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Role of FODMAPs in Patients With Irritable Bowel Syndrome: A Review

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Abstract

Irritable bowel syndrome (IBS) is a condition characterized by abdominal pain, bloating, flatus, and altered bowel habits. The role of dietary components in inducing IBS symptoms is difficult to explore. To date, foods are not considered a cause but rather symptom-triggering factors. Particular interest has been given to the so-called FODMAPs (fermentable oligo-, di-, and monosaccharides and polyols). We aimed to summarize the evidence from the most common approaches to manage suspected food intolerance in IBS, with a particular interest in the role of FODMAPs and the effects of a low FODMAP diet. We reviewed literature, consulting PubMed and Medline by using the search terms *FODMAP(s), fructose, lactose, fructans, galactans, polyols (sorbitol, mannitol, maltitol, xylitol, erythritol, polydextrose*, and *isomalt*), *irritable bowel syndrome*, and *functional gastrointestinal symptoms*. FODMAP-restricted diets have been used for a long time to manage patients with IBS. The innovation in the so-called FODMAP concept is that a global restriction should have a more consistent effect than a limited one in preventing abdominal distension. Even though all the potential low FODMAP diets provide good relief of symptoms in many patients, there is just a little relief in others. Several studies highlight the role of low FODMAP diets to improve symptoms in patients with IBS. The evidence on this dietary approach supports the hypothesis that a low FODMAP diet should be the first dietary approach. However, many points remain to be clarified, including the evaluation of possibly significant nutrition concerns. (*Nutr Clin Pract*.XXXX;xx:xx-xx)

Keywords

diet therapy; gastrointestinal diseases; oligosaccharides; disaccharides, monosaccharides; FODMAP; irritable bowel syndrome

Irritable bowel syndrome (IBS) is a clinical condition characterized by abdominal pain, bloating, flatus, and altered bowel habits.[1,2] Several studies conducted using barostat and similar devices indicate that these symptoms may be induced by luminal distension in association with visceral hypersensitivity. This suggests that dietary factors could modify intestinal luminal distension by increasing water and gas volume and thus may be suitable targets for therapy.[1,2] The role of dietary components in inducing IBS symptoms is difficult to explore. Several studies have suggested a possible role for food allergy or food intolerance in IBS pathogenesis.[1,3] Food allergy is defined as a reproducible adverse reaction arising from specific immune responses occurring on exposure to specific food antigens. Whenever similar reactions occur without evidence of immunologic mechanisms, they are named "food intolerance."[3] The latter has been considered in IBS pathogenesis, but questionable outcomes have been obtained due to issues surrounding diagnostic tools and difficulties in conducting well-designed dietary trials. In addition, accurate identification of the foods contributing to symptoms is difficult to achieve and fraught with complexity, given that meals are often complex mixtures of dietary components, and the timing of symptom onset can vary, both with different foods and with the same food in different patients.[4–8] However, recent evidence has suggested that foods do not seem to be the cause of the condition, only the triggering factors of symptom onset.[9] As aforesaid, identification of trigger foods could be extremely difficult, especially in the case of food intolerance.[3] Many published studies report specific food intolerance using patient questionnaires, although this is an unreliable method given the mix of foods included in meals and snacks and the likelihood of pinpointing the wrong culprit.[10,11] At the same time, there is a consistent lack of clear evidence for "food allergy" in IBS and also on rechallenge with suspect trigger foods, which has not been successful in identifying reliable immunologic markers.[12]

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In recent decades, the role of dietary components has been better explored and highlighted. Some studies report that certain food components can contribute to symptom onset due to malabsorption of carbohydrates[9,13] and stimulate hypersensitivity through food chemical ingestion.[11] Moreover, a new clinical condition—nonceliac gluten sensitivity (NCGS)—entered this complex situation, and it has been suggested that it may be important in causing IBS in a subgroup of patients,[14–16] although contradictory data seem to deny a role for the gluten-free diet in the treatment of these IBS-like patients.[17] More recently, international literature has paid specific attention to the so-called FODMAPs (fermentable oligo-, di-, and monosaccharides and polyols; ie, fructose, lactose, fructans, galactans, and polyols). They form a heterogeneous group of poorly absorbed, short-chain carbohydrates, which seem to be possible IBS symptom inducers and whose restriction from the diet could produce beneficial effects in patients with IBS.[9,18–56]

Therefore, the aim of our article is to summarize the latest evidence and applications of the most common research approaches to manage suspected food intolerance in IBS. Particular interest will be paid to the role of FODMAPs and to the effects of a low FODMAP diet in patients with IBS.

Methods

This review is based on a PubMed and Medline search, conducted in November 2014, for all available articles with the search terms, alone and matched to each other: *FODMAP(s), fructose, lactose, fructans, galactans, polyols* (*sorbitol, mannitol, maltitol, xylitol, erythritol, polydextrose*, and *isomalt*), *irritable bowel syndrome*, and *functional gastrointestinal symptoms*. The references of identified eligible articles were also searched for further studies. The search provided 391 eligible studies, of which the abstract and, whenever possible, full text were read and analyzed. Considering the specific interest of our research, to provide a practical point of view to evaluate, diagnose, and manage possible FODMAP intolerance in IBS and patients with functional gastrointestinal (GI) symptoms, we excluded papers not written in English, letters to the editor, case reports, studies that are too small (<5 patients studied), exclusive biochemical and experimental research, reviews reporting data about the same original studies, and research otherwise not of our specific interest (ie, matching error). We considered 40 articles: 31 original studies and 9 reviews (Figure 1 and Tables 1 and 2).[9,18–56]

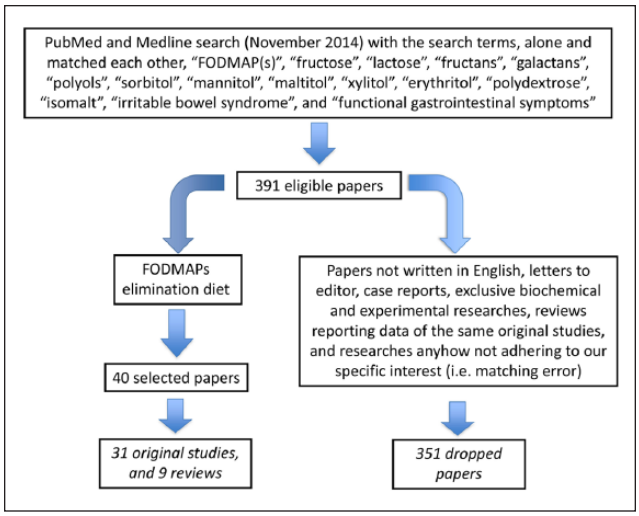

Figure 1. Method of research and selection of papers suitable for the review. FODMAPs, fermentable oligo-, di-, and monosaccharides and polyols.

What Are FODMAPs, and How Much Is Too Much?

During the past several decades, and probably in conjunction with urbanization, reports conflict about whether sugar intake has increased.[57] Nonetheless, several studies performed in the United States agree on the same point: the proportion of sugar intake made up of fructose is increasing.[58] The even greater consumption of fruit juice, as well as the use of high-fructose corn syrup (which contains 42%–55% fructose) as sweeteners in many manufactured foods, seems to play the leading role. In the past 4 decades, the proportion of energy from high-calorie sweeteners has increased to about 22% of the total daily calorie intake, of which more than 80% can be attributed to increased consumption of soft drinks and/or sugared fruit drinks.[57–62] To date, there are no direct studies of time trends in fructan ingestion, but indirect evidence indicates changes in their consumption patterns.[60] The intake of major sources of fructans, such as pasta and pizza, has increased, and at the same time the type of fructan in the diet is changing.[61–63] The widespread use of fructans is attributable both to the unique technological benefits in food manufacture (they improve palatability and stability of foods) and to the putative nutrition benefits as "functional foods."[61] There are no data available on polyol intake trends, but it is likely that their use as food additives has increased with the desire to produce "sugar-free" products to lower energy intake and to protect dentition.[57,58,62–65]

Throughout the 1980s and 1990s, evidence (especially observational cohort studies) of a possible induction of functional bowel disorders and IBS symptoms due to the poorly absorbed, short-chain carbohydrates and polyols (lactose, fructose, and sorbitol) has confirmed that dietary restriction of all three together could cause symptomatic relief.* More recent studies confirmed the above-mentioned results.† However, it is clear that these sugars are not the only answer. A deeper examination of the international literature on the biochemistry and physiology of digestion of other carbohydrates suggests

*References 18, 25, 27, 31, 36, 38, 39, 41, 43, 49.
†References 19–22, 29, 30, 33, 34, 40, 44, 45, 51.

