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Consensus document on exclusion diets in irritable bowel syndrome (IBS)

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This consensus document is being published simultaneously into Spanish and English language in The Spanish Journal of Gastroenterology (Revista Española de Enfermedades Digestivas) and into English language in Nutrición Hospitalaria because of its special interest.

ABSTRACT

This paper summarizes the contents of a consensus document on exclusion diets in irritable bowel disease that was developed by a task force from SEPD, FEAD, SENPE, FESNAD, SEÑ, SEEN, SEGHN, SEDCA and ADENYD. The complete document is available at the FEAD and in SENPE websites.

Irritable bowel syndrome is a highly prevalent functional digestive disorder where, in addition to drugs, therapy includes diet and acquisition of healthy habits as basic elements for its control. In order to facilitate dietary counseling for these patients in daily practice, the present consensus document on the role of exclusion diets was developed. To this end, consensus opinions were collected from various experts in the national scientific societies aiming at establishing recommendations applicable to the health care of patients with irritable bowel syndrome.

Key words: Consensus document. Irritable bowel syndrome. FODMAP. Gluten. Lactose. Education for health. Exclusion diets.

INTRODUCTION

Irritable bowel syndrome (IBS) is a condition that has become highly relevant in our healthcare setting. This is due to its high prevalence among the population, chronic nature, deep impact on patient life, and lack of curative treatment. It is precisely this latter fact that explains why patients with IBS receive various therapies on an ongoing basis. Because of this, patients and their practitioners seek strategies to control IBS symptoms, which often include modifications of dietary habits. Diets that exclude selected foods are increasingly used, and some of them are radical in that they involve basic components of our dietetic pattern. Not always are these diets accurate, evidence-based, or adequately monitored. Exclusion diets must be used both prudently and only when indicated since they may have a detrimental impact on nutritional and health status.

Because of the above, the Fundación Española de Enfermedades Digestivas (FEAD), together with the Federación Española de Sociedades de Nutrición, Alimentación y Dietética (FESNAD), have favored the development of a joint, consensus document on exclusion diets in the setting of IBS. This consensus document has been jointly written by several scientific societies (Sociedad Española de Patología Digestiva [SEPD], FEAD, Sociedad Española de Nutrición Clínica y Metabolismo [SENPE], FESNAD, Sociedad Española de Nutrición [SEÑ], Sociedad Española de Endocrinología y Nutrición [SEEN], Sociedad Española de Gastroenterología, Hepatología y Nutrición Pediátrica [SEGHN], Sociedad Española de Dietética y Ciencias de la Alimentación

[SEDCA] y Asociación de Enfermeras en Nutrición y Dietética [ADENYD]), which have provided their specific outlook and knowledge. It is addressed to all practitioners involved in the health care of patients with IBS, including Primary Care physicians, nutritionists, gastroenterologists, pediatricians, etc. An easily readable format was also sought to render the paper useful in clinical practice, providing a clear view on who should receive exclusion diets, how and when, in the setting of IBS. Recommendations included in the present consensus document are based on current understanding and expert consensus reports as identified in the references. We are confident that this paper will clarify concepts and improve the management of IBS patients by applying objective criteria for the exclusion of lactose, gluten, or FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) from the diet.

BIOLOGICAL BASIS OF FOOD EXCLUSION IN IRRITABLE BOWEL SYNDROME

The gastrointestinal (GI) tract processes 8 to 9 l of fluid/day with a reabsorption efficiency of 98%, so that merely 100 to 200 ml are passed in the feces. The bowel also extracts nutrients, vitamins, and minerals from ingested food, excluding antigens and microbes, and excretes waste materials as a result of a special molecular architecture combined with regulatory mechanisms that involve the autocrine, luminal, paracrine, immune, neuronal, and endocrine systems.

The intestinal mucosal barrier includes the luminal surface with commensal microbiota and a mucus layer over 100 μm thick, the columnar epithelium and underlying extracellular matrix, and the lamina propria, which contains the innate and adaptive immune systems as well as both blood and lymphatic vessels. In the small bowel (SB) 600-fold by virtue of the circular Kerckring's folds, villi and crypt structure, and microvilli, which increase the small intestinal surface area from 3,300 cm^2 to 2 million cm^2 (1).

Food intolerance is very common in functional digestive disorders (FDDs), both in functional dyspepsia and irritable bowel syndrome (IBS). Many patients with IBS associate the ingestion of a wide range of foods with the development of abdominal bloating and pain (2,3), and 62% make dietary adjustments (4) such as reduced consumption of dairy products, spicy foods, wheat, alcohol, and some fruits or vegetables rich in poorly absorbable short-chain carbohydrates and sugar alcohols, and increased consumption of fruits rich in fermentable oligosaccharides, monosaccharides, and polyols (FODMAPs) (5,6). Up to 4.7% of patients may have latent celiac disease, and while malabsorption of lactose and other sugars does not seem to be more common in IBS patients than in the general population, patients often attribute their symptoms to ingestion of wheat and dairy products, hence other mechanisms may be involved.

This may occur through direct interactions between diet components and potentially sensitized

intestinal mucosal receptors, or may be mediated by changes in the intestinal flora's metabolic capacity, bile acid and digestive enzyme secretion, intestinal hormone release, changes in epithelial morphology and functioning (7), impaired colonic motility and intraluminal distension, immune responses or impaired signaling between the bowel and brain, and cognitive factors. For instance, FODMAPs are osmotically active and increase water contents in the intestinal lumen. They undergo fermentation with production of hydrogen, carbon dioxide, methane, short-chain fatty acids (SCFAs), and lactate. Many patients with IBS report symptoms in response to gluten- or wheat-containing products despite negative celiac serology and normal SB morphology, which has been called "non-celiac gluten/wheat sensitivity." Gluten may induce a mild immune response in patients with IBS, which may be associated with exaggerated responses in enteric and sensorial nerves, and compromised intestinal barrier function (8,9). An increase in the intestinal density of sensorial fibers expressing transient receptor potential (subfamily V, TRPV) cation channels seems to play a role in the response to spicy, hot foods seen in patients with IBS (10). Although up to 20% of patients with IBS are positive that they are allergic to specific foods, IgE-mediated food allergies have not been convincingly associated with the pathogenesis of IBS, and the role of measurements of IgGs against food components remains unclear.

Bacterial microbiota and metabolic capacity

The intestinal lumen is home to a wide range of microbes, the so-called intestinal microbiota, primarily made up of bacteria but also archaea, fungi, viruses, and phages. Although more than 1,000 bacterial species and wide interindividual differences have been identified, the intestinal microbiota includes a limited number of phyla, with Bacteroidetes, Firmicutes, and members of Proteobacteria and Actinobacteria being predominant (11). This ecosystem is key to balance in immune responses, intestinal epithelium functioning, barrier function, and metabolic capacity.

