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REVIEW

Controversies and reality of the FODMAP diet for patients with irritable bowel syndrome

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Abstract

Since its first trial showing evidence of efficacy for managing symptoms of irritable bowel syndrome, the fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet has been gaining popularity but not without criticism. Application of the diet has changed from a rigid list of "allowed" and "not allowed" foods to a structured program of initial FODMAP restriction followed by food reintroduction and finally personalization so that patients are empowered to adjust their diet themselves to achieve good predictability of symptoms. Safety concerns of the diet have centered around its initial elimination leading to compromise of nutritional and psychological health, but careful patient assessment and management, preferably through a FODMAP-trained dietitian, will reduce the risk of such negative health outcomes. Most negative attention for the FODMAP diet has been the notion that it will ruin the microbiota. Controlled studies have indicated that reducing FODMAP intake has no effects on bacterial diversity but will reduce total bacterial abundance, and higher FODMAP intakes will increase health-promoting bacteria, supporting the concept of the full FODMAP program, including attaining a minimal "maintenance" level of FODMAP restriction. This review addresses all these concerns in detail and how to overcome them, including the use of a "FODMAP-gentle" diet, describing restriction of a select few foods very concentrated in FODMAPs. This version of the diet is commonly applied in practice by experienced FODMAP-trained dietitians but is not clearly described in literature. Careful direction and assessment of response or nonresponse will decrease the risks of over-restriction and under-restriction of diet.

Introduction

The understanding, diagnosis, and treatment of irritable bowel syndrome (IBS) has grown considerably over the past two decades. IBS is a chronic, nonfatal condition that waxes and wanes in its severity. Any dietary approach ideally would cure the condition, but this is not possible according to our current understanding of the multifactorial pathogenesis. As a palliative measure, it ideally should work in the longer term, be able to cope with the fluctuating severity, and have only minor interference with the quality of life of the patient. Of the dietary approaches proposed, evidence for efficacy is largely restricted to one diet, the fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet. The emergence of a FODMAP diet as a treatment of IBS has been a game changer. Studies from around the globe have shown efficacy over placebo, and 50–87% of adult IBS sufferers benefit.[1–5] However, practical application of the diet requires good familiarity and some finesse in a heterogeneous IBS population. As the diet progresses to an individualized regimen, there are different paths upon which the maintenance phase can be reached, but these paths are not well documented. With increasing knowledge and application of a low-FODMAP diet comes many questions and controversies. This review will address the interpretation of the relevance of dietary FODMAPs in its uncertainties particularly from the perspective of the delivery of the FODMAP diet.

The ideal dietary approach. Approaches to trialing and evaluating diets to treat IBS have involved elimination of specific whole food triggers, such as milk and wheat, "healthy eating" principles, or extreme diets, such as the "paleo" diet, which have vague rationales and are usually wrongly promoted as "healthy" instead of therapeutic. They also tend to be overly restrictive and recommended for ongoing application rather than defined timeframe of implementation. Moreover, they generally only have one format without defined opportunities for de-restriction. These issues build concerns around nutritional inadequacies and

righteous eating behavior (discussed later) but are also likely to challenge continuing adherence. Because of the extremely restrictive nature of these diets that invariably reduce carbohydrate intake, many of the diets probably do have efficacy with reduction of symptoms of IBS, although this largely remains anecdotal. However, a more targeted, less severe approach, such as a FODMAP diet, should maximize initial efficacy with less restriction, offer a "way out" with planned de-restriction, and maintain long-term efficacy in a safe way.

The evolution of the FODMAP diet. Individual FODMAPs, such as lactose and fructose, have been known to contribute to IBS symptoms for many years.[6] From learning of the similar gastrointestinal fate of FODMAPs, their mechanism of action in the context of IBS, and their composition in our diet, the concept of considering all the FODMAPs together for a dietary therapy was born.[7] Initially, a primitive version of a FODMAP diet that concentrated on fructose and fructans (the so-called fructose malabsorption diet) was based on limited food composition knowledge and applied to IBS patients on an ongoing basis without subsequent derestriction.[8] Since then, knowledge of its possible negative associations[3,9–11] and the observation that tolerances to foods differed across individuals led to the current three-step FODMAP diet. This protocol details how to initially restrict, then reintroduce foods, and finally personalize a diet for long-term IBS management and has been described in detail elsewhere.[12,13] This protocol has not been formally assessed in randomized controlled trials, but several studies of the longer-term efficacy when individualization of the diet is achieved have now been published. The response to a liberalized version of a low-FODMAP diet seemed to last. This has been reviewed in detail by Mitchell *et al*.[14]

Who should deliver the diet?. From its development, a FODMAP diet has been dietitian-led as all of the early studies involved dietitian researchers.[2,5,15] Reports are emerging from prospective research where an unstated health professional has delivered the diet with a dietitians acting as troubleshooter[16] to retrospective experience where a nurse trained in delivering the diet has been the sole educator.[17] Unfortunately, access to a dietitian varies across the globe[18] and, even if a dietitian is available, knowledge and training in a low-FODMAP diet will be highly variable. Such training of dietitians has ranged from self-education utilizing books or Internet information, face-to-face courses, or webinars 1 h to 1 day in duration to detailed educational programs that involve education about IBS, patient assessment, dietary and non-dietary therapeutic options, and detailed training in how to deliver the diet. Many people who wish to try the diet may not involve health professionals and go directly to books, Internet sites, dietary sheets with food lists, or digital applications. Because the optimal delivery of dietary modification like the FODMAP program requires a combination of education in physiology, food composition and identification, reading of food labels, and a dynamic process of restriction then reintroduction, the educative process is an inherent weakness that may potentially lead to markedly varying quality of adherence to the program itself. Caution must be exercised in overinterpreting heterogeneous response rates to the diet seen in clinical trials. Delivery might not be ideal because of, for example, the needs to maintain blinding of the participants.[4,19]

In practice, patients with IBS who are advised to try a low-FODMAP diet are either referred to a dietitian specializing in IBS, a generalist dietitian, or group education[20] or simply given educational handout or directed to self-guided resources via the Internet or smartphone apps. Survey data from the USA indicate that gastroenterologists advocate for a FODMAP diet, but most only use educational handouts. Only one in five will refer to a dietitian, and most do not have access to a specialized dietitian.[21] This may influence general awareness of a FODMAP diet in IBS sufferers, particularly in the USA. Indeed, approximately half of IBS patients do not follow any dietary plan, and only one quarter of patients are aware of a FODMAP diet in a recently published US survey.[22] The use of physician assistants and nurse practitioners to deliver therapeutic or other interventions that require more time than physicians are able to provide is being actively encouraged as potentially cost-effective ways of delivering non-pharmacological therapies.[23,24] Nevertheless, as patient awareness grows together with the intense search of Internet information, health professionals will be questioned about the FODMAP approach, and many will be ill-equipped to offer informed advice. Furthermore, many patients will initiate dietary change on the suggestion of the multiple Internet sites that are not shy of providing firm advice. In other words, the majority of patients, at least in the USA, are being educated in the FODMAP diet via diet sheets and Internet sites. Unfortunately, the quality of such information is generally fair at best. For example, food lists provide conflicting lists of high and low-FODMAP foods,[25] and the advice provided has a low readability and lacks context of how and why the diet is applied, is often not based on evidence, and may be contradictory and often contrary to current recommendations.[26]

Thus, to achieve optimal implementation of the FODMAP diet, there is a need for ready access to training for health professionals and reliable advice for consumers. As outlined earlier, the FODMAP diet is a program of restriction and reintroduction that optimally is delivered in the setting of knowledge of the conditions and awareness of the suitability of the diet to the individual. Courses specifically targeting dietitians have been designed and instituted by tertiary educational bodies such as Monash University, King's College London, and Michigan University. Such courses gain recognition by professional bodies. There are also privately run educational programs, but care must be taken in choosing those not scrutinized by professional bodies, and conflicts of interest may be a problem.

