



*Review*

## **Role of IgG food test in patients with allergic diseases**

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**Abstract:** The role of immunoglobulin G (IgG) food elimination in allergic diseases is controversial. This main aim is to clarify the beneficial effects of specific immunoglobulin G (sIgG) food elimination on improving allergic diseases. International guidelines disagree about the beneficial roles of IgG food elimination on allergic diseases. However, many studies have proven the role of IgG food elimination on allergic diseases. In atopic dermatitis children, studies have shown that milk, egg, wheat, and soya are positive for sIgGs and there sIgG elimination will improve atopic dermatitis. In allergic rhinitis, the sIgG4 food test is usually positive to seafood, and IgG food elimination will improve both allergic rhinitis and asthma symptoms. In asthma, persistent IgE egg sensitizers have higher sIgG1 to egg than partial IgE egg sensitizers. Additionally, high sIgG1 to egg is a risk factor for future asthma (with sensitivity of 64% and specificity of 74%). In asthma, persistent sIgG1 egg sensitization is risk for future asthma and IgG food elimination will improve asthma (especially milk and egg). In chronic urticaria, the most common positive sIgGs to food are cola nut, yeast, wheat, red kidney bean, pea, corn, and egg white in Saudi Arabia. Women and patient aged < 40 years have higher positive sIgG rates to several foods. In food intolerance, IgG food elimination will improve the symptoms of food intolerance. Furthermore, primary prevention of food intolerance can be achieved by early IgG food elimination. In conclusion, despite those most international guidelines disagree about the beneficial role of IgG food elimination on allergic diseases; some studies support its role. This test may be used if patients' symptoms do not improve after the IgE food tests. Moreover, IgG food companies should offer cheap short lists, such as ImuPro Screen 22 foods or ImuPro Screen Plus 44 foods.

**Keywords:** IgG; IgG food test; IgE; allergic diseases; asthma; allergic rhinitis; atopic dermatitis; atopy

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## 1. Introduction

Immunoglobulin G (IgG) is among the four main IgGs secreted during bacterial, viral, or fungal infections. However, the role of IgG in allergic cascades is vague. However, IgG is well known for its role in anaphylaxis. Antigens can induce anaphylaxis by activation of both the classical and alternative complement pathways. The role of IgG in anaphylaxis is to compete with the antigens by binding to the same IgE receptors. In this way, IgG can prevent the occurrence of anaphylaxis. However, this role can be applied to a small quantity of antigen, as IgG can not prevent anaphylaxis in cases with large antigen quantities [1].

IgG secretion (type III hypersensitivity) does not happen immediately after an exposure to a trigger, similar to type I hypersensitivity reactions, but it may take a longer time to occur (up to several days). That is why we name the IgG reaction as delayed in comparison to the IgE reaction, which is referred as an immediate reaction. Therefore, the diagnosis of type III reaction is difficult in comparison to the diagnosis of type I reaction, which is easier. The same can be applied to food intolerance (type III IgG-mediated) in comparison to food allergy (type I hypersensitivity). Thus, the diagnosis of food intolerance (type III hypersensitivity) is difficult, as compared to that of food allergy (type I hypersensitivity), which is easier [2].

The mechanism of food intolerance is not well understood because it does not occur via the IgE mechanism (non-IgE mediated). One of the possible non-IgE mechanisms for food intolerance is the IgG cascade, which can occur via type III hypersensitivity reaction, indicating that the food antigens will trigger IgG secretion via type III hypersensitivity reaction. These secreted specific IgGs (sIgGs) against certain foods will trigger the chronic inflammation cascade, leading to the appearance of food intolerance symptoms. This concept may explain why doing an IgG food test for food intolerance is beneficial [3].

The enzyme-linked immunosorbent assay (ELISA) and radio allegro sorbent type are indirect immunoassay (IA) in vitro tests, which are used to detect sIgGs against foods. The first step in IA is to mix the patients' blood with a substrate, which contains anti-IgG against suspected foods. Second, a radioactive substance, an anti-substrate, is then added. Finally, the level of radioactivity of the suspected food is measured. If the radioactivity is high, the sIgG against the suspected food is high and considered positive [4].

