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TOPIC HIGHLIGHT

2015 Advances in Irritable Bowel Syndrome

Food allergy in irritable bowel syndrome: The case of non-celiac wheat sensitivity

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Abstract

Irritable bowel syndrome (IBS) is one of the most common gastrointestinal disorders, having a prevalence of 12%-30% in the general population. Most patients with IBS attribute their symptoms to adverse food reactions. We review the role of diet in the pathogenesis of IBS and the importance of dietary factors in the management of these patients. The MEDLINE electronic database (1966 to Jan 2015) was searched using the following keywords: "food", "diet", "food allergy", "food hypersensitivity", "food intolerance", "IBS", "epidemiology", "pathogenesis", "pathophysiology", "diagnosis", "treatment". We found 153 eligible papers; 80 were excluded because: not written in English, exclusive biochemical and experimental research, case reports, reviews, and research otherwise not relevant to our specific interest. We selected 73 papers: 43 original papers, 26 reviews and 4 letters to the editor. These papers focused on IBS pathogenesis, the association between IBS and atopy, and between IBS and food allergy, the relationship between IBS and non-celiac wheat sensitivity, the role of diet in IBS. Pending further scientific evidence, a cautious approach is advisable but the concept of food allergy should be included as a possible cause of IBS, and a dietary approach may have a place in the routine clinical management of IBS.

Key words: Irritable bowel syndrome; Food allergy; Food intolerance; Non-celiac wheat sensitivity; Atopy; Asthma; Elimination diet

Core tip: Starting from the late evidences about the non-celiac wheat sensitivity, we reviewed the role of diet in the pathogenesis of irritable bowel syndrome and the importance of dietary factors in the management of these patients. We found 183 papers about the matter, selecting 73 for review. We concluded that food allergy could be a possible cause of irritable bowel syndrome, and a dietary approach should be implemented in clinical practice.

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INTRODUCTION

With prevalence ranging from 12%-30% of the general population, and even if it is only 5%-10% using recent diagnostic criteria, irritable bowel syndrome (IBS) is one of the most common gastrointestinal disorders. The disease is usually diagnosed in younger patients (*i.e.*, < 50 years of age) and is more common in women[1,2]. It has always been counted among the chronic functional gastrointestinal disorders, characterized by abdominal discomfort or pain, abnormal bowel habits, and often bloating and abdominal distension. Symptom patterns remain the cornerstone of diagnosis and classification of functional gut disorders (*i.e.*, the Rome Ⅲ criteria). They may be categorized as diarrhea-predominant (D-IBS), constipation-predominant (C-IBS), mixed diarrhea and constipation (M-IBS), and unclassified (U-IBS) IBS[3,4]. Although IBS does not seem to be associated with the development of serious diseases or mortality, it reduces the patient's quality of life considerably. Symptom severity varies in different patients, from tolerable to severe, interfering with daily activity, causing an impairment similar to some major chronic diseases, such as congestive heart failure, hepatic cirrhosis, renal insufficiency, and diabetes[5,6]. Data from an international survey on 1966 responding IBS patients (83% female, 91% white, 78% United States/Canada), stressed the relevance of impaired health status: restriction of 73 d/year of activity on average, poor health-related quality of life, particularly with dietary restrictions, mood disturbance, and interference with daily activity. To receive treatment that would make them symptom-free, patients would give up 25% of their remaining life (average 15 years), and 14% would risk a 1/1000 chance of death[7]. In addition, this condition represents an economic burden to society as a result of the low productivity of IBS patients and the excessive use of healthcare resources[8,9]. Conventional IBS treatment consists of antispasmodics, antidepressants, and medications modifying bowel habit, depending on whether diarrhea or constipation is the predominant disorder. The notorious long-term inadequacies of current drug therapy lead to much patient dissatisfaction, and a tendency for patients to seek a variety of alternative remedies, especially of a dietary nature[10,11], because 20%-65% of them attribute their symptoms to adverse food reactions[12-14]. However, there are surprisingly few studies focusing on the relationship between IBS symptoms and diet, thus this issue is still controversial[15-23]. This represents a glaring gap that needs to be addressed.

METHODOLOGY OF THE REVIEW

Recently published data on the relationship between gastrointestinal functional disorders (including IBS) and adverse food reactions showed that the number of studies has increased since 2000: from 54 to 77 publications per 2.5-year interval for "adverse food reactions", and from 454 to 991 for "food allergy", up to June 2013[24]. The present review aims to elucidate the role of diet in the pathogenesis of IBS and the importance of dietary factors in the management of these patients. We searched the MEDLINE electronic database (1966 to Jan 2015) using the following keywords alone and in different combinations: "food", "diet", "food allergy", "food hypersensitivity", "food intolerance", "IBS", "epidemiology", "pathogenesis", "pathophysiology", "diagnosis", and "treatment". The search was restricted to papers published in English or at least having an abstract in English. We retrieved potentially relevant articles and reviewed their reference lists to identify studies missed by our search strategy. At the end of our search, we found a total of 153 eligible papers; 80 were excluded because: not written in English, exclusive biochemical and experimental research, case reports, reviews reporting data of the same original studies, and research otherwise not relevant to our specific interest (*i.e.*, matching error). In the end we selected 73 papers, specifically 43 original papers, 26 reviews, and 4 letters to editor.

IBS PATHOGENESIS: NOT ONLY A SOMATIZATION DISORDER

To date IBS pathogenesis remains uncertain, even though multiple factors, such as altered small bowel and/or colonic motility (slow, fast or uncoordinated), visceral hypersensitivity ("visceral hyperalgesia"), imbalance in neurotransmitters, genetic factors, psychological dysfunction, infections, and inflammation, may lead to the development and maintenance of symptoms[25,26].

The evidence of a correlation between IBS and the microorganisms that reside in the gut in physiological or pathological conditions has been highlighted in an IBS patient subgroup. Some authors point to a small intestinal bacterial overgrowth (SIBO)-like condition as one possibility, whose diagnosis is often based on indirect measures (lactulose breath test), leading to symptoms due to fermentation and gas production in the small intestine[27,28]. In this context, some IBS patients describe acute onset of persistent symptoms after an episode of gastroenteritis, characterized by at least two of the following: fever, vomiting, diarrhea, or positive stool culture. New IBS onset develops after

infective gastroenteritis in 4%-31% of people, and the odds of developing IBS seem to be significantly higher in subjects with prior gastroenteritis compared to controls[29-34]. These data are confirmed by the prevalence of post-infection IBS among patients with IBS that ranges between 3% and 35%[35,36]. Nevertheless, a simple explanation of post-infection IBS does not yet exist, but enteric infections surely affect gut physiology, causing a persistent low-grade mucosal inflammation in some patients[37].

Colon mucosa histology of patients with IBS who did not describe any pre-existing acute infection gastroenteritis found similar low-grade inflammatory changes on post-infection patients, suggesting a more general "inflammatory hypothesis" for IBS[38,39]. Furthermore, this mucosal inflammation could be a clue for a role of food allergy in an IBS subgroup; histology can be characterized by increased numbers of jejunum and terminal ileal mucosa mast cells[40-47], eosinophils[46,48,49], T lymphocytes [T helper (T_H)2 and T_H17][47,49-51], B lymphocytes and plasma cells[52]. This inflammatory infiltrate causes typical abnormalities on the intestinal nerve plexus and nociceptive structures: *i.e.*, association of mast cells to enteric and colonic visceral-nociceptive sensory neurons, unmyelinated nerves in the lamina propria at the ileo-caecal junction, and substance-P positive nerves[53-56], and direct T cell-neural interaction, lymphocyte infiltration in the myenteric plexus[57], and increased circulating gut-homing lymphocytes expressing β7 integrin[58]. Obviously, an intense pattern of expression of pro-inflammatory and neuro-stimulating molecules support such substantial change in the normal intestinal mucosa morphostructural framework. Specific histopathology staining has found increased tissue concentration of histamine (and H1R and H2R receptors)[59-61], serotonin[62,63], substance P, vasoactive intestinal peptide[64], inducible nitric oxide synthase (iNOS)[65,66], pro-inflammatory cytokines [*i.e.*, interferon (IFN)-γ, interleukin (IL)-1β, tumor necrosis factor (TNF)-α, IL-4 and IL-13 [(the latter are T_H2 cytokines, leading to up-regulation of transforming growth factor (TGF)-β and increased cyclooxygenase-2 and prostaglandin E2 expression within smooth muscle)], chemotactic chemokines [*i.e.*, monocyte chemotactic protein-1 (CCL2), macrophage inflammatory protein-1β (CCL4), and CXCL16][67,68], and a high TNF-producer/low IL-10-producer cell phenotype[69]. Strengthening the role of inflammation, increased fecal levels of IgE, tryptase, eosinophil cationic protein and eosinophil protein X have also been found[70-74]. All these quantitative data suffer from a great overlap between IBS patients and controls; however, it is generally accepted that the mucosal immune system seems to be activated in at least a subset of patients suffering from IBS. In these subjects it is noteworthy that mucosal inflammation and local activation of the immune system can be attributable to either exogenous factors, including food antigens and changes in the resident microbial flora, or endogenous chemical irritants, such as bile salts. Mucosal immune cell activation results in changes in the function of submucosal and myenteric neurons, linking these two effector systems in the genesis of gastrointestinal function disorders (*e.g.*, intestinal permeability, secretion, absorption, blood flow, visceral sensitivity, and motility)[33,38,39,74,75].