How the diet should be delivered. The latest published reviews advise that a structured protocol comprising three phases should be followed by IBS patients: (i) FODMAP restriction, which will reduce FODMAP intake below an arbitrary cutoff level to temporarily over-restrict the diet; (ii) provocation test (reintroduction), which help to identify the impact of specific FODMAPs and their doses on symptoms; and (iii) personalization, involving development of a long-term plan of dietary manipulation.[12] This protocol seems to work well for the majority of IBS sufferers. However, this "top-down" method of treatment may not be suitable for some patients, particularly if other aspects

of health are compromised. An example of this is a patient with other dietary restrictions already in place who may be at risk of nutritional inadequacy or in someone with an active eating disorder in whom restrictive eating behavior would be harmful for psychological and possibly physical health. Avoiding the use of a dietary therapy or using a "bottom-up" approach to therapy by applying a mild FODMAP restriction,[27] termed "FODMAP gentle" may be applied. Table 1 describes the populations where a FODMAP-gentle diet could be used. A drawback of using a bottom-up approach is that there may not be a clarity of response, meaning that nonresponse may be due to insufficient FODMAP restriction rather than wrong therapy. The traditional published FODMAP protocol should be utilized in the majority of IBS sufferers unless there is indication to use FODMAP-gentle approach.

Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols gentle. A FODMAP-gentle diet describes the reduction of a few foods that are highly concentrated in FODMAPs and/or reduction of a few targeted FODMAPs. Further dietary restriction is applied if necessary. Applying a "FODMAP-gentle" diet has some evidence of efficacy as suggested by Böhn *et al*., comparing a low-FODMAP diet with the National Institute for Health and Care Excellence guidelines. They added to the National Institute for Health and Care Excellence diet avoidance of "gas-producing foods,"[28] which are all foods most concentrated in FODMAPs, such as milk, onion, legumes, polyol sweeteners, wheat bran, and prune juice.[29] Table 2 describes this FODMAP-gentle diet based on our current knowledge of food composition.

Table 2 Description of a FODMAP-gentle diet

Food group	High FODMAP foods to restrict on a FODMAP-gentle diet
Grains	Wheat and rye
Vegetables	Onion, leek, cauliflower, and mushrooms
Fruit	Apple, pear, dried fruit, stone fruit, and watermelon
Dairy	Milk and yoghurt
Meat/alternatives	Legumes

FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols.

Difficulties in response to a FODMAP diet. Both response and nonresponse to a low-FODMAP diet will bring potential matters for consideration. The most common issues arising from the initial restriction of FODMAPs are either the diet is so effective that patients are unwilling to reintroduce food or a lack of response to the diet.

You cannot get people to reintroduce. Patients who respond well to strict restriction but are reluctant to reintroduce more FODMAPs into the diet present challenging scenarios. There is no evidence base for dealing with this situation, but, in clinical practice, this has been approached by applying non-dietary therapies, such as psychological or drug/supplementary therapy. These strategies aim to provide the patient confidence to lessen dietary restriction and also may have some efficacy in symptom management. As with any dietary restriction, there is risk for food aversions to develop, and expectation of symptoms is likely to provoke a response irrespective of symptom physiology. IBS populations are frequently affected by nocebo responses.[30] There is good argument that applying a psychological therapy, such as gut-directed hypnotherapy, is well suited for patients refractory to basic treatment in primary care,[31] and instinctually, this psychological support would also be useful in those reluctant to reintroduce food, who may also have abnormal psychology developed around eating behavior.

The diet is not working. Nonresponse or partial response to a low-FODMAP diet may be due to many factors. Firstly, the diagnosis of IBS might not be correct. Gastrointestinal symptoms related to untreated celiac disease often resolve with a gluten-free diet. Protein hypersensitivity, commonly associated with lymphocytic duodenits and/or eosinophilic infiltration, has been described and appears to respond in both short term and long term to appropriate restriction.[32,33] Inflammation associated with inflammatory bowel disease does not respond to FODMAP restriction.[34,35] Secondly, poor adherence to the diet, either knowingly or unknowingly, should be considered. There may be many hidden yet still very concentrated sources of FODMAPs (e.g. onion powder) that can contribute to symptoms. Thirdly, if the patient's habitual FODMAP intake is naturally low, the impact of a low-FODMAP

