



Role for food-specific IgG-based elimination diets

Kate Hicks

*Department of Health Sciences, University of York,
Heslington, York, UK, and*

Gillian Hart

YorkTest Laboratories Ltd, York Science Park, York, UK

Abstract

Purpose – Evidence has suggested that elimination diets based on food-specific IgG measurement can lead to improvements in chronic ill health symptoms. This paper aims to review the evidence from studies on food-specific IgG measurement and dietary change.

Design/methodology/approach – A literature review of studies on the putative role for food-specific IgG-based elimination diets was undertaken.

Findings – The use of fully standardised clinically evaluated food-specific IgG tests as a basis for elimination diet could lead to a considerable improvement in many patients' quality of life.

Originality/value – This unique review captures evidence for a viable alternative to the time consuming and expensive elimination diet/food challenge approach.

Keywords Food products, Diet, Personal health

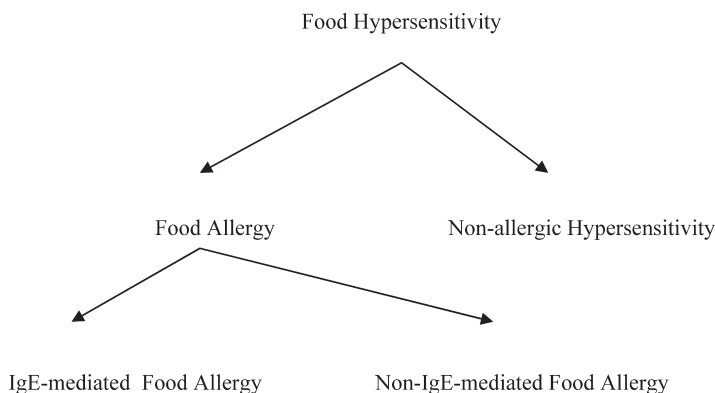
Paper type General review

Introduction

The range of symptoms associated with adverse reactions to food (food hypersensitivity) is wide and includes itching, eczema, urticaria, angioedema, asthma, rhinitis, intestinal symptoms and headache (Zuberbier *et al.*, 2004). Reported prevalence of food hypersensitivity varies widely from 3 to 35 per cent (reviewed in Madsen, 2005), with others claiming higher rates up to 45 per cent (Allergy UK Report, 2007). There are several proposed mechanisms by which an individual may have an adverse reaction to food. According to a recent review of nomenclature, food hypersensitivity may be either allergic or non-allergic, the latter including adverse reactions due to enzyme deficiencies and pharmacologically active food components (Johansson *et al.*, 2004; Figure 1). Food allergy refers to cases where immunological mechanisms are demonstrated and includes IgE- and non-IgE-mediated allergy.

The current gold standard approach for confirming non-IgE-mediated allergy, is to follow an elimination diet, excluding all except a few foods, for a few days to a few weeks. Once the symptoms are controlled, this is followed by challenge with foods one at a time (preferably double-blind, placebo-controlled challenge) to identify the offending foods. The clinical usefulness of this approach is limited by the fact that it is very expensive, lengthy and requires a high level of patient compliance (Bruijnzeel-Koomen *et al.*, 1995). Furthermore, it may give rise to false negative challenges, for example due to an insufficient dose of challenge food, insufficient duration of challenge, or long lag times post-challenge before symptom exacerbation (Freed, 2002). It is also clear that it is well nigh impossible to test all the different combinations of food types that may be causing the problems. Hence there is a need for more simple tests to make the identification of offending foods in patients with non-IgE-mediated food allergy more feasible in clinical practice. In addition, it has also been suggested





Source: Johansson *et al.* (2004)

Figure 1.
Adverse reactions to food

that patients may be more compliant to a diet based on the results of a laboratory test as it may be considered to be more “scientific” (Zar *et al.*, 2005a).

It has been proposed that food-specific IgG antibodies play a role in the underlying mechanism of non-IgE-mediated food allergy and that the measurement of these antibodies in patients with suspected food allergy may be useful in identifying offending foods. The proposal originated from *in vitro* studies of the putative role of IgG antibodies in allergy and from the measurement of food-specific IgG antibodies in patients. For example, studies have suggested that specific IgG₄ subclass antibodies to cow’s milk and egg may be associated with degranulation of basophils and mast cells, and that this response may be independent of the IgE-mediated response (Hindocha and Wood, 1985; Beauvais *et al.*, 1990). Furthermore, elevated levels of food-specific IgG have been observed in the serum of certain atopic and food hypersensitive individuals (Merrett *et al.*, 1984), though the elevated IgG₄ levels may occur ultimately as a consequence of an IgE-mediated response.