On the other hand, the classical pathogenic hypothesis is that IBS represents a disturbance of the "brain-gut axis", referring to the bi-directional communication between the gut (luminal wall and enteric nervous system) and the central nervous system, including the hypothalamic-pituitary axis. In this context female gender, family history of IBS, history of physical or sexual abuse, and co-morbid psychiatric disorders are strong IBS risk factors. In addition, up to 70% of the patients referred to tertiary centers with IBS meet diagnostic criteria for anxiety or depression[76-78]. However, a link between this "classical pathogenesis" and inflammation exists. Some studies sustain that stressful early life events and/or psychiatric co-morbidity mediate low-level inflammation and mast cell and lymphocyte infiltration of the bowel. Many studies on IBS link the events observed at the cellular level to anxiety and depression. Increased gastrointestinal symptoms, due to stronger intestinal cell immune activity, are directly linked to anxiety and depression. Furthermore, a certain correlation has been shown between inflammatory cytokine release (IL-1β, IL-6, and TNF-α,) and mood. These data support the histopathology evidence promoting the idea of a three-way relationship between IBS (as well as other functional gastrointestinal disorders), mood disturbance, and immune dysregulation[79-81]. Further complicating this framework is the established existence of a complex immune response system, which cannot be reduced only to T_H1 and T_H2 responses, but includes several pathways described as a mosaic of overlapping T_H1/T_H2 responses mediated by T_H17 and T_H22 cells[82].

ATOPY AND IBS

It has been suggested that IBS, and its related low-grade inflammation, can be the expression of a systemic allergic (or "atopic") disorder induced by foods (food allergy or food hypersensitivity). Several lines of evidence support this hypothesis (Table 1). An increased airway responsiveness to inhaled methacholine and/or reversibility with bronchodilators has been shown in IBS patients with no clinical evidence of asthma or other atopic disease compared to control groups (*i.e.*, positive disease controls with inflammatory bowel disease and healthy controls)[83,84]. Nevertheless, contrasting data come from a study on 42 IBS patients and 42 matched healthy controls that does not confirm increased bronchial hyper-responsiveness[85].

Analysis of this same issue from the opposite point of view has evidenced that patients with bronchial

Table 1 Summary of studies on irritable bowel syndrome and atopy

Ref.	Study design	Patients	Topic	Main results
White *et al*[83], 1991	Case-control observational study	11 IBS patients 11 healthy controls 11 organic gut diseases patients	IBS and bronchial hyper-responsiveness	FEV1 reduction induced by methacholine in IBS patients was significantly greater than that observed in healthy subjects. FEV1 decrease in patients with organic disease was not different from that in normal subjects
Yazar *et al*[84], 2001	Case-control observational study	133 IBS patients 137 healthy controls	IBS and asthma	Twenty-one (15.8%) IBS patients and 2 (1.45%) patients from the control group had the diagnosis of asthma. FEV1, flow after 50% of the vital capacity has been exhaled, peak expiratory flow rate, and maximal mid-expiratory flow rate were significantly different
Jun *et al*[85], 2005	Case-control observational study	42 IBS patients 42 healthy controls	IBS and bronchial hyper-responsiveness	No statistical difference was found between the two groups with respect to FEV1, FVC, FVC/FEV1, and FEF(25-75)
Roussos *et al*[86], 2003	Case-control observational study	150 asthma patients 130 other pulmonary disease patients 120 healthy controls	IBS and asthma	IBS prevalence was significantly higher in asthmatics (62/150, 41.3%) than in subjects with other pulmonary disorders (29/130, 22.3%) and healthy controls (25/120, 20.8%). None of the asthma medications were associated with increased or decreased likelihood of IBS
Ozol *et al*[87], 2006	Case-control observational study	125 asthma patients 95 healthy controls	IBS and asthma	IBS was found in 29.6% and 12.7% ($P < 0.005$) respectively of asthma patients and healthy controls. Food allergy was reported in 7.2% and 2.1% ($P > 0.05$) respectively for the two groups. No significant association between asthma related parameters, IBS, and food allergy could be found
Powell *et al*[88], 2007	Retrospective study	7235 patients attending a general practice	IBS, asthma and allergic rhinitis	IBS was more common in patients with asthma (9.9%) and allergic rhinitis (7.9%) compared to patients with chronic diseases (4.9%, $P < 0.002$ and 4.9%, $P < 0.05$ respectively) or the remaining non-asthmatic population (5.5%, $P < 0.001$ and 5.5%, $P < 0.02$ respectively)
Cole *et al*[89], 2007	Nested case-control study	91237 people with asthma 24518 people without asthma	IBS and asthma	Incidence of IBS among people with asthma was 20% higher than in non-asthmatic patients; no association was found between oral steroid intake and IBS among people with asthma
Huerta *et al*[90], 2002	Population-based cohort study	50000 people with asthma 50000 people without asthma	IBS and asthma	IBS incidence in the asthma cohort was 2.5 per 1000 persons/years and 2.0 in the general population, with a RR of 1.3. In the asthma cohort, oral steroid users had RR of 0.5 for developing IBS, without any difference between short- and long-term users
Panicker *et al*[91], 2008	Case-control observational study	138 asthma patients 145 healthy controls	IBS and asthma	A large proportion (39.13%) of asthmatics had IBS compared to controls (7.93%) ($P < 0.001$). IBS was reported in 87% of cases using inhalers, and in 13% with additional oral theophylline ($P < 0.001$). As many as 66.6% cases, had IBS with relatively short duration of asthma (1-5 yr, $P < 000$)
Hunskar *et al*[92], 2012	Cohort study	817 subjects exposed to giardia 1128 subjects not exposed to giardia	Post-infection IBS and asthma	IBS was found in 47.8% of subjects with asthma compared with 45.3% in those without asthma ($P = 0.662$) in the giardia exposed group. For controls, corresponding percentages were 23.9% and 12.2% ($P < 0.001$)
Tobin *et al*[93], 2008	Prospective study	125 consecutive: allergy/ immunology ($n = 39$), gastroenterology ($n = 36$) general medicine ($n = 50$)	IBS and atopic diseases	The likelihood of IBS was significantly higher in patients with seasonal allergic rhinitis (2.67 times; $P = 0.03$), allergic eczema (3.85 times; $P = 0.001$), and depression (2.56 times; $P = 0.04$). Patients reporting atopic symptoms (seasonal allergic rhinitis, asthma, and allergic eczema) were 3.20 times (95%; $P = 0.02$) more likely to fulfill IBS criteria
Jones *et al*[94], 2014	Retrospective study	30000 patients from primary care medical records	FGIDs and atopic diseases	In patients suffering from IBS alone, functional dyspepsia alone and multiple functional gastrointestinal disorders, there was higher asthma prevalence compared to controls (OR = 1.43, 1.41 and 1.92 respectively)
Olén *et al*[96], 2014	Birth cohort study	2610 children	Recurrent abdominal pain and atopic diseases in children	237 (9%) children reported abdominal pain when 12 yr old. Asthma in the first two years of life and food allergy at age 8 yr were significantly associated with abdominal pain at 12 yr ($P < 0.001$). There was an increased risk of abdominal pain at 12 yr in children sensitized to food allergens at 4 or 8 yr
Smith *et al*[97], 1985	Prospective study	29 patients with perceived food hypersensitivity	Self-reported food hypersensitivity and allergy	17 (60%) of the 26 patients were positive to skin prick tests to inhalant allergens