Table 1 Possible contraindications for dietary therapy in IBS population

Possible contraindication	Associated negative impact from diet	FODMAP gentle or no dietary therapy?
Active eating disorder	Psychological health and nutritional status	No therapy
Malnutrition	Nutritional status	FODMAP-gentle
Other dietary restrictions in place	Nutritional status	FODMAP-gentle
Children	Nutritional adequacy and establishing good eating habits	FODMAP-gentle
Comorbidity with negative risk associated with altered diet (e.g. IBD and pregnancy)	Altered microbiota and nutritional adequacy	FODMAP-gentle
Unwillingness to apply diet	Non-adherence	FODMAP-gentle or no therapy
Poor capability to understand and/or apply diet	Non-adherence	FODMAP-gentle or no therapy

FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome.

diet would be less. This was seen in a study by Böhn and colleagues,[28] where the subjects' mean habitual oligosaccharide intake of 2.7 g/day was much less than that seen on other trials estimating usual FODMAP intake (3.8–5.6 g/day) and more comparable with low-FODMAP diet (mean oligosaccharide 1.6–3.3 g/day).[2,4,11] Fourthly, specific phenotypes of IBS may be less responsive to the diet. Mechanistic studies have demonstrated that FODMAPs exert symptoms through luminal distension[15,36–38]; thus, it is perceived that IBS patients with visceral hypersensitivity would benefit the most from the therapy. Theoretically, IBS that may be caused by solely altered motility or mucosal and immune function, which is difficult to distinguish, would not benefit from a low-FODMAP diet; these predictors of response have not been well studied. Lastly, the patient's expectation of response may be another reason for failure. With dietary therapies becoming more popular and accessible, misuse and misunderstanding of the role of diet may be the problem. A common misconception among the community is that FODMAPs are the cause rather than a FODMAP diet being a treatment for IBS and will inevitably lead to the expectation that symptoms will be completely resolved with this diet. This is rarely the case considering that IBS is impacted by several factors. Misunderstanding can lead to overanalysis of food intake and a fixation on righteous eating or orthorexia nervosa, a condition in which a patient will avoid food that they believe to be harmful.[39] Commonly, patients will present with extended self-initiated food and symptom diaries and limit their social activities around food. Concern about reintroducing or testing the impact of food is also common among these people. Thorough explanation of the multiple factors involved in the pathophysiology of IBS and sometimes application of non-dietary treatments, such as psychological or pharmacological strategies, may be useful to divert attentions from food, improve understanding, and then encourage reintroduction and personalization of diet.

Predictors of nonresponse. Because of the need for considerable effort in learning the diet and the healthcare professional's time involved, it would be useful to predict in whom the diet should be avoided. The first group is those with an apparent contraindication to the strict low-FODMAP approach. These are discussed in the succeeding texts. The second group comprises those in whom the indication is appropriate but where predictors of poor response are identified. With high rates of efficacy of the diet, the predictors used would need to carry a high negative predictive value to be clinically applicable. In terms of symptom patterns, published studies have not been powered to answer such a question. Predominant stool pattern has been implied to be a predictor of response, presumably because it is expected that FODMAPs will increase water load to the colon, and this will subsequently be reflected in the fecal water content. This notion comes from the use of lactulose and sorbitol, both FODMAPs, in the treatment of constipation. However, the dose used to achieve laxation is high, and usual dietary intake seldom reaches such levels. At lower lactulose intake, fecal water is not increased.[40] Furthermore, in the pivotal feeding studies where the effects of crossing over from a low to typical FODMAP diet and vice versa were compared, fecal water content changed minimally.[41] It might be different for an individual who has a high intake of FODMAPs (as originally described for "fruit juice diarrhea" in children[42]). Recent randomized controlled trials investigating the efficacy of a low-FODMAP diet have only targeted diarrhea-predominant IBS (IBS-D) patients,[1] and this was possibly based on this premise or in order to have less heterogeneity of study subjects or both. Indeed, efficacy rates are not higher in IBS-D populations compared with IBS allcomers and, while studies have not been powered to look at subgroups of IBS, earlier studies have shown improvement in constipation-predominant IBS and IBS with mixed bowel habits groups.[2,3]

