

REVIEW ARTICLE

Is there a role of food allergy in irritable bowel syndrome and functional dyspepsia? A systematic review

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Abstract A significant proportion of adults believe they suffer from food allergy, and 20–65% of patients with irritable bowel syndrome (IBS) attribute their symptoms to something in food that activates an abnormal response. This systematic review evaluates the role of food allergy in aetiology and management of these disorders. Activation of gastrointestinal mucosal immune system may be one of the causative factors in the pathogenesis of functional dyspepsia and IBS. This activation may result from effects of bacterial infection or other luminal factors including commensal microbial flora and food antigens. Some studies have reported on the role of food allergy in IBS; only one epidemiological study on functional dyspepsia and food allergy has been published. The mechanism by which food activates mucosal immune system is uncertain, but food specific IgE and IgG4 appeared to mediate the hypersensitivity reaction in a subgroup of IBS patients. Exclusion diets based on skin prick test, RAST for IgE or IgG4, hypoallergic diet and clinical trials with oral disodium cromoglycate have been conducted, and some success has been reported in a subset of IBS patients. Further well-controlled studies are needed to establish whether food allergy plays a role in the pathophysiology of functional dyspepsia and IBS.

Keywords cytokines, food allergy, functional dyspepsia, irritable bowel syndrome, mast cells, neuroimmune.

INTRODUCTION: DEFINITION

There is an increasing appreciation of the role of the intraluminal milieu to the development of functional gastrointestinal disorders. This has been highlighted by recent observations of changes in mucosal and neuromuscular function in animal models as well as in patients with these disorders. Therapeutic benefit of antibiotics¹ or probiotics² confirms the potential role of modulating the intraluminal bacterial flora. However, given the high frequency with which patients report association of symptoms with food ingestion, it is relevant to systematically explore the evidence for an association of food allergy or intolerance to manifestation of these functional gastrointestinal disorders.

In 1916, Cooke and Van der Veer were the first to consider food allergy as a potential factor in the causation of gastrointestinal symptoms in patients with asthma and hay fever.³ Loveless⁴ and Graham *et al.*⁵ verified the association between the ingestion of food and development of symptoms in adults in the 1950s.

Food adverse reactions consist of any abnormal reaction after the ingestion of a food, and include food allergy, food intolerance and food aversions. Food intolerance is an adverse physiologic reaction, which is mediated by non-immunologic reaction and may be due to factors within foods, such as toxins (e.g. food poisoning) or pharmacologic agents (e.g. caffeine or tyramine), enzyme deficiency of the host (e.g. lactase deficiency) or idiosyncratic responses induced by

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unknown mechanism. Food aversions are psychological avoidance responses to any type of foods.

METHODOLOGY OF SYSTEMATIC REVIEW

We searched the MEDLINE electronic database (1966–March 2005) using the following keywords singly and in different combinations: food allergy, food hypersensitivity, functional dyspepsia (FD), irritable bowel syndrome (IBS), epidemiology, diagnosis, pathogenesis, pathophysiology, treatment. The search was restricted to papers published or having at least an abstract in the English language. We also hand-searched the references of the individual papers retrieved. We retrieved potentially relevant articles and reviewed their reference lists to identify studies that our search strategy may have missed. As shown in Table 1, the evidence is assessed using Jadad criteria (Table 2).⁶

EPIDEMIOLOGY

The prevalence of food allergies is greatest in the first few years of life, affecting about 6% of infants less than 3 years of age,⁷ and decreases over the first decade. In adults, the prevalence of food allergies is lower, and was estimated at 3.7% in a recent US study.⁸ On the other hand, in several population studies,^{9–12} 20–45% of adults believe that they suffer from adverse reactions to food, and 20–65% of patients with IBS attribute their symptoms to adverse food reactions.^{13,14} Such perceived adverse reactions may be caused by different mechanisms, and the majority of adverse food reactions are non-immunologic in origin, with lactose intolerance the most common adverse reaction worldwide.¹⁵ One uncontrolled study observed a high prevalence of FD and IBS in patients with adverse reactions to food.¹⁶ The role of adverse physiologic reactions to food such as lactose intolerance in IBS patients is unclear.^{17,18} Although perceived food allergy is often not verified by double-blind placebo-controlled food challenge, a perception of food allergy may be associated with a subset of patients with IBS or FD.