Lillestøl *et al*[98], 2010	Prospective study	71 patients with perceived food hypersensitivity	Self-reported food hypersensitivity and allergy	66 (93%) patients suffered from IBS and 43 (61%) had atopic diseases (predominantly rhinoconjunctivitis). Atopic patients had increased density of IgE-bearing cells and intestinal permeability but gastrointestinal symptoms did not differ between groups (P = 0.02). IgE-positive cells and intestinal permeability did not differ between patients who were sensitized to inhalants and those who were only sensitized to food
Berstad *et al*[99], 2012	Prospective study	84 patients with perceived food hypersensitivity	Self-reported food hypersensitivity, IBS, chronic fatigue and fibromyalgia	83 patient were diagnosed with IBS, 58% with severe symptoms. 85% reported symptoms suggestive of chronic fatigue and 71% fibromyalgia. These symptoms could not be explained either by IgE-mediated food allergy or by organic pathology
Lind *et al*[100], 2013	Case-control observational study	38 patients with self-reported food allergy 42 healthy controls	Self-reported food hypersensitivity, IBS, fatigue	FIS scores were higher in patients (median 85.0, interquartile range 36.8-105.3) than in controls (median 14.0, interquartile range 3.0-29.0, $P \leqslant 0.0001$)
McKee *et al*[12], 1987	Observational study	40 IBS patients	IBS and elimination diet	Patients received an antigen-exclusion. 15% showed improvement in their IBS-symptoms. A further 12.5% reported increased well-being but this did not seem to be related to the exclusion of any particular food. The diarrhea prevalent subgroup responded the best (3/8) whereas the constipation subgroup consistently failed to improve
Heizer *et al*[17], 2009	Review	NA	IBS and elimination diet	25% of IBS patients reported their symptoms may be caused or exacerbated by one or more dietary components. Diet restricted in fermentable, poorly absorbed carbohydrates, including fructose, fructans, sorbitol, and other sugar alcohols seemed to be beneficial
Zar *et al*[101], 2005	Prospective study	25 IBS patients	IBS and elimination diet	Patient IgG4 antibodies to milk, eggs, wheat, beef, pork and lamb were measured, and were commonly elevated. Significant improvement was reported in pain severity (P < 0.001), pain frequency (P = 0.034), bloating severity (P = 0.001), satisfaction with bowel habits (P = 0.004) and effect of IBS on life in general (P = 0.008) at 3 and 6 mo of elimination diet
Atkinson *et al*[102], 2004	Randomized trial	150 IBS patients	IBS and elimination diet	Patients received either a diet excluding all foods to which they had raised IgG antibodies or a sham diet for 3 mo. The true diet resulted in a 10% (26% in fully compliant) greater reduction in symptom score than the sham diet
Bolin[103], 1980	Randomized trial	20 patients suffering from persistent diarrhea	IBS and DSCG	18 patients reported significant improvement in diarrhea while taking sodium cromoglycate and this did not correlate with the presence of other atopic diseases, history of food intolerance, or lactase deficiency
Paganelli L *et al*[104], 1990	Prospective study	14 IBS patients	IBS, elimination diet and DSCG	7 (50%) patients improved after elimination diet with (5/7) and without (2/5) DSCG
Lunardi *et al*[105], 1991	Double-blind cross-over trial	20 IBS patients	IBS and DSCG	18 patients completed the study; analysis of patients' diary card scores showed a statistically significant difference in favor of DSCG
Stefanini *et al*[106], 1992	Prospective study	101 IBS patients (diarrhea type)	IBS, atopy and DSCG	Patients were then tested for 48 commercial alimentary antigens by SPT and underwent 8 wk of oral DSCG. Symptom improvement was observed in 67% of the 74 SPT-positive patients, whereas only in 41% of the 27 SPT-negative patients
Stefanini *et al*[107], 1995	Multicenter trial	428 IBS patients (diarrhea type)	IBS, elimination diet and DSCG	IBS symptoms improved in 60% of patients treated with elimination diet and in 67% of those treated with DSCG. In both groups clinical results were significantly better in the patients positive to the skin prick test than in the negative ones
Leri *et al*[108], 1997	Randomized study	120 IBS patients (diarrhea type)	IBS, elimination diet and DSCG	66 patients had positive SPT; they were randomly treated with elimination diet (30) or with elimination diet plus DSCG. 18 (60%) of the 30 patients that had received the only exclusion diet reported symptom improvement, whereas 32 of the 36 patients (89%) who had undergone both dietary and DSCG treatments showed an improvement that was clinically and statistically significant (P = 0.01)

DSCG: Disodium cromoglycate; FCV: Forced vital capacity; FEF: Forced expiratory flow; FEV1: Forced expiratory volume in 1 s; FGIDs: Functional gastrointestinal disorders; FIS: Fatigue impact scale; IBS: Irritable bowel syndrome; RR: Relative risk; SPT: Skin prick test; NA: Not available.

asthma and allergic rhinitis (or other atopic disease) have higher prevalence of IBS compared to patients suffering from other pulmonary disorders and healthy subjects[86,87]. For example, Powell *et al*[88], in a retrospective case control study of more than 7000 patients in a general practice setting in the United Kingdom, demonstrated an excess of IBS among patients with general practitioner-diagnosed allergic conditions (bronchial asthma and allergic rhinitis). The odds ratio (OR) for IBS among bronchial asthma patients was two-fold that of controls, indicating a substantial association between these conditions[88]. Cole *et al*[89] found a similar pattern for IBS prevalence in asthmatics; no association was found in this study with the asthma therapy (*e.g.*, use of oral steroids), but another study showed reduction of risk of IBS development in asthma patients by use of oral steroids. These findings could suggest a beneficial effect of steroid treatment in IBS, thus entailing a possible role of inflammation in IBS pathogenesis[90]. Their findings were replicated by Panicker *et al*[91], who reported an OR for IBS of almost 3 in an allergy out-patient sample in Kuwait, and afterwards by Hunskar *et al*[92] in Norway. In 2008, a prospective study by Tobin *et al*[93] used structured questionnaires administered to 125 consecutive patients admitted to allergy/immunology, gastroenterology, and general medicine clinics to confirm this evidence. The allergy/immunology clinic reported a significantly higher rate of IBS than the general medicine clinic, and surprisingly similar to that reported in the gastroenterology department. Patients reporting atopic symptoms (seasonal allergic rhinitis, asthma, and allergic eczema) were 3.20 times more likely (95%CI: 1.20-8.50, $P = 0.02$) to fulfill the criteria for IBS. Therefore, the authors defined a subgroup of IBS patients ("atopic IBS") who have typical IBS symptoms in association with atopic manifestations. Significantly, the likelihood of IBS was significantly higher in patients also suffering from depression[93]. More recently, Jones *et al*[94] examined the matching of IBS, functional dyspepsia, and chronic idiopathic constipation diagnosis, with 4 atopic conditions (allergic rhinitis/hay fever, conjunctivitis, eczema and bronchial asthma) from 30000 primary care medical records in the United Kingdom, using the Health Improvement Network (THIN), over a minimum 5 year period. The validity of gastrointestinal disorder diagnoses has been shown, and the diagnostic records in THIN have been validated[95]. The authors considered factors known to be involved in functional gastrointestinal disorders, including age, gender and mood disorders (*i.e.*, anxiety and depression) to determine whether these factors may explain the association. Atopic conditions were found in excess among all functional gastrointestinal disorder groups compared to controls. In particular, in the groups with IBS alone, functional dyspepsia alone, and multiple functional gastrointestinal disorders, there was higher asthma prevalence compared to controls. The excess was generally highest among patients with multiple functional gastrointestinal disorders, and was only partly explained by the "three-way interconnection" among functional gastrointestinal disorders, atopic conditions and mood disorders[94]. In a birth cohort study of 2610 children, Olén *et al*[96] examined the association between allergy-related diseases (asthma, allergic rhinitis, eczema and food allergy) or sensitization (*i.e.*, allergen-specific IgE detection) and recurrent abdominal pain of functional origin, a specific phenotype of IBS in children. The authors showed that all allergy-related diseases were associated with concurrent abdominal pain and that the risk increased with increasing number of allergy-related diseases. Asthma in the first two years of life and food allergy at age 8 years were significantly associated with abdominal pain at 12 years. There was an increased risk of abdominal pain at 12 years in children sensitized to food allergens at 4 or 8 years, but in stratified analyses, this was confined to children whose parents had not reported food allergy at the time of sensitization[96].

