FOOD REACTIONS
The Facts

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WHAT’S IN A NAME?

- Food Allergy
  - Only IgE reactions are considered true food allergies.

- Food Intolerance
  - Not a true food allergy: could be enzyme deficiency, chemical reactions, aversion. May also refer to IgG-mediated reactions or other immune reactions to food.

- Food Sensitivity
  - Not true food allergy: could be enzyme deficiency, chemical reactions, aversion. May also refer to IgG-mediated reactions or other immune reactions to food.
DEFINITIONS

- **Antigen** is any substance that elicits antibody production.
- **Allergen** is any substance that causes an allergy (IgE).
- **Immunoglobulin** and **antibody** are terms used interchangeably. There are 5 major immunoglobulins:
  - IgE – only 1 to 2 % of immunoglobulins are IgE
  - IgG – most abundant in serum, crosses placenta
  - IgA – immunoglobulin produced in greatest numbers in a day. Found in mucous membranes
  - IgM - produced at onset of infections
  - IgD – function not well understood
Major immunoglobulin-mediated food reactions

- IgE – Type I hypersensitivity reaction (Immediate)
- IgG – Type III hypersensitivity reaction (Delayed)
- IgA – mucosal damage (Delayed)
FOOD ALLERGY: TYPE I HYPERSENSITIVITY

- IgE mediated
- Rapid onset
  - Immediate onset
  - Immediate plus late phase
- Observable reactions
  - hives
  - anaphylaxis

Wiki - public
### Symptoms associated with IgE Food Reactions

<table>
<thead>
<tr>
<th>Respiratory</th>
<th>Skin</th>
<th>Digestive</th>
</tr>
</thead>
<tbody>
<tr>
<td>• laryngeal edema</td>
<td>• eczema</td>
<td>• abdominal cramping</td>
</tr>
<tr>
<td>• asthma / wheezing</td>
<td>• angioedema</td>
<td>• nausea</td>
</tr>
<tr>
<td>• rhinitis, ↑ mucous secretion</td>
<td>• acute urticaria</td>
<td>• vomiting</td>
</tr>
<tr>
<td>• lip, tongue swelling</td>
<td></td>
<td>• diarrhea</td>
</tr>
<tr>
<td>• oral allergy syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• sneezing</td>
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</tr>
</tbody>
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*World Allergy Organization*
FOOD SENSITIVITY: TYPE III HYPERSENSITIVITY - IgG

- Type III hypersensitivity is an IgG mediated reaction caused by the deposition of antigen: antibody immune complexes at tissue sites.

- With excess antigen, small complexes tend to deposit in blood vessel walls where they can cause tissue injury.

*Circulating IgG antibodies encounter food antigens & form circulating immune complexes (CICs)*

*CICs can deposit in tissue and release inflammatory cytokines*

FOOD SENSITIVITY: TYPE III HYPERSENSITIVITY - IgG

- Half-life of IgG is 23 to 96 days in serum
- IgG antibodies form ~ 30 days after antigen recognition
- 4 sub-types of IgG:
  - IgG₁  IgG₂  IgG₃  IgG₄
  - IgG₄ may be protective against IgE reactions

# Symptoms Associated with IgG Food Reactions

<table>
<thead>
<tr>
<th>Systemic</th>
<th>Skin</th>
<th>Lungs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Rashes</td>
<td>Food-induced bronchitis, asthma</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Redness</td>
<td></td>
</tr>
<tr>
<td>Sweating</td>
<td>Swelling</td>
<td></td>
</tr>
<tr>
<td>Chills</td>
<td>Scaling (eczema, psoriasis)</td>
<td></td>
</tr>
<tr>
<td>Weakness</td>
<td>Thickening of skin</td>
<td></td>
</tr>
<tr>
<td>Reduced tolerance for exertion</td>
<td>Pruritus</td>
<td></td>
</tr>
</tbody>
</table>

SYMPTOMS ASSOCIATED WITH IgG REACTIONS

**Digestive**
- Abdominal pain
- Bloating
- Nausea
- Vomiting
- Diarrhea

**Brain**
- Disordered thinking/feeling
- Memory disturbances
- Behavioural problems

**Musculoskeletal**
- Food-allergic arthritis
- Pain
- Stiffness
- Swelling

## Comparing IgE and IgG

<table>
<thead>
<tr>
<th>Consideration</th>
<th>Immunoglobulin E</th>
<th>Immunoglobulin G</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of reaction</td>
<td>Rapid</td>
<td>Delayed</td>
</tr>
<tr>
<td>Duration of reaction</td>
<td>Brief (hours)</td>
<td>Prolonged (days to weeks)</td>
</tr>
<tr>
<td>Origin of response</td>
<td>Mast cells</td>
<td>Circulating immune complexes (CICs) macrophage overload</td>
</tr>
<tr>
<td>Food that trigger</td>
<td>Any food</td>
<td>Commonly consumed foods</td>
</tr>
<tr>
<td>Food quantity</td>
<td>Small amount of food can trigger response</td>
<td>Dose dependent - more reactive food means bigger reaction</td>
</tr>
<tr>
<td>Patient awareness</td>
<td>Subject usually aware of food trigger</td>
<td>Subjects usually unaware of food trigger</td>
</tr>
<tr>
<td>Persistence</td>
<td>Reactions may persist for life or resolve spontaneously</td>
<td>Symptoms may occur for months after elimination of reactive foods</td>
</tr>
</tbody>
</table>

*Adapted from Nutr Clin Pract. 2010;25(2):192-98*
LABORATORY TESTS FOR FOOD ALLERGY / SENSITIVITY

- IgE
  - *In vivo*
  - *In vitro*

- IgG
  - *In vitro*
Testing for Food Reactions – IGE

In vivo

- Skin prick test
  - Looking for histamine response
  - 90% sensitivity, 50% specificity
- Oral food challenge (DBPCFC)
  - Hospitals or allergy clinics only

Waserman and Watson Allergy, Asthma & Clinical Immunology 2011, 7(Suppl 1):S7
TESTING FOR FOOD REACTIONS – IgE

In vitro

- ImmunoCAP is highly sensitive and specific quantitative analysis
  - Provocation unnecessary
  - Antihistamine use is acceptable

- Food specific IgE via ELISA
  - Only unbound IgE is measured in serum.
  - Half-life of IgE antibodies is short (approx 1 day).
EVIDENCE OF EFFICACY - IgE

- **ImmunoCAP**
  - Specific IgE useful to identify potential allergens, but not considered diagnostic.  
    \( J \text{ Allergy Clin Immunol. } 2010; 126(6):S1-S58 \)
  - ImmunoCAP IgE antibody levels predicted clinical reactivity (positive food challenge) with >95% certainty for egg, milk, peanut, and fish.  
    \( J \text{ Allergy Clin Immunol. } 2010; 125:S116-25 \)

- **Total IgE**
  - Helminths stimulate IgE production  \( \text{World Allergy Organization} \)
  - Chronic intermittent hive reactions may be due to parasite infection.  \( J \text{ Parasitol. } 2003 \text{ Jun;89(3):490-2. Eur Rev Med Pharmacol Sci.} \)
TESTING FOR FOOD SENSITIVITY

- measures levels of IgG antibodies to food antigens via ELISA
  - Total IgG (all four subclasses)
    - Studies showing clinical relevance most often use total IgG
  - IgG4 subclass only
    - 10 to 15% of healthy patients have IgG4 deficiency.
IS FOOD SENSITIVITY A CLINICAL CONDITION

- Gluten sensitivity is a recognized diagnosis
  - the 14th International Celiac Symposium June 2011 recognized gluten sensitivity as a diagnosis separate from wheat allergy or celiac disease
  - Criteria for diagnosis include elevated IgG and IgA antibodies to gliadin (gluten protein), negative celiac sera and biopsy and symptoms consistent with either celiac disease or wheat allergy.
- Evidence continues to evolve regarding the clinical relevance of IgG food sensitivity reactions.
FOOD SENSITIVITY TEST: CLINICAL BENEFITS

- GI Conditions:
  - Irritable Bowel Syndrome (IBS)
  - Crohn’s
  - Dyspepsia

- Migraine Headaches

- Obesity
**FOOD SENSITIVITY IgG - IBS**

- 150 outpatients tested for food-specific IgG
  - Randomized to ‘true’ diet or ‘sham’ diet
  - After 6 weeks, 10% reduction in symptoms. (p=0.024)
  - After 12 weeks, 26% reduction. (p<0.001)


- Open label, 20 IBS patients
  - Food specific IgG testing done
  - Significant reduction in # stools/day and pain scale (p<0.05) after 1 year

FOOD SENSITIVITY IgG - CROHN’S DISEASE

- 40 Crohn’s patients
  - IgG levels to specific foods measured
  - Symptom diary kept
  - Randomized (blinded) to true or sham diet for 6 weeks then crossover to alternate diet.
  - Decreased stool frequency, abdominal pain and increased overall well being in patients that adhered to diet excluding IgG reactions (true diet) compared to sham diet group.

_Bentz S et al. Digestion 2010;81:252–264_
Elimination of IgG reactive foods led to improvement in migraine headaches:

- 43/56 migraine patients reported no migraine after one to six months of elimination diet (removing reactive foods from diet)
- Most common reactive foods in migraineurs: dairy, wheat, eggs, yeast

**FOOD SENSITIVITY IgG - MIGRAINE**

- Double-blind randomized cross-over trial of 30 patients
  - 6 week baseline diet
  - IgG food testing
  - Randomized to either exclusion diet or inclusion diet, 2 week washout, then cross-over to opposite diet
  - In elimination diet phase there was statistically significant reduction in attack count, # headache days, number of attacks requiring acute medication and total medication use.
  - No significant difference in attack severity or attack duration

Alpay K et al. *Cephalalgia*. 2010; 30(7): 829–837
Food Sensitivity IgG - Obesity

- Obese juveniles have significantly elevated C-reactive protein, and greater intima media thickness and elevated IgG antibodies to foods compared to normal weight controls.
- Tight correlation between elevated IgG antibodies and increased CRP/intima media thickness.
- Findings raise “possibility, that anti-food IgG is pathogenetically involved in development of atherosclerosis and obesity.”

Suspected IgG reaction

- Omit suspected food for approximately 5 days. Food antigen is cleared, but IgG antibodies are still being produced and present in high numbers.
- On day 6 – consume a large amount of the suspected food. If food is truly IgG reactive, it will provoke a large immune response and an exacerbation of symptoms.

REPRODUCIBILITY OF RESULTS

Hodsdon looked at the reproducibility of IgG food test from a CLIA accredited laboratory RMA refers testing to

- Two samples from same patient (split sample) – 100% within one reactivity level
- Four samples from one patient on 4 different days over the course of a week - 99% within one reactivity level

<table>
<thead>
<tr>
<th>Result</th>
<th>Split Sample</th>
<th>Four samples / 1 week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identical</td>
<td>95%</td>
<td>82%</td>
</tr>
<tr>
<td>Within one reactivity level</td>
<td>5%</td>
<td>17%</td>
</tr>
</tbody>
</table>

Hodsdon W, Zwickey H. NMJ.2010;2(3):8-13
LABORATORY TEST SUMMARY

- No *in vitro* test is considered diagnostic for food allergy, sensitivity or intolerance.

- Reproducibility of results and evidence of clinical benefits are the only measures of ‘accuracy’ of non-diagnostic tests.
USEFUL REFERENCES


SUMMARY

- IgE food reactions are the only true food allergies.
- *In vitro* tests are **not** considered diagnostic of food allergy.
- The terms food sensitivity and food intolerance are not universally defined.
- *In vitro* tests for food sensitivity/food intolerance include IgG and non-specific immune testing (leukocytotoxic / neutrophil degranulation)