Food Allergy and Intolerance in IBS

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Abstract: Irritable bowel syndrome (IBS) is a very common functional gastrointestinal disorder. IBS is likely to be a multifactorial condition resulting from a number of different mechanisms such as disordered motility, visceral hypersensitivity, abnormal central processing, psychological factors, genetic factors, gut inflammation, and dietary factors. Many patients with IBS give a history of adverse food reactions, but the foods identified to be relevant have been highly variable. Food hypersensitivity can be mediated by immunoglobulin E–dependent and –independent mechanisms involving mast cells, eosinophils, and other immune cells. Recent clinical and experimental studies suggest that there is a possible role for food hypersensitivity in IBS, with improvement of IBS symptom severity in a subset of patients on elimination diets, but the underlying mechanisms in IBS have yet to be fully understood. This review considers the evidence for the role of food hypersensitivity in IBS, based on the available epidemiologic and pathophysiologic data, and the clinical implications.

Keywords
Food allergy, IgE, IgG, irritable bowel syndrome

Irritable bowel syndrome (IBS) is a very common functional gastrointestinal disorder, affecting 10–20% of the adults in the United States.[1] However, the pathophysiology of IBS remains poorly understood, although it is likely to be a multifactorial condition involving a number of different mechanisms such as disturbed motility, visceral sensitivity, central processing, genetic factors, psychological factors, and inflammation.[2-5] Adverse food reaction may also play an important role in IBS, as up to 65% patients with IBS report that their symptoms are related to specific foods.[6,7] To evaluate the role of adverse food reactions in IBS is difficult, but there is now increasing interest because dietary elimination and rechallenge studies suggest that symptom response in a subgroup with IBS may depend on immunoglobulin (Ig) status.[8-10]

The aim of this article is to review the evidence of a role of food hypersensitivity in IBS; we will focus on epidemiologic and pathophysiologic data of clinical relevance to examine this issue.

Definition of Food Intolerance and Food Hypersensitivity

Adverse food reactions include any abnormal responses to food, and are further classified as food intolerance or food hypersensitivity/allergy.[11] The term food intolerance encompasses nonimmunologically mediated adverse reactions to food, which resolve following dietary elimination and are reproduced by food challenge. This includes the direct effects of pharmacologically active constituents of foodstuffs (eg, tyramine in cheese or caffeine in coffee) and enzyme deficiencies (eg, lactose and fructose intolerance). Food allergy/hypersensitivity is used to describe conditions in which an immunological mechanism (IgE- or non–IgE-mediated) may be demonstrable (eg, cow's milk, peanut, or soybean allergy).[12,13]

Prevalence of Food Hypersensitivity and Allergy in IBS

Although the prevalence of perceived adverse food reactions is high, with up to 20% of the general population reporting skin allergy, asthma, intestinal symptoms, headaches, and behavioral changes related to foods, the actual prevalence of true food hypersensitivity or intolerance is estimated to be 5% in the general population.[14-16] The prevalence of food hypersensitivities is greatest in the first few years of life, affecting about 6% of infants less than 3 years of age in the United States, but decreases with age.[15] The perception of food hypersensitivity in IBS seems to be higher than in the general population, with 20–65% of IBS patients attributing their symptoms to food hypersensitivity.[7,17,18] In fact, patients with IBS often report that specific foods aggravate their symptoms.[19] However, there are discrepancies between perceived food hypersensitivity or food intolerance and actual food allergies in patients with IBS. Dainese and colleagues[20] reported that more than 50% of IBS patients were found sensitized to some food or inhalant by skin prick test without any typical clinical signs, but patients were unable to identify potentially offending foods.

Gut Barrier and Oral Intolerance

Food allergy represents an abnormal response of the mucosal immune system to antigens delivered through the oral route. The gastrointestinal mucosal barrier is a complex physical (mucus, epithelial cell tight junctions, acid, and enzymes) and immunologic (natural killer cells, polymorphonuclear leukocytes, macrophages, epithelial cells, toll-like receptors, lymphocytes, Peyer patches, secretory IgA, and cytokines) structure. Despite the complex mucosal barrier, about 2% of ingested food antigens are absorbed and transported throughout the normal mature gut wall.[21,22] Even though intact foreign food antigens routinely penetrate the gastrointestinal tract, they infrequently induce clinical symptoms because of the development of oral tolerance to dietary proteins in most individuals.[23] Recent studies suggested that antigen-presenting cells, especially intestinal epithelial cells and dendritic cells, and regulatory T cells play a central role in oral tolerance.[24,25] However, the underlying immunologic mechanisms involved in oral tolerance induction are not fully understood.

