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From Food Map to FODMAP in Irritable Bowel Syndrome

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10.1 Introduction

Irritable bowel syndrome (IBS) is one of the most common gastrointestinal diseases in the general population, with a prevalence ranging from 12 % to 30 %, mainly affecting younger patients (i.e., <50 years of age) and women [1]. As in other chronic functional gastrointestinal disorders, abdominal discomfort or pain, abnormal bowel habits, and often bloating and abdominal distension are the main clinical features. Their diagnosis is based on symptom patterns (i.e., the Rome III criteria), which also allow categorization in diarrhea-predominant (D-IBS), constipation-predominant (C-IBS), mixed diarrhea and constipation (M-IBS), and unclassified (U-IBS) IBS [2]. Symptom severity ranges from tolerable to severe, both between different patients and in the same patient, affecting patients' quality of life considerably as in some major chronic diseases [3]. Depending on whether diarrhea or constipation is the predominant disorder, antispasmodics, antidepressants, and medications modifying bowel habit represent the main conventional IBS treatments. Unfortunately, most patients report long-term inadequacy of current drug therapy and a tendency to seek a variety of alternative remedies, especially of a dietary nature (up to 65 % of them attribute their symptoms to adverse food reactions) [4]. However, the relationship between IBS symptoms and diet is still controversial,

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because of research quality and low number of scientific studies [5]. This represents a glaring gap that needs to be addressed.

10.2 IBS Pathogenesis

Development and maintenance of IBS symptoms has been attributed to multiple factors, such as altered small bowel and/or colonic motility (slow, fast, or uncoordinated), visceral hypersensitivity ("visceral hyperalgesia"), imbalance in neurotransmitters, genetic factors, infections, inflammation, and psychological dysfunction [6].

A correlation between IBS and the microorganisms that reside in physiological or pathological conditions in the gut has been stressed in some subgroups. In particular, small intestinal bacterial overgrowth (SIBO) could be responsible for increased fermentation and gas production in the small intestine, leading to symptoms [7]. To date authors do not agree on the possible pathogenic mechanisms of postinfectious IBS, but the evidence of persistent low-grade mucosal inflammation in some patients could explain how enteric infections affect gut physiology [8].

Similar histological abnormalities have also been found in colon mucosal biopsies of patients with IBS who did not describe any preexisting acute infectious gastroenteritis, suggesting a more general "inflammatory hypothesis" for IBS [9]. Increased numbers of jejunum and terminal ileal mucosa mast cells – a clue for a role for food allergy in an IBS subgroup [10], eosinophils [10], T lymphocytes (T helper [T_H]2 and T_H17) [11], B lymphocytes, and plasma cells [12] – characterize this inflammation. This composite infiltrate interacts with the intestinal nerve plexus and nociceptive structures [13]. Further evidence of the inflammatory theory of IBS lies in the increased IgE, tryptase, eosinophil cationic protein, and eosinophil protein X fecal levels [14]. Either exogenous factors, including food antigens and changes in the resident microbial flora, or endogenous chemical irritants, such as bile salts, might be responsible for mucosal inflammation and local activation of the immune system. In particular, mucosal immune cell activation results in changes in the function of submucosal and myenteric neurons, linking these two effector systems in the genesis of gastrointestinal function disorders [15].

These pathogenic hypotheses might apparently conflict with the classical one that IBS represents a disturbance of the "brain-gut axis." In this context female gender, family history of IBS, history of physical or sexual abuse, and comorbid psychiatric disorders are strong IBS risk factors [16]. Some studies sustain that either stressful early life events or psychiatric comorbidity or both mediate low-level inflammation as well as lymphocytes and mast cell infiltration of the bowel. Thus, an increasing number of researchers promote the idea of a three-way relationship between IBS, mood disturbance, and immune dysregulation [17].

10.3 The Facts: Diet in IBS Patients

Most IBS patients assign a significant role to diet in their symptom onset or persistence, and over 60 % of them would like to know what kind of foods should be avoided [5, 6]. Unfortunately, only 1–3 % of them are diagnosed as suffering from

food allergy using current medical methods. The discrepancy between self-perception and diagnostic tools is a major source of frustration both for patients and health care professionals, who are unable to provide reliable answers and support [18]. Several studies agree that 60 % of IBS patients experience worse symptoms following food ingestion, 28 % within 15 min after eating, and 93 % within 3 h. The most common foods singled out are wheat products (pasta, bread, pizza), cow's milk and milk-derived products, tomato, eggs, certain meats, fish/shellfish, cabbage, peas/beans, onion, hot spices, garlic, apple, peach, citrus, fried food, smoked products, fats, food additives, nuts, hazelnuts, chocolate, alcohol, and caffeine [14, 19].

Böhn et al. examined a cohort of 197 adult IBS patients with food allergy/intolerance, IBS symptoms, somatic symptoms, depression and general anxiety, and gastrointestinal-specific anxiety, using quality of life questionnaires. Eighty-four percent of subjects reported symptoms related to at least one food, and over 70 % noted symptoms after intake of food items with incompletely absorbed carbohydrates (i.e., fermentable oligo-, di-, and monosaccharides and polyols, FODMAPs) such as dairy products, beans/lentils, apple, flour, and plum. Noteworthy, self-reported food intolerance was associated with reduced quality of life (sleep, physical status, and social interactions) [20]. A Norwegian population-based cross-sectional study reported that 70 % of IBS subjects perceived a food intolerance (mean 4.8 food items), 62 % limited or excluded foods from their diet (mean 2.5 food items), and 12 % drastically modified daily intake causing nutritional deficiencies in the long run [21]. Data emerging from many studies is the lower consumption of spaghetti, pasta, couscous, and rice in IBS than in controls. The first three products are made using durum wheat, which tends to be high in gluten and FODMAPs, while the last tends to be low [22]. Similarly, lactose is considered one of the main causes of IBS symptoms. Therefore, these patients have a lower consumption of milk and other dairy products often self-inducing important nutritional deficits. Furthermore, IBS patients have been reported to have a significantly lower intake of retinol (vitamin A) equivalent, β-carotene, and magnesium, due to a lower consumption of certain vegetables (tomatoes, raw vegetables, etc.). Controversially, they report a higher consumption of pears, peach, grapes, melon, mango, and plums, which are rich in FODMAPs and documented as possible trigger factors of symptoms [22].

Finally, 12 % of IBS patients either limit or avoid alcohol intake due to self-reported intolerance [19].

In conclusion, IBS patients try to avoid certain food items rich in gluten and FODMAPs, even though the higher consumption of some FODMAP-rich fruits and vegetables remains questionable. The total calories, carbohydrates, proteins, and fat intake does not seem to differ from the general population, but such dietary restrictions could be responsible for their low calcium, phosphorus, vitamin B2, and vitamin A intake.

10.4 A Possible Role for Food Allergy and Intolerance

The large amount of evidence on dietary components causing IBS symptoms has not clarified the possible pathogenic mechanisms underlying this relationship. Physicians have suggested a possible role for food allergy or food intolerance.

"Food allergy" (or sensitivity or hypersensitivity) is defined as "reproducible adverse reaction arising from specific immune responses occurring on exposure to specific food antigens." Whenever similar reactions occur without evidence of immunological mechanisms, they are named "food intolerance" [23].

