Food Allergies and Sensitivities: Observing the Complete Picture

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Diagnosing and treating adverse reactions to foods is a cornerstone of naturopathic practice. About 25% of Canadians believe they have allergic reactions to foods; but according to strict diagnostic guidelines only 8% of young children and 2% of adults in western countries actually experience food allergies per se.1, 2

Skin prick ‘scratch’ testing is often the default method performed in allergy office settings; however it has poor positive predictive value for foods (i.e. many asymptomatic patients have reactions to food allergen extracts). In addition, many patients with either gut-limited immune reactions or delayed-type immune reactions display negative skin prick tests.3-5 Many NDs then, knowing that elimination diets are challenging for patients, are left wondering what science can tell us about these other reactions, if blood panels are an effective and valid way of establishing these reactions, and how might these tests guide our clinical decision making?

Before addressing these questions, it’s important to establish a common nomenclature. In the opinion of the authors, much of the confusion surrounding the efficacy of food reaction testing, and non-IgE tests in particular, has arisen from indiscriminate use of the terms food allergy, food sensitivity and food intolerance. Use of the term ‘food allergy’ to describe IgG food reactions has created the impression that functional and integrative physicians are equating IgE food allergies with IgG food reactions. This has led critics to dismiss IgG testing as lacking clinical utility because its results do not correlate with IgE tests.6 Unfortunately, this runs the very real risk of ignoring the relevance of IgG food reactions as a separate clinical condition, plus it discounts the progress that can be achieved through properly designed elimination diets for a variety of challenging health conditions. Additionally, there is emerging evidence that IgA antibody responses to foods may be of clinical significance, and evidence that the classical food allergy response may have a combination of IgE and non-IgE immune-mediated reactions.3, 4 Globally, our understanding of adverse reactions to foods is changing as new information continues to emerge in gastroenterology, immunology and related scientific fields.

After a careful review of recent literature on the immunology of food hypersensitivity responses, we recommend that naturopathic doctors and allied functional and integrative physicians standardize the use of the term food sensitivity to describe non-IgE immune mediated reactions. As defined, food sensitivity could be used to describe both IgG and IgA food reactions, although it typically refers to IgG reactions unless otherwise stated. Sensitivity is defined as a “degree of susceptibility”, a term consistent with the variability of clinical symptoms associated with IgG and IgA food reactions.7 Food sensitivity would then be the preferred term for immunological reactions not mediated by IgE response. This clearly differentiates IgG and IgA food reactions from the classical definition of food allergy involving IgE response and mast cell degranulation. Furthermore, we suggest that the term food intolerance be used exclusively to describe non-immune mediated reactions like enzyme deficiencies (as in the case of lactose intolerance) or chemical reactions.

Per Brandtzaeg, one of the most respected researchers in the area of food allergies, diagrammed the relationship between immune and non-immune reactions in his 2010 Nature Reviews paper, adapted below for ND clinical use (with the label food sensitivity added to describe non-IgE mediated reactions).3 We believe using the nomenclature described in Figure 1 (page 34) to distinguish the different types of food reactions helps clarify that food sensitivity is a distinct phenomenon, with distinct symptomatology and treatments.

Testing for Food Allergies and Food Sensitivities

In the process of reviewing clinical history, considering allergic exposures and possible adverse changes to digestive immunity, practitioners may consider blood testing for food allergy or sensitivity as a guide in deciding which foods to eliminate and/or challenge or as a confirmation for presenting symptoms. In conventional circles, the clinical utility of serum ELISA (enzyme linked immunosorbent assay) testing for immediate hypersensitivity (IgE) reactions is well established, while use of this method for delayed hypersensitivity reactions (IgG) remains controversial, if not outright derided. Lavine’s article in the Canadian Medical Association journal illustrated this point, declaring that IgG testing is “not a recognized diagnostic tool for food allergy” and suffers from a “paucity of evidence”.6 The CMAJ article, which cited little of the current research on food allergy immunology, received wide coverage in the Canadian popular press.8 Our argument is
that Lavine’s assertions about the ineffectiveness of IgG testing for food allergies misses a crucial point: that IgG reactions to food are a distinct clinical condition — an immunological reaction characterized by deposition of antibody-antigen complexes in blood vessels and symptoms appearing hours to days after ingestion of the offending food.9

The goal of this current review is to survey the available evidence regarding testing methods for the three main antibody groups (IgE, IgG and IgA) from a scientific as well as a clinical standpoint, and give examples where this testing is of significant utility in the context of appropriate clinical follow up by a skilled naturopathic physician.

Testing for IgE response: deciphering food allergy

Classical food allergy is essentially an IgE response. Although only 0.02% of circulating antibodies are IgE, they can pack a powerful punch, including life-threatening anaphylactic reactions. The half-life of IgE is approximately one day, which means the antibodies disappear from the blood very quickly once exposure has ceased. This can make it challenging to identify acute intermittent reactions as the antibodies may not be circulating in serum long enough to be detected post-reaction.

In an IgE reaction, the high affinity of IgE for receptor sites on the mast cell results in attachment of IgE to mast cells. IgE attachment ‘primes’ the mast cell, readying it to act quickly if there is a subsequent exposure. When exposure to the same antigen reoccurs, the antigen cross-links to the cell-bound IgE and causes the immediate release of pharmacologically active substances. These inflammation causing chemicals cause fluids to flood into cells, resulting in vasodilation, edema, mucus secretion, smooth muscle constriction, increased pain response, and chemotaxis, all of which can result in symptoms like: sneezing, wheezing, rhinitis, increased mucous secretion, abdominal cramping, angioedema, urticaria and anaphylaxis.3,9

The double-blind placebo-controlled food challenge (DBPCFC) is considered the gold standard for diagnosis of IgE food reactions. In a DBPCFC, patients are given capsules every 30 to 60 minutes that contain either placebo or the suspected reactive food. The patient is observed for symptoms, and the test ends when symptoms arise or the allergist concludes that sufficient allergen has been consumed (usually 4 to 8 hours). Due to the possibility of provoking life-threatening anaphylactic reactions, DBPCFC is currently only performed in hospitals or allergy specialty clinics, leaving it outside the scope of both naturopathic and conventional primary care medicine.10

Skin tests (either intradermal or skin prick) are widely used because of their simplicity, rapid results, low cost, ability to test multiple allergens at one time, and good sensitivity. During a skin test (ST), a small amount of allergen is injected under the skin, and the patient is observed for signs of a reaction (e.g. hives, swelling, redness) at the site of injection. ST is contraindicated in pregnancy, generalized skin disease and with current use of antihistamines.11 The sensitivity and specificity statistics for ST can vary significantly depending on the allergen extract used, site of testing (forearm, upper back, lower back), and age of patient, which means there is little consensus as to the true reliability of this test.3

In vitro (blood tests) are often used when skin tests are contraindicated (e.g. antihistamine or beta blocker use, anaphylactic reaction to previous skin test) or considered impractical (e.g. no access to allergist, unwillingness to submit to test). In vitro immunosorbent assays (e.g. ELISA, FEIA, RAST) bind a specific allergen to a solid phase ‘sorbent’ and then add the patient serum to the solid phase. If antibodies to a specific allergen are present in patient serum, they are detected by an enzyme-linked or radio-labeled anti-human IgE antibody. The quantity of IgE antibody present is measured and expressed as either units of IgE or as a class score. Fluoro-enzymeimmunoassay (also known as FEIA, ImmunoCAP, or CAP) is rapidly replacing the radio-allergosorbent test (RAST) and appears to be the most accurate in vitro IgE test; predicting clinical reactivity in some cases with >95% certainty.12
The high sensitivity of the FEIA means that recent exposure to suspected food antigens is not necessary for reactions to be measured. The main disadvantage of the FEIA however, is its high cost, which discourages screening of multiple allergens. Multi-allergen (e.g. 96 General Food IgE) ELISA tests are more affordable, but lack the sensitivity of the FEIA and are less likely to identify rapid onset, severe, short duration (i.e. acute) IgE reactions. Multi-allergen ELISA tests appear to be most useful for identifying non-acute IgE reactions to regularly consumed foods.