The number and diversity of bacteria vary along the GI tract, from $0-10^3$ bacteria per ml in the acidic stomach environment to 10^5 per ml in the SB and up to 10^{12} per ml in the colon (12). This composition is affected by intestinal pH, oxygen, and available nutrients (13). The SB is characterized by the presence of high oxygen levels, digestive enzymes, antimicrobial peptides, and increased motility. The colon has an anaerobic environment with reduced motility and high levels of undigested nutrients. Lifestyle and diet are determinants of microbiota composition and function (14,15). Furthermore, microbiota composition patterns are highly predictive of health status (16). The intestinal microbiota exhibits a high metabolic capacity, and contributes to the synthesis of vitamins (B, K) and the conversion of dietary residues, endogenous compounds (e.g., mucins), bile acids, and xenobiotics (17).

Carbohydrate metabolism

Fermentation of complex carbohydrates such as fibers and resistant starches usually results in short-chain fatty acids (SCFAs), particularly acetate, propionate, and butyrate. Since these fatty acids are fuel for our intestinal cells and represent signaling molecules to which we are responsive, they are deemed to be beneficial. Patients with IBS have significantly higher levels of fecal acetate and propionate when compared to control individuals (18), which might be associated with IBS symptoms. A wide variety of bacteria may produce butyrate, including *Faecalibacterium prausnitzii*, *Eubacterium rectale*, *Eubacterium halli*, and *Roseburia intestinalis* (19). Propionate may be fermented by *Bacteroides spp* and *Veillonella spp*, but propionate is also carried in the portal circulation to the liver, where it can be used. Propionate fermentation often results in simultaneous acetate production by a wide variety of microbes in the gut, albeit acetate represents the primary fermentation product to some bacteria, including *Ruminococcus obeum* (20). Carbohydrate fermentation also results in the production of hydrogen and carbon dioxide. Therefore, impaired handling of intestinal gas, which is consistently described in IBS, may well bear some relation to the development of dysbiosis.

Hydrogen may serve as energy source for a variety of microbes, including methanogenic archaea, reductive acetogens, and sulfate reducers. *Methanobrevibacter smithii* is the most common methanogen in the human bowel. Sulfate reducers may also use hydrogen as a source of energy, which results in the formation of sulfide, a toxic compound considered as harmful for our health. Although the relative volumes of bowel gases released in the breath have been used to relate FDD symptoms to *in-situ* intestinal microbial fermentation, cross-feeding between different microbial populations may change the relative concentrations of hydrogen, methane and sulfide in the breath; for instance, hydrogen methanogenesis will result in a drop in gas volume.

Protein metabolism

While most proteins are digested and absorbed in the SB, a high-protein diet may lead to relevant protein loads in the colon. Less extensively studied than carbohydrate fermentation, microbial protein fermentation is considered to be potentially harmful for health as it may generate toxic products such as amines, ammonia, N-nitrous oxide, sulfur, and phenolic compounds (21). Prolonged epithelial exposure to these molecules may result in adverse changes, including carcinogenesis. Potential protein sources for fermentation include the diet and host-derived compounds. Since bacteria favor carbohydrate over protein fermentation, protein-rich, carbohydrate-poor diets, typical in western countries, may promote protein

fermentation in the bowel. A recent study showed that fecal protease concentrations were higher in patients with IBS as compared to healthy controls, which suggests an increase in protein metabolism in the colon (22).

Lipid metabolism

In contrast to carbohydrates and proteins, fat is thought to not reach the colon microbiota. An indirect effect of dietary fat assimilation is to facilitate the diffusion of bacterial components such as lipopolysaccharides across the epithelium, which may lead to low-grade inflammation (23).

Many studies demonstrate microbiota changes in patients with IBS (24). *Faecalibacterium prausnitzii* and *Akkermansia muciniphila* seem to be decreased in IBS whereas potentially pathogenic groups such as *Proteobacteria* have an increased presence. However, there is no consensus on the microbial species that consistently correlate (whether positively or negatively) with IBS clinical manifestations. Therefore, longitudinal studies involving repeat microbiota sampling will obviously be crucial to tell cause from consequence or coincidence. These studies may include interventions with specific diets or supplements, specific drug therapies, or novel strategies such as fecal microbiota transplantation.

Bile acids (BAs)

The two main BAs (cholic acid and chenodeoxycholic acid) are synthesized from cholesterol by hepatocytes; conjugated with taurine and glycine, they are then excreted in the bile. In the SB, BAs play a central, vital role in the digestion and absorption of liposoluble vitamins and fats. A highly efficient enterohepatic circulation ensures preservation of secreted BAs, with fecal losses lower than 10%. While a fraction of BAs is passively absorbed, the primary preservation mechanism is active absorption via a sodium-dependent transporter located in the apical surface of enterocytes in the terminal ileum. Ileal BA absorption and hepatic secretion are closely associated through a feedback loop that is partly mediated by the fibroblast growth factor 19 (FGF-19), secreted by ileal enterocytes in response to high intracellular BA levels. FGF-19 secretion is in turn mediated by the nuclear farnesoid X receptor (25). FGF-19 then binds FGF receptor 4 and its Klotho-beta (KLB) co-receptor in hepatocytes in order to inhibit cytochrome P450 7A1, the enzyme that limits BA synthesis rate (26).

As primary BAs, they go through the small bowel, and approximately 15% are deconjugated by the microbiota; the small fraction of primary BAs that reaches the colon is deconjugated by colonic bacteria and transformed by bacterial 7-hydroxylase in secondary BAs (deoxycholic acid

and lithocholic acid, respectively). While lithocholic acid is minimally absorbed, up to 50% of deoxycholic acid is reabsorbed and reconstituted in the liver to enter the bile.

BAs have a variety of physiological effects that are relevant to FDDs. These include effects on intestinal motility and secretion, mucosal permeability, and visceral sensation (27,28). The first step in the bacterial metabolism of BAs is performed by the enzyme bile salt hydrolase, which deconjugates primary BAs into primary BAs and free amino acids; the former may undergo a number of additional enzymatic transformations, including dehydroxylation, dehydrogenation, and sulfatation, to yield secondary or tertiary BAs (29).

High-fat diets stimulate BA secretion and may increase colonic water secretion and motor activity, as well as induce microbiota changes in IBS. Thus, fecal BA levels have been associated with stool form and frequency, relative BA deficiency with IBS and constipation (30), and excessive BA with IBS and diarrhea (31). Primary BA malabsorption has been shown to affect 32% of people with unexplained diarrhea, and may be even more prevalent among patients with IBS and diarrhea (32).