There are several sIgG food test companies in Saudi Arabia. The most famous companies include ImuPro, BeFunctional Labs (food print test), and MADx MicroArray Diagnostics (Fox Xplorer test). ImuPro provides several IgG foods lists, which are as follows: ImuPro Screen 22 foods, ImuPro Screen Plus 44 foods, ImuPro Basic 90 foods, and ImuPro Complete 270 foods. The BeFunctional Labs (food print test) lists include general foods, foods for vegetarians, herbs and spicy foods, and vegan foods. MADx MicroArray Diagnostics (Fox Xplorer test) is the only company providing a list of 286 foods. It may be a good idea to provide different lists with different prices. Cheap small lists are a good solution, which is suitable for most patients.

## 2. Evidence against the role of IgG food test in allergic diseases (international guidelines)

The most important international guidelines are discussed below.

### *2.1. American Academy of Allergy, Asthma, & Immunology (AAAAI)*

AAAAI has mentioned that the diagnosis of food intolerance is clinical only and that there is no test available for its diagnosis. Moreover, it pointed out that the sIgG food test is useless for several reasons. First, AAAAI has refused the commercial abuse of sIgG food test without evidence-based findings. Second, AAAAI has rejected the idea that food elimination can be made for multiple food allergies depending on the sIgG food test. Third, the sIgG positivity to certain food indicates only a physiological reaction or tolerance to that food; it does not mean allergy to that food. Fourth, non-medical people abuse this test without medical advice, and they start food elimination based on the test results. Fifth, people change their eating habits based on the test results [5].

### *2.2. Canadian Society of Allergy and Clinical Immunology (CSACI)*

CSACI was published in 2012. It is not interested in this test based on five points. First, this test is available for health and non-health workers, which will enable its abuse. Second, patients can buy the tools of this test direct from pharmacies without medical advice. Third, the sIgG food test companies distribute advertisements for this test in clinics without doctors' permission. Fourth, this test is expensive and no medical evidence can support its benefit. Fifth, parents start food elimination for their children without medical advice (depending on the test results). This may affect child nutrition, especially with the essential food avoidance, like wheat and egg [6].

### *2.3. European Academy of Allergy and Clinical Immunology (EAACI)*

The EAACI position paper was published in 2008, which focused mainly on the role of IgG4. It does not support the role of IgG4 in the diagnosis of both food allergy and intolerance due to several reasons: asymmetry between positive IgG results and patient symptoms; absence of evidence supporting the idea of IgG4 histamine release; absence of randomized blind clinical studies supporting the role of IgG4 in this area; IgG4 can indicate the presence of tolerance to certain foods showing sIgG positivity; and this paper has clarified that positive IgG indicates a physiological response to food only [7].

## **3. Evidence supporting the role of IgG food test in allergic diseases**

Below are the studies supporting the beneficial role of IgG food test in allergic diseases.

### *3.1. Role of IgG food test in atopic dermatitis*

In one prospective study conducted in China in 2018, the study sample was divided into the experimental and control groups. The experimental group comprised 216 atopic kids (140 kids in the eczema group, 76 kids with other allergies in the allergy group), whereas the control group included 80 kids without allergies. The sIgG food test was performed on all kids. The sIgG positivity rate was high (91.4% and 93.4% in the eczema and allergy groups, respectively). However, the p value was not significant between the two groups. Nevertheless, the p value was significant between both the

eczema and allergy groups, when compared to the control group (Table 1). Milk and egg were the major foods that were positive for sIgG (70%) [8].

**Table 1.** The comparison between both (eczema and allergy groups) versus control group.

	The sIgG positivity rate	Significance between eczema and allergy groups	Significance between both groups and control (80)
Eczema group (140)	91.4%	P > 0.05	P < 0.05

A cross-sectional study involving kids from Holland in 1999 investigated the correlation between sIgGs and sIgEs and foods and inhalants allergy triggers. The study sample was divided into the experimental and control groups. The experimental group included 120 atopic kids (58 kids with atopic dermatitis, 62 kids with other atopies). The control group comprised 140 normal kids. Both groups underwent sIgG food tests. The rate of positive sIgGs against foods is higher in the experimental group than in the control group. In the atopic dermatitis group, both sIgG and sIgE positivities are correlated to egg white and a mixture of wheat and rice. In the other atopy group, sIgG positivity is related to egg white, orange, and cow's milk. Therefore, sIgG and sIgE positivities are correlated to certain foods and inhalants in atopic kids [9].

