



FOOD INTOLERANCE (Food IgG Antibodies)

Theory, Facts & Fallacies

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Scientific Director CNS



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INTRODUCTION

Introduction **1**

Definitions

Antibodies

Significance

IgG vs IgG4

Mechanisms

Inflammation

Diseases

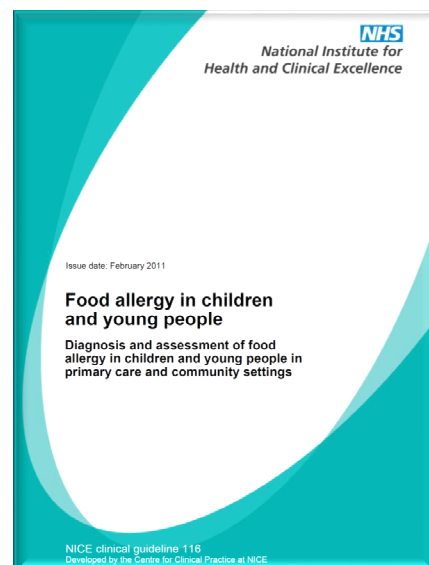
Developments

Conclusion

Food 'allergy' in the UK: 500% increase in hospital admissions seen since 1990.

In the past we tended to see the immediate type of reaction, but now we are seeing much more of serious delayed reactions.

Why has there been such an increase?



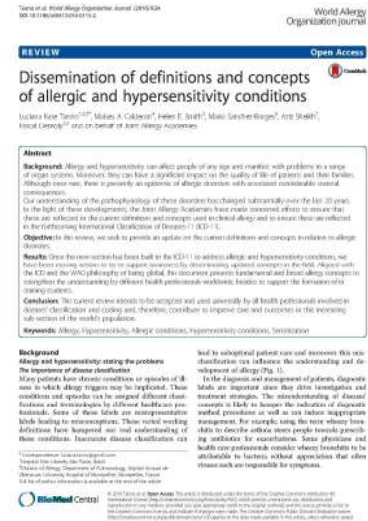


ADVERSE FOOD REACTIONS

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Tanno LK, Calderon MA, Smith HE, Sanchez-Borges M, Sheikh A, Demoly P; Joint Allergy Academies. *World Allergy Organ J.* 2016 Aug 9;9:24. doi: 10.1186/s40413-016-0115-2. eCollection 2016.

- Allergy and hypersensitivity, previously perceived as simple and rare disorders, are now common and increasingly a major global public health problem.
- Numerous reports over the last 20 years have been indicating that the world is dealing with an allergy epidemic.
- They are complex conditions able to be expressed in many different organs and in any age, having a significant impact on the quality of life of patients and their families.
- All health care professionals, in whatever role may thus encounter patients with allergic conditions.



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- The prevalence of migraine, asthma, dermatitis and irritable bowel syndrome has been continuously increasing
- Etiological studies suggest that these diseases may be related to adverse food reactions (food hypersensitivity)
- Numerous studies have found that the levels of food-specific IgG's and IgG subclasses in serum are significantly higher in individuals with food hypersensitivity
- IgG-mediated immunologic responses play an important role in the pathogenesis of adverse food reactions



IgG GUIDED DIET

Geoffrey Hardman, Gillian Hart. Nutrition & Food Science Vol. 37 No. 1, 2007 pp. 16-23

NFS 37,1

Dietary advice based on food-specific IgG results

Geoffrey Hardman
Centre for Health Economics, University of York, Heslington, York, UK, and
Gillian Hart
YorkTest Laboratories Ltd, York Science Park, York, UK

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Abstract

Purpose - To provide evidence that elimination diet based on food-specific IgG test results is an effective, reliable and valid aid to the management of chronic medical conditions.
Design/methodology/approach - A postal survey, commissioned by Allergy UK, was carried out with 5286 subjects reporting a wide range of chronic medical conditions, who had taken a food-specific IgG enzyme-linked immunosorbent assay (ELISA) test. Questionnaires, issued three months after the results, were analysed to investigate the effect of eliminating the foods identified by the test. To check for response bias, a separate group of patients who had not responded were interviewed by telephone. The analysis and reporting of the data was carried out at the University of York.

Findings - 18 patients who rigorously followed the diet 73.6 per cent had a noticeable improvement in their condition. Of patients who benefited from following the recommendations 88.2 per cent felt the benefit within three weeks. Those who reported more than one condition were more likely to report noticeable improvement, 82.3 per cent of those that dieted rigorously and reported three or more co-morbidities showed noticeable improvement in their condition. For those who dieted rigorously and reported high benefit, 92.1 per cent noticed a return of symptoms on reintroduction of the offending foods.
Originality/value - These data provide evidence for the use of elimination diet based on food-specific IgG blood test results as an aid to management of the symptoms of a range of chronic medical conditions.

Keywords Food products, Diet
Paper type Research paper

Introduction

A role for food-specific IgG antibodies in the underlying mechanism of food intolerance (non-IgE mediated food allergy) has been proposed, as has the measurement of food-specific antibodies as a strategy for identifying foods to which a patient may be sensitive (Marinkovich, 1990). It is proposed that the presence of food-specific IgG indicates a potential sensitivity to that particular food and that the patient may achieve benefit by eliminating the foods from their diet. Recent study showed a consistent increase in IgG antibody titres across the three Irritable Bowel Syndrome (IBS) subgroups compared to controls for wheat, beef, pork, lamb, and soya bean (Zur et al., 2005), and a clinically significant improvement in symptoms has been observed in IBS patients eliminating foods identified by such a method (Atkinson et al., 2004). However, the exact role of IgG antibodies as markers of food intolerance is proved is not clear. IgG antibodies to food antigens are often present in healthy individuals and are generally considered to be part of the normal immune response to food allergens (Haines, 1995).

Food intolerance has been associated with a myriad of chronic symptoms including headaches (Rees et al., 2005), intestinal and skin symptoms (Stumpson and McCoslin, 1985), behavioural changes and respiratory disorders (Pillay, 1988). Currently, the best accepted method for diagnosing and confirming food intolerance is empirical, by elimination diet and subsequent challenge (Kodjic, 2002). Using this method patients



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SURVEY RESULTS – ALLERGY UK 2007 MAIN MEDICAL CONDITION REPORTED		% WHO REPORTED MODERATE TO HIGH BENEFIT
Gastrointestinal	IBS, Crohn's Disease	80%
Respiratory	Asthma, breathing difficulties	78%
Neurological	Migraine, Headaches	72%
Dermatological	Eczema, Acne, Psoriasis	76%
Musculo-skeletal	Arthritis, Rheumatoid Arthritis	64%
Psychological	Depression, ADHD, Panic Attacks	81%
Other	Bloating, Lethargy, general feeling of Malaise	79%

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Food intolerance has been associated with a myriad of chronic symptoms including headaches (Rees *et al.*, 2005), intestinal and skin symptoms (Sampson and McCoslett, 1982), behavioural changes and respiratory disorders (Polkari, 1988). Currently, the best accepted method for diagnosing and confirming food intolerance is empirical, by elimination diet and subsequent challenge (Kodjifile, 2002). Using this method patients



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How do we define food allergy and intolerance?





STANDARD CLASSIFICATION

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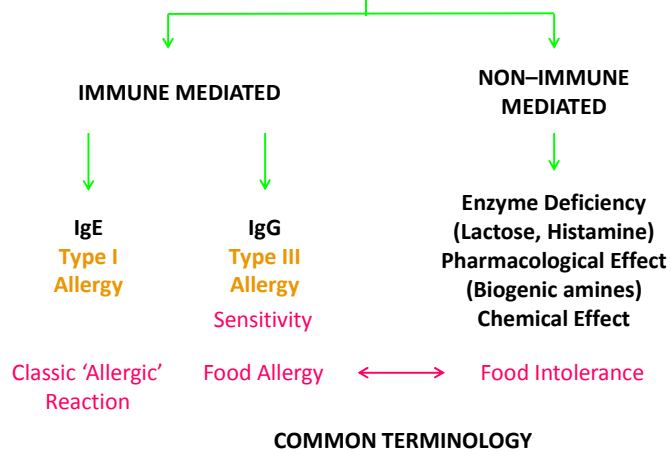
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ADVERSE REACTION TO FOOD



COMMON TERMINOLOGY



CLASSIFICATION OF ALLERGIC REACTIONS

Classified in four groups as defined by Gell and Coombs in 1963

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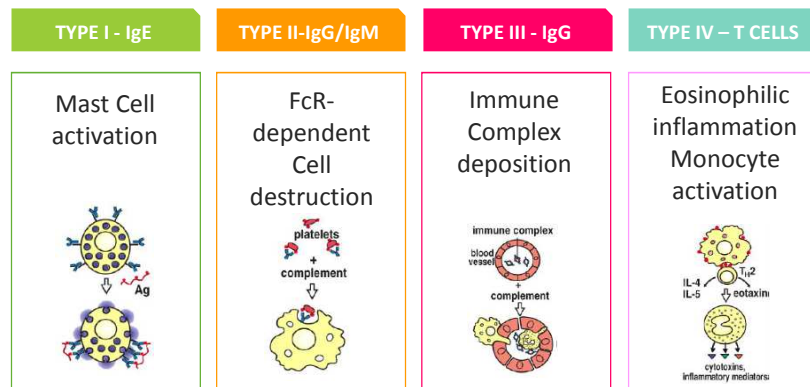
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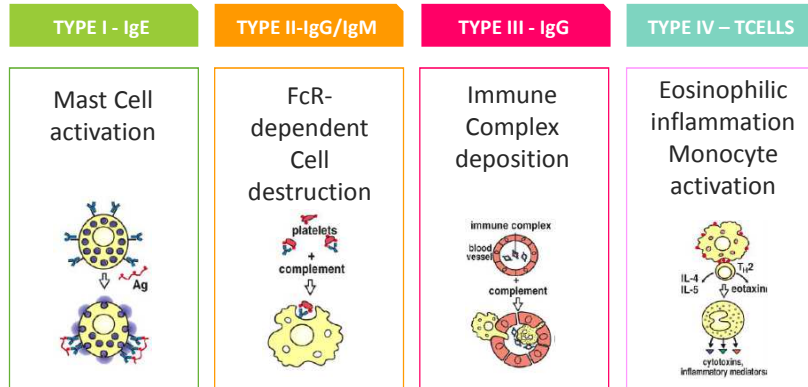
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CLASSIFICATION OF ALLERGIC REACTIONS

Classified in four groups as defined by Gell and Coombs in 1963

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- Concepts in medicine and the new knowledge generated in the last few years have substantially changed our view of the immune system and its interaction with the environment and external agents.
- Such developments in pathophysiology, pharmacology and clinical practice necessitate reviewing current definitions and terminologies.

World Allergy Organization Journal
90-101/16WAOJ201610

REVIEW Open Access

Dissemination of definitions and concepts of allergic and hypersensitivity conditions

Luciana Kato Tanno^{1,2*}, Malak A. Calzavara³, Helen E. Smith⁴, Maria Sanchez-Borges⁵, Anis Sheik⁶, José Luis García⁷ and on behalf of Joint Allergy Academies

Abstract
Background: Allergy and hypersensitivity can affect people of any age and manifest with problems in a range of organ systems. Moreover they can have a significant impact on the quality of life of patients and their families. Although their prevalence is generally an epidemic of allergic disorders with associated considerable societal consequences, our understanding of the pathophysiology of these disorders has changed substantially over the last 20 years. In the light of these developments, the Joint Allergy Academies have made concerted efforts to ensure that these are reflected in the current definitions and concepts used in clinical allergy and to ensure these are reflected in the international biomedical classification of Diseases (ICD-11).
Objective: In this review, we seek to provide an update on the current definitions and concepts relevant to allergic conditions.
Results: Over the recent past has been built by the ICD-11 to address allergic and hypersensitivity conditions, we have been moving towards a more robust consensus by disseminating updated concepts to the field. Alignment with the ICD and the WHO classification of being global, the consensus presents a formal and broad allergy consensus framework for understanding by relevant health professionals worldwide, besides to support the harmonization of language across countries.
Conclusions: The current review intends to accept and also identify all health professionals involved in clinical classification and codes and, therefore, contribute to improve care and outcomes in the increasing sub-section of the world's population.
Keywords: Allergy, Hypersensitivity, Allergic conditions, Hypersensitivity conditions, Sensitization

Background
Allergy and hypersensitivity: stating the problem
 Many patients have chronic conditions or episodes of ill health in which allergy triggers may be implicated. These conditions and episodes can be assigned different clinical features and terminology in different health care environments. Some of these labels are nonrepresentative labels leading to miscommunication. These varied working definitions have hampered our real understanding of these conditions. International disease classification systems are essential for epidemiological surveillance and to support patient care and research. This review identifies the need to update the current definitions and concepts used in clinical allergy and to ensure these are reflected in the international biomedical classification of Diseases (ICD-11).
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FOOD INTOLERANCE (IgG)

Introduction

Definitions **2**

Antibodies

Significance

IgG vs IgG4

Mechanisms

Inflammation

Diseases

Developments

Conclusion




“45% of the population suffer from a food intolerance”

- Non-specific / multiple symptoms
- Most people are undiagnosed
- **Many clients will be affected**




What are IgG antibodies
& what is their significance ?






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ANTIBODY CLASSIFICATION



Monomer
IgD, IgE, IgG




Dimer
IgA



Pentamer
IgM

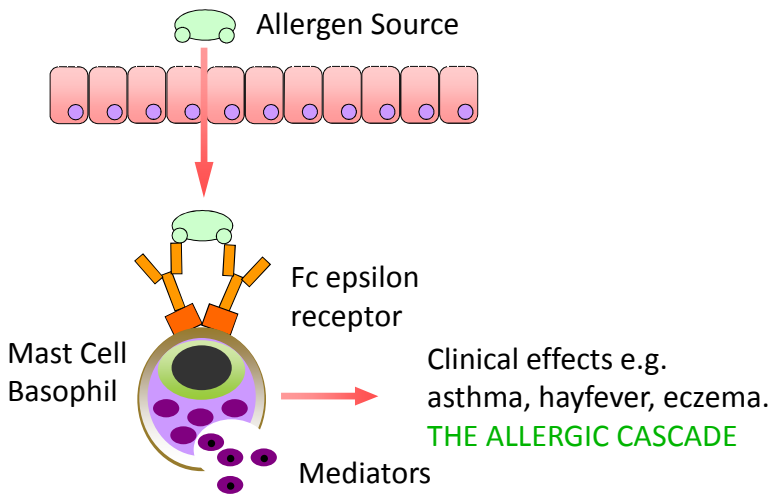
Name	Types	Description
IgA	2	Found in gut, respiratory tract, urogenital tract, saliva, tears and breast milk. First line immune defense system against invading pathogens
IgD	1	Antigen receptor on B cells that haven't been exposed to antigens. Can produce immune response via mast cells and basophils
IgE	1	Binds antigens and triggers histamine response from mast cells and basophils. Type I hypersensitivity
IgG	4	Provides the majority of antibody-based immunity against pathogens. Can cross placenta to give passive immunity to fetus.
IgM	1	Expressed at the surface of B cells. Use in early stages of B cell immunity before there is sufficient IgG

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ANTIBODY PRODUCTION – PROVOCATION IgE ALLERGY




THE ALLERGIC CASCADE

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ANTIBODY CLASSIFICATION



Monomer
IgD, IgE, IgG




Dimer
IgA



Pentamer
IgM

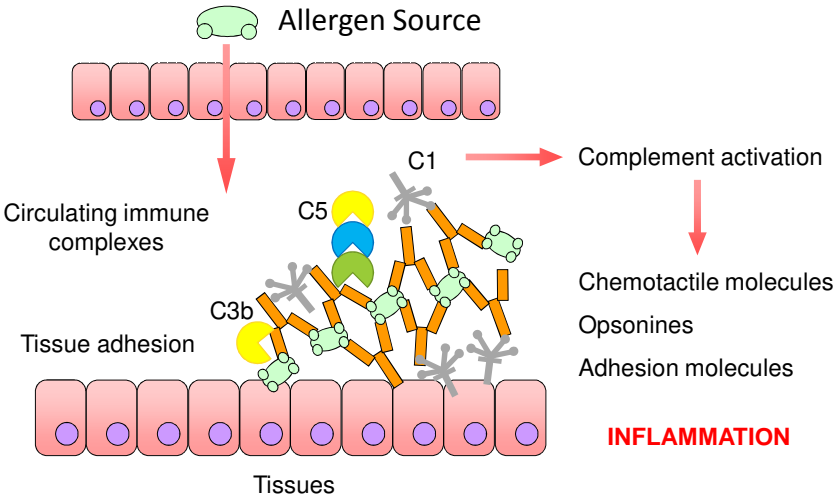
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ANTIBODY PRODUCTION – CIRCULATING IMMUNE COMPLEXES (CIC)



The diagram illustrates the complement activation pathway. It starts with an **Allergen Source** (represented by a green car) releasing antigens that bind to antibodies on the surface of **Tissues** (represented by a row of pink cells). This leads to the formation of **Circulating immune complexes**. The activation of **C1** (orange Y-shape) leads to **Complement activation**, which produces **C3b** (yellow Y-shape) and **C5** (blue Y-shape). **C3b** is involved in **Tissue adhesion** to the tissue cells. **C5** leads to **Chemotactile molecules**, **Opsonines**, and **Adhesion molecules**, which ultimately result in **INFLAMMATION**.

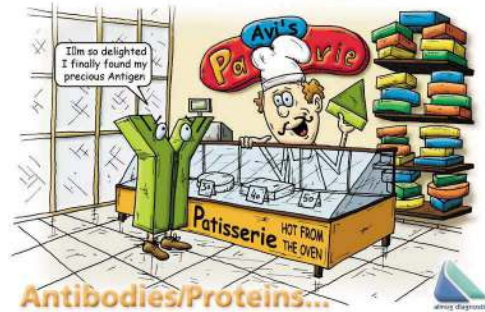
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WHAT DOES THE PRESENCE OF IgG ANTIBODIES MEAN?


Whilst it is a normal physiological phenomenon to produce IgG antibodies to foods, we have to remember that the presence of such antibodies in the serum constitutes an immunological defence reaction against the food



Oral tolerance is the normal state and it is not a normal reaction to develop high levels of antibodies to all foods that are consumed regularly.



What about IgG₄ antibodies & their significance ?




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IgG SUBCLASS PROPERTIES

PROPERTY	IgG1	IgG2	IgG3	IgG4
Neutralisation	++	++	++	++
Activation of complement pathway	++	+	+++	
Opsonisation	+++	+	++	
Binding to macrophages	++	+	+++	++
Binding to neutrophils	+		+	

IgG1 and IgG3 have strong **pro-inflammatory** properties
 IgG4 has protective, **anti-inflammatory** properties
 IgG4 deficiency seen in 10 to 15% of healthy patients

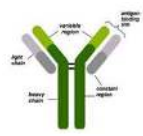


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IgG4 FUNCTION

- Acts as a 'blocking agent' against the actions of IgE
- Catches and neutralises the (food) antigen before IgE can bind to it
- IgG4 acts to prevent acute allergic reactions (Type I allergy) occurring
- No complement activation and no opsonising capacities
- No involvement with Type III (IgG-mediated) food intolerance**
- Invalid measurement, to detect 'delayed-onset' food intolerance**





THE BOTTOM LINE FOR ALLERGY DIAGNOSIS

R. C. Aalberse, S. O. Stapel, J. Schuurman and T. Rispens. Clinical & Experimental Allergy, 39, 469–477

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- IgG4 by itself is unlikely to be a cause of allergic symptoms. In general, the presence of allergen-specific IgG4 indicates that anti-inflammatory, tolerance-inducing mechanisms have been activated.
- The existence of the IgG4 subclass, its up-regulation by anti-inflammatory factors and its own anti-inflammatory characteristics may help the immune system to dampen inappropriate inflammatory reactions.

REVIEW

Immunoglobulin G4: an odd antibody

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*Amgen and Academic Medical Centre, University of Amsterdam, Amsterdam; the Amsterdam and Vrije Universiteit, the Netherlands

Clinical & Experimental Allergy

Summary
Despite its well-known association with IgE-mediated allergy, IgG4 antibodies still have several poorly understood characteristics. IgG4 is a very unusual antibody: the antibody is involved in a continuous process of half-molecule (i.e. a heavy and attached light-chain) exchange. This process, also referred to as 'Fab-arm exchange', results usually in oligomeric antibodies with two different antigen-combining sites. While these antibodies are heterodimers, they will behave as monomeric antibodies in most situations. Another aspect of IgG4 will poorly understood, is its tendency to mimic IgE (immunological factor (IF) activity by interacting with IgE on a cell-surface, in contrast to conventional IgG, which binds to its variable domain, the activity of IgG4 is located in its constant domain. This is potentially a source of false positives in IgE antibody assays. Because regulation of IgG4 production is dependent on help by T-helper type 2 (Th2) cells, the IgG4 response is largely restricted to non-microbial antigens. This Th2-dependency associates the IgG4 and IgE responses. Another typical feature is the transient regulation of IgG4 in its tendency to appear only after prolonged immunisation. In the context of IgE-mediated allergy, the appearance of IgG4 antibodies is usually associated with a decrease in symptoms. This likely is due, at least in part, to an allergen-blocking effect as the most cell level and/or at the level of the antigen-presenting cell (apoptotic IgG4-facilitated activation of T cells). In addition, the favourable association reflects the enhanced production of IL-10 and other anti-inflammatory cytokines, which drive the production of IgG4. While in general IgG4 is being associated with non-activating characteristics, in some situations IgG4 antibodies have an association with pathology. Two striking examples are protracted disease and sclerosing diseases such as autoimmune pancreatitis. The mechanistic basis for the association of IgG4 with these diseases is still unclear. However, the association with sclerosing diseases may reflect an excessive production of anti-inflammatory cytokines triggering an over-activating expansion of IgG4-producing plasma cells. The bottom line for allergy diagnosis is that IgG4 antibody is unlikely to be a cause of allergic symptoms. In general, the presence of allergen-specific IgG4 indicates that anti-inflammatory, tolerance-inducing mechanisms have been activated. The existence of the IgG4 subclass, its up-regulation by anti-inflammatory factors and its own anti-inflammatory characteristics may help the immune system to dampen inappropriate inflammatory reactions.

Introduction
In the 1960s, it was discovered that the five classes of antibodies present in all mammals (IgM, IgG, IgA, IgE and IgD) could be subdivided into subclasses. In contrast to the IgG classes, these subclasses developed relatively recently after most of the evolutionary diversification of the mammalian species. As a consequence, the human subclasses do not have clear structural homologues in, for example, the mouse. Nevertheless, there is often some functional homology between subclasses among mice and man, although this is not reflected in their amino acid sequence. The human IgG subclasses have been assigned numbers according to their time of discovery. This numbering scheme corresponds to their abundance in plasma. IgG1 is the most abundant (~50% of total IgG), IgG4 the least abundant (~0.5%). In contrast, the number assignment to the rodent IgG subclasses initially reflected their electrophoretic mobility: rodent IgG1 is relatively fast (α-acidic), while rodent IgG2 has a lower mobility, and so on.



(EAACI) Task Force Report. 2008

European Academy of Allergy & Clinical Immunology (EAACI) Task Force Report. 2008

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- Testing of IgG to foods is considered irrelevant for the laboratory work-up of food allergy or intolerance.
- Testing for IgG4 against foods is not recommended as a diagnostic tool.
- Due to lack of any controlled studies on the diagnostic value of IgG testing in food allergy, it should not be performed in the case of food-related complaints. (Papers cited 1982 – 2006)

Position paper

Testing for IgG4 against foods is not recommended as a diagnostic tool: EAACI Task Force Report*

Sharon B. Dwyer¹, R. Aalberse², S. O. Stapel², S. Valleron³, E. F. Knudsen⁴, S. D. Strickland⁵, S. Valleron⁶, J. K. M. M. van der Schoot⁷, S. Valleron⁸, S. Valleron⁹, S. Valleron¹⁰

Abstract
Serum diagnosis for food allergy is performed with IgE antibody assays. However, the presence of food-specific IgG antibodies, but not IgG4, is not considered to be a diagnostic tool for food allergy. This position paper discusses the clinical relevance of the regional history and the clinical food-specific IgG antibody response in a positive controlled food challenge (FC). When IgE-mediated food allergy cannot be established by regular diagnostic procedures, it is not uncommon that diagnosed patients, who blame food components for their problems, seek further for confirmation of their presumed autoimmune etiology, looking for test results that may be in line with their expectations. Commercial laboratories all over Europe are currently offering broad-based IgG testing against foods to the public, claiming that these tests represent reliable tools for the diagnosis of food allergy. This idea is probably



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IgG & FOOD ALLERGY – LEAP STUDY

LEAP Study team N Engl J Med 2015;372:803-13

- **Conclusions:** The early introduction of peanuts significantly decreased the frequency of the development of peanut allergy among children at high risk for this allergy and modulated immune responses to peanuts.
- Increases in levels of peanut-specific IgG antibody occurred predominantly in the consumption group.
- Observations indicate that IgG is associated with a protective role against the development of allergy.



What are the mechanisms of IgG mediated food intolerance ?





INTESTINAL PERMEABILITY

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Ménard S, Cerf-Bensussan N, Heyman M. *Mucosal Immunol.* 2010 May;3(3):247-59. doi: 10.1038/mi.2010.5. Epub 2010 Mar 10. PMID: 20404811

nature publishing group

REVIEW

See REVIEW page 213
See COMMENTARY page 209

- In intestinal diseases, increased permeability to large molecules mostly (food antigens, microbial fragments) can have a role in exacerbating inappropriate immune responses

Multiple facets of intestinal permeability and epithelial handling of dietary antigens

S Ménard¹, N Cerf-Bensussan¹ and M Heyman¹

The intestinal epithelium, the largest interface between the host and environment, regulates fluxes of ions and nutrients and limits host contact with the massive load of luminal antigens. Local protective and tolerogenic immune responses toward luminal content depend on antigens sampling by the gut epithelial layer. Whether, and how exaggerated, the entrance of antigenic macromolecules across the gut epithelium might initiate and/or perpetuate chronic inflammation as well as the respective contribution of paracellular and transcellular permeability remains a matter of debate. To this extent, experimental studies involving the *in vivo* assessment of intestinal permeability using small inert molecules do not necessarily correlate with the uptake of larger dietary antigens. This review analyzes both the structural and functional aspects of intestinal permeability with special emphasis on antigen handling in healthy and diseased states and consequences on local immune responses to food antigens.

INTRODUCTION

The intestinal epithelium forms a selective barrier, which filters fluxes of nutrients, regulates ion and water movements, and limits host contact with the massive intraluminal load of dietary antigens and microbes. However, this barrier is not fully impermeable to macromolecules: in the steady state, the transcellular passage of small amounts of food-derived antigens and microorganisms participates in the induction of a homeostatic immune response dominated by immune tolerance to dietary antigens¹ and the local production of secretory immunoglobulin A (IgA)², preventing pathogenic and commensal microbes from entering intestinal compartments. Conversely, primary or secondary defects of the intestinal barrier can lead to excessive entrance of dietary or microbial-derived macromolecules, which are putative contributors to the pathogenesis of a spectrum of human diseases, including food allergy and inflammatory bowel diseases (IBD), and could even be related to autoimmune diseases and metabolic syndromes³. Reinforcing the intestinal barrier and more particularly the paracellular pathway has recently been suggested as a therapeutic strategy to treat or prevent diseases driven by luminal antigens. Delineating how antigens are transported across the epithelium in healthy and diseased states should help in the design of appropriate therapeutic tools.

Herein, we will discuss the multiple pathways involved in the intestinal transport of luminal food antigens and analyze the contribution of the paracellular and transcellular pathways.

DIETARY ANTIGENS ARE AVAILABLE FOR INTESTINAL TRANSPORT

Although the majority of dietary proteins are totally digested by digestive enzymes and are absorbed in the form of nutrients (amino acids or dipeptides/tripeptides), some however can reach both the low pH of the gastric fluid and proteolytic enzyme hydrolysis⁴, meaning that large immunogenic peptides or intact proteins are capable of reaching the small intestinal lumen.⁵ For example, β-lactoglobulin, a major cow's milk allergen, is stable under acidic conditions and resists digestion by pepsin, whereas the resistance of gluten gliadins to digestive enzymes is a major factor underlying celiac disease (CD). The high protein content (20%) of gliadin prevents their efficient intraluminal digestion and leads to the release of large trypsin (35- and 26-mer immunogenic peptides)⁶ able to activate the human proteinase CD11⁷ T cells in celiac patients. The deleterious role of resistant protein digestion is highlighted by the increased risk of food allergy reported in patients taking antacid medication, which thereby impairs gastric protein digestion.⁸ Despite this

Supplies 2009. www.nature.com/journalData/immunology/33/3/247-59
Received 15 December 2009; accepted 20 January 2010; published online 13 March 2010; doi:10.1038/mi.2010.5



IgG AND THE GUT MICROBIOME

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Hippe B, Remely M, Bartosiewicz N, Riedel M, Nichterl C, Schatz L, Pummer S, Haslberger A. *Endocr Metab Immune Disord Drug Targets.* 2014 Mar;14(1):67-75.

Endocrine, Metabolic & Immune Disorders - Drug Targets. 2014; 14: 67-75.
Abundance and Diversity of GI Microbiota Rather than IgG₄ Levels Correlate with Abdominal Inconvenience and Gut Permeability in Consumers Claiming Food Intolerances

Berit Hippe¹, Marlene Remely¹, Natalie Bartosiewicz¹, Monika Rodef², Claudia Nichterl¹, Lidia Schatz¹, Susana Pummer¹ and Alexander Haslberger^{1,3*}

- Pilot study analysed interactions of gastrointestinal microbiota, gut permeability, nutrition, IgG levels, and their impact or correlation on food intolerances and well-being.
- Anti-inflammatory effects of *Faecalibacterium prausnitzii* or *Lactobacilli* and gut barrier functions of *Akkermansia* may have a key role in food intolerances.

As an inappropriate tolerance to food antigens has been associated with mechanisms of response [1] or paralysis of T-cells [5] and failure in the production of regulatory T-cells

intolerance are well described [16]. In contrast many aspects [17] in the area of non-IgE-mediated intolerance remain poorly understood [18-20]. Various food components, and also a number of natural and artificial food additives have been discussed as non-IgE mediated adverse reactions [21, 22]. Furthermore, the role of IgG antibodies in these antibodies remains highly controversial. IgG₄ formed in the initial response after contact with a new food antigen. With further exposure to the antigen, a change in the formation of IgG antibodies occurs in their place [23]. Following this change the amount of IgG₄ rises from 3% up to 50%. High IgG₄ concentrations may indicate an immune conflict of the immune system with food antigens. The synthesized IgG₄ antibodies are supposed to neutralize, but may also block the IgE-mediated allergic response [24]. Actual increased allergies show increased IgG₄ levels in 50% of cases. However, the identification of the triggering food is difficult as the organisms often strip after hours or days. In many of these IgG₄ mediated immune responses a disturbed intestinal permeability, leading to a constant

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IgG AND THE GUT MICROBIOME

Hippe B, Remely M, Bartosiewicz N, Riedel M, Nichterl C, Schatz L, Pummer S, Haslberger A
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 Abundance and Diversity of GI Microbiota Rather than IgG Levels Correlate with Abdominal Inconvenience and Gut Permeability in Consumers Claiming Food Intolerances

Berit Hippe¹, Marlene Remely¹, Natalie Bartosiewicz², Monika Riedel², Claudia Nichterl¹, Ladin Schatz², Susana Pummer² and Alexander Haslberger^{1,2}*

- Even in absence of diagnosed milk intolerance, discomfort increased, if the IgG levels were high or Lactobacilli and Bifidobacteria levels were low.
- The analytical strategy to include the analysis of major commensal gastrointestinal microbiota groups in addition to food intolerances, IgG levels, resulted in significant correlations.

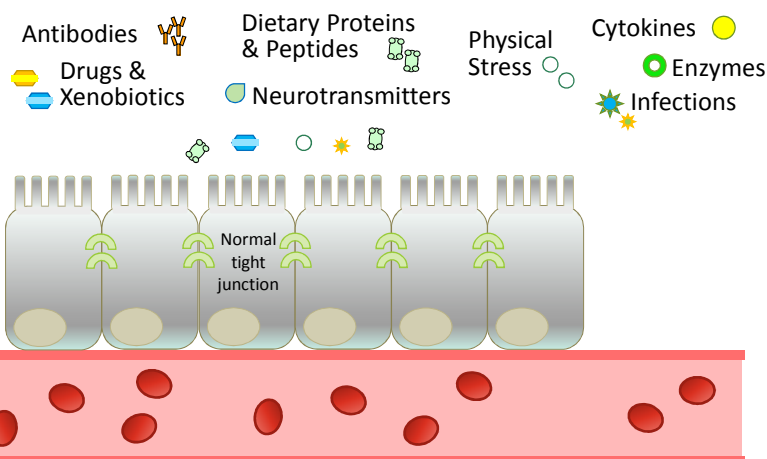
problem in the western world and according to the World Allergy Organization (WAO), 250-300 million people are affected. The trend continues to rise, especially in children [2]. In Europe, 2-6% of people suffer from a food allergy, while intolerances are estimated at 20% [3]. Genetic aspects such as single nucleotide polymorphisms [4], environmental influences such as the described "hygiene hypothesis" [5], and stress from the social environment [6, 7] have been linked to intolerances. Recently aspects of gut microbiota and gut permeability are in discussion for their role in food intolerance [7].

An inappropriate tolerance to food antigens has been associated with mechanisms of apoptosis [8] or paralysis of T-cells [9] and failure in the production of regulatory T-cells [17] in the area of non-IgE-mediated intolerances remains poorly understood [18-20]. "Natural" food components, and also a number of natural and artificial food additives have been discussed for non-IgE-mediated allergic reactions [21, 22]. Furthermore, the role of IgG antibodies in these intolerances remains highly controversial. IgG is formed in the natural response after contact with a new food antigen. With further exposure to the antigen, a change in the formation of IgG antibodies occurs in time place [23]. Following this change the amount of IgG rises from 3% up to 50%. High IgG concentrations may indicate an immune conflict of the immune system with food antigens. The synthesized IgG antibodies are supposed to neutralize cells, but may also block the IgE-mediated allergic response [24]. Actual tolerated allergens show increased IgG levels in 50% of cases. However, the identification of the triggering food is difficult in the symptoms often slip after hours or days. In many of these IgG-mediated immune responses a disturbed intestinal permeability, leading to a constant


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'LEAKY GUT' SYNDROME










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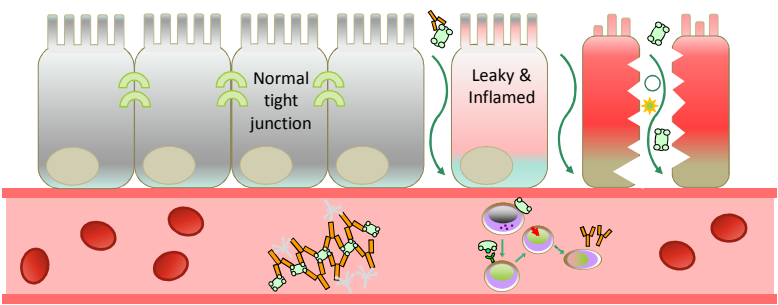
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‘LEAKY GUT’ SYNDROME

Antibodies  Dietary Proteins & Peptides  Physical Stress  Cytokines 

 Drugs & Xenobiotics  Neurotransmitters  Enzymes

 Infections



Blood Brain
Barrier Breach


Inflammation

FOOD ALLERGY & INTOLERANCE

Autoimmunity

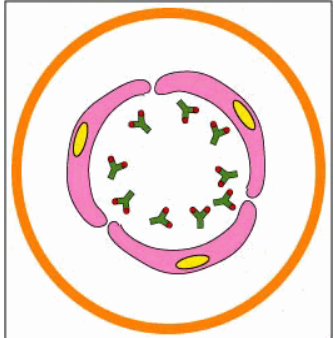
Malabsorption
& nutrient deficiency

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IMMUNE COMPETENCY AND ‘TOTAL LOAD’



- With an efficient immune response, the half-life of a complex may be a few minutes which may **NOT** elicit symptoms
- An overload of antigen or poor immunity, will lead to deposition of large complexes in the tissues and probable symptoms.

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FOOD IMMUNE COMPLEXES

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R. PAGANELLI, R. J. LEVINSKY & D. J. ATHERTON Department of Immunology, The Institute of Child Health, London. Clin. exp. Immunol. (1981) 46, 44-53.

- The formation of an antigen-antibody complex in the circulation is a normal physiological method of antigen elimination.
- However, there is a great deal of evidence suggesting that increased levels of circulating immune complexes are associated with a variety of diseases in which the complexes, once deposited in the tissues, cause damage by activating complement and other effector mechanisms.

Clin. exp. Immunol. (1981) 46, 44-53.

Detection of specific antigen within circulating immune complexes: validation of the assay and its application to food antigen-antibody complexes formed in healthy and food-allergic subjects

R. PAGANELLI, R. J. LEVINSKY & D. J. ATHERTON Department of Immunology, The Institute of Child Health, London (Accepted for publication 17 April 1981)

SUMMARY

A simple two-step method for the detection of specific antigen within immune complexes is described. The immune complexes are precipitated from serum by polyethylene glycol, dissociated by incubation in acid pH buffer and adsorbed onto the surface of polystyrene tubes. The antigen is detected by the binding of a radio-labelled affinity-purified specific antibody. The assay can detect the antigen within both antigen- and antibody-excess immune complexes of any immunoglobulin class, and can also allow semiquantitative comparison of different samples. Immune complexes containing food proteins antigen after eating have been found in the serum of both normal subjects and atopic patients; the latter group showed higher mean levels of antigen-specific immune complexes. The method can be adapted for large-scale screening of clinical samples for suspected antigens if suitable antisera are available.

INTRODUCTION

Circulating soluble immune complexes (IC) are thought to play a role in a variety of diseases (WHO, 1977). These include systemic lupus erythematosus, certain forms of glomerulonephritis, rheumatoid arthritis, chronic inflammatory bowel disease, certain malignancies as well as parasitic infections. They have also been described in healthy subjects and in physiological conditions such as pregnancy (Masson, Didier & Cambien, 1977). The fact that immune complexes are found in such diverse clinical conditions indicates their heterogeneity and indeed such differences in immunoglobulin class, complement-binding capacity as well as size have been described in different diseases (Levinsky & Soothill, 1979). The great variety of methods used for the detection of immune complexes depend on these different physicochemical or biological properties. Hence, some characterization of immune complexes in disease can be achieved by using several methods in combination, but to date none of these have reliably been able to detect the antigen within the immune complex. Recently we have become interested not only in immune response to antigens entering the host through the gastrointestinal mucosal surface but also in the mechanisms whereby food antigen entry fails to elicit damaging reactions in normal individuals. It is well recognized that the gut mucosa is not completely impermeable to macromolecules (Walker & Isenbacher, 1974) and that the amounts absorbed are sufficient to immunize (Peterson & Gowd, 1963) since low levels of antibodies to food antigens may be detected in most healthy subjects (May et al., 1977). The

Correspondence: Dr R. J. Levinsky, Department of Immunology, The Institute of Child Health, 30 Guilford Street, London WC1N 1EH. 0009-916X/1981/0046-0044\$2.00 © Blackwell Scientific Publications



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Severance EG, Gressitt KL, Halling M, Stallings CR, Origoni AE, Vaughan C, Khushalani S, Alaedini A, Dupont D, Dickerson FB, Yolken RH. Neurobiol Dis. 2012 Dec;48(3):447-53. doi: 10.1016/j.nbd.2012.07.005. Epub 2012 Jul 16.

- In conclusion, a significant portion of C1q activation in non-recent onset schizophrenia can be attributed to the formation of immune complexes with the food antigens, milk caseins and wheat gluteins.
- Our data provide a starting point to examine if perinatal exposure to food antigens in susceptible individuals represents a plausible means by which C1 activation could ultimately result in symptoms and behaviour characteristic of schizophrenia.



Complement C1q formation of immune complexes with milk caseins and wheat gluteins in schizophrenia

Emily C. Severance^{1,2}, Kaitlin L. Gressitt¹, Meredith Halling¹, Cassie R. Stallings³, Andrea E. Origoni⁴, Crystal Vaughan¹, Sunil Khushalani¹, Armin Alaedini¹, Didier Dupont¹, Faith B. Dickerson¹, Robert H. Yolken¹

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ABSTRACT

Immune system factors including complement pathway activation are increasingly linked to the etiology and pathophysiology of schizophrenia. Complement protein, C1q, binds to and helps to clear immune complexes composed of immunoglobulins against antigens. The antigen excess (AE) immune complexes and wheat gluten have been reported in individuals with schizophrenia. Here, we assessed the extent to which these food antigens might precipitate the immune complexes of complement C1q in serum from individuals with schizophrenia (n = 38), non-recent onset schizophrenia (n = 42), and non-psychiatric controls (n = 42). C1q precipitated from the serum of individuals with schizophrenia, non-recent onset schizophrenia (OR = 8.82, p < 0.008), non-recent onset schizophrenia (OR = 3.13, p < 0.03) compared to controls. Specific immune complexes composed of C1q, wheat gluten, and casein were detected in the serum of individuals with schizophrenia (OR = 10.1, p < 0.001) compared to controls. C1q precipitated from the serum of individuals with schizophrenia with more casein- or non-gluten-related antigens, the presence of C1q antibodies, and a diminished amount of immune complex complement. In conclusion, complement activation may be a useful biomarker to diagnose schizophrenia early during the course of the disease. Future prospective studies should evaluate the impact of casein- and gluten-free diets on C1q activation in schizophrenia.

Introduction

Immune system factors are becoming increasingly linked to the etiology and pathophysiology of complex neurodevelopmental brain disorders such as schizophrenia and autism (Kasper et al., 2010; Brown, 2011; Brown and Patterson, 2011; Cohen, 1981; Origoni et al., 2011; Barch and Lendvai, 2002; Nevo and Yirmey, 2011; So et al., 2006; Selman et al., 2008; Yolken and Torrey, 2008).

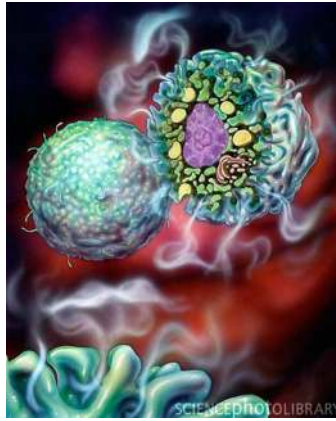
We have reported strong associations between schizophrenia and a variety of infectious disease and food-derived antigens (Yolken et al., 2010, 2010; Lander et al., 2006; Yolken et al., 2006; Severance et al., 2010a, 2011a, 2012; Yolken and Torrey, 2008). If antigenic exposure plays a role in the pathogenesis of schizophrenia, we might expect that immune responses involved in early stages of antigen clearance are also affected.

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IgG & MAST CELL ACTIVATION?

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Mast cells are found in connective tissue and basophils are a type of white blood cell.

They contain histamine and other mediators, used for fighting infection

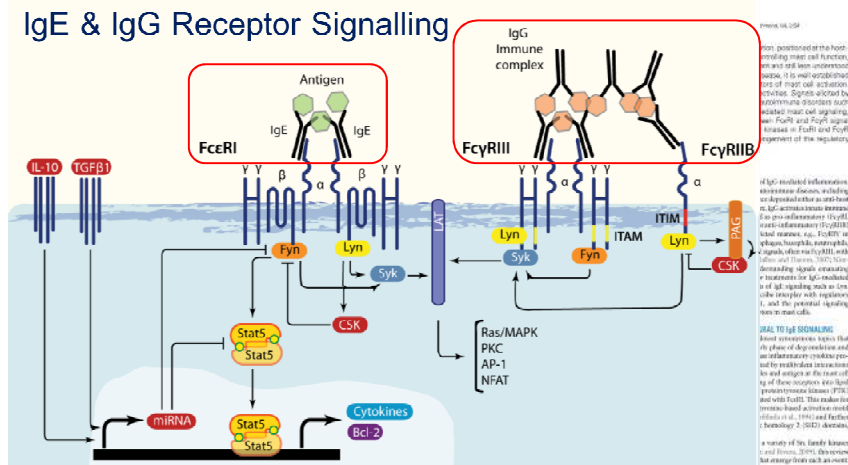


IgG & MAST CELL ACTIVATION?

Pullen NA, Falanga YT, Morales JK, Ryan JJ. *Front Immunol.* 2012 May 11;3:117. doi: 10.3389/fimmu.2012.00117. eCollection 2012. PMID: 22593761

Frontiers in Immunology
 REVIEW ARTICLE
 The Fyn-STAT5 pathway: a new Frontier in IgE- and IgG-mediated mast cell signaling

IgE & IgG Receptor Signalling



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MAST CELL INVOLVEMENT IN INFLAMMATORY DISEASE

● Strong association
● Medium association
● Weak association

Biochim Biophys Acta. 2012 January ; 1822(1): 21–33.

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MECHANISM OF IgG FOOD INTOLERANCE

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What diseases and conditions have been associated with raised levels of food IgG antibodies?

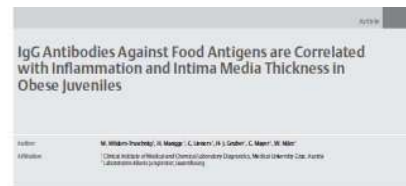


INFLAMMATION & OBESITY

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Wilders-Truschig M, Mangge H, Lieners C, Gruber H, Mayer C, März W. *Exp Clin Endocrinol Diabetes*. 2008 Apr;116(4):241-5. Epub 2007 Dec 10. PMID: 18072008

- Obese children have significantly higher IgG antibody values directed against food antigens than normal weight children.
- Anti-food IgG antibodies are tightly associated with low grade systemic inflammation.
- These findings raise the possibility, that anti-food IgG are pathogenically involved in the development of obesity and atherosclerosis.



Abstract
 Objective: Systemic low grade inflammation may contribute to the development of obesity, insulin resistance, diabetes mellitus and atherosclerosis. We evaluated the association between IgG antibodies specific for food components, low grade inflammation and early atherosclerosis in obese and normal weight juveniles.
 Methods: Methods and Procedures: We determined IgG antibodies directed against food antigens, C-reactive protein (CRP) and the thickness of the intima-media layer (IMT) of the carotid arteries in 32 obese children and in 36 normal weight children.
 Results: Obese juveniles showed a highly significant increase in IMT ($p < 0.0001$), CRP values ($p < 0.0001$) and anti-food IgG antibody concentrations ($p < 0.0001$) compared to normal weight juveniles. Anti-food IgG showed tight correlations with CRP ($r = 0.5533; p < 0.0001$) and IMT ($r = 0.5000; p < 0.0001$) and remained highly significant in a multiple regression model.
 Discussion: We show here that obese children have significantly higher IgG antibody values directed against food antigens than normal weight children. Anti-food IgG antibodies are tightly associated with low grade systemic inflammation and with the IMT of the carotid arteries. These findings raise the possibility that anti-food IgG is pathogenically involved in the development of obesity and atherosclerosis.



FOODPRINT AND INFLAMMATION STUDY

Average Drop 53.3%

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Patient ID	Received Date	Result mg/L	Grade	Received Date	Result mg/L	Grade	% Drop
55195	09/11/2015	1.2	2	08/02/2016	1.2	2	4.5
55196	09/11/2015	3.3	4	29/02/2016	0.4	1	87.1
55197	09/11/2015	4.7	4	10/02/2016	0.5	2	88.7
55202	09/11/2015	1.5	3	10/02/2016	1.1	2	24.4
55205	09/11/2015	3.6	4	22/02/2016	1.0	2	70.7
55206	09/11/2015	1.8	3	22/02/2016	0.8	2	58.3
55210	09/11/2015	7.6	4	16/03/2016	6.1	4	19.8
55355	16/11/2015	5.1	4	10/02/2016	4.8	4	5.7
55482	23/11/2015	3.6	4	14/03/2016	2.0	3	45.7
55483	23/11/2015	2.8	3	08/02/2016	0.7	2	74.6
55490	23/11/2015	1.0	2	22/02/2016	0.6	2	41.2
57101	22/02/2016	1.5	3	22/02/2016	0.4	1	73.9
57479	09/03/2016	2.1	3	23/05/2016	0.5	1	73.8
57486	09/03/2016	3.7	4	25/05/2016	2.1	3	42.5
57558	14/03/2016	7.8	4	23/05/2016	0.9	2	88.5
57397	07/03/2016	9.3	4	23/05/2016	0.5	1	94.8
57478	09/02/2016	5.2	4	25/05/2016	1.7	3	66.7
*56504	23/03/2016	3.7	4	25/05/2016	4.1	4	+10.9
57900	04/04/2016	3.7	4	GP Result	2.6	3	30.5

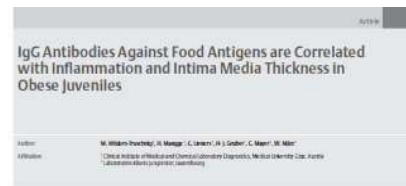
	GRADE	RISK
Grade 1 / 2		Low Risk
Grade 3		Moderate Risk
Grade 4		High Risk



INFLAMMATION & OBESITY

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Wilders-Truschig M, Mangge H, Lieners C, Gruber H, Mayer C, März W. Exp Clin Endocrinol Diabetes. 2008 Apr;116(4):241-5. Epub 2007 Dec 10. PMID: 18072008



atherosclerosis. Especially, as described for the IBS above, a dietary elimination therapy based on the presence of IgG antibodies to food components may be indicated. Such a dietary therapy may be effective in reducing low grade inflammation and thereby preventing clinical consequences like type 2 diabetes and atherogenesis.

Obese juveniles showed a highly significant (P < 0.001) elevated CRP (> 5.0001) and anti-food IgG antibody levels (> 0.2001) compared to normal juveniles. Anti-food IgG showed high correlation with CRP (> 0.5001+0.5001 and > 0.5001+0.5001) and correlated highly to a multiple regression model. We show here that obese children with elevated IgG antibody levels against food antigens show moderate inflammation. IgG antibodies are associated with low grade inflammation and with the IMT of the carotid arteries. These findings indicate that anti-food IgG is pathogenetically involved in the development of obesity and atherosclerosis.



Food Intolerances in Athletes – Understanding the Performance Impact

<http://www.runtothefinish.com/2014/09/food-intolerances-in-athletes.html>

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Impacts on the athlete:

- Increased inflammation results in muscle soreness and slows down recovery time
- Increases stress on the body leading to fatigue as the body needs more rest
- Prevents nutrients from being fully absorbed
- Weakens the immune system.
- Causes weight gain
- Can impact breathing by inflaming the air ways



IgG WEIGHT and Quality of Life

Lewis, Woolger, Melillo, Alonso et al. Obesity & Weight loss Therapy 2012 2:1

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- 120 subjects with a mean age of 45.5 and BMI of 20> avoided positive foods for 90 days
- Body composition, blood pressure & quality of life measured at baseline 30,60 and 90 day follow up.
- On average participants lost 1lb a week and 3 inches from the waist Reduction in weight, BMI, waist and hip circumferences, blood pressure
- Improvements in all indicators of quality of life including mental quality.

Lewis et al. • Obesity and Weight Loss Therapy 2012, 2:1
http://dx.doi.org/10.1186/1745-0213-2-1

Obesity & Weight Loss Therapy

Research Article

Eliminating Immunologically-Reactive Foods from the Diet and its Effect on Body Composition and Quality of Life in Overweight Persons

John E. Lewis¹, Josh M. Woolger¹, Angeline Melillo¹, Yvonne Alonso¹, Spencer Melillo¹, Sarah R. Jones¹, David Kamali¹, Andrea Sandoz¹, Thomas A. Smith¹, David Long¹, Heidi Galloway¹, Kathy Stender¹ and Janet Tomlinson^{1*}

¹Department of Physical Education, University of North Carolina at Greensboro, Greensboro, NC, USA

Abstract

Background: Observe the relationship between chronic disease and poor nutritional habits, using strategies to address the issue of poor health in the U.S. to improve the quality of overweight people's health. The goal is to reduce the risk of chronic disease by eliminating immunologically-reactive foods from the diet. The goal is to reduce the risk of chronic disease by eliminating immunologically-reactive foods from the diet. The goal is to reduce the risk of chronic disease by eliminating immunologically-reactive foods from the diet.

Objective: The study assessed the effect of an IgG-mediated food sensitivity diet in combination with a food elimination diet on body composition and secondary outcomes in people who wanted to lose weight and were overweight.

Methods: A total of 120 subjects aged 18 and over took part in the study. Subjects had to eliminate all reaction foods from their diet for 90 days. Study participants: Body composition, blood pressure, and quality of life were measured at baseline and 30, 60, and 90-day follow-up.

Results: Subjects who eliminated IgG-mediated reaction foods from their diet had reductions in weight, body mass index, waist and hip circumferences, body fat, blood pressure, and improvements in all indicators of quality of life measured at the 30, 60, and 90-day follow-up.

Conclusions and Context: Subjects were able to improve their body composition and quality of life by removing immunologically-reactive foods from their diet. This trial was registered at ClinicalTrials.gov (NCT01212121).

Keywords: Food Sensitivity Testing, Elimination Diet, Obesity, Quality of Life

Introduction

Chronic diseases, such as cardiovascular disease, obesity, and diabetes, account for the majority of deaths in the U.S. each year, and the cost of these diseases accounts for more than 70% of the national medical cost [1]. In addition, behavioral trends such as poor diet and lack of physical activity are the leading causes of chronic disease. These trends have significant dietary behaviors in the case and prevention of health and disease, including obesity and heart disease. Thus, the best strategy for improving the health of the nation and reducing the number and cost of chronic diseases lies in changing behaviors and eating habits.

Chronic disease and obesity in the adult population is a result of different predispositions, although the degree of the effect of age factors may vary from person to person. Many people believe that dietary habits contribute to their condition, and some also believe that dietary habits, although not necessarily cause their condition, may worsen their condition. Both have the diet may be beneficial. Determining how diet affects the body is difficult due to the complexity of diet, which includes the amount and variety of food consumed, the timing of meals, and the individual's genetic, hormonal, and lifestyle characteristics. The diet may affect the body in a number of ways, including the amount and variety of food consumed, the timing of meals, and the individual's genetic, hormonal, and lifestyle characteristics. The diet may affect the body in a number of ways, including the amount and variety of food consumed, the timing of meals, and the individual's genetic, hormonal, and lifestyle characteristics.

Discussion: Immunologically-reactive foods may be caused by...

*Corresponding author: John E. Lewis, 1201 S. Main Street, Room 1000, PO Box 26170, Greensboro, NC 27402-6170, USA; Email: lewisj@uncg.edu

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Research Papers

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- Delayed food allergy
- Irritable Bowel Syndrome (IBS)
- Inflammation, obesity & arthritis
- Migraine
- Asthma / respiratory diseases
- Crohn's disease
- Behaviour problems (schizophrenia & autism)

Research Article
Antibodies against Food Antigens in Patients with Anitistic Spectrum Disorders

Laura de Niz, Ana Carolina, Fabiana de Aguiar, Maria Pia Braga, Ana Sampaio, Rita Cordeiro, Sebastião Abrahão, Nilda Mendes, Karen M. Laurson, Cláudia Schmidt, Patrícia Luciani, Inês Moreira, Carlos Teixeira, Gláucia Franca, Antonia Paschoa, and Carolina Botelho

Abstract
 The aim of this study was to evaluate the presence of antibodies against food antigens in patients with anitistic spectrum disorders (ASDs). The study included 100 patients with ASDs (50 with autism spectrum disorder [ASD] and 50 with Asperger's disorder [AS]) and 100 healthy controls. The results showed that the prevalence of antibodies against food antigens was significantly higher in the ASD group compared to the healthy controls. The most common antibodies were against egg, milk, and wheat. The results suggest that food allergies are more prevalent in patients with ASDs, which may contribute to the development of these disorders.



DELAYED ALLERGY

Dixon HS. Otolaryngol Head Neck Surg. 2000 Jul;123(1 Pt 1):48-54. PMID: 10889481

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- Elimination of IgG positive foods is successful in significantly decreasing symptoms
- In all 80 patients studied 71% achieved a 75% or greater improvement level

Treatment of delayed food allergy based on specific immunoglobulin G RAST testing

HAMILTON S. DIXON, MD, FACS, Georgia

This preliminary, descriptive study after extensive clinical experience demonstrates specific IgG RAST done in 114 consecutive patients with strong positive histories for delayed food allergy. Elimination of the positive foods was the sole means of treatment. The symptoms leading to the food were detailed and the method of workup is reviewed. The overall results demonstrated a 71% success rate for all symptoms achieving at least a 75% improvement level. Of particular interest was the group of patients with chronic, disabling symptoms, unresponsive to other intensive treatments. When as 70% obtained 75% or more improvement, 20% of those patients obtained 100% relief. (Otolaryngol Head Neck Surg 2000;123:48-54)

Food allergy has remained a very controversial subject, especially with pediatricians and traditional allergists. Whereas IAT was once dismissed as a false, discredited, and unproven test, the recent recognition of delayed hypersensitivity reactions in part has led to the use of immunologic testing. The most recent use of immunologic testing has not been made in a single article but in two separate papers. Furthermore, the prevalence of cyclic or delayed food allergy has never been well established in the literature. Thus the clinical standpoint, delayed food allergy has no cause-and-effect relationship. Therefore the symptoms are unresponsive to both parent and pharmacologic therapy, elimination diets, introduction of foods, and other reconstructive measures are usually not helpful. For many years, traditional allergists have used various tests and have paid more for foods, along with intensive testing. Many false-positive and false-negative results have made these tests unreliable, especially only 20% accurate.¹

Challenge testing has been the gold standard for delayed food allergy and was accurate in 70% of cases. Even more difficult is the double-blind placebo-controlled food challenge. Unless exact rules are followed, reproducibility of challenge is low,² and its applicability has led to subsequent use in clinical practice.

Cross-reactive food testing has been shown to be accurate only in well-controlled laboratories with highly trained technicians. Results have often been equivocal, especially in office laboratories. The most precise test, the ALCAT, may hold more promise, but it is still not in general use.

Transcortin-sensitization testing has also been shown to be efficacious in 8 published double-blind studies, with 75% to 80% accuracy demonstrated.³⁻⁸ Completed double-blind studies using a combination of food challenges and provocative-challenge testing on patients with chronic, disabling, and unresponsive allergic symptoms have been reluctant to accept this test because it is not immediately reproducible due to the nature of type III hypersensitivity. This non-occurring test is used by only a small number of allergists. Patient compliance in any practice has been poor because patients must make multiple visits and travel long distances to complete the necessary history of skin tests. This problem has left many patients with incomplete workups and a continuation of confusing symptoms.

Thus there is currently no standardized, accepted test for delayed food allergy. Furthermore, the prevalence of delayed food allergy as a significant cause of illness has not been well reported. It is more traditional allergists are unaware of its importance, referring to this problem as food intolerance, which is regarded as meaningless and is usually thought to be associated with chemical sensitivity caused by additives and food color.

Specific IgG testing for foods has been controversial for several reasons: (1) IgG reflects exposure to the food; (2) IgG levels occur in the normal population;⁹ (3) IgG is a protective antibody; (4) IgG is thought by some to be more specific for classical food allergy than total specific IgG;¹⁰ (5) some food reactions are immunologic; (6) there is little explanation between RAST classes (types) and severity of symptoms;¹¹ (7)



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Table 3. Order of symptom improvement in 80 atopic patients after elimination of positive foods by specific IgG tests

Symptom	No. reported	≥75% improvement	100% improvement
Diarhea	20	90%	45%
Cramps	13	84%	38%
Cough	22	77%	36%
Cervical headache	15	73%	20%
Nausea	17	70%	24%
Burping	13	69%	15%
Hoarseness	20	65%	15%
Throat clearing	29	65%	28%
Nasal drainage	36	63%	17%
Fullness in ears	17	64%	29%
Nasal congestion	40	62%	20%
Asthma	13	61%	15%
Sinus headache	33	60%	24%
Gas	26	57%	12%
Itchy eyes	19	57%	26%
Sneezing	20	55%	20%
Ear popping	11	54%	27%
Watery eyes	15	53%	6%
Fatigue after meals	31	51%	23%
Dizziness	24	50%	21%
Ringing in ears	18	50%	5%
Skin rash	12	50%	8%
Chronic fatigue	25	48%	0%
Migraine headache	19	47%	16%
Itchy skin	14	35%	7%

Symptom not included if reported fewer than 10 times.

Treatment of delayed food allergy based on specific immunoglobulin G RAST testing

HAMILTON S. DIXON, MD, Boca Raton, Florida

This preliminary, descriptive study after extensive clinical experience demonstrates specific IgG food RASTs done in 114 consecutive patients with strong positive histories for delayed food allergy. Elimination of the positive foods was the sole means of treatment. The symptoms leading to the test are detailed, and the method of testing is reviewed. The overall results demonstrated a 71% success rate for all symptoms achieving at least a 75% improvement level. Of particular interest was the group of patients with chronic, disabling symptoms, unresponsive to other alternative treatments. When as 70% obtained 75% or more improvement, 20% of those patients obtained 100% relief. (Cochrane J Allergy Clin Immunol 2002;123:48-54)

Food allergy has remained a very controversial subject, especially with pediatricians and traditional allergists. Thomas Jiff was the first to use RASTs with 1969. However, explaining immediate hypersensitivity, the exact mechanism for delayed hypersensitivity remains in part obscure. The exact role of immune complexes, complement, and IgG in type III delayed hypersensitivity has not been made to a simple extent for the very reason. Furthermore, the prevalence of cyclic or delayed food allergy has never been well established in the literature. From the clinical standpoint, delayed food allergy has an onset-and-effect relationship. Therefore the symptoms go unaccompanied by both gastric and obstructive. History, elimination diets, immunotherapy of foods, and other conservative measures are usually not helpful. For many years, traditional allergists have used various tests and some patients do feel foods, along with absolute testing. Many false-positive and false-negative

From the Department of Otolaryngology-Head and Neck Surgery, University of Miami, Miami, Florida; and the Department of Otolaryngology-Head and Neck Surgery, University of Miami, Miami, Florida. Received at the Annual Meeting of the American Academy of Otolaryngology, San Diego, CA, September 23, 1998. Reprint requests: Hamilton S. Dixon, MD, 1200 North Dixie Hwy, Ste. 200, Boca Raton, FL 33432-2744. Copyright © 2002 by the American Academy of Otolaryngology-Head and Neck Surgery Foundation, Inc. 0007-1226/02/123-0048-07. DOI: 10.1097/00006123-200212300-00048

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MIGRAINE – IgG-MEDIATED?

Julio Pascual and Agustín Oterino. Cephalalgia 0(00) 1–3. International Headache Society 2010

- Increased IgG antibodies and cytokines would lead to an inflammation response, which seems to play an important role in the pathophysiology of migraine attacks.
- Supporting this hypothesis, a recent study has shown that anti-food IgG antibodies in obese juveniles are associated with systemic inflammation
- These data are interesting, as obesity seems to be a risk factor in the development of chronic migraine.

IgG-mediated allergy: A new mechanism for migraine attacks?

Julio Pascual and Agustín Oterino

Despite recent advances offered by modern neuroimaging and genetic techniques, the pathophysiology of migraine has not been fully clarified. As pointed out by Silber and Laine 50 years ago, a series of observations reported that their migraine attacks are usually precipitated by dietary items (1). In a survey analyzing the prevalence of dietary migraines in 500 new migraine patients, Purfield et al found in 1984 that 19.2% of migraine patients reported sensitivity to cheese, 18.2% to chocolate and 11.1% to citrus fruit (2). The same year, Moina et al published a paper in the *Lancet* with the categorical title "Migraine Is a Food-Allergic Disease", describing the treatment of just nine patients with severe refractory migraines with other sodium citrate/ergotamine of placebo after the patients ate foods previously identified as provocations (3). Sodium citrate/ergotamine exerted a protective effect, which made the authors conclude that a food-allergy reaction is the cause of migraines, at least in this group of patients with dietary precipitants. Definitive proof that this is a reproducible fact, however, has proved elusive. In other studies objective evidence of hypersensitivity was found in very few cases, and those reporting a reduction in migraine during formal diets not only include a low number of patients, but mostly make no witness attempt to control the dietary strategy from the patients, pay insufficient attention to placebo effect and include an unreliable prevalence of atopic diseases in migraine patients. One of the obstacles to acceptance of the dietary hypothesis is the lack of a clear scientific explanation of the mechanism implicated in the development of migraine attacks supposedly precipitated by food. The first obvious proposed mechanism was an allergy mediated by IgE antibodies. Theoretically, the interaction of a food constituent with a specific IgE antibody would produce a response by activation of complement or degradation of mast cells. Several independent studies have failed to find elevated IgE levels or complement activation during migraine attacks, even in patients with a history of food-precipitated headaches (4,5).

These results, together with the finding that these patients are usually sensitive to several and different foods, led to the next proposal for a common pathogenic mechanism: antigenic stimulation between these disparate foods seemed less likely than sharing a common chemical constituent (2). Investigators tried to confirm the so-called "amine hypothesis" first by clinical challenge tests with substances like tyramine or phenylethylamine. An elegantly executed by Purfield (5), the results of these studies can be interpreted as inconclusive. The next step was to investigate the amines' metabolic routes. Could the elimination pathways of such amines be deficient in dietary migraine patients? There are two major biosynthetic pathways for these substances in humans: oxidation by monoamine oxidase (MAO) to phenylethylamine/tyramine acid and naphthol by phenylethylamine/tyramine to water-soluble conjugates. MAO, a mitochondrial enzyme, exists in two forms in humans, with different substrate specificities. MAO-A predominates in gut, muscle and liver and preferentially inactivates catecholamines and serotonin. The human placenta contains both MAO-A, which metabolizes phenylethylamine, benzylamine and methylhistamine. Tyramine and dopamine are substrates for both forms (6). The ready availability of placental led to MAO-B being the only form to be studied in migraine patients. Many studies have found a low placental MAO-B activity but only during migraine attacks, both in dietary and non-dietary patients (5). The significance of these findings remains uncertain. The explanation route has also been explored in migraine patients. A reduced urinary output of naphthol tyramine metabolites after an oral tyramine load in subjects with food-sensitive migraine



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IBS AND MIGRAINE

Aydinlar EI, Dikmen PY, Tiftikci A, Saruc M, Aksu M, Gunsoy HG, Tozun N. *Headache*. 2013 Mar;53(3):514-25. Epub 2012 Dec 6. PMID: 23216231

- **Conclusions:** Our findings indicate that food elimination based on IgG antibodies in migraine patients who suffer from concomitant IBS may effectively reduce symptoms from both disorders with possible positive impact on the quality of life of the patients as well as potential savings to the health-care system.

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Research Submission

IgG-Based Elimination Diet in Migraine Plus Irritable Bowel Syndrome

Elif Başar Aydınlar, MD, Pinar Yalınay Dikmen, MD, Ayşe Tiftikçi, MD, Murat Saruc, MD, Murat Aksoy, Hülya G. Gencer, Neriman Tozun, MD

Objectives.—To evaluate therapeutic potential of the immunoglobulin G (IgG)-based elimination diet among migraine patients with irritable bowel syndrome (IBS).

Background.—Food elimination has been suggested as an effective and inexpensive therapeutic strategy in patients with migraine and concomitant IBS in the past studies.

Methods.—A total of 21 patients (mean [standard deviation] age: 36.8 [12.2] years; 85.7% females) diagnosed with migraine and IBS were included in this double-blind, randomized, controlled, crossover clinical trial composed of baseline control diet, one diet (elimination or provocation diet), and second diet (interchange of elimination or provocation diet).

Results.—IgG antibody titer against 276 food allergens revealed mean (standard deviation) titer/total titer to be 2.13 (14.1). Compared with baseline levels, elimination diet per se was associated with significant reductions in attack count (4.8 [2.1] vs 2.7 [2.0], $P < .001$), maximum attack duration (2.4 [0.4] vs 1.1 [1.1] days, $P < .001$), mean attack duration (1.8 [0.2] vs 1.1 [0.3] days, $P < .001$), maximum attack severity (visual analog scale: 6.1 [1.4] vs visual analog scale: 4.5 [0.5], $P < .001$), and number of attacks with acute medication (4.4 [1.5] vs 1.9 [1.8], $P < .001$). There was a significant reduction in pain-relieving severity (1.8 [1.3] vs 1.2 [0.6], $P < .05$), pain-relieving within the first 16 days (1.2 [0.5] vs 1.1 [1.1], $P < .05$), and improvement obtained in quality of life (1.4 [1.4] vs 1.2 [1.8], $P < .05$) by the elimination diet as compared with provocation diet.

Conclusions.—Our findings indicate that food elimination based on IgG antibodies in migraine patients who suffer from concomitant IBS may effectively reduce symptoms from both disorders with possible positive impact on the quality of life of the patients as well as potential savings to the health-care system.

Key words: migraine, irritable bowel syndrome, elimination diet, immunoglobulin G antibody, food antigen

(Headache March 2013;53:514-25)

From the Department of Neurology, Ahi Evran University School of Medicine, Istanbul, Turkey (E. Aydınlar and P. Y. Dikmen); Department of Gastroenterology, Ahi Evran University School of Medicine, Istanbul, Turkey (A. Tiftikçi, M. Saruc, and N. Tozun); Department of Nutrition and Dietetics, Ahi Evran Health Group, Istanbul, Turkey (M. Aksoy and H. G. Gencer).

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Accepted for publication October 1, 2012.

Conflict of Interest: The authors declare that they have no conflict of interest.

Funding: The study is supported by Immuno Diagnostic Laboratories, Istanbul, Turkey.

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What is the current medical opinion about IgG ?



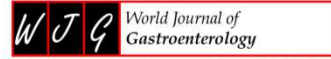


IBS: A ROLE FOR IgG

Mansueto P, D'Alcamo A, Seidita A, Carroccio A. World J Gastroenterol. 2015 Jun 21;21(23):7089-109. Review. PMID: 26109796

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- Irritable bowel syndrome (IBS) is one of the most common GI disorders, having a prevalence of 12%-30%.
- Most patients with IBS attribute their symptoms to adverse food reactions.
- Review of publications (1966 to 2015)
- Studies reported that serum IgG levels are higher in patients with IBS and food allergy history, perhaps related to an inflamed or "leaky" gut.
- Hypersensitivity reactions may play a role in causing IBS symptoms in a subset of patients.



World J Gastroenterol 2015 Jun 21; 21(23): 7089-109

Food allergy in irritable bowel syndrome: The case of non-celiac wheat sensitivity

Pasquale Mansueto, Alberto D'Alcamo, Aurelio Seidita, Antonio Carroccio

Abstract
Irritable bowel syndrome (IBS) is one of the most common gastrointestinal disorders, having a prevalence of 12%-30% in the general population. Most patients with IBS attribute their symptoms to adverse food reactions. We review the role of diet in the pathogenesis of IBS and the importance of dietary factors in the management of these patients. The MEDLINE electronic database (1966 to Jan 2015) was searched using the following keywords: "food", "diet", "food allergy", "food hypersensitivity", "food intolerance", "IBS", "epidemiology", "pathogenesis", "pathophysiology", "diagnosis", "treatment". We found 153 eligible papers, 80 were excluded because: not written in English, exclusive biochemical and experimental research, case reports, reviews, and research otherwise not relevant to our specific interest. We selected 73 papers: 43 original papers, 20 reviews and 4 letters to the editor. These papers focused on IBS pathogenesis, the association between IBS and allergy, and between IBS and food allergy; the relationship between IBS and non-celiac wheat sensitivity; the role of diet in IBS. Pending further scientific evidence, a cautious approach is advisable but the concept of food allergy should be included as a possible cause of IBS, and a dietary approach may have a place in the routine clinical management of IBS.

Key words: Irritable bowel syndrome; Food allergy; Food intolerance; Non-celiac wheat sensitivity; Allergy; Allergic; Elimination diet

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Case Up: Starting from the late evidence about the non-celiac wheat sensitivity, we reviewed the role of diet in the pathogenesis of irritable bowel syndrome and the importance of dietary factors in the management of these patients. We found 153 papers about the matter, selecting 73 for review. We concluded that food allergy could be a possible cause of irritable bowel syndrome, and a dietary approach should be implemented in clinical practice.

WJG | www.wjg.com 7089 June 21, 2015 | Volume 21 | Issue 23



IBS: A ROLE FOR IgG

Mansueto P, D'Alcamo A, Seidita A, Carroccio A. World J Gastroenterol. 2015 Jun 21;21(23):7089-109. Review. PMID: 26109796

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- Patients might have selective gut permeability to food allergens. The increase of food-specific IgG titers could be a specific reaction, rather than a non-specific response to increased gut mucosal permeability.
- Pending further scientific evidence, a cautious approach is advisable but the concept of food allergy should be included as a possible cause of IBS, and a dietary approach may have a place in the routine clinical management of IBS.



World J Gastroenterol 2015 Jun 21; 21(23): 7089-109

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Pasquale Mansueto, Alberto D'Alcamo, Aurelio Seidita, Antonio Carroccio

Abstract
Irritable bowel syndrome (IBS) is one of the most common gastrointestinal disorders, having a prevalence of 12%-30% in the general population. Most patients with IBS attribute their symptoms to adverse food reactions. We review the role of diet in the pathogenesis of IBS and the importance of dietary factors in the management of these patients. The MEDLINE electronic database (1966 to Jan 2015) was searched using the following keywords: "food", "diet", "food allergy", "food hypersensitivity", "food intolerance", "IBS", "epidemiology", "pathogenesis", "pathophysiology", "diagnosis", "treatment". We found 153 eligible papers, 80 were excluded because: not written in English, exclusive biochemical and experimental research, case reports, reviews, and research otherwise not relevant to our specific interest. We selected 73 papers: 43 original papers, 20 reviews and 4 letters to the editor. These papers focused on IBS pathogenesis, the association between IBS and allergy, and between IBS and food allergy; the relationship between IBS and non-celiac wheat sensitivity; the role of diet in IBS. Pending further scientific evidence, a cautious approach is advisable but the concept of food allergy should be included as a possible cause of IBS, and a dietary approach may have a place in the routine clinical management of IBS.

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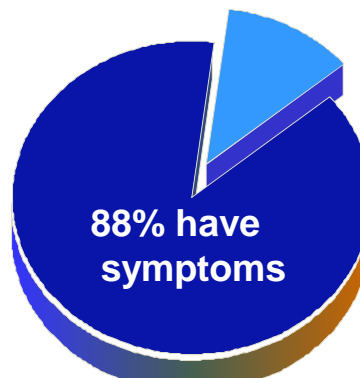
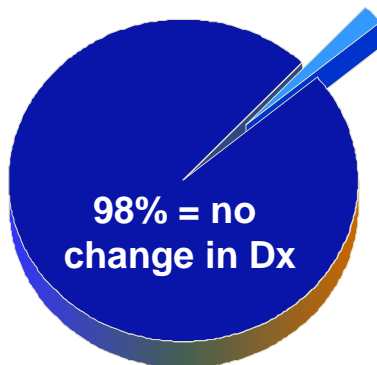
WJG | www.wjg.com 7089 June 21, 2015 | Volume 21 | Issue 23



IBS PROGNOSIS

Heaton, Thompson. Irritable Bowel Syndrome. 1999 Health Press, Oxford

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IgG EVALUATION

Mullin GE, Swift KM, Lipski L, Turnbull LK, Rampertab SD. Nutr Clin Pract. 2010 Apr;25(2):192-8. Review. PMID: 20413700

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- Literature review (2010) evaluating the validity of tests used to assess food reactions
- Food hypersensitivity, food allergy, food sensitivity, food intolerance testing and adverse food reactions
- IgG-based testing showed promise, with clinically meaningful results
- Proven useful as a guide for elimination diets
- Further investigation into the clinical application is required

Techniques, Materials, Devices

Testing for Food Reactions: The Good, the Bad, and the Ugly

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An increasing number of commercial tests for food allergies are marketed to consumers and healthcare practitioners with unproven claims. The aim of this article is to provide an evidence-based review of the tests and procedures that currently are used for patients with suspected food allergy. A systematic review of the literature evaluating the validity of tests and procedures used in food reactions was performed using conventional search engines (eg, PubMed, CINAHL) as well as consumer sites (eg, Google, Bing). The National Library of Medicine Medical Subject Headings (MeSH) terms food hypersensitivity was used along with food allergy testing, food sensitivity testing, food intolerance testing, and adverse food reactions. Of the results obtained, testing for immunoglobulin E (IgE)-mediated food allergy was best represented in PubMed. IgE-based testing continues to be the gold standard for suspected food allergies. Among modalities used by many conventional and

alternative practitioners, immunoglobulin G (IgG)-based testing showed promise, with clinically meaningful results. It has been proven useful as a guide for elimination diets, with clinical impact for a variety of diseases. Molecular release testing and antigen leukocyte cellular antibody testing were only reported on consumer sites. Further investigation into the validity and the clinical application of these tests and procedures is required. Discussing the basis for food reactions continues to present a diagnostic challenge, and testing for food allergies in the context of an appropriate clinical history is paramount to making the correct diagnosis. (Nutr Clin Pract 2010;25:192-198)

Keywords: food sensitivity; food hypersensitivity; allergy and immunology; immunoglobulin E; immunoglobulin G; skin tests

More than 50 million Americans suffer from allergies yearly. Allergy, ranking as the sixth leading cause of chronic disease in the United States, was responsible for a staggering \$18 billion U.S. healthcare expenditures in 2001.¹ Of those with allergies, up to 25% of adults report symptoms that may be related to foods. However, testing for food reactions can be challenging for both the patient and the clinician. Many healthcare practitioners have not received formal training in allergy and immunology and, as a result, may not be familiar with the proper application and interpretation of available test results.

In the context of the clinical history, both serum antibodies and allergy skin testing can be of considerable assistance in identifying (or excluding) the particular allergens that may be causing the patient's

symptoms. Numerous tests are available on the market and are being used by conventional and alternative practitioners to assess for food reactions. There are 2 main categories of tests available: allergy skin tests (skin prick testing) and measurements of allergen-specific antibodies from blood. We review the various tests along with the published evidence for food reactions for the clinician.

Food Allergies

A food allergy is typically defined as an adverse immune response to the proteins in a food. This may occur as the result of a humoral response (immunoglobulin E [IgE] antibodies), a cellular response (ie, T cells), or both. IgE-mediated food allergies affect between 1% and 2% of individuals in the U.S. and United Kingdom, specifically, these allergies are seen in 1% of adults and 6%-8% of children.² The prevalence of food allergies in American children seems to be on the rise, now affecting 3 million children, according to the Centers for Disease Control and Prevention.³ Certain foods are more common allergens among specific age groups, accounting for the majority of immediate food allergies in young children

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ALLERGY VS INTOLERANCE

- Introduction
- Definitions
- Antibodies
- Significance
- IgG vs IgG4
- Mechanisms
- Inflammation
- Diseases
- Developments

Conclusion 10

Category	Allergy	Intolerance
Food	e.g. peanut, shellfish	e.g. gluten, dairy
Mediated	IgE antibodies	IgG antibodies
Rate of Response	Immediate after ingestion	Delayed up to 72 hrs after ingestion
Mechanism	Rapid production of histamine	Gradual formation of Ag/Ab complexes
Symptoms	Classical 'allergic' response	Many symptoms affecting any part of the body
Severity	Can be fatal	Not life-threatening
Permanence	Can last lifetime	Can be reversed or reduced by elimination of foods
Diagnosis	Often self-diagnosed	Rarely self- diagnosed
Skin-prick test	Positive	Negative



CHARACTERISTICS OF IgE & IgG MEDIATED REACTIONS TO FOOD

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Conclusion 10

IgE Mediated - Allergy	IgG Mediated - Intolerance
Incidence is relatively low	Incidence is relatively high
Result from infrequent exposure	Result from frequent exposure
Very predictable short term symptoms	Chronic, variable symptoms
Offending food is usually obvious	Offending food frequently not suspected
Basophil/Mast Cell triggered reactions	Immune complex trigger
Histamine/Leukotriene release	Inflammatory response
Patient aware of offending food	Patient rarely aware of offending food
Antibody persistent for years	Antibody declines within one month
In vitro testing for serum IgE confirmation	In vitro testing for serum IgG shows food offenders and extent of gut permeability
Permanent food avoidance & immunotherapy	Eliminate then rotate food(s), heal gut, improve digestion



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