**Name of journal: World Journal of Gastroenterology**

**ESPS Manuscript NO: 17075**

**Columns: Topic Highlight**

**2015 Advances in Irritable Bowel Syndrome**

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

Mansueto P *et al*. Food allergy in non-celiac wheat sensitivity

Pasquale Mansueto, Alberto D’Alcamo, Aurelio Seidita, Antonio Carroccio

**Pasquale Mansueto, Alberto D’Alcamo, Aurelio Seidita, Antonio Carroccio,** Biomedical Department of Internal Medicine and Specialist, University Hospital of Palermo, 90141 Palermo, Italy

**Antonio Carroccio,** Internal Medicine Department, Hospital of Sciacca (Agrigento), 92019 Agrigento, Italy

**Author contributions:** All the authors reviewed international literature performing a critical revision for important intellectual content.

**Conflict of interest:** All the authors have no conflicts to declare.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Correspondence to: Antonio Carroccio, Professor,** Internal Medicine Department, Hospital of Sciacca (Agrigento), via Ciaculli 207, 90124 Palermo, Italy.acarroccio@hotmail.com

**Telephone:** +39-925-84757

**Fax:** +39-925-962492

**Received:** February 10, 2015

**Peer-review started:** February 11, 2015

**First decision:** March 26, 2015

**Revised:** April 4, 2015

**Accepted:** May 7, 2015

**Article in press:**

**Published online:**

**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

**© The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

**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.

Mansueto P, D’Alcamo A, Seidita A, Carroccio A. Food allergy in irritable bowel syndrome: the case of non-celiac wheat sensitivity. *World J Gastroenterol* 2015; In press

**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 [TH]2 and TH17)[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 TH2 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 TH1 and TH2 responses, but includes several pathways described as a mosaic of overlapping TH1/TH2 responses mediated by TH17 and TH22 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 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 rhinoconjuctivitis) 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 15min after eating and 93% within 3h. 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 the most important daily-required dietary source of calcium (50%-75%), phosphorus (20%-30%), and vitamin B2 (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 B2[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]. Andre *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, buck-wheat, 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 ≥ 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 TH2 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*[180] 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 interdisciplinary, 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.

**REFERENCES**

1 **Ford AC**, Moayyedi P, Lacy BE, Lembo AJ, Saito YA, Schiller LR, Soffer EE, Spiegel BM, Quigley EM; Task Force on the Management of Functional Bowel Disorders. American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. *Am J Gastroenterol* 2014; **109** Suppl 1: S2-26; quiz S27 [PMID: 25091148 DOI: 10.1038/ajg.2014.187]

2 **Canavan C**, West J, Card T. The epidemiology of irritable bowel syndrome. *Clin Epidemiol* 2014; **6**: 71-80 [PMID: 24523597 DOI: 10.2147/CLEP.S40245]

3 **Rome Foundation**. Guidelines--Rome III Diagnostic Criteria for Functional Gastrointestinal Disorders. *J Gastrointestin Liver Dis* 2006; **15**: 307-312 [PMID: 17203570]

4 **Drossman DA**, Dumitrascu DL. Rome III: New standard for functional gastrointestinal disorders. *J Gastrointestin Liver Dis* 2006; **15**: 237-241 [PMID: 17013448]

5 **Mönnikes H**. Quality of life in patients with irritable bowel syndrome. *J Clin Gastroenterol* 2011; **45** Suppl: S98-101 [PMID: 21666428 DOI: 10.1097/MCG.0b013e31821fbf44]

6 **Agarwal N**, Spiegel BM. The effect of irritable bowel syndrome on health-related quality of life and health care expenditures. *Gastroenterol Clin North Am* 2011; **40**: 11-19 [PMID: 21333898 DOI: 10.1016/j.gtc.2010.12.013]

7 **Drossman DA**, Morris CB, Schneck S, Hu YJ, Norton NJ, Norton WF, Weinland SR, Dalton C, Leserman J, Bangdiwala SI. International survey of patients with IBS: symptom features and their severity, health status, treatments, and risk taking to achieve clinical benefit. *J Clin Gastroenterol* 2009; **43**: 541-550 [PMID: 19384249 DOI: 10.1097/MCG.0b013e318189a7f9]

8 **Spiegel BM**. The burden of IBS: looking at metrics. *Curr Gastroenterol Rep* 2009; **11**: 265-269 [PMID: 19615301 DOI: 10.1007/s11894-009-0039-x]

9 **Nellesen D**, Yee K, Chawla A, Lewis BE, Carson RT. A systematic review of the economic and humanistic burden of illness in irritable bowel syndrome and chronic constipation. *J Manag Care Pharm* 2013; **19**: 755-764 [PMID: 24156644]

10 **Spanier JA**, Howden CW, Jones MP. A systematic review of alternative therapies in the irritable bowel syndrome. *Arch Intern Med* 2003; **163**: 265-274 [PMID: 12578506 DOI: 10.1001/archinte.163.3.265]

11 **Wald A**, Rakel D. Behavioral and complementary approaches for the treatment of irritable bowel syndrome. *Nutr Clin Pract* 2008; **23**: 284-292 [PMID: 18595861 DOI: 10.1177/0884533608318677]

12 **McKee AM**, Prior A, Whorwell PJ. Exclusion diets in irritable bowel syndrome: are they worthwhile? *J Clin Gastroenterol* 1987; **9**: 526-528 [PMID: 3680901 DOI: 10.1097/00004836-198710000-00007]

13 **Nanda R**, James R, Smith H, Dudley CR, Jewell DP. Food intolerance and the irritable bowel syndrome. *Gut* 1989; **30**: 1099-1104 [PMID: 2767507 DOI: 10.1136/gut.30.8.1099]

14 **Bischoff SC**, Herrmann A, Manns MP. Prevalence of adverse reactions to food in patients with gastrointestinal disease. *Allergy* 1996; **51**: 811-818 [PMID: 8947339 DOI: 10.1111/j.1398-9995.1996.tb04471.x]

15 **Shaw AD**, Brooks JL, Dickerson JW, Davies GJ. Dietary triggers in irritable bowel syndrome. *Nutr Res Rev* 1998; **11**: 279-309 [PMID: 19094251 DOI: 10.1079/NRR19980019]

16 **Burden S**. Dietary treatment of irritable bowel syndrome: current evidence and guidelines for future practice. *J Hum Nutr Diet* 2001; **14**: 231-241 [PMID: 11424515 DOI: 10.1046/j.1365-277X.2001.00284.x]

17 **Heizer WD**, Southern S, McGovern S. The role of diet in symptoms of irritable bowel syndrome in adults: a narrative review. *J Am Diet Assoc* 2009; **109**: 1204-1214 [PMID: 19559137 DOI: 10.1016/j.jada.2009.04.012]

18 **Morcos A**, Dinan T, Quigley EM. Irritable bowel syndrome: role of food in pathogenesis and management. *J Dig Dis* 2009; **10**: 237-246 [PMID: 19906102 DOI: 10.1111/j.1751-2980.2009.00392.x]

19 **Eswaran S**, Tack J, Chey WD. Food: the forgotten factor in the irritable bowel syndrome. *Gastroenterol Clin North Am* 2011; **40**: 141-162 [PMID: 21333905 DOI: 10.1016/j.gtc.2010.12.012]

20 **Bischoff SC**, Mayer JH, Manns MP. Allergy and the gut. *Int Arch Allergy Immunol* 2000; **121**: 270-283 [PMID: 10828717 DOI: 10.1159/000024340]

21 **Zar S**, Kumar D, Benson MJ. Food hypersensitivity and irritable bowel syndrome. *Aliment Pharmacol Ther* 2001; **15**: 439-449 [PMID: 11284772 DOI: 10.1046/j.1365-2036.2001.00951.x]

22 **O'Sullivan M**, O'Morain C. Food Intolerance: Dietary Treatments in Functional Bowel Disorders. *Curr Treat Options Gastroenterol* 2003; **6**: 339-345 [PMID: 12846943 DOI: 10.1007/s11938-003-0026-5]

23 **Zigich S**, Heuberger R. The relationship of food intolerance and irritable bowel syndrome in adults. *Gastroenterol Nurs* 2013; **36**: 275-282 [PMID: 23899486 DOI: 10.1097/SGA.0b013e31829ed911]

24 **Raithel M**, Weidenhiller M, Hagel AF, Hetterich U, Neurath MF, Konturek PC. The malabsorption of commonly occurring mono and disaccharides: levels of investigation and differential diagnoses. *Dtsch Arztebl Int* 2013; **110**: 775-782 [PMID: 24300825 DOI: 10.3238/arztebl.2013.0775]