Another interesting field of study includes the patients with self-reported food allergy. In a study performed in patients with self-reported food allergy there was an increased prevalence of both IBS and atopic disease (*e.g.*, bronchial asthma and rhinoconjunctivitis) compared to healthy subjects. These authors studied a small group composed of 29 patients with perceived food allergy and IBS, and found a high prevalence of atopic disease: about 60%, as defined by 3 or more positive skin prick tests (SPT) to inhalant allergens[97]. More recently, Lillestøl *et al*[98] explored the association between atopic diseases, gastrointestinal symptoms, and possible gastrointestinal manifestations of atopic disease in 71 adult patients with gastrointestinal complaints self-attributed to food allergy. The authors evaluated symptoms, SPT, serum markers of allergy (total and specific IgE, tryptase, and eosinophil cationic protein), intestinal permeability, IgE- and tryptase-positive cells and eosinophils in duodenal biopsies. The diagnosis of food allergy was based on double-blind placebo-controlled food challenges (DBPCFC), the method which is considered the gold standard in adverse food reaction diagnosis (see below). The authors demonstrated that 93% of the patients suffered from IBS and 61% patients had atopic diseases (predominantly rhinoconjunctivitis). Atopic patients had increased density of IgE-bearing cells (mainly mast cells) and intestinal permeability compared to non-atopic patients, but gastrointestinal symptoms (*i.e.*, IBS-like presentation) did not differ between groups. IgE-sensitization was mainly against inhalants and pollen-associated food allergens. The numbers of IgE-positive cells and the intestinal permeability did not differ between patients who were sensitized to inhalants and those who were only sensitized to food. However, DBPCFC were negative in most of the patients, and the clinical significance of such

sensitization was uncertain. In the article, however, the DBPCFC challenge method was not described and this limits the opportunity to evaluate the results[98]. In this context, it has been also demonstrated that perceived food allergy in IBS patients may be associated with more severe and debilitating illness. Berstad *et al*[99] in a prospective study enrolling 84 patients referred for perceived food allergy assessed the severity of their intestinal and extra-intestinal symptoms. All but 1 patient were diagnosed with IBS, according to the Rome Ⅲ criteria. The large majority of subjects reported extra-intestinal symptoms; 85% reported symptoms suggestive of chronic fatigue, and 71% fibromyalgia. These symptoms could not be explained either by IgE-mediated food allergy or by organic pathology. The authors conclude that comorbidity (the triad of IBS, chronic fatigue, and musculoskeletal pain) demonstrated in 71% of examined patients, might be caused by a common underlying cause[99]. Lind *et al*[100] reported similar results, validating a Norwegian translation of the Fatigue Impact Scale (FIS); the impact of fatigue among 38 patients with self-reported food allergy and IBS was greater than among the 42 healthy controls.

Finally, to strengthen the possible pathogenic association between food allergy and IBS, several studies demonstrated a positive response to elimination diets and disodium cromoglycate (DSCG)[12,17,101-108], suggesting that in a subset of IBS patients, symptoms can be attributed to food allergy.

FACTS: DIET IN IBS PATIENTS

Most patients with IBS believe that diet plays a significant role in their symptoms, and 63% desire to know what kind of foods they should avoid (15-23). The current medical diagnostic methods allow diagnosis of food allergy only in 1%-3% of them. This discrepancy is a major source of frustration both for patients and for health care professionals, who are unable to provide appropriate answers and support[109-112]. Nevertheless, several studies agree in reporting that 60% of IBS patients worsen their symptoms following food ingestion; 28% within 15 min after eating and 93% within 3 h. Many IBS patients identify specific foods as responsible for their symptoms, most commonly implicating wheat products (pasta, bread, pizza), cow's milk and milk-derived products, tomato, eggs, certain meats, fish/shellfish, cabbage, peas/beans, onion, hot spices, garlic, apple, peach, citrus, fried food, smoked products, fats, food additives, walnuts, hazelnuts, chocolate, alcohol, and caffeine[13,72,113-119]. Table 2 summarizes the data of the literature about the frequency of the different foods acting as trigger factors in IBS.

Böhn *et al*[120] examined which food groups and specific food items IBS patients report causing gastrointestinal symptoms, and investigated the association between gastrointestinal and psychological symptoms and quality of life. All of the 197 adult IBS patients completed questionnaires on food allergy, IBS symptoms, somatic symptoms, depression and general anxiety, gastrointestinal-specific anxiety, and quality of life. 84% of them reported symptoms related to at least one food, and over 70% noted symptoms after intake of food items with incompletely absorbed carbohydrates, *i.e.*, Fermentable Oligo-, Di-, and Monosaccharides and Polyols (FODMAP), dairy products, beans/lentils, apple, flour, and plum. Patients also experienced gastrointestinal symptoms from foods rich in biogenic amines, *i.e.*, histamine and tyramine, such as tuna, salami, cheese, and wine/beer (58%), or histamine-releasing foods: pork, milk, and wine/beer (43%). More than half (52%) of IBS patients also considered fried and fatty foods as possible symptom triggers. The authors concluded that self-reported food allergy was associated with reduced quality of life (sleep, physical status and social interactions)[120]. Similarly, Carlson *et al*[121] studied perceived food allergy in 25 child-parent pairs through a questionnaire and focus groups. The majority of children participating were classified as either having IBS or abdominal migraine. The median number of foods identified as producing gastrointestinal symptoms was 11, and the top 3 self-identified trigger foods were spicy foods, pizza and cow's milk. Children identified coping strategies, including eating smaller portions, modifying foods, or avoiding the food altogether. Interestingly, all of them reported a certain degree of impairment in school performance, sports, and social activities[121].

Such evidence indicates a certain selectivity in dietary intake in IBS patients with perceived food allergy, but no difference was detected between them and community health controls by dietary survey[122-126]. On the other hand, a Norwegian population-based cross-sectional study on food allergy and IBS showed that 70% of subjects perceived a food allergy (mean 4.8 food items related to symptoms), 62% limited or excluded food items from their daily intake (mean 2.5 food items reduced or eliminated), and 12% made drastic changes in their diet potentially causing nutritional deficiencies in the long run. However, no association was pointed out among perceived food allergy, food allergy diagnostic tests (*i.e.*, serum total IgE and food-specific IgE, IgA antibodies against lactalbumin, lactoglobulin, casein and ovalbumin, total IgA, IgA and IgG against gliadin and gluten), and lactose malabsorption (H2 and CH4 breath test)[127]. Data that are fairly consistent in the already mentioned studies, and in many others, confirm the lower consumption of spaghetti, pasta, couscous, and rice in IBS than in controls. The first three are products made using durum wheat, which tend to be high in gluten and FODMAP, while rice tends to be low[128,129]. Another common belief is that lactose could be the main cause of IBS symptoms. Therefore these patients consume less milk and other dairy products[128,130-132], but it must be remembered that dairy products represent

Table 2 Identification of foods triggering symptoms in irritable bowel syndrome patients

Ref.	Patients	Diagnostic methods	Foods	Comment
Nanda *et al*[13], 1989	91 of 200 IBS patients reported symptomatic improvement after 3 wk of elimination diet	Open challenge	Cheese 35.2% Onions 35.2% Milk 31.9% Wheat 29.7% Chocolate 27.5% Butter 25.3% Yoghurt 24.7% Coffee 24.2% Eggs 23.3% Nuts 18.0% Others 34.1%	73 of the 91 improved patients were able to identify one or more foods responsible for their symptoms in the open challenge. All except one remained well on clinical follow-up
Carroccio *et al*[71], 2011	160 IBS patients	DBPCFC to wheat and milk	Wheat and milk 18.75% Only milk 3.75% Only wheat 2.5%	40 (25%) patients were found to suffer from food hypersensitivity. These patients had increased levels of fecal eosinophil cationic protein and tryptase, indicating that they might cause inflammation in patients with IBS
Dainese *et al*[112], 1999	128 IBS patients	Self-reported intolerance questionnaires *vs* SPT	Milk (28.8% *vs* 3%) Wheat (17.5% *vs* 1.5%) Pepper (2.5% *vs* 6%) Peanut (6.3% *vs* 6%) Pear (5% *vs* 7.5%) Tomato (12.5% *vs* 9%) Onion (3.8% *vs* 9%) Celery (2.5% *vs* 9%) Banana (2.5% *vs* 9%) Carrot (0% *vs* 10.5%) Garlic (0% *vs* 10.5%) Parsley (0% *vs* 16%) Walnut (6.3% *vs* 18%) Apple (10% *vs* 18%)	More than 50% of IBS patients were found sensitized to some food or inhalant without any symptom. There is a substantial lack of correlation between self-perceived food intolerance and SPT sensitization
Locke *et al*[115], 2000	76 IBS patients of 643 subjects from Olmsted County general population	Self-reported intolerance questionnaires	Beans 22.3% Chocolate 23.6% Dairy products 52.6% Eggs 21.0% Nuts 23.6% Onions 57.8% Spicy food 81.5%	Among the 643 subjects, IBS symptoms were reported by 12% (76). IBS was significantly associated with use of analgesics, food allergy or sensitivity
Farah *et al*[116], 1985	13 of 49 patients suspected of food intolerance after elimination diet	DBPCFC	1/13 peas 1/13 coffee 1/13 eggs	After DBPCFC 3 patients were confirmed to suffer from food intolerance. Authors found that 10 patients reacted to placebo, suggesting a psychogenic cause for their disturbances
Carlson *et al*[121], 2014	25 children suffering from gastrointestinal disorders and their parents	Child-reported intolerance questionnaires *vs* parent- reported intolerance questionnaires	Spicy food 68% *vs* 60% Pizza 52% *vs* 48% Cow's milk 56% *vs* 48% Fired foods 48% *vs* 36% Fast Foods 40% *vs* 40% Sodas 40% *vs* 36% Cheese 40% *vs* 36%	Specific foods are perceived to exacerbate gastrointestinal symptoms in children with functional gastrointestinal disorders. No differences were found in severity or frequency of symptoms with ingestion of the foods between children and parents with respect to the 10 most frequent foods/food types
Böhn *et al*[126], 2013	197 IBS patients	Self-reported intolerance questionnaires	Dairy products 49.2% Beans 36.0% Apple 27.9% Wheat 24.4% Fried foods 52.3% Plum 23.4% Peas 19.3% Chocolate 16.8% Foods rich in biogenic amines (58%) Histamine-releasing foods (43%)	Most IBS patients believe that certain foods could be triggers of their symptoms. They identified FODMAP containing foods, histamine-releasing foods, fried foods and foods rich in biogenic amines as the main culprits. Self-reported food intolerance seems to be associated with high symptom burden and reduced quality of life