The role of IgE-mediated and non-IgE-mediated allergic response in IBS has been studied for a long time, producing only conflicting data and no consistent evidence. The first studies evaluated that possible association are from the mid-1980s, but several have been conducted more recently [5, 24]. The results of these recent studies are reported in Tables 10.1 and 10.2. Authors mainly focused on the conventional methods (total serum IgE test, skin prick test (SPT), radioallergosorbent test (RAST), search for IgE fragment crystallizable (FC) in fecal extracts, elimination diets, and rechallenges) to diagnose IgE-mediated allergies in patients reporting IBS-like symptoms [5, 25]. The main discrepancy found in these studies is between self-perceived food intolerance and the positive results of diagnostic tests [25]. Two hypotheses were proposed to explain these results: (1) low serum-specific IgE levels and (2) inadequate allergenic preparations used for SPT and ImmunoCAP. These hypotheses would explain the low prevalence of wheat IgE-mediated enteropathy, including food allergy in IBS patients [26].

Inadequacy of the conventional methods (SPT and serum food allergen-specific IgE levels) to identify IgE-mediated responses in IBS patients led us to evaluate the efficacy of flow cytometric cellular allergen stimulation test (FLOW-CAST) in the diagnosis of food allergy in 120 consecutive IBS patients [27]. We concluded that this diagnostic test might supplement or better replace routine allergy tests [27].

The substantial lack of agreement on the role of typical IgE-mediated allergic reactions in IBS pathogenesis has led physicians to explore alternative hypotheses. In particular, hypersensitivity reactions induced by a different antibody class (i.e., IgG) seem to be of some importance (Table 10.3).

10.4.1 IBS and Food Intolerance

Other physicians instead focused nonimmunologic responses to food antigens (i.e., food intolerances), but questionable outcomes have been seen both due to issues surrounding diagnostic tools and difficulties in projecting well-designed dietary trials. Triggers for symptom onset or worsening have been historically identified in caffeine, alcohol, fiber, and fats, although strong evidence is conflicting in some and lacking in most. Correct identification of symptom-inducing foods is difficult to achieve both because meals are 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 [19]. However, most evidence identifies foods as the triggering factors of symptom onset rather than as a cause of the condition [28].

The role of dietary components in inducing IBS symptoms has been better explored, with some studies reporting how certain food components can contribute to causing carbohydrate malabsorption [28, 29]. In the last decade, several authors have approached the study and management of suspected food intolerance in IBS,

Table 10.1 Systemic IgE-mediated allergic response in IBS patients

Authors	Year of publication	Populations	Techniques	Results
Petitpierre M et al.	1985	24 IBS patients, 12 atopic and 12 nonatopic	Total serum IgE test, SPT and RAST to various food antigens, 3-week-long low-allergenic diet followed by open challenge, blind dietary provocation test	Fourteen patients identified one or more foods and food additives able to evoke typical IBS symptoms. Nine of these, all from the atopy group, had elevated total serum IgE and positive SPT, suggesting a systemic IgE-mediated food allergy
Zwetchkenbaum J et al.	1988	10 IBS patients with atopy	SPT and open elimination diet	A significant cutaneous reaction was found in 6, whose symptoms improved on elimination diet. Subsequent rechallenge with the offending food allergens failed to produce IBS symptoms
Barau E et al.	1990	Seventeen children with clinical IBS symptoms	Urinary elimination of lactulose and mannitol in fasting condition then after specific food ingestion (selected on a suggestive clinical history or positive SPT or RAST)	Nine had modification of intestinal permeability; all had a personal and/or family history of allergy and/or high total IgE and responded to food exclusion
André et al	1995	312 food allergy patients diagnosed on history, positive SPT and RAST. 95 healthy subjects	Search of IgE FC in fecal extracts	236/312 food allergy patients (73 %) found positive, whereas none of 95 controls were positive. Subgroup analysis showed that 32/312 patients satisfied IBS criteria; 22 of them (68.8 %) were found to have detectable IgE FC in feces
Bischoff SC et al.	1996	375 adult patients of a gastroenterology outpatient clinic	Preliminary selection by clinical signs of atopic disease, elevated IgE (total and/or specific against food antigens), eosinophilia, and responsiveness to DSCG therapy. Confirmation test by endoscopic allergen provocation and/or elimination diet and rechallenge	32 % of subjects complained of abdominal symptoms as a consequence of an adverse food reaction. 14.4 % of them were suspected of suffering from a food allergy. 3.2 % were confirmed as suffering from food allergy

(continued)

Table 10.1 (continued)

Authors	Year of publication	Populations	Techniques	Results
Dainese R et al.	1999	128 consecutive IBS patients	SPT for foods	80/128 (62.5 %) patients self-reported adverse reactions to foods. SPTs were positive in 67/128 patients (52.3 %). Significant differences were proven between the reported foods and sensitization tests
Soares RL et al.	2004	43 subjects divided in group I (IBS), group II (functional dyspepsia), and group III (healthy controls)	SPT for 9 food allergens	SPT was positive in 19.4 % of group I, 2.3 % of group II, and 4 % of group III, with significant differences between group I and the others. However, none of the volunteers with IBS reported intolerance to any isolated food
Jun DW et al.	2006	105 subjects divided in 3 different groups: IBS treated group, IBS untreated group, and control group	SPT for foods and inhalant allergens	SPT was positive in 38.6 % of treated IBS patients, 16.1 % of untreated IBS patients and 3.3 % of controls ($p<0.01$). The more frequently identified foods were saury, rice, mackerel, buckwheat, sweet potatoes, celery, onions, and trumpet shell; on the contrary, patients reported to be intolerant to dairy products, raw foods, spicy foods, coffee, and alcohol
				Thus, no correlation could be proven between patients' intolerance and SPT results
Uz E et al.	2007	53 C-IBS, 19 D-IBS, and 28 M-IBS and 25 healthy controls	Total IgE, SPT for 11 common allergens, and ECP and eosinophil counts	SPT positivity, mean IgE and ECP levels were higher in patients than in controls, but there was no statistically significant difference among IBS subgroup. Foods rich in dietary fibers, gas-producing agents, or foods containing significant amounts of carbohydrates were the main responsible for SPT positivity

C-IBS constipation-predominant IBS, *D-IBS* diarrhea-predominant IBS, *DSCG* disodium cromolyn glycate, *ECP* eosinophil cationic protein, *IBS* irritable bowel syndrome, *FC* fragment crystallizable, *M-IBS* mixed diarrhea and constipation IBS, *RAST* radioallergosorbent test, *SPT* skin prick test