Table 1. Original Research Selected for Review, in Chronological Order.

Authors	Year of Publication	Type of Publication	Design of the Study	No. of Patients and Controls	GI Disorder	Results
Andersson and Nygren[18]	1978	Original research	Prospective observational study	4 patients, 4 controls	Diarrhea and colic pains	Patients under fructose-free diet might have partial fructose malabsorption.
Ravich et al[41]	1983	Original research	Prospective observational study	16 healthy participants	None	Incomplete absorption of fructose should be considered a possible case of GI symptoms.
Stone-Dorshow and Levitt[48]	1987	Original research	Randomized controlled trial	15 healthy participants (10 intervention group, 5 controls)	None	Adaptation of colonic bacteria to carbohydrate malabsorption is variable and may depend on quantity or nature of the carbohydrate.
Rumessen and Gudmand-Hoyer[43]	1988	Original research	Prospective observational study	25 patients	Functional bowel disease	GI distress may be provoked by malabsorption of small amounts of fructose, sorbitol, and fructose-sorbitol mixtures in patients with functional bowel disease.
Symons et al[49]	1992	Original research	Prospective observational study	15 patients, 24 healthy controls	IBS (Rome II criteria)	IBS symptoms increased in parallel with increasing dose. No significant correlation was observed between the increase in symptom score and the increase in peak hydrogen concentration.
Götze and Mahdi[31]	1992	Original research	Prospective observational study	293 patients	Recurrent abdominal pain, meteorism, or diarrhea	Fructose malabsorption may be the cause of functional gut disorders.
Fernández-Bañares et al[27]	1993	Original research	Prospective observational study	25 patients, 12 healthy controls	IBS-like symptoms	Sugar malabsorption may be implicated in the development of abdominal distress in a subset of patients with functional bowel disease.
Mishkin et al[36]	1997	Original research	Prospective observational study	520 patients	Functional dyspepsia	Multiple sugar malabsorption is common when lactose maldigestion/malabsorption is present.
Clausen et al[23]	1998	Original research	Prospective observational study	12 healthy participants	None	Fecal volume in carbohydrate-induced diarrhea is proportional to the osmotic force of the malabsorbed saccharide.
Evans et al[25]	1998	Original research	Prospective observational study	15 patients	IBS (Rome II criteria)	Carbohydrate malabsorption can provoke symptoms in patients with IBS; no association can be proved between such a phenomenon and jejunal hypersensitivity or dysmotility.
Rumessen and Gudmand-Hoyer[42]	1998	Original research	Single-blind, crossover randomized trial	16 healthy participants	None	GI symptoms after fructans increased with increasing dose and decreasing chain length. The overall GI effects of short-chain fructans seem similar to those of lactulose.
Ledochowski et al[34]	2000	Original research	Prospective observational study	53 fructose malabsorbers	Meteorism and/or diarrhea	Fructose- and sorbitol-reduced diets reduced GI symptoms and improved mood and early signs of depression.

(continued)

Table 1. (continued)

Authors	Year of Publication	Type of Publication	Design of the Study	No. of Patients and Controls	GI Disorder	Results
Goldstein et al[30]	2000	Original research	Prospective observational study	94 patients with IBS, 145 patients with functional gut disorder	IBS and IBS-like symptoms not fulfilling Rome II criteria	Combined sugar malabsorption is common in functional bowel disorders. Dietary restriction should be implemented before institution of drug therapy.
Rana et al[40]	2001	Original research	Prospective observational study	25 patients, 25 healthy controls	IBS (Rome II criteria)	Patients with diarrheal type of IBS have a higher incidence of lactose intolerance compared with spastic and mixed IBS.
Choi et al[21]	2003	Original research	Prospective observational study	183 patients	IBS-like symptoms	Fructose intolerance may cause unexplained GI symptoms.
Beyer et al[20]	2005	Original research	Prospective observational study	15 healthy participants	None	Fructose, in amounts commonly consumed, may result in mild GI distress in healthy people.
Fernández-Bañares et al[28]	2006	Original research	Prospective observational study	36 patients	IBS (Rome II criteria)	A malabsorbed sugar-free diet might be a long-term effective therapy in patients with IBS.
Shepherd and Gibson[44]	2006	Original research	Retrospective observational study	62 patients	IBS-like patients	Comprehensive fructose malabsorption dietary therapy achieves a high level of sustained adherence and good symptomatic response.
Shepherd et al[9]	2008	Original research	Double-blinded, randomized, quadruple arm, placebo-controlled challenge	25 patients	IBS-like symptoms	Dietary restriction of fructose and/or fructans is likely to be responsible for symptomatic improvement.
Choi et al[22]	2008	Original research	Prospective observational study	80 patients	IBS (Rome II criteria)	IBS symptoms improves on fructose-restricted diet despite moderate impact on lifestyle.
Skoog et al[45]	2008	Original research	Double-blind, randomized, crossover study	30 patients, 20 healthy controls	IBS-like patients	Prevalence of fructose intolerance is not significantly different in health and IBS. Current methods for identifying fructose intolerance should be modified to more closely reproduce fructose ingestion in daily life.
Barrett et al[19]	2009	Original research	Prospective observational study	Crohn's disease (n = 91), ulcerative colitis (n = 56), functional GI disorders (n = 201), celiac disease (n = 136), healthy volunteers (n = 71)	Various, according to the specific disease	Carbohydrate malabsorption and early rise in breath hydrogen after lactulose are normal physiologic phenomena.

(continued)

Table 1. (continued)

Authors	Year of Publication	Type of Publication	Design of the Study	No. of Patients and Controls	GI Disorder	Results
Ong et al[37]	2010	Original research	Single-blind, crossover intervention trial	15 patients, 15 healthy controls	IBS (Rome II criteria)	FODMAPs induce hydrogen production in the intestine and induce GI and systemic symptoms in patients with IBS.
Zhao et al[51]	2010	Original research	Prospective observational study	31 patients, 32 healthy controls	IBS (Rome III criteria)	SIBO increases the likelihood of lactose intolerance in patients with IBS as a direct result of lactose fermentation in the small intestine, independent of orocecal transit time and visceral sensitivity.
Staudacher et al[47]	2011	Original research	Prospective observational study	82 patients (39 standard diet, 43 low FODMAP diet)	IBS (Rome II criteria)	A low FODMAP diet is more effective than standard dietary advice for IBS symptom control.
Staudacher et al[46]	2012	Original research	Randomized controlled trial	41 patients (19 in intervention group, 22 in control group)	IBS (Rome II criteria)	FODMAP-restricted diet was effective in managing IBS symptoms. A reduction in concentration and proportion of luminal bifidobacteria after a 4-week diet was found.
De Roest et al[24]	2013	Original research	Prospective observational study	90 patients	IBS (Rome II criteria)	Low FODMAP diet shows efficacy for patients with IBS in controlling symptoms.
Yao et al[50]	2014	Original research	Double-blinded, placebo-controlled trial	20 patients, 21 healthy controls	IBS (Rome II criteria)	Polyols induce GI symptoms in patients with IBS independently of their absorptive patterns, suggesting that the dietary restriction of polyols may be efficacious.
Halmos et al[32]	2014	Original research	Double-blinded, randomized, crossover, placebo-controlled challenge	30 patients, 8 healthy controls	IBS (Rome II criteria)	Diet low in FODMAPs effectively reduced functional GI symptoms.
Halmos et al[54]	2014	Original research	Randomized controlled trial	27 patients, 6 healthy participants	IBS (Rome II criteria)	A low FODMAP diet has a marked effect on gut microbiota composition compared with a typical Australian diet, reducing total bacterial abundance and increasing fecal pH.
Pedersen et al[53]	2014	Original research	Prospective observational study	19 patients	IBS (Rome III criteria)	Quality of life in patients with IBS significantly improved during low FODMAP diets.