DIAGNOSTIC USEFULNESS OF FOOD EXCLUSION IN IBS

IBS is a common functional digestive disorder, its prevalence being estimated at 10-20% (33,34). This condition also represents a significant impact on patient quality of life (34,35). IBS diagnosis is established by means of careful history taking, including Rome IV criteria (Table 1), exclusion of alarm signs and symptoms (Table 2), and diagnostic testing on an individual basis (36). This syndrome is classified in four subtypes according to the defecation pattern predominating (Bristol scale): IBS with predominant constipation (IBS-C), with predominant diarrhea (IBS-D), mixed (IBS-M), and unclassified (IBS-U) (37).

Abdominal pain and distension are the symptoms that predominate in IBS, in association with changes in bowel rhythm (constipation or diarrhea). Symptom severity may vary over time. Therefore, in order to reach the right diagnosis, other intestinal and extraintestinal conditions must be ruled out, as well as drugs that may induce IBS-like complaints. All this requires a thorough case history and physical examination (36).

Multiple studies suggest the potential role of diet as symptom trigger in IBS (38,39). It is estimated that 84% of patients diagnosed with IBS associate symptom development or aggravation with the ingestion of at least one type of food (40).

Consequently, dietary changes or restrictions represent the most common mechanism patients use to try and control their symptoms, so that 62% of affected individuals limit their diet without advice from a gastroenterologist or nutritionist (40,41). Most common restrictions include the

exclusion of foods containing lactose, wheat, and selected fruits and vegetables. Thus, a detailed dietary history must be taken, highlighting the role of specific foods or their components as causal factors of symptoms (Table 3).

From all the above, food challenge or exclusion testing with potential dietary symptom triggers over a given period of time might be deemed an additional diagnostic criterion for IBS.

In patients with IBS, the incidence of lactose malabsorption is not higher than in control populations, but intolerance symptoms do manifest more often. Because of this, lactose-restricted diets are now considered to be useful in assessing symptom course.

In this regard, it was recently reported that the prevalence of IBS has increased in parallel with the growing use of fructose, processed foods, and additives. Berg LK et al. (42) have proposed a diagnostic instrument for the assessment of fructose intolerance. It is based on a visual analog scale to record symptoms following a low-fructose diet and a challenge with this same compound. The authors point out that, compared with the hydrogen breath test, this diagnostic tool has a sensitivity of 0.84, a specificity of 0.76, a PPV of 0.83, and a NPV of 0.79. Therefore, a fructose exclusion diet and subsequent fructose challenge may represent a new tool for diagnosing these patients.

A FODMAP-restricted diet might also be considered (43) as a diagnostic test for symptom assessment, but this has not been evaluated.

Furthermore, the IBS subtype where dietary exclusion/challenge testing is most useful should also be established. This strategy might also improve symptoms in other conditions (celiac disease [CD], non-celiac gluten sensitivity, and inflammatory bowel disease, among others) (44,45), where its diagnostic accuracy remains to be established.

The diagnosis of IBS and its subtypes is therefore based on the identification of diagnostic criteria (currently, Rome IV criteria) and the exclusion of alarm data. An adequate dietary history is key for diagnosis completion and treatment guidance. While exclusion diet and subsequent challenge with specific symptom-related foods may be promising as a diagnostic tool in IBS, exclusion duration and challenge timing have not been standardized, and neither have the substances to be used or its diagnostic accuracy.

FODMAP EXCLUSION IN IBS

Scientific evidence

In the dietary management of IBS two lines of intervention have been established. The first line includes a regular eating pattern of five or six meals with restriction of alcohol, caffeine, spicy foods, fat, and gas-producing foods, and fiber distributed throughout the day; the second line

consists of a FODMAP-restricted diet (46,47).

This type of dietary therapy comprises two phases. In the first phase FODMAPs are severely restricted for four to eight weeks; in the second phase, excluded foods are gradually reintroduced according to individual tolerance to end up with a diet as scarcely restrictive as possible (top-down method) (48). While this is the most common treatment available, FODMAP dietary contents may also be managed the other way round (bottom-up method), that is, first only restricting high-FODMAP foods, and then also withdrawing lower-FODMAP foods until tolerance is achieved (48).

Low-FODMAP diet is defined as a diet poor in fermentable oligosaccharides (fructooligosaccharides, galactooligosaccharides), disaccharides (lactose), monosaccharides (fructose), and polyols (sorbitol, mannitol, maltitol, xylitol) (49). Fructans and fructooligosaccharides are naturally present in foods such as garlic and wheat; galactooligosaccharides in pulses; lactose in dairy products; fructose in some fruits including apple and pear, and polyols in stoned fruits. Table 6 lists foods to be excluded from a low-FODMAP diet, as well as foods allowed.

These compounds may reach the colon unabsorbed, and here they increase luminal water contents due to the higher osmotic load they provide. They also induce gas production from fermentation. All this results in abdominal bloating and brings about IBS complaints (50-52).

Recently, the British Dietetic Association published a systematic review discussing the randomized controlled trials reported from January 1985 through October 2015 (53). Upon analyzing seven trials meeting the authors' inclusion criteria using a low-FODMAP diet for three, four or six weeks (54-57) improved symptoms in diarrhea-predominant IBS and mixed-type IBS, but not in constipation-predominant IBS, with a level of evidence B. Furthermore, a fructose-restricted diet improved abdominal pain, bloating, and stool frequency after four weeks (58). This study had a lower, C level of evidence. Regarding a comparison of the effectiveness of a low-FODMAP diet *versus* the National Institute for Health Care dietary regimens, results were similar with a level of evidence C (56). Also with a level of evidence C, low-FODMAP diets were shown to have an effectiveness similar to that of probiotic administration (*L. rhamnosus GG*) in diarrhea-predominant IBS and mixed IBS with predominant diarrhea (55).

Given the difficulty of correctly designing a double-blind, randomized study with a prolonged intervention period, the scientific evidence available thus far is limited (59). Primary limitations of reported studies include: a) lack of appropriate control group; b) absence of blind studies; c) too short therapy durations; and d) reduced number of subjects (60). However, despite this, countries such as Japan and the United Kingdom have included this type of diet in treatment

regimens for IBS.

The fact that low-FODMAP diets are highly restrictive must be highlighted. They may reduce the ingestion of dietary nutrients such as calcium and fiber. Thus, in order to provide non-deficient diets despite restrictions, such dietary regimens should be controlled by experienced dietitians. They will provide patients with adequate information, both oral and in writing, on high-FODMAP foods and their potential alternatives to achieve a balanced diet (61).