Table 10.2 Local IgE-mediated allergic response in IBS patients

Authors	Year of publication	Populations	Techniques	Results
Santos J et al.	1999	8 patients with food allergy and 7 healthy volunteers	Jejunal food challenge. Closed-segment perfusion technique was used to investigate the effects on luminal release of tryptase, histamine, prostaglandin D(2), eosinophil cationic protein, peroxidase activity, and water flux	A rapid increase in intestinal release of tryptase, histamine, prostaglandin D(2), and peroxidase activity was found, whereas no increase of eosinophil cationic protein could be detected. Release of these mediators notably increase water secretory response
Arslan G et al.	2002	20 patients (7 patients with food allergy and 13 with food intolerance)	Duodenal mucosa challenge with allergen extracts via a nasoduodenal tube. Endosonography was used to identify the response	Increased mucosal thickness was found in 11 patients, but no significant difference was found between the allergic and the intolerance group
Arslan G et al.	2005	32 patients with chronic abdominal complaints self-attributed to food hypersensitivity/allergy	Duodenal mucosa challenge with allergen extracts via a nasoduodenal tube. External ultrasound was used to identify the response	14 (44%) of the 32 patients had a sonographic response (increased wall thickness, diameter, peristalsis, and/or luminal fluid) after challenge. A positive sonographic response was significantly related to a positive SPT and DBPCFC
Coëffier M et al.	2005	25 patients with food allergy and 14 control patients	Analysis by real-time RT-PCR of the levels of epsilonGT, IL-4, IL-13, IFN-gamma, IL-4Ralpha, STAT6 and FcepsilonRIalpha mRNA on cecum biopsies	EpsilonGT and IL-4 expression were increased in food allergy patients, whereas IL-13, IFN-gamma, IL-4Ralpha, STAT6 and FcepsilonRIalpha were not altered
Lidén M et al.	2008	21 patients with primary Sjogren's syndrome and 18 healthy controls	Rectal challenge with CMP using the mucosal patch technique to measure nitric oxide production and myeloperoxidase release	A post-challenge inflammatory response was identified in 38% of patients as a sign of CMP sensitivity not linked to serum IgE or IgG/IgA antibodies to milk proteins. All CMP-sensitive patients suffered from IBS, diagnosed according to Rome III criteria

CMP cow's milk proteins, *DBPCFC* double-blind placebo-controlled food challenge, *IBS* irritable bowel syndrome, *IL* interleukin, *RT-PCR* real-time polymerase chain reaction, *SPT* skin prick test

Table 10.3 Non-IgE-mediated allergic response in IBS patients

Authors	Year of publication	Populations	Techniques	Results
El Rafei A et al.	1989	25 patients with suspected food allergy	DBPCFC, specific IgG4 and IgE levels dosage	Increased serum IgG4 or IgE levels were found in 63 % of patients with a positive history of food allergy. IgG4 or IgE increased in 91 % DBPCFC-positive patients
Niec AM et al.	1998	7 clinical trials	Meta-analysis	15–71 % response rate to exclusion diet; the most commonly incriminated foods were milk, wheat, eggs, potatoes, and celery. All studies suffered from limitations in their trial designs
Atkinson W et al.	2004	150 IBS patients	Patients received either an elimination diet based on IgG positivity or a sham diet for 12 weeks, excluding the same number of foods but not those to which they had antibodies	IBS symptom severity score showed a 10 % greater reduction in the IgG-based elimination diet. Patients with a greater number of sensitivities, as determined by the IgG test, reported a greater reduction in symptoms
Zar S et al.	2005	25 IBS patients	Analysis of food-specific IgG4 antibody-guided exclusion diet on symptoms and rectal compliance	Patients reported significant improvement in pain severity and frequency, bloating severity, satisfaction with bowel habits, and overall quality of life. Rectal compliance increased significantly, but the thresholds for urge to defecate/ discomfort were unchanged
Zar S et al.	2005	108 IBS patients (52 D-IBS, 32 C-IBS, and 24 M-IBS) and 43 controls	SPT, IgG4, and IgE against common food antigens	IgG4 titers to wheat, beef, pork, and lamb were significantly higher in IBS patients than controls. In addition, IgE titers had no significant difference between the groups, and SPT was positive for only a single antigen in 5 of 56 patients. Authors concluded that no correlation could be found between the IgG4 antibody elevation and patients' symptoms
Drisko J et al.	2006	20 IBS patients	Response to food-specific IgG-based elimination diet	All patients reported significant improvement in symptoms, stool frequency, and quality of life

Zuo XL et al.	2007	37 IBS patients and 20 controls	Serum IgG and IgE antibody titers to 14 common foods	Higher titers for some food-specific IgG antibodies (crab, egg, shrimp, soybean, and wheat) were found in IBS patients, but there was no significant correlation between symptom severity and IgG antibody titers
Guo H et al.	2012	77 D-IBS patients and 26 controls	Preliminary dosage of food-specific IgG, followed by a 12-week IgG-based elimination diet	39 (50.65 %) patients with D-IBS compared with four (15.38 %) controls were positive to food-specific IgG. All symptom scores decreased after elimination diet
Ligaarden SC et al.	2012	269 subjects with IBS and 277 control subjects	Food- and yeast-specific IgG and IgG4 antibodies	After correction for subject characteristics and diet, no significant differences of food-specific IgG and IgG4 antibody levels were found between groups
Aydinlar EI et al.	2013	21 patients with migraine and IBS	Preliminary IgG antibody tests against 270 food allergens. Evaluation of patients at baseline (usual diet), after a first diet (elimination or provocation diets), and after a second diet (interchange of elimination or provocation diets)	Food elimination based on IgG antibodies effectively reduced symptoms with a positive impact on the quality of life

C-IBS constipation-predominant IBS, *DBPCFC* double-blind placebo-controlled food challenge, *D-IBS* diarrhea-predominant IBS, *IBS* irritable bowel syndrome, *M-IBS* mixed diarrhea and constipation IBS, *SPT* skin prick test

looking at FODMAPs with increasing interest, focusing on the effects of a low FODMAP diet [28, 30–34]. More recently, a new clinical entity – non-celiac gluten sensitivity (NCGS) – has burst into this complex "world," and it has been suggested that it may be important in a subgroup of IBS patients [35–37], although contradictory data seem to deny the role of a gluten-free diet in the treatment of these patients [38].

10.5 What Are FODMAPs?

Several studies have explored the changes in dietary composition during the last few decades, in particular how it could have been modified by urbanization. Reports conflict about whether sugar intake has increased, but agree on the same focus point: the proportion of sugar intake made up of fructose is increasing. In this context, the intakes of fruit juices as well as the use of high-fructose corn syrup (which contains 42–55 % fructose) as sweeteners in many manufactured foods seem to play the leading role [39]. However, no direct studies of time trends in fructan ingestion are available, but indirect evidence indicates changes in their consumption patterns. Pasta and pizza intake, major sources of fructans, has increased exponentially, and at the same time, the type of fructans in the diet is changing. Similarly, even if no direct data is available about intake of polyols, it is likely that their use as food additives to produce "sugar-free" products has led to increased consumption [39].