25 **Barbara G**, De Giorgio R, Stanghellini V, Cremon C, Salvioli B, Corinaldesi R. New pathophysiological mechanisms in irritable bowel syndrome. *Aliment Pharmacol Ther* 2004; **20** Suppl 2: 1-9 [PMID: 15335408 DOI: 10.1111/j.1365-2036.2004.02036.x]

26 **Lee YJ**, Park KS. Irritable bowel syndrome: emerging paradigm in pathophysiology. *World J Gastroenterol* 2014; **20**: 2456-2469 [PMID: 24627583 DOI: 10.3748/wjg.v20.i10.2456]

27 **Pimentel M**, Chow EJ, Lin HC. Eradication of small intestinal bacterial overgrowth reduces symptoms of irritable bowel syndrome. *Am J Gastroenterol* 2000; **95**: 3503-3506 [PMID: 11151884 DOI: 10.1111/j.1572-0241.2000.03368.x]

28 **Grace E**, Shaw C, Whelan K, Andreyev HJ. Review article: small intestinal bacterial overgrowth--prevalence, clinical features, current and developing diagnostic tests, and treatment. *Aliment Pharmacol Ther* 2013; **38**: 674-688 [PMID: 23957651 DOI: 10.1111/apt.12456]

29 **McKendrick MW**, Read NW. Irritable bowel syndrome--post salmonella infection. *J Infect* 1994; **29**: 1-3 [PMID: 7963621 DOI: 10.1016/S0163-4453(94)94871-2]

30 **Neal KR**, Hebden J, Spiller R. Prevalence of gastrointestinal symptoms six months after bacterial gastroenteritis and risk factors for development of the irritable bowel syndrome: postal survey of patients. *BMJ* 1997; **314**: 779-782 [PMID: 9080994 DOI: 10.1136/bmj.314.7083.779]

31 **Rodríguez LA**, Ruigómez A. Increased risk of irritable bowel syndrome after bacterial gastroenteritis: cohort study. *BMJ* 1999; **318**: 565-566 [PMID: 10037630 DOI: 10.1136/bmj.318.7183.565]

32 **Spiller RC**. Postinfectious irritable bowel syndrome. *Gastroenterology* 2003; **124**: 1662-1671 [PMID: 12761724 DOI: 10.1016/S0016-5085(03)00324-X]

33 **Ishihara S**, Tada Y, Fukuba N, Oka A, Kusunoki R, Mishima Y, Oshima N, Moriyama I, Yuki T, Kawashima K, Kinoshita Y. Pathogenesis of irritable bowel syndrome--review regarding associated infection and immune activation. *Digestion* 2013; **87**: 204-211 [PMID: 23712295 DOI: 10.1159/000350054]

34 **Grover M**, Camilleri M, Smith K, Linden DR, Farrugia G. On the fiftieth anniversary. Postinfectious irritable bowel syndrome: mechanisms related to pathogens. *Neurogastroenterol Motil* 2014; **26**: 156-167 [PMID: 24438587 DOI: 10.1111/nmo.12304]

35 **Ohman L**, Simrén M. New insights into the pathogenesis and pathophysiology of irritable bowel syndrome. *Dig Liver Dis* 2007; **39**: 201-215 [PMID: 17267314 DOI: 10.1016/j.dld.2006.10.014]

36 **Porter CK**, Thura N, Riddle MS. Quantifying the incidence and burden of postinfectious enteric sequelae. *Mil Med* 2013; **178**: 452-469 [PMID: 23707833 DOI: 10.7205/MILMED-D-12-00510]

37 **Rhodes DY**, Wallace M. Post-infectious irritable bowel syndrome. *Curr Gastroenterol Rep* 2006; **8**: 327-332 [PMID: 16836945 DOI: 10.1007/s11894-006-0054-0]

38 **Ohman L**, Simrén M. Pathogenesis of IBS: role of inflammation, immunity and neuroimmune interactions. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 163-173 [PMID: 20101257 DOI: 10.1038/nrgastro.2010.4]

39 **Camilleri M**, Lasch K, Zhou W. Irritable bowel syndrome: methods, mechanisms, and pathophysiology. The confluence of increased permeability, inflammation, and pain in irritable bowel syndrome. *Am J Physiol Gastrointest Liver Physiol* 2012; **303**: G775-G785 [PMID: 22837345 DOI: 10.1152/ajpgi.00155.2012]

40 **Gui XY**. Mast cells: a possible link between psychological stress, enteric infection, food allergy and gut hypersensitivity in the irritable bowel syndrome. *J Gastroenterol Hepatol* 1998; **13**: 980-989 [PMID: 9835312 DOI: 10.1111/j.1440-1746.1998.tb00558.x]

41 **O'Sullivan M**, Clayton N, Breslin NP, Harman I, Bountra C, McLaren A, O'Morain CA. Increased mast cells in the irritable bowel syndrome. *Neurogastroenterol Motil* 2000; **12**: 449-457 [PMID: 11012945 DOI: 10.1046/j.1365-2982.2000.00221.x]

42 **Doyle LA**, Sepehr GJ, Hamilton MJ, Akin C, Castells MC, Hornick JL. A clinicopathologic study of 24 cases of systemic mastocytosis involving the gastrointestinal tract and assessment of mucosal mast cell density in irritable bowel syndrome and asymptomatic patients. *Am J Surg Pathol* 2014; **38**: 832-843 [PMID: 24618605 DOI: 10.1097/PAS.0000000000000190]

43 **Philpott H**, Gibson P, Thien F. Irritable bowel syndrome - An inflammatory disease involving mast cells. *Asia Pac Allergy* 2011; **1**: 36-42 [PMID: 22053295 DOI: 10.5415/apallergy.2011.1.1]

44 **Guilarte M**, Santos J, de Torres I, Alonso C, Vicario M, Ramos L, Martínez C, Casellas F, Saperas E, Malagelada JR. Diarrhoea-predominant IBS patients show mast cell activation and hyperplasia in the jejunum. *Gut* 2007; **56**: 203-209 [PMID: 17005763 DOI: 10.1136/gut.2006.100594]

45 **Wang SH**, Dong L, Luo JY, Gong J, Li L, Lu XL, Han SP. Decreased expression of serotonin in the jejunum and increased numbers of mast cells in the terminal ileum in patients with irritable bowel syndrome. *World J Gastroenterol* 2007; **13**: 6041-6047 [PMID: 18023097 DOI: 10.3748/wjg.13.6041]

46 **Walker MM**, Warwick A, Ung C, Talley NJ. The role of eosinophils and mast cells in intestinal functional disease. *Curr Gastroenterol Rep* 2011; **13**: 323-330 [PMID: 21552990 DOI: 10.1007/s11894-011-0197-5]

47 **Ortiz-Lucas M**, Saz-Peiró P, Sebastián-Domingo JJ. Irritable bowel syndrome immune hypothesis. Part one: the role of lymphocytes and mast cells. *Rev Esp Enferm Dig* 2010; **102**: 637-647 [PMID: 21142384]

48 **Walker MM**, Talley NJ. Functional gastrointestinal disorders and the potential role of eosinophils. *Gastroenterol Clin North Am* 2008; **37**: 383-95, vi [PMID: 18499026 DOI: 10.1016/j.gtc.2008.02.007]

49 **Walker MM**, Talley NJ, Prabhakar M, Pennaneac'h CJ, Aro P, Ronkainen J, Storskrubb T, Harmsen WS, Zinsmeister AR, Agreus L. Duodenal mastocytosis, eosinophilia and intraepithelial lymphocytosis as possible disease markers in the irritable bowel syndrome and functional dyspepsia. *Aliment Pharmacol Ther* 2009; **29**: 765-773 [PMID: 19183150 DOI: 10.1111/j.1365-2036.2009.03937.x]

50 **Fu Y**, Tong JJ, Pan Q, Wang WF, Zou KF, Qian W, Hou XH. [Phenotypic analysis of Th cells in colon and peripheral blood in patients with irritable bowel syndrome]. *Zhonghua Yi Xue Za Zhi* 2009; **89**: 2120-2123 [PMID: 20058616]

51 **Zanini B**, Lanzarotto F, Villanacci V, Carabellese N, Ricci C, Lanzini A. Clinical expression of lymphocytic duodenosis in "mild enteropathy" celiac disease and in functional gastrointestinal syndromes. *Scand J Gastroenterol* 2014; **49**: 794-800 [PMID: 24941349 DOI: 10.3109/00365521.2014.919017]