Monsbakken *et al*[127], 2006	84 IBS patients	Self-reported intolerance questionnaires	Milk 41.7% Cheese 14.3% Eggs 11.9% Peas 21.4% Onions 35.7% Cabbage 34.5% Wheat 14.3% Coffee 26.2% Chocolate 25.0% Beer 16.9%	70% of subjects perceived a food intolerance (mean 4.8 food items related to symptoms), 62% limited or excluded food items from their daily intake (mean 2.5 food items reduced or eliminated), and 12% made drastic changes in their diet potentially causing nutritional deficiencies in the long run
Parker *et al*[130], 2001	122 IBS patients	LHBT, lactose elimination diet and DBPCFC (with 5/10/15 g of lactose)	33/122 (27%) positive to LHBT 9/33 (27.7%) improved on lactose elimination diet 5/9 (55.5%) worsened on DBPCFC with 15 g of lactose	Lactose intolerance was demonstrated in IBS patients with positive (33/122) or negative (13/122) LHBT. DBPCC were inconclusive
Yang *et al*[131], 2013	60 IBS patients *vs* 60 controls	LHBT and self-reported lactose intolerance	18% *vs* 3% with 10 g LHBT 47% *vs* 22% with 20 g LHBT 85% *vs* 68% with 40 g LHBT 63% *vs* 22% with self- reported intolerance	The risk of lactose intolerance is related to the dose ingested and is higher in IBS patients than in controls. Self-reported intolerance is associated with avoidance of dairy products
Dainese *et al*[132], 2014	51 IBS patients	LHBT (50 g) and self-reported lactose intolerance	21/51 (41.1%) self-perceived lactose intolerance 24/51 (47%) positive LHBT 14/51 (27.4%) reported symptoms during LHBT	Patients who experienced symptoms during LHBT had more severe IBS symptoms and higher anxiety, depression, and fatigue scores. Increase in hydrogen production and in the severity of IBS influenced the symptoms of lactose intolerance during LHBT
Carroccio *et al*[145], 2010	24/120 IBS patients who underwent DPBCFC after elimination diet	DBPCFC and flow-CAST	12.5% cow milk only on DBPCFC 8.3% wheat only on DBPCFC 79.1% both cow milk and wheat on DBPCFC 86.3% cow milk on Flow-CAST 85.7% wheat on Flow-CAST	Flow-CAST had higher sensitivity than serum total IgE and serum food-specific IgE, both in the diagnosis of cow's milk allergy and wheat protein allergy. Flow-CAST diagnostic accuracy proved higher than the two traditional techniques both for cow's milk allergy and for wheat protein allergy diagnoses

DBPCFC: Double blind place controlled food challenge; FODMAP: Fermentable Oligo-, Di-, and Monosaccharides And Polyols; IBS: Irritable bowel syndrome; LHBT: Lactose hydrogen breath test; SPT: Skin prick tests.

the most important daily-required dietary source of calcium (50%-75%), phosphorus (20%-30%), and vitamin B_2 (riboflavin) (30%) in the Western world[133]. Trying to compensate for this restriction, IBS patients are counted among the major consumers of alternative milk products (soy, rice and oat milk)[128,134], but despite such replacement, IBS patients were found to have a low intake of calcium, phosphorus and vitamin B_2[128,134]. Furthermore, IBS patients reported a lower consumption of certain vegetables (tomatoes, raw vegetables, raw broccoli, cabbage, mushrooms, green beans, onion, leeks, garlic, and paprika)[128,134]. This is most likely the reason for the significantly lower intake of retinol (vitamin A) equivalent, β-carotene and magnesium observed in these patients[128,134]. Controversially, they report a higher consumption of pears, peach, grapes, melon, mango, and plums; these fruits and vegetables are rich in FODMAP and documented as possible symptom trigger factors[128,134].

Finally, due to self-reported intolerance to various alcoholic beverages, lower alcohol consumption was found in IBS subjects, and as many as 12% either limit or avoid such beverages[117,127,128]. However, this latter evidence does not enjoy complete agreement among physicians. Two studies reported equal or higher alcohol intake in IBS patients than in the general population[135,136].

In conclusion, the total intake of calories, carbohydrates, proteins and fat does not seem to differ in IBS and the general population, whereas the former tend to avoid certain food items rich in gluten and FODMAP, even if the higher consumption of some FODMAP-rich fruits and vegetables remains questionable. Such dietary restrictions could be responsible for their low calcium, phosphorus, vitamin B2, and vitamin A intake.

FOOD ALLERGY AND IBS

IgE-mediated allergic food reactions

There is no consistent evidence and only conflicting data for a role of IgE-mediated allergic response in IBS, perhaps especially in patients with concomitant atopy. Among the first studies evaluating a possible association, Petitpierre *et al*[137] analyzed 24 IBS patients, 12 atopic (*i.e.*, allergy prone) and 12 non-atopic, who underwent total serum IgE test, SPT, radioallergosorbent test (RAST) to various food allergens, and 3 wk of low-allergenic diet followed by open challenge. Responders underwent blind dietary provocation. In 14 patients one or more foods and food additives produced the typical IBS symptoms. Nine

of these, all from the atopy group, had elevated total serum IgE and positive SPT, which suggest systemic IgE-mediated food allergy[137]. In another study, 10 IBS patients with atopy were included, and exposed by SPT to common food allergens; food allergy was demonstrated in 6 of them, whose symptoms improved on an open elimination diet. However, subsequent rechallenge with the offending food allergens failed to produce IBS symptoms[138]. Barau *et al*[139] examined the intestinal permeability of 17 children with clinical symptoms of IBS, analyzing the differential urinary elimination of lactulose and mannitol, orally ingested at the same dosage. Patients were tested first in fasting condition, then after specific food ingestion (selected on a suggestive clinical history or positive SPT and RAST). Nine patients had modification of intestinal permeability after food ingestion. All had a personal and/or family history of allergy and/or high total IgE, and responded to food exclusion[139]. André *et al*[140] showed increased IgE fragment crystallizable (Fc) in fecal extracts of 236/312 food allergy patients (73%) whose diagnosis was based on history, positive SPT and RAST. In contrast, all the 95 healthy subjects had undetectable fecal IgE Fc. In the subgroup analysis of IBS patients, 22 of the 32 (68.8%) were found to have detectable IgE Fc in feces. The simultaneous measurement of α-1-antitrypsin in the serum and feces excluded the possibility of plasma protein (including IgE) extravasation as responsible for these findings[140].