Another approach to predicting response/nonresponse is to define characteristics of the fecal microbiota before application. Looking at the microbial composition, either by 16S rRNA sequencing[43] or by the use of microarray-type technology to compare with "normal" profiles,[44,45] has been predictive of nonresponders, but the negative predictive value of the tests has been poor. If they were used in routine practice, many patients who would benefit from the dietary approach would be excluded. Of more promise is a metabolomic approach of examining the pattern of volatile organic compounds released from feces, which had an almost 100% accuracy in a retrospective examination of patients with IBS-D from a trial.[46] Whether the algorithms derived are predictive in prospective groups and in patients with non-diarrhea-predominant IBS remains to be seen.

Breath test-directed individualization of the diet. It has been suggested that breath testing for fructose and/or lactose malabsorption is predictive of response to a low-FODMAP diet, with conflicting interpretations of results.[47,48] Poor reproducibility and the lack of malabsorption occurrence that is specific to an IBS cohort compared with healthy comparator are some limitations in its use,[49–51] and also, the common misconception that breath tests are diagnostic is misleading and often discourages acceptance of patients' true diagnosis of IBS and understanding of its pathophysiology.

Limitations of assessing efficacy of a FODMAP diet in patients with irritable bowel syndrome.

Dietary trials are not the same as drug trials and carry many limitations in their execution and interpretation.[52] There are always challenges in designing placebo diets and properly blinding subjects. This may be particularly difficult for a FODMAP diet in certain countries where the diet is well known to the general community. Finding FODMAP-naïve people in Australia, the birthplace of FODMAPs, is becoming more challenging. Everyone eats and has their own opinions of diet, which may not be physiologically accurate. A good example of this is the specific increase in symptoms from FODMAPs and not gluten in blinded IBS subjects who have self-perceived gluten sensitivity.[53] It is well established that placebo and nocebo responses are high in studies using IBS subjects.[30] Additionally, eating behavior is often changed when being observed or recorded, and it may be that study participants become more adherent to diets or even change their habits, such as eating "healthier" when records are kept.[52,54] Background diets are infrequently controlled or sometimes not even considered in data interpretation.[55] Furthermore, assessing an IBS population has its own shortcomings, and subjective assessments, which are the basis of all validated IBS scoring systems, do not seem to match objective

markers of changes in stool form,[41] and often, the symptoms of IBS have no objective measures.

Fear-mongering associated with a FODMAP diet. As with any new treatments, criticisms follow, but some relating to a FODMAP diet have been unjustified. Statements commonly heard about a FODMAP diet that are often misleading include the following:

- "A FODMAP diet is too hard to follow": At first glance of long food lists of "forbidden foods," one may be forgiven for thinking that a FODMAP diet is too difficult to apply and maintain, particularly if patients are merely provided extended food lists with no guidance on how to translate the information to their lifestyle. However, there is now sufficient evidence to indicate that IBS subjects who have followed some version of a FODMAP diet for several months overcome the perceived difficulties of the diet if there is symptom improvement.[8,56] Furthermore, one observational study showed that the majority of IBS patients feel seeing a dietitian and receiving written information were important in supporting good dietary adherence.[56] In addition to improving adherence, a well-trained dietitian can target attention to the changes to each patient's individual current intake and make allowances for dietary flexibility, such as allowing more legumes for vegetarians[57] or eating out more freely. Alternatively, a FODMAP-gentle approach may be applied (Table 2). This message of personalization is sometimes lost in publications that describe strict, controlled diets for assessment in trial form or reviews compiled by those without experience in the real-world application of dietary therapy. Finally, as with any treatment, support from the prescriber is vital for its success. Practitioners, including gastroenterologists and dietitians, who do not advocate for the FODMAP diet will likely discourage adherence, which would also increase likelihood of poor response.
- "A low FODMAP diet is for life": The protocol of initial restriction and eventual personalization of a FODMAP diet[12] allows a systematic method of establishing the minimal level of restriction needed for symptom control. The majority of patients can ultimately lessen their FODMAP restriction without compromising symptom control,[14] use diet to predict symptoms, and manipulate food choice according to the state of their IBS (e.g. flare of symptoms or quiescent period). Most patients would consider they are no longer on the diet, even though food choice is modified according to FODMAP content of foods in the longer term.
- "FODMAPs are bad for me": This is a common perception, usually thought by patients using symptoms as a marker of poor gut health. Data indicate the opposite that FODMAPs exhibit prebiotic actions[9,58,59] and are substrates for bacterial fermentation yielding short-chain fatty acids[60] with health-promoting and potential anti-inflammatory effects.[61] Like any medical therapy, attaining the minimal therapeutic dose is desirable to reduce the risk of adverse health consequences. Furthermore, usual dietary intake of FODMAPs does not induce symptoms in healthy subjects.[2]
- "A FODMAP diet will ruin the microbiota": There are many attention around gut microbiota and treatments that may positively or negatively alter it, including dietary FODMAPs, because they exert prebiotic activity.[58,59] Therefore, it would be expected that a low-FODMAP diet would reverse this prebiotic effect, but this is not necessarily the case. Several well-controlled studies assessing varying FODMAP intake have shown that a low-FODMAP diet has no effects on bacterial diversity, a marker of good gut health, among patients with IBS, Crohn's disease, or healthy subjects.[4,9,10,43,62] Total bacterial abundance decreases in these patient populations,[9,35] but the health significance of this is unknown and possibly favorable as indicated in a study in which fecal water from patients on a low-FODMAP diet increased markers of inflammation when infused into a rat colon.[63] The putatively negative indicator for health is that a low-FODMAP diet will reduce relative abundance of specific good bacteria, including butyrate-producing and butyrate-promoting bacteria and bifidobacteria in some studies.[4,9,10,28,64] Probiotic supplementation corrected this change in one study.[4] Studies investigating the more liberal phases of a FODMAP diet have not been completed, but change in relative bacterial abundance related more to increases induced by the control diet compared with habitual intake rather than a reduction during a low-FODMAP diet. Mean daily intake of approximately 5-g oligosaccharides seems to restore the microbiome,[9–11] lending further support to the promotion of the full FODMAP program, including maintenance phase.

"New" FODMAP. The term, "FODMAP," refers to carbohydrates with certain characteristics related to their slow or no absorption in the small intestine and ready fermentability when exposed to bacterial populations. The often-quoted list of FODMAP groups—fructose in excess of glucose, polyols, lactose, fructo-oligosaccharides, and galacto-oligosaccharides—was never meant to include all FODMAPs but just to cover the vast majority of dietary FODMAPs of relevance to dietary manipulation. "New" FODMAPs might include the following.

Passively absorbed monosaccharides. The pentose monosaccharide, xylose, was used in a test of small intestinal absorptive capability because it is passively and slowly absorbed. It is also fermentable.[65] Xylose would, therefore, behave like sorbitol. This is sometimes forgotten as occurred in a recent study when it was used as a placebo for a prebiotic in a study comparing a Mediterranean diet plus prebiotic with low-FODMAP diet plus xylose.[64] The use of a FODMAP as placebo in the low-FODMAP arm was curious and complicated interpretation of the results.[66] The presence of xylose is not well characterized in food but thought to be found in some fruits and vegetables. Food-related xylose may be clinically relevant. Arabinose is added to foods and has direct (slow absorption and fermentable) and indirect FODMAP effects (inhibition of sucrose digestion).[67]

Other non-digestible oligosaccharides. There are other dietary oligosaccharides that are not hydrolyzed in the small intestine. It is thought that isomalto-oligosaccharides (derive from soybean) and xylo-oligosaccharides (found in bamboo shoots and some fruit and vegetables) are not commonly consumed, but quantitative lists

of food content are not available, and their role in inducing symptoms via dietary intake is probably low, although may play a greater role in some cultures, such as in Japan.