A large epidemiologic study has identified infectious gastroenteritis as the most significant environmental risk factor for the development of IBS,[26] suggesting that previous infection and persistent low-grade inflammation may play an important role in the pathogenesis of functional gut diseases. This may be because of impairment of the complex immune response of the gastrointestinal mucosa, which results in a breakdown of oral tolerance.

Food Intolerance and Exclusion Diets

In 1982, Jones and colleagues[27] demonstrated a symptomatic response to a 1-week elimination diet in IBS patients. Since then, several studies have reproduced these findings, demonstrating a benefit from exclusion diets in up to two thirds of IBS patients, with the diarrhea-predominant subgroup showing the highest response rate.[20,28,29] Niec and coworkers[19] performed a systematic review of clinical trials that used dietary exclusion followed by food challenge. Milk, wheat, and eggs were most frequently identified to cause symptom exacerbation, and a possible common factor was salicylate or amine content. However, all studies had methodologic limitations, including inadequate patient selection, appropriateness of and duration of exclusion diets, and methods of food challenge. Double-blind placebo-controlled trials of exclusion diets are considered the gold standard, but they are technically difficult to perform. Most of the studies have used an open dietary elimination and challenge design, and thus could not exclude the role of psychological factors or placebo response.

Food Allergy/Hypersensitivity

Food allergy can involve many different organ systems including the oral cavity, digestive tract, skin, and respiratory tract.[30-33] Whereas dermatologic, respiratory, and systemic manifestations of food allergy are well recognized, those reactions manifesting primarily in the digestive tract can be difficult to recognize, diagnose, and treat.

Food allergy can be categorized into IgE-dependent (type I or immediate) and IgE-independent (delayed or cell-mediated) immune reactions. An immune-mediated food hypersensitivity response has been suggested

as the underlying mechanism in a proportion of patients with IBS.[18,28,29]

IgE-Mediated Food Hypersensitivity

Acute-phase IgE-mediated food allergic reactions typically start within minutes to 1 hour, and may affect the skin (urticaria, angioedema, flushing, pruritus), the respiratory tract (sneezing, rhinorrhea, congestion, cough, wheezing, difficulty breathing), and the gastrointestinal tract (nausea, vomiting, diarrhea, cramping, abdominal pain).[34-36] This acute phase causes activation of mast cells and basophils with release of histamine, leukotrienes, and other mediators known to be responsible for a number of effects in the gastrointestinal tract.[37] However, there is little evidence of a relationship between acute-phase IgE-mediated food allergy and symptoms in IBS.

Delayed reactions following immediate IgE-mediated hypersensitivity start within 2–24 hours after allergen challenge and are characterized by a cellular infiltration of the tissue with granulocytes (basophils, eosinophils) and lymphocytes (mainly Th2 cells).[38,39] These immune reactions to food antigens are believed to play a role in milk and soy protein enteropathies and celiac disease.[40]

Several studies have tried to establish a relationship between IgE level and food allergy in IBS using total serum IgE, food-specific IgE (radioallergosorbent test [RAST]), and IgE-mediated skin prick as markers of food hypersensitivity.[41,42] Petitpierre and associates evaluated total serum IgE titers in 12 atopic and 12 nonatopic patients with IBS who were defined by a personal and family history, atopic symptoms, positive immediate skin test, and RAST.[29] All patients were given an exclusion diet for 3 weeks with subsequent food provocation. The level of serum IgE was elevated in 9 of 12 atopic and 0 of 12 nonatopic subjects; 14 out of 24 specific offending foods were found and confirmed by blind challenges. Barau and colleagues[46] observed enhanced intestinal permeability induced by food ingestion in 9 of 17 children with symptoms of IBS with a personal and/or family history of allergy and/or raised total IgE. These studies suggest that IgE-mediated food allergies may be important in the subgroup of patients with atopy, although food allergy is unlikely to explain symptoms in most patients with IBS. Other uncontrolled studies have reported that the efficacy of oral disodium cromoglycate treatment was almost as good as diet restriction in IBS patients with diarrheal symptoms and a positive prick test for certain foods.[44,45]