PATHOPHYSIOLOGY OF FOOD ALLERGY IN ADULTS

It has been estimated that humans consume approximately 100 ton of food during a lifetime,¹⁹ but the fact that only a small portion of the population develops symptoms in relation to the ingestion of food leads to the inference that the gastrointestinal system is uniquely designed to avoid potentially deleterious

immune responses to foods. While the gastrointestinal tract acts as a conduit, allowing the transfer of nutrients from the intestinal lumen to the systemic circulation, it also protects against invasion by microbes and other antigens including foods. The gastrointestinal barrier is a complex structure that serves to protect the host against invading pathogens and allergens. It has several components: non-specific defence systems and innate or adaptive immune responses.

The non-specific defence systems consist of gastric acid, digestive enzymes, mucus, an intact epithelial layer forming tight junctions and peristaltic movement. For example, in mice, inhibition of acid secretion by injection of ranitidine or omeprazole was shown to increase sensitization to food antigens.²⁰ The innate immune responses include alternative complement pathways, natural killer cells, polymorphonuclear leukocytes, macrophages, toll-like receptors which are usually associated with the luminal membrane of gut epithelial cells,²¹ antimicrobial peptides such as defensins and cathelicidins²² and reparative factors called trefoil peptides.²³ Adaptive immune responses consist of intraepithelial and lamina propria lymphocytes, Peyer's patches, secretory IgA and cytokines. These provide an active barrier to foreign antigens. Working together, these factors may prevent the development of food allergy. Several studies have shown that intestinal permeability measured by using polyethylene glycol (PEG), mannitol/lactulose, L-rhamnose/lactulose or horseradish peroxidase (HRP) was increased in patients with food allergy compared to healthy volunteers.^{24–28} In contrast, there is a small study that did not find any difference of intestinal permeability between food allergy patients and healthy volunteers.²⁹ Overall, these results may indicate that intestinal permeability is increased in patients with food allergy, and that the increased permeability may be secondary to inflammatory events such as infection, ischemic injury or malnutrition.

Yet, despite these barriers, about 2% of ingested food antigens are absorbed even through the mature gut and they are transported throughout the body in an intact form that may result in immunological responses.³⁰ The neonate or infant is exposed to dietary antigens since 'closure' of the gut, which is determined by non-immunologic as well as immunologic mechanisms in the gut,³¹ is required for tolerance to develop. Oral tolerance, as characterized by Chase³² in 1946, refers to a state of active inhibition of immune responses to an antigen by means of prior exposure to that antigen through the oral route.³³ Thus, food antigens generally do not cause clinical symptoms because most

Table 1 Clinical trials in IBS patients

Reference	Subjects	Treatment	Challenge protocol	Result	Follow-up	Jadad score (0-5)*
Jones <i>et al.</i> ⁷⁵ Study 1	25, IBS	Low allergenic, 1 week	Open food, daily	14/21 (67%) specific offending foods found	Not recorded	0
Study 2	6, symptom-free subjects from study 1	Same diet during challenges only	DB nasogastric daily	10/12 DB challenges provoked symptoms	Not recorded	5
Study 3	5, selected patients from study 1	Same diet, 4 days	SB disguised in unspecified flavoured soup daily	100% symptomatic with SB challenges	Not recorded	1
Bentley <i>et al.</i> ⁷⁶	27, IBS	Low allergenic, unknown duration	Open food 3 days apart; DBPC in responders	14/21 (67%) remission after ED; 10/21 (47.7%) specific offending foods found; 3/8 (37.5%) confirmed by DB challenge	3 responders remained well; duration not stated	2
Farah <i>et al.</i> ⁷⁷	49, GI clinic patients with symptoms sug- gestive of food intol- erance	Low allergenic, 2 weeks	DBPC; open food 1 week apart in responders	13/49 (26.5%) remission after ED; 8/49 (16.3%) specific offending foods found; 3/8 (37.5%) confirmed by DB challenge	6-18 months	5
Petitpierre <i>et al.</i> ⁷⁸	24, IBS (12, atopic; 12, non-atopic)	Low allergenic, 3 weeks	Open and single-blind; unspecified frequency	7/24 (29.2%) symptoms unchanged; 3/24 (12.5%) remission with ED but negative challenges; 14/ 24 (58.3%) specific offending foods found and confirmed by blind challenges	6 months	0
McKee <i>et al.</i> ⁷⁹	40, IBS	Low allergenic, 1 week	Open, unspecified frequency	6/40 (15%) remission during ED	Not recorded	0
Zwetchkenbaum <i>et al.</i> ⁸⁰	10, IBS	Exclusion of foods and same-food families linked to IBS symptoms from food diaries; 2 weeks	Open for 2 days apart	6/9 (66.7%) symptoms unchanged with ED; 3/9 (33.3%) remission with ED, challenges negative; 0/9 (0%) AFRs identified	Not recorded	1