A significant aspect to bear in mind regarding the follow-up of low-FODMAP diets is the intestinal microbiota. A low-FODMAP diet may alter the composition of the gut microbiota. A reduction of fructans and galactooligosaccharides may bring about a decrease in the beneficial bacteria included in the microbiota. In this regard, two studies have shown that a low-FODMAP diet for 3-4 weeks results in a reduction in *Bifidobacteriaceae* (55,62). This is interesting as patients with IBS have been seen to have lower levels of fecal *Bifidobacteriaceae* (55,62,63), and a negative association has been found between the fecal amount of these bacteria and abdominal pain (64-66). Therefore, should dysbiosis be a cause of IBS, although no clear evidence supports this hypothesis as yet, the effect of a low-FODMAP diet would be counterproductive. These diets also result in a reduction of butyrate-producing bacteria, and increased numbers of mucus-degrading bacteria. However, the clinical transcendence of these changes remains unknown. Also, available data are insufficient to establish whether adverse changes in the gut microbiota may be avoided with the concomitant use of a low-FODMAP diet and probiotics.

As it was pointed out above, following symptom remission with FODMAP restriction, FODMAP-containing foods are gradually reintroduced. Available data suggest that 75% of patients tolerate FODMAP reintroduction with only moderate restrictions and still retain symptom control. However, evidence is still limited in this regard. Finally, the fact should be mentioned that while low-FODMAP diets may improve IBS symptoms, and hence are expected to improve quality of life, they may also have negative aspects such as financial costs, implementation burden, and downside impact on patient daily life (e.g., the habit of eating out). This may ultimately lead to reduced quality of life.

Whom is it recommended?

It is recommended for patients with diarrheic or mixed IBS who do not respond to treatment with the standard diet included in the NICE guidelines (regular eating schedule, no copious meals, reduced ingestion of fat, insoluble fiber, caffeine, and gas-producing foods such as pulses, cabbage, and onion). Level of evidence B. Grade of recommendation B.

Complete or partial restriction?

Using the top-down approach, FODMAP exclusion should be complete over the first 4-8 weeks, until symptom remission. High-FODMAP foods are then gradually reintroduced until patient tolerance is reached. This is usually prescribed for patients who do not usually ingest high amounts of FODMAPs, are intensely symptomatic, or prefer this strategy. Level of evidence B. Grade of recommendation B.

Using the bottom-up approach, FODMAP exclusion is partial and starts with foods with higher FODMAP contents; this restriction lasts for 4-8 weeks until tolerance is achieved. This is usually prescribed for patients who consume high amounts of FODMAPs, are moderately symptomatic, or prefer this strategy.

For how long?

The complete FODMAP exclusion phase will last for about 4-8 weeks. Afterwards, controlled, gradual exposure to each FODMAP group will ensue for three days in order to identify individual tolerance. Level of evidence B. Grade of recommendation B.

Reintroduction of normal diet

Once the tolerance thresholds for the various FODMAPs have been identified, dietary FODMAP contents will be adapted thereto in order to prescribe as few restrictions as possible, and minimize potential deleterious effects on the microbiota, colonocyte metabolism, and long-term nutritional status.

What controls will we need?

Any low-FODMAP diet should be implemented under the supervision of an experienced dietician specialized in gastroenterology. Level of evidence B. Grade of recommendation B.

It is recommended that any nutritional deficiencies present prior to a low-FODMAP diet be identified and treated with supplementation, and then followed up during the intervention period. Also, intake of fiber, calcium, iron, zinc, folic acid, and vitamin D should be monitored during any low-FODMAP diet, particularly in patients unable to afford alternative low-FODMAP foods.

LACTOSE EXCLUSION IN IBS

Scientific evidence

Lactose intolerance is a disorder that follows lactose ingestion in the presence of lactase

deficiency. This deficiency may result in lactose malabsorption when the unabsorbed sugar reaching the colon is fermented by colonic bacteria with gas production (hydrogen, methane, etc.). As a consequence, multiple intolerance symptoms may develop, including abdominal pain, bloating, borborygmus, diarrhea, and even vomiting (69).

Intolerance may be classified as:

- Congenital lactase deficiency. This is an extremely rare pediatric condition of which only about 40 cases have been reported worldwide, primarily in Finland. It was initially described in 1959 by Holzel et al. It must not be mistaken for primary or secondary deficiency.
- Primary lactase deficiency. This results from a physiological decrease in lactase secretion with age that may be seen in all mammals, although humans have developed gene mutations that allow secretion during adulthood, particularly in some races (e.g., Caucasians).
- Secondary lactase deficiency. It is due to lactase deficiency because of diseases that involve the SB wall. Most significant among these are CD, non-celiac gluten sensitivity, Crohn's disease, gastrointestinal infection, cow's milk protein enteropathy, drugs such as NSAIDs, antibiotics, etc., and other causes such as gastropathy, giardiasis, malnutrition, carcinoid syndrome, etc. (68,69).

Lactose malabsorption and intolerance affect a high percentage of the population. In Spain, 15% of northern populations and over 40% in southern areas are estimated to suffer from this condition, which is even more common among immigrants from South America and Africa (70,71).

The potential incidence of lactose intolerance in people with IBS is worthy of mention here. A recent study shows that lactose malabsorption is as common in healthy individuals as in patients with IBS; however, the intolerance associated with malabsorption is more severe in the latter group. This study enrolled a group of patients with IBS and a group of healthy volunteers. Both groups underwent hydrogen breath testing after lactose overloading, which measured malabsorption extent; they also had their abdominal circumference measured before and after testing in order to objectively assess intestinal gas formation. Results showed that with equal levels of malabsorption, as measured with hydrogen breath, patients with IBS had more symptoms, and these were more severe, when compared to healthy controls. The study concludes that patients with IBS do not have higher levels of lactose malabsorption *versus* the general population, albeit they do have higher levels of intolerance, as they are particularly hypersensitive; their symptoms are more severe and, most importantly, "worse lived" when compared to the general population (72).

All in all, we may consider that there is scientific evidence to support lactose exclusion as

potentially effective for health improvement in IBS.

Whom is it recommended?

Lactose exclusion is to be recommended when symptoms are identified in association with the ingestion of dairy products or evidence of lactose malabsorption is present.

Complete or partial?

Lactose exclusion may be partial, then patient response is monitored and lactose ingestion may be increased accordingly. However, it is advisable that exclusion be initially complete, and then subjected to nutrition monitoring (73).

For how long?

Exclusion duration cannot be established beforehand; response to exclusion may be assessed after 4-8 weeks.

Lactose-containing foods to be avoided include:

- Processed cow's milk contains at least 4.7% lactose.
- Similar proportions are found in the raw milk of other mammals.
- Butter may be considered as a lactose-containing food or otherwise depending on its preparation process; some processes separate water-soluble components from milk fats.
- Intolerant individuals may tolerate traditionally prepared yogurt since the bacteria involved are lactase producers.
- Traditionally prepared hard cheese and mild-aged cheese may be eaten, as their fermentation process and fats result in decreased lactose contents.
- Also, traditional methods for cheese ageing (over two years) reduce lactose to almost zero. This may be different for cheese manufactured with modern procedures.

Other foods to be avoided include pastry cream, liquid cream, commercial purées, bechamel sauce, sliced bread, milk-containing cocoa products, and fruit shakes.

Reintroduction of normal diet

On a gradual, step-by-step basis, ensuring that lactose-containing products are increasingly well tolerated, and no symptoms suggest that IBS worsens with lactose ingestion. Nevertheless, even when IBS is not caused by lactose malabsorption, patients with IBS and lactose intolerance do benefit from lactose exclusion in terms of symptoms.

Nutritional monitoring will provide balance between potential lactose intolerance and IBS.

GLUTEN EXCLUSION IN IBS

Scientific evidence

IBS is a condition with a prevalence of 7-25% (74,75). It manifests with abdominal symptoms without organic cause that are typically associated with meals; 90% of patients relate them to some specific food, and two thirds of them restrict their dietary intake (76). One of these foods is gluten (protein portion of cereals, such as wheat, oat, rye), which induces similar symptoms in CD.

In patients with IBS who do better with a gluten-free diet (GFD), gluten-related disorders must be ruled out (77); 30% of celiac patients were formerly categorized as IBS sufferers (78,79), and high rates of final diagnosis with CD (2-42%) and non-celiac gluten sensitivity (NCGS) are reported (52-93%) (80). The prevalence of CD in the duodenal biopsies of patients with suspected IBS may be four times higher than expected (81).

Gluten-related disorders may be divided into three categories:

1. Wheat allergy: an allergic reaction to gluten mediated by eosinophils in the bowel. There is no genetic predisposition, diagnosis is clear, and gluten exclusion may save lives by preventing anaphylaxis (82).
2. Celiac disease: an autoimmune systemic disorder mediated by acquired autoimmunity (T-cells); it primarily affects the digestive system of genetically susceptible individuals (HLA DQ2/8) (83). Its prevalence of 1-3% has increased in recent years as a result of improved diagnosis (Table 7). In the adult, it may manifest both with diarrhea and constipation, hence it may involve patients categorized with IBS of any subtype (84). Gluten exclusion relieves symptoms, prevents complications, and improves quality of life (85)
3. Non-celiac gluten sensitivity: mediated by innate immunity with failed adaptive response; duodenal infiltration with lymphocytes may be present, and no complications develop (Table 6). A prevalence of up to 10% has been estimated in Spain (86). Discrepancies exist regarding its definition, and up to 30% of patients with NCGS in initial series might be now diagnosed with CD according to current criteria (80,87,88).

A review of adult patients diagnosed with NCGS (89) showed highly heterogeneous studies: variable gluten doses (2-52 grams/day), periods (1-6 weeks), and placebos. It concluded that over 80% of subjects diagnosed with NCGS would not retain their diagnosis in a placebo-controlled, double-blind study.

Furthermore, NCGS symptoms may be triggered by wheat proteins other than gluten, by short-chain carbohydrates (FODMAPs), or by ATIs (amylase-tryptase inhibitors) in wheat. It is because

of this that Guandalini and Polanco (90) suggested using the designation “wheat intolerance syndrome.”

Most NCGS studies find improvement in the placebo group, but only 16% had gluten-related symptoms and 40% of these improved with placebo (94), the so-called “nocebo effect.” This effect may be statistically prevented, but such adjustment was never performed. In studies on food intolerance in IBS, two thirds may have exhibited nocebo effects (90). In the study by Barmeyer (91), over 50% of patients on GFD remained on such a diet after one year despite lack of response.

Several studies of GFD in patients with IBS-D found a decrease in stool number in up to 60% of subjects (92,93) with improved intestinal permeability (92,94) and epithelial changes observed with endomicroscopy (95).

In a study of patients with IBS (88) who received an initial course of GFD for four weeks, and were then randomized to receive wheat capsules or placebo, 30% were diagnosed with NCGS, even though 10-40% of these met CD criteria. There is also a group of patients with atopic conditions, food hypersensitivity, and eosinophilic infiltration that, according to some authors (88), should be classified with wheat allergy.

Six clinical trials have explored the role of gluten in IBS (Table 7). All have methodological issues: failure to rule out CD, nocebo effect, and failure to differentiate gluten from other dietary compounds except in one case, who found no differences *versus* FODMAPs (96).

Therefore, IBS and NCGS are not synonyms, but some patients initially diagnosed with IBS may improve with a gluten-free diet; however, only a reduced number will do so because of gluten itself, and may then be diagnosed with NCGS. No markers allow to identify the subgroup of patients who will experience improvement. Response to GFD may occur later than seen in studies (91).

An association between NCGS and CD-risk haplotype HLA DQ2/8 was initially found (97), but was later found to be inconsistent. It has a sensitivity of 25% and specificity of 52% for the diagnosis of NCGS (91).

NCGS may only be diagnosed after excluding other conditions, and assessing its improvement/worsening following gluten withdrawal/reintroduction. Hence, gluten should be blindly reintroduced in patients with IBS on GFD, since only 14-30% will experience relapse (98-100).

To conclude, gluten exclusion cannot be universally recommended in IBS since evidence is limited by the poor quality of studies. Also, 0.5% of the general population (101) follow a GFD in the absence of gluten-related disorders, and British guidelines (76) recommend that IBS patients

on GFD be informed of the low evidence of benefit and the risks of diets that may be deficient in calories and nutrients (fiber, folic acid, niacin, vitamin B12, vitamin E, vitamin A, phosphorus, calcium, zinc, selenium) and rich in saturated fat (102,103), as well as expensive and inconvenient.

Whether NCGS is a transient or permanent disorder remains unknown, hence response to gluten reintroduction should be regularly assessed (104,105).

Whom is it recommended?

NCGS is a gluten-related disorder that may partly account for IBS. However, the evidence supporting universal gluten exclusion for all patients with IBS is low (RCTs with limited quality). Patients with IBS already on a GFD should be informed of their low evidence of benefit and of their risk (grade of recommendation C: expert opinion).

Complete or partial?