A number of investigators have performed the gastrointestinal equivalent of skin testing for assessing mucosal evidence of food hypersensitivity. The technique involves injecting the gastrointestinal mucosa (gastric, duodenal, or colon) with a panel of antigens and looking endoscopically for a wheal-and-flare response.[46,47] Bischoff and associates[46] reported a positive colonoscopic allergen provocation test in 54 of 70 patients with abdominal symptoms suspected to be related to food allergy, whereas no reaction in response to antigen was found in 5 healthy volunteers. This positive reaction was correlated with intestinal mast cell and eosinophil activation, as well as with the patient's history of adverse reactions to food, but not with serum concentrations of total or specific IgE or with skin test results.

IgG-Mediated Food Hypersensitivity

IgG antibodies to food are detectable in healthy individuals, although usually at rather low levels. Furthermore, studies in healthy children have demonstrated high levels of IgG antibody to milk and egg in the early years of life, which gradually diminish with increasing age.[48,49] Although IgG food antibodies are often a normal finding and can vary with age, raised titers of IgG are seen in patients with asthma, hay fever, eczema and atopic dermatitis[50,54]; IgG4 antibodies levels were higher than normal in patients with eczema and/or asthma.[52-54] However, the results of exclusion diets based on IgG food antibodies in food-related disorders have been contradictory.[55,56]

In a recent, randomized controlled trial, Atkinson and associates[8] assessed the therapeutic potential of an elimination diet based on the presence of IgG antibodies to food in patients with IBS. One-hundred-fifty outpatients with IBS were randomized to receive either a diet excluding all foods to which they had elevated IgG antibodies, or a sham diet excluding the same number of foods but not those to which they had antibodies. After 12 weeks, the true diet resulted in a 10–26% greater reduction in symptom score than the sham diet, and this was related to compliance (Figure 1). Global rating scores of symptom relief also significantly improved in the true diet group. On the reintroduction phase of eliminated foods, a significantly greater deterioration was observed in subjects in the true diet group compared with those in the sham group. However, this study had some limitations, including a small effect of the true diet compared to the sham diet, exclusion of significantly different foods, and use of only a symptom assessment to determine the efficacy of the dietary interventions.

Zar and colleagues[9,10] also demonstrated that patients with IBS have elevated food-specific IgG4 antibodies to common food antigens. They tested the response to an exclusion diet based on elevated food-specific IgG4 antibodies in 25 patients with IBS for 6 months; symptom assessment and rectal compliance and sensitivity were measured with a barostat. At 3 months, a significant improvement was seen in IBS symptoms, namely pain severity, pain frequency, bloating severity, and satisfaction with bowel habits; this improvement was maintained

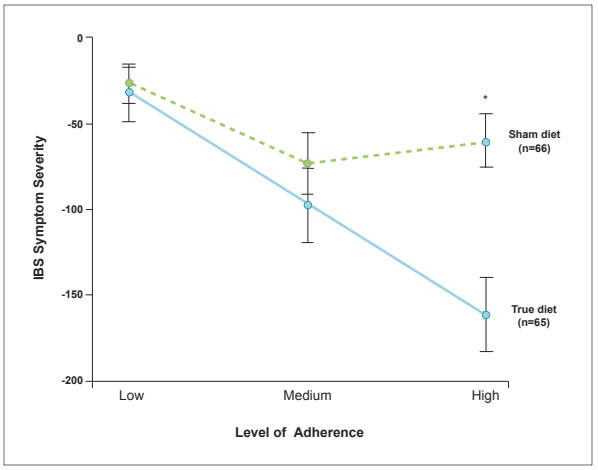

Figure 1. Mean change in symptom severity scores at 12 weeks according to degree of adherence. Difference between the groups with high adherence: 101 (95% confidence interval, 54–147); *P< 0.001.

Reproduced from Atkinson et al. *Gut*. 2004;53:1459-1464.

