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TOPIC HIGHLIGHT

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Irritable bowel syndrome and food interaction

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Abstract

Irritable bowel syndrome (IBS) is one of the most common gastrointestinal disorders in Western countries. Despite the high prevalence of this disorders, the therapeutic management of these patients is often unsatisfactory. A number of factors have been suggested to be involved in the pathogenesis of IBS, including impaired motility and sensitivity, increased permeability, changes in the gut microbiome and alterations in the brain-gut axis. Also food seems to play a critical role: the most of IBS patients report the onset or the exacerbation of their symptoms after the meals. Recently, an increasing attention has been paid to the role of food in IBS. In this review we summarize the most recent evidences about the role of diet on IBS symptoms. A diet restricted in fermentable, poorly absorbed carbohydrates and sugar alcohols has beneficial effects on IBS symptoms. More studies are needed to improve our knowledge about the relationship between food and IBS. However, in the foreseeable future, dietary strategies will represent one of the key tools in the therapeutic management of patients with IBS.

Key words: Irritable bowel syndrome; Fermentable, poorly absorbed carbohydrates and sugar alcohols; Gut microbiota; Food intolerance; Gluten

Core tip: The most of irritable bowel syndrome patients reported food as a trigger of gastrointestinal symptoms and self-referred intolerance to certain food items. However, it is difficult identify which items are involved in symptoms triggering because food is a complex milieu of several chemicals, almost all potentially able to induce symptoms *via* several ways. It has been proposed three pathogenic mechanisms by which food items might induce symptoms: *via* immune activation (food hypersensitivity), *via* direct action of bioactive molecules (food chemicals) and *via* luminal distension.

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INTRODUCTION

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder characterized by abdominal pain or discomfort associated with abnormal bowel habit. Since the absence of reliable biomarkers, Rome Ⅲ diagnostic criteria define IBS as recurrent abdominal pain or discomfort for at least 3 d per month in the past 3 mo, associated with 2 or more of the following: improvement with defecation, onset associated with a change in the frequency of stool or onset associated with a change in the form (appearance) of stool. Based on stool form, IBS is

classified in IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), mixed IBS (IBS-M) and unsubtyped IBS (IBS-U)[1]. Prevalence of IBS in the industrialized world is approximately 10%-15%, which makes IBS one of the most common GI disorders[2]. The pathogenesis of IBS is not completely understood, but several factors seem to play a role in the pathogenesis of IBS, including dysregulation of the brain-gut axis with impaired gut motility and sensibility, psyco-social factors, genetic factors, impaired gut barrier function and changes in the gut microbiome[3].

Food plays a key role in IBS: more than 60% of patients with IBS report the onset or worsening of symptoms after meals, within 15 min in 28% and within 3 h in 93% of these patients[4]. The most of IBS patients (84%) reported meal-related symptoms to at least one food item. In addition, self-reported food intolerance is associated with higher symptoms severity score and reduced quality of life[5-7]. In line with this, patients try to identify and remove the food items they do not tolerate: a cross-sectional study showed that 62% of IBS patients limited or excluded food items from the diet[8].

The role of food as trigger of GI symptoms in functional disorders is well-known, while it is much more difficult to pinpoint what food groups or items are involved in symptoms onset or worsening in IBS. For this reason, dietary recommendations for functional gastrointestinal disorders (FGIDs) are limited and largely based more upon empiricism or pathophysiology knowledge rather than randomized clinical trials or guideline consensus. The lack of a specific nutritional training and scientific evidences explains the skepticism of most primary care practitioners and gastroenterologists about dietary advices, that often are limited to change fiber intake or to reduce lipids consumption.

In the last years, the potential role of food in the management of IBS has been revisited[9]. Searching PubMed (MeDLINe) database using the terms "food" and "irritable bowel syndrome", we have found that the number of published papers increased from 7 in 1997 to 108 in 2011. This renewed interest has led to new advances in the pathophysiology and management of IBS, but also to new sources of confusion. For example, increasing attention has been paid to the role of wheat in GI symptoms. Recent studies have supported the existence of a subgroup of IBS patients with undiagnosed non-celiac gluten sensitivity, defined as a condition of morphological, immunological, or functional disorder that responds to gluten exclusion[10]. However, the existence of a objective clinical entity is controversial and recent evidences seem to reappraise the role of gluten in GI symptoms in these patients, focusing the attention on fermentable, poorly absorbed, short-chain carbohydrates present in wheat[11].