In an old cross-sectional study published in 1989, 276 atopic dermatitis kids were enrolled. These kids had never had food elimination. At baseline, both sIgEs and sIgGs against egg, milk, soya, and mite were measured; the kids were also asked to clean their sleeping rooms and eliminate the abovementioned foods. After 140 days, both sIgE and sIgGs of some kids had improved, whereas others had not. Both sIgEs and sIgGs against the above mentioned foods were re-measured again. The sIgG values were dramatically reduced in the kids with improvement as compared the kids without improvement. Possibilities for the unimproved kids are either incomplete (sleeping rooms cleaning or foods elimination). This means that food elimination in atopic dermatitis kids will decrease the sIgGs levels [10].

### 3.2. Role of IgG food test in allergic rhinitis

In a comparative study done in Malaysia in 2001. the sIgG, sIgG4, and sIgE levels were measured in 143 allergic rhinitis patients who are allergic to foods also. Allergic rhinitis diagnosis was diagnosed either by using a questionnaire or performing a skin prick test. The sIgG tests were positive for shrimp in 47 patients, crab in 46 patients, and both in 50 patients. sIgE and sIgG4 positivities were correlated to crab allergy, indicating that, in allergic rhinitis patients, both sIgEs and sIgG4s can be linked to shrimp and crab allergies. This paper confirmed that allergic rhinitis and foods are correlated based on the IgG food test results [11].

In 2016, a case report investigated the effect of IgG food elimination on allergic rhinitis and asthma. In this report, a 10-year-old girl complained of allergic rhinitis and asthma symptoms. Both sIgE and sIgG tests against foods were performed. Then, the foods showing sIgG positivity were excluded from her diet. The clinical symptoms of both allergic rhinitis and asthma were evaluated at 1 and 8 months post-food elimination. After 8 months of avoidance, both allergic rhinitis and asthma clinical symptoms were improved dramatically. Therefore, avoidance of positive sIgG foods in children can improve both allergic rhinitis and asthma symptoms [12].

### 3.3. Role of IgG food test in asthma

Currently, it is well known that the continuing sIgE sensitization to eggs is a risk factor for future asthma in kids. A cohort study conducted in the UK in 2004 investigated the role of sIgE sensitization to egg in asthmatic kids. The study sample comprised 46 newborns of atopic parents who were followed to determine whether they will develop asthma in the future or not. The state of sIgE sensitization to egg was tested by skin prick test at 1 and 2 years of age. Accordingly, the state of sIgE sensitization to egg was classified as follows: transient (skin prick test (SPT) positive to egg at 1 year of age only) and persistent (SPT positive to egg at 1 and 2 years of age) egg sensitization. sIgGs to ovalbumin subclasses (sIgG, sIgG1, and sIgG4) were measured at baseline, 6 months, 1 year, and 5 years. The results showed that the sIgG1 level was significantly higher in the persistent egg sensitizers than in the transient egg or non-egg sensitizers. It was concluded that a high level of sIgG1 to egg (in persistent egg sensitizers) is a risk factor for future asthma. Additionally, sIgG1 levels > 14500 units at 1 year can predict future development of asthma with 64% sensitivity and 74% specificity [13].

A prospective clinical trial conducted in Malaysia in 2004 enrolled 22 asthmatic kids (13 and 9 kids in the experimental and control groups). It is a good study, but it has a small sample size. The experimental group was ordered to avoid milk and egg for 8 weeks, whereas the control group was ordered to eat normally. The levels of sIgGs to both beta lactoglobulin and ovalbumin and peak flow meter were taken for both groups at baseline, 7 days, and 8 weeks. After 8 weeks, results showed obviously the good effects of this step. In the experimental group, the levels of sIgGs to ovalbumin and beta lactoglobulin were decreased significantly, whereas, in the control group, the levels of IgGs ovalbumin were increased significantly. Additionally, after 8 weeks, the peak flow meter was increased in the experimental group. This paper shows the beneficial effects of milk and egg avoidance on the sIgG levels and asthma symptoms [14].