Assays have been developed that measure food-specific IgG in patients’ serum, and referencing studies have been conducted measuring food-specific IgG levels in patients and control subjects. In addition others have compared food-specific IgG levels with the results of specific food challenges. The proposed role of specific IgG is, however, controversial given that these antibodies are often present in healthy individuals suggesting that they are part of the normal physiological response to food ingestion (Rumbo *et al.*, 1998; Kruszewski *et al.*, 1994; Johansson *et al.*, 1984). In addition, it has been proposed that IgG antibodies may be protective and actually block the allergic reaction, rather than playing a pathogenic role; association cannot necessarily be taken to mean causation (Dannaeus and Inganas, 1981; AAAI Position Statement, 1995). The present article provides an overview of the current evidence regarding the clinical potential of food-specific IgG tests.

Food-specific IgG tests

Food-specific IgG tests generally either measure all subclasses of food-specific IgG antibody (IgG₁, IgG₂, IgG₃ and IgG₄) or just IgG₄. The IgG₄ subclass has been proposed as being more specific for food allergy than total food-specific IgG (el Rafei *et al.*, 1989;

Awazuhara *et al.*, 1997), whilst other studies have implicated the involvement of other IgG subclasses (Shakib *et al.*, 1986; Morgan *et al.*, 1990).

The tests involve measuring food-specific IgG in patients' blood samples using either an enzyme linked immunosorbant assay (ELISA) or a radioallergosorbant (RAST) assay method. Food-specific IgG titres are reported as positive or negative relative to an arbitrary cut-off, set by the individual laboratories performing the tests. Patients are advised to avoid or reduce intake of the "positive" food(s), i.e. those to which they have elevated levels of food-specific IgG, in an attempt to gain relief from their symptoms. Further nutritional advice regarding maintenance of a balanced diet may be provided in the form of a guidebook or consultation with a nutritionist.

These tests are not standardised, nor are specific normal ranges and cut-offs defined, since neither food allergens nor food-specific IgG solutions of known concentration and character are commercially available. For this reason, it is necessary for each of the different tests available to be clinically evaluated to show efficacy, for example by the performance of randomised controlled trials investigating the effectiveness of an elimination diet based on the test results. Alternatively, a test must be shown to be equivalent to a test that has been clinically validated to show that it is effective.

Effectiveness of IgG test-based elimination diets

A pragmatic line of research is to determine whether the elimination of foods to which an individual has significantly elevated levels of IgG is clinically effective, irrespective of the actual role of food-specific IgG antibodies in food allergy. A search of the published literature has identified only one randomised controlled trial (RCT; Atkinson *et al.*, 2004), the gold standard in clinical trial design, and seven studies that did not include a control group (referred to here as "non-RCT" studies; Zar *et al.*, 2005a; Rees *et al.*, 2005; Dixon, 2000; Dockhorn, 1987; Hardman and Hart, 2007; Marinkovich, 1996; Zwetchkenbaum and Burakoff, 1988). All studies are summarised in Table I.

The only published RCT of this approach was a double-blind, placebo-controlled trial conducted in 150 patients with irritable bowel syndrome (IBS) recruited from a specialist outpatient clinic in secondary care (Atkinson *et al.*, 2004). The RCT results indicated that food elimination based on the results of the YorkTest Laboratories' ELISA for food-specific IgG antibodies ("true diet") resulted in significantly improved symptoms compared to a "sham diet" comparison group. IBS patients randomised to true diet had, after 12 weeks, a ten percentage point greater reduction in IBS symptom score than patients allocated to a sham (placebo) diet ($p = 0.024$), which eliminated the same number of foods but not those to which patients had raised IgG. Importantly, there was a greater reduction in symptoms for patients fully adhering to the true diet but not those adhering to the sham diet group (26 per cent greater reduction in true diet vs sham diet group; $p < 0.001$). This finding is important as it supports the proposal that the IgG-based diet is an active treatment which if not adhered to does not seem to have an effect. The study did not attempt to confirm hypersensitivity to "IgG-positive" foods by performing individual food challenges. Instead, at the end of 12 weeks, patients in both groups were asked to resume consumption of all the foods they had been advised to eliminate in order to assess the effect of their reintroduction. After four weeks, reintroduction of the eliminated foods led to a 24 per cent greater deterioration in symptoms in those on the true diet compared to those on the sham diet ($p = 0.003$). This observation further supports the notion that the intervention is an active treatment, in that patients only gain benefit if they adhere to the IgG-based elimination diet.

