SCIENTIFIC BACKGROUND

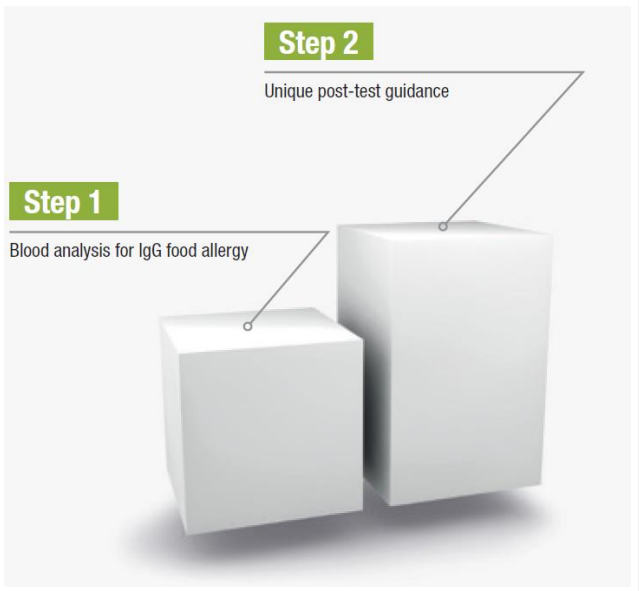
ImuPro
Right Food. Better Health.

Content

SCIENTIFIC BACKGROUND

1. Introduction

IgG food allergies (type III) are causing more and more health challenges. Such IgG-mediated allergies often remain undetected because the symptoms only occur a few hours or even days after the consumption of a trigger food, making them extremely difficult to identify. Fortunately, a reliable diagnostic test and nutritional concept can help: ImuPro.

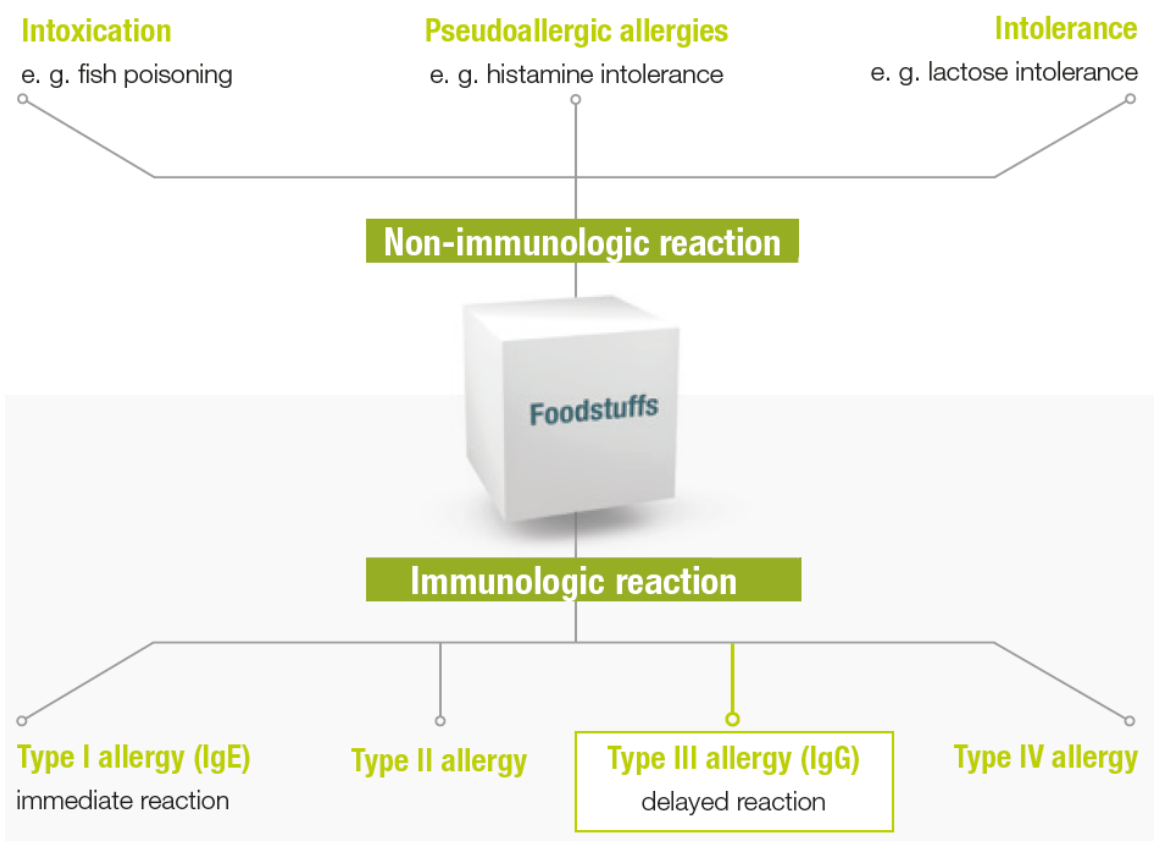


ImuPro combines a sophisticated and reliable blood analysis for IgG food allergies with unique post-test guidance. With ImuPro you will find out whether or not an IgG food allergy could be the cause of your patients' chronic complaints.