In this paper, we performed a literature review about the putative pathogenic mechanisms of food in IBS as well as the recent evidences supporting the role of food as a means of therapeutic strategies in the management of IBS. Since a great number of papers have been published in the last years, we focused mainly on high-quality works.

PUTATIVE MECHANISMS

It should be remembered that food is a complex milieu of nutrients. On the other side, the ingestion of food activates a complex response of GI tract that allows the transfer of nutrients from the intestinal lumen to the systemic circulation through the processes of digestion, absorption and expulsion of needless elements. The great complexity of food composition and GI physiology explain why it is difficult to identify single food items involved in IBS symptoms triggering or worsening.

Several mechanisms have been proposed to explain how food triggers GI symptoms in IBS. Gibson propose at least three pathogenic mechanisms by which food items might induce GI symptoms in functional bowel disorders: *via* immune activation (food hypersensitivity), *via* direct action of bioactive molecules (food chemicals), and *via* luminal distension[12].

A long-standing debate is whether or not immunological mechanisms are involved in the pathogenesis of IBS. In the last decades, it has been suggested that increased epithelial barrier permeability leads to immune activation and low-grade inflammation, that could play a crucial role in the pathogenesis of IBS[13]. Since the gut is the gatekeeper that controls nutrients access, it is not difficult to imagine that food antigens in definite conditions could trigger low-grade inflammation that would change the motor and sensory function of the gut in a group of susceptible individuals[14].

Adverse food reactions may play an important role in GI symptoms triggering, as many patients report an exacerbation of symptoms after food ingestion[15]. There is no international consensus for the terms of "food intolerance". This expression should be referred to non-immunological non-toxic adversion to food[16]. Chemicals with potential bioactivity such as salicylates, amines and glutamates are natural, pharmacologically active substances that are believed to cause adverse reactions, such as anaphylactoid reactions, urticaria, and asthma in susceptible individuals by a non-immune direct effect on mast cells to produce cysteinyl leukotrienes. However, bioactive chemicals would be able to trigger GI symptoms including nausea, vomiting, abdominal pain, bloating or diarrhea[17] and a line of evidences support the role of these molecules in IBS[15]. Although several mechanisms have been proposed to explain the pathogenesis of these symptoms, it has been hypothesized that chronic exposure to food chemicals may induce visceral hypersensitivity to luminal stimuli through the activation and overexpression of TRP channels on enteric nervous system neurons. In addition, some evidences in murine model suggest that salicylate intolerance may involve mast cells production of cysteynil leukotriens, which promote smooth muscle contraction and increase vascular permeability[18]. Salicylates, glutamates and amines have been the principal targets of elimination diet treating groups, with

Table 1 Estimated food allergy rates in North America[21]

Prevalence	Infant/child	Adult
Milk	2.5%	0.3%
Egg	1.5%	0.2%
Peanut	1.0%	0.6%
Tree nuts	0.5%	0.6%
Fish	0.1%	0.4%
Shellfish	0.1%	2.0%
Wheat, soy	0.4%	0.3%
Sesame	0.1%	0.1%
Overall	5.0%	3%-4%

Table 2 Pathophysiologic classification of allergic reactions to food[19]

Immunopathology	Disorder
IgE dependent	Urticaria and atopic eczema
	Rhinitis or asthma
	Oral allergy syndrome (angioedema of lips and tongue)
	Nausea, abdominal pain, diarrhea or constipation
Non IgE dependent	Atopic dermatitis
	Celiac disease
	Eosinophilic esophagitis, gastritis, gastroenteritis, enterocolitis and proctitis

contrasting results[15].