Table 1 (Continued)

Reference	Subjects	Treatment	Challenge protocol	Result	Follow-up	Jadad score (0-5)*
Nanda <i>et al.</i> ¹³	200, IBS	Low allergenic, 3 weeks	Open for 2 days	91/189 (47.9%) remission during ED; 73/189 (38.6%) specific offending foods found by open food challenge	14.7 months average for responders; 12.5 months for non-responder	1
Atkinson <i>et al.</i> ⁸⁵	150, IBS who had raised IgG antibodies to foods	True diet (excluding all foods to which they raised IgG antibodies)/Sham diet (excluding the same number of foods), 12 weeks	Open for 4 weeks	10% greater reduction in symptom score in the true diet group than the sham diet group. ($P = 0.024$). Open reintroduction of diet; 24% greater deterioration in symptoms in the true diet group. ($P = 0.003$)	Not recorded	5
Bolin ⁸³	20, Persistent diarrhoea	DSCG/Placebo, 4 weeks, cross-over design		8/20 (40%) remission during DSCG	Not recorded	5
Lunardi <i>et al.</i> ⁸⁴	20, IBS	DSCG/Placebo, 8, 4 weeks washout, cross-over design		15/18 (83%) remission during DSCG	Not recorded	4
Stefanini <i>et al.</i> ⁸¹	101, IBS-diarrhoea (improved after an ED and worsened after a challenge)	DSCG, 8 weeks		Improvement of symptoms, 50/74 (67%) of the SPT-positive patients 11/27 (40%) of the SPT-negative patients ($P < 0.05$)	Not recorded	1
Stefanini <i>et al.</i> ⁸²	428, IBS-diarrhoea (Multicentre study)	DSCG/Low allergenic, 1 month		Improvement of symptoms, 118/175 (68%) during DSCG 103/171 (60%) during low allergenic	Not recorded	1

ED, elimination diet; DB, double-blind; AFR, adverse food reactions; DSCG, disodium cromoglycate; * See Table 2.

Table 2 The Jadad scale⁶

Item	Points
Randomization	
Study described as randomized	+1
Randomization method described and appropriate	+1
Randomization method described and inappropriate	-1
Blinding	
Study described as double blind	+1
Blinding method described and appropriate	+1
Blinding method described and inappropriate	-1
Blinding method not described	0
Study not described as blind	0
Withdrawals and dropouts	
Withdrawals and dropouts described	+1
Withdrawals and dropouts not described	0

individuals acquire oral tolerance. Some studies showed that exclusive breast-feeding in infants may promote the development of oral tolerance and prevent some food allergy and atopic dermatitis in infancy,^{34,35} whereas other studies have reported an increased risk for development of atopic eczema and food allergies in breast-fed infants.^{36,37} Tolerance is, therefore, key to the maintenance of immunologic homeostasis in the gut and the prevention of disease. The fact that mice raised in a germ-free environment from birth fail to develop normal tolerance³⁸ suggests that commensal gut flora could play an important role in the development of oral tolerance.

Sensitization to food antigens could be attributed to immaturity of the host or breakdown of these defence mechanisms due to a variety of factors such as enteric infections³⁹ or genetic alterations.^{40,41} Sensitization could lead to the development of food allergy. Sensitization may occur in the gastrointestinal tract after ingestion of a food, considered a traditional or class-1 food allergy, or after inhalation of an airborne allergen that cross-reacts with a specific food, considered a class-2 food allergy.⁴² In adults, peanuts, tree nuts, fish and shellfish are responsible for most allergic reactions in North America.⁴³ The list of foods inducing allergic reactions varies somewhat in different countries where cultural habits result in ingestion of different kind of foods.¹⁵ Food allergy is an abnormal or exaggerated immunologic response to a food antigen, and it can be mediated by a classic type 1, immediate hypersensitivity, IgE-mediated reaction to the offending food, or by type 4 delayed hypersensitivity, cell-mediated response, or a mixed IgE and cell-mediated response.