52 **Vicario M**, González-Castro AM, Martínez C, Lobo B, Pigrau M, Guilarte M, de Torres I, Mosquera JL, Fortea M, Sevillano-Aguilera C, Salvo-Romero E, Alonso C, Rodiño-Janeiro BK, Söderholm JD, Azpiroz F, Santos J. Increased humoral immunity in the jejunum of diarrhoea-predominant irritable bowel syndrome associated with clinical manifestations. *Gut* 2014; Epub ahead of print [PMID: 25209656 DOI: 10.1136/gutjnl-2013-306236]

53 **Barbara G**, Stanghellini V, De Giorgio R, Cremon C, Cottrell GS, Santini D, Pasquinelli G, Morselli-Labate AM, Grady EF, Bunnett NW, Collins SM, Corinaldesi R. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. *Gastroenterology* 2004; **126**: 693-702 [PMID: 14988823 DOI: 10.1053/j.gastro.2003.11.055]

54 **Barbara G**, Wang B, Stanghellini V, de Giorgio R, Cremon C, Di Nardo G, Trevisani M, Campi B, Geppetti P, Tonini M, Bunnett NW, Grundy D, Corinaldesi R. Mast cell-dependent excitation of visceral-nociceptive sensory neurons in irritable bowel syndrome. *Gastroenterology* 2007; **132**: 26-37 [PMID: 17241857 DOI: 10.1053/j.gastro.2006.11.039]

55 **Yang Y**, Zhou D, Zhang W. [Mast cells of ileocecal junction in irritable bowel syndrome]. *Zhonghua Nei Ke Za Zhi* 1997; **36**: 231-233 [PMID: 10374283]

56 **Pang X**, Boucher W, Triadafilopoulos G, Sant GR, Theoharides TC. Mast cell and substance P-positive nerve involvement in a patient with both irritable bowel syndrome and interstitial cystitis. *Urology* 1996; **47**: 436-438 [PMID: 8633418 DOI: 10.1016/S0090-4295(99)80469-5]

57 **Törnblom H**, Lindberg G, Nyberg B, Veress B. Full-thickness biopsy of the jejunum reveals inflammation and enteric neuropathy in irritable bowel syndrome. *Gastroenterology* 2002; **123**: 1972-1979 [PMID: 12454854 DOI: 10.1053/gast.2002.37059]

58 **Ohman L**, Isaksson S, Lundgren A, Simrén M, Sjövall H. A controlled study of colonic immune activity and beta7+ blood T lymphocytes in patients with irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2005; **3**: 980-986 [PMID: 16234043 DOI: 10.1016/S1542-3565(05)00410-6]

59 **Cremon C**, Carini G, Wang B, Vasina V, Cogliandro RF, De Giorgio R, Stanghellini V, Grundy D, Tonini M, De Ponti F, Corinaldesi R, Barbara G. Intestinal serotonin release, sensory neuron activation, and abdominal pain in irritable bowel syndrome. *Am J Gastroenterol* 2011; **106**: 1290-1298 [PMID: 21427712 DOI: 10.1038/ajg.2011.86]

60 **Sander LE**, Lorentz A, Sellge G, Coëffier M, Neipp M, Veres T, Frieling T, Meier PN, Manns MP, Bischoff SC. Selective expression of histamine receptors H1R, H2R, and H4R, but not H3R, in the human intestinal tract. *Gut* 2006; **55**: 498-504 [PMID: 16299042 DOI: 10.1136/gut.2004.061762]

61 **Deiteren A**, De Man JG, Pelckmans PA, De Winter BY. Histamine H₄ receptors in the gastrointestinal tract. *Br J Pharmacol* 2015; **172**: 1165-1178 [PMID: 25363289 DOI: 10.1111/bph.12989]

62 **Berstad A**, Raa J, Valeur J. Tryptophan: 'essential' for the pathogenesis of irritable bowel syndrome? *Scand J Gastroenterol* 2014; **49**: 1493-1498 [PMID: 25000845 DOI: 10.3109/00365521.2014.936034]

63 **Keszthelyi D**, Troost FJ, Jonkers DM, van Eijk HM, Lindsey PJ, Dekker J, Buurman WA, Masclee AA. Serotonergic reinforcement of intestinal barrier function is impaired in irritable bowel syndrome. *Aliment Pharmacol Ther* 2014; **40**: 392-402 [PMID: 24943480 DOI: 10.1111/apt.12842]

64 **Sohn W**, Lee OY, Lee SP, Lee KN, Jun DW, Lee HL, Yoon BC, Choi HS, Sim J, Jang KS. Mast cell number, substance P and vasoactive intestinal peptide in irritable bowel syndrome with diarrhea. *Scand J Gastroenterol* 2014; **49**: 43-51 [PMID: 24256141 DOI: 10.3109/00365521.2013.857712]

65 **Paragomi P**, Rahimian R, Kazemi MH, Gharedaghi MH, Khalifeh-Soltani A, Azary S, Javidan AN, Moradi K, Sakuma S, Dehpour AR. Antinociceptive and antidiarrheal effects of pioglitazone in a rat model of diarrhoea-predominant irritable bowel syndrome: role of nitric oxide. *Clin Exp Pharmacol Physiol* 2014; **41**: 118-126 [PMID: 24471407 DOI: 10.1111/1440-1681.12188]

66 **Mete R**, Tulubas F, Oran M, Yılmaz A, Avci BA, Yildiz K, Turan CB, Gurel A. The role of oxidants and reactive nitrogen species in irritable bowel syndrome: a potential etiological explanation. *Med Sci Monit* 2013; **19**: 762-766 [PMID: 24029778 DOI: 10.12659/MSM.889068]

67 **Darkoh C**, Comer L, Zewdie G, Harold S, Snyder N, Dupont HL. Chemotactic chemokines are important in the pathogenesis of irritable bowel syndrome. *PLoS One* 2014; **9**: e93144 [PMID: 24667736 DOI: 10.1371/journal.pone.0093144]

68 **Akiho H**, Deng Y, Blennerhassett P, Kanbayashi H, Collins SM. Mechanisms underlying the maintenance of muscle hypercontractility in a model of postinfective gut dysfunction. *Gastroenterology* 2005; **129**: 131-141 [PMID: 16012943 DOI: 10.1053/j.gastro.2005.03.049]

69 **van der Veek PP**, van den Berg M, de Kroon YE, Verspaget HW, Masclee AA. Role of tumor necrosis factor-alpha and interleukin-10 gene polymorphisms in irritable bowel syndrome. *Am J Gastroenterol* 2005; **100**: 2510-2516 [PMID: 16279907 DOI: 10.1111/j.1572-0241.2005.00257.x]

70 **Kolmannskog S**, Haneberg B. Immunoglobulin E in feces from children with allergy. Evidence of local production of IgE in the gut. *Int Arch Allergy Appl Immunol* 1985; **76**: 133-137 [PMID: 3967940 DOI: 10.1159/000233679]

71 **Carroccio A**, Brusca I, Mansueto P, Soresi M, D'Alcamo A, Ambrosiano G, Pepe I, Iacono G, Lospalluti ML, La Chiusa SM, Di Fede G. Fecal assays detect hypersensitivity to cow's milk protein and gluten in adults with irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2011; **9**: 965-971.e3 [PMID: 21839707 DOI: 10.1016/j.cgh.2011.07.030]

72 **Goepp J**, Fowler E, McBride T, Landis D. Frequency of abnormal fecal biomarkers in irritable bowel syndrome. *Glob Adv Health Med* 2014; **3**: 9-15 [PMID: 24891989 DOI: 10.7453/gahmj.2013.099]

73 **Däbritz J**, Musci J, Foell D. Diagnostic utility of faecal biomarkers in patients with irritable bowel syndrome. *World J Gastroenterol* 2014; **20**: 363-375 [PMID: 24574706 DOI: 10.3748/wjg.v20.i2.363]

74 **Chadwick *VS***, Chen W, Shu D, Paulus B, Bethwaite P, Tie A, Wilson I. Activation of the mucosal immune system in irritable bowel syndrome. *Gastroenterology* 2002; **122**: 1778-1783 [PMID: 12055584 DOI: 10.1053/gast.2002.33579]

75 **Ford AC**, Talley NJ. Mucosal inflammation as a potential etiological factor in irritable bowel syndrome: a systematic review. *J Gastroenterol* 2011; **46**: 421-431 [PMID: 21331765 DOI: 10.1007/s00535-011-0379-9]

76 **Surdea-Blaga T**, Băban A, Dumitrascu DL. Psychosocial determinants of irritable bowel syndrome. *World J Gastroenterol* 2012; **18**: 616-626 [PMID: 22363132 DOI: 10.3748/wjg.v18.i7.616]