Luminal distension is another mechanism by which food induces GI symptoms. It is well-known the presence of visceral hypersensitivity in the majority of patients with IBS, resulting in a lower painful threshold of gut wall stretching. The presence of certain nutrients in food, in particular short chain carbohydrates, could induce or worsen GI symptoms in IBS patients *via* two main actions. First, these small molecules are osmotically active and increase luminal water volume in distal ileum and colon. Secondly, short chain carbohydrates are substrates for colonic bacterial fermentation, resulting in the production of gas. The increase of intra-luminal water and gas volume leads to luminal distension that induces GI symptoms in subjects with lower pain threshold or impaired motility pattern such as patients with functional GI disorders[19].

FOOD HYPERSENSITIVITY

The term food allergy is used to describe an adverse immune response to food. Food allergy can be classified on the basis of immunopathologic mechanisms in IgE-mediated (considered type I hypersensitivity) and non-IgE-mediated reactions (including type Ⅲ and Ⅳ hypersensitivity)[20]. In the Table 1 are reported estimated rates of food allergies in North America[21].

Classic IgE-mediated food allergies are classified as type- I immediate hypersensitivity reaction. These allergic reactions have an acute onset (from seconds to one hour) and may have extremely heterogeneous clinical manifestations[20]. Although it is relatively easy to recognize the allergic manifestations of skin, such as urticaria and atopic eczema, and respiratory tract, such as rhinitis or asthma, the GI tract can be affected by food allergies in several ways: oral allergy syndrome (angioedema of lips and tongue), nausea, abdominal pain, diarrhea or constipation. Rarely, food allergy manifested as signs and symptoms that can occur in IBS (diarrhea associated to abdominal pain)[22]. The spectrum of food allergies also includes delayed-onset diseases, that can be mediated by intestinal mucosal mechanisms involving not only IgE but also T cells, mast cells and eosinophils that produce proinflammatory mediators. Belong of this kind of disease: atopic dermatitis, celiac disease or eosinophilic GI diseases, such as esophagitis, gastritis, gastroenteritis, enterocolitis and proctitis (Table 2).

The increased prevalence of atopic conditions in patients with diarrhea-predominant IBS[23] and the positive response to oral sodium cromoglycate treatmentin these patients[24]. suggest that food hypersensitivity could play a role in pathogenesis of IBS.

An equivalent of prick test in the gut mucosa, the so-called colonoscopic allergen provocation test (COLAP), showed promising initial results. Food antigens selected according to the patients' history of food intolerance and the presence of specific IgE in serum were injected into the mucosa of the cecum during colonoscopy in seventy adult patients with chronic abdominal symptoms and suspected gastrointestinal food allergy and in five healthy volunteers. COLAP test was positive in response to at least one food antigen in 77% of patients, whereas no reaction was detected in the five healthy volunteers. Moreover, in the clinical follow up over a period of at least 6 months, a food eliminiation diet induced a significant improvement of symptoms in 29 of 35 patients (83%) with positive COLAP test. The researchers concluded that allergic reactions may play a part in a subgroup of patients with irritable bowel syndrome and COLAP test may improve the clinical management of these patients, supporting this "intestinal prick test" as a valuable diagnostic tool of GI food allergy[25].

Several researchers focused on the role of food-specific IgG and IgG4. Although dietary antigens physiologically induce the production of IgG4, the hypothesis that these immunoglobulin are involved in IBS stems from the observation that IBS patients had higher IgG4 titers to certain antigens, such as wheat, beef, pork and lamb, compared to controls[26]. Moreover, two studies revealed that a food elimination diet based on serum IgG/IgG4 antibodies is able to improve overall symptoms in IBS[26,27]. Despite the initial promising results of COLAP test and elimination diet based on serum IgG/IgG4 antibodies, there have been no further published reports of these tests[28].

In conclusion, the role of hypersensitivity in IBS remains uncertain. Clinical trials, *in vitro* and epidemiological studies have suggested a potential role of allergic mechanisms in the pathogenesis of IBS, but further studies are needed to elucidate this relationship. To date, food allergy and IBS should be considered as two distinct clini-

cal entities. Food allergy should be considered in case of uncontrolled symptoms in patients with IBS-like symptoms and when a clear allergic response to a specific food has been identified. Unfortunately, there is not a gold standard procedure for food allergy diagnosis. At present, skin prick tests and the radioallergosorbent test, the most used tests to investigate IgE-mediated allergy, suggest only individual sensitization but they are not sufficient *per se* to diagnose food allergy. For this reason, suspected food allergy needs to be confirmed by a double-blind, placebo-controlled food challenge[20].

Fat hypersensitivity

Lipids are a complex group of chemical substances including triglycerides, and its constituent fatty acid, as well as cholesterol, phospholipids and sterol. Fat is not a simply nutrient, in fact, lipids are able to modulate the responses of the gut to various stimuli. In patients suffering from FGIDs, such as irritable bowel syndrome, some of these modulatory mechanisms, being abnormal, may lead to the onset of gastrointestinal symptoms[29]. In fact, it has been hypothesized that in irritable bowel syndrome, as well as in other FGIDs, patients display intestinal hypersensitivity and exaggerated reflexes after normal stimuli, for example after fat ingestion[30]. These patients complain symptoms such as fullness, bloating and nausea after lipids intake much more frequently and at lower fat load than healthy subjects. It has been described that lipids through the inhibition of small bowel motility and the delaying of intestinal transit may cause gas retention and, then, abdominal bloating[31]. On the other hand, many evidences show that lipids stimulate colonic motor activity through a mechanism known as "gastrocolonic reflex". Such reflex seems to be upregulated in IBS patients and may lead to post-prandial diarrhea. Simrén *et al*[32] have, also, demonstrated that duodenal lipid load increased rectal sensitivity and perception of rectal distension in IBS patients, inducing different symptoms in the constipated and diarrheal subtypes of IBS with the same mechanism. In fact, if C-IBS patients experience rectal distension as pain, D-IBS subjects report primarily rectal urgency. However, although association between lipids intake and gastrointestinal symptoms has been observed, only few studies report lower dietary fat consumption in IBS patients if compared to healthy subjects.

FOOD CHEMICALS

Salicylates

Although, aspirin and other non steroidal anti-inflammatory drugs are the best studied compounds belonging to salicylates, salicylic acid and its derivates are present in many foods in different concentrations[33]. Salicylate intolerance is defined as a nonspecific antigen-induced pseudoallergic hypersensitivity reaction characterized by systemic and local manifestations[15,18-33].

Symptoms of acetylsalicylic acid intolerance are caused by overproduction of leukotriene metabolites (leukotrien B4, C4, D4, E4) and a reduction of prostaglandin, prostacyclin and thromboxan as consequence of cyclooxygenase inhibition. It has been hypothesized that in patients intolerant to salicylate the inhibition of these enzymes may be higher than in healthy subjects[34].

The typical triad of intolerance to salicylic acid comprises the occurrence of polyposis nasi, nonallergic asthma and angioedema as well as laryngeal edema following contact with substances containing acetylsalicylic acid. Further clinical manifestations of salicylate intolerance may include gastrointestinal symptoms such as abdominal pain, swelling, meteorism, colitis and diarrhea.

However, the presentation of such gastrointestinal symptoms, accompanied or not by typical systemic manifestations, may create diagnostic difficulties; in fact, the diagnosis of salicylate intolerance may be considered once other causes have been excluded.

The variety of symptoms of salicylate intolerance is linked to the different expression and concentration of cytokines in the different tissues. In fact, for example, leukotriene B4 is primarily involved in inflammation, leukotriene C4 is responsible of typical pseudo allergic mechanisms while leukotrienes C4, D4 and E4 cause bronchoconstriction, bronchial hyperreactivity, mucus production and vasodilatation[35]. These mechanisms have been used to explain intolerance to acetylsalicylic acid and, although it is possible to hypothesize that other salicylate derivates may induce symptoms sharing similar pathogenesis, further studies are needed.