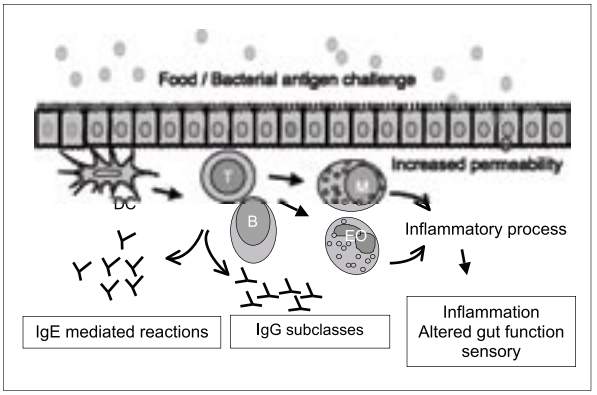

Figure 2. Mechanism of food hypersensitivity–induced irritable bowel syndrome (IBS). Altered epithelial permeability leads to an increased antigen load, with antigen-presenting cells, including dendritic cells (DC), resulting in activation of B lymphocytes (B) producing IgE/IgG, and T lymphocytes (T) producing cytokines. Mast cell (M) and eosinophil (EO) activation leads to the release of various chemical mediators. Together, these events may lead to altered gut function, minor inflammation, and abnormal mucosal sensitivity in a subset of patients with IBS.

at the 6-month follow-up for all parameters. Moreover, symptom improvement was associated with changes in objective physiologic data (ie, an increase in rectal compliance as measured by barostat). Limitations included the small sample size and lack of a control group. The authors suggested that serum IgG4 antibody testing may provide an objective and rapid method for selecting an exclusion diet when treating IBS patients. However, IgG4 production may represent a physiologic response of the gut immune system to dietary antigen challenge.[57,58] Transient alterations in the permeability of gut mucosa from any insult might theoretically increase the antigenic load presented to the mucosal immune system. An increased IgG4 antibody response may thus be a secondary phenomenon and represent a normal physiologic rather than a pathologic response of the gut immune system. Therefore, further well-controlled double-blind exclusion diet studies based on IgG and IgG subclass are warranted.

Lessons for Clinical Practice

The limited understanding of the relevance of food intolerance or allergy in IBS has resulted in a lack of diagnostic or therapeutic options in terms of dietary manipulation for the condition. To try to identify offending food antigens, some studies have evaluated skin prick tests and foods-specific serum IgE and IgG antibodies,[8,29,43,44] but the data are not sufficient to change management in IBS. After skin prick tests, introduction of elimination diets or disodium cromoglycate has been reported to improve symptoms in IBS, but the data remain inconclusive.[44,59] It is too soon to routinely recommend serum IgE or IgG testing for food hypersensitivity followed by an elimination diet in IBS, as there is not enough evidence or experience.

Conclusion

IBS is a common disorder of the gastrointestinal tract and causes significant morbidity as well as consuming substantial healthcare resources. Patients with IBS frequently complain about an exacerbation of symptoms after food ingestion. This association could be explained by an exaggerated gastrocolonic response, abnormal eating behavior, or psychologic distress rather than food allergy or intolerance. Nevertheless, recent dietary elimination and food challenge studies have demonstrated an improvement in IBS symptomatology in a subgroup with IBS and suggest diet has a role in the pathogenesis.[60] The mechanisms by which food may mediate pathophysiologic alterations in IBS remain to be elucidated (Figure 2). Further work into the underlying mechanisms is warranted before management change can be justified.

References

1. Drossman DA, Camilleri M, Mayer EA, et al. AGA technical review on irritable bowel syndrome. *Gastroenterology*. 2002;123:2108-2131.
2. Whitehead WE, Engel BT, Schuster MM. Irritable bowel syndrome: physiological and psychological differences between diarrhea-predominant and constipation-predominant patients. *Dig Dis Sci*. 1980;25:404-413.
3. Poitras P, Riberdy Poitras M, Plourde V, Boivin M, Verrier P. Evolution of visceral sensitivity in patients with irritable bowel syndrome. *Dig Dis Sci*. 2002;47:914-920.
4. Neal KR, Barker L, Spiller RC. Prognosis in post-infective irritable bowel syndrome: a six year follow up study [see comment]. *Gut*. 2002;51:410-413.