Complete, as studies were carried out with complete gluten exclusion (grade of recommendation A) (106-108). In patients with IBS without evidence of gluten-related disease, exclusion should only be considered in the setting of a low-FODMAP diet as it is doubtful that a favorable response in patients with NCGS may result from reduced FODMAP rather than gluten ingestion.

For how long?

For at least eight weeks in order to assess efficacy, although most studies identify improvements within one week. In the absence of improvement, NCGS diagnosis should be deemed uncertain (grade of recommendation A).

Reintroduction of normal diet

Response to normal diet reintroduction should be regularly assessed in a masked, double-blind fashion to avoid the nocebo effect (grade of recommendation A).

What controls will be needed?

Diet must be supervised by an expert to ensure compliance and prevent nutritional deficiencies (grade of recommendation C).

NUTRITIONAL CONSEQUENCES OR IMPACT OF LACTOSE, GLUTEN, AND FODMAP EXCLUSION IN ADULT PATIENTS

A low-FODMAP diet entails removal of basic foods such as some cereals and derivatives (mainly wheat, oat, and rye), lactose-containing dairy products, pulses, and multiple fruits and vegetables (109).

In the review published in March 2017 by Catassi G. et al (110), most studies thus far reporting on the effects of the low-FODMAP diet in adult patients with IBS (111-125) had a dietary intervention period of three to four weeks (115). Only two of 17 studies had longer dietary therapies, of nine and 16 months, respectively (111,113), of which only one assessed and ensured adequate calcium and fiber ingestion (113).

Given the lack of long-term studies on the nutritional consequences of low-FODMAP diet, and given the type of food exclusion involved (wheat, oat, rye, and lactose-rich dairy products, among other foods), the authors hypothesized that the potential risks of its long-term use might be inferred from the data available for other well-known food exclusion regimens such as gluten-free and lactose-free diet (110).

For years, patients on GFD have been known to have a higher risk for deficient fiber, calcium, iron, zinc, magnesium, folic acid, and vitamin B12 ingestion (126,127); now we know that many gluten-free products are unbalanced because of higher contents in fat and sugar, and two- to three-fold less protein as compared to their gluten-containing counterparts (128). Furthermore, a recent long-term, prospective cohort study carried out in the USA in 110,017 non-celiac subjects on GFD associated this diet with an increase in cardiac events (129), which is in contrast with the benefits GFD seemingly has on cardiovascular disease in celiac patients (130). The authors report that the increase in cardiovascular disease seen in these non-celiac patients on GFD may result from reduced ingestion of beneficial wholegrains (129).

As regards fiber intake, deficiencies may be higher with low-FODMAP diets because of restricted pulse, fruit, and vegetable consumption; this may be particularly harmful for patients suffering from IBS with constipation (110).

Finally, GFD has also been recently associated with higher risk for contamination with arsenic, mercury and other metals (131) from soil, water, and fertilizers; their impact on health is uncertain but might involve an increased risk for cancer and other chronic conditions (132,133). Increased exposure to these GFD contaminants may result from higher ingestion of rice (134) and gluten-free rice derivatives (135), but further studies are needed to establish the actual risk associated with this exposure.

Regarding the restriction of lactose-containing dairy products, it may result in decreased calcium intake since dairy foods are a major calcium source; intestinal calcium absorption is enhanced by lactose, hence may also be reduced (136,137), which may favor vitamin D deficiency (138), a

condition highly prevalent in patients with IBS (139). In case of severe lactose intolerance, such deficiencies may be prevented by consuming lactose-free dairy products (milk, yogurts, cheese) or calcium- and vitamin D-enriched vegetable drinks (rice milk, almond milk, oat milk, etc.); however, let us recall that most people with lactase deficiency may even tolerate small amounts of lactose (less than 12 g, equivalent to a cup), particularly when combined with other foods or taken fractionated throughout the day (140-142). In this way, these individuals may tolerate small amounts of milk or naturally fermented, low-lactose dairy products such as yogurt, kefir or cheese.

Catassi G. et al (110) also report that low-FODMAP diet may be poor in antioxidants such as flavonoids, carotenoids, and vitamin C, naturally present in some of the excluded vegetables (e.g., cauliflower, onion, garlic), and in phenolic acids and anthocyanins, present in wheat and fruits (110,143).

Despite these reasonable hypotheses, based on studies using short-term low-FODMAP diet or other exclusion diets, a recently reported study fails seemingly to confirm such potential nutritional consequences (144).

O’Keeffe et al. (144), in addition to studying the long-term effects of low-FODMAP diet on clinical response, also explored its nutritional adequacy, dietary acceptability, and food-related quality of life. This study enrolled 375 patients who received a stringent low-FODMAP diet for at least six weeks. After this short period of time patients were instructed to reintroduce FODMAP-rich foods up to tolerance level. The long-term study was performed in 103 patients over six to 18 months. Of 103 patients, 84 followed a “FODMAP adapted diet” (including subjects on strict low-FODMAP diet, FODMAP-rich diet to tolerance levels, and low-FODMAP diet 50% of time) and 19 returned to their “usual” diet. No significant long-term differences in energy and nutrient ingestion were found between groups, except for folic acid and vitamin A, which was higher in the “FODMAP-adapted” group. In both groups, 95% of patients reached dietary reference values for daily energy and most nutrients, including carbohydrates, fiber and calcium, which had been reduced in prior short-term studies (112,117,145).

Despite these good results, the authors are aware of multiple study limitations, including low participation in the initial sample, only 27%, in comparison to similar studies; the study design itself, without control arm or blinding; and the use of food frequency questionnaires as tools to assess dietary intake, as they tend to underestimate or overestimate ingestion of certain foods (146). Along the same lines, another recent randomized, single-blind study by Vincenzi M et al. (147), reported in June 2017, established that low-FODMAP diet does not seem to cause folic acid or vitamin D deficiencies after three months. This study is pending publication of results at

six months' follow-up.

According to extant evidence, it would be reasonable to consider that low-FODMAP diet, when rightly supervised by an experienced dietician, may be nutritionally adequate in the long run (148). However, prolonged FODMAP restriction may have physiological effects on intestinal microbiome, colonocyte metabolism, and nutritional status that should not be underestimated and require further research (112,114,148).

EDUCATION TO ACQUIRE HEALTHY EATING HABITS. COMMUNICATING WITH THE PATIENT WITH IBS

Diet and eating habits have become highly relevant in the dietary management of IBS. In this regard, educational interventions by health practitioners may promote morbidity control, reduce healthcare burden, and improve patient quality of life.

Background

Many chronic diseases are associated with unhealthy diets (156); accordingly, unhealthy eating habits may be thought of as risk behaviors related both to incidence and morbidity, as well as to healthcare burden. In an attempt to diminish this predicament emphasis has been placed on an integral, holistic approach to the needs of people suffering from said conditions (150). Education is now prioritized as a tool for improving patient self-management and quality of life (151).

