

# Significance of antibody measurements in food related immune response

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The human organism has developed a very high degree of tolerance towards food proteins. But in some condition, especially when the gut barrier is impaired, the immune system might recognize incompletely digested food proteins as foreign and activate the immune system to neutralize and destroy these food fragments.

The immune response to food can be categorized in 3 categories:

1. Production of IgE,
2. Production of IgG
3. Production of IgA

## Type III allergy causes classic symptoms

Ad 1: IgE antibodies are responsible for acute allergic reactions, classified as Type 1 allergy, which mainly affect the mucosa, the skin and circulation. Classic symptoms are: rash, itching of skin and mucosa, Quincke's edema, anaphylaxis. IgE receptors are located all over the mucosa and react immediately after contact with the antigen. They activate the degranulation of mast cells and massive release of histamine. Symptoms occur rapidly, between seconds and 30 minutes after ingestion of the responsible food.

2-4% of adults and up to 8% of children are believed to be affected by IgE mediated allergy.

Normally no blood testing is needed to identify the responsible food. IgE tests are mainly performed for confirmation.

An IgE screening to a high number of foods is completely useless.

## IgG antibodies are responsible for delayed immune reactions to food

Ad2: IgG antibodies are so-called second line defense antibodies and are responsible for delayed immune reactions to food. They are classified as Type 3 allergy. Food needs to pass the gut barrier in order to form circulating immune complexes. Phagocytes are attracted to destroy the immune complex. These immune complexes are either destroyed in circulation, with in general no manifestation of symptoms, or fixed to a tissue where they are destroyed locally. If this becomes an ongoing process, due to regular intake of the antigenic food, specific symptoms may occur and become chronic, depending on which organ has fixed the immune-complex.

Symptoms generally appear after 2-3 hours up to 2-3 days after ingestion of the responsible food. Therefore it is practically impossible to associate an ingested food with a chronic symptom. In order to identify the responsible food, it is interesting to screen a lot of food for IgG, in order not to miss the important ones. It is believed that in approximately 50% of patients suffering from chronic inflammatory diseases, delayed food allergies - mediated by IgG - may play an important role. Due to their relatively long half-life time, IgG are persistent antibodies and extremely suitable to identify immune reactions to foreign food antigens. IgG antibodies disappear from circulation from 2-3 months up to 2 years depending of the initial blood concentration, if the respective food is totally avoided.

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## IgA antibodies to food are linked to distinct pathologies

Ad3: IgA is a first line antibody, which is produced in the early stage of an immune reaction. It has a very short half-life time and disappears when the second line antibodies (IgG) are produced. IgA antibodies to food have been reported to be involved in some distinct pathologies, such as IgA-mediated nephropathy. They can form immune-complexes with food antigens and are predominantly deposited in the kidney in sensitized subjects and lead to glomerulonephritis. Testing for IgA to food should be strictly limited to this pathology.

## Validity of antibody testing

IgE testing is strictly limited to classic food allergy and its value is questionable as 99% of all food allergies can be identified without testing, due to the extremely short time of appearance of symptoms and the ingestion of food.

## Differentiation of IgG (all subclasses) and IgG4

Contrary to the widespread opinion among allergists that it is a physiological phenomenon when human organism produces IgG antibodies to foodstuffs, we have to keep in mind that the presence of IgG/IgG4 in the serum always constitutes an immunological defense reaction against the foodstuff.

Why should it be normal that the organism develops a defense reaction against a harmless and not reproducible food protein? If this assumption were correct, every Western European would have antibodies to gluten, yeast, egg, wheat, and milk. This, however, is not the case, of course.

« Oral tolerance » is the normal case and it is not a normal reaction of the body to develop antibodies to all foodstuffs that are consumed regularly.

If IgG antibodies are detected, they may be specific total IgG or IgG4 antibodies depending on the case.

Which antibodies are produced mainly depends on which cytokines were produced during the initial sensitization. They determine whether a classical food allergy (IgE-mediated) or an asymptomatic food allergy or immune complexes - that later result in chronic inflammatory processes and thus in a delayed food allergy (IgG1-IgG3-mediated) - develop.

A differentiated examination of the specific properties of the different antibody classes may help to better understand the issue.

## The classic food allergy

The genes for the decryption of IgE and IgG4 antibodies are located next to each other on chromosome 14. They are read one after the other. Their production depends on the interleukin pattern present. If mainly IL-4 (interleukin 4) is produced, one can assume that mainly IgE is produced and a real so-called type I allergy develops. It is marked by an immediate reaction after the consumption of the corresponding food and may be fatal in case of anaphylactic shock.

A small portion of the population (2-6%) shows an up regulation of IL-4. This group develops a type I allergy. All others react by producing IL-10 in case of contact with the allergen (sensitization).

## The asymptomatic food allergy

If mainly IL-10, having anti-inflammatory properties, is produced in case of sensitization, mainly IgG4 will be produced. IgG4 is considered to be the "blocking antibody" of IgE, i.e. IgG4 blocks „the access of IgE“ to the allergen. The concentration of IgG4 is about 10,000 times higher than the concentration of IgE and it can therefore bind more quickly and frequently to the allergen than IgE. Since IgG4 releases only about 1% of the quantity of histamine that is released by IgE, nearly all patients do not show allergic symptoms. Symptoms, even mitigated, may only occur in patients with DAO deficiency (approx. 3%) that is in case of insufficient histamine detoxification.

Thus, IgG4 is a measure for an "overcome" or asymptomatic type I allergy. Therefore, a de-sensitization attempts to trigger the production of IgG4. IgG4 is considered to be a measure for the tolerance towards an antigen. The higher the IgG4/IgE ratio, the greater the success of desensitization. Thus, in 95-97% of the patients, IgG4 has positive properties since the antibodies counteract a type I allergy. (The allergens are caught by IgG4 so that less of them can react with IgE and trigger symptoms.)

## IgG4 by itself is unlikely to cause allergic symptoms

Allergists assess this as a normal reaction of the body and therefore deny the significance of IgG4 for the diagnosis of food allergies. This is understandable since according to "evidence based" criteria there is a clear ratio of 97% to 3% in favor of IgG4.

The IgE/IgG4 ratio is a measure for the potential allergic reaction:

- high IgE/IgG4: high probability of an allergic reaction
- high IgG4/IgE: low probability of an allergic reaction

The bottom line for allergy diagnosis: 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.

Immunoglobulin G4: An odd antibody. Aalberse RC, Stapel SO, Schuurman J, Rispens T. Clin Exp Allergy 2009, 39(4):469-77

The main function of IgG4, however, is presumably to interfere with immune inflammation induced by complement-fixing antibodies, or, in the case of helminthes infection or allergy, by IgE antibodies.

IgG4 breaking the rules. Rob C Aalberse and Janine Schuurman. Immunology 2002, 105(1): 9–19.

## The delayed food allergy

If other interleukins (IL-12, IFN) are generated, mainly IgG antibodies of the classes IgG1, IgG2 and IgG3 are produced. They are pro-inflammatory and are responsible for food-related chronic diseases. Every time a foodstuff is consumed against which IgG1, IgG2 or IgG3 is present, an immune complex develops that deposits preferably there where individual-specific defects of the body exist. These "activated sites" may be small lesions that had already become inflamed earlier (e.g. joints), organs affected by infections (e.g. intestine) or damage caused by environmental toxins (e.g. mercury) for example in the thyroid gland. It is not easy to foresee which symptom will occur since it depends decisively on the patient's state of health. In case of regular consumption of the foodstuffs against which IgG1-IgG3 antibodies are present, the deposition of immune complexes results in a chronic inflammation.

This is true except for unspecific systemic reactions for which low-grade inflammations play a main role (high blood pressure, iron deficiency, metabolic syndrome, overweight). In these cases, it has turned out that every positive antibody and / or the corresponding food contributes to a reaction.

IL-12 as an adjuvant for the enhancement of protective humoral immunity.

Metzger DW. Expert Rev Vaccine, 2009 8(5):515-8.

Enhancement of humoral immunity by interleukin-12. Metzger DW, Buchanan JM, Collins JT, Lester TL, Murray KS, Van Cleave VH, Vogel LA, Du. Ann NY Acad Sci., 1996, 31(795):100-15

## Properties of IgG4 and / or specific total IgG

IgG4 is considered to be a non-inflammatory antibody, which means that it cannot generate any chronic inflammatory processes. The reason for that is that IgG4 can neither activate the complement, nor opsonize the corresponding antigen. However, these two actions are the prerequisite for the identification and destruction of the formed complex by phagocytes. This destruction is the inflammatory reaction.

- Without opsonisation and complement activation there is no inflammatory reaction!!!
- IgG1 and IgG3 have strong pro-inflammatory properties.
- IgG4 has protective, anti-inflammatory properties.

### Opsonisation:

Phagocytes can identify an antigen only after it has been marked and thus made visible. This is carried out by antibodies. Among the IgG antibodies, mainly IgG1 and IgG3 have this ability, whereas IgG4 has no opsonising activity. Thus, IgG4 cannot mark the antigens in a way, so that phagocytes can't identify them.

### Complement:

The complement system consists of about 30 proteins that are involved in the regulation of the inflammatory reaction. They are involved both in the activation and in the termination of the inflammation cascade. IgG4 is not able to activate the complement system either.

Inhibition of complement activation by IgG4 antibodies. Van der Zee JS, van Swieten P, Aalberse RC. Clin Exp Immunol., 1986, 64(2):415-22

### Conclusion:

To identify food allergens, which cause chronic inflammatory diseases, only the testing for total specific IgG to food is indicated.

IgE is only indicated in case of immediate type 1 allergy.

IgG4 testing alone is not recommended and unsuitable to detect food responsible for acute type allergy and delayed type allergy.