77 **Coss-Adame E**, Rao SS. Brain and gut interactions in irritable bowel syndrome: new paradigms and new understandings. *Curr Gastroenterol Rep* 2014; **16**: 379 [PMID: 24595616 DOI: 10.1007/s11894-014-0379-z]

78 **Fadgyas-Stanculete M**, Buga AM, Popa-Wagner A, Dumitrascu DL. The relationship between irritable bowel syndrome and psychiatric disorders: from molecular changes to clinical manifestations. *J Mol Psychiatry* 2014; **2**: 4 [PMID: 25408914 DOI: 10.1186/2049-9256-2-4]

79 **Andreasson AN**, Jones MP, Walker MM, Talley NJ, Nyhlin H, Agréus L. Prediction pathways for innate immune pathology, IBS, anxiety and depression in a general population (the PopCol study). *Brain Behav Immun* 2013; **32**: e46 [doi: 10.1016/j.bbi.2013.07.170]

80 **Buckley MM**, O'Mahony SM, O'Malley D. Convergence of neuro-endocrine-immune pathways in the pathophysiology of irritable bowel syndrome. *World J Gastroenterol* 2014; **20**: 8846-8858 [PMID: 25083058 DOI: 10.3748/wjg.v20.i27.8846]

81 **Qin HY**, Cheng CW, Tang XD, Bian ZX. Impact of psychological stress on irritable bowel syndrome. *World J Gastroenterol* 2014; **20**: 14126-14131 [PMID: 25339801 DOI: 10.3748/wjg.v20.i39.14126]

82 **Raphael I**, Nalawade S, Eagar TN, Forsthuber TG. T cell subsets and their signature cytokines in autoimmune and inflammatory diseases. *Cytokine* 2014; Epub ahead of print [PMID: 25458968 DOI: 10.1016/j.cyto.2014.09.011]

83 **White AM**, Stevens WH, Upton AR, O'Byrne PM, Collins SM. Airway responsiveness to inhaled methacholine in patients with irritable bowel syndrome. *Gastroenterology* 1991; **100**: 68-74 [PMID: 1983850]

84 **Yazar A**, Atis S, Konca K, Pata C, Akbay E, Calikoglu M, Hafta A. Respiratory symptoms and pulmonary functional changes in patients with irritable bowel syndrome. *Am J Gastroenterol* 2001; **96**: 1511-1516 [PMID: 11374691 DOI: 10.1111/j.1572-0241.2001.03748.x]

85 **Jun DW**, Lee OY, Yoon HJ, Lee HL, Yoon BC, Choi HS, Lee MH, Lee DH, Kee CS. Bronchial hyperresponsiveness in irritable bowel syndrome. *Dig Dis Sci* 2005; **50**: 1688-1691 [PMID: 16133970 DOI: 10.1007/s10620-005-2916-y]

86 **Roussos A**, Koursarakos P, Patsopoulos D, Gerogianni I, Philippou N. Increased prevalence of irritable bowel syndrome in patients with bronchial asthma. *Respir Med* 2003; **97**: 75-79 [PMID: 12556015 DOI: 10.1053/rmed.2001.1409]

87 **Ozol D**, Uz E, Bozalan R, Türkay C, Yildirim Z. Relationship between asthma and irritable bowel syndrome: role of food allergy. *J Asthma* 2006; **43**: 773-775 [PMID: 17169830 DOI: 10.1080/02770900601031789]

88 **Powell N**, Huntley B, Beech T, Knight W, Knight H, Corrigan CJ. Increased prevalence of gastrointestinal symptoms in patients with allergic disease. *Postgrad Med J* 2007; **83**: 182-186 [PMID: 17344573 DOI: 10.1136/pgmj.2006.049585]

89 **Cole JA**, Rothman KJ, Cabral HJ, Zhang Y, Farraye FA. Incidence of IBS in a cohort of people with asthma. *Dig Dis Sci* 2007; **52**: 329-335 [PMID: 17211701 DOI: 10.1007/s10620-006-9530-5]

90 **Huerta C**, García Rodríguez LA, Wallander MA, Johansson S. Risk of irritable bowel syndrome among asthma patients. *Pharmacoepidemiol Drug Saf* 2002; **11**: 31-35 [PMID: 11998549 DOI: 10.1002/pds.666]

91 **Panicker R**, Arifhodzic N, Al Ahmad M, Ali SA. Association and symptom characteristics of irritable bowel syndrome among bronchial asthma patients in Kuwait. *Ann Thorac Med* 2010; **5**: 37-42 [PMID: 20351959 DOI: 10.4103/1817-1737.58958]

92 **Hunskar GS**, Langeland N, Wensaas KA, Hanevik K, Eide GE, Mørch K, Rortveit G. The impact of atopic disease on the risk of post-infectious fatigue and irritable bowel syndrome 3 years after Giardia infection. A historic cohort study. *Scand J Gastroenterol* 2012; **47**: 956-961 [PMID: 22746290 DOI: 10.3109/00365521.2012.696681]

93 **Tobin MC**, Moparty B, Farhadi A, DeMeo MT, Bansal PJ, Keshavarzian A. Atopic irritable bowel syndrome: a novel subgroup of irritable bowel syndrome with allergic manifestations. *Ann Allergy Asthma Immunol* 2008; **100**: 49-53 [PMID: 18254482 DOI: 10.1016/S1081-1206(10)60404-8]

94 **Jones MP**, Walker MM, Ford AC, Talley NJ. The overlap of atopy and functional gastrointestinal disorders among 23,471 patients in primary care. *Aliment Pharmacol Ther* 2014; **40**: 382-391 [PMID: 24961872 DOI: 10.1111/apt.12846]

95 **Herrett E**, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol* 2010; **69**: 4-14 [PMID: 20078607 DOI: 10.1111/j.1365-2125.2009.03537.x]

96 **Olén O**, Neuman Å, Koopmann B, Ludvigsson JF, Ballardini N, Westman M, Melén E, Kull I, Simrén M, Bergström A. Allergy-related diseases and recurrent abdominal pain during childhood - a birth cohort study. *Aliment Pharmacol Ther* 2014; **40**: 1349-1358 [PMID: 25270840 DOI: 10.1111/apt.12965]

97 **Smith MA**, Youngs GR, Finn R. Food intolerance, atopy, and irritable bowel syndrome. *Lancet* 1985; **2**: 1064 [PMID: 2865536 DOI: 10.1016/S0140-6736(85)90927-4]

98 **Lillestøl K**, Helgeland L, Arslan Lied G, Florvaag E, Valeur J, Lind R, Berstad A. Indications of 'atopic bowel' in patients with self-reported food hypersensitivity. *Aliment Pharmacol Ther* 2010; **31**: 1112-1122 [PMID: 20163379 DOI: 10.1111/j.1365-2036.2010.04261.x]

99 **Berstad A**, Undseth R, Lind R, Valeur J. Functional bowel symptoms, fibromyalgia and fatigue: a food-induced triad? *Scand J Gastroenterol* 2012; **47**: 914-919 [PMID: 22594347 DOI: 10.3109/00365521.2012.690045]

100 **Lind R**, Berstad A, Hatlebakk J, Valeur J. Chronic fatigue in patients with unexplained self-reported food hypersensitivity and irritable bowel syndrome: validation of a Norwegian translation of the Fatigue Impact Scale. *Clin Exp Gastroenterol* 2013; **6**: 101-107 [PMID: 23869173 DOI: 10.2147/CEG.S45760]

101 **Zar S**, Mincher L, Benson MJ, Kumar D. Food-specific IgG4 antibody-guided exclusion diet improves symptoms and rectal compliance in irritable bowel syndrome. *Scand J Gastroenterol* 2005; **40**: 800-807 [PMID: 16109655 DOI: 10.1080/00365520510015593]

102 **Atkinson W**, Sheldon TA, Shaath N, Whorwell PJ. Food elimination based on IgG antibodies in irritable bowel syndrome: a randomised controlled trial. *Gut* 2004; **53**: 1459-1464 [PMID: 15361495 DOI: 10.1136/gut.2003.037697]

103 **Bolin TD**. Use of oral sodium cromoglycate in persistent diarrhoea. *Gut* 1980; **21**: 848-850 [PMID: 6777263 DOI: 10.1136/gut.21.10.848]

104 **Paganelli R**, Fagiolo U, Cancian M, Sturniolo GC, Scala E, D'Offizi GP. Intestinal permeability in irritable bowel syndrome. Effect of diet and sodium cromoglycate administration. *Ann Allergy* 1990; **64**: 377-380 [PMID: 2108592]

105 **Lunardi C**, Bambara LM, Biasi D, Cortina P, Peroli P, Nicolis F, Favari F, Pacor ML. Double-blind cross-over trial of oral sodium cromoglycate in patients with irritable bowel syndrome due to food intolerance. *Clin Exp Allergy* 1991; **21**: 569-572 [PMID: 1742648 DOI: 10.1111/j.1365-2222.1991.tb00848.x]

106 **Stefanini GF**, Prati E, Albini MC, Piccinini G, Capelli S, Castelli E, Mazzetti M, Gasbarrini G. Oral disodium cromoglycate treatment on irritable bowel syndrome: an open study on 101 subjects with diarrheic type. *Am J Gastroenterol* 1992; **87**: 55-57 [PMID: 1728124]

107 **Stefanini GF**, Saggioro A, Alvisi V, Angelini G, Capurso L, di Lorenzo G, Dobrilla G, Dodero M, Galimberti M, Gasbarrini G. Oral cromolyn sodium in comparison with elimination diet in the irritable bowel syndrome, diarrheic type. Multicenter study of 428 patients. *Scand J Gastroenterol* 1995; **30**: 535-541 [PMID: 7569760 DOI: 10.3109/00365529509089786]

108 **Leri O**, Tubili S, De Rosa FG, Addessi MA, Scopelliti G, Lucenti W, De Luca D. Management of diarrhoeic type of irritable bowel syndrome with exclusion diet and disodium cromoglycate. *Inflammopharmacology* 1997; **5**: 153-158 [PMID: 17694364 DOI: 10.1007/s10787-997-0024-7]

109 **Rona RJ**, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, Sigurdardottir ST, Lindner T, Goldhahn K, Dahlstrom J, McBride D, Madsen C. The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol* 2007; **120**: 638-646 [PMID: 17628647 DOI: 10.1016/j.jaci.2007.05.026]

110 **Leung PS**, Shu SA, Chang C. The changing geoepidemiology of food allergies. *Clin Rev Allergy Immunol* 2014; **46**: 169-179 [PMID: 24535418 DOI: 10.1007/s12016-014-8411-5]

111 **Savage J**, Johns CB. Food allergy: epidemiology and natural history. *Immunol Allergy Clin North Am* 2015; **35**: 45-59 [PMID: 25459576 DOI: 10.1016/j.iac.2014.09.004]

112 **Dainese R**, Galliani EA, De Lazzari F, Di Leo V, Naccarato R. Discrepancies between reported food intolerance and sensitization test findings in irritable bowel syndrome patients. *Am J Gastroenterol* 1999; **94**: 1892-1897 [PMID: 10406255 DOI: 10.1111/j.1572-0241.1999.01226.x]

113 **Jones VA**, McLaughlan P, Shorthouse M, Workman E, Hunter JO. Food intolerance: a major factor in the pathogenesis of irritable bowel syndrome. *Lancet* 1982; **2**: 1115-1117 [PMID: 6128447 DOI: 10.1016/S0140-6736(82)92782-9]

114 **Bentley SJ**, Pearson DJ, Rix KJ. Food hypersensitivity in irritable bowel syndrome. *Lancet* 1983; **2**: 295-297 [PMID: 6135828 DOI: 10.1016/S0140-6736(83)90285-4]

115 **Locke GR**, Zinsmeister AR, Talley NJ, Fett SL, Melton LJ. Risk factors for irritable bowel syndrome: role of analgesics and food sensitivities. *Am J Gastroenterol* 2000; **95**: 157-165 [PMID: 10638576 DOI: 10.1111/j.1572-0241.2000.01678.x]

116 **Farah DA**, Calder I, Benson L, MacKenzie JF. Specific food intolerance: its place as a cause of gastrointestinal symptoms. *Gut* 1985; **26**: 164-168 [PMID: 3967835 DOI: 10.1136/gut.26.2.164]

117 **Simrén M**, Månsson A, Langkilde AM, Svedlund J, Abrahamsson H, Bengtsson U, Björnsson ES. Food-related gastrointestinal symptoms in the irritable bowel syndrome. *Digestion* 2001; **63**: 108-115 [PMID: 11244249 DOI: 10.1159/000051878]

118 **Reding KW**, Cain KC, Jarrett ME, Eugenio MD, Heitkemper MM. Relationship between patterns of alcohol consumption and gastrointestinal symptoms among patients with irritable bowel syndrome. *Am J Gastroenterol* 2013; **108**: 270-276 [PMID: 23295280 DOI: 10.1038/ajg.2012.414]

119 **MacDermott RP**. Treatment of irritable bowel syndrome in outpatients with inflammatory bowel disease using a food and beverage intolerance, food and beverage avoidance diet. *Inflamm Bowel Dis* 2007; **13**: 91-96 [PMID: 17206644 DOI: 10.1002/ibd.20048]

120 **Böhn L**, Störsrud S, Törnblom H, Bengtsson U, Simrén M. Self-reported food-related gastrointestinal symptoms in IBS are common and associated with more severe symptoms and reduced quality of life. *Am J Gastroenterol* 2013; **108**: 634-641 [PMID: 23644955 DOI: 10.1038/ajg.2013.105]

121 **Carlson MJ**, Moore CE, Tsai CM, Shulman RJ, Chumpitazi BP. Child and parent perceived food-induced gastrointestinal symptoms and quality of life in children with functional gastrointestinal disorders. *J Acad Nutr Diet* 2014; **114**: 403-413 [PMID: 24360501 DOI: 10.1016/j.jand.2013.10.013]

122 **Jarrett M**, Heitkemper MM, Bond EF, Georges J. Comparison of diet composition in women with and without functional bowel disorder. *Gastroenterol Nurs* 1994; **16**: 253-258 [PMID: 8075160 DOI: 10.1097/00001610-199406000-00004]

123 **Saito YA**, Locke GR, Weaver AL, Zinsmeister AR, Talley NJ. Diet and functional gastrointestinal disorders: a population-based case-control study. *Am J Gastroenterol* 2005; **100**: 2743-2748 [PMID: 16393229 DOI: 10.1111/j.1572-0241.2005.00288.x]

124 **Sicherer SH**, Sampson HA. Food allergy: recent advances in pathophysiology and treatment. *Annu Rev Med* 2009; **60**: 261-277 [PMID: 18729729 DOI: 10.1146/annurev.med.60.042407.205711]

125 **Williams EA**, Nai X, Corfe BM. Dietary intakes in people with irritable bowel syndrome. *BMC Gastroenterol* 2011; **11**: 9 [PMID: 21291551 DOI: 10.1186/1471-230X-11-9]

126 **Böhn L**, Störsrud S, Simrén M. Nutrient intake in patients with irritable bowel syndrome compared with the general population. *Neurogastroenterol Motil* 2013; **25**: 23-30.e1 [PMID: 22937900 DOI: 10.1111/nmo.12001]

127 **Monsbakken KW**, Vandvik PO, Farup PG. Perceived food intolerance in subjects with irritable bowel syndrome-- etiology, prevalence and consequences. *Eur J Clin Nutr* 2006; **60**: 667-672 [PMID: 16391571 DOI: 10.1038/sj.ejcn.1602367]

128 **Ostgaard H**, Hausken T, Gundersen D, El-Salhy M. Diet and effects of diet management on quality of life and symptoms in patients with irritable bowel syndrome. *Mol Med Rep* 2012; **5**: 1382-1390 [PMID: 22446969 DOI: 10.3892/mmr.2012.843]

129 **Biesiekierski JR**, Rosella O, Rose R, Liels K, Barrett JS, Shepherd SJ, Gibson PR, Muir JG. Quantification of fructans, galacto-oligosacharides and other short-chain carbohydrates in processed grains and cereals. *J Hum Nutr Diet* 2011; **24**: 154-176 [PMID: 21332832 DOI: 10.1111/j.1365-277X.2010.01139.x]

130 **Parker TJ**, Woolner JT, Prevost AT, Tuffnell Q, Shorthouse M, Hunter JO. Irritable bowel syndrome: is the search for lactose intolerance justified? *Eur J Gastroenterol Hepatol* 2001; **13**: 219-225 [PMID: 11293439 DOI: 10.1097/00042737-200103000-00001]

131 **Yang J**, Deng Y, Chu H, Cong Y, Zhao J, Pohl D, Misselwitz B, Fried M, Dai N, Fox M. Prevalence and presentation of lactose intolerance and effects on dairy product intake in healthy subjects and patients with irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2013; **11**: 262-268.e1 [PMID: 23246646 DOI: 10.1016/j.cgh.2012.11.034]

132 **Dainese R**, Casellas F, Mariné-Barjoan E, Vivinus-Nébot M, Schneider SM, Hébuterne X, Piche T. Perception of lactose intolerance in irritable bowel syndrome patients. *Eur J Gastroenterol Hepatol* 2014; **26**: 1167-1175 [PMID: 25089542 DOI: 10.1097/MEG.0000000000000089]

133 . Geissler C. Human Nutrition. 11th edition. Elsevier Churchill Livingstone, London 2005. NO PMID

134 **Prescha A**, Pieczyńska J, Ilow R, Poreba J, Neubauer K, Smereka A, Grajeta H, Biernat J, Paradowski L. Assessment of dietary intake of patients with irritable bowel syndrome. *Rocz Panstw Zakl Hig* 2009; **60**: 185-189 [PMID: 19803452]

135 **Ligaarden SC**, Lydersen S, Farup PG. Diet in subjects with irritable bowel syndrome: a cross-sectional study in the general population. *BMC Gastroenterol* 2012; **12**: 61 [PMID: 22676475 DOI: 10.1186/1471-230X-12-61]

136 **El-Salhy M**, Ostgaard H, Gundersen D, Hatlebakk JG, Hausken T. The role of diet in the pathogenesis and management of irritable bowel syndrome (Review). *Int J Mol Med* 2012; **29**: 723-731 [PMID: 22366773 DOI: 10.3892/ijmm.2012.926]

137 **Petitpierre M**, Gumowski P, Girard JP. Irritable bowel syndrome and hypersensitivity to food. *Ann Allergy* 1985; **54**: 538-540 [PMID: 4014782]

138 **Zwetchkenbaum J**, Burakoff R. The irritable bowel syndrome and food hypersensitivity. *Ann Allergy* 1988; **61**: 47-49 [PMID: 3389571]

139 **Barau E**, Dupont C. Modifications of intestinal permeability during food provocation procedures in pediatric irritable bowel syndrome. *J Pediatr Gastroenterol Nutr* 1990; **11**: 72-77 [PMID: 2117653 DOI: 10.1097/00005176-199007000-00015]

140 **André F**, André C, Colin L, Cavagna S. IgE in stools as indicator of food sensitization. *Allergy* 1995; **50**: 328-333 [PMID: 7573816 DOI: 10.1111/j.1398-9995.1995.tb01156.x]

141 **Simonato B**, De Lazzari F, Pasini G, Polato F, Giannattasio M, Gemignani C, Peruffo AD, Santucci B, Plebani M, Curioni A. IgE binding to soluble and insoluble wheat flour proteins in atopic and non-atopic patients suffering from gastrointestinal symptoms after wheat ingestion. *Clin Exp Allergy* 2001; **31**: 1771-1778 [PMID: 11696054 DOI: 10.1046/j.1365-2222.2001.01200.x]

142 **Jun DW**, Lee OY, Yoon HJ, Lee SH, Lee HL, Choi HS, Yoon BC, Lee MH, Lee DH, Cho SH. Food intolerance and skin prick test in treated and untreated irritable bowel syndrome. *World J Gastroenterol* 2006; **12**: 2382-2387 [PMID: 16688829]

143 **Soares RL**, Figueiredo HN, Maneschy CP, Rocha VR, Santos JM. Correlation between symptoms of the irritable bowel syndrome and the response to the food extract skin prick test. *Braz J Med Biol Res* 2004; **37**: 659-662 [PMID: 15107926 DOI: 10.1590/S0100-879X2004000500005]

144 **Uz E**, Türkay C, Aytac S, Bavbek N. Risk factors for irritable bowel syndrome in Turkish population: role of food allergy. *J Clin Gastroenterol* 2007; **41**: 380-383 [PMID: 17413606 DOI: 10.1097/01.mcg.0000225589.70706.24]

145 **Carroccio A**, Brusca I, Mansueto P, Pirrone G, Barrale M, Di Prima L, Ambrosiano G, Iacono G, Lospalluti ML, La Chiusa SM, Di Fede G. A cytologic assay for diagnosis of food hypersensitivity in patients with irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2010; **8**: 254-260 [PMID: 19932763 DOI: 10.1016/j.cgh.2009.11.010]

146 **Ebo DG**, Hagendorens MM, Bridts CH, Schuerwegh AJ, De Clerck LS, Stevens WJ. In vitro allergy diagnosis: should we follow the flow? *Clin Exp Allergy* 2004; **34**: 332-339 [PMID: 15005724 DOI: 10.1111/j.1365-2222.2004.01891.x]

147 **Moneret-Vautrin DA**, Sainte-Laudy J, Kanny G, Frémont S. Human basophil activation measured by CD63 expression and LTC4 release in IgE-mediated food allergy. *Ann Allergy Asthma Immunol* 1999; **82**: 33-40 [PMID: 9988204 DOI: 10.1016/S1081-1206(10)62657-9]

148 **Sanz ML**, Gamboa PM, Antépara I, Uasuf C, Vila L, Garcia-Avilés C, Chazot M, De Weck AL. Flow cytometric basophil activation test by detection of CD63 expression in patients with immediate-type reactions to betalactam antibiotics. *Clin Exp Allergy* 2002; **32**: 277-286 [PMID: 11929494 DOI: 10.1046/j.1365-2222.2002.01305.x]

149 **Carroccio A**, Brusca I, Mansueto P, D'alcamo A, Barrale M, Soresi M, Seidita A, La Chiusa SM, Iacono G, Sprini D. A comparison between two different in vitro basophil activation tests for gluten- and cow's milk protein sensitivity in irritable bowel syndrome (IBS)-like patients. *Clin Chem Lab Med* 2013; **51**: 1257-1263 [PMID: 23183757 DOI: 10.1515/cclm-2012-0609]

150 **Bischoff SC**, Mayer J, Wedemeyer J, Meier PN, Zeck-Kapp G, Wedi B, Kapp A, Cetin Y, Gebel M, Manns MP. Colonoscopic allergen provocation (COLAP): a new diagnostic approach for gastrointestinal food allergy. *Gut* 1997; **40**: 745-753 [PMID: 9245928 DOI: 10.1136/gut.40.6.745]

151 **Kristjansson G**, Serra J, Lööf L, Venge P, Hällgren R. Kinetics of mucosal granulocyte activation after gluten challenge in coeliac disease. *Scand J Gastroenterol* 2005; **40**: 662-669 [PMID: 16036526 DOI: 10.1080/00365520510015566]

152 **Lidén M**, Kristjánsson G, Valtysdottir S, Venge P, Hällgren R. Cow's milk protein sensitivity assessed by the mucosal patch technique is related to irritable bowel syndrome in patients with primary Sjögren's syndrome. *Clin Exp Allergy* 2008; **38**: 929-935 [PMID: 18498540 DOI: 10.1111/j.1365-2222.2008.02983.x]

153 **Arslan G**, Ødegaard S, Elsayed S, Florvaag E, Berstad A. Food allergy and intolerance: response to intestinal provocation monitored by endosonography. *Eur J Ultrasound* 2002; **15**: 29-36 [PMID: 12044850 DOI: 10.1016/S0929-8266(02)00004-6]

154 **Arslan G**, Gilja OH, Lind R, Florvaag E, Berstad A. Response to intestinal provocation monitored by transabdominal ultrasound in patients with food hypersensitivity. *Scand J Gastroenterol* 2005; **40**: 386-394 [PMID: 16028432 DOI: 10.1080/00365520510012163]

155 **Arslan G**, Lillestøl K, Mulahasanovic A, Florvaag E, Berstad A. Food hypersensitivity reactions visualised by ultrasonography and magnetic resonance imaging in a patient lacking systemic food-specific IgE. *Digestion* 2006; **73**: 111-115 [PMID: 16788291 DOI: 10.1159/000094042]

156 **Santos J**, Bayarri C, Saperas E, Nogueiras C, Antolín M, Mourelle M, Cadahia A, Malagelada JR. Characterisation of immune mediator release during the immediate response to segmental mucosal challenge in the jejunum of patients with food allergy. *Gut* 1999; **45**: 553-558 [PMID: 10486364 DOI: 10.1136/gut.45.4.553]

157 **Fritscher-Ravens A**, Schuppan D, Ellrichmann M, Schoch S, Röcken C, Brasch J, Bethge J, Böttner M, Klose J, Milla PJ. Confocal endomicroscopy shows food-associated changes in the intestinal mucosa of patients with irritable bowel syndrome. *Gastroenterology* 2014; **147**: 1012-20.e4 [PMID: 25083606 DOI: 10.1053/j.gastro.2014.07.046]

158 **Hoveyda N**, Heneghan C, Mahtani KR, Perera R, Roberts N, Glasziou P. A systematic review and meta-analysis: probiotics in the treatment of irritable bowel syndrome. *BMC Gastroenterol* 2009; **9**: 15 [PMID: 19220890 DOI: 10.1186/1471-230X-9-15]