Importance of eating habits in the dietary management of IBS

Restriction of selected foods has been shown to entail potential nutritional deficiencies; obviously, restrictive therapies should foster regular eating habits based on recommended dietary allowances, as put forth in the recent document titled "*The food pyramid*" (152). Despite limited evidence regarding the association of healthy eating habits with IBS symptoms, the aforementioned paper discusses the importance of patient counseling, with emphasis on lifestyle as related to eating habits.

Importance of a health team intervention model in the dietary management of IBS. Educating patients with IBS

Intervention model

Initial guidelines for the dietary management of IBS lacked an integral critical assessment, particularly regarding first-line approaches (153). This conventional development has led to patient issues, including dissatisfaction with practitioner interactions (154) and/or deficient

knowledge (155,156). Given their transcendence, patient-reported difficulties (poor accessibility for concern resolution, uncertainty-derived worrying, etc.) may be associated with treatment noncompliance (155,157), self-prescribed dietary adjustments (156) or presence of irregular eating habits (158,159), all of them documented in this population.

Given that adherence to dietary treatment is key for prescription regimen effectiveness in IBS (160), and the deficiencies found in its management are incongruous with guideline compliance by health professionals, it is advisable that education be focused on the needs identified in patients with IBS (161).

Education in the management of chronic diseases

Educational interventions are the responsibility of health professionals, and a most recommended measure in the key areas of models developed for the management of chronic diseases (162-169). All of them argue that education improves quality of care for chronic patients. In this setting should the meaning of therapeutic education, and of its goals, be understood (WHO, 1988). This involves helping patients to learn and develop multiple skills, and improving several health parameters, increasing personal satisfaction, and diminishing anxiety with reduced numbers of complications and costs.

Education in the management of IBS

Overall, modifying eating habits is effort-intensive for health teams, and also results in patient difficulties. The significance of functional disorders like IBS depends not only on symptom severity but also on biopsychosocial factors such as associated gastrointestinal and extraintestinal symptoms, extent of involvement, and perception and behavior forms (170). Dietary and lifestyle interventions must cover cognitive and behavioral aspects, particularly when patients show a special interest in understanding dietary changes, survival strategies, and the causes of their disease (171).

Some studies demonstrate the potential benefits of education in the setting of IBS. A holistic approach dealing both with body and mind of patients with IBS is associated with therapy benefits (160,161), and may be appropriate to facilitate behavior changes as related to dietary management (171,172). IBS regimens should emphasize a better understanding of IBS patient expectations, as well as the therapeutic value of patient-professional communication (173). It is also important that care models be developed that promote learning and experience sharing, connecting the patients' perception of their health issue, needs, and life status with the transference of knowledge and skills by health providers (174). The first-line intervention

approach to IBS recommends that health providers foster self-management by imparting knowledge to patients with IBS, a strategy that must prevail over any other considerations (175). Diet counseling, as developed by trained professionals, promotes the adoption of and adherence to a healthier diet, improves quality of life, and reduces morbidity in IBS (176-179). A diary recording food ingestion and symptom development will help identify products that trigger or worsen complaints (180). Providing nutritional orientation in consultation sessions will reassure patients with IBS (177) and ensure adequate intakes while avoiding nutritional deficiencies. The importance of an approach focused on self-management and patient education in the first line of intervention has been already highlighted (153).

Recommendations

- Dietary management in IBS requires an integral, holistic approach including involvement extent, perception style, and patient behavior.
- Given the complexity of dietary management in IBS, appropriate regimens are insufficient; patients must also understand them, adhere to them, and be willing to comply.
- It is important that patients be involved as active subjects in the change process, using education as a cornerstone to facilitate communication and efficient self-management.

CONCLUSIONS

The present paper was meant to capture a consensus on the role of exclusion diets in IBS. To this end, the consensus opinions of various experts representing the major Spanish scientific societies were collected to establish a set of recommendations applicable to healthcare practice for patients with IBS. Thus, we strived to collect scientific evidence on food exclusions while avoiding highly restrictive, poorly substantiated or controlled diets.

IBS is a highly prevalent functional disorder of the digestive system where dietary management and healthy habits, in addition to drug therapy, are key control measures. Furthermore, the exclusion of dietary components such as lactose or FODMAPs has diagnostic added value. For cases of IBS with diarrhea unresponsive to conventional dieting, FODMAP exclusion is effective under professional supervision for 4-8 weeks. If successful, tolerated FODMAPs will be gradually reintroduced. For IBS with diarrhea associated to lactose ingestion, lactose should be excluded from the diet for 4-8 weeks, and then slowly reintroduced according to symptom-free tolerability. For IBS with diarrhea, supervised gluten exclusion in a complete though transient fashion may be considered; subsequently, gluten may be reintroduced, blindly if feasible, in order to rule out the possibility of non-celiac gluten sensitivity.

All things considered, the therapeutic approach to patients with IBS must be an integral one comprising all available measures, including education for health and coordinated action by practitioners such as doctors, nutritionists, and nurses, in order to optimize IBS symptom control and improve patient quality of life.

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Accepted Article

Table 1. Rome IV criteria for the diagnosis of irritable bowel syndrome

Recurrent abdominal pain, on average at least one day per week in the last three months, associated with two or more of the following:

- Related to defecation
- Associated with a change in stool frequency
- Associated with a change in stool form (appearance)

Criteria should be fulfilled at least for the last three months, with symptom onset at least six months before diagnosis

In IBS-C:	In IBS-D:	In IBS-M:	In IBS-U:
<ul style="list-style-type: none"> – 25% of hard stools (Bristol 1-2) and < 25% of liquid stools (Bristol 6-7) – Predominant bowel habit based on stool form on days with at least one abnormal bowel movement – Predominant constipation may only be established when patient is assessed off medications for the treatment of impaired bowel habit 	<ul style="list-style-type: none"> – > 25% of liquid stools (Bristol 6-7) and < 25% of hard stools (Bristol 1-2) – Predominant bowel habit based on stool form on days with at least one abnormal bowel movement – Predominant diarrhea may only be established when patient is assessed off medications for the treatment of impaired bowel habit 	<ul style="list-style-type: none"> – > 25% of liquid stools (Bristol 6-7) and > 25% of hard stools (Bristol 1-2) 	<ul style="list-style-type: none"> – < 25% of liquid stools (Bristol 6-7) and < 25% of hard stools (Bristol 1-2)

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Table 2. Alarm criteria

- Family or personal history of colorectal cancer, intestinal polyposis, inflammatory bowel disease, and celiac disease
- Symptom onset after 50 years of age
- Recent changes in usual defecation rhythm
- Presence of signs and symptoms suggestive of organicity:
 - Night-time symptoms
 - Fever
 - Anemia, leukocytosis
 - Unintentional weight loss not accounted for by other causes
 - Blood in feces
 - Significant abdominal pain
 - Pathological physical examination including: palpable abdominal mass, visceromegalies, adenopathies, goiter, abnormal digital rectal exam, etc.