DIAGNOSIS OF FOOD ALLERGY IN ADULTS

Allergy to specific foods is suspected by many patients, but is confirmed objectively in very few. Although relatively rare in adults compared to infants and young children, food allergy should be considered in patients with characteristic signs and symptoms or suggestive immunologic responses or biopsy findings when other causes for the symptoms are not identified.

Diagnosis of food allergy requires a suspicion that certain symptoms or signs may be caused by or be related to food allergy. Clinical evaluation should be used to rule out non-immunological adverse reactions to food such as lactose, sorbitol or fructose intolerance, pharmacologic effects of ingested caffeine, histamine or tyramine, psychological disorders manifesting with gastrointestinal symptoms, and pathological gastrointestinal diseases. This involves careful history, physical examination and diagnostic tests such as breath hydrogen tests for lactose,⁴⁴ fructose⁴⁴ or sorbitol.⁴⁵ When food allergy is considered possible, the next step is confirmation of diagnosis and identification of the implicated foods by appropriate skin and/or *in vitro* testing, followed by double-blind, placebo-controlled food challenges.⁴⁶⁻⁴⁸ A careful history may establish a suspicion of a food-induced allergic reaction, the type of food involved and the timing of ingestion relative to symptom onset. This timing may suggest which allergic mechanism (IgE-mediated, mixed IgE and cell-mediated or cell-mediated) was likely involved. IgE-mediated reactions are typically rapid in onset; non-IgE mediated disorders become evident hours to days after allergen ingestion. It is less likely to identify the implicated food in chronic disorders compared to situations associated with acute reactions to food.

There is no gold standard diagnostic procedure for gastrointestinal food allergy.⁴⁹ The methods include *in vitro* tests, *ex vivo* stimulation tests or *in vivo* provocation tests. Skin prick tests and the radioallergen sorbent test (RAST) for IgE suggest the presence of systemic food-specific IgE, or so-called sensitization. However, sensitization can exist without clinical reactions and, hence, a positive test does not imply food allergy. Colonoscopic allergen provocation test (COLAP) assesses local IgE responses and appears mechanistically more convincing, but its clinical relevance is still unclear.⁵⁰ Other laboratory techniques have not proven useful in blinded studies. At present, a double-blind, placebo-controlled food challenge is considered the only conclusive method for diagnosing food allergy.¹⁵ However, it is associated with several practical problems: the lack of a read-out

system, the variable time interval between ingestion and the onset of symptoms, and the lack of discrimination between food allergy and food intolerance.⁴⁹

ROLE OF FOOD ALLERGY IN FUNCTIONAL DYSPEPSIA

Functional dyspepsia is conventionally defined as persistent or recurrent pain or discomfort centred in the upper abdomen that is not relieved by defecation or caused by organic diseases.⁵¹ Genetic predisposition, psychological factors, inflammation and *Helicobacter pylori* infection may contribute to the development of FD, although the aetiology is unknown. Patients with FD often report that meals rich in fat cause discomfort.⁵² There are no controlled studies to investigate the association between food allergy and FD.

A case-control study from Italy investigated the incidence of several gastrointestinal diseases in 236 adult patients with food allergy or intolerance, and data from patients admitted to hospitals in the same region were used for comparison.¹⁶ The prevalence of FD was 2–4% higher in patients with adverse reactions to food relative to controls. Further, well-controlled studies are needed to evaluate the relationship between food allergy and FD.

ROLE OF FOOD ALLERGY IN IBS

Multiple factors such as altered bowel motility, visceral hypersensitivity, psychological dysfunction, genetic factors, imbalance in neurotransmitters and infection and inflammation may lead to the development and maintenance of symptoms of IBS, but the pathogenesis of IBS still remains uncertain.⁵³

A subgroup of IBS patients describes an acute onset of persistent symptoms after an episode of gastroenteritis characterized by at least two of the following: fever, vomiting, diarrhoea or positive stool culture.⁵⁴ In 1962, Chaudhary and Truelove reported for the first time that 34 of 130 patients with irritable colon syndrome dated the onset of their symptoms to an attack of either bacillary or amebic dysentery.⁵⁵ After four decades, recent studies have shown that 4–31% of people develop new onset IBS after infective gastroenteritis,^{56–62} and the odds of developing IBS was significantly higher in the group with prior gastroenteritis compared to a control group in some of these studies.^{60–62} However, a recent prospective cohort study showed that there was no significant difference in the incidence of IBS between those exposed to enteric infection during travel and the non-exposed groups.⁶³