Poorly absorbed, short-chain carbohydrates and polyols (lactose, fructose, and sorbitol) were tested throughout the 1980s and 1990s (especially observational cohort studies), to identify their role as symptom inducer in functional bowel disorders and IBS. Authors agree they act in a dose-dependent manner and that a dietary restriction of all three together could bring symptomatic relief [30, 31, 34]. However, international literature about the biochemistry and physiology of digestion denotes how other carbohydrates are involved in IBS-like symptom onset. Fructo-oligosaccharides (fructans or FOS) and galacto-oligosaccharides (galactans or GOS) are short-chain carbohydrates incompletely absorbed in the human gastrointestinal tract. In particular, patients report worsening of symptoms whenever these sugars are consumed in combination (e.g., lactose with fructans, fructose with sorbitol, etc.), indicating their additive effects [33, 40]. Other potential culprits seem to be incompletely absorbed polyols, i.e., mannitol, maltitol, and xylitol, used as artificial sweeteners, but also found naturally in foods [41]. In 2005, a team of Australian researchers theorized that foods containing these poorly absorbed, short-chain carbohydrates worsen the symptoms of some digestive disorders and coined the acronym FODMAPs, grouping them all together according to their chain length [42]. Characteristics shared by all these short-chain highly osmotic carbohydrates are the poor absorption in the small intestine and the rapid fermentation by gut bacteria. These specific features are responsible for increased gas production, bowel distension, bloating, cramping, and diarrhea – all symptoms of IBS, triggered in association with intrinsic visceral hypersensitivity [43].

FODMAP intake varies across ethnic and dietary groups due to different dietary behavior. Fructose and fructans are most widespread in the North American and Western European diets; therefore, they should be considered the ones to which nearly all patients with IBS are exposed in their everyday diet.

10.6 Possible Mechanisms of FODMAP Triggering of IBS Symptoms

How FODMAPs exert their effects on IBS patients is still uncertain, but some researchers are studying the matter. The poor absorbability of FODMAPs in the small intestine has been considered a possible starting point, as shown using an ileostomy model. Carbohydrates increase water content in the output from the stoma, mainly because of an osmotic effect. This effect could easily explain diarrhea in some individuals [29]. Undseth et al. used magnetic resonance imaging to study the osmotic effect of FODMAPs by the analysis of small bowel water content (SBWC). Fructose, lactulose, inulin, or mannitol meals but not a glucose meal increase water content in patients suffering from D-IBS but not in healthy volunteers [44].

Other authors focused on gas production after FODMAP fermentation in the gut. Ong et al. designed a single-blind, crossover, short-term, interventional study to assess gas production during low and high FODMAP diets in IBS patients and healthy volunteers. The high FODMAP diet produced higher levels of breath hydrogen in both groups; interestingly, IBS patients were found to have higher levels during each dietary period than the controls. The latter reported just increased flatus production on a high FODMAP diet, whereas IBS patients complained of rapid onset of gastrointestinal symptoms and lethargy. Conversely on a low FODMAP diet, breath hydrogen production (and consequently symptom score in IBS patients) was reduced both in healthy volunteers and in patients. This study confirms the additive bacterial fermentative nature of the short-chain carbohydrates (with production of short-chain fatty acids [SCFA], including butyrate, and gases such as carbon dioxide, hydrogen, and in some people methane) and their role in causing gastrointestinal symptoms [33]. In the context of bacterial fermentation, Brighentini et al. found that the speed of hydrogen production is inversely proportional to FODMAP chain length [45], and Clausen et al. indicated the fermentative rather than osmotic effect of short-chain carbohydrates after entering the colon [46].

Another research line points to FODMAP effects on gastrointestinal motility [47]. To assess such effects on gastrointestinal motility, Madsen et al. evaluated 11 healthy volunteers in a double-blind crossover investigation. The subjects ingested a glucose solution or a mixture of fructose and sorbitol, in random order, marked with (99m) Tc-diethylenetriaminepentaacetic acid. The mouth-to-cecum transit of the radiolabeled marker was faster, and the percentage content of the marker in the colon was higher after ingestion of the fructose-sorbitol mixture than after ingestion of glucose [48]. Both the osmotic effect of FODMAPs and a contemporary activation of neural feedback pathways and/or hormonal changes from SCFA production, secondary to FODMAP bacterial fermentation, might be responsible for this increased gut motility [49].

In addition, in animal models (rats), fructo-oligosaccharides were responsible for injury of the colonic epithelium and increased intestinal permeability [50].

FODMAP ingestion effects go beyond the gastrointestinal tract, being responsible for systemic effects. Mild depression has been reported in women with IBS, after fructose and lactose intake [51], improving when free fructose is eliminated from the diet.

FODMAPs also affect the intestinal flora of these patients. Patients with IBS have fewer *Lactobacillus* spp. and *Bifidobacterium* spp. in their intestinal flora than healthy individuals. These bacteria bind to epithelial cells, inhibit pathogen adhesion, and enhance barrier function; in addition, they do not produce gas upon fermenting carbohydrates, an effect which is amplified as they also inhibit *Clostridium* spp. growth. Bacteria such as *Clostridium* spp. break down FODMAPs, induce gas production, and cause large intestine distension, with abdominal discomfort and pain [52].

All this evidence could lead us to think that all the different carbohydrates making up the large family of FODMAPs have similar physiological effects and therefore should be considered together. That is true only to a limited extent. Although all exert an osmotic effect, this varies according to the molecular weight and rapidity of absorption of the specific carbohydrate. Absorption across the small intestinal wall varies according to the dose and speed of intestinal transit and for fructose the luminal glucose content (glucose facilitates fructose absorption) and individual absorptive capacity via fructose-specific transporters. Thus, fructose and polyols have a greater osmotic effect than fructans and galacto-oligosaccharides, whereas their luminal concentration will fall more distally because of their slow absorption as opposed to no absorption for oligosaccharides. Conversely, oligosaccharides will have greater fermentative effects since they are not absorbed [53].

These hypotheses are consistent with current knowledge of IBS pathogenesis, among which, visceral hypersensitivity is the most important. Gut distention, due to increased gas production and other mechanisms, abnormally stimulates the enteric nervous system, which reacts by altering its motility patterns. The brain analyzes such changes and interprets them as bloating, discomfort, and pain. Dietary components that could stimulate this mechanism should have the following features: (a) poorly absorbed in the proximal small intestine, (b) composed of small molecules (i.e., osmotically active), (c) rapidly fermented by bacteria (potentially they should be fermented both by small intestinal and cecal bacteria, expanding, at the same time, the bacterial population, i.e., a "prebiotic" effect), and (d) associated with hydrogen production. All these seem to describe dietary FODMAPs. In others words, to better highlight an abovementioned concept, FODMAPs do not cause IBS [30], but represent possible triggers for symptom onset, and their intake reduction might reduce patient complaints.

10.7 Low FODMAP Diet Benefits for IBS Patients

Diets based on fructose, with or without sorbitol, and lactose restriction, have been used for a long time, in the management of patients suffering from functional gut symptoms and IBS. Unfortunately, conflicting results have been reported in

literature [30, 31, 34]. The very limited success of this approach is the probable cause of the slow spread of this kind of diet. Noteworthy, limited FODMAP restriction ignores the evidence that there is potentially a great amount of FODMAPs in the everyday diet, all of which have similar end-effects in the bowel. Recently, authors have embraced the "FODMAP concept" or approach: a global FODMAP restriction should have a far greater and more consistent effect than a limited one. Thus, reduction of the intake of all poorly absorbed short-chain carbohydrates should be more effective in preventing luminal distension (and consequently symptom onset) than merely concentrating on one of these [54].