Lactulose. This synthetic disaccharide is used first as a laxative and, secondly, to lower colonic pH by virtue of its fermentation to reduce absorption of nitrogenous molecules in patients with hepatic encephalopathy. In the latter setting, it is often clinically forgotten that lactulose is a FODMAP and will induce bloating and abdominal discomfort at doses lower than those that cause diarrhea (identical to lactose in patients with severe hypolactasia).

Nutraceuticals and functional foods. Oligosaccharides with prebiotic actions are now commonly utilized in the food and "health" industry. These include types of fructo-oligosaccharides, galacto-oligosaccharides, and xylo-oligosaccharides that are included in symbiotic preparations, yoghurts, or simply as supplements. Arbinose is added to foods for diabetics or the obese as it inhibit sucrase activity.[67] Their FODMAP actions are quite evident in studies where the doses are moderately high. An example is in a study of the effect of FOS on disease activity in patients with Crohn's disease. FOS did not improve inflammation but induced functional-type symptoms.[55]

Inulin. This fructan is frequently added to foods such as yoghurts. It can have variable numbers of fructose molecules such that most inulins are a mixture of oligosaccharides and polysaccharides. Unfortunately, average chain length is not stated on food labels or in functional foods. Inulin behaves like a FODMAP in its ability to be fermented and to induce gut symptoms, but, at least, longer chain inulins have minimal osmotic effect in the small intestine as shown by magnetic resonance imaging.[38] However, inulins are usually considered in the list of FODMAPs.

Deficiency of other brush border hydrolases in the small intestine. The story of low activity of lactase in the brush border with subsequent maldigestion of lactose, which then exerts osmotic effects and is fermented by bacteria in the colon, is well established, and hypolactasia is very common. The activity of other brush border hydrolases is gaining more attention. A general schema of such hydrolase activities is shown in Figure 1. Reduced activities of any of the other brush border hydrolases will potentially result in maldigestion of dietary disaccharides and of maltose and dextrins from amylase-mediated digestion of starch. Congenital deficiencies of sucrase-isomaltase and trehalase are well described, being relatively common in Greenland and Alaska but not in the USA or Europe, and result in gastrointestinal symptoms consistent with those induced by carbohydrate malabsorption.[68] Recent studies in adult populations have indicated that the presence of common and rare polymorphisms of sucrase-isomaltase that are associated with reduced activity of the expressed protein are more common in patients with non-constipation-predominant patients with IBS with odds ratio of 1.36 for the more common 15Phe variant.[69] The practice of measuring hydrolase activities in duodenal biopsies is relatively common in pediatrics, and reduced activities on one or combined enzymatic activities are frequently observed; for example, in a systematic review of more