159 **Coëffier M**, Lorentz A, Manns MP, Bischoff SC. Epsilon germ-line and IL-4 transcripts are expressed in human intestinal mucosa and enhanced in patients with food allergy. *Allergy* 2005; **60**: 822-827 [PMID: 15876314 DOI: 10.1111/j.1398-9995.2005.00782.x]

160 **Kamisawa T**, Zen Y, Pillai S, Stone JH. IgG4-related disease. *Lancet* 2015; **385**: 1460-1471 [PMID: 25481618 DOI: 10.1016/S0140-6736(14)60720-0]

161 **Brito-Zerón P**, Ramos-Casals M, Bosch X, Stone JH. The clinical spectrum of IgG4-related disease. *Autoimmun Rev* 2014; **13**: 1203-1210 [PMID: 25151972 DOI: 10.1016/j.autrev.2014.08.013]

162 **Barnes RM**, Johnson PM, Harvey MM, Blears J, Finn R. Human serum antibodies reactive with dietary proteins. IgG subclass distribution. *Int Arch Allergy Appl Immunol* 1988; **87**: 184-188 [PMID: 3192305 DOI: 10.1159/000234670]

163 **Fälth-Magnusson K**, Kjellman NI, Magnusson KE. Antibodies IgG, IgA, and IgM to food antigens during the first 18 months of life in relation to feeding and development of atopic disease. *J Allergy Clin Immunol* 1988; **81**: 743-749 [PMID: 3356852 DOI: 10.1016/0091-6749(88)91048-2]

164 **Husby S**, Oxelius VA, Teisner B, Jensenius JC, Svehag SE. Humoral immunity to dietary antigens in healthy adults. Occurrence, isotype and IgG subclass distribution of serum antibodies to protein antigens. *Int Arch Allergy Appl Immunol* 1985; **77**: 416-422 [PMID: 4018884 DOI: 10.1159/000233819]

165 **Johansson SG**, Dannaeus A, Lilja G. The relevance of anti-food antibodies for the diagnosis of food allergy. *Ann Allergy* 1984; **53**: 665-672 [PMID: 6391294]

166 **Quinti I**, Papetti C, D'Offizi G, Cavagni G, Panchor ML, Lunardi C, Paganelli R. IgG subclasses to food antigens. *Allerg Immunol* (Paris) 1988; **20**: 41, 43-44 [PMID: 3293604]

167 **Shanahan F**, Whorwell PJ. IgG-mediated food intolerance in irritable bowel syndrome: a real phenomenon or an epiphenomenom? *Am J Gastroenterol* 2005; **100**: 1558-1559 [PMID: 15984981 DOI: 10.1111/j.1572-0241.2005.50009.x]

168 **Perelmutter L**. IgG4: non-IgE mediated atopic disease. *Ann Allergy* 1984; **52**: 64-69 [PMID: 6364895]

169 **Finn R**, Smith MA, Youngs GR, Chew D, Johnson PM, Barnes RM. Immunological hypersensitivity to environmental antigens in the irritable bowel syndrome. *Br J Clin Pract* 1987; **41**: 1041-1043 [PMID: 3504322]

170 **el Rafei A**, Peters SM, Harris N, Bellanti JA. Diagnostic value of IgG4 measurements in patients with food allergy. *Ann Allergy* 1989; **62**: 94-99 [PMID: 2919809]

171 **Drisko J**, Bischoff B, Hall M, McCallum R. Treating irritable bowel syndrome with a food elimination diet followed by food challenge and probiotics. *J Am Coll Nutr* 2006; **25**: 514-522 [PMID: 17229899 DOI: 10.1080/07315724.2006.10719567]

172 **Guo H**, Jiang T, Wang J, Chang Y, Guo H, Zhang W. The value of eliminating foods according to food-specific immunoglobulin G antibodies in irritable bowel syndrome with diarrhoea. *J Int Med Res* 2012; **40**: 204-210 [PMID: 22429360 DOI: 10.1177/147323001204000121]

173 **Aydinlar EI**, Dikmen PY, Tiftikci A, Saruc M, Aksu M, Gunsoy HG, Tozun N. IgG-based elimination diet in migraine plus irritable bowel syndrome. *Headache* 2013; **53**: 514-525 [PMID: 23216231 DOI: 10.1111/j.1526-4610.2012.02296.x]

174 **Niec AM**, Frankum B, Talley NJ. Are adverse food reactions linked to irritable bowel syndrome? *Am J Gastroenterol* 1998; **93**: 2184-2190 [PMID: 9820394 DOI: 10.1111/j.1572-0241.1998.00531.x]

175 **Ortolani C**, Bruijnzeel-Koomen C, Bengtsson U, Bindslev-Jensen C, Björkstén B, Høst A, Ispano M, Jarish R, Madsen C, Nekam K, Paganelli R, Poulsen LK, Wüthrich B. Controversial aspects of adverse reactions to food. European Academy of Allergology and Clinical Immunology (EAACI) Reactions to Food Subcommittee. *Allergy* 1999; **54**: 27-45 [PMID: 10195356 DOI: 10.1034/j.1398-9995.1999.00913.x]

176 **Beyer K**, Teuber SS. Food allergy diagnostics: scientific and unproven procedures. *Curr Opin Allergy Clin Immunol* 2005; **5**: 261-266 [PMID: 15864086 DOI: 10.1097/01.all.0000168792.27948.f9]

177 **Hunter JO**. Food elimination in IBS: the case for IgG testing remains doubtful. *Gut* 2005; **54**: 1203; author reply 1203 [PMID: 16009694]

178 **Philpott H**, Nandurkar S, Lubel J, Gibson PR. Alternative investigations for irritable bowel syndrome. *J Gastroenterol Hepatol* 2013; **28**: 73-77 [PMID: 23033865 DOI: 10.1111/j.1440-1746.2012.07291.x]

179 **Zar S**, Benson MJ, Kumar D. Food-specific serum IgG4 and IgE titers to common food antigens in irritable bowel syndrome. *Am J Gastroenterol* 2005; **100**: 1550-1557 [PMID: 15984980 DOI: 10.1111/j.1572-0241.2005.41348.x]

180 **Zuo XL**, Li YQ, Li WJ, Guo YT, Lu XF, Li JM, Desmond PV. Alterations of food antigen-specific serum immunoglobulins G and E antibodies in patients with irritable bowel syndrome and functional dyspepsia. *Clin Exp Allergy* 2007; **37**: 823-830 [PMID: 17517095 DOI: 10.1111/j.1365-2222.2007.02727.x]

181 **Ligaarden SC**, Lydersen S, Farup PG. IgG and IgG4 antibodies in subjects with irritable bowel syndrome: a case control study in the general population. *BMC Gastroenterol* 2012; **12**: 166 [PMID: 23170971 DOI: 10.1186/1471-230X-12-166]

182 **Sewell WA**. IgG food antibodies should be studied in similarly treated groups. *Gut* 2005; **54**: 566 [PMID: 15753547]

183 **Dapoigny M**, Stockbrügger RW, Azpiroz F, Collins S, Coremans G, Müller-Lissner S, Oberndorff A, Pace F, Smout A, Vatn M, Whorwell P. Role of alimentation in irritable bowel syndrome. *Digestion* 2003; **67**: 225-233 [PMID: 12966230 DOI: 10.1159/000072061]

184 **Lea R**, Whorwell PJ. The role of food intolerance in irritable bowel syndrome. *Gastroenterol Clin North Am* 2005; **34**: 247-255 [PMID: 15862933 DOI: 10.1016/j.gtc.2005.02.005]

185 **Biesiekierski JR**, Newnham ED, Irving PM, Barrett JS, Haines M, Doecke JD, Shepherd SJ, Muir JG, Gibson PR. Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial. *Am J Gastroenterol* 2011; **106**: 508-14; quiz 515 [PMID: 21224837 DOI: 10.1038/ajg.2010.487]

186 **Carroccio A**, Mansueto P, D'Alcamo A, Iacono G. Non-celiac wheat sensitivity as an allergic condition: personal experience and narrative review. *Am J Gastroenterol* 2013; **108**: 1845-152; quiz 1853 [PMID: 24169272 DOI: 10.1038/ajg.2013.353]

187 **Mansueto P**, Seidita A, D'Alcamo A, Carroccio A. Non-celiac gluten sensitivity: literature review. *J Am Coll Nutr* 2014; **33**: 39-54 [PMID: 24533607 DOI: 10.1080/07315724.2014.869996]