A research trial designed as a retrospective uncontrolled audit by Shepherd et al. was the first to confirm the role of a low FODMAP diet in managing gastrointestinal complaints. Patients with IBS and fructose malabsorption underwent a low fructose/fructan (and polyol, if the patients noted symptom induction) diet. Seventy-four percent of patients reported abdominal symptom improvement, with a durable efficacy closely related to dietary compliance. However, this study suffers from a significant weakness in its retrospective approach that greatly undermines its reliability, especially in a field where "placebo effect" is particularly widespread [34]. To resolve this issue and prove the efficacy of a low FODMAP diet, the same author designed 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). Twenty-five patients with IBS, who had documented fructose malabsorption as well as a previously demonstrated durable (3–36 months) symptomatic response to reduction of dietary FODMAPs, were enrolled in the study. Abdominal symptoms recurred in 70–80 % of patients, in a dose-dependent way, when fed with pure forms of FODMAPs, especially with fructose plus fructans; this proved an additive effect, especially if compared to 15 % complaining of the same abdominal symptoms when fed a similar diet spiked with placebo [28]. Although conducted according to the strictest scientific rules, this study has the weakness of being carried out in a single center in Australia. This specific feature has made other studies necessary to confirm these preliminary observations.

In 2012, Staudacher et al. performed a randomized, controlled, non-blinded trial in 41 United Kingdom patients with IBS. Physicians investigated the effects of fermentable carbohydrate restriction on gastrointestinal symptoms, luminal microbiota, and SCFA. Patients were randomly assigned to intervention diet or habitual diet group for 4 weeks. Patients in the intervention group more frequently reported symptom reduction compared with controls. In addition, even though the total luminal bacteria at follow-up did not differ between groups, when adjusted for baseline, the intervention group had lower concentrations of bifidobacteria. Finally, no difference in total or individual fecal SCFA could be found between groups. Unfortunately, this study also had several other weaknesses: small sample size, use of a "habitual" diet, which varied from patient to patient, the lack of a standardized low FODMAP diet, and differences in patient-provider contact time [40]. In 2014, going back to Australia, a randomized, placebo-controlled, single-blind, crossover study, evaluated the effect of different diets in a group of 30 patients with IBS and 8 healthy

individuals. Subjects were randomly assigned to groups receiving 21 days of either a diet low in FODMAPs or a typical Australian diet, followed by a washout period of at least other 21 days, before crossing over to the alternate diet. IBS patients effectively reduced symptoms on the low FODMAP diet. Noteworthy, with no difference in IBS subgroup, patients reported the greatest symptom improvement within the first 7 days. No significant changes were found between diets in healthy controls. Although better designed than prior studies, the crossover design, the use of a "typical" Australian diet, and the small sample size make it difficult to apply the results of this study to all IBS patients [32]. In the same period, Pedersens et al. conducted a randomized, controlled, unblinded trial in 123 IBS patients [55]. Patients underwent one of the following diets for 6 weeks: low in FODMAPs, high *Lactobacillus rhamnosus* GG, and a normal Danish/Western diet. At week 6, a statistically significant reduction in the IBS severity score system was observed in the low FODMAP group and *Lactobacillus rhamnosus* GG group compared to the normal Danish/Western diet group. However, adjusted linear regression analysis showed a statistically significant improvement of IBS severity score in the low FODMAP diet group vs. normal Danish/Western diet group, but not in *Lactobacillus rhamnosus* GG group vs. normal Danish/Western diet group. Finally, quality of life was not significantly altered in any of the three groups. Analysis of IBS subgroups showed the results were significant for the D-IBS and M-IBS subtypes, but not for the C-IBS subtype, in both low FODMAP and *Lactobacillus rhamnosus* GG treatment groups. The unblinded design and absence of both a placebo capsule group and a standardized preprepared low FODMAP diet make it difficult to interpret this study [56].

Other studies comparing effects of a low FODMAP diet to normal diets are reported in Table 10.4.

10.8 Diagnosis of FODMAP "Malabsorption"

The clinical and pathophysiological features of FODMAPs are not yet clear, and the difficulty of establishing a diagnosis of FODMAP malabsorption is even more trying. Usually, after an accurate clinical history, including dietary and lifestyle assessment, with a focus on potential food intolerance, patients undergo clinical investigations in accordance with local/national guidelines. The most frequently required investigations are blood and fecal tests, endoscopy and/or radiological imaging to rule out any organic disease. In the absence of organic disease or food allergy, patients are diagnosed as suffering from a functional gastrointestinal disorder. Unfortunately to date diagnosis of food intolerance in most areas is still impossible, and only a few tests are clinically useful to identify specific food intolerance. Breath hydrogen levels provide a reliable measure of sugar absorption. A significant rise in breath hydrogen following test sugar intake demonstrates poor absorption with subsequent fermentation by intestinal microflora [57]. Positivity to a breath test could allow the identification of carbohydrates responsible of symptom onset and whose exclusion from the diet could reduce intestinal discomfort. In contrast, a

Table 10.4 FODMAP diet comparative studies

Authors	Year of publication	Study design	Populations	Intervention	Results
Staudacher HM et al.	2011	Nonrandomized comparative study	82 consecutive patients with IBS	Standard (i.e., National Institute for Health and Clinical Excellence, NICE, dietary guidelines, which include either use of probiotics or exclusion diets or increasing fiber intake or decreasing fiber intake) versus FODMAP dietary advice	To assess symptom reduction, all the patients compiled specific standardized questionnaires, which pointed out more satisfaction in the low FODMAP group, with significant improvements in bloating, abdominal pain, and flatulence
Chumpitazi BP et al.	2015	Double-blind crossover intervention	35 children with Rome III IBS	Patients were randomized, after a 1-week baseline diet period, to a low FODMAP diet or typical American childhood diet, followed by a 5-day washout period before crossing over to the other diet	Compared to baseline, children had fewer daily abdominal pain episodes on a low FODMAP diet and more episodes on the typical American childhood diet. Children who responded to the low FODMAP diet would have a different microbiome composition and associated microbial metabolic capacity compared to those who did not respond
Ong DK et al.	2010	Single-blind crossover intervention	15 IBS patients and 15 healthy subjects	Low (9 g/day) or high (50 g/day) FODMAP diet for 2 days	In IBS patients, the high FODMAP diet increased gastrointestinal symptoms and lethargy, whereas in healthy volunteers only flatus production increased. Both groups had increased production of breath hydrogen on a high FODMAP diet, but IBS patients had higher levels than the controls. Breath methane did not increase in patients with IBS on the high FODMAP diet, but was reduced in healthy subjects

(continued)

Table 10.4 (continued)