At the moment, elimination diet represents the best way to diagnose and manage salicylate as well as other food chemicals intolerance, but, considered the widespread presence of these substances in foods (Table 3), too severe alimentary restrictions should be avoided for the risk of unpalatable diets and malnutrition. Moreover, all studies, which report that dietary manipulation may be a valid treatment choice in IBS patients, have important limitations in their trial designs, including inadequate patient selection, appropriateness and duration of exclusion diets, and methods of food challenge[15].

LUMINAL DISTENSION

Milk

The enzyme activity of lactase, a β-galactosidase present on the apical surface of enterocytes in the small intestinal brush border, physiologically starts to decline within the first few months of life in most of mammalian. In humans, approximately 70% of the adult population has a decreased lactase activity[36]. In people with lactase deficiency, lactose is not hydrolyzed and absorbed in the small bowel, but passes through the gastrointestinal tract into the colon into where bacterial fermentation produces gas and short-chain fatty acids and other products that can cause luminal distension and induce GI symptoms[37].

The typical symptoms of lactose intolerance are similar to those in IBS and include abdominal pain, bloating, flatus, diarrhoea, borborygmi. Conversely, patients with

Table 3 Food sources of salicylate reported in literature[15,18,33]

Food	State	Significant source of salicylate
Pepper (red chili)	Fresh	1.20
Sweet potato (white)	Fresh	0.50
Apricot	Fresh	2.58
Apricot	Canned	1.42
Apricot	Nectar	0.14
Orange	Fresh	2.39
Pineapple	Fresh	2.10
Almonds	Fresh	3.0
Raspberries	Fresh	3.14
Dates	Fresh	3.73

IBS more frequently report perceived intolerance to milk or dairy products compared to healthy individuals[8].

Despite the similarity between IBS and lactose intolerance, the prevalence of lactose intolerance in IBS patients is similar compared to controls[38] and testing patients for lactose intolerance or the use of lactase supplementation is not justified[39].

On the other side, subjective perception of intolerance for milk is not a useful criteria to identify people with lactose malabsorption. Vernia *et al*[40] tried to define the relationship between self-referred perception of milk intolerance and lactose intolerance. In this study, 475 consecutive IBS patients underwent a hydrogen breath test after an oral load of lactose. Data analysis of 201 age- and sex-matched pairs of IBS patients classified according to self-reported milk tolerance/intolerance showed that the prevalence of positive HBT was similar in milk "tolerant" (68.6%) and "intolerant" patients (75.6%), confirming that self-reported milk intolerance does not help in identifying lactose intolerance in IBS patients.

However, it is plausible to hypothesize that not lactose but milk-specific component may play a role in IBS symptoms and reducing milk and dairy products in the diet could represent an appropriate strategy in the management of IBS.

Fermentable oligosaccharides, disaccharides, monosaccharides and polyols

In the last couple of years, increasing evidences support the efficacy for the management of IBS of a diet with lower amounts of fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs)[41]. Scientific evidences showed that they are individually involved as a trigger for symptoms in patients with functional disorders[42-44]. At the base of the concept of enclosing these sugars into one group would be the common pathogenetic mechanism by which they contribute to symptoms burden in IBS: when FODMAPs are poorly absorbed through the small intestine, they pass in the bowel and increase intestinal luminal water content through their osmotic activity and induce gas production due to fermentation by gut bacteria. The increased content of water and gas causes luminal distension that induces GI symptoms in IBS patients. In addition, products of fermentation such as short-chain fatty acids could be involved in symptom generation[12].

The low FODMAP diet approach involves the reduction, not complete avoidance, of these sugars in the diet. Based on the knowledge of the FODMAP status of foods, foods are classified into high and low FODMAP content and the latter food consumption is encouraged (Table 4). In a first period of 6-8 wk, all known or suspected types of food with high content in FODMAP groups are strictly restricted from the diet, in order to determine the benefit of FODMAP restriction. Subsequently, individual FODMAPs are reintroduced to test their individual tolerance of each FODMAP *via* a series for food challenges[44]. As the authors rightfully acknowledge, restricting the intake of FODMAPs excludes a wide variety of foods from the diet with the potential risk to affect nutrient intake.