A case report published in China in 2015 described cases of two asthmatic patients who were followed up before and after 91 days of dependable sIgG food elimination. For continuous assessment, the sIgG food levels were evaluated four times at baseline and 21, 49, and 91 days, respectively. The results showed that all asthma clinical parameters were improved gradually over time. The first parameter was the demand for asthma medications; the need for asthma inhalers, oral montelukast, and oral antihistamines was decreased. The second parameter was asthma symptoms; the episodes of exacerbation were decreased, blood oxygen saturation was increased, lung wheezes were reduced, and severity of symptoms was decreased. These results mean that the asthma symptoms can improve a lot after sIgG food elimination [15].

### 3.4. Role of IgG food test in urticaria

In a retrospective study performed in a university hospital in Riyadh, Saudi Arabia in 2016, the sIgG food status of patients with positive allergy tests was assessed. The study data were collected between 2010 and 2015. Seventy-one adult patients were enrolled in the study, with the majority of the participants having chronic urticaria. The sIgG positivity rates were high for several foods (Table 2). Women had higher sIgG positivity rates for certain foods than men (Table 3). Patients aged < 40 years have higher sIgG positivity rates for certain foods also (Table 4) [16].

**Table 2.** Rates of IgG positivity to foods among chronic urticaria patients.

Related food	The sIgG positivity rate
Cola nut	80.3%
Yeast	78.9%
Wheat	77.5%
Red kidney bean	71.8%
Pea	63.4%
Corn	62%
Egg white	62%

**Table 3.** Sex distribution of sIgG positivity rates in patients with chronic urticaria for certain foods.

	The sIgG positivity rate in females	The sIgG positivity rate in males	P value
Wheat	74%	25.5%	<0.001
Corn	77.3%	22.7%	<0.001
Cola nut	71.9%	28.1%	<0.001

**Table 4.** Age distribution of sIgG positivity rates in patients with chronic urticaria for certain foods.

Highers sIgGs	Significance
Gliadin	P < 0.003
Egg white	P < 0.03
Barley	P < 0.05

### 3.5. Role of IgG food test in food intolerance

In 2021, a recent Chinese study with a large sample evaluated the levels of sIgG against foods in 2368 food intolerance patients. The sIgG positivity rate to foods was high (82.7%). Women were more likely to show sIgG positivity to egg (54.7%), shrimp (29%) and milk (26%). Accordingly, food elimination was done depending on the sIgG test results. After food elimination, most food intolerance symptoms were improved in most of the patients. Hence, food intolerance symptoms can be improved after food elimination, which is dependent on the IgG food test results [17].

Can we prevent food intolerance by early avoidance of sIgG positive foods? One study may have provided an answer to this question. In 2019, this study conducted in China evaluated the sIgG levels of 312 food intolerance patients. Fourteen foods were found to show sIgG positivity; these include crab (42.3%), shrimp (21.5%), egg (18.7%), and milk (16.99%). Subsequently, food elimination was done depending on the sIgG food results. After food avoidance, the skin and gastrointestinal tract, respiratory, and CNS symptoms were improved. The study findings may indicate primary prevention of food intolerance by early avoidance of sIgG positive foods. However, this is still controversial and needs more research [18].

### 3.6. Common foods showing sIgG positivity

A previous study done in Saudi Arabia with the largest sIgG food sample was reported. ImuPro has used their database. The study sample included 1644 patients who had undergone sIgG food test in the past. Results showed that the common positive sIgG food panels differed between adults and children. The common positive sIgG food panel in adults is shown in Table 5. In the children panel, the most common food positive for sIgG is cow's milk (95.74%) followed by oats (92.2%). However, despite the fact that these two panels are different, we can say that gluten and dairy products are the commonest in Saudi Arabia [19].