Several studies suggest that low-grade mucosal inflammation may play a role in the pathogenesis of IBS in both unselected and postinfectious IBS patients. The mucosal inflammation is characterized by increased numbers usually of ileal mast cells,^{63–67} increased nitric oxide synthetase (iNOS),⁶⁸ lymphocyte infiltration in the myenteric plexus⁶⁹ and an increase in T lymphocytes.⁷⁰ Although there is a great deal of overlap in the quantitation data of controls and IBS for all these markers to inflammation, it is generally accepted that the mucosal immune system seems to be activated, at least in a subset of patients with IBS.⁷¹ It is important to note that mucosal inflammation and immune system activation in the mucosa of these IBS patients can also be caused by other factors, including food antigens, changes in the resident microbial flora or endogenous chemical irritants such as bile salts. Mucosal activation of these immune cells results in changes in the function of submucosal and myenteric neurons,^{72,73} linking these two effector systems in the causation of disorders of gastrointestinal functions, e.g., secretion, absorption, blood flow and motility.

RELATIONSHIP OF FOOD ALLERGY, IMMUNE HYPERSENSITIVITY AND IBS

The mucosal surface of the gastrointestinal tract defends the organism from the constant challenge of antigens, such as microorganisms, and enables assimilation of antigens from food that remains innocuous in most individuals. In order to maintain the homeostasis of the gut, the intestine is in a state of continuous immune responsiveness, with a delicate balance between concomitant facilitation and suppression of inflammatory responses. However, food antigens can activate the mucosal immune system when there is immaturity of the gut barrier, pathological destruction of that barrier, infection or inflammation and genetic susceptibility.⁷⁴ It is hypothesized that mucosal immune activation caused by food antigens may contribute to the development of food allergy and IBS, but further work is needed in order to understand the interaction of food with the gastrointestinal immune system.

There are several lines of evidence suggesting that IBS can be caused by food allergy or generalized immune hypersensitivity. First, several studies demonstrate a positive response to elimination diets and disodium cromoglycate (DSCG), and these may indicate that, in a subset of IBS patients, symptoms can be attributed to food allergy or food intolerance (Table 1).^{13,75–85} Second, the prevalence of atopic

conditions is increased in patients with diarrhoea-predominant IBS,^{81,86} and airway responsiveness to inhaled methacholine was increased in IBS patients with no clinical evidence of atopic disease in comparison to two control groups (healthy controls and positive diseases controls with inflammatory bowel disease⁸⁷). Third, a recent study revealed that patients with bronchial asthma have an increased prevalence of IBS relative to the patients with other pulmonary disorders and healthy subjects.⁸⁸

The mechanisms underlying food allergy may be mediated by IgE and/or IgG antibodies in these patients.

IgE-mediated food hypersensitivity⁸⁹

Several studies suggest a causative role of IgE-mediated food hypersensitivity in a subgroup of IBS patients, typically those with atopy.^{50,78,90-92} Petitpierre *et al.* evaluated 24 IBS patients, 12 atopic, 12 non-atopic, who underwent total serum IgE test, skin prick test, RAST to various food antigens, and 3 weeks of low-allergenic diet followed by open challenge.⁷⁸ Responders underwent blind dietary provocation. In 14 patients, one or more foods and food additives reproduced the typical IBS symptoms. Nine of these 14 patients showed elevated total serum IgE and positive skin tests which suggest systemic IgE-mediated food hypersensitivity. All these patients had evidence of atopy. In another study, nine of 17 paediatric IBS patients with personal and/or family history of allergy and/or raised total serum IgE levels had increased intestinal permeability (estimated by the differential urinary elimination of oral lactulose and mannitol) in response to food challenges.⁹³