FODMAPs, fermentable oligo-, di-, and monosaccharides and polyols; GI, gastrointestinal; IBS, irritable bowel syndrome; SIBO, small intestinal bacterial overgrowth.

Table 2. Published Reviews Selected for Evaluation, in Chronological Order.

Authors	Year of Publication	Results
Gibson et al[29]	2007	Restricting dietary intake of free fructose and/or fructans may have durable symptomatic benefits in patients with IBS.
Gibson[38]	2011	Dietary restriction of FODMAPs is an effective therapy in most patients with functional bowel symptoms and should be first-line therapy.
Magge and Lembo[33]	2012	The reduction of FODMAPs in a patient's diet may improve functional GI symptoms.
McKenzie et al[35]	2012	FODMAP elimination diet seems to improve GI symptoms in patients with IBS, but there is a lack of high-grade evidence.
Putkonen et al[39]	2013	FODMAP restriction is efficacious for functional GI symptoms, but potentially negative effects on microbiota deserve attention.
Fedewa and Rao[26]	2014	Current research shows that the FODMAP diet may be effective in treating some patients with IBS.
Staudacher et al[55]	2014	Efficacy of fermentable carbohydrate restriction in IBS has been proven by several researchers, who also found significant changes in gut microbiota.
El-Salhy et al[52]	2014	FODMAPs seem responsible for endocrine activity from specialized GI cells, increasing GI motility and sensation and triggering IBS symptoms.
Mullin and Shepherd[56]	2014	Diet in the management of IBS has become increasingly important in recent years, with several studies trying to validate the relationship between certain foods (FODMAPs) and symptom onset.

FODMAPs, fermentable oligo-, di-, and monosaccharides and polyols; GI, gastrointestinal; IBS, irritable bowel syndrome.

involvement of fructo-oligosaccharides (fructans or FOS) and galacto-oligosaccharides (galactans or GOS); they are also short-chain carbohydrates and are incompletely absorbed in the human GI tract.[23,26,37,42,47,48] Other potential culprits seem to be incompletely absorbed polyols (ie, mannitol, maltitol, and xylitol), used as artificial sweeteners, but also found naturally in foods.[50] Grouping these poorly absorbed, short-chain carbohydrates according to their chain length resulted in the acronym FODMAP.[66–70]

Historically, this term was specifically coined, in 2005, by a group of Australian researchers who theorized that foods containing these forms of carbohydrates worsen the symptoms of some digestive disorders, such as IBS and inflammatory bowel disease (IBD).[71] These short-chain highly osmotic carbohydrates are poorly absorbed in the small intestine and are rapidly fermented by bacteria in the gut, causing increased gas production, bowel distension, bloating, cramping, and diarrhea—all symptoms of IBS, triggered in association with intrinsic visceral hypersensitivity.[72]

More specifically, free fructose is a simple sugar requiring no digestion, which can arrive in the intestinal lumen either as a free hexose in foods or following enzyme-mediated hydrolysis of sucrose or saccharose, a disaccharide composed of the monosaccharides fructose and glucose.[73] It is absorbed by the small intestinal epithelium via 2 mechanisms: (1) in cotransport with glucose (GLUT-2) and, when in equimolar amounts with glucose, fructose is taken up efficiently (eg, following sucrose hydrolysis), due to the insertion of GLUT-2 (a glucose/fructose-specific transporter) into the apical membrane of the enterocyte[73] and (2) by a specific alternative transporter (GLUT-5): in the case of excess relative to glucose, free fructose is taken up by GLUT-5, which is present on the apical border of enterocytes throughout the small intestine. Since the concentration of fructose is higher in the lumen than in the intestinal epithelial cells, a concentration gradient allows the fructose to flow down into the latter, assisted by transport proteins, but this mechanism is low capacity (ie, saturation at low levels).[73] If the free fructose load is sufficiently large, its malabsorption is universal. However, about 40% of the general population exhibit very limited ability to absorb free fructose and are considered to have "fructose malabsorption."[73,74] Apples, cherries, mangoes, pears, watermelon (among fruits), asparagus, artichokes, sugar snap peas (among vegetables), honey, and high-fructose corn syrup are the most common foods containing fructose.[73,74]

Lactose is a disaccharide, made up of 2 sugar units (glucose and galactose), naturally occurring in mammalian milk, including cows, sheep, and goats. Whenever an individual has an insufficient level of lactase (a condition that can be found in 15%–100% of populations), the enzyme needed to hydrolyze the disaccharide to its constituent monosaccharides and whose levels can be influenced by factors such as genetics, ethnicity (Asian, African American, Hispanic, Native American, Alaska Native, and Pacific Islander), and other gut disorders, lactose behaves as a FODMAP.[75] Nevertheless, this is a concentration-dependent process, since it has been demonstrated that symptoms only occur in lactose malabsorbers when lactose is ingested in quantities in excess of 7 g, since most people have

some degree of lactase activity.[76] Common foods rich in lactose are milk, yogurt, ice cream, custard, and soft cheeses.[72]

FODMAP oligosaccharides are fructans (linear or branched fructose polymers with a glucose terminal end and a chain length, or degree of polymerization, less than 10, the naturally occurring storage carbohydrates of a variety of vegetables) and galactans, whose digestion and absorption are impossible for humans because they do not have enzymes to break them down.[77–79] Thus, they are not absorbed in the small intestine and are rapidly fermented, causing gas formation.[77] Fructans can be found in several foods belonging to the large families of fruits, cereals, legumes, nuts, and vegetables such as peach, persimmon, watermelon (among fruits), artichokes, beetroot, Brussels sprouts, chicory, fennel, garlic, leek, onion, peas (among vegetables), wheat, rye, barley (among grains and cereals), pistachios (among nuts and seeds), lentils, chickpeas (among legumes), and chicory drinks.[77,78] Wheat is a major source of fructans in the diet, containing 1%–4% fructans in solid matter.[77] It is the main constituent of bread, pasta, breakfast cereals, cakes, cookies, and crackers. Rye also contains fructans, whose chain length is longer than that found in wheat, the one thing that could make them less osmotically active or as rapidly fermented.[77–81] An additional source of fructans is inulin (a long-chain fructan, with a chain length or degree of polymerization greater than 10), which is increasingly being added to foods for its putative probiotic effects.[82–85] The main GOS dietary forms are raffinose, which is composed of 1 molecule of fructose, 1 glucose, 1 galactose, and 1 stachyose, whose composition is the same as raffinose except for 1 more galactose molecule.[79] Raffinose and stachyose cannot be broken down to their simple sugar constituents because humans lack the enzyme α-galactosidase that hydrolyzes the galactosidic linkages.[86] The primary dietary sources of galactans are certain legumes, such as baked beans, red kidney beans, chickpeas, lentils, and soy products, but can also be found in green and yellow (wax) beans, Brussels sprouts, and cabbage.[86,87] Large amounts of galactans due to increased consumption of legumes, commonly used as important alternative sources of protein in specific diets, are often consumed by vegetarians, particularly those following vegan diets. Other cuisines that are based on these foods, such as the Indian (many curries and soups) and Mexican ("chili con carne" and refried beans), are likely to provide greater intake of galactans.[77–79,86,87]

Polyols (ie, sorbitol, mannitol, maltitol, xylitol, erythritol, polydextrose, and isomalt) are sugar alcohols.[88] They appear to have primary roles in plants as energy reserves and agents of osmolarity, but recently they have been used as sugar substitutes by the food industry to produce low-calorie food products.[88,89] Only about one-third of what is consumed is actually absorbed, and the proportion varies depending on different polyols and individuals. Polyols are probably slowly absorbed by passive diffusion: a system of active transport in the small intestine epithelial barrier has not been demonstrated.[89] The rate of absorption is related to 3 factors. First, the diffusion depends on molecular size, occurring through "pores" in the epithelium. Second, there is variation of pore size along the small intestine, with larger pores proximally. Finally, pore size is affected by mucosal disease (eg, pore size decreases in celiac disease).[89] So it is not surprising that studies on the absorption of some polyols, such as sorbitol and mannitol, have highlighted considerable individual variation and a fermentation extent strictly dependent on intake amount.[88,89] Sorbitol tends to be more common in fruits, whereas mannitol is found more commonly in vegetables. Common foods in this group are apples, apricots, avocado, blackberries, cherries, nectarines, pears, plums, prunes (among fruits), cauliflower, mushrooms, and snow peas (among vegetables). As aforesaid, polyols are also used as artificial sweeteners, being identified by the following additive numbers on food packages: E420 (sorbitol), E421 (mannitol), E965 (maltitol), E967 (xylitol), and E953 (isomalt). Finally, sorbitol is often found in foods rich in free fructose and has been marketed as a laxative; this latter feature has made a warning necessary on the boxes of candy, whenever used as a sweetener, especially in sugarless chewing gum.[66,88,89]

Obviously, differences in dietary habits make the relative consumption of different FODMAP subgroups vary across ethnic and dietary groups. In North American and Western European diets, fructose and fructans are by far the most widespread in the diet and therefore the ones to which nearly all patients with IBS are exposed in their everyday diet (Table 3).

Benefits of a Low FODMAP Diet for Patients With IBS

FODMAP-restricted diets have been used for a long time, with varying success, in the management of patients with functional gut symptoms and IBS. The best examples are restriction of fructose, with or without sorbitol, and lactose.‡ However, the very limited success of this approach is the most likely reason why this kind of diet has not been widely used. A limited restriction of FODMAPs ignores the likelihood that there is a potentially large amount of FODMAPs in the everyday diet, each of which has similar end effects in the bowel.[28,90] The innovation in the so-called FODMAP concept or approach is that a global restriction should have a far greater and more consistent effect than a limited one.[28] Thus, the central focus should be to reduce the intake of all poorly absorbed short-chain carbohydrates, rather than merely concentrating on one of these, to be more effective in preventing luminal distension. Such a global approach should optimize symptom control in patients with IBS, reducing carbohydrates that have similar actions (high osmotic power and rapid fermentation).[28]

Shepherd et al[44] were the first to confirm the role of a low FODMAP diet in managing GI complaints by means of a research trial designed as a retrospective evaluation of patients with IBS and fructose malabsorption on a low-fructose/fructan diet (and polyols, if the patients noted symptom induction), balancing fructose (but not fructans) with glucose

‡References 18–21, 25, 30, 33, 34, 36, 38–40, 43–45, 49, 51.

Table 3. Main FODMAPs and Their Alimentary Origin.

Food Component	Dietary Form	Foods
Monosaccharide	Fructose	*Fruits*: apples, pears, nashi pears, clingstone peaches, mango, sugar snap peas, watermelon, cherries, tinned fruit in natural juice *Honey* *Vegetables*: asparagus, artichokes, sugar snap peas *Sweeteners*: fructose, high-fructose corn syrup *Large total fructose dose*: concentrated fruit sources; large servings of fruit, dried fruit, fruit juice
Disaccharides	Lactose	*Milk*: cow, goat, and sheep (regular and low fat) *Ice cream* *Custards* *Yogurt* (regular and low fat) *Cheeses*: soft and fresh (eg ricotta, cottage)
Oligosaccharides	Fructans and/or galactans	*Fruits*: watermelon, custard apple, white peaches, rambutan, persimmon *Vegetables*: artichokes, asparagus, beetroot, Brussels sprouts, broccoli, cabbage, fennel, garlic, leeks, okra, onions, peas, shallots *Cereals*: wheat and rye when eaten in large amounts (eg, bread, pasta, couscous, crackers, biscuits), barley *Nuts and seeds*: pistachios *Legumes*: chickpeas, lentils, red kidney beans, baked beans *Inulin*
Polyols	Sorbitol, mannitol, maltitol, xylitol, erythritol, polydextrose, and isomalt	*Fruits*: apples, apricots, cherries, lychee, nashi pears, nectarines, pears, peaches, plums, prunes, watermelon *Vegetables*: avocado, cauliflower, mushrooms, snow peas *Sweeteners*: sorbitol (E420), mannitol (E421), xylitol (E967), maltitol (E965), isomalt (E953), and others ending in *-ol* *Laxative*

Data from Gibson and Shepherd.[71,72,90] FODMAPs, fermentable oligo-, di-, and monosaccharides and polyols.

by supplementing foods with excess free fructose with free glucose. Abdominal symptom improvement on this dietary regimen was reported by 74% of patients. Efficacy was durable and closely related to dietary compliance (ie, better in those compliant than noncompliant). However, the main weakness of the study was that it was a retrospective analysis; it is universally known that a retrospective analysis of diet experience is not the ideal way to determine whether efficacy was due to a placebo effect, which is notoriously high in clinical trials of patients with IBS.[44] Efficacy of the diet was confirmed by a randomized, double-blind, placebo-controlled, quadruple-arm crossover, rechallenge trial with fructose, fructans, fructose plus fructans, and glucose (as placebo), at varying doses (low, medium, or high), in 25 patients with IBS, as defined by the Rome II criteria: all patients should have documented fructose malabsorption (positive fructose hydrogen breath test following a 35-g fructose load) as well as a previously demonstrated durable symptomatic response (3–36 months) to reduction of dietary FODMAPs. Abdominal symptoms, such as pain, bloating, and flatulence, recurred in a dose-dependent way in 70%–80% of patients when fed with pure forms of FODMAPs, especially with fructose plus fructans; this proved to have an additive effect, especially compared with 15% reporting the same abdominal symptoms with a similar diet spiked with placebo (glucose).[9] A possible weakness of the above-reported studies is the origin: they have all been carried out by a single center in Australia. This specific feature has made a subsequent comparative study of this dietary approach necessary, which was performed in the United Kingdom and demonstrated the superiority of a low FODMAP diet compared with a dietary approach previously considered best practice (ie, National Institute for Health and Clinical Excellence diet). The low FODMAP intake group reported satisfaction with their symptom response compared with the standard group. Symptom score data showed better overall symptom response in the low FODMAP group compared with the standard diet group. More specifically, the most significant improvements were achieved in bloating, abdominal pain, and flatulence.[35,47] The same beneficial effects of a low FODMAP diet have been confirmed by a more recent study, which included patients with IBS who underwent hydrogen/methane breath testing for fructose and lactose malabsorption and had received dietary advice regarding the low FODMAP diet. Particular attention should be paid to the greater symptomatic improvement in those with fructose malabsorption compared with the others. An association between fructose malabsorption and better efficacy of the diet

may reflect large amounts of fructose in the diet of these patients.[24] Finally, in an Australian study in 2014, a group of patients with IBS and healthy individuals (controls matched for demographics and diet) were randomly assigned to groups that received 21 days of either a diet low in FODMAPs or a typical Australian diet, followed by a washout period of at least 21 days, before crossing over to the alternate diet. In this controlled crossover study, the patients with IBS effectively reduced functional GI symptoms when consuming a diet low in FODMAPs.[32]

However, there is no evidence that fructose and/or lactose malabsorption and/or FODMAP consumption is more frequent in patients with functional bowel symptoms (including IBS) than in those without such factors. In other words, FODMAPs cannot be considered the cause of functional bowel disorders but rather represent a dietary trigger and an opportunity for treatment.[19]

Table of FODMAP Content of Foods: Strengths and Weaknesses

Thanks to the above-mentioned studies, it was possible to gain better and more specific knowledge about food composition to fine-tune the FODMAP approach.[90] This included the consideration of a broader range of FODMAPs, including FOS, GOS, and mannitol, in addition to fructose, lactose, and sorbitol. Today, a low FODMAP diet avoids these 6 carbohydrates, with published tables of food composition available for fruits, vegetables, breads, and cereals.[91–93] Great importance should also be given to the possibility of simply and accurately assessing FODMAP consumption in individuals and specific populations, such as disease groups. Recently, Halmos et al[54] calculated that the mean FODMAP content of an Australian mixed diet is 23.7 g/d, ranging from 16.9–30.6 g/d.