In an extensive laboratory analysis, high levels of IgG antibodies specific to particular food proteins are identified. Testing foods individually allows the patients to change their diet very selectively based on their results and limits the level of restriction required, increasing their chance of success.

Along with the ImuPro test results, comprehensive nutritional guidelines and professional support are provided for you and your patients.

2. IgG food allergy



With IgG food allergies (type III), the immune system reacts to harmless food allergens and produces specific IgG antibodies. Due to medicines, infections, mycosis, stress and environmental poisons, the integrity of the intestinal wall can be damaged and food components can slip between the intestinal cells. In some cases this triggers an immune response and the immune system starts to produce specific IgG antibodies against them.

These antibodies and the food antigens form immune complexes which can adhere to organs and tissues. When the immune complexes are destroyed by phagocytic cells and the complement system, the surrounding tissues can be damaged. This leads to low-grade inflammatory conditions which can become chronic. The symptoms are delayed.

2.1 Development of type III allergies to food

Food is certainly no direct threat to the organism. In contrast, it is necessary for a sufficient supply of energy, nutrients and micronutrients, to allow normal functions of a living cell or the organism. The human organism has developed a high degree of tolerance to food and particularly to food proteins - as long as they enter the organism in the manner intended, through an intact gut barrier. The gut barrier is composed of the mucus, the physiological flora, secretory IgA (sIgA) and the physical barrier of enteric cells.

An intact gut barrier is key for tolerance.

Unfortunately the gut barrier faces continuous ongoing aggressions like:

- Infections
- Dysbiosis
- Colonisation by Candida albicans or parasites
- Inappropriate diets
- Incomplete digestion
- Alcohol abuse
- Drugs of all kinds
- Heavy metals
- Excessive exercise leading to gut ischemia
- Psychological stress etc.

Enteric cells are glued together by the so-called tight junctions. They prevent food from by-passing the cells and force them to enter the organism by passing through the cells. If the **gut barrier is impaired**, the tight junctions may break up, increasing the permeability of the gut and leading to leaky gut syndrome. This condition is held responsible for the development of type III allergies.

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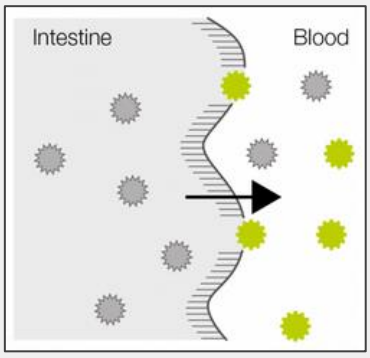
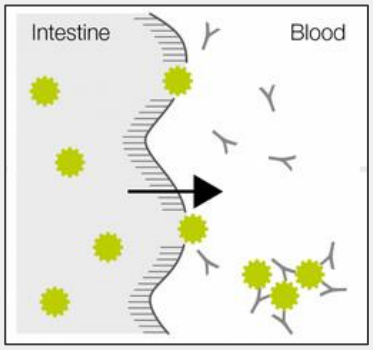
Food that passes through the enteric cells is not attacked by the immune system. In contrast, **food that by-passes** the enteric cells might be recognised as foreign and induces an immune reaction whereby antibodies are formed in order to destroy the invading proteins. In rare cases IgE is formed, leading to type I allergies which in certain cases can even lead to life threatening conditions.



Intestinal wall is damaged: food components can slip between intestinal cells

Formation of immune complexes

Broadly speaking, the immune system consists of two parts: the innate immune system and the adaptive immune system, which is an immune defense acquired during the course of a lifetime. With special receptors, so-called toll-like receptors (TLRs), the innate immune system is capable of recognizing foreign aggressors without prior contact and without prior formation of antibodies. This innate system is extremely important for the survival of newborns, since their intestinal mucosa is not yet fully formed (and would therefore let a large number of infectious germs pass) and they do not have their own antibodies.



Immune system starts response: formation of immune complexes

TLRs have been described and identified by scientists. (1) TLRs are passed on by the germ line cells and do not differ individually. In other words, if the reaction to foods were directed by the innate immune system, all human beings would react to the very same foods, just the way they react to infectious pathogens. This, of course, is not the case.

TLRs recognise specific regions which are typical for the pathogenicity of an infectious pathogen. Of course, foods do not pose a direct threat to our organism. They cannot multiply within the body. Therefore, there is no reason why the organism would have to defend itself against common foods – considering that these are the basis for its survival.

If food proteins enter the blood stream through a damaged intestinal barrier, it is the adaptive immune system that starts a reaction, not the innate immune system.

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The normal immune reaction is to form **IgG antibodies** which generally do not lead to severe acute symptoms. These IgG antibodies recognise the food for which they have been formed. They are also transferred from mother to baby in the third trimester of pregnancy. The IgG antibodies fix to the food proteins to form an **immune complex** in the blood stream. They are called circulating immune complexes.

By fixing to the antigen, they change their confirmation and the immune complexes become **visible to phagocytic cells.** Phagocytes are “blind” - they only recognise antigens which are marked. Antibodies and fragments of the complement system carry out this task. Primarily these are IgG antibodies of the classes 1, 2 and 3. IgG4 is not able to do this; hence IgG4 is not pro-inflammatory, but rather a protective antibody (see also chapter 2.4).

The ability of the IgG classes 1, 2 and 3 to form an antigen is called “opsonisation”. By binding to the antigen the antibody changes its spatial arrangement. It is recognised by IgG receptors on the granulocytes and induces the destruction of the immune complex formed. Simultaneously, the IgG antibody induces an activation of the complement system which attracts further granulocytes (chemotaxis).

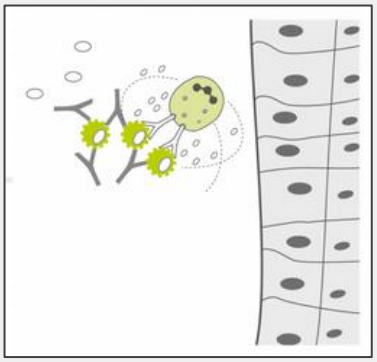
Thus, in terms of processes, the IgG antibodies are the first to bind to the antigen and to activate the complement system, in this way attracting the granulocytes which then destroy the immune complex.

If phagocytes bind to the circulating immune complex, they release certain cytokines, inflammation mediators, proteases and oxygen radicals, in order to **destroy the immune complex. This is an inflammatory reaction.**

Inflammation is a protective response intended to fight infections and in case of tissue injury eliminate the initial cause of cell injury as well as the necrotic cells and tissues resulting from the original insult and to initiate the process of repair under one condition: if it takes place occasionally and for a limited time. If the **inflammatory reaction becomes chronic** because the inducer of the inflammation is food that is consumed regularly, then the protective effect of inflammation turns into a threat to our health.

2.2 How does type III allergy to food cause symptoms?

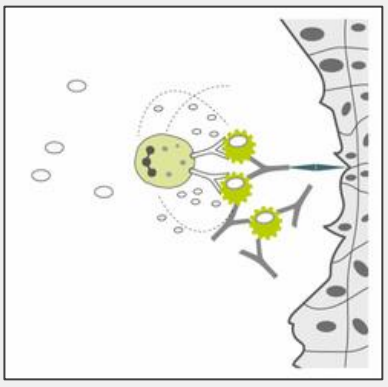
There are certain scenarios; common to all of them is the fact that inflammatory mediators like TNF-α are formed and may exhibit effects that affect the whole body.



Immune complexes are destroyed: inflammatory process without tissue damage may result in systemic symptoms (e. g. hypertension, metabolic disorders)

The immune complex is destroyed in circulation.
This is the normal situation. In this case, patients often don't experience specific symptoms. **Unspecific symptoms** can be fatigue and retention of water, reflected by an **unexplained variation of body weight**. In the long term, due to continuous generation of TNF-α, cardiovascular, hormonal and metabolic disorders might develop.

The immune complex is fixed to a tissue.
Trauma, surgery or infections may sensitise tissues by formation of adhesion molecules. These **adhesion molecules** have the capacity to **fix circulating immune complexes**. For example, deposition of circulating immune complexes formed by enteric bacteria with antibodies has long been discussed as a cause of chronic joint inflammation. If the immune complex is fixed to a tissue, it is also destroyed locally and the **tissue will be partially attacked** by excessive production of proteases and oxygen radical. This leads to tissue damage and specific symptoms (2, 3).



Immune complexes are destroyed: inflammatory process with tissue damage may result in specific symptoms (e. g. IBS, migraine)

If the food forming the immune complex is eaten regularly, a **chronic inflammatory reaction** is induced in the tissue concerned. **Symptoms do not appear immediately**. It may take several months before a symptom becomes apparent. Often it starts to appear gradually, but intensifies with time. As normally no association is made with an adverse food reaction and the food is not avoided, symptoms may become chronic.

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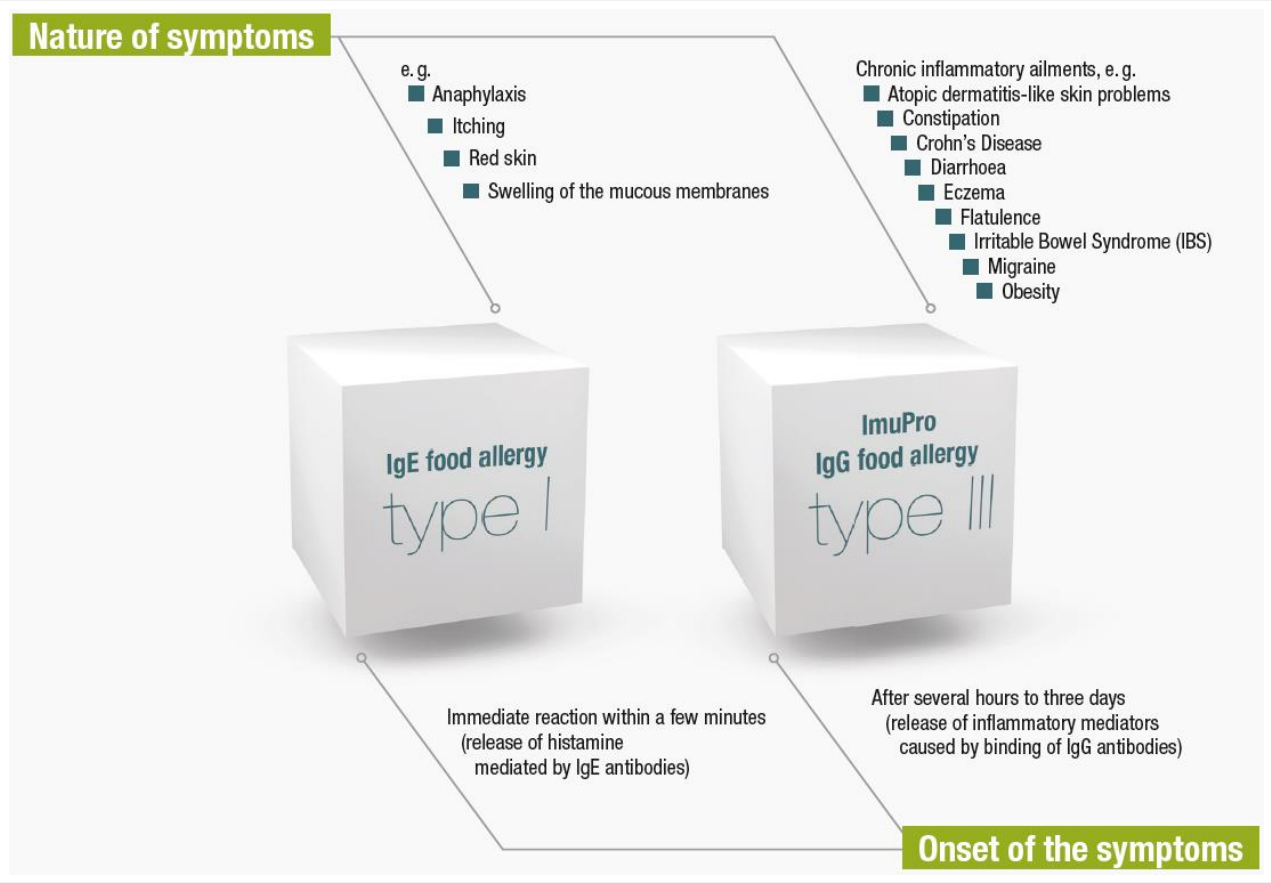
At present time, it is **not predictable which food causes which kind of symptom** in an individual. Individual susceptibilities vary considerably in respect of the genetic predisposition, the reaction of the immune system, organ repair capability, but probably also in respect of the kind of epitope recognised by the antibody.

Therefore a given food may exhibit **different symptoms in different patients.** It is not advisable to recommend the avoidance of food for one patient because this recommendation was successful for another. Avoidance of food should only be performed individually based on reliable test results.



2.3 What is the difference between an IgE food allergy and an IgG food allergy?

By definition, **IgG food allergies (type III)** are characterised by the formation of circulating immune complexes formed by an antigen and its corresponding IgG. In contrast to **type I allergy**, caused by IgE antibodies, symptoms are not acute but delayed, appearing after two to three hours at the earliest and up to three days. While IgE-mediated allergies are related to acute severe conditions, IgG-mediated allergies are considered to be responsible for chronic inflammatory diseases (4, 5, 6, 7, 8, 9, 10).

2.4 Significance of IgG4

IgG4 is considered to be the “blocking antibody” of IgE, i.e. IgG4 blocks IgE. The concentration of IgG4 is about ten thousand 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 one percent of the quantity of histamine that is released by IgE, nearly all patients do not show allergic symptoms. Thus IgG4 is a measure for an “overcome” or asymptomatic type I allergy.

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.

IgG4 can neither activate the complement nor opsonise the corresponding antigen. However, these two actions are the prerequisite for the identification and destruction of the formed immune complex by phagocytes. Hence, IgG4 does not play a role in delayed food allergies.

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

Overview of the properties of the IgG subclasses

Function	IgG1	IgG2	IgG3	IgG4
Neutralisation	++	++	++	++
Opsonisation	+++	+	++	-
Complement activation	++	+	+++	-
Transplacentral	+	+	+	+
Extravascular diffusion	+++	+++	+++	+++
Average serum concentration mg/ml	9	3	1	0.5
Reaction type	Type II	Type IV	Type III	Type I
Binding to mononuclear cells	++	(+)	+++	++
Binding to neutrophils	+	-	+	-

According to: Immunology, Roitt, Brostoff, Male; 6th edition, 2001, Mosby

3. Cross-reactions

The immune system produces so-called **antibodies to fight foreign invaders.**
The best known antibodies are: IgA, IgM, IgG, IgE. Each of them has different properties and tasks to fulfil to fight foreign agents. Common to all of them is that they **do not recognise the invader as a whole,** but recognise specific or less specific parts of it, most of the time parts of certain proteins from the invader. These parts are called epitopes.

This means: If **two different invaders have common epitopes**, under certain circumstances an antibody produced to recognise invader one may also recognise invader two - although the immune system has never encountered invader two before. This does not mean that the reaction to the second agent is false; it is a so-called **cross-reaction.** The same problem exists in classic type I allergy (IgE).

3.1 Relevance for ImuPro

If we transfer this to the **ImuPro results**, it might be that IgG antibodies to a food have been detected, even though the food was never eaten before. This reaction is not necessarily a false positive, but could be a cross-reaction.

Example: Your patient has been tested positive to oysters, but he is sure that he has never eaten oysters before. This could be a cross-reaction to dust mites. Dust mites and all invertebrates - like mussels, oysters, lobster, crab, scampi etc. - have a common antigenic protein, called tropomyosin; the quantity of tropomyosin differs from species to species. So if your patient is sensitised to dust mites, he might have a positive test result to one or several of the seafoods mentioned above. It is also possible that he has been previously sensitised to another seafood. Whether or not a cross-reaction occurs depends on the epitope, on the amount of the protein present in the different species and on its accessibility. So your patient might be positive to one or two of the seafoods, but not to all.

Note: In the particular case of seafood as a cross-reaction to dust mites, we recommend changing the mattress and pillows and using an anti-dust mite mattress protection in the future. Reaction to seafood might always be an indication for a sensitisation to dust mites.

Cross-reaction exists between a huge variety of foods but also between non-food and food. Certain pollen in particular may exhibit a high number of cross-reactions to food. The most prominent are birch and mugwort.

The table below shows the best known cross-reactions between food and non-food allergens.

Mugwort					
Aniseed	Apple	Artichoke	Camomile	Cardamom	Carrots
Celeriac	Cinnamon	Coriander	Cucumber	Cumin	Fennel
Garlic	Ginger	Grape	Kiwi	Lychee	Mango
Melon	Nutmeg	Oregano	Paprika	Parsley	Pepper
Potato	Sunflower seed	Tomato			
Birch tree					
Almond	Apple	Apricot	Carrots	Cherry	Fig
Hazelnut	Kiwi	Lychee	Nectarine	Pear	Plum
Soy	Walnut				
House dust mite					
Crayfish	Lobster	Mussels (blue)	Octopus	Oysters	Scallop
Shrimp, prawn	Snails	Squid, cuttlefish			
Latex					
Avocado	Banana	Fig	Kiwi	Mango	Melon
Papaya	Peach	Potato	Spinach	Sweet chestnut	Tomato
Grass pollen					
Beans	Lentil	Peanut	Peas	Pumpkin	Tomato

Note: This list is intended to give an overview of possible cross-reactions. No liability is assumed for either its completeness or accuracy.

3.2 How to deal with cross-reactions?

Cross-reactions are not false positive reactions. So they should first be **considered as "real" reactions.** It is known that not all diagnostically revealed cross-reactions lead to clinically relevant symptoms. This again applies to type I allergy (IgE) or type III allergy (IgG). Therefore a **provocation diet is essential** to evaluate the clinical impact of the diagnosed cross-reaction. If no symptoms or no increase of body weight appears after the provocation, it is highly probable that no clinical impact can be expected from that food.

4. The ImuPro Concept

The main pillars of ImuPro are: elimination, rotation and reintroduction. They are the foundation of the following three phases:

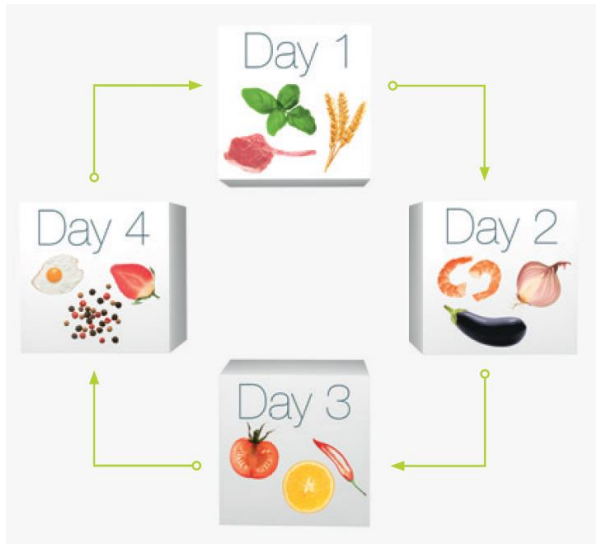
1. Elimination phase
2. Provocation phase
3. Stabilisation phase

4.1 Elimination phase

The first key to success is to identify and **avoid pro-inflammatory foods**. Allopathic and holistic therapies are less or not successful in treating chronic inflammatory diseases if the agent causing this process is not removed.

The second key to success is to **rotate food**, in order

- to allows for a varied diet supplying all necessary micronutrients and avoiding monotony,
- to reduce the environmental risk (foods contaminated with environmental agents like nitrate),
- to avoid unintended nutritional mistakes (ignorance of prohibited food contained in presumably allowed food) and
- to avoid the appearance of IgG to newly introduced food.



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Interpretation of results:

The ImuPro test determines the presence and concentration of specific IgG antibodies to a broad variety of foodstuffs. Based on the results of the antibody titre, the foodstuffs are then categorised into three groups:

- **Not elevated**: no IgG detected or level is below cut-off value, food is allowed for consumption, respecting the rotation principle
- **Elevated:** elevated levels of IgG detected, foods have to be avoided strictly for five to eight weeks
- **Highly elevated**: elevated levels of IgG detected, foods have to be avoided strictly for five to eight weeks

No difference is made between the concentration of IgG in respect to time and the strictness of avoidance. All positive foods have to be treated equally!

The amount of IgG in serum does not necessarily correlate with the intensity of symptoms. Furthermore, not all IgG positive foods (just as for IgE positive allergens in type I allergy) are responsible for specific symptoms.

The work of Jönsson et al (10) showed that certain factors need to be present to induce a systemic inflammatory reaction: IgG, the antigen, neutrophils and IgG receptors. To induce specific symptoms or diseases, immune complexes need to be deposited in the tissue where they lead to local inflammatory reactions. The specific symptoms are not necessarily dependent on the amount of IgG present, but they are dependent on the amount of tissue adhesion molecules present.

Why does the initial elimination take five to eight weeks?

- If a food is responsible for the symptoms reported by the patients, a positive effect should be seen within the time frame when the concerned food is strictly avoided. Only in some difficult cases like Parkinson's disease, Multiple Sclerosis, degenerative osteoarthritis or progressed stages of diseases, may it take longer. In these cases, it is the responsibility of the treating physician to prolong the elimination phase.

- Not all positive foods cause specific symptoms. Therefore, it might not be useful to avoid a food for a long period of time as it complicates the compliance of the patient and unnecessarily increases the number of foods to be avoided.

- A minimum avoidance of five weeks is easily feasible for the patients. A rapid success – after one week for most symptoms motivates them to stay compliant for this short time, together with the perspective of reintroducing certain foods again soon.

- After five to eight weeks, the susceptibility to food has not disappeared yet. IgG antibodies are still present. This enables the patient to quickly find out which food causes which symptom during the following provocation phase and to focus on these foods.

4.2 Provocation phase

The provocation phase (also regarded as the gold standard in type I allergy) aims:

- to identify the IgG-positive foods which induce specific symptoms or lead to inflammatory reactions in the patient's body.
- to identify which food causes which symptom.
- to enable the patient to concentrate on particular foods causing health issues
- to facilitate the following stabilisation phase by reducing the number of foods to be avoided and increasing the compliance.

After five to eight weeks of complete avoidance of **all IgG positive food**, the patient may now consume these foods one by one, in order to determine the effect a particular food has on the health situation of the patient.

How to introduce a food correctly?
It is recommended to start with food from the class "elevated". Foods from this class have lower concentrations of IgG, which tend to disappear faster than higher levels (IgG has a half-life of about 23 days (11)). After having finished with the foods of this group, the patient moves on to the group "highly elevated".

Alternative approach: In particular cases, it is also possible to start with the preferred food of the patient and then carry on as described above. Often patients want to know whether their preferred foods are causing them problems, whether they have to avoid them permanently or whether they will be allowed to consume again them after a short time. This can be psychologically important in individual cases.

When reintroducing a food:

- The patient should eat the **food in its pure form** if possible. For example if a patient has a reaction to yeast and gluten, he should not use bread as it contains both and it will remain unclear which one caused the problem.
- Only **one type of food at a time** should be introduced.

Reintroduction is generally done during one day. It is important that the patient consumes this product on multiple occasions over the day to guarantee that the amount ingested is enough to induce a response. Then the food is avoided again for the rest of the provocation phase (= three days).

During the following three days the patient has to observe if any **symptoms reappear** or if an **increase in body weight** of approximately one kilogram or more occurs.

Alternative approach: In particular cases or in doubt, the patient may reintroduce a food for up to three days in a row and then avoid it again for three days. The provocation phase will then last six days instead of four. During these six days, it is observed whether any of the symptoms previously present have reappeared or whether an increase in body weight as mentioned above has occurred.

Note: In any case, it is important to observe reappearance of symptoms for three days because IgG mediated symptoms are delayed and may only reappear within three days after consumption.

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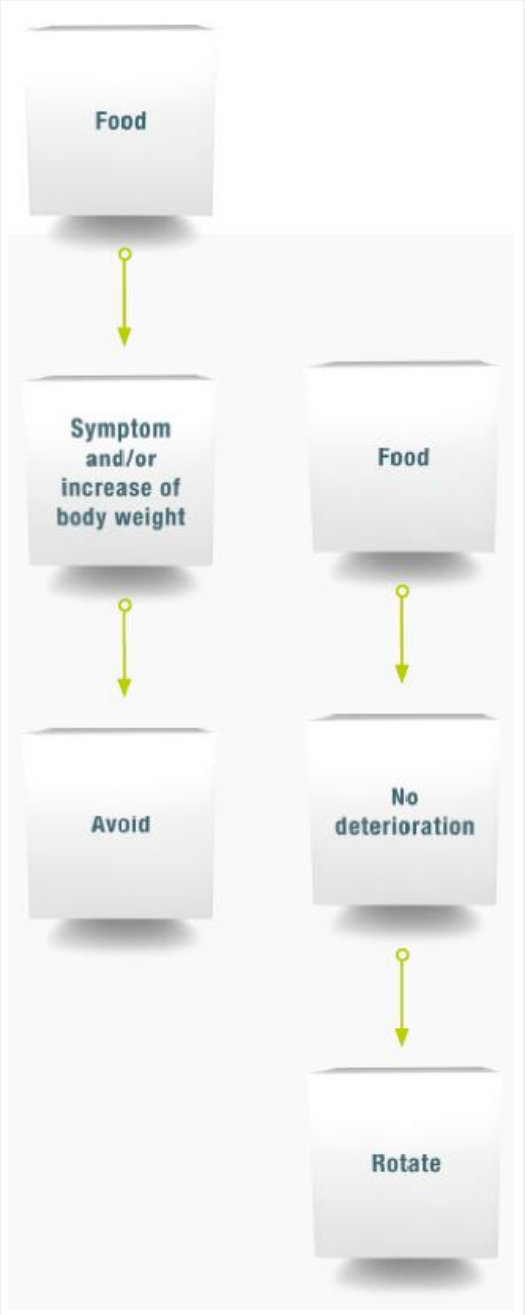

If **neither a symptom nor an increase in body weight** has occurred, the patient can consume the food in rotation.

If a **symptom has reappeared,** the food has to be avoided strictly for at least one year.

If **only an increase in body weight** has occurred, the food is inducing an inflammatory reaction. The increase of body weight occurs due to water retention caused by the reacting food. There are two ways to proceed in this case:

- If **systemic symptoms** exist, e.g. hypertension, increased body weight, metabolic disorders, chronic iron deficiency and particularly in sport medicine, it is recommended to avoid this food for at least one year.

- In particular cases where **no systemic symptoms** exist, but where the focus is put on specific ailments like joint pain, migraine, Crohn's disease etc., it might be a good idea to allow these foods in strict rotation, in order to facilitate the avoidance of food that causes specific symptoms (e. g. joint pain).

Although these foods do not induce a specific symptom yet, they still represent a certain threat for the future. We know that an IgG-positive food that does not induce a symptom at present is able to do so in the future when a sensitisation to a tissue occurs. Particular attention should be paid to this, especially when new symptoms appear in the future.

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Why do not all IgG positive foods cause symptoms?

Several reasons may explain this phenomenon:

- No receptor present to fix the circulating immune complex
- Cross-reaction of the food in-vitro
- Unspecific reaction of patient's serum due to unknown interference

No receptor present to fix the circulating immune complex

If no receptor for a circulating immune complex exists, the immune complex will not be fixed in or on the epithelium of the tissue and will not be destroyed locally.

The consequences of immune complexes destroyed in circulation may differ from patient to patient. The common feature is **low-grade systemic inflammation** which expresses itself differently depending on the health situation and the genetic predisposition of the patient. Common to all will be the **partial blockage of insulin receptors** by the action of **TNF-α** (12, 13). Whether or not a patient experiences any problems with this phenomenon will depend on the ability to metabolise glucose. If no previous impairment of the glucose metabolism is present, the patient will not experience any health impact, although this may change in future.

Another consequence of systemic inflammation may be **hypertension**. But not everybody who has IgG to foodstuffs will develop hypertension (14). Only if certain genetic polymorphisms exist may inflammation caused by food lead to hypertension.

Whether or not a food leading to systemic reaction has to be avoided, depends on the health situation of the patient and the judgment of the physician.

Cross-reaction of the food in-vitro

ImuPro is an in-vitro diagnostic test. Common to all in-vitro diagnostics is that they **do not reflect hundred percent of the body's reaction.** Although the reaction observed is correct, it may be that in-vivo the same reaction does not happen. This depends on the nature of the epitope and the concentration of the epitope in the food. It also makes a difference whether the epitope is destroyed during digestion for one food but not for the other.

A particular form of cross-reaction is the cross-reaction to so-called **Carbohydrate Cross-reaction Determinants (anti-CCD)**. This phenomenon is also observed in IgE allergy testing and is known as anti-CCD reactions. In type I allergy, anti-CCDs are produced due to exposure to pollen. Pollen – food cross-reactions are common.

Latex and insect venom can also lead to anti-CCD production. In some ImuPro results, all animal derived antigens remain negative while most or all plant derived foods are positive. It is not known if these reactions are clinically significant. Only the provocation test can give the answer.

Unspecific reaction of patient's serum

In rare cases, unspecific reactions of patient's serum of unknown aetiology can be observed. It is presumed to be caused by **super-activation of the immune system**, as observed after multi-vaccinations. This is particularly the case with infants.

Severe leaky gut syndrome may also cause unspecific reactions. This phenomenon is also known as cross-linked fixation of antibodies. After treating the leaky gut syndrome, these unspecific reactions may disappear again.

4.3 Stabilisation phase

After having identified his personal triggers, the patient now knows which food causes him health problems. He has the choice to concentrate on all trigger foods, including foods causing specific symptoms and foods causing systemic issues (food only leading to an increase in body weight). Or he may only concentrate on the few foods causing specific symptoms, if it is advisable in his case.

The stabilisation phase aims

- to substantially improve the health of the patient in future
- to eliminate IgG to food
- to extend the variety of food consumed and thus the enjoyment of eating
- to enable the patient to reintroduce the food again after all IgGs have been eliminated

During the stabilisation phase the patient **avoids the trigger foods for at least one year.** The foods that did not cause any symptoms and/or gain in body weight overnight during the provocation phase may be reintroduced into the diet. It is advisable to eat the reintroduced foods only once a week to enable the body to eliminate IgG antibodies against it.

In most chronic ailments, avoidance of IgG-positive food can lead to **partial or complete remission of symptoms.** To achieve this, the avoidance of the concerned food should be as strict as possible.

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The human immune system hosts so-called **memory cells** (15). These are specialised B-lymphocytes which - together with plasma cells - carry the message that a certain protein is to be considered as foreign and to be destroyed. It is believed that these memory cells can have a life span of one to two years. If no stimulation of these memory cells takes place in this time, they will die out and the **immune system's memory is lost,** meaning the patient should **re-tolerate the food again** (17).

Of course this is in part a theoretical hypothesis, but experiences in the past do confirm it - at least in part. For some ubiquitous allergens, it may be more difficult to eliminate the memory cells. But if the food is consumed in rotation later, no sufficient IgG should be formed to induce health issues.

This is also true for IgG positive foods not leading to symptoms. If they are not consumed regularly but in rotation, no health issues should be expected in future. The **key to long lasting success is rotation**, particularly during but also after the stabilisation phase.

5. Summary

1 Elimination phase

Foods to avoid
- strict 5-8 week elimination

Allowed foods
- 4-day rotation

2 Provocation phase

Avoided foods
- 1-day reintroduction
- 3-day observation

Allowed foods
- rotation

3 Stabilisation phase

Trigger foods
- 1-year avoidance

Allowed foods
- rotation

SCIENTIFIC BACKGROUND

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