The Fc fragment of IgE contains the C-terminal domains of the heavy immunoglobulin chains; it has no antigen-binding sites or effector functions. Andre *et al.* showed increased Fc fragment of IgE in faecal extracts of 236/312 patients (73%) with food hypersensitivity based on history, positive skin prick test and RAST test. In contrast, 95 healthy subjects had undetectable faecal IgE.⁹⁴ In a subgroup analysis, 22 of the 32 (68.8%) IBS patients were found to have detectable Fc fragment of IgE in faeces. In 70 adult patients with abdominal symptoms suspected to be related to food allergy and in five healthy volunteers, the COLAP test was performed by Bischoff *et al.*⁵⁰ Food antigens were selected according to the patients' history of food intolerance and presence of specific IgE in serum. Three food antigens were injected into the mucosa of the cecum during colonoscopy. A standard set of three antigens (milk, wheat, hazelnut) was used for chal-

lenge in the five healthy volunteers. The mucosal weal and flare reaction was classified semiquantitatively 20 min after challenge using a scale of 0-4: 0 = no reaction, 1 = questionable reaction, 2 = moderate reaction (<1 cm diameter), 3 = strong reaction (1-2 cm) and 4 = maximal reaction (>2 cm). The reaction was classified as positive if the grade of weal or flare reaction was ≥ 2 . Colonoscopic allergen provocation test was positive in response to at least one food antigen in 77% (54/70) overall and a similar 74% (39/53) with a putative diagnosis of IBS. In contrast, no reaction was detected in the five healthy volunteers. Biopsies taken from the test positive site showed both mast cell and eosinophil activation.⁹⁴ Following the dietary elimination of suspected food antigens in COLAP positive patients, 29/35 (89%) reported a significant clinical response after 3 months. The COLAP results corresponded strongly to a positive history of food intolerances, but they corresponded poorly to results of skin prick tests and specific serum IgE levels. These findings suggest that, in IBS patients, clinically relevant food antigens can be identified by the COLAP test, but not by skin test and measurement of specific serum IgE. The data also suggest that the mechanism of intestinal food allergy in IBS seems to be different from the classic type-1 hypersensitivity reactions of the skin or the respiratory mucosa. Prospective studies are needed to confirm the clinical relevance of these observations.

IgG-mediated food hypersensitivity

Although several studies suggested that IgG and IgG4 production may be part of a normal immunologic response to dietary antigens,^{91,92,95,96} other studies have demonstrated that serum IgG4 levels are elevated in patients with a history of food allergy or IBS.⁹⁷⁻¹⁰⁰ IgG4 receptors are located on basophils and mast cells and are distinct from IgE receptors.¹⁰¹ An increased prevalence of serum IgG antibodies to dietary proteins was demonstrated in 58 IBS patients compared with 46 controls, suggesting that IgG food antibodies may have some role in IBS.⁹⁷ Similarly, food specific IgG4 antibodies to common food antigens are elevated in IBS patients.¹⁰⁰ El Rafei *et al.* compared specific IgG4 and IgE levels to double-blind food challenges in 25 patients with suspected food allergy. They observed raised serum IgE or IgG4 levels in 63% of patients with a positive history of food hypersensitivity and either IgE or IgG4 in 91% of patients.⁹⁷ Similar results have been reported in other studies.^{99,102} These results suggest that the combination of specific IgE and IgG4 antibodies to food

antigens may be useful in evaluating patients with suspected food allergy.

Atkinson *et al.* assessed the therapeutic potential of dietary elimination based on the presence of IgG antibodies to food in 150 IBS outpatients;⁸⁵ they were randomized to receive for 12 weeks either an elimination diet or a sham diet. After 12 weeks, the elimination diet resulted in a 10% greater reduction in IBS symptom severity score than the sham diet ($P = 0.024$). The reduction in severity score was 26% in fully compliant patients ($P < 0.001$ vs sham diet). Following reintroduction of foods in both groups, more patients in the elimination diet group showed worsening of global rating compared with the sham diet group ($P = 0.047$). Further controlled studies are needed to confirm these provocative findings that evaluate the role of specific serum IgG in the diagnosis and treatment of IBS patients.

FOOD INTOLERANCE IN IBS

A recent population-based study, using a valid self-report questionnaire, reported that IBS symptoms are associated with reporting of many 'food allergies', which could not be discriminated from food intolerance.¹⁰³ The next section critically appraises the studies of adverse food reactions in IBS.