Authors	Year of publication	Study design	Populations	Intervention	Results
De Roest RH et al.	2013	Prospective observational study	90 IBS patients	Dietary advices regarding the low FODMAP diet	All the patients experienced a beneficial effect in symptom control; in particular larger symptomatic improvement was proven in subjects with fructose malabsorption compared to the others
Mazzawi T et al.	2013	Prospective observational study	46 IBS patients	Dietary advices regarding the low FODMAP diet	Patients had to complete 4 questionnaires prior to and 3 months after receiving a dietary interview. IBS symptom score decreased once the patients had received dietary guidance. The total score for quality of life increased significantly after dietary guidance sessions. No statistical differences were pointed out in calories, carbohydrate, fiber, protein, fat, or alcohol intake following the dietary interview. Consumption of certain fruits and vegetables that were rich in FODMAPs, as well as insoluble fibers, decreased
Pedersen N et al.	2014	Prospective observational study	19 IBS patients	Six weeks free diet followed by 6 weeks low FODMAP diet	Patients were asked to record their symptoms on a web application. A significant improvement in disease activity was observed during both the control and low FODMAP diet periods, IBS quality of life changed significantly only during the second
Huamán JW et al.	2015	Prospective observational study	30 IBS patients	Low FODMAP diet for 2 months	At the end of the study period, more than 70 % of patients reported a positive impact of the low FODMAP diet in controlling overall symptoms and specific symptoms, such as functional abdominal bloating, flatulence, abdominal pain, diarrhea, and fatigue. By contrast, constipation was controlled in only 48 % of patients

Ostgaard H et al.	2012	Retrospective observational study	36 IBS patients, 43 IBS patients who had received dietary guidance 2 years earlier, and 35 healthy controls	Dietary advices versus free diet	IBS patients voluntarily avoided certain foods, some of which belong to FODMAPs, but at the same time, they had a higher consumption of other foods rich in FODMAPs. In addition, they avoided other foods that are crucial for their health. The group of IBS patients who had received dietary advices avoided all FODMAP-rich foods, consumed more foods with probiotic supplements, and did not avoid food sources that were crucial to their health. These patients, compared to unguided IBS patients, had improved quality of life and reduced symptoms
Zubek J et al.	2012	Case series	40 IBS patients who underwent low FODMAP diet	Low FODMAP diet for 4–12 weeks	Patients reported a statistically significant reduction for bloating, abdominal pain, and diarrhea
O'Meara C et al.	2013	Case series	27 symptomatic IBS patients	Instruction on avoidance of dietary FODMAPs and individually tailored nutritional advices	14/27 patients were revalued after receiving dietary advices; 13/14 had satisfactory relief of global IBS symptoms; 10/12 patients reported an improvement in abdominal pain; 13/14 an improvement in bloating; 11/12 an improvement in flatulence; 10/13 an improvement in fecal urgency
MCgeoch V et al.	2014	Case series	80 IBS patients on low FODMAP diet	Low FODMAP diet	46/80 patients were enrolled (other patients did not present at follow-up visit); patients reported a lower incidence of each IBS symptom. The biggest improvements were reported for bloating (93%) and flatulence (92%)

(continued)

Table 10.4 (continued)

Authors	Year of publication	Study design	Populations	Intervention	Results
Rao SS et al.	2015	Systematic review	Adult patients with IBS on low FODMAP diet	NA	Authors found only 6 eligible studies on FODMAP-restricted diets, whose heterogeneity and methodological quality did not allow them to perform a meta-analysis. Overall IBS symptoms improved in 4/4 studies, C-IBS symptoms in 1/3 studies, and 3 studies did not meet inclusion criteria
Marsh A et al.	2015	Meta-analysis	Adult patients with IBS on low FODMAP diet	NA	A significant decrease in IBS symptom severity scores and increase in IBS quality of life scores was found for individuals on a low FODMAP diet in RCTs and nonrandomized interventions. In addition, a low FODMAP diet significantly reduced severity of both overall symptoms and specific symptoms such as abdominal pain and bloating in the RCTs. Similar results were pointed out in nonrandomized interventions

C-IBS constipation-predominant IBS, *IBS* irritable bowel syndrome, *RCT* randomized controlled trials

negative breath test proves complete absorption of the sugar suggesting that intake of that specific carbohydrate should not influence patient symptoms. Therefore, breath hydrogen testing to define absorption of a fructose and/or lactose load is very useful as it can reduce the extent of the necessary dietary restriction [57]. Routinely, to diagnose FODMAP malabsorption, fructose (testing dose of 35 g), lactose (testing dose of 25–50 g), and sorbitol (testing dose of 10 g) breath tests are performed. Nevertheless, physicians should remember that there are three other FODMAPs (fructans, galactans, and mannitol) acting as potential triggers of IBS symptoms. No specific breath test is available for fructans and galactans, since they are always malabsorbed and fermented, whereas mannitol breath test is rarely performed, as it is not a widespread component in the diet and can be investigated as a trigger through simple dietary elimination and rechallenge [57].

However, breath tests have a moderate degree of false positivity. As an example, IBS patients suffering from SIBO, diagnosed by lactulose breath test, a reliable and noninvasive test for the diagnosis of this condition, might have falsely abnormal breath tests for fructose, lactose, and sorbitol [58].

10.9 Tables of the FODMAP Content of Foods: Strengths and Weaknesses

A number of studies offer more specific knowledge about food composition, in particular, FODMAP content, which allows us to better modify the dietary regimens of IBS patients. The broader range of FODMAPs, including FOS, GOS, and mannitol, in addition to fructose, lactose, and sorbitol, forces us to avoid all these carbohydrates in low FODMAP diets, with elimination of an extended spectrum of foods. Such large restrictions are required to publish tables of food composition on fruits, vegetables, breads, and cereals [59]. The impact of dietary modification of FODMAPs can have on functional gut symptoms should shift the focus to the possibility of simply and accurately assessing FODMAP intake in individuals and specific populations. In this context, administration of food frequency questionnaires (FFQs) is a simple and useful assessment. The Monash University Comprehensive Nutrition Assessment Questionnaire (CNAQ), a 297-item comprehensive, semi-quantitative FFQ, has shown its efficacy in estimating intake of macro- and micronutrients, FODMAPs, and glycemic index/load, in an Australian population. Barret et al. validated this FFQ proving how this tool allows patients to identify a wide range of low FODMAP foods and manage their IBS with less restrictive diets [60].

One of the most important limits to the spread of a low FODMAP diet is the development of tables assessing FODMAP-rich and FODMAP-poor foods. To date, published lists of food composition report only a limited description of FODMAP content. The recent development of FODMAP content measuring methodologies, together with a systematic examination of fruits, vegetables, and cereals, partially overcome this issue. However, the strongest limitation is the absence of a unique and widely approved cutoff level indicating a food as “high” or not in FODMAPs. This is further complicated by the direct relationship between the total amount of

FODMAPs ingested and whether symptoms will be induced or not. Several studies have tried to assess possible cutoff levels to avoid symptom induction [34, 59]. The preliminary results hint that the total dose for therapeutic benefit in IBS population should be less than 0.5 g FODMAPs per sitting or less than 3 g FODMAPs per day. Unfortunately, CNAQ showed that these values are considerably lower than the amount obtainable through a strict diet [34].

10.10 Practical Low FODMAP Diet Management

The efficacy shown by a low FODMAP diet allows its use as a potentially effective treatment option for IBS patients, under the monitoring of an expert dietitian. A preliminary step, because of the variability of response to diet and the possible coexistence of a food allergy, is to identify the predictors of both of these different conditions. Reports of atopic history, symptoms related to mast cell activation, or concurrent systemic manifestations, such as urticaria or asthma, should direct our focus to an IgE-mediated food allergy.