5. Floch MH, Narayan R. Diet in the irritable bowel syndrome. *J Clin Gastroenterol*. 2002;35(1 suppl):S45-S52.
6. 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.
7. Simren M, Mansson A, Langkilde AM, et al. Food-related gastrointestinal symptoms in the irritable bowel syndrome. *Digestion*. 2001;63:108-115.
8. 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.
9. 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.
10. 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.
11. Sampson HA. Food allergy. Part 1: immunopathogenesis and clinical disorders. *J Allergy Clin Immunol*. 1999;103(5 pt 1):717-728.
12. Strobel S. Epidemiology of food sensitivity in childhood—with special reference to cow's milk allergy in infancy. *Monogr Allergy*. 1993;31:119-130.
13. Kay AB, Lessof MH. Allergy: conventional and alternative concepts. A report of the Royal College of Physicians Committee on Clinical Immunology and Allergy. *Clin Exp Allergy*. 1992;22(suppl 3):1-44.
14. Sampson HA. Update on food allergy. *J Allergy Clin Immunol*. 2004;113: 805-819.
15. Bock SA. Prospective appraisal of complaints of adverse reactions to foods in children during the first 3 years of life. *Pediatrics*. 1987;79:683-688.
16. Young E, Stoneham MD, Petruckevitch A, et al. A population study of food intolerance. *Lancet*. 1994;7;343:1127-1130.
17. Locke GR 3rd, Zinsmeister AR, Talley NJ, et al. Risk factors for irritable bowel syndrome: role of analgesics and food sensitivities. *Am J Gastroenterol*. 2000;95:157-165.
18. Zar S, Kumar D, Benson MJ. Food hypersensitivity and irritable bowel syndrome. *Aliment Pharmacol Ther*. 2001;15:439-449.
19. Niec AM, Frankum B, Talley NJ. Are adverse food reactions linked to irritable bowel syndrome? *Am J Gastroenterol*. 1998;93:2184-2190.
20. Dainese R, Galliani EA, De Lazzari F, et al. Discrepancies between reported food intolerance and sensitization test findings in irritable bowel syndrome patients. *Am J Gastroenterol*. 1999;94:1892-1897.
21. Macdonald TT, Monteleone G. Immunity, inflammation, and allergy in the gut. *Science*. 2005;307:1920-1925.
22. Husby S, Foged N, Host A, Svehag SE. Passage of dietary antigens into the blood of children with coeliac disease: quantification and size distribution of absorbed antigens. *Gut*. 1987;28:1062-1072.
23. Chase MW. Inhibition of experimental drug allergy by prior feeding of the sensitizing agent. *Proc Soc Exp Biol*. 1946;61:257-259.
24. Warshaw AL, Walker WA, Isselbacher KJ. Protein uptake by the intestine: evidence for absorption of intact macromolecules. *Gastroenterology*. 1974;66:987-992.
25. Mowat AM. Anatomical basis of tolerance and immunity to intestinal antigens. *Nat Rev Immunol*. 2003;3:331-341.
26. Rodriguez LA, Ruigomez A. Increased risk of irritable bowel syndrome after bacterial gastroenteritis: cohort study. *BMJ*. 1999;318:565-566.
27. Jones VA, McLaughlan P, Shorthouse M, et al. Food intolerance: a major factor in the pathogenesis of irritable bowel syndrome. *Lancet*. 1982;2:1115-1117.
28. Bentley SJ, Pearson DJ, Rix KJ. Food hypersensitivity in irritable bowel syndrome. *Lancet*. 1983;2:295-297.
29. Petitpierre M, Gumowski P, Girard JP. Irritable bowel syndrome and hypersensitivity to food. *Ann Allergy*. 1985;54:538-540.
30. Atherton DJ, Sewell M, Soothill JF, et al. A double-blind controlled crossover trial of an antigen-avoidance diet in atopic eczema. *Lancet*. 1978;1:401-403.
31. Novembre E, de Martino M, Vierucci A. Foods and respiratory allergy. *J Allergy Clin Immunol*. 1988;81:1059-1065.
32. Pelikan Z. Nasal response to food ingestion challenge. *Arch Otolaryngol Head Neck Surg*. 1988;114:525-530.
33. Chehade M, Mayer L. Oral tolerance and its relation to food hypersensitivities. *J Allergy Clin Immunol*. 2005;115:3-12
34. Sampson HA, McCaskill CC. Food hypersensitivity and atopic dermatitis: evaluation of 113 patients. *J Pediatr*. 1985;107:669-675.