Type of study	Indication	Subjects	Tests used	Duration	Results	Author
Randomised, double-blind, placebo-controlled	IBS	150 adults with IBS attending out-patient clinic in secondary care (UK)	IgG ELISA (all subclasses) for 29 foods	12 weeks	All 150 patients were IgG positive to one or more foods. True diet resulted in a 10% greater reduction in IBS symptom severity score than the sham diet ($p = 0.024$). 54% of patients fully adhering to true diet self-reported significant improvement, compared to 15% on sham diet. Reintroduction of eliminated foods led to a 24% greater deterioration in symptoms in those on the true diet compared to those on the sham diet.	Atkinson <i>et al.</i> (2004)
Open, non-controlled, prospective	IBS	25 adults with IBS	IgG ₄ radioimmuno-fluorescence assay for 16 foods	Six months	All 25 patients were IgG positive to one or more foods. Significant improvement reported in pain severity ($p < 0.001$), pain frequency ($p = 0.034$), bloating severity ($p = 0.001$), satisfaction with bowel habits ($p = 0.004$) and effect of IBS on life in general ($p = 0.008$) at three months; maintained at six months. Rectal compliance significantly increased at six months ($p = 0.01$); thresholds for urge to defecate unchanged.	Zar <i>et al.</i> (2005a)

(continued)

Table I.
Clinical studies of the effectiveness of food IgG test-based elimination diets

Type of study	Indication	Subjects	Tests used	Duration	Results	Author
Open, non-controlled, prospective	Migraine	61 adults with migraine (high-impact headache) recruited from primary care general practices (UK)	IgG ELISA (all subclasses) for 113 foods	Two months	60 out of 61 patients were IgG positive to one or more foods. 28 and 38% (of 46 and 39 patients still in the study) self-reported "considerable" benefit (score of 4 or 5 on a scale 0-5) at one and two months, respectively. Patients who self-reported rigorous adherence to diet received more benefit from diet, compared to less strict adherers. 68% of patients who re-introduced foods reported a return of migraine symptoms. Proportion of patients tested with positive results not reported. Most common offending foods not reported. 72% of patients responding to the survey self-reported improvement as 3, 4 or 5 on a scale of 0-5 (increasing to 76% of patients who rigorously adhered to diet). 78% of patients who re-introduced foods reported a return of symptoms (increasing to 92.3% of patients who rigorously adhered to diet and showed high benefit).	Rees <i>et al.</i> (2005)
Open, non-controlled, retrospective survey	Various	5,286 patients	IgG ELISA (all subclasses) for 113 foods	Three months		Hardman and Hart (2007)

(continued)

Type of study	Indication	Subjects	Tests used	Duration	Results	Author
Open, non-controlled, prospective	Various: nasal, sinus and throat symptoms, fatigue, itchy skin, behaviour	114 patients with a positive history of symptoms consistent with delayed food allergy	IgG RAST (for foods eaten ≥ 2 /week by the patient)	Patients followed-up for four to 22 months	109 out of 114 patients were IgG positive to one or more foods. Not possible to report the common offending foods as each patient was tested for a different panel of foods. 71% of the 80 patients who partially/completely adhered to diet (50% of all patients entering study) achieved a $\geq 75\%$ level of improvement of all symptoms (self-reported level of improvement collected during personal interview). No re-introduction of foods.	Dixon (2000)
Open, non-controlled	Various: respiratory symptoms, headache, rash, gastro-intestinal symptoms	50 children; various symptoms	IgE and IgG RAST for four foods (milk, egg, corn, wheat)	Not reported	17 and 32 out of 46 patients were IgE and IgG positive, respectively, for one or more of the foods tested. Milk, egg and wheat more commonly positive than corn. Elimination of both IgE- and IgG-positive foods led to improved symptoms in 70% of patients	Dockhorn (1987)
					No re-introduction of foods	

(continued)

Table I.

Table I.