Several studies supported the potential benefits of restricting a spectrum of FODMAPs in the diet in IBS[45,46]. Recently, in a randomized double-blind controlled crossover study, Halmos *et al*[47] demonstrated that a diet low in FODMAPs for a 3 wk period effectively reduced overall gastrointestinal symptoms -abdominal pain, bloating and bowel habit dissatisfaction- in a group of 30 unselected IBS patients, compared to a standard Australian diet.

In a non-randomized study, the low FODMAP diet was more effective than United Kingdom national dietary guidelines for symptom control in a series of consecutive patients with IBS who attended a follow-up dietetic outpatient visit for dietary management of their symptoms[45].

Other studies are needed to assess the long-term efficacy and safety of FODMAP restriction as well as to identify patient profiles that predict dietary response. However, low FODMAP diet represents the one of the most promising emerging strategies in the management of IBS.

Wheat

Many individuals complaining GI symptoms benefit from gluten withdrawal, although they cannot be classified as either celiac diseases or wheat allergy[48,49]. The hypothesis that gluten is able to induce IBS-like symptoms in non-coeliac people is not new[50,51]. Gluten has been considered the culprit of the causal relationship between wheat ingestion and GI symptoms. Indeed, recent literature has supported the existence of a subgroup of IBS patients with undiagnosed non-celiac gluten sensitivity, defined as a condition of morphological, immunological, or functional disorder that responds to gluten exclusion[10]. The existence of this condition is suggested by clinical trials showing that gluten-free diet was able to relieve GI symptoms in a randomized, double-blind, placebo-controlled, rechallenge trials[52]. Biesiekierski *et al*[52] confirmed the existence of gluten sensitivity in patients with IBS-D in a randomized, double-blind, placebo-controlled, rechallenge trial. In this study, 34 IBS patients who reported symptomatic relief after a GFD for at least 6 wk were enrolled. Nineteen patients received 16 g of non fermentable gluten per day *via* bread and a muffin, whereas the

Table 4 Food sources of fermentable oligosaccharides, disaccharides, monosaccharides and polyols[44]

	High FODMAP food source	Low-FODMAP food source
Excess fructose	Fruits (apples, pears, nashi pears, clingstone peaches, mango, sugar snap peas, watermelon, tinned fruit in natural juice) Honey Sweeteners (fructose)	Fruit (banana, blueberry, carambola, durian, grapefruit, grape, honeydew melon, kiwifruit, lemon, lime, mandarin, orange, passionfruit, paw paw, raspberry, rockmelon, strawberry, tangelo) Honey substitutes (maple syrup, golden syrup) Sweeteners (any except polyols)
Lactose oligosaccharides	Milk (cow, goat and sheep) Ice cream Yoghurt Soft cheeses	Milk (lactose-free, rice milk) Cheese (hard cheeses, camembert) Yoghurt (lactose-free) Ice cream substitutes (gelati, sorbet) Butter
Polyols	Vegetables (artichokes, asparagus, beetroot, Brussels sprout, broccoli, cabbage, fennel, garlic, leeks, okra, onions, peas, shallots) Cereals (wheat and rye when eaten in large amounts) Legumes (chickpeas, lentils, red kidney beans, baked beans) Fruits (watermelon, custard apple, white peaches, rambutan, persimmon)	Vegetables (bamboo shoots, bokchoy, carrot, celery, capsicum, choko, choy sum, corn, eggplant, green beans, lettuce, chives, parsnip, pumpkin, silverbeet, spring onion, tomato) Onion/garlic substitutes (garlic-infused oil) Cereals (gluten-free and spelt bread/cereal products)
Fructans and/or galactans	Fruits (apples, apricots, cherries, longon, lychee, nashi pears, nectarine, pears, peaches, plums, prunes, watermelon) Vegetables (avocado, cauliflower, mushrooms, snow peas) Sweeteners (sorbitol, mannitol, xylitol, maltitol, isomalt	Fruits (banana, blueberry, carambola, durian, grapefruit, grape, honeydew melon, kiwifruit, lemon, lime, mandarin, orange, passionfruit, paw paw, raspberry, rockmelon) Sweeteners (sucrose, glucose)

other 15 patients received gluten-free bread and a muffin. In the gluten group, 68% reported that symptoms were not adequately controlled compared with 40% in gluten-free group ($P = 0.0001$). Moreover, patients in the gluten-free group reported significantly greater improvements in GI symptoms such as pain, bloating, stool consistency and tiredness compared to patients in gluten group. Researchers suggested that gluten sensitivity may be a distinct clinical entity in a subset of patients with IBS.