35. Sicherer SH. Food allergy. *Lancet*. 2002;360:701-710.
36. Sicherer SH, Teuber S; Adverse Reactions to Foods Committee. Current approach to the diagnosis and management of adverse reactions to foods. *J Allergy Clin Immunol*. 2004;114:1146-1150.
37. Gauchat JF, Henchoz S, Mazzei G, et al. Induction of human IgE synthesis in B cells by mast cells and basophils. *Nature*. 1993;365:340-343.
38. Macfarlane AJ, Kon OM, Smith SJ, et al. Basophils, eosinophils, and mast cells in atopic and nonatopic asthma and in late-phase allergic reactions in the lung and skin. *J Allergy Clin Immunol*. 2000;105(1 pt 1):99-107.
39. Bischoff SC, Mayer JH, Manns MP. Allergy and the gut. *Int Arch Allergy Immunol*. 2000;121:270-283.
40. Crowe SE, Perdue MH. Gastrointestinal food hypersensitivity: basic mechanisms of pathophysiology. *Gastroenterology*. 1992;103:1075-1095.
41. Zwetchkenbaum J, Burakoff R. The irritable bowel syndrome and food hypersensitivity. *Ann Allergy*. 1988;61:47-49.
42. Bischoff S, Crowe SE. Gastrointestinal food allergy: new insights into pathophysiology and clinical perspectives. *Gastroenterology*. 2005;128:1089-1113.
43. 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.
44. Stefanini GF, Saggioro A, Alvisi V, et al. 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.
45. Stefanini GF, Prati E, Albini MC, et al. Oral disodium cromoglycate treatment on irritable bowel syndrome: an open study on 101 subjects with diarrheic type. *Am J Gastroenterol*. 1992;87:55-57.
46. Bischoff SC, Mayer J, Wedemeyer J, et al. Colonoscopic allergen provocation (COLAP): a new diagnostic approach for gastrointestinal food allergy. *Gut*. 1997;40:745-753.
47. Reimann HJ, Lewin J. Gastric mucosal reactions in patients with food allergy. *Am J Gastroenterol*. 1988;83:1212-1219.
48. Okahata H, Nishi Y, Mizoguchi N, et al. Development of serum Dermatophagoides farinae-, ovalbumin- and lactalbumin-specific IgG, IgG1, IgG4, IgA and IgM in children with bronchial asthma/allergic rhinitis or atopic dermatitis. *Clin Exp Allergy*. 1990;20:39-44.
49. Barnes RM, Lewis-Jones MS, Allan S, et al. Development and isotype diversity of antibodies to inhalant and dietary antigens in childhood atopic eczema. *Clin Exp Dermatol*. 1993;18:211-216.
50. Gwynn CM, Smith JM, Leon GL, Stanworth DR. Role of IgG4 subclass in childhood allergy. Lancet. 1978;1:910-911.
51. Shakib F, McLaughlan P, Stanworth DR, et al. Elevated serum IgE and IgG4 in patients with atopic dermatitis. *Br J Dermatol*. 1977;97:59-63.
52. Shakib F, Brown HM, Phelps A, Redhead R. Study of IgG sub-class antibodies in patients with milk intolerance. *Clin Allergy*. 1986;16:451-458.
53. Merrett J, Barnetson RS, Burr ML, Merrett TG. Total and specific IgG4 antibody levels in atopic eczema. *Clin Exp Immunol*. 1984;56:645-652.
54. Merrett J, Burr ML, Merrett TG. A community survey of IgG4 antibody levels. *Clin Allergy.* 1983;13:397-407.
55. Johansson SG, Dannaeus A, Lilja G. The relevance of anti-food antibodies for the diagnosis of food allergy. *Ann Allergy*. 1984;53(6 pt 2):665-672.
56. Morgan JE, Daul CB, Lehrer SB. The relationships among shrimp-specific IgG subclass antibodies and immediate adverse reactions to shrimp challenge. *J Allergy Clin Immunol*. 1990;86(3 pt 1):387-392.
57. Husby S, Oxelius VA, Teisner B, et al. 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.
58. Barnes RM, Harvey MM, Blears J, et al. IgG subclass of human serum antibodies reactive with dietary proteins. *Int Arch Allergy Appl Immunol*. 1986;81:141-147.
59. Zwetchkenbaum J, Burakoff R. The irritable bowel syndrome and food hypersensitivity. *Ann Allergy*. 1988;61:47-49.
60. Lea R, Whorwell PJ. The role of food intolerance in irritable bowel syndrome. *Gastroenterol Clin North Am*. 2005;34:247-255.