Considering the different nature of each FODMAP, it is not surprising that not all of these carbohydrates will be symptom triggers for all patients. Malabsorbed FODMAPs due to altered gut flora, visceral hypersensitivity, and motility disorders, typical of IBS patients, are the ones most likely to play a major role in inducing symptoms [33]. Noteworthy, fructans and galactans are always malabsorbed and fermented by intestinal microflora. The remaining FODMAPs will induce symptoms only in the proportion of IBS patients that malabsorbs them. In this regard, lactose and fructose malabsorption in white IBS patients is estimated to be 25 % and 45 %, respectively [30]. Finally, polyols are incompletely absorbed, but their low amounts found naturally in foods as well as in sugar-free products and medications is usually well tolerated in most people [30].

Breath tests should be considered useful diagnostic tools helping physicians to implement personalized specific low FODMAP diet, but they cannot be considered mandatory. Where breath tests cannot be performed, a trial of a full low FODMAP diet can be conducted, followed by challenge with each carbohydrate (fructose, lactose, sorbitol, and mannitol) initially avoided. As a final step, small amounts of fructans and galactans may be tested to assess the level of tolerance, even though they are associated with gas-induced symptoms, even in healthy subjects [33].

Nowadays, the low FODMAP diet has been mainly evaluated as a dietician-delivered diet. A one-to-one patient-dietitian setting, together with the use of written educational material and recipe books, has been used, but some group education sessions have been tested with apparent success and cost reduction [61].

Noteworthy, some patients report using instructions and diet sheets by themselves to manage their symptoms. Physicians should be cautious of this approach, discouraging patients to continue without a dietician's consultation, due to the lack of sufficient ad hoc studies and the possible dietary self-induced imbalance. Rao et al. tried to create a systematic approach to patients at the first consultation. (1) Define patient's lifestyle and alimentary behavior. Physicians should address

patients with direct questioning and ask them to compile pre-completed food record diaries (for at least a 7-day period). This approach allows the identification of daily FODMAP intake. (2) Explain the scientific basis of FODMAP physiopathology in IBS. Patients must be aware of the role of FODMAPs to increase the likelihood of lasting diet compliance. (3) Provide specific dietary instructions. (4) Discuss techniques to avoid unintentional FODMAP intake. Patients often report great difficulty handling situations where food preparation cannot be controlled. (5) Instruct patients about the need for a strict and long-term diet. Patients sensitive to FODMAPs often observe symptom improvement within the first week of a restricted diet. However, it has been found that there is a clear increase in efficacy over the first 6 weeks, so it is recommended to attempt strict adherence for at least 6–8 weeks. If the diet has shown little efficacy after 8 weeks, it may be discontinued [62].

These preliminary steps allow physicians to assess symptom response on a strict FODMAP diet. Obviously such a limited diet cannot be continued for long; thus, it should be a must to define individual tolerance. Single carbohydrate reintroduction allows this process ensuring maximum variety in the diet, to avoid overrestrictions and reduce the risk of nutritional inadequacy. Rechallenge must be taken separately for each carbohydrate with food as simple as possible to avoid overlaps. Whenever patients report inadequate response to the diet, specific questioning is required to determine the adherence and modify any deficiency. If adherence is indicated, attention should be paid to reduce intake of resistant starch and both insoluble and soluble fiber [43].

Adherence to a low FODMAP diet has been found to be relatively high, in particular after adequate instruction. Unwillingness to undertake dietary recommendations, difficulties accessing and increased expense of wheat-free foods, and dislike of the taste represented the main barriers to adherence [34].

10.11 Limitations and Potential Concerns of the Low FODMAP Diet in IBS Patients

The presented data show that a low FODMAP diet could lead to symptom control in specific subclasses of IBS patients, but it is far from being effective in all of them. Foods represent just the trigger of symptom onset, and since diets do not influence the pathophysiological substrate of IBS, intermittent symptoms remain in many patients, albeit at a tolerable level [32].

Requiring further and better definition is the security of long-term low FODMAP diets; such a restrictive diet is at risk of being nutritionally inadequate. In this context, some preliminary data come from Staudacher et al. who reported that a strict 4-week-long low FODMAP diet reduced total carbohydrate intake, including both total sugars and starches; however, total energy, protein, fat, and non-starch polysaccharide levels did not change. In addition, authors found a reduction of total calcium intake in patients following a restricted diet for more than 4 weeks [40]. However, a restricted low FODMAP diet should not compromise nutritional adequacy, eliminating whole categories of food. Expert dietician

consultation is important in food substitution with suitable alternatives from the same food group. The greatest difficulties are with legumes (including chickpeas, baked beans, red kidney beans, and lentils), since these all contain fructans and galactans. Fortunately, in a low FODMAP diet, foods such as seeds, nuts, and quinoa are encouraged, as well as eating legumes in small amounts [43]. As reported by Staudacher et al. [40], reduction in fiber intake might be a consequence of the restriction of wheat-based products, so patients should be advised, as part of dietary counseling, to ensure adequate intake of resistant starch and non-starch polysaccharides. In addition, FODMAPs (particularly oligosaccharides, such as inulin) are prebiotic, increasing growth of bacteria with known health benefits (especially *Bifidobacterium* spp.), and precursors for SCFA production, known to be important for colonic health. Thus, it is likely that a low FODMAP diet would counteract the prebiotic actions of FODMAPs and reduces SCFA production [59]. In this context, 26 IBS patients and 6 healthy subjects were randomly allocated in one of two dietetic regimens differing only in FODMAP content and then crossed over after a washout period. Participants collected a 5-day fecal sample during their habitual diet and after 17 days of a low FODMAP diet and Australian diet. Analysis of stool found greater microbial diversity, reduced total bacterial abundance, higher fecal pH, but similar SCFA concentrations during the low FODMAP diet compared with the Australian diet. Prebiotic bacteria, namely, *Bifidobacterium* spp., concentrations were similar in the two diets, but total bacterial abundance decreased on low FODMAP diet. On the contrary, the Australian diet increased relative abundance of butyrate-producing *Clostridium* cluster XIVa and mucus degrading-associated *Akkermansia muciniphila* and reduced mucus degrading-associated *Ruminococcus torques*. This study indicates that FODMAP reduction is not "antiprebiotic." Noteworthy, even if no reduced prebiotic effect by FODMAPs was found, there was a reduction in total bacterial abundance. The functional and health implications of such changes need further studies, to exclude possible adverse effects in the long term [63]. Hence, it is important to emphasize that patients receiving this dietary restriction should be monitored for long-term effects on health, and more data are needed regarding benefits vs. harms [58].

For all the abovementioned reasons, a strict long-term low FODMAP diet must be discouraged. Reintroduction of FODMAP foods should be instituted as soon as possible after achieving a good symptomatic response. This will allow identification of the cutoff level of food restriction that each patient requires to adequately control symptoms without encountering nutritional imbalances [42].

10.12 IBS and NCGS

Having assessed the role of food as a possible trigger for symptom onset in IBS patients, we must recognize a role of primary importance for wheat, the basis of most popular diets in the Western world [35–37, 64]. Several reasons have been proposed to explain its role as symptom inducer: (1) high fructans content, as

member of the family of FODMAPs; (2) autoimmune disorder trigger; and (3) high IgE and non-IgE-mediated allergenicity.