Elimination diets and food challenge in IBS

Eight studies investigated the effect of dietary exclusion followed by food challenge (Table 1).^{13,75–80,85} In 1982, Jones *et al.* evaluated the role of specific foods in induction of symptoms of IBS patients.⁷⁵ A study of 25 consecutive IBS patients tested the effect of a 1-week elimination diet composed of a single meat, a single fruit and distilled or spring water, followed by open challenge with the suspected single food. Two-thirds (14/21) of patients discovered that their symptoms cleared and recurred on food challenge. The foodstuffs commonly implicated were wheat, corn, dairy products, coffee, tea and citrus fruits. Six of the 14 patients were then randomized in a double-blind, challenge study which confirmed food-related symptoms. Mechanistically, rectal PGE2 levels were increased after administration of food. However, other markers for immune activation were not altered, arguing against an immunological cause for these intolerances. Bentley *et al.* studied 27 patients with IBS.⁷⁶ Food hypersensitivity was confirmed in three of the 27 patients, and these three patients were atopic. In a separate study of 49 patients suspected of having specific food intolerance, only three proved to have specific food intolerance

on double-blind challenge.⁷⁷ Intolerance is often suspected, but is verifiable only in a minority of such patients. McKee *et al.* studied 40 patients with IBS; 15% showed evidence of food intolerance. Some patients with diarrhoea-predominant or alternating bowel habit responded to an exclusion diet. In contrast, the constipation-predominant IBS group consistently failed to improve.⁷⁹ Although serum IgG antibody seems not to be a reliable indicator of food hypersensitivity in IBS,⁸⁰ a recent controlled study demonstrated that food elimination based on IgG antibodies may be effective in reducing symptoms in IBS patients who had elevated serum IgG to specific food antigens.⁸⁵ The Oxford, UK group followed for more than 1 year 73 IBS patients who were able to identify individual food intolerance during open challenges. All but one patient had prolonged benefit after exclusion diet.¹³

In summary, several studies have demonstrated 15–71% response rates to exclusion diets in IBS patients.¹⁰⁴ The wide range of response rate can be attributed to the lack of standardized protocols, which may impact on the validity of studies. Double-blind, placebo-controlled challenges identified problem foods in 6–58% of cases, with milk, wheat and eggs being the most commonly implicated foods.^{75–77} It is important to note that lactose intolerance and celiac disease could be the cause of symptoms because they were not excluded in these studies. Diarrhoea-predominant IBS patients had a higher symptomatic response rate compared to other subgroups.^{75–77} The symptomatic improvement was shown to persist even at 1-year follow-up.¹³ However, all studies had major limitations in trial design including inadequate patient selection, poor compliance, duration and appropriateness of exclusion diets and methods of food challenge. These limitations, as well as the potential for macro- and micronutrient deficiencies resulting from elimination diets also may limit their usefulness in IBS patients.

Disodium cromoglycate trials in IBS

Disodium cromoglycate inhibits the release of inflammatory mediators such as histamine, leukotrienes and slow reacting substance of anaphylaxis by inhibiting degranulation of mast cells following contact with an allergen in rats or humans.^{105,106} Disodium cromoglycate has been used successfully in atopic patients with suspected food-induced exacerbation of symptoms.^{107–109} In 20 patients with persistent diarrhoea, DSCG was assessed in a double-blinded, placebo-controlled, cross-over design; eight of 20 patients receiving DSCG noted significant improvement in diarrhoea whereas no patients receiving placebo