Type of study	Indication	Subjects	Tests used	Duration	Results	Author
Open, non-controlled trial, retrospective	Various: malaise, fever, rash, arthritis, gastrointestinal symptoms, headache	55 patients with symptoms suggestive of adverse reactions to foods, negative for all specific IgE tests and IgG positive to one or more foods	IgG multiple allergosorbant test chemiluminescent assay (36 allergens)	Patients followed up at one year	All 55 patients were IgG positive to one or more foods (this was a selection criteria), 90% of the 31 patients that adhered for one year (51% of all patients entering study) achieved symptomatic improvement, as determined by patient interviews (compared to 30% of the 24 non-adherers). Adherers had significant drops in specific IgGs after one year food exclusion diet; non-adherers did not ($p < 0.001$)	Marinkovich (1996)
Open, non-controlled, prospective	IBS	Ten adults with IBS	IgG RAST for 20 foods and skin scratch tests with 42 foods	Two weeks	All ten patients were IgG positive to one or more foods. Elimination of positive foods indicated by both IgG RAST and skin scratch tests led to improved symptoms in three out of ten patients. All three improvers were openly challenged with excluded foods. No positive challenges.	Zwetchkenbaum and Burakoff (1988)

The seven “non-RCT” studies were performed in patients with a range of chronic symptoms including IBS, other gastro-intestinal symptoms, migraine, nasal, sinus and throat symptoms, fatigue, itchy skin and behavioural problems (for examples see Pelikan, 1988; Sampson and McCaskill, 1985). Patients were advised to avoid foods to which they had significantly raised levels of IgG (and IgE in one study, Dockhorn, 1987; and positive skin scratch test results in another study, Zwetchkenbaum and Burakoff, 1988) and were followed-up for two weeks to 22 months. The studies reported considerable improvement in patients’ symptoms following dietary elimination of IgG-positive foods, with 30 per cent to over 70 per cent of patients reporting significant improvement (Rees *et al.*, 2005; Hardman and Hart, 2007; Dixon, 2000; Marinkovich, 1996).

In addition to the subjective measurement of symptom improvement, Zar *et al.* (2005a) also reported improvement in patients with IBS in terms of an objective endpoint, rectal compliance. This is a widely measured parameter of rectal function determined clinically by recording pressure changes associated with volume infusion into a rectal balloon. A significant increase was seen at six months compared to baseline (5.42 ± 2.33 mL/mmHg at baseline vs 7.75 ± 4.22 mL/mmHg at six months; $p = 0.011$). Three out of the eight non-RCT studies reported the response when patients re-introduced offending foods (Zwetchkenbaum and Burakoff, 1988; Rees *et al.*, 2005; Hardman and Hart, 2007). In one case, none of the three patients who improved on elimination diet experienced a return of symptoms when challenged with excluded foods (Zwetchkenbaum and Burakoff, 1988), whereas the other two studies indicated that approximately 70 per cent of patients who re-introduced foods reported a return of symptoms.

A limitation of these “non-RCT” studies, which lack a control group, is that the observed improvement in symptoms may be a result of factors other than the IgG test-based elimination diet. Chronic symptoms tend to fluctuate and it is possible that on average, if patients sought medical care and were then enrolled onto a study during a period of severe symptoms, then this would be followed by a period of reduced symptoms (regression to the mean). In addition, some or all of the reported improvement in symptoms may have been due to the placebo effect. However, a number of findings in these studies are important and encouraging. Firstly, three studies reported higher benefit for those patients who fully adhered to diet, compared to less strict adherers (Rees *et al.*, 2005; Marinkovich, 1996; Hardman and Hart, 2007). This association is a necessary finding if there is any causal link between the intervention and improvement in symptoms but it is not proof of causality as it may just reflect a higher placebo effect in rigorous adherers, as would be expected. Furthermore, the causal association may be operating in the reverse direction, whereby those patients experiencing a reduction in symptoms are more motivated to comply with the exclusion diet. Secondly, some of the studies had long follow-up periods (six months to 22 months) and indicated that for some patients the benefit persisted for a relatively long time (Zar *et al.*, 2005a; Marinkovich, 1996; Dixon, 2000), which may indicate that the response was not simply due to a relatively short-term placebo effect. Lastly, the fact that subjective, self-reported IBS symptom improvement was associated with objective physiological improvement in rectal compliance in one study suggests that the response may be real, rather than simply placebo effect (Zar *et al.*, 2005a). The observation in three studies that patients experienced a return of symptoms when challenged with excluded foods is important as it strengthens the proposal that the foods may be causing or contributing to symptoms, and that

avoidance of IgG-positive foods is an effective intervention. However, this was not seen in the study by Zwetchkenbaum and Burakoff (1988).