Extending the perspective over the longtime encoded disorders, researchers' attention is shifting to non-celiac gluten sensitivity (NCGS) [65].

The NCGS is a syndrome characterized by intestinal and extraintestinal symptoms related to the ingestion of gluten-containing food, in subjects that are not affected by either celiac disease (CD) or wheat allergy (WA) [37, 64, 65]. In 2013, Biesiekierski et al. tested 37 subjects with IBS, based on Rome III criteria, and NCGS. Authors aimed to investigate if IBS symptoms were related to gluten intake rather than FODMAPs. Participants were randomly assigned to groups given a 2-week gluten-free and reduced FODMAP diet and were then placed on a high-gluten diet (16 g/day), a low-gluten diet (2 g/day), or placebo diet (no gluten), for 1 week. After a washout period of at least 2 weeks, patients were randomized to the second arm and, then, again after a 2-week-long washout period, to the third arm. During the diet challenges, a visual analogue scale was used to assess symptoms. Twenty-two participants then crossed over to groups given gluten or control diets for 3 days. In all participants, gastrointestinal symptoms consistently and significantly improved during reduced FODMAP intake, but significantly worsened when their diets included gluten or whey protein. However, gluten-specific effects were observed in only 8 % of participants, and the worsening of symptoms across dietary arms was thought to be due to stress put on the patients due to the need for frequent clinic visits rather than due to diet differences [38]. According to these results, the authors concluded that NCGS does not exist and that the symptoms in the self-reported gluten-sensitive patients were due to the FODMAP content in the wheat. However, looking at the study's supplemental file, it emerged that among 149 patients initially recruited, only 40 were included in the study, and more than two-thirds of the patients were excluded since they had the DQ2 or the DQ8 alleles or an increase in duodenal mucosa lymphocytes. It is well known that both of these are very frequent characteristics in NCGS patients. By excluding these patients, the Australian colleagues introduced a selection bias, and we suggest that they have studied another kind of NCGS patients, preselecting only those without any immunologic activation [38].

In NCGS, patients complain of IBS-like symptoms, often related to extraintestinal manifestations, which disappear on a gluten-free diet. This evidence, however, has not eliminated all doubts about what is actually responsible for the clinical manifestations of this new disease (gluten or other components of wheat), thus we suggested the term "non-celiac wheat sensitivity" (NCWS) [66]. With a prevalence ranging from 0.55 % to 6 % of the general United States population, NCWS represents an extremely widespread problem [65]. Usually, it affects females (male to female ratio ranging between 1:2.5 and 1:4) [37, 65] in the third-fourth decades of life [37].

Unfortunately, to date physicians have not managed to identify a specific marker for this disease, so it is mainly defined by "negative" criteria: (1) lack of the key CD criteria (e.g., autoimmunity and histology), (2) no evidence of IgE-mediated wheat allergy, and (3) response to wheat elimination diet (implemented in a blinded fashion

to avoid a possible placebo/nocebo effect) [64, 67]. Clinical manifestations usually occur soon after wheat ingestion, improving or disappearing (within hours or few days) on gluten elimination diet and relapsing following its reintroduction. Gastrointestinal disorders and systemic manifestations are complexly weaved in NCWS, but they can also occur separately [36, 64]. Gastrointestinal involvement consists of IBS-like symptoms, such as abdominal pain, bloating, and bowel habit abnormalities, whereas systemic manifestations are extremely variable: fatigue, foggy mind, headache, depression, joint and muscle pain, leg or arm numbness, dermatitis (from skin rash to eczema), anemia, and several others [37, 65]. The very frequent presence of extraintestinal symptoms is an important argument to exclude FODMAPs as the cause of NCGS. Furthermore, as a confirmation of a prevalent or exclusive immunologic pathogenesis of NCGS, there is the recent evidence that higher proportions of patients with NCWS develop autoimmune disorders (mainly Hashimoto's thyroiditis), have an elevated frequency of antinuclear antibodies (ANA) in the serum, and showed DQ2/DQ8 haplotypes compared with patients with IBS [68].

In any case, NCWS pathogenesis is still largely undetermined and debated [64]. Proposed pathogenic mechanisms are (1) non IgE-mediated wheat allergy [37, 65], (2) activation of the innate immunity mechanisms by amylase-trypsin inhibitors (ATIs) [65], and (3) gastrointestinal neuromuscular abnormalities induced by the gliadin, leading to smooth muscle hyper-contractility and indirectly to increase in luminal water content [69]. At the current level of knowledge, researchers agree that there is a reasonable overlap between NCWS and IBS, and NCWS and IBS patients might easily crossover.

10.13 Low FODMAP Diet or Gluten-Free Diet in NCWS? This Is the Question

The coexistence of gluten and fructans in wheat has recently raised the question of which of the two evidence-based dietary approaches, gluten-free diet or low FODMAP diet, physicians should advise to IBS patients [59]. A consistent number of patients increasingly recognize an association between gut symptoms and/or fatigue and ingestion of wheat products, such as pasta and bread. An Australian survey of 1,184 IBS adults reported that 8 % avoid wheat or consume a gluten-free diet to relieve their symptoms [70].

Even if a low FODMAP diet, being more restrictive, offers a higher chance of symptomatic response, a gluten-free diet could remove a specific pathogenic factor. To date, no consensus has been reached. A gluten-free diet might be used if the clinic is geared toward an exclusion diet followed by DBPC rechallenge, especially in patients with biomarkers suggesting gluten-related relevant pathogenic events: circulating antibodies to whole gliadin, high in vitro basophil activation, increased fecal eosinophil cationic protein and tryptase, and increased duodenal IEL density (>25/100 enterocytes) with or without eosinophil infiltration. Non-responder subjects should be tested with a low FODMAP diet. Alternatively, a low FODMAP diet might be used as the first approach, and in those with insufficient response, gluten

could be removed as the second step. If an adequate response occurs, then non-wheat-based FODMAP intake can be cautiously increased [53].

Conclusion

Emerging evidence argues with increasing insistence for the role of food intolerance in the management of IBS symptoms. Food components should be considered not as etiological elements of IBS, but as symptom triggers. Thus, changes in dietary intake might allow consistent improvement in symptoms and quality of life even if they do not represent a cure and don't influence the pathogenic mechanisms. To date, physicians are focusing on the role of a low FODMAP diet in symptom improvement in many patients suffering from IBS. The increasing evidence for this dietary approach supports the hypothesis that it should be the first dietary modification in patients suffering from IBS. However promising, this dietary approach still leaves many questions unanswered, including the evaluation of possibly significant nutritional concerns. This point must be stressed, and patients should be discouraged from undertaking a low FODMAP diet without adequate support from a dietitian. To further complicate the extended framework of IBS triggers, there are many other food components besides carbohydrates worthy of being studied. Among these, dietary fats might change visceral hypersensitivity, whereas naturally occurring chemicals, widespread in foods, could interact with gut receptors or have direct actions on the enteric nervous system and mast cells. Finally, the role of wheat and gluten in IBS is far from being completely understood, and physicians should always consider the possible use of a sequential dietetic approach (low FODMAP/gluten-free diet).

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