**Table 5.** The most common foods positive for sIgG among adults in Saudi Arabia.

IgG positive foods	Rate
Oats	82.5%
Barley	79.1%
Rye	76.1%
Cow's milk	75%
Wheat	74.9%
Kamut	74.6%
Spelt	74.6%
Gluten	73.9%

A large cross-sectional study conducted in Italy enrolled 6879 patients. The sIgG blood levels to 44 foods were measured. The sIgG test results showed positivity to various foods, but the most common products were cow's milk, goat milk, eggs, and yeasts. This study concluded that sIgG food test can be used to delay food sensitivities. Given that the two abovementioned studies were not linked to clinical allergic diagnosis, it was important to add the clinical diagnosis to both studies to identify which allergic diseases are more commonly associated with positive sIgG food tests [20].

## 4. Executive summaries

### 4.1. Atopic dermatitis

(1) In atopic dermatitis children, the sIgG positivity rate is significantly higher in the eczema and allergy groups than in the control group (especially for milk and egg).

(2) Positive sIgGs and sIgEs are mostly associated in atopic kids (eczematous or non-eczematous), especially for egg white, mixture of wheat and rice, orange, cow's milk, and inhalants.

(3) In atopic dermatitis kids, food elimination will lower the levels of both sIgEs and sIgGs to foods, especially egg, milk, and soya.

### 4.2. Allergic rhinitis

(1) In allergic rhinitis patients, the sIgG4 food test is usually positive to seafoods in Malaysia and possibly to other foods in other countries.

(2) Food elimination (which is dependent on the sIgG food test results) leads to the improvement of symptoms in both allergic rhinitis and asthma.

#### 4.3. Asthma

(1) Asthmatics who are persistent egg IgE sensitizers (SPT positive to egg at both 1 and 2 years) showed the following findings:

a. Persistent IgE egg sensitizers have higher sIgG1 to egg than transient egg and non-egg sensitizers.

b. In persistent sensitizers, a high level of sIgG1 to egg is a risk factor of future asthma (sIgG1 level at 1 year of >14500 units can predict future asthma with a sensitivity of 64% and a specificity of 74%).

(2) In asthmatics, food avoidance, especially to milk and egg, will lower the sIgG levels to both ovalbumin and beta lactoglobulin and will improve the peak flow meter readings.

(3) In asthmatics, IgG dependable food avoidance will:

a. Decrease the need to use asthma inhalers, oral montelukast, and oral antihistamines.

b. Improve the asthma parameters:

i. Decrease exacerbations, lung wheezes, and asthma symptom severity.

ii. Increase blood oxygen saturation.

#### 4.4. Urticaria

In chronic urticaria patients (in Saudi Arabia):

a. The most common foods with sIgG positivity are cola nut, yeast, wheat, red kidney bean, pea, corn, and egg white.

b. Women have a significantly higher positive sIgG rates than men for certain foods (wheat, corn, and cola nut).

c. Patients aged < 40 years have higher positive sIgG rates for certain foods (gliadin, egg white, and barely).

#### 4.5. Food intolerance

(1) In food intolerance patients, food elimination, which is dependent on IgG food test results, will lead to symptom improvement, especially in women with IgG positivity to egg, shrimp, and milk.

(2) Primary prevention of food intolerance can be done by early avoidance of triggers (depending on the IgG food test results).

#### 4.6. Common foods showing sIgG positivity

(1) In Saudi Arabia:

a. the most common foods showing sIgG positivity in adults are oat, barley, rye, cow's milk, wheat, Kamut, spelt, and gluten.

b. the most common foods showing sIgG positivity in children are cow's milk and oat.



c. In general, gluten and dairy products are the most common foods showing sIgG positivity in Saudi Arabia.

(2) In Italy, sIgG is positive mainly to cow's milk, dairy products, goat milk, egg, and yeasts.

## 5. Conclusions

The present study indicated that IgG food test can be performed if patients do not show improvement in symptoms after the IgE food tests. Moreover, as a solution for high cost of IgG food test, IgG food companies should offer cheap short IgG food test lists, which include the commonest food allergens, such as ImuPro Screen 22 foods or ImuPro Screen Plus 44 foods.

## Conflict of interest

The author declares no conflict of interest associated with this paper.

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