Bischoff *et al*[14] examined 375 adult patients in a gastroenterology outpatient clinic by history, SPT, measurements of laboratory parameters, and intestinal provocation with food allergens by colonoscopy. Thirty-two percent of subjects complained of abdominal symptoms as a consequence of an adverse food reaction. According to clinical signs of atopic disease, elevated total IgE, specific IgE against food allergens, eosinophilia and responsiveness to DSCG, 14.4% of them were suspected of suffering from a food allergy. The diagnosis was confirmed in 3.2% by endoscopic allergen provocation (see below), and/or elimination diet and rechallenge[14]. A different approach to show IgE involvement in IBS was applied by Simonato *et al*[141], who examined the sera of 20 patients, previously diagnosed as suffering from IBS and complaining of symptoms after wheat ingestion (with symptom improvement on elimination diet and their re-appearance after open wheat challenge). Even though only 50% of them were positive for wheat-specific IgE detection by SPT and ImmunoCAP system, immunoblotting analysis established that all had IgE binding to soluble and insoluble wheat proteins. The authors concluded that conventional methods used for the diagnosis of IgE-mediated hypersensitivity are inadequate for the allergological screening of this subgroup of patients. Two hypotheses were proposed to explain these results: (1) low serum specific IgE levels; and (2) inadequate allergenic preparations currently used for SPT and CAP for the diagnosis of food allergy to wheat. If correct, such hypotheses would explain why wheat IgE-mediated enteropathy has been rarely reported, opening a new perspective on the prevalence of food allergy in IBS patients[141]. Conflicting data come from Dainese *et al*[112], who demonstrated self-reported adverse reactions to one or more foods in 62.5% of 128 consecutive IBS patients, but with significant discrepancy between the reported food allergy and sensitization test findings (*i.e.*, SPT). The same discrepancy was found by Jun *et al*[142], who evaluated the results of the SPT for foods and inhalant allergens in 105 subjects forming three different target groups: treated group, undergoing treatment for IBS due to more severe symptoms, untreated group whose IBS symptoms did not require treatment, and control group with no IBS symptoms. SPT results were positive in 38.6% of treated IBS patients, 16.1% of untreated IBS patients, and 3.3% of controls ($P < 0.01$). Patients reported being intolerant to dairy products, raw foods, spicy foods, coffee, and alcohol. On the contrary, SPT were positive for saury (a fish belonging to Scomberesocidae), rice, mackerel, buckwheat, sweet potatoes, celery, onions, and trumpet shell, so no correlation was found between patient's allergy and SPT results[142]. A Brazilian study, by Soares *et al*[143], examined the cutaneous response to 9 food allergens in 43 volunteers (students and employees of the School of Medicine of Universidade Federal Fluminense). Participants were divided into 3 groups according to Rome Ⅱ criteria: group Ⅰ (IBS), group Ⅱ (functional dyspepsia), and group Ⅲ (healthy controls). SPT were positive in 19.4% of group Ⅰ, 2.3% of group Ⅱ, and 4% of group Ⅲ, with significant differences between the number of positive responses obtained in group Ⅰ (IBS) and the other 2 groups. However, none of the volunteers with IBS reported allergy to any isolated food. Authors concluded that higher reactivity to food antigens in group Ⅰ suggests that intestinal permeability may be greater in patients with IBS[143]. Uz *et al*[144], who evaluated SPT to 11 common allergens, total IgE, eosinophilic cationic protein and eosinophil counts in 100 Turkish patients satisfying the Rome Ⅱ criteria and 25 healthy controls, obtained similar results in a completely different geographic area. IBS patients were divided according to their main clinical feature (53 had constipation predominant, 19 had diarrhea predominant, and 28 had alternating type IBS). The authors found that SPT positivity, mean IgE, and eosinophilic cationic protein were more common in patients than in controls, but no statistically significant difference could be shown between IBS subgroups. SPT are positive with foods rich in dietary fiber (such as cereals, fruits and vegetables), gas-producing agents (such as cereals and onion), or foods containing significant amounts of carbohydrates (*i.e.*, fructose or sorbitol), which may be incompletely absorbed (such as apple, banana, and strawberry)[144].

The inadequacy of the conventional methods

(SPT and serum food allergen-specific IgE levels) to identify IgE-mediated responses in IBS patients could probably explain our results in a recent study[145]. We evaluated the efficacy of an *in vitro* basophil activation assay in the diagnosis of food allergy in 120 consecutive IBS patients. In addition, we included as control groups 40 healthy subjects, and 40 patients suffering from gastrointestinal disorders other than IBS. Flow cytometric basophil activation test (Flow-CAST) is a diagnostic allergological technique based on the demonstration of altered membrane phenotypes on allergen-activated basophils, with up-regulation, surface expression, and cytofluorometric detection of CD63[146]. Severity of symptoms and possible self-perceived food allergy were assessed by 2 predesigned questionnaires. All the enrolled patients underwent preliminary serum total and food allergen-specific IgE determination, together with the Flow-CAST, and then underwent a 4-wk elimination diet, with the exclusion of wheat, cow's milk, eggs, tomato, chocolate, and any other self-reported food intolerance. Patients reporting symptom improvement after elimination diet (44/120, 26%) underwent DBPCFC with wheat and cow's milk (1 wk wash-out interval between the two challenges). The 24 patients who had positive DBPCFC (3 only to cow's milk, 2 only to wheat, and 19 to both cow's milk and wheat) were diagnosed as suffering from IBS and food allergy. Comparing the results of immunologic assays in the different groups we found a higher sensitivity of Flow-CAST *vs* serum total IgE and serum food-specific IgE, both in the diagnosis of cow's milk allergy and wheat protein allergy. Similarly, diagnostic accuracy of Flow-CAST proved higher than the two traditional techniques both for cow's milk allergy and wheat protein allergy diagnoses. We concluded that as already shown for some inhalant IgE-mediated allergic reactions[146-148], this diagnostic test might supplement or better replace routine allergy tests (SPT and serum total and allergen-specific IgE) for the diagnosis of IgE-mediated food allergy[145]. Unfortunately, even if promising, this diagnostic technique has limitations since its effectiveness is quite variable. In particular, some years after our first study, we compared the diagnostic accuracy of two different methods of *in vitro* basophil activation tests: we used the first in the previous mentioned study, which was performed on blood samples after centrifugation and leukocyte separation, while the second was performed on whole blood samples. We found that in food allergy diagnosis, basophil activation test on separate leukocytes had a sensitivity of 86% and a specificity of 91%, whereas the test on whole blood had a sensitivity of 15%-20% and a specificity of 73% ($P < 0.0001$ compared to the other method)[149].

Is there a role for local IgE-mediated reactions in IBS?

To our knowledge, no other study since 2007 has investigated the possible relationships between IBS and IgE-mediated food allergy by using SPT for serum food-specific IgE detection. Therefore, the question remains open. In addition, some data suggest a different mechanism from the classic type-1 hypersensitivity reactions in intestinal IgE-mediated food allergy in IBS patients. It has been proposed that an IgE-mediated reaction could be localized and limited to the intestinal mucosa.

In 1997 Bischoff *et al*[150] questioned this hypothesis, performing the colonoscopic allergen provocation (COLAP) test on 70 adult patients with abdominal IBS-like symptoms, suspected of being related to food allergy, and 5 healthy volunteers. Food allergens were selected according to the patient's history of food allergy and presence of specific IgE in serum. In the 5 healthy volunteers a standard set of three allergens (milk, wheat, hazelnut) was used for challenge. All enrolled subjects underwent colonoscopy during which 3 food allergens were injected into the cecal mucosa. The mucosal wheal and flare reaction were semi-quantitatively classified 20 min after challenge using a 0-4 scale and reaction was classified as positive for grade $\geqslant$ 2. In 74% of subjects with a putative diagnosis of IBS, COLAP test was positive in response to at least one food allergen. In contrast, no reaction was detected in the 5 healthy volunteers. Biopsies from the positive test site showed both mast cell and eosinophil activation. Consequently, COLAP positive subjects underwent 3 mo of dietary elimination of suspected food allergens; 89% reported a significant clinical response. COLAP results strongly correlated with positive history of food allergy, but poorly with SPT results and specific serum IgE levels. These findings strengthen the idea of a local IgE mediated mechanism, which can be identified by the COLAP test but not by SPT and measurement of specific serum IgE[150,151]. Similarly, Lidén *et al*[152] evaluated the mucosal response (*i.e.*, nitric oxide production and myeloperoxidase release, measured using the mucosal patch technique) to a rectal challenge with cow's milk protein (CMP) in 21 patients with primary Sjogren's syndrome and 18 healthy controls. An inflammatory response after CMP challenge was identified in 38% of patients as a sign of CMP sensitivity not linked to serum IgE or IgG/IgA antibodies to milk proteins. All CMP sensitive patients suffered from IBS, diagnosed according to Rome Ⅲ criteria. Half of the positive patients had already suspected that their gastrointestinal symptoms could be induced by CM intake[152]. In three different studies Arslan *et al*[153-155], used endosonography, transabdominal ultrasonography and magnetic resonance imaging to visualize local intestinal reactions in response to direct intraduodenal administration of suspected allergens (luminal provocation). The challenge caused a rapid intestinal reaction, characterized by thickening of the intestinal wall, increased peristalsis, and influx of large amounts of fluid into the lumen. Notably, the latter