Total IgE determination in serum may also be a useful diagnostic screening tool in naturopathic practice. According to Sanz et al, atopic adults with Total IgE greater than 1000 kU/L (1000 UI/mL) always have at least one positive specific IgE to a particular antigen.13, 14 Elevated Total IgE accompanied by clinical symptoms related to allergy suggest the need for specific IgE testing to identify the allergen(s) responsible for these symptoms. That said, Total IgE may also be elevated in parasite infections, Hodgkin’s disease, aspergillosis, autoimmune disease and hyper-IgE syndrome.11

Deciphering Food Sensitivity

Using the model proposed by Brandtzaeg (Figure 1), the term food sensitivity describes non-IgE mediated reactions, which includes IgG and IgA. Since IgG antibodies represent about 75 to 80% of circulating serum immunoglobulins, IgG reactions to specific foods are common. However, it is important to understand that the presence of elevated IgG antibodies to a specific food is not proof of a clinically relevant food sensitivity, just as elevated serum IgE levels are not proof of a clinically relevant food allergy.15 Similar to IgE, elevated IgG antibodies should be considered in the context of the patient’s diet and symptoms. Foods rarely consumed, or consumed on an intermittent basis are much less likely to provoke symptoms. The dose-dependent nature of IgG food reactions means that foods frequently consumed, or those consumed in excess, are most likely to provoke clinically significant symptoms.9 Symptoms associated with IgG reactions can include: fatigue, digestive symptoms (constipation, diarrhea, bloating, abdominal discomfort etc.), joint pain and stiffness, memory disturbances, and skin conditions.

The mechanism of action by which IgG antibodies to specific foods results in clinical symptoms has yet to be fully defined, however experimental evidence indicates that inflammatory processes appear to be a key element.16 The immune response that best describes IgG food specific reactions and their relationship to inflammation is the Type III hypersensitivity reaction (see figure 3).3 In a Type III hypersensitivity reaction, IgG antibodies form to absorbed food antigens and bind with the food antigens to form a circulating immune complex (CIC). CICs are routinely removed by macrophages from the liver, but when excess antigen is present (i.e. food is frequently consumed, or consumed in large quantity), small CICs deposit in blood vessel walls and release inflammatory cytokines that can cause tissue injury.17 In fact, clinical evidence of the link between inflammation and elevated IgG to specific foods appeared in a study of obese juveniles, which found a tight correlation between elevated food-specific IgG and elevated C-reactive protein, a marker of inflammation.18 This mechanism offers a possible insight into the reason why IgG elevations are not always clinically significant. Specifically – foods that are consumed in small amounts or infrequently may elicit an IgG reaction, but macrophages are able to remove the CICs and prevent tissue deposition and release of inflammatory cytokines.

Testing for IgG response

There is currently no ‘gold standard’ laboratory test for food sensitivity, as it is still not a recognized diagnosis. Nevertheless, several laboratory tests are in common use including, but not limited to, the ELISA IgG test and the antigen leukocyte cellular antibody test (ALCAT); known generically as cell size variability method.

The cell size variability test (antigen leukocyte cellular antibody test or ALCAT) is marketed as a chemical sensitivity/food intolerance test. In cell size variability testing, patient blood is combined with the food/chemical or drug. Once sufficient time has passed to trigger the appropriate pathway (e.g. immune, toxic or pharmacologic), changes in the leukocyte size/volume are measured. The mechanism by which foods or chemicals induce this change is not understood, but is believed to involve the release of inflammatory mediators. Unfortunately, no well-designed, peer-reviewed clinical trials have been published that validate the cell size variability method. On the other hand, two published peer-reviewed papers found unacceptably high variability in split samples for the cell size variability method,18, 19 with one of the investigating teams concluding: “Cell size variability testing for food allergies proved to be completely random in all tests.”19 It is difficult to see how this lack of reliability can lead to useful clinical decision making, although additional peer-reviewed research may provide greater insight into the clinical value of this test.
Enzyme-linked immunosorbent assay (ELISA) for IgG food specific antibodies is the food sensitivity testing method most widely utilized in North America. Unfortunately there is no standard method for testing IgG food sensitivities, with some laboratories isolating and testing the IgG4 subclass of IgG and others measuring Total IgG (subclasses 1, 2, 3 and 4) to specific foods.

