP diet. For example, concurrent ingestion of a probiotic cocktail successfully restored the relative abundance of Bifidobacteria, but this provided no symptomatic advantage.[43] Whether this correction has other health benefits is unknown. Concurrent use of a synthetic GOS failed to change bifidobacterial density or provide symptomatic benefit.[68]

Our attention on adding value to the diet has focused on the potential role of fiber supplements. The rationale for this was threefold. First, there is a risk of reducing fiber intake even under the guidance of an experienced dietitian.[29,38] Secondly, reducing FODMAP intake has little impact on the quality of feces, provided habitual fiber intake is not very high (as was originally observed in children with so-called "fruit-juice diarrhea"[69]). This was also

demonstrated in a pivotal cross-over feeding study, whereby fecal water content and objective ratings of fecal appearance were similar, comparing low with typical FODMAP intake.[70] Satisfaction with stools improved with FODMAP reduction, but that endpoint is independent of fecal water content. Fiber that changes fecal characteristics might benefit patients with abnormal stool patterns. Thirdly, reducing FODMAP intake diminishes the total fermentable carbohydrate load to the colon and, when no attention is paid to intake of nonstarch polysaccharide and resistant starch, the distal colon potentially becomes starved of putatively beneficial metabolites of carbohydrate fermentation, such as butyrate,[71] and protein fermentation increases[72] evidenced by increased fecal concentrations of branched-chain fatty acids and increased density of sulfate-reducing Bilophila.[65,72,73] Findings from studies in rats, pigs, and healthy humans suggest that supplementation with a combination of fermentable fiber (providing substrate to saccharolytic bacteria) and a minimally fermentable fiber (to push fermentation distally) enables uniform distribution of carbohydrate fermentation around the bowel, even on a FODMAP restricted diet.[74–76] In fact, a randomized, double-blind, triple-cross-over feeding study in 26 patients with IBS consuming low-FODMAP diets showed that concurrent supplementation of minimally fermentable sugarcane bagasse alone improved the quality of the feces (dry stools were moister, wet stools drier).[77] When sugarcane bagasse was cosupplemented with fermentable resistant starch, carbohydrate fermentation increased and was evenly distributed around the colon.[78] Importantly, the supplements tested in two different cohorts of patients with IBS were well tolerated and did not diminish the symptomatic benefits of the low-FODMAP diet[77] Thus, fiber supplements with specific characteristics may add value to the benefits of restricting FODMAPs alone.

Conclusions

Diet therapies are powerful tools in chronic gastrointestinal diseases, but, as discovered on the FODMAP diet journey, they are complex therapies and not without risks. Engagement of an expert gastrointestinal dietitian is critical for optimal and safe application of the FODMAP and other therapeutic diets and enabling assessment of patients for suitability and risks, education regarding the implementation and practical aspects of the diet, regular follow up and individualization of the approach. These skills are unique to dietitians and not inherent in traditionally trained clinicians, including gastroenterologists. Hence, the real-world application of this diet requires additional skills and an evaluation of risks as well as benefits. The ideal clinical scenario would be to enhance the nutritional training of gastroenterologists (be it via medical schools or specialist training programs) and the gastroenterological training of dietitians to enable specialization in this field. At a minimum, active engagement with a gastroenterological dietitian is encouraged to improve the quality of life of both patients with functional gut symptoms and of the treating doctors.

Acknowledgments

Nil.

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