event is a typical feature of immediate IgE-mediated food allergy responses, due to degranulation and release of mediators from mucosal mast cells[156]. In the same way, Fritscher-Ravens *et al*[157] examined structural/functional changes of intestinal mucosa after food challenge in 36 IBS patients with suspected food allergy, and in 10 patients with Barrett's esophagus (controls without IBS symptoms), using confocal laser endomicroscopy (CLE), for real-time visualization. Diluted food allergens (wheat, soy, cow's milk, and yeast) were directly administered to the duodenal mucosa through the endoscope working channel. CLE showed a real-time response (*i.e.*, epithelial breaks/leaks/gaps forming, inter-villous space widening [possibly results in increased permeability], and IEL increase) in 22 of 36 patients (CLE^+); the remaining 14 patients (CLE^-) and controls had no response to the challenge. Symptom scores improved more than 50% in CLE^+ patients after a 4-wk exclusion diet and increased up to 74% at 12 mo; as expected, symptoms continued in CLE^- patients[157]. This might exclude a possible placebo effect of the exclusion diet because classic placebo-controlled studies have shown that in IBS the placebo effect is generally shorter-lived[158]. In addition, considering that many of the examined patients had known non-gastrointestinal atopic disease, it is likely they could have a high density of IgE-armed mast cells in their duodenal mucosa; thus, a local IgE-mediated reaction seems an even more reasonable explanation of the visualized changes[98]. A demonstration of *in situ* induction of IgE without systemic IgE responses has been suggested by the evidence of a localized mucosal up-regulation of IL-4 and ε germline transcripts in food allergy. Coëffier *et al*[159] suggest in their study that circulating immunoglobulin analysis may provide misleading insights into genuine mucosal allergic responses. Further uncertainty is added by findings on abdominal ultrasound assessment following duodenal allergen challenge, which suggest the unreliability of DBPCFC in identifying genuine intestinal allergic responses. Abnormal findings of duodenal wall swelling and fluid exudation were seen not only in patients with positive DBPCFC, but also in several DBPCFC negative symptomatic patients. It is thus possible that organic symptoms due to genuine mast cell-mediated mucosal allergic responses may be misdiagnosed as psychologically-mediated in at least some patients[154].

Non IgE-mediated allergic food reactions in IBS: A role for IgG

Although there is no general agreement, this type of hypersensitivity reaction may play a role in causing IBS symptoms in a subset of patients. Different antibody classes (*i.e.*, IgG) seem to be of some importance in food-related allergies in IBS. In particular, the IgG4 subclass, which is found to be involved in some specific pathologic entities (*e.g.*, autoimmune pancreatitis), are synthesized under the influence of T_H2 cytokines and might induce histamine release, exactly like IgE antibodies[160,161]. This concept, however, seems to be unclear and controversial. Although several studies suggested that IgG and IgG4 production may be part of a normal immunologic response to dietary antigens[162-168], other studies reported that serum IgG and IgG4 levels are higher in patients with IBS and food allergy history, perhaps related to an inflamed or "leaky" gut. Therefore, these patients might have selective gut permeability to food allergens and the increase of food-specific IgG and IgG4 titers could be a specific reaction, rather than a non-specific response to increased gut mucosal permeability[101,102,169-174]. However, due to the low sensitivity or specificity of tests used to support this hypothesis, their clinical use has been proposed with conflicting results[167,175-181]. Finn *et al*[169] were the pioneers in this field, demonstrating an increased prevalence of serum IgG antibodies against dietary proteins in 58 IBS patients compared to 46 controls, and suggesting that IgG food antibodies may have some role in IBS. Afterwards, el Rafei *et al*[170] compared specific IgG4 and IgE levels to DBPCFC in 25 patients with suspected food allergy. They observed increased serum IgG4 or IgE levels in 63% of patients with a positive history of food allergy and either IgG4 or IgE in 91% of diagnosed patients. These results suggest that the combination of specific IgG4 and IgE antibodies to food allergens may be useful in evaluating patients with suspected food allergy[170].

Atkinson *et al*[102] assessed the therapeutic potential of dietary elimination based on the presence of IgG antibodies to food. Authors selected 150 IBS outpatients who were randomized to receive either an elimination diet or a sham diet for 12 wk, excluding the same number of foods but not those to which they had antibodies. After 12 wk, the IgG based elimination diet resulted in a 10% greater reduction in IBS symptom severity score than the sham diet. The data were significantly higher (26%) considering only fully compliant patients. Reduction in symptoms was higher in patients exhibiting a greater number of sensitivities, as determined by the IgG test, if they adhered to the true diet but not the sham diet. Following reintroduction of foods, more patients in the IgG based elimination diet group showed worsening of global rating than the sham diet group. The authors concluded that many patients with IBS would prefer a dietary solution to their problem rather than having to take medication, and the economic benefits of this approach to health services are obvious. It is well known that patients spend large sums of money on a variety of unsubstantiated tests in a vain attempt to identify dietary allergies. The results of this study suggest that "assay of IgG antibodies to food may have a role in helping patients identify candidate foods"[102]. However, the study was strongly criticized

both for including imbalanced groups and because IgG food antibodies were not compared between IBS patients and healthy control individuals[177,182].

Zar *et al*[101] examined 25 patients with IBS and their IgG4 titers to 16 foods (milk, eggs, cheese, wheat, rice, potatoes, chicken, beef, pork, lamb, soya bean, fish, shrimps, yeast, tomatoes and peanuts), evaluating the effect of a food-specific IgG4 antibody-guided exclusion diet on symptoms and rectal compliance. IgG4 antibodies to milk, eggs, wheat, beef, pork and lamb were commonly elevated, and foods were excluded for 6 mo. Significant improvement was reported in pain severity, pain frequency, bloating severity, satisfaction with bowel habits, and effect of IBS on life in general. Rectal compliance increased significantly, but the thresholds for urge to defecate/discomfort were unchanged. This study also suffers from the great flaw of control group absence[101]. In a small open label pilot study, Drisko *et al*[171] enrolled 20 patients with IBS, who had failed standard medical therapies, treating them with food elimination diets based on the results of serum IgG food and mold panels, followed by controlled food challenge. Authors obtained a sustained clinical response and significant improvement in overall well-being and quality of life[171]. Similar results were recently obtained in a Chinese trial. A group of 77 D-IBS patients and 26 healthy controls were tested for specific serum IgG antibodies against 14 common food allergens. Food-specific IgG antibodies were identified in 50.6% patients and 15.3% controls. Thirty-five patients with D-IBS and food allergy (as identified by specific IgG antibody positivity) agreed to consume diets that excluded the identified food for 12 wk. After 4 wk of dietary therapy, most symptoms of D-IBS had improved, and by 12 wk, all symptom scores (abdominal pain, bloating level and frequency, abdominal distension, diarrhea frequency, stool shape, general feelings of distress, and total symptom score) decreased significantly compared to the baseline[172]. A double-blind, randomized, controlled, cross-over clinical trial, composed of baseline (usual diet), first diet (elimination or provocation diets), and second diet (interchange of elimination or provocation diet) phases, involved 21 patients diagnosed with migraine and IBS. It was demonstrated that food elimination based on IgG antibodies in this specific subgroup of IBS patients may effectively reduce symptoms from both disorders with possible positive impact on the quality of life, as well as potential savings to the health-care system[173]. Finally, a systematic review of 7 clinical trials showed a 15%-71% response rate to diet exclusion, and the most commonly incriminated foods included milk, wheat, eggs, potatoes, and celery. However, all studies had major limitations in their trial designs, including inadequate patient selection, appropriateness and duration of exclusion diets, and methods of food challenge[174].