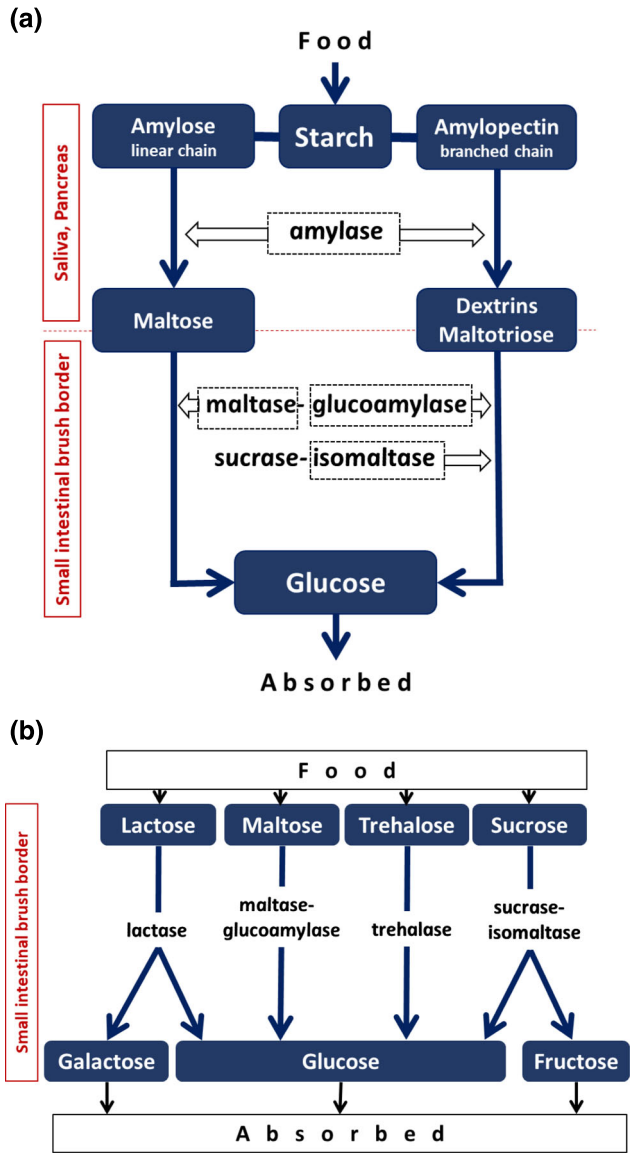

Figure 1 Schematic of the human digestion of (a) starch into glucose and (b) disaccharides into monosaccharides, for intestinal absorption. [Color figure can be viewed at wileyonlinelibrary.com]

than 30,000 tests from a spectrum, of patients, lactase was reduced in 39%, maltase in 13%, sucrase in 9%, and isomaltase in 9%, and pan-disaccharidase deficiencies may occur in up to 10%.[70] While duodenal inflammation tended to be associated with reduced activities, the clinical relevance of the findings remains uncertain for a few reasons. Firstly, the normal values for the enzyme activities are uncertain and often based upon old studies. For instance, some authors quote a study in which findings in jejunal biopsies from 15 adults and 17 children who were apparently healthy are the source of normative data.[71] Activities in duodenal biopsies are also said to be lower than those in the jejunum. Secondly, the level of measured activity that has clinical relevance (i.e. will lead to maldigestion of substrate and symptoms) is not known. Thirdly, the efficacy of dietary approaches to dealing with such deficiencies

is surprisingly poorly studied. Dietary manipulation in children with sucrase-isomaltase deficiency has had limited success.[68] In other words, identifying low enzyme activities is poorly translated in to evidence-based therapies. Interestingly, a *post hoc* analysis of a trial investigating efficacy of a low-FODMAP diet in IBS-D showed better response to the diet in those not carrying hypomorphic sucrose-isomaltase gene variant, suggesting potential indicator for nonresponse to the diet or a marker that additional disaccharides and oligosaccharides associated with amylase-digested starch (Fig. 1) would be considered FODMAPs in a subgroup of IBS subjects with sucrose-isomaltase hypomorphic variants.[72] The use of replacement enzymes such as sucrosidase has evidence of benefit,[68] but the therapy is limited by its expense. The way forward has to involve three strategies. Firstly, diagnostic criteria have to be refined, perhaps with the use of genetic testing, possibly breath testing with strict control over confounders (as earlier discussed) and enzymatic activities in duodenal biopsies having defined true normal values. Secondly, the relevance of the definition of the physiology to clinical symptoms warrants careful examination. Thirdly, dietary strategies that are practical need to be developed and assessed for efficacy. Thus, in adults with functional gut symptoms, defining the physiology of an individual's brush border hydrolases seems of limited evidence-based value in clinical practice but more intense research into diagnostic methods, design of therapeutic strategies, and evaluation of efficacy.

Conclusions

The FODMAP diet is well established in its efficacy for managing symptoms of IBS, but with increasing popularity comes controversies and inappropriate application of the diet. Up-skilling health professional to guide its use in patients is essential to avoid nutritional and psychological problems and to promote acceptable adherence. Understanding of a FODMAP diet includes how to direct structured protocols of FODMAP restriction, reintroduction, and personalization and also when and how to apply a FODMAP-gentle diet. Careful direction and assessment of response will decrease the risks of over-restriction and under-restriction of diet. Future research to improve our knowledge and application of a FODMAP diet will involve better understanding of how new FODMAPs, such as xylose and arabinose, and sucrose and dextrins in a minority, are relevant in the FODMAP paradigm.

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