

IgG to foods: a test not ready for prime time

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Current Opinion in Allergy and Clinical Immunology 2007, 7:257–258

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1528-4050

In 1988, the Practice Standards Committee of the American Academy of Allergy and Immunology (now the American Academy of Allergy, Asthma and Immunology) examined the published literature related to the theory that assays measuring circulating food-immune complexes (IgG or IgE antibodies to food antigens) were useful as tests for sensitivity to specific foods [1]. The Practice Standards Committee concluded that the value of the measurement of food-immune complexes toward the diagnosis of food allergy remained unproven and did not have a place in current clinical practice. During the 1990s, several commercial laboratories continued to offer assays for detection of food immune complexes, but the test of the current decade is the measurement of specific IgG to foods. Such tests are claimed to identify non-IgE-mediated hypersensitivity to foods that may be associated with a myriad of disorders, from fatigue and myalgia to obesity and irritable bowel syndrome. Currently, there is direct-to-consumer advertising for panels of IgG to foods, and direct marketing by some companies to primary care physicians to order these tests. In the United States and several European countries, 'mainstream' allergy diagnostic laboratories now offer IgG assays to foods, though these may not be covered by a patient's medical insurance. The assays may measure total IgG, all subclasses, just IgG4, or some combination thereof. Some companies also construct a 'rotary diet' for the patient to follow at home, which limits intake of foods from identified food groups to only once per cycle after a pathologist on staff has reviewed the tests, though most laboratories do not get involved in the practice of medicine in this way. Such dietary prescriptions can be hard to follow [2], and are without proven benefit, as no double-blind, placebo-controlled series have been published that critically evaluate their effectiveness [3].

In view of the continuing concern that ordering a panel of food-specific IgG may be seen by some patients and physicians as a substitute for a thorough history, physical exam and indicated diagnostic testing, we have again

reviewed the literature related to IgG testing for foods. This topic was briefly touched upon in our reviews of unproven diagnostic procedures in 2003 and 2005 [4,5]. In the past 2 years, several more publications on the utility of elimination diets based on IgG testing to foods in irritable bowel syndrome have been published, but no studies were located on specific IgG testing in other disorders advertised by some of the laboratories as being related to food hypersensitivities, specifically chronic fatigue, fibromyalgia, headache and sleep disturbance. Another critical issue for such measurements is the reproducibility and the need for a ring test, wherein blinded samples are divided and sent to different laboratories with replicates.

Zar *et al.* [6] assayed food-specific IgG4 in a commercial UK laboratory in 108 irritable bowel syndrome patients and 43 controls and found significantly elevated IgG4 levels to wheat, lamb, beef, pork and soy when compared with controls. This same group [7] then used food-specific IgG4 to design elimination diets for 25 patients with irritable bowel syndrome (13 with diarrhea-predominant, 10 with constipation-predominant, and two with alternating symptoms), but data at 6 months were only available on 15. There was no placebo diet group. Patients eliminated an average of eight foods, with the most common being foods common in a Western diet, including milk, eggs, beef, pork, wheat and tomatoes. Subjects reported significant overall improvement. Rectal compliance and thresholds for discomfort and the urge to defecate were measured in 12 patients at baseline, but it was not noted how many were again tested at 6 months. Rectal compliance was reported to improve significantly, but not discomfort threshold values. As there was no placebo group, it is difficult to further interpret these data, considering the far-ranging improvements that can be seen with the placebo effect. Drisko *et al.* [8] placed 20 patients on elimination diets for 1 year. The diet was based on IgG testing performed in a commercial laboratory. Throughout the rest of the paper, however, the authors discuss the detection of serum IgG antigen-antibody complexes, so what was actually measured is not clear. The diet intervention lasted variably from 21 to 28 days before foods were added back over several months to be eaten in a rotation (rotary diet), if tolerated, along with probiotic supplements taken twice per day. They reported that subjects who followed the diet improved, but there was no placebo group, probiotics were also given, and the potential for a placebo effect was huge.

In irritable bowel syndrome, there may indeed be true, proven benefits from dietary change, but IgG to the food may reflect foods commonly consumed rather than those contributing to symptoms. There may be other food-specific immune effects, immune dysregulation, peptide effects or effects of dietary components on gut microflora composition, irrespective of IgG values. We could even foresee future assays for specific IgG to foods as predictive of clinical tolerance in some disorders. For example, in IgE-mediated food allergy, the new development of elevated levels of IgG4 to foods may be correlated with the development of clinical tolerance to the food in oral immunotherapy trials, and not with worsening of clinical food allergy. Enrique *et al.* [9] reported a trial of sublingual immunotherapy with hazelnut for hazelnut food allergy in 23 patients, half randomized to active treatment and half to placebo. Fifty percent of those on active treatment were able to tolerate 20 g of hazelnut at the end of the trial and showed increases in hazelnut-specific IgG4. Buchanan *et al.* [10] recently completed a pilot study of egg oral immunotherapy in seven children with IgE-mediated egg allergy, all of whom improved during the course of the study. Two were able to reach a state of complete oral tolerance. Hen's egg-specific IgG rose significantly in these subjects. It is also known, however, that patients with IgE-mediated cow's milk allergy have increased specific IgG1 and IgG4 compared with healthy controls [11,12] and, in a recent study [12], subjects with previous IgE-mediated cow's milk allergy who now tolerated cow's milk on oral food challenge actually had low levels of specific IgG1 and IgG4. Thus, what is the exact role of IgG, its subclasses and the IgA isotype in food hypersensitivity overall? This is certainly a question for further research and emphasizes that it is far too early to encourage patients or insurers to spend money on blood test panels that are suited for research, not clinical, applications at this time.

Such IgG testing appears to have become big business; however, the actual expenditures and profits for this testing modality are not reported separately in publicly available financial reports from large laboratories that report to stockholders. Allergy and immunology professional societies need to better inform physicians and other healthcare practitioners of the evidence for

specific diagnostic tests and the potential waste of money when tests that are still in 'research mode' are broadly accessed. As noted above, increased IgG may indicate acquisition of clinical tolerance to a food in cases of resolving IgE-mediated food allergy. How these studies compare with measurements of food-specific IgG in irritable bowel syndrome or other disorders with possible food hypersensitivity is still unknown, especially as trials that appropriately blind interventions in irritable bowel syndrome are difficult to design and implement. The best route to maintain a healthy skepticism about the 'latest' tests, and keep healthcare dollars where they are needed most, may be through education of health insurance companies and national providers.

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