188 **Carroccio A**, Mansueto P, Iacono G, Soresi M, D'Alcamo A, Cavataio F, Brusca I, Florena AM, Ambrosiano G, Seidita A, Pirrone G, Rini GB. Non-celiac wheat sensitivity diagnosed by double-blind placebo-controlled challenge: exploring a new clinical entity. *Am J Gastroenterol* 2012; **107**: 1898-906; quiz 1907 [PMID: 22825366 DOI: 10.1038/ajg.2012.236]

189 **Mullin GE**, Shepherd SJ, Chander Roland B, Ireton-Jones C, Matarese LE. Irritable bowel syndrome: contemporary nutrition management strategies. *JPEN J Parenter Enteral Nutr* 2014; **38**: 781-799 [PMID: 25085503 DOI: 10.1177/0148607114545329]

190 **Sapone A**, Bai JC, Ciacci C, Dolinsek J, Green PH, Hadjivassiliou M, Kaukinen K, Rostami K, Sanders DS, Schumann M, Ullrich R, Villalta D, Volta U, Catassi C, Fasano A. Spectrum of gluten-related disorders: consensus on new nomenclature and classification. *BMC Med* 2012; **10**: 13 [PMID: 22313950 DOI: 10.1186/1741-7015-10-13]

191 **Carroccio A**, Rini G, Mansueto P. Non-celiac wheat sensitivity is a more appropriate label than non-celiac gluten sensitivity. *Gastroenterology* 2014; **146**: 320-321 [PMID: 24275240 DOI: 10.1053/j.gastro.2013.08.061]

192 **Volta U**, De Giorgio R. New understanding of gluten sensitivity. *Nat Rev Gastroenterol Hepatol* 2012; **9**: 295-299 [PMID: 22371218 DOI: 10.1038/nrgastro.2012.15]

193 **Volta U**, Tovoli F, Cicola R, Parisi C, Fabbri A, Piscaglia M, Fiorini E, Caio G. Serological tests in gluten sensitivity (nonceliac gluten intolerance). *J Clin Gastroenterol* 2012; **46**: 680-685 [PMID: 22138844 DOI: 10.1097/MCG.0b013e3182372541]

194 **Volta U**, Caio G, Tovoli F, De Giorgio R. Non-celiac gluten sensitivity: questions still to be answered despite increasing awareness. *Cell Mol Immunol* 2013; **10**: 383-392 [PMID: 23934026 DOI: 10.1038/cmi.2013.28]

195 **Aziz I**, Sanders DS. Emerging concepts: from coeliac disease to non-coeliac gluten sensitivity. *Proc Nutr Soc* 2012; **71**: 576-580 [PMID: 22954208 DOI: 10.1017/S002966511200081X]

196 **Mooney PD**, Aziz I, Sanders DS. Non-celiac gluten sensitivity: clinical relevance and recommendations for future research. *Neurogastroenterol Motil* 2013; **25**: 864-871 [PMID: 23937528 DOI: 10.1111/nmo.12216]

197 **Catassi C**, Bai JC, Bonaz B, Bouma G, Calabrò A, Carroccio A, Castillejo G, Ciacci C, Cristofori F, Dolinsek J, Francavilla R, Elli L, Green P, Holtmeier W, Koehler P, Koletzko S, Meinhold C, Sanders D, Schumann M, Schuppan D, Ullrich R, Vécsei A, Volta U, Zevallos V, Sapone A, Fasano A. Non-Celiac Gluten sensitivity: the new frontier of gluten related disorders. *Nutrients* 2013; **5**: 3839-3853 [PMID: 24077239 DOI: 10.3390/nu5103839]

198 **Volta U**, Bardella MT, Calabrò A, Troncone R, Corazza GR; Study Group for Non-Celiac Gluten Sensitivity. An Italian prospective multicenter survey on patients suspected of having non-celiac gluten sensitivity. *BMC Med* 2014; **12**: 85 [PMID: 24885375 DOI: 10.1186/1741-7015-12-85]

199 **DiGiacomo DV**, Tennyson CA, Green PH, Demmer RT. Prevalence of gluten-free diet adherence among individuals without celiac disease in the USA: results from the Continuous National Health and Nutrition Examination Survey 2009-2010. *Scand J Gastroenterol* 2013; **48**: 921-925 [PMID: 23834276 DOI: 10.3109/00365521.2013.809598]

200 **Qiao SW**, Iversen R, Ráki M, Sollid LM. The adaptive immune response in celiac disease. *Semin Immunopathol* 2012; **34**: 523-540 [PMID: 22535446 DOI: 10.1007/s00281-012-0314-z]

201 **Cianci R**, Pagliari D, Landolfi R, Frosali S, Colagiovanni A, Cammarota G, Pandolfi F. New insights on the role of T cells in the pathogenesis of celiac disease. *J Biol Regul Homeost Agents* 2012; **26**: 171-179 [PMID: 22824744]

202 **Di Sabatino A**, Vanoli A, Giuffrida P, Luinetti O, Solcia E, Corazza GR. The function of tissue transglutaminase in celiac disease. *Autoimmun Rev* 2012; **11**: 746-753 [PMID: 22326684 DOI: 10.1016/j.autrev.2012.01.007]

203 **Inomata N**. Wheat allergy. *Curr Opin Allergy Clin Immunol* 2009; **9**: 238-243 [PMID: 19318930 DOI: 10.1097/ACI.0b013e32832aa5bc]

204 **Keet CA**, Matsui EC, Dhillon G, Lenehan P, Paterakis M, Wood RA. The natural history of wheat allergy. *Ann Allergy Asthma Immunol* 2009; **102**: 410-415 [PMID: 19492663 DOI: 10.1016/S1081-1206(10)60513-3]

205 **Junker Y**, Zeissig S, Kim SJ, Barisani D, Wieser H, Leffler DA, Zevallos V, Libermann TA, Dillon S, Freitag TL, Kelly CP, Schuppan D. Wheat amylase trypsin inhibitors drive intestinal inflammation via activation of toll-like receptor 4. *J Exp Med* 2012; **209**: 2395-2408 [PMID: 23209313 DOI: 10.1084/jem.20102660]

206 **Verdu EF**, Huang X, Natividad J, Lu J, Blennerhassett PA, David CS, McKay DM, Murray JA. Gliadin-dependent neuromuscular and epithelial secretory responses in gluten-sensitive HLA-DQ8 transgenic mice. *Am J Physiol Gastrointest Liver Physiol* 2008; **294**: G217-G225 [PMID: 18006603 DOI: 10.1152/ajpgi.00225.2007]

207 **Choi S**, DiSilvio B, Fernstrom MH, Fernstrom JD. The chronic ingestion of diets containing different proteins produces marked variations in brain tryptophan levels and serotonin synthesis in the rat. *Neurochem Res* 2011; **36**: 559-565 [PMID: 21207140 DOI: 10.1007/s11064-010-0382-1]

**P-Reviewer:** Hirahara N, Owczarek D **S-Editor:** Ma YJ **L-Editor:** **E-Editor:**

**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*[85], 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*[86], 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*[87], 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*[88],(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*[89], 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*[90], 2007 | Nested case-control study | 91,237 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*[91], 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*[92]*,* 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 years, *P <* 000). |
| Hunskar *et al*[93], 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*[94], 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*[95], 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*[97], 2014 | Birth cohort study | 2610 children | Recurrent abdominal pain and atopic diseases in children | 237 (9%) children reported abdominal pain when 12 years old. Asthma in the first two years of life and food allergy at age 8 years were significantly associated with abdominal pain at 12 years (*P <* 0.001). There was an increased risk of abdominal pain at 12 years in children sensitized to food allergens at 4 or 8 years. |
| Smith *et al*[98], 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*[99], 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*[100]*,* 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[101]*, 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* ≤ 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 IBSpatients 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*[104], 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*[105], 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[106], 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*[107], 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*[108], 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*[109], 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*[110]*,* 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*[111], 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 second; FGIDs: Functional gastrointestinal disorders; FIS: Fatigue impact scale; IBS: Irritable bowel syndrome; RR: Relative risk; SPT: Skin prick tests.

**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*[72], 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*[113], 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*[116], 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*[117], 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*[122], 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*[127], 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*[128], 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*[131], 2001 | 122 IBS patients | LHBT, lactose elimination diet and DBPCFC (with 5/10/15g 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 15g of lactose | Lactose intolerance was demonstrated in IBS patients with positive (33/122) or negative (13/122) LHBT. DBPCC were inconclusive. |
| Yang *et al*[132], 2012 | 60 IBS patients *vs* 60 controls | LHBT and self-reported lactose intolerance | 18% *vs* 3% with 10 g LHBT  47% *vs* 22% with 20g 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*[133], 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*[146], 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.