The impact that dietary modification of FODMAPs can have on functional gut symptoms and the putative role that FODMAPs might play in the pathogenesis of specific GI diseases have been highlighted.[24,25] In this regard, administration of food frequency questionnaires (FFQ) is the method of choice. Broad food composition in an Australian population has been studied using the Monash University Comprehensive Nutrition Assessment Questionnaire (CNAQ), a 297-item comprehensive, semiquantitative FFQ, to estimate consumption of macro- and micronutrients, FODMAPs, and glycemic index/load.[94] This FFQ has been validated by comparing FFQ responses on 2 occasions, plus four 1-week semiquantitative food records kept during a 12-month period, in a broad range of participants, and the data were analyzed using 4 statistical methods. The CNAQ will probably be a useful tool for future investigation of FODMAPs and other dietary components in chronic disease and GI disorders.[94]

Even though several studies have demonstrated the efficacy of a low FODMAP diet in treating IBS symptoms, there are many limitations in developing tables of FODMAP-rich and FODMAP-poor foods.[93–95] To date, only a limited description of FODMAP content can be found in published lists of food composition. This limitation has been only partially overcome by the development of methods to measure FODMAP content, together with a systematic examination of fruits, vegetables, and cereals.[93] However, the biggest limitation is in the absence of a unique and widely approved cutoff level of FODMAP content, which should dictate whether a food must be classified as "high" FODMAP content or not. This is further complicated by the fact that the total FODMAPs ingested, rather than just the consumption of a single food containing FODMAPs in any one meal, is a major factor in determining whether symptoms will be induced. In the original description of the diet, only careful clinical observation (obtaining feedback from patients regarding foods that they identified as triggers for symptoms) allowed the identification of cutoff values.[92–94] The reported foods were examined for trends in the pooled food composition table. For example, foods and beverages containing >0.5 g fructose in excess of glucose per 100 g, >3 g fructose in an average serving quantity regardless of glucose intake, and >0.2 g fructans per serving were considered at risk of inducing symptoms.[44,92,93,95]

Therefore, according to this first study, the total dose indicated for therapeutic benefit in the IBS population is less than 0.5 g FODMAPs per sitting or less than 3 g FODMAPs per day. These values are considerably lower than the amount obtainable through the diet, as suggested in a validated FFQ of an average Australian diet.[44,94]

Possible Mechanisms of FODMAP Triggering of IBS Symptoms

The mechanisms by which FODMAPs produce effects have been studied in 2 separate trials. Using an ileostomy model, it was confirmed that FODMAPs consumed in meals are poorly absorbed in the small intestine.[13] Interestingly, an osmotic effect of the carbohydrates has been suggested by the increased water content of the output from the stoma. This may well be the physiologic mechanism inducing diarrhea in some individuals.[13] In this context (ie, osmotic effect of FODMAPs), magnetic resonance imaging analysis allowed studying the small bowel water content (SBWC). It was higher after a meal containing mannitol, but not a glucose meal, in patients with IBS with diarrhea but not in healthy volunteers.[96] The second research line was a single-blind, crossover, short-term, interventional study, aimed to assess breath hydrogen during low and high FODMAP diets in healthy volunteers and in patients with IBS. Higher levels of breath hydrogen were produced with the high FODMAP diet both in healthy volunteers and in patients with IBS, who proved to have higher levels during each dietary period than the controls.[37] GI symptoms (abdominal pain, bloating, wind, heartburn, and nausea) and lethargy were significantly and quickly induced by the high FODMAP diet in patients with IBS, while only increased flatus production was reported by healthy volunteers. Conversely, breath hydrogen

production was reduced both in healthy volunteers and in patients with IBS when consuming a low FODMAP diet, with consequential reduction in GI symptom scores in the IBS population.[37] This confirms the additive bacterial fermentative nature (with production of short-chain fatty acids, including butyrate, and gases such as carbon dioxide and hydrogen) of the short-chain carbohydrates and their role in the induction of bloating, abdominal distension and pain, and excessive flatus.[37] In this different context (bacterial fermentation), Brighenti et al[97] showed that hydrogen production speed is inversely proportional to FODMAP chain length. Just a few years later, a study analyzing activity of the short-chain carbohydrates after entering the colon indicated that the fermentative rather than osmotic effects predominated in most people.[23]

Other studies by Piche et al[98,99] point out how FODMAPs might also generate IBS symptoms through motility effects (ie, acceleration of small intestinal and colon transit and increase in gastroesophageal reflux). These effects could be connected to the already described osmotic effect of FODMAPs and an activation of neural feedback pathways and/or hormonal changes from short-chain fatty acid production at the same time, secondary to FODMAP bacterial fermentation. In this context, several GI endocrine cell abnormalities have been reported in patients with IBS in response to luminal stimuli (mostly ingested nutrients). Specialized cells release hormones into the lamina propria, where they exert paracrine/endocrine activity. FODMAPs seem responsible for such endocrine responses, increasing GI motility and sensation, thereby triggering IBS symptoms.[52]

Furthermore, an injury of the colon epithelium and increased intestinal permeability have been shown in animal models, including rats fed with fructo-oligosaccharides. These rats also developed more severe colitis when infected with *Salmonella* species.[100] This finding may be particularly relevant given the evidence that 7%–30% of patients with acute gastroenteritis subsequently develop postinfection IBS.[101]

FODMAPs may also be responsible for systemic effects, such as mild depression with fructose and lactose malabsorption in women with IBS.[102] This depression seems to improve when free fructose is eliminated from the diet.[34] A possible pathogenic mechanism could be identified in the lower levels of circulating tryptophan, suggesting secondary deficiency in serotonin synthesis, in patients with fructose malabsorption on an unrestricted diet.[103]

The pathogenic role of FODMAPs in IBS symptoms is probably also associated with the intestinal flora of these patients.[104–106] Bacteria, such as *Clostridium* species, break down FODMAPs with gas production, thus causing large intestine distension, with abdominal discomfort or pain.[104] Patients with IBS have fewer *Lactobacillus* and *Bifidobacterium* species in their intestinal flora than do healthy individuals. These bacteria have been shown to bind to epithelial cells, inhibiting pathogen adhesion and, at the same time, enhancing barrier function.[104–106] Furthermore, these bacteria species do not produce gas upon fermenting carbohydrates, an effect that is amplified as they also inhibit *Clostridium* species growth. Increased tolerance to FODMAPs could be achieved by replacing the intestinal flora with these beneficial bacteria.[104–106]