**IgG4 Subclass Testing:** Research shows IgG4 can bind to mast cells and prevent IgE-facilitated activation of T-cells – suggesting that elevated IgG4 dampens inflammation caused by IgE reactions (i.e. induces tolerance).\(^{20}\) However, IgG4 by itself is not considered a likely cause of allergic symptoms, nor is elevated IgG4 considered diagnostic for food allergy.\(^ {20, 21}\)

**Total IgG Testing** (Subclasses IgG1, IgG2, IgG3, and IgG4): Most of the positive clinical research on food sensitivities to date has utilized Total IgG determinations of food specific IgG, and positive clinical data for IgG-guided elimination in several conditions is detailed below:

- **Irritable Bowel Syndrome (IBS):** A landmark study by Atkinson, published in Gut in 2004 investigated IgG food sensitivities in 150 patients with IBS. In this study, patients were tested for IgG reactions to 29 different foods, and then randomized to either a sham diet or a ‘true’ diet. Both patient and investigator were blinded as to which group was assigned. After 6 weeks, there was a 10% reduction in symptoms and after 12 weeks, a 26% reduction (p <0.001) in the ‘true’ diet group compared to the sham diet.\(^ {22}\) These findings have been replicated by several other investigators.\(^ {23-25}\)

- **Migraine:** Clinical research suggests IgG food sensitivity may also play a role in migraine headaches. Three peer-reviewed studies have shown significant decreases in migraine headaches when IgG reactive foods were eliminated from the diet.\(^ {26-28}\)

- **Crohn’s Disease:** A small randomized, double-blind, six-week cross-over trial by Bentz et al in 2010 investigated IgG food sensitivities in Crohn’s disease patients. Crohn’s patients in the true diet group experienced an 11% decrease in stool frequency (when true diet was adopted in the first 6 weeks), reduced abdominal pain, and improvement in general well-being compared to the sham diet.\(^ {29}\)

- **Diabetes, Cardiovascular Disease and Obesity:** Both Ahmed and Kohno found that children with insulin dependent diabetes mellitus (IDDM) had significantly higher IgG to specific food antigens than healthy controls.\(^ {30,31}\) A recent study by Lewis et al on obesity found that patients who eliminated
IgG reactive foods from their diet lost nearly 500 grams per week, 7 cm from the waist, and 3.5 cm from the hips over the course of 90 days. And, the Wilders-Truschnig study previously cited found a strong correlation between increased intima media thickness and elevated IgG antibodies to specific foods.

Reliability of Food Sensitivity Testing: The hallmark of a clinically relevant test is one that has high sensitivity and specificity: this means the test is sensitive enough to catch early stages of the disease, and is specific enough that it is not falsely identifying healthy patients as having a disease. The fact that food sensitivity tests are not diagnostic (i.e. disease is not measurable or quantifiable), means that sensitivity and specificity data cannot be determined. Therefore, others measures of reliability must be considered, with reproducibility of results and accreditation by a licensing body being of particular interest.

Reproducibility of IgG results was first called into question by Miller in 1997 when widely different results for the same sample were reported (76%, 29% and 22% of foods reactive) from three different laboratories performing IgG food sensitivity tests. However, a 2010 study comparing ELISA Total IgG from one laboratory to the cell size variability method from another laboratory reported very little variation in split-sample results for ELISA IgG (95% of food reactions were identical and the other 5% within one zone) compared to highly variable results for the cell size variability method (34% of foods were identical, another 28% were within one zone). In a test of consistency of results over time (one week), IgG had a low coefficient of variance (0.05) compared to cell size variability (0.55), which indicates a high degree of reproducibility for IgG ELISA. The intra-class correlation (how strongly points within a group agree with one another) was also highly correlated (0.99) for IgG ELISA compared to cell size variability (0.01). Overall, the Hodsdon study showed that highly reproducible results for ELISA IgG are possible, albeit without specifically considering the issue of inter-laboratory variability.

Laboratory accreditation offers protection to the public by ensuring that external laboratory professionals oversee a laboratory’s quality control and quality assurance on a regular basis, and that industry standards are maintained. In Canada, accrediting bodies include the College of Physicians and Surgeons and OLA (Ontario Laboratory Accreditation), while in the United States, accreditation of laboratories is maintained by CLIA (Clinical Laboratory Improvement Amendments) and CAP (College of American Pathologists).
Laboratory testing for IgG reactions is a common tool in naturopathic practice. The following facts should assist NDs in obtaining the most clinically relevant results for their patients:

- The half-life of an IgG antibody is between 23 and 96 days, which makes it challenging to identify reactive foods solely through elimination diets or observation. This also means it can take more than a year for food-specific IgG antibodies to disappear after elimination from diet.
- It takes approximately 30 days to generate an antibody to a specific food if it has been avoided long-term or there has been no previous exposure. Consequently, when a food has been meticulously avoided for six months or more, it may be necessary to reintroduce it six weeks prior to sample collection in order to avoid a false negative result.
- For foods that are consumed regularly or intermittently, two servings of a reactive food twice a week for three weeks prior to sample collection is generally considered sufficient exposure prior to testing for IgG antibodies.
- Because of the high concentration of IgG antibodies circulating in blood, a very small volume of blood (i.e., the amount in a dried blood spot) can be used to measure antibodies to multiple antigens.
- If several foods in the same family are reactive, it is recommended that other foods in that food family also be eliminated from the diet.
- If IgG testing is impractical, a 6-day elimination of the suspected food, followed by reintroduction on day 7 is suggested. Serum levels of the food antigens will decline over the six days, but IgG antibody levels will remain high. When the suspected food antigen is consumed in significant quantity on day 7 – reactive foods will produce a significant symptom flare as the circulating IgG antibodies react immediately with the food antigen.

IgA testing: GI sensitivity/immune response

Following Brandtzaeg’s model (see Figure 1), non-IgE mediated food reactions would also include IgA food sensitivities. Although IgG is the immunoglobulin present in greatest quantity in serum, IgA is the antibody produced in the greatest quantity in normal mucosal tissue, particularly the gut.

The point of the IgA defense system is to prevent excessive penetration of both commensal microbes (probiotic or ‘good’ bacteria) and food antigens through the gut mucosa into the intestinal lamina propria. Antigens that do make their way into the lamina propria may initially trigger IgG responses and eventually classical systemic IgE responses, in susceptible individuals. Oral tolerance to antigens, then, is also part of this IgA system, which is initially established in the neonatal period, as the infant is exposed to microbes and an increasing number of foods.

Research shows that newborns have very little IgA, because they have not been exposed to microbes in utero. But, within the first month of life, the number of cells capable of producing IgA increases 75-fold a result of normal exposure to commensal microbes in the environment. This is a crucial point; development of proper mucosal immunity during the first year of life is a combination of colonisation by appropriate microbial colonies in the gut (and other mucosal surfaces including the lungs and nasal passages), and production of IgA immunoglobulins in response. IgA deficiency itself has been linked in numerous studies to food allergy susceptibility in children. This also underlines the potential benefits of rebalancing these microbial colonies with symbiotic therapy (pre- and pro-biotics) in infants who receive antimicrobial therapies for infections.

IgA is an unmistakably important immunoglobulin, but the significance of elevated IgA to specific foods remains unclear. Our current understanding of elevated IgA to specific foods is that it is most likely an indicator of antigen exposure and mucosal damage. For example, elevated gliadin IgA antibodies in a celiac patient is considered a sign of non-compliance with the gluten-free diet, or may be an early sign of mucosal damage caused by undiagnosed celiac disease. The manufacturer of FEIA (fluoroenzymeimmunosorbent assay) for IgA clearly states that there are no recommended cut-off values for specific IgA antibodies as they are simply markers for antigen exposure and not directly associated with a disease. In other words, elevated IgA to a specific food suggests mucosal damage and possibly loss of oral tolerance. However, with the exception of anti-gliadin IgA, there is no published evidence that global elimination of IgA reactive foods results in clinical improvement of symptoms.

Summary: where do we go from here?

For the naturopathic clinician, the bottom line for diagnosis of food related problems remains (and should remain) a carefully constructed clinical presentation, review of systems, relevant allergen exposures, and consideration of current digestive functioning and healthy bacteria. In this context, ELISA testing for food related reactions can confirm history-related symptoms, and/or serve as a guide to elimination and/or rotation diets. When carefully constructed and with appropriate clinical follow up, these diets are nutritionally sound and relatively simple for patients to follow. Food re-introduction, rather than long-term avoidance, may be a realistic goal if functional mucosal immunity (an IgA response) is restored.
and results in increased oral tolerance to established food allergens. Thus, appropriate use of food sensitivity testing can help guide clinical decision making that takes into account the totality of the patient's clinical picture, as well as addressing the underlying causes of many of their presenting health challenges.

About the Authors

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References