The uncertainty in the measurement of IgG and IgG4 to identify possible food allergy is further increased by the discrepancy in the studies by the authors above. For example, Zar *et al*[179] examined 108 IBS patients (52 D-IBS, 32 C-IBS, and 24 M-IBS) and 43 controls, measuring IgG4 and IgE titers and SPT to 16 common foods including milk, eggs, cheese, wheat, rice, potatoes, chicken, beef, pork, lamb, fish, shrimps, soya bean, yeast, tomatoes, and peanuts. IgG4 titers to wheat, beef, pork, and lamb were significantly higher in IBS patients than controls, whereas the antibody titers to potatoes, rice, fish, chicken, yeast, tomato, and shrimp were not significantly different. In addition, IgE titers showed no significant difference between the groups. SPT was positive for only a single antigen in 5 of 56 patients tested with the same panel of foods. Nevertheless, no correlation could be found between the IgG4 antibody elevation pattern and patient symptoms[179]. Similarly, Zuo *et al*[180] found higher titers for some food-specific IgG antibodies (crab, egg, shrimp, soybean, and wheat), in 37 Chinese subjects with IBS compared to 20 controls, and no significant correlation between symptom severity and IgG antibody titers. As in the Zar *et al*[179] study the positivity of food allergen-specific IgE antibodies of the two groups did not show any significant difference[180]. Ligaarden *et al*[181] designed a case control study, including 269 subjects with IBS and 277 control subjects, which, after correction for subject characteristics and diet, demonstrated no significant differences in food-specific IgG and IgG4 antibody levels between groups. Of some interest was the evidence of lower IgG values against egg and beef, and higher values against chicken were associated with more severe symptoms. The authors suggested that subjects with severe IBS symptoms may consume lower quantities of egg and beef (often reported as offending food items) and higher quantities of chicken (that seems to be better tolerated) when symptoms are severe and may subsequently have lower levels of IgG against egg and beef and higher levels of IgG antibodies against chicken[181].

OVERALL CONSIDERATIONS ABOUT FOOD ALLERGY AND IBS STUDIES

Summarizing, several studies demonstrated a variable response rate to exclusion diets in IBS patients, ranging from 15%-71%; the lack of standardized protocols, which may influence validity of studies, might explain this wide range of response rate. Elimination diets and subsequent DBPCFC identified problematic foods in 6%-58% of cases, with wheat, milk, and eggs being the most commonly implicated foods. Noteworthy: lactose or other carbohydrate intolerance and celiac disease were not always excluded in these studies, so they potentially could be the cause of symptoms. Diarrhea-predominant IBS patients had a higher symptomatic response rate compared to other subgroups, with response to

diet persisting even at 1-year follow-up. However, inadequate patient selection, poor compliance, appropriateness and duration of exclusion diets, and methods of food challenge were major limitations common in almost all trial designs. The potential for macro- and micronutrient deficiencies resulting from elimination diets, may also limit their usefulness in IBS patients[23,136,183,184].

NON-CELIAC WHEAT SENSITIVITY AND IBS

The importance of food components as possible triggers of IBS has been particularly stressed for wheat[185-188]. Mullin *et al*[189] recently reviewed the dietary management of IBS patients, pointing out how wheat may act as symptom inducer for several reasons: high fructans content and other members of the family of highly fermentable FODMAP; autoimmune (*e.g.*, celiac) disorder trigger; high IgE and non IgE-mediated allergenicity (among the top 8 food allergens).

In this context, gaining more attention day by day, is the new nosological entity known as "non-celiac gluten sensitivity" (NCGS)[190]. NCGS patients usually present with IBS-like symptoms, often associated with extra-intestinal manifestations, which disappear on a gluten-free diet. However, to date there is no consensus about which components of wheat might be responsible, and because there is no definite proof that gluten is really the culprit, we have suggested the term "non-celiac wheat sensitivity" (NCWS)[191]. NCWS represents an extremely widespread problem, whose prevalence ranges between 0.55% to 6% of the general United States population. Currently NCWS is mainly defined by "negative" criteria: physicians consider the diagnosis in all cases that lack the key CD criteria (presence of anti-tissue transglutaminase (anti-tTG) antibodies, and endoscopic or histologically significant enteropathy, *i.e.*, Marsh 3, do not satisfy the criteria for IgE-mediated wheat allergy, but respond to wheat elimination diet (implemented in a blinded fashion to avoid a possible placebo/nocebo effect)[190,192-198]. Its onset is reported in the third-fourth decades of life and a study by our group, including the largest series of NCWS patients in the literature, showed a median age of 28 years[188], and a higher prevalence in females (male to female ratio ranging between 1:2.5 and 1:4)[188,190,193,199]. Symptoms and signs that usually characterize NCWS occur soon after gluten ingestion, improving or disappearing (within hours or a few days) on gluten withdrawal and relapsing following its reintroduction. Clinical presentation is a combination of gastrointestinal disorders and systemic manifestations[186,187]. In particular, gastrointestinal involvement consists of IBS-like symptoms, such as abdominal pain, bloating, and bowel habit abnormalities (either diarrhea and/or constipation), whereas systemic manifestations range from fatigue to foggy mind, headache and depression, joint and muscle pain, leg or arm numbness, dermatitis (eczema or skin rash), or anemia[188,190,193,199]. IBS-like symptoms are usually more frequent than extraintestinal ones, but most patients usually report having experienced at least 2 of the extraintestinal manifestations, primarily foggy mind and fatigue[188,190,193,199].

Probably the main issue concerning NCWS is its possible pathophysiology. Wheat, and in particular one of its components: gliadin, is known to induce both autoimmune and allergic responses (Ig-E mediated allergic reactions), in CD and wheat allergy, respectively[187,200-204]. On the contrary, NCWS pathogenesis is still largely unknown. Among several pathogenic mechanisms, we might mention (1) activation of innate immunity mechanisms by amylase-trypsin inhibitors (ATI); these are plant-derived proteins that inhibit enzymes of common parasites in wheat. *In vitro* and *in vivo* studies suggest that wheat ATI induce innate immune responses that involve monocytes, macrophages, and dendritic cells[205]; (2) gastrointestinal neuromuscular abnormalities, leading to smooth muscle hyper-contractility, and indirectly a rise in luminal water content; this mechanism could be linked to an HLA-restricted predisposition[206,207]; (3) high FODMAP content leading to increased motility and gas production; and (4) non IgE-mediated wheat allergy[188,190,193]. Recently we retrospectively reviewed the features of a large group of IBS-like patients, fulfilling the NCWS criteria. Data of 206 patients, previously diagnosed as NCWS and cow's milk protein intolerant, who self-reported multiple food allergy, and 50 IBS patients were reviewed. Patients were diagnosed by undergoing a standard 4-wk elimination diet with the exclusion of wheat, cow's milk, eggs, tomato, chocolate and any other self-reported food intolerance, followed by a DBPC wheat and cow milk challenge, at an interval of at least 4 wk from each other and always when the patients were completely asymptomatic. Notably, a history of food allergy in infancy was more frequently reported in NCWS patients (40/206, 19%) than in IBS controls (2/50, 4%, $P = 0.01$), as was the coexistence of an atopic disease (73/206, 35% and 3/50, 6% respectively; $P = 0.0001$). Similar results suggesting the hypothesis of multiple food allergy in such subgroups of NCWS patients, are: positive serum anti-gliadin IgG (134/206, 65% *vs* 7/50, 14% in IBS controls; $P = 0.0001$), positive serum anti-betalactoglobulin IgG (80/206, 39% *vs* 7/50, 14% in IBS controls; $P = 0.001$), positive *in vitro* basophil activation assay (166/206, 80% *vs* 2/50, 4% in IBS controls; $P = 0.0001$) and Intraepithelial eosinophil infiltration in the colon mucosa (154/206, 75% *vs* 0/50 in IBS controls; $P = 0.0001$). These data made us conclude that patients with NCWS and multiple food allergy have several clinical, laboratory, and histological characteristics suggesting a non-IgE-mediated food allergy[186,188].

Finally, there is a reasonable overlap between NCWS and IBS and several patients classified in one of the two groups could be better included in the other. The prospective for the future is a better understanding of the pathophysiological background (similarities and differences) of the two nosological entities, which could facilitate the physician's clinical management and improve the patient's quality of life.

CONCLUSION

IBS affects a large proportion of the general population and it can significantly affect quality of life. This aspect is a financial burden to the national health system for both direct costs (estimated in the United States from $1562 to $7547 per year in 2013) and indirect costs (ranging from $791 to $7737 per year). Its etiology still remains elusive. The individual's perception of illness, chronicity, and diagnostic uncertainty, based on symptom criteria alone, force physicians to undertake extensive and often negative investigations. Recently, food allergy has re-emerged as involved in many chronic disorders, including IBS; thus, it must be considered in diagnosis and management. For the first time, a pathophysiological basis for IBS is being discovered, but further work is needed to advance current understanding of the exact mechanisms by which the gastrointestinal immune system handles food and microbial antigens in health and disease. However, pending further scientific evidence, a cautious approach is advisable, and it should include the concept of food allergy as a possible cause of IBS; a dietary approach can find a place in routine clinical management of IBS. Taken together, the reported findings suggest that clinical management of patients with gastrointestinal complaints self-attributed to food should be inter-disciplinary, attending to the gastroenterological, allergological, psychological, as well as dietary aspects of the condition. Guidance concerning food management, which includes individualized restriction of wheat and certain FODMAP-rich food items, may reduce IBS symptoms. However, additional research is required for accurate IBS diagnosis and treatment strategies.

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