Following studies failed to find a specific marker or pathogenetic mechanisms supporting the idea that gluten sensitivity is an objective clinical entity. Despite the lack of evidences, the mass media have publicized the advantages of GFD leading many patients to exclude gluten from diet. Two years later, the same group of researchers conducted a placebo-controlled, crossover rechallenge study in 37 subjects with gluten sensitivity and IBS. After a two weeks run-in on a gluten-free and low FODMAP diet test, subjects were placed on high-gluten (16 g gluten/d), low-gluten (2 g gluten/d and 14 g whey protein/d), or control (16 g whey protein/d) diets for 1 wk, followed by a washout period of at least 2 wk. Twenty-two participants then crossed over to groups given gluten (16 g/d), whey (16 g/d), or control (no additional protein) diets for 3 d. In all participants, gastrointestinal symptoms improved during reduced FODMAP intake and similarly worsened when their diets included gluten or whey protein. Participants were then rechallenged gluten (16 g/d), whey (16 g/d), or control (no additional protein) diets for 3 d and during this rechallenge symptoms increased by similar levels among groups, again regardless of the protein source. The researchers concluded that gluten sensitivity might not be a discrete entity and that gluten might not be a specific trigger of functional gut symptoms once dietary FODMAPs are reduced[11].

In conclusion, no clear evidences support that gluten may induce GI symptoms in individuals without CD. The observed effects of GFD in GI symptoms relief may be due to the fact that many gluten-containing cereals are high in fermentable, poorly absorbed,short-chain carbohydrates that seem to have a critical role in triggering IBS symptoms[12].

DIET AND GUT MICROBIOTA

Gut microbiota is individual-specific and is influenced by the genetic and environmental factors. In particular is well-known the role of nutrition in changes of gut bacteria[53,54]. In a recent study, researchers found that gut microbiota is able to rapidly switch between herbivorous and carnivorous functional profiles after a short-term macronutrient changes in diet[55].

Recently, the intestinal microbiota has been proposed as an etiological factor in physiopathology and pathogenesis of IBS[56]. Supporting the role of gut bacteria in IBS are studies that document the onset of IBS symptoms after an acute gastroenteritis and the qualitative and quantitative changes of bacteria composition that occur in IBS subtypes[57]. In a recent study, researchers aimed to assess the microbiota composition by molecular analysis of fecal samples from 62 patients with IBS patients and 46 healthy individuals. They found that gut microbiota of IBS patients differed significantly from that of controls. In particular, the microbiota of IBS patients had a 2-fold increased ratio of the Firmicutes to Bacteroidetes[58]. However, the role of microbiota is still unclear due to

methodological problems, influence of confounding factors and large differences between studies.

In agreement with this observation, we can speculate that diet-induced changes to the gut microbiota may contribute to the onset or worsening of IBS symptoms, as well as beneficial effects of certain nutrients on IBS symptoms could be, at least partially, mediated by changes in gut bacteria.

CONCLUSION

Food is able to trigger IBS symptoms in a great part of patients. Food related mechanisms involved in to trigger symptoms seem generally referred to food hypersensitivity, action of bioactive molecules and luminal distension. Intestinal microbiota aberration has a crucial role in luminal distension and considering that microbiota is often modified by dietary habits so we have closed the circle. The food changes the microbiota which in turn induces the abnormal fermentation of food ingested. A great attention is now directed to food containing FODMAP that are able to determine IBS symptoms both *via* microbiota aberration and luminal distension. Finally, studies oriented to define relationship between IBS and food could be a comprehensive strategy to improve medical therapy of IBS.

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