Table 3. Medical history taking in IBS

- Rome IV criteria (Table 1)
- Exclusion of alarm signs and symptoms (Table 2)
- Differential diagnosis with other diseases and with drugs that may induce IBS-like manifestations
- Detailed physical examination
- Assessment of symptoms supportive of diagnosis:
 - Symptom chronicity
 - Association with other functional digestive and non-digestive disorders
 - Psychological determinants
- Dietary history: potential symptom-triggering foods or food components

Table 4. High-FODMAP foods that are advised against

<i>High-FODMAP foods that are advised against</i>	
Fructose	Fruits: apple, ripe banana, mango, pear, fruit preserves, watermelon Sweeteners: fructose, high-fructose corn syrup Fruit concentrates. Fruit juices, dehydrated fruits Honey Corn syrup
Lactose	Milk (cow, sheep, goat) Yogurt Cheese: soft, uncured cheeses Custard Ice cream
Fructans	Vegetables: garlic, artichoke, eggplant, broccoli, cabbage, Brussels sprouts, onion, chicory, asparagus, leek, beet Cereals: wheat and rye in large amounts (e.g., bread, biscuit, couscous, pasta) Fruits: cherimoya, persimmon, watermelon
Galactans	Pulses: beans, chickpeas, lentils
Polyols	Fruits: avocado, apricot, cherry, plum, prune, lychee, apple, peach, nectarine, pear, watermelon Vegetables: cauliflower, common mushroom, sweet corn, green pepper Sweeteners: sorbitol, mannitol, xylitol
<i>Foods allowed</i>	
Fruits	Banana, blueberry, cranberry, grape, grapefruit, melon, kiwi, lemon, lime, mandarin, orange, passion fruit, papaya, pineapple, raspberry, strawberry, rhubarb With moderate consumption: avocado, cherry, coconut, blackberry

*See additives.

Table 5. Diagnostic criteria for celiac disease

The "4 out of 5" rule
<ol style="list-style-type: none">1. Typical symptoms of celiac disease<ul style="list-style-type: none">– E.g., chronic diarrhea, delayed growth in children, iron-deficiency anemia2. Serum celiac IgA antibodies, positive in high titers<ul style="list-style-type: none">– 10 x upper limit of normal (IgG antibodies in subjects with IgA deficiency)3. Haplotype HLA-DQ2 or DQ8c<ul style="list-style-type: none">– Also with half heterodimer (HLA-DQB1*02 positive)4. Celiac enteropathy in small bowel biopsy<ul style="list-style-type: none">– Including Marsh 3 lesions, Marsh 1-2 lesions associated with positive celiac serology in low/high titers, or Marsh1-3 lesions associated with subepithelial IgA deposits5. Response to gluten-free diet<ul style="list-style-type: none">– Clinical and histological response in patients with negative serology

Table 6. Diagnostic criteria for non-celiac gluten sensitivity (NCGS)

1. Gluten ingestion results in rapid development of intestinal and extraintestinal symptoms
2. Symptoms rapidly subside on dietary gluten withdrawal
3. Negative IgE and skin test results to wheat
4. Negative serology for celiac disease (IgA anti-EmA, anti-TG2 antibodies)
5. Positive IgG anti-gliadin antibodies in 50% of patients
6. Duodenal biopsies: normal or with moderately increased intraepithelial lymphocytes
7. Haplotype HLA-DQ2 and/or HLA-DQ8: positive in 40% of patients

Table 7. Reported clinical trials on gluten and IBS

<i>Author</i>	<i>Study population</i>	<i>Design</i>	<i>Objective</i>	<i>Result</i>
Biesiekierski et al. (107)	34 patients with IBS after a period on GFD 56% with CD-risk haplotype	Double-blind, randomized, controlled study Randomization to receive 16 or 0 g of gluten for six weeks	Effect on gastrointestinal and other symptoms Intestinal permeability with fecal lactoferrin measurement	Improvement with GFD in 68% of gluten group vs 40% of placebo group. Relief of abdominal pain and non-digestive symptoms such as fatigue. No effect on flatulence or nausea, though
Biesiekierski et al. (96)	37 asymptomatic patients with IBS and NCGS on a GFD 56% had risk haplotype	Double-blind, randomized trial Two weeks with low-FODMAP diet Then, randomization to receive placebo (16 g of soy protein), low-dose gluten (2 g) or high-dose gluten (16 g) for one week 22 were crossed to gluten, serum protein or control for two weeks	Effect of gluten in patients on low-FODMAP diet, as measured by symptoms and both serum and intestinal inflammation markers	All three groups improved with low-FODMAP diet, and then similarly worsened after intervention Only 8% improved with gluten exclusion
Shahbazhani et al. (108)	72 patients with IBS	Double-blind, placebo-controlled study, including 148 subjects; 72	Effect of gluten after reintroduction in patients with IBS on GFD	83% of those with gluten experience worsening symptoms <i>versus</i> 25% in the placebo group

		completed the initial six weeks on GFD, and were randomized to receive 52 vs 0 g of gluten for six weeks		
Vázquez Roque et al. (97)	45 patients with IBS-D 50% with CD-risk haplotype, homogeneously distributed in both groups	Randomized, controlled trial Randomization to receive GFD vs placebo for four weeks	Effect of gluten on permeability markers (lactulose and mannitol excretion), cytokine production, and clinical data 28 underwent rectosigmoidoscopy	Greater number of stools and higher permeability in the gluten arm No histological changes Differences are seen in those CD-risk haplotype
Zanwar et al. (104)	60 patients with IBS who had responded to GFD Patients with CD and wheat allergy were excluded	For four weeks gluten is dosed <i>versus</i> placebo in a randomized, double-blind, controlled fashion	Assessment before and after GI symptoms	Symptoms (abdominal pain, bloating, fatigue) worsened at one week after reintroduction
Elli et al. (98)	98 patients with IBS who had responded to GFD	Double-blind, randomized, crossover trial Reintroduction of gluten <i>versus</i> placebo (5.6 g gluten capsules)	Assessment of quality of life items (VAS, SF 36) Transaminases, CRP, and iron status are measured	28% of patients responded to GFD <i>versus</i> 14% to placebo