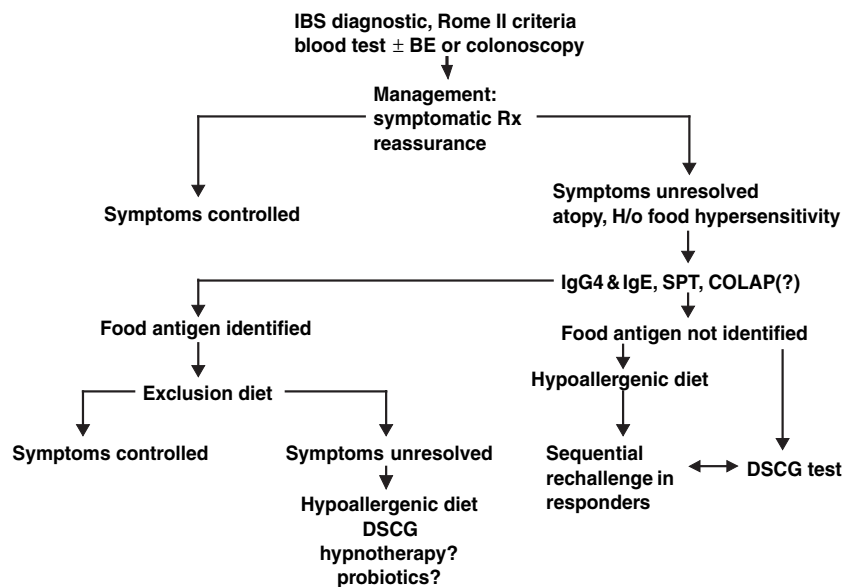


Figure 1 Proposed algorithm for managing food hypersensitivity-induced IBS (adapted from Ref. 110). BE, barium enema; SPT, skin prick test; COLAP, colonoscopic allergen provocation test; H/O, history of; DSCG, disodium cromoglycate

showed significant improvement in diarrhoea.⁸³ In a small double-blind, placebo-controlled study, oral DSCG seemed to be a useful treatment in patients with IBS and proven food intolerance.⁸⁴ Two uncontrolled, unblinded studies have evaluated the effect of oral cromolyn sodium in patients with IBS.^{81,82} Stefanini *et al.* conducted an 8-week trial of oral DSCG, which resulted in significant symptomatic improvement in diarrhoea-predominant IBS patients.⁸¹ In a multicentre trial of 428 diarrhoea-predominant IBS patients, 1-month trials of oral DSCG or elimination diet were shown to be equally effective, odds ratio for improvement was 0.7 (95% CI for odds ratio: 0.6–3.5).⁸²

These data suggest that DSCG may be effective in a subgroup of IBS patients, and a positive response to DSCG may help select patients who are likely to benefit from dietary manipulation. However, two early studies included small numbers of patients and the others were not randomized controlled studies. Thus, further controlled studies with long-term follow-up in IBS patients are needed to confirm the beneficial effects of DSCG and to identify characteristics of the IBS patients who are likely to improve.

PROPOSED MANAGEMENT ALGORITHM FOR FOOD ALLERGY IN IBS

From the above review, it appears that food allergy may be associated with development of symptoms in a subgroup of IBS patients who have a history of exacerbation of symptoms on ingesting specific foods or atopy. Assessment of food allergy includes a combination of skin prick test and food specific serum IgE

and IgG4 antibodies, which may be useful in isolating the causative food antigen. Exclusion diet based on these tests or a hypoallergenic diet with sequential reintroduction of individual foodstuffs can be used in such IBS patients, but this approach is time-consuming and associated with low compliance, and the development of macro- and micronutrient deficiencies may limit their application in clinical practice.

Zar *et al.* recently proposed an algorithm for diagnosing and treating food allergy in IBS patients including experimental therapies such as hypoallergenic diet, DSCG or other approaches (Fig. 1).¹¹⁰ While this algorithm appears reasonable, based on the published evidence reviewed above, it is still necessary to demonstrate its effectiveness in practice.

CONCLUSIONS

The pathogenesis of functional bowel disorders remains unclear. Food allergy may be one of the factors contributing to the development of these disorders. There have been no controlled studies on the role of food allergy in FD, and further epidemiological studies (only one published to date) are needed to clarify whether food allergy is related to FD.

Food allergy or intolerance is associated with failure of tolerance mechanisms. The gastrointestinal mucosal immune system may be activated in association with the development of symptoms in a subgroup of IBS patients. Such activation can result from gastrointestinal infections, microbial flora and food antigens. The mechanism by which food activates the mucosal immune system in IBS patients is not known, but an

immunologically based reaction has been postulated. Food specific IgE and IgG antibodies can mediate hypersensitivity reactions in IBS patients,¹¹¹ sensitizing the mucosal mast cells, which in turn secrete several chemical messengers (e.g. transmitters, cytokines) capable of mediating sensorimotor dysfunction of the bowel. Clinical trials with exclusion diets based on immunologic tests, hypoallergic diets or DSCG suggest that they have potential in reducing symptoms in the subgroup of IBS patients who have a clear history of adverse food reactions. Further well designed studies are needed to clarify the mechanisms of food-induced activation of the gut mucosal immune system in IBS, how food intolerance or allergy induces neuroenteric effector systems, and how to identify the subgroup of IBS patients in whom it is beneficial and cost-effective to evaluate and treat for food allergy.

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