Finally, it is of some importance to note that FODMAPs are commonly added to enteral formula, in the form of FOS and inulin.[107,108] Enteral nutrition (EN) is frequently used as the main source of nutrition in hospitalized patients, so it is reasonable to hypothesize that EN provides more FODMAPs than usual dietary consumption in these latter patients, increasing the risk of diarrhea, one of the most common complications of EN.[108] Halmos et al[54,108] were the first to assess this hypothesis through a retrospective study investigating all possible predictors of diarrhea in hospitalized patients, with a particular focus on 7 enteral formulas, whose FODMAP contents ranged from 10.6–36.5 g/d vs the reported 16.9–30.6 g/d of a mixed Australian diet (both values well in excess of the suggested 3 g/d reported for low FODMAP diets).[47] Any variables that could possibly contribute to diarrhea were analyzed, and specific data were collected.[107,108] Inpatients with a longer length of stay and receiving EN for a longer period were positively associated with development of diarrhea. All the enteral formulas, excluding Isosource 1.5 (Nestlé Health Science, Lutry, Switzerland), were positively related to diarrhea onset. Analysis of the specific composition of Isosource 1.5 proved the FODMAP content (just 10.6 g/d) was the only significant difference: 30%–53% lower than all the other formulas.[107] These data were obtained through methods previously validated for food analysis—that is, high-performance liquid chromatography (HPLC) and enzymatic assays.[92,93] Recently, in another retrospective study, the same author assessed Isosource 1.5, which had a protective effect against developing diarrhea. However, the FODMAP content of commercial enteral formulas is not shown in product information, and a prospective randomized study is needed to test the role of FODMAPs in EN-associated diarrhoea.[108]

All of these insights are consistent with current understanding of the pathophysiological mechanisms that underlie IBS. Among these, visceral hypersensitivity is the most important; distension of the gut due to increased gas production and other mechanisms abnormally stimulates the enteric nervous system, which reacts by altering its motility patterns and sending messages to the brain that may be interpreted as bloating, discomfort, and pain.[108–111] Dietary components that putatively lead to luminal distension in the regions of interest have the following characteristics: (1) poorly absorbed in the proximal small intestine; (2) formed by small molecules (ie, osmotically active); (3) rapidly fermented by bacteria, potentially fermented by small intestinal and cecal bacteria, expanding the bacterial population at the same time (ie, a "probiotic" effect); and (4) associated with hydrogen production.[109–112] Dietary FODMAPs are the best fit for these mechanisms. In others words, to better highlight the concept, FODMAPs do not cause IBS but are the possible trigger for symptom onset and

represent an opportunity to reduce the patient's symptoms.[111] All of this steers us away from the more traditional concepts of fructose and lactose "intolerance" vs fructose and lactose "malabsorption." Concisely, visceral hypersensitivity is the main cause of a disproportionate reaction, mediated by the intestinal nervous system, to the ingestion of carbohydrates such as fructose and lactose and therefore not bound to any phenomenon of malabsorption. Delivery of dietary FODMAPs to the large intestine is a normal phenomenon, which will not cause any disproportioned reaction without the underlying presence of visceral hypersensitivity.[109,111] Therefore, a low FODMAP diet reduces osmotic effects, fermentation, and associated gas production and is likely to minimize the distension induced by food, thereby reducing symptom severity.[111,112] Alterations in the number, composition, function, and location of the microbiota could represent other factors concurring to pathogenesis of IBS symptoms.[104–106] It has been shown that some patients with IBS may have small intestinal bacterial overgrowth (SIBO). Such a condition could cause increased permeability in the small intestine and fermentation of malabsorbed carbohydrates in the narrow lumen of the small intestine, subsequently inducing abdominal pain and discomfort. These patients may have more predominant methane-producing bacteria that, when fermenting carbohydrates, delay intestinal transit and cause constipation.[109–112]

Diagnosis of FODMAP "Malabsorption"

To date, diagnosis of food intolerance in most areas is still unfortunately impossible. A reliable measure of test sugar absorption can be provided by assessment of breath hydrogen levels.[113] A significant rise in breath hydrogen following test sugar intake demonstrates poor absorption with subsequent fermentation by intestinal microflora. In patients with IBS, a positive breath test could allow the identification of carbohydrates causing symptom onset and whose exclusion from the diet could reduce intestinal discomfort. Contrariwise, a negative breath test proves the complete absorption of the sugar, suggesting that the patient can continue to consume this sugar without affecting his or symptoms.[113] Therefore, breath hydrogen testing to determine absorption of a fructose and/or lactose load is very useful since it can reduce the necessary restriction of diet. Lactose intolerance can also be detected both by a lactose tolerance test, measuring the amount of blood glucose after oral lactose consumption, and by detection of lactase activity through small bowel (duodenal) biopsy.[113] Breath hydrogen testing is not strictly necessary for the diagnosis of food intolerance; the fully restricted diet can be initiated, but altering the diet entails a risk of nutrition compromise, and in general it is a good principle not to restrict foods if not necessary.[113,114] The breath tests that allow detection of FODMAP malabsorption are routinely conducted with fructose (testing dose of 35 g), lactose (testing dose of 25–50 g), and sorbitol (testing dose of 10 g). Nevertheless, careful physicians should remember that 3 other FODMAPs need to be considered as potential triggers for IBS symptoms. A specific breath test for fructans and galactans is not available, since they are always malabsorbed and fermented.[113,114] Furthermore, the mannitol breath test is rarely offered since it is not a widespread component in the diet and can be investigated as a trigger through simple dietary elimination and rechallenge.[113]

Even if the use of breath tests to identify intolerance to FODMAPs could be useful, physicians should be aware of false positives. For example, it has been demonstrated that in patients with IBS with SIBO, diagnosed by lactulose breath test, a reliable and noninvasive test for the diagnosis of this condition (even if several recent studies suggest that the test can be flawed in diagnosing it), sugar breath tests (fructose, lactose, and sorbitol hydrogen breath tests), may be falsely abnormal. SIBO eradication with a 1-week course of antibiotics normalizes sugar breath tests in most patients.[114] These results suggest that in the presence of SIBO, sugars could be nonspecifically fermented by the large amount of intestinal bacteria, causing abnormal hydrogen production and consequently a mistaken diagnosis of FODMAP intolerance.[114] An alternative hypothesis to explain the false positives of the test could be damage of the small bowel mucosa, caused by bacterial overgrowth, inducing a transient enzymatic or carrier protein deficiency and then multiple sugar malabsorption. Appropriate antibiotic therapy to eradicate the SIBO allows mucosa regeneration and healing, reverting to a negative breath test. Therefore, testing for SIBO should be performed before other sugar breath tests to avoid a misdiagnosis of sugar malabsorption.[114]

Practical Low FODMAP Diet Management

FODMAP Tolerance Assessment

The efficacy of the low FODMAP diet suggests that if dietetic expertise is available, it should be the first-line treatment. Since response to diet is variable and some patients could have a food allergy as well, it is important for physicians to better target a low FODMAP diet, identifying the predictors of both conditions. Symptoms may provide some hints: atopic history; symptoms referable to mast cell activation, such as flushing and tingling in the mouth; or concurrent systemic manifestations, such as urticaria or asthma, should direct considerations to food allergy.[115] However, it has been suggested that the classic symptoms of IBS (bloating and frequent lower abdominal pain relieved by defecation) could also be due to a non–IgE-mediated food allergy.[116,117]

By definition, FODMAPs are different carbohydrates characterized by some identical features; considering their different nature, it is not surprising that not all FODMAPs will be symptom triggers for all patients. Only those that are malabsorbed are likely to play a role. It is important to keep in mind that

fructans and galactans are always malabsorbed and fermented by intestinal microflora.[42,118,119] So, if in healthy people, the result of consumption of these sugars is gas production and flatulence, then in patients with IBS, in whom conditions such as altered gut flora, visceral hypersensitivity, and motility disorders are present, they could induce symptom onset.[37] The remaining FODMAPs will induce symptoms only in the proportion of patients with IBS that malabsorbs them. In this regard, the prevalence of fructose and lactose malabsorption in white patients with IBS is 45% and 25%, respectively.[19] The sugar polyols, sorbitol and mannitol, are incompletely absorbed, but their low amounts found naturally in foods as well as in sugar-free products and medications are usually well absorbed in most people.[19,25,120] Several differences between healthy individuals and those with IBS in small intestinal handling of sorbitol and mannitol have been found in a randomized, double-blind, placebo-controlled crossover study.[50] Patients with IBS not only seem to absorb twice as much of these polyols, but they seem to do it more quickly for mannitol than for sorbitol compared with healthy individuals, who, in contrast, do not seem to present any difference in absorption rate between mannitol and sorbitol. Several hypotheses have been proposed to identify the cause of such differences, but further studies are required. One possibility is slower orocecal transit in patients with IBS. A lengthening of time of transit allows greater absorption of molecules that are passively and slowly absorbed.[50] Alternatively, the differences in absorption patterns between healthy individuals and patients with IBS might reflect epithelial abnormalities, which have been reported in some subgroups of patients with IBS. Despite superior absorption, both sorbitol and mannitol induce specifically abdominal symptoms, suggesting that some mechanism(s) other than (or in addition to) their fermentation are involved. Fluid distension of the small intestine has been proposed because of the osmotic effect induced by slowly absorbed polyols in most of the small intestine.[50] Such observations suggest that polyol dietary restriction should be included in low FODMAP diets for patients with IBS, irrespective of their ability to absorb them according to breath hydrogen results. Therefore, in this context, breath testing to assess polyol absorption, as is frequently performed for fructose and lactose, may not be clinically useful or relevant.[50,121] Even though breath tests are useful diagnostic tools helping physicians to implement specific and personalized low FODMAP diets, they cannot be considered mandatory, and the exclusion of polyols may still be appropriate in these patients.[113,121] If breath testing cannot be performed, a trial of a complete low FODMAP diet can be conducted, followed by a rechallenge of any of the potentially well-absorbed carbohydrates (fructose, lactose, sorbitol, and mannitol).[121] Tolerance to fructans and galactans can then be tested. In large amounts, these carbohydrates will always contribute to gas-associated symptoms, a phenomenon that can be observed even in healthy individuals for extreme amounts. However, small amounts of fructans and galactans may be tested to assess the level of tolerance in patients with IBS.[37]

Approach to Patients With Suspected FODMAP Intolerance

Nowadays, low FODMAP diets have been evaluated only as a dietitian-guided diet. This has mostly been achieved in a one-to-one setting, together with the use of written educational material (information sheets or detailed publications) and recipe books, but group education sessions have also been used with apparent success.[122] No data are available about the efficacy of using instructions and diet sheets by patients themselves. However, physicians should be cautious in undertaking such an approach, due to the lack of sufficient ad hoc studies. The strategy that should be used consists of 2 different phases: (1) preliminary consultation and start of a low FODMAP diet and (2) challenge by FODMAP reintroduction.[56] The first phase could be performed by physicians assisted by expert dietitians according to the following key points:

- *Define qualitatively and quantitatively the patient's typical eating practices and lifestyle.* This first evaluation is important to identify the FODMAPs to which the patient has daily exposure. Useful methods to obtain such information are precompleted food recording diaries (compiled for at least a 7-day period) and direct questioning during the consultation.
- *Explain the scientific basis of FODMAP malabsorption and subsequent fermentation to the patient.* This step is of great importance to provide a basis for better understanding of food choice and increase the likelihood of compliance.
- *Provide specific dietary instructions (Table 4).*
- *Discuss techniques to handle situations where food preparation cannot be controlled, such as eating away from home (eg, restaurants, school camps, and eating at friends' homes).*
- *Trial diet.* To ensure symptoms are well controlled, a strict trial of the low FODMAP diet should be performed for the first 6–8 weeks.

Assessment of symptom response under a strict FODMAP diet will subsequently lead to discussions of individual tolerance. Reintroduction of single carbohydrates, hence testing tolerance, is a vital stage of the dietetic process to ensure maximum variety in the diet, to avoid overrestriction and reduce a risk of nutrition inadequacy due to long-term diets.[56] Rechallenge includes consumption of, for example, fructose (2 tsp honey), lactose (125–250 mL milk or 200 g yogurt), fructans (2 slices wheat bread or 1 clove of garlic), galactans (1/2 cup lentils or legumes), sorbitol (4 dried apricot halves), and mannitol (1/2 cup mushrooms). Whenever response to the diet is inadequate, specific questioning is required to determine compliance to the

Table 4. Suggestions for Correct Management of FODMAP Intake.

Dietary Advice	Note(s)
Reduce dietary fructose load, especially in the form of free fructose.	Unless complete fructose absorption has been demonstrated by breath hydrogen testing.
Encourage food intake characterized by fructose/glucose balance or where glucose is in excess of fructose.	Advise coingestion of free glucose to "balance" excess of free fructose problematic foods.
Avoid foods that contain significant free fructose in excess of glucose.	
Restrict lactose-containing foods.	Whenever lactose malabsorption is demonstrated on breath hydrogen or lactose tolerance testing.
Avoid foods that are a substantial source of fructans and galactans.	Diets where it is possible to find the highest levels of fructans and galactans are vegan, Indian, and Mexican cuisines.
Avoid polyols.	Advise the patients about their role as sweeteners in several foods, chewing gums, drinks, and so on.

diet, modifying any deficiency. If compliance is established, attention should be paid to reducing resistant starch and both insoluble and soluble fiber intake. Physicians should always consider other possible triggers such as gluten and/or food chemicals, as well as other factors influencing GI system activity such as caffeine, fat, meal size, and regularity.[72]

Low FODMAP Diet Compliance

Patient compliance with a low FODMAP diet, if correctly introduced, is remarkably good. Shepherd et al[44] found compliance (complete or nearly so) with the diet in about 75% of patients by retrospective review. The study analyzed patients with proven fructose malabsorption and symptoms of IBS who had been instructed about fructose malabsorption after a median of 14 months (range, 2–40 months) of dietary intervention, paying particular attention to diet compliance, difficulties in consuming a correct diet, and strategies used by patients to avoid contamination. The main barriers to compliance included an unwillingness to undertake dietary recommendations, difficulties accessing (and increased expense) of wheat-free specialty foods, and dislike of the taste of these foods. Another possible cause, particularly important in modern society, is the necessity of eating out due to work and social concerns. Finally, most patients implemented the dietary strategies by self-selecting alternative foods.[24,44]

Gearry et al[122] found a particularly good response to the diet in a population of patients with inflammatory bowel disease and functional gut symptoms, with higher education status, working no more than 35 hours per week and using appropriate cookbooks, suggesting that the diet does require effort and time commitments.

Low FODMAP Diet in Patients With IBS: Limitations and Potential Concerns

Despite all the potential of low FODMAP diets, they are far from being a panacea for patients with IBS. Surely, they provide good relief of symptoms in many patients (ie, those with bloating and diarrhea), but it is of little relevance in some others.[47] Further studies are required to identify predictive factors of benefit apart from dietary compliance.[44] Since the diet does not influence the pathophysiologic substrate of IBS, intermittent symptoms remain in many patients, albeit at a now tolerable level. Symptomatic hyperresponsiveness to the reintroduction of FODMAPs in the diet has recently been described,[32] but no specific mechanism has been clearly identified to date. Experimental data showed that in rats fed fructose-poor diets, GLUT-5 expression falls, as does the ability to absorb fructose from the small intestine.[123] Whether or not this occurs in humans and contributes to IBS symptoms, fructose reintroduction in the diet warrants further investigation.[123,124]

A feature of greater importance, requiring further and better definition, is the safety of long-term low FODMAP diets. Restrictive diets are at risk of being nutritionally inadequate and potentially expensive. In general, by the very definition of a low FODMAP diet, it should not compromise nutrition adequacy (ie, it should not eliminate whole categories of foods, as is the case for several other types of diet). Foods are substituted with a suitable alternative within the same food group. The greatest difficulties are found with legumes (including chickpeas, baked beans, red kidney beans, and lentils), since these all contain fructans and galactans.[92,93] Fortunately, people on a low FODMAP diet can still enjoy tofu, and foods such as seeds, nuts, and quinoa are encouraged, as well as eating legumes in small amounts.[72] Reduction in fiber intake might be a consequence of the restriction of wheat-based products, but physicians should opportunely advise the patients as part of dietary counseling to ensure continuing adequate intake of resistant starch and nonstarch polysaccharides.[125] A possible detrimental effect of an elimination diet, although characterized by a wide variety of foods, such as a low FODMAP diet, is nevertheless present, because patients greatly reduce the intake of fiber and eliminate some carbohydrates, such as inulin, characterized by probiotic effects (ie, induction of selective bacterial proliferation, especially bifid bacteria).[124–126] For

example, possible interactions between the diet and luminal indices associated with colorectal carcinogenesis require elucidation.[95,118,126,127] For all these reasons, a strict, long-term, low FODMAP diet is not recommended. Rather, after achieving good symptomatic response, a reintroduction of FODMAP foods should be instituted as soon as possible to find the level of food restriction that the individual requires to adequately control symptoms without encountering nutrition imbalance. A low FODMAP diet is also not recommend for healthy people because of concerns regarding changes in luminal microflora and fiber intake.[70]

FODMAPs and Wheat Sensitivity

In recent years, increasing interest has surrounded the condition named "nonceliac gluten sensitivity."[128] Patients with NCGS show IBS-like symptoms, often associated with extraintestinal manifestations, which disappear on a gluten-free diet. However, it is not known which components of wheat cause the symptoms in patients with NCGS, and because there is no definite proof that gluten is really the culprit, we suggested the term *nonceliac wheat sensitivity* (NCWS).[129] Obviously, the first diagnostic approach for these patients must be to exclude a celiac disease diagnosis. Consequently, to match the criteria for NCGS, these patients must be negative for celiac disease (CD) serology (anti–endomysial antibodies and/or anti–tissue transglutaminase IgA and IgG) and must have a normal duodenal histopathology. Furthermore, these patients must have negative immune allergy tests to wheat since wheat allergy also must be excluded. These individuals show clinical symptoms that can overlap with CD symptoms and show a resolution of symptoms when started on a gluten-free diet, implemented in a blinded fashion to avoid a possible placebo effect of the dietary intervention.[128] Very recently, Biesiekierski et al,[17] in a placebo-controlled, crossover rechallenge study, did not find any evidence of specific effects of gluten in patients with NCGS placed on diets low in FODMAPs. Consequently, the authors suggested that NCGS might not be a real entity and that it might be confounded by FODMAP restriction. Accordingly, they concluded that at least in their highly selected cohort, gluten might not be a specific trigger of functional gut symptoms once dietary FODMAPs are reduced. This point of view considers the toxic effect of gluten in patients with NCGS, previously demonstrated in several other studies and by these authors themselves, only as a contribution to the FODMAP dietary load.[17] It should be said, however, that the patient population included in the above study was highly selected. To be sure to exclude patients with celiac disease, the authors excluded all patients carrying the HLA-DQ2 or HLA-DQ8 haplotype who have a simple duodenal lymphocytosis with normal villi/crypts ratio (Marsh 1 histology). In this way, they excluded more than 55% of the patients (82 of 149) initially recruited.[17]

Furthermore, previous studies had demonstrated that HLA-DQ2 and duodenal lymphocytosis are frequent findings in patients with NCGS. A retrospective study of ours, which included the most numerous NCGS patient population published so far, showed that about 50% of patients with NCGS had the DQ2 haplotype and that a higher percentage showed duodenal lymphocytosis.[16] Another study by Wahnschaffe et al[130] demonstrated that HLA-DQ2 expression is a useful marker to identify a subgroup of patients with diarrhea IBS who are likely responders to a gluten-free diet. Furthermore, Vazquez-Roque et al[131] provided a mechanistic explanation for the observation that gluten withdrawal may improve patient symptoms in IBS, showing also that biological effects of gluten were associated with the HLA-DQ2 or HLA-DQ8 genotype. Thus, the exclusion of HLA-DQ2 patients having normal villi at duodenal histology very probably does not permit studying a relevant percentage of patients with NCGS who have immunologic activation at the basis of their gluten-related symptoms. This probable role for an immune reaction in a percentage of patients with NCGS is suggested by mucosal studies[132] and by the high levels of serum anti-gliadin IgG antibodies (the "old antibodies" toward the native gliadin) found in NCGS, which fall on gluten-free diets.[133]

Finally, there are several elements supporting the hypothesis that a percentage of patients with NCGSs have a pathogenic mechanism based on non-IgE food allergy, a condition that can cause duodenal lymphocytosis.[15] On the other hand, the concern to exclude a CD diagnosis by excluding from the study on NCGS the patients with IBS who have a duodenal lymphocytosis is not justified, since no current guidelines consider CD diagnosis in patients with normal villi and negative CD-specific serum antibodies.[15,133]

The association between IBS, FODMAPs, and wheat sensitivity has been recently stressed by Mullin et al.[56] Their review of the dietary management of patients with IBS points out how wheat may provoke symptoms for several reasons: autoimmune disorder trigger, high fructans contents and member of the family of highly fermentable FODMAPs, and high IgE-mediated and non–IgE-mediated allergenicity (among the top 8 food allergens).

In conclusion, regarding the role of FODMAPs in NCGS, we think that the literature data support the hypothesis that a low FODMAP diet can be useful in a percentage of these patients, probably those in whom a "biochemical-digestive mechanism" plays a prevalent role in causing the symptoms (Figure 2). However, as we have already suggested, we think that NCWS is a heterogeneous condition, which includes different subgroups of patients who have different pathogenic mechanisms: strong data suggest a direct pathogenic role of wheat-cereal proteins (not only gluten) in a subgroup, probably the biggest subgroup of these patients.[15,134]

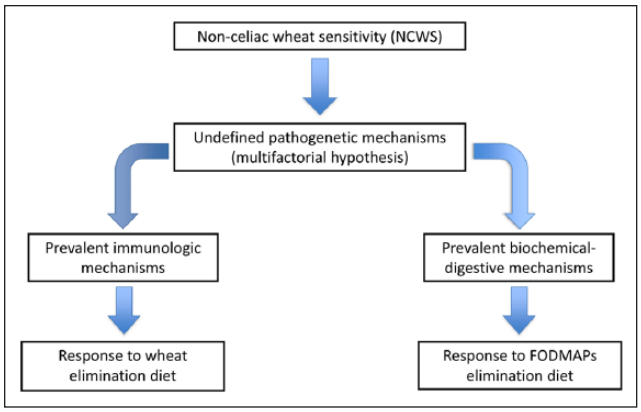

Figure 2. Possible pathogenic role of FODMAPs in nonceliac wheat sensitivity symptoms. FODMAPs, fermentable oligo-, di-, and monosaccharides and polyols.

Conclusion

There is emerging evidence for the role of food in triggering IBS symptoms (FODMAPs, IgE-mediated food allergies, and non-IgE food sensitivities and intolerances) and the relief provided by specific elimination diets. Changes in dietary intake, even if they do not represent a cure and do not influence the pathogenic mechanisms, allow improvement in symptoms and quality of life. To date, several studies highlight the role of low FODMAP diets, which improve symptoms in many patients with IBS. The increasing evidence supporting this dietary approach, as well as its relative ease of implementation, supports the hypothesis that a low FODMAP diet should be the first dietary approach in patients with IBS. However, many points remain to be clarified, including the evaluation of possibly significant nutrition concerns, especially in patients who do not have the help of a dietitian. Further studies are required to better identify those who can benefit from a low FODMAP diet and those in whom this diet should not be applied. Biomarkers to identify non–IgE-mediated food allergy and better methods to reveal problem food types are also required. Besides carbohydrates, there are many other food components worthy of study; among these, dietary fat has been shown to change visceral hypersensitivity, and naturally occurring chemicals widespread in foods can interact with receptors in the gut or have direct, possibly pharmacologic, actions on the enteric nervous system and mast cells.

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