Despite the fact that the patient groups studied and the method of patient selection were very different, in all studies the vast majority of patients enrolled were IgG-positive to at least one food (70-100 per cent). In the five studies that reported the foods that were commonly IgG-positive, milk and egg were common to them all, and wheat was common to four out of five (Zwetchkenbaum and Burakoff, 1988; Atkinson *et al.*, 2004; Zar *et al.*, 2005a; Rees *et al.*, 2005; Dockhorn, 1987 in IBS, migraine and mixed symptom patients, respectively). Different additional IgG-positive foods were listed for each study. This is consistent with the findings of elimination and challenge studies in patients with IBS in which dairy products, eggs and wheat were identified as the most common foods to exacerbate IBS symptoms in both open and double-blind challenges (Niec *et al.*, 1998). The studies indicated that patients are generally IgG-positive for several foods (mean of five to seven foods; Rees *et al.*, 2005; Atkinson *et al.*, 2004), indicating that a “standard” elimination diet just excluding two or three foods may not be sufficient. Instead it may be necessary to identify all a patient’s problem foods to achieve optimal symptomatic improvement, but this remains to be investigated in an RCT.

Only one study re-measured food-specific IgG at the end of the food elimination period and a drop in levels for the excluded foods was observed (Marinkovich, 1996). The association between reduced IgG levels for excluded foods and symptomatic improvement is consistent with the hypothesis that the food-specific IgG may be playing a direct role in symptom initiation or exacerbation. However, such an association may just reflect exposure, with levels dropping when foods are removed from the diet.

Food-specific IgG titres in patients

There is a group of studies that measure levels of food-specific IgG in patients and control subjects to assess whether food-specific IgG is present in higher levels in those with symptoms compared with healthy subjects (Rumbo *et al.*, 1998; Kruszewski *et al.*, 1994; Johansson *et al.*, 1984). A number of studies have demonstrated significantly higher levels of food-specific IgG (either IgG₄ or all four subclasses of IgG) in certain patient groups. For example, Finn *et al.* (1987), demonstrated that a higher proportion of patients with IBS were IgG-positive for three common food components compared to blood donor control subjects (35 vs 17 per cent for ovalbumin, $p < 0.01$; 37 vs 23 per cent for cow’s milk, $p < 0.05$; 21 vs 12 per cent for gliadin, not statistically significant). In another study, significantly higher IgG₄ titres to five out of 16 foods tested (wheat, beef, pork, lamb and soya bean) were observed in patients with IBS compared to healthy control subjects (Zar *et al.*, 2005b). Another study compared levels of IgG subclass antibodies to three cow’s milk proteins (β -lactoglobulin, α -lactalbumin and α -casein) in adults with asthma, eczema or both due to milk hypersensitivity with IgG levels in two control groups: blood donors and adults with asthma or eczema due to inhalant allergy (Shakib *et al.*, 1986). Apart from one blood donor, high levels of IgG subclass antibodies to all three milk proteins were found only in the patients with milk hypersensitivity. The most frequently detected antibody was anti- α -casein IgG₄, high in eight out of 19 milk hypersensitive individuals. The authors concluded that some adult cases of milk hypersensitivity, particularly those with eczema, may be diagnosed by detecting raised serum levels of IgG subclass antibodies to milk proteins. It should be noted that in this study these milk sensitive individuals had negatives skin prick

and RAST test results for milk indicating that these individuals were suffering from a food allergy that was not mediated by IgE.

Separately, shrimp-specific IgG₂ and IgG₄ antibodies were shown to be significantly higher in individuals with a history of immediate, adverse reactions to shrimp compared to control subjects (Morgan *et al.*, 1990). Iacono *et al.* (1995) measured anti- β -lactoglobulin IgG antibody levels in three groups of children aged one month to six years: cow's milk protein allergy (CMPA) patients, patients with non-CMPA gastrointestinal symptoms and healthy controls. The level was significantly higher in children with CMPA. The authors concluded that anti- β -lactoglobulin IgG was a useful diagnostic marker for CMPA and, using their laboratories' arbitrary cut-off, the authors reported that the assay had a sensitivity of 83-96 per cent and a specificity of 81-97 per cent. The same group confirmed the presence of elevated anti- β -lactoglobulin IgG in infants and children with CMPA compared to control subjects in a further study (Cavataio *et al.*, 1996). However, it is not entirely clear from these studies if these patients were considered to have IgE-mediated (immediate CMPA) or non-IgE mediated (delayed CMPA), or both.

Another study has shown IgG antibodies to dietary antigens to be strikingly increased in the gut of patients with rheumatoid arthritis and that food problems related to this may reflect an adverse additive effect of multiple reactions mediated, for example, by immune complexes promoting autoimmune reactions in the joints (Hvatum *et al.*, 2006). This follows evidence that a breakdown in gastrointestinal intolerance to dietary antigens may play a role in the immunopathogenesis of rheumatoid arthritis (O'Farrelly *et al.*, 1988, 1989). The finding that food-specific IgG levels are higher in patients with inflammatory bowel disease, compared to healthy controls (Inns *et al.*, 2007), is consistent with the hypothesis that the food-specific IgG antibodies may be directly involved in symptom initiation or exacerbation. The additional information in this study of a correlation between food antibodies and patient reported food hypersensitivity in ulcerative colitis is also interesting and requires follow up.

Other studies, however, have found no difference in food-specific IgG titres between patients with suspected or confirmed food hypersensitivity and control subjects. For example, Merrett and colleagues (Merrett *et al.*, 1983) found no difference in IgG₄ titres to cheese, milk, orange and chocolate between patients with dietary migraine, patients with non-dietary migraine and healthy controls. Other studies in children with confirmed clinical reactions to milk did not find a consistent pattern of elevated anti-milk IgG in patients compared to control subjects (Firer *et al.*, 1987; Burks *et al.*, 1990; Host *et al.*, 1992; Hidvegi *et al.*, 2002).

Discussion

There is a need for a simple, convenient test to help the management of food hypersensitivity and identify offending foods in patients with persistent symptoms and/or those patients in whom non-IgE-mediated food allergy is strongly suspected. Currently, the best available option is the time consuming and laborious elimination and challenge method, which means eating a very restricted diet for up to several weeks and requires high levels of patient compliance.

A number of "non-RCT" studies in patients (see Table I) with a wide range of chronic symptoms have been published, reporting significant benefit from excluding foods identified by an IgG test in 30 per cent to over 70 per cent of patients. Where reported, many patients who reintroduced IgG-positive foods experienced a return of symptoms.

Importantly, it was found that patients who strictly adhered to their elimination diet gained more benefit compared to less strict adherers, a necessary finding if there is any causal link between IgG test-based food elimination and the observed improvement in symptoms. The only randomised placebo-controlled trial (Atkinson *et al.*, 2004) did show that a food-specific IgG ELISA test-based diet was more effective than a placebo diet in patients with IBS. The positive results of the RCT in patients with IBS indicate that this type of intervention is worthy of further investigation and additional RCTs are needed to explore the full potential of using IgG test-based elimination diets in other conditions.

There remain a large number of questions regarding the production of food-specific IgG antibodies in health and disease, and their role in food allergy. Following the positive results of the first published RCT of an IgG test-based elimination diet, a putative mechanism by which food-specific IgG antibodies may be detrimental in IBS has been proposed (Shanahan and Whorwell, 2005). Thus studies directly investigating the mechanism by which food-specific IgG antibodies may be operating in IBS and food allergy in general are now needed.

An important aspect of food-specific IgG tests is that they are not standardised. "Normal" levels of food-specific IgG in healthy individuals are not well defined, hence the cut-off between a positive and negative result is arbitrarily set by the individual laboratories performing the tests. Consequently, the results for a single patient using differently derived food-specific tests can vary. It is important that a validated reference method (External Quality Assurance Scheme) is established in future to ensure consistency between methods.

Conclusion

The use of fully standardised clinically evaluated food-specific IgG tests could lead to a considerable improvement in many patients' quality of life, and could provide a viable alternative to the time consuming and expensive elimination diet/food challenge approach.

References

- AAAI Position Statement (1995), "Measurement of specific and nonspecific IgG4 levels as diagnostic and prognostic tests for clinical allergy", *Journal of Allergy and Clinical Immunology*, Vol. 95, pp. 652-4.
- Allergy UK (2007), *Stolen Lives 3: The Food Allergy and Food Intolerance Report*, Allergy UK, Swanley.
- Atkinson, W., Sheldon, T.A., Shaath, N. and Whorwell, P.J. (2004), "Food elimination based on IgG antibodies in irritable bowel syndrome: a randomised controlled trial", *Gut*, Vol. 53, pp. 1459-64.
- Awazuhara, H., Kawai, H. and Maruchi, N. (1997), "Major allergens in soybean and clinical significance of IgG4 antibodies investigated by IgE- and IgG4-immunoblotting with sera from soybean-sensitive patients", *Clinical and Experimental Allergy*, Vol. 27, pp. 325-32.
- Beauvais, F., Hieblot, C., Burtin, C. and Benveniste, J. (1990), "Bimodal IgG4-mediated human basophil activation. Role of eosinophils", *Journal of Immunology*, Vol. 144, pp. 3881-90.
- Bruijnzeel-Koomen, C., Ortolani, C., Aas, K. *et al.* (1995), "Adverse reactions to food. European Academy of Allergology and Clinical Immunology Subcommittee", *Allergy*, Vol. 50, pp. 623-35.
- Burks, A.W., Williams, L.W., Casteel, H.B. *et al.* (1990), "Antibody response to milk proteins in patients with milk-protein intolerance documented by challenge", *Journal of Allergy and Clinical Immunology*, Vol. 85, pp. 921-7.

- Cavataio, F., Iacono, G., Montalto, G. *et al.* (1996), "Gastroesophageal reflux associated with cow's milk allergy in infants: which diagnostic examinations are useful?", *American Journal of Gastroenterology*, Vol. 91, pp. 1215-20.
- Dannaeus, A. and Inghanas, M. (1981), "A follow-up study of children with food allergy. Clinical course in relation to serum IgE- and IgG-antibody levels to milk, egg and fish", *Clinical Allergy*, Vol. 11, pp. 533-9.
- Dixon, H.S. (2000), "Treatment of delayed food allergy based on specific immunoglobulin G RAST testing", *Otolaryngology – Head & Neck Surgery*, Vol. 123, pp. 48-54.
- Dockhorn, R.J. (1987), "Clinical studies of food allergy in infants and children", *Annals of Allergy*, Vol. 59, pp. 137-40.
- el Rafei, A., Peters, S.M., Harris, N. and Bellanti, J.A. (1989), "Diagnostic value of IgG4 measurements in patients with food allergy", *Annals of Allergy*, Vol. 62, pp. 94-9.
- Finn, R., Smith, M.A., Chew, D. *et al.* (1987), "Immunological hypersensitivity to environmental antigens in the irritable bowel syndrome", *British Journal of Clinical Practice*, Vol. 41, pp. 1041-3.
- Firer, M.A., Hoskings, C.S. and Hill, D.J. (1987), "Humoral immune response to cow's milk in children with cow's milk allergy. Relationship to the time of clinical response to cow's milk challenge", *International Archives of Allergy and Applied Immunology*, Vol. 84, pp. 173-7.
- Freed, D.L. (2002), "False-negative food challenges", *Lancet*, Vol. 359 No. 9310, pp. 980-1.
- Hardman, G. and Hart, G. (2007), "Dietary advice based on food-specific IgG results", *Nutrition and Food Science*, Vol. 37, pp. 16-23.
- Hidvegi, E., Cserhati, E., Kereki, E. *et al.* (2002), "Serum immunoglobulin E, IgA, and IgG antibodies to different cow's milk proteins in children with cow's milk allergy: association with prognosis and clinical manifestations", *Pediatric Allergy and Immunology*, Vol. 13, pp. 255-61.
- Hindocha, P. and Wood, C.B. (1985), "Histamine release from human leucocytes by IgG4 subclass in the sera of allergic children", *Allergy*, Vol. 40, pp. 523-8.
- Host, A., Husby, S., Gjesing, B. *et al.* (1992), "Prospective estimation of IgG, IgG subclass and IgE antibodies to dietary proteins in infants with cow milk allergy. Levels of antibodies to whole milk protein, BLG and ovalbumin in relation to repeated milk challenge and clinical course of cow milk allergy", *Allergy*, Vol. 47, pp. 218-29.
- Hvatum, M., Kanerud, L., Hällgren, R. and Brandtzaeg, P. (2006), "The gut–joint axis: cross reactive food antibodies in rheumatoid arthritis", *Gut*, Vol. 55, pp. 1240-7.
- Iacono, G., Carroccio, A., Cavataio, F. *et al.* (1995), "IgG anti-betalactoglobulin (betalactotest): its usefulness in the diagnosis of cow's milk allergy", *Italian Journal of Gastroenterology*, Vol. 27, pp. 355-60.
- Inns, S.J., Emmanuel, A.V., Hurel, S. and Bloom, S.L. (2007), "Prevalence of IgG food-specific antibodies in IBD: a case-control study", *Gastroenterology*, Vol. 132, Supplement 2, p. A-655.
- Johansson, S.G., Bieber, T., Dahl, R. *et al.* (2004), "Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003", *Journal of Allergy and Clinical Immunology*, Vol. 113, pp. 832-6.
- Johansson, S.G., Dannaeus, A. and Lilja, G. (1984), "The relevance of anti-food antibodies for the diagnosis of food allergy", *Annals of Allergy*, Vol. 53, pp. 665-72.
- Kruszewski, J., Raczka, A., Klos, M. and Wiktor-Jedrzejczak, W. (1994), "High serum levels of allergen specific IgG-4 (asIgG-4) for common food allergens in healthy blood donors", *Archivum Immunologiae et Therapiae Experimentalis*, Vol. 42, pp. 259-61.
- Madsen, C. (2005), "Prevalence of food allergy: an overview", *Proceedings of the Nutrition Society*, Vol. 64, pp. 413-7.

- Marinkovich, V. (1996), "Specific IgG antibodies as markers of adverse reactions to foods", *Monographs in Allergy*, Vol. 32, pp. 221-5.
- Merrett, J., Barnetson, R.S., Burr, M.L. and Merrett, T.G. (1984), "Total and specific IgG4 antibody levels in atopic eczema", *Clinical and Experimental Immunology*, Vol. 56, pp. 645-52.
- Merrett, J., Peatfield, R.C., Rose, F.C. and Merrett, T.G. (1983), "Food related antibodies in headache patients", *Journal of Neurology, Neurosurgery and Psychiatry*, Vol. 46, pp. 738-42.
- Morgan, J.E., Daul, C.B. and Lehrer, S.B. (1990), "The relationships among shrimp-specific IgG subclass antibodies and immediate adverse reactions to shrimp challenge", *Journal of Allergy and Clinical Immunology*, Vol. 86, pp. 387-92.
- Niec, A.M., Frankum, B. and Talley, N.J. (1998), "Are adverse food reactions linked to irritable bowel syndrome?", *American Journal of Gastroenterology*, Vol. 93, pp. 2184-90.
- O'Farrelly, C., Marten, D., Melcher, D. *et al.* (1988), "Association between villous atrophy in rheumatoid arthritis and a rheumatoid factor and gliadin-specific IgG", *Lancet*, Vol. 2 No. 8615, pp. 819-22.
- O'Farrelly, C., Price, R., McGillivray, A.J. and Fernandes, L. (1989), "IgA rheumatoid factor and IgG dietary protein antibodies are associated in rheumatoid arthritis", *Immunological Investigations*, Vol. 18, pp. 753-64.
- Pelikan, Z. (1988), "Nasal response to food ingestion challenge", *Archives of Otolaryngology – Head and Neck Surgery*, Vol. 114, pp. 525-30.
- Rees, T., Watson, D., Lipscombe, S. *et al.* (2005), "A prospective audit of food intolerance among migraine patients in primary care clinical practice", *Headache Care*, Vol. 2, pp. 105-10.
- Rumbo, M., Chirido, F.G., Anon, M.C. and Fossati, C.A. (1998), "Detection and characterization of antibodies specific to food antigens (gliadin, ovalbumin and beta-lactoglobulin) in human serum, saliva, colostrum and milk", *Clinical and Experimental Immunology*, Vol. 112, pp. 453-8.
- Sampson, H.A. and McCaskill, C.C. (1985), "Food hypersensitivity and atopic dermatitis: evaluation of 113 consumers", *Journal of Paediatrics*, Vol. 107, pp. 669-75.
- Shakib, F., Brown, H.M., Phelps, A. *et al.* (1986), "Study of IgG sub-class antibodies in patients with milk intolerance", *Clinical Allergy*, Vol. 16, pp. 451-8.
- Shanahan, F. and Whorwell, P.J. (2005), "IgG-mediated food intolerance in irritable bowel syndrome: a real phenomenon or an epiphenomenon?", *American Journal of Gastroenterology*, Vol. 100, pp. 1558-9.
- Zar, S., Mincher, L., Benson, M.J. and Kumar, D. (2005a), "Food-specific IgG4 antibody-guided exclusion diet improves symptoms and rectal compliance in irritable bowel syndrome", *Scandinavian Journal of Gastroenterology*, Vol. 40, pp. 800-7.
- Zar, S., Benson, M.J. and Kumar, D. (2005b), "Food-specific serum IgG4 and IgE titers to common food antigens in irritable bowel syndrome", *American Journal of Gastroenterology*, Vol. 100, pp. 1550-7.
- Zuberbier, T., Edenharter, G., Worm, M. *et al.* (2004), "Prevalence of adverse reactions to food in Germany – a population study", *Allergy*, Vol. 59, pp. 338-45.
- Zwetchkenbaum, J. and Burakoff, R. (1988), "The irritable bowel syndrome and food hypersensitivity", *Annals of Allergy*, Vol. 61, pp. 47-9.

Corresponding author

Gillian Hart can be contacted at: gill.hart@yorktest.com