Review

Food-Specific IgG Antibodies: Decoding Their Dual Role in Immune Tolerance and Food Intolerance

Jenny Valentina Garmendia , Juan Bautista De Sanctis * , Alexis Hipólito García *

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Review

Food-Specific IgG Antibodies: Decoding Their Dual Role in Immune Tolerance and Food Intolerance

Jenny Valentina Garmendia [1], Juan Bautista De Sanctis [1,2,*] and Alexis Hipólito García [3,*]

[1] 1 Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry, Palacky University, Olomouc, The Czech Republic

[2] The Czech Advanced Technology and Research Institute (Catrin), Palacky University, Olomouc, The Czech Republic

[3] Institute of Immunology Nicolás E. Bianco Colmenares, Faculty of Medicine, Universidad Central de Venezuela, Los Chaguaramos, Caracas 1040, Venezuela

* Correspondence: Dr Alexis Hipólito García (alexisgarcia27@gmail.com. Dr. Juan Bautista De Sanctis juanbautista.desanctis@upol.cz

Abstract: Food-specific IgG antibodies, particularly those of the IgG4 subclass, have generated significant debate regarding their role in immune tolerance versus food intolerance. This article comprehensively reviews the literature on the subject, exploring evidence from healthy individuals and patient populations with varied clinical conditions. On one hand, IgG—especially IgG4—is frequently detected in individuals without adverse food reactions and may represent a normal adaptive immune response to constant dietary antigen exposure, contributing to the development of regulatory T-cell–mediated tolerance. On the other hand, several studies have linked elevated food-specific IgG levels with conditions characterized by increased intestinal permeability and inflammation, including eosinophilic esophagitis, irritable bowel syndrome, inflammatory bowel disease, and autoimmune disorders. The review discusses multiple investigations where IgG-guided elimination diets have yielded symptomatic improvements, suggesting a potential benefit for targeted dietary interventions. However, these findings are tempered by the observation that IgG antibodies are commonly present in asymptomatic individuals, thereby questioning their specificity as markers of adverse food reactions. Current diagnostic guidelines from leading allergy and immunology organizations discourage routine IgG testing for food allergies and intolerances, highlighting that these antibodies might instead indicate exposure or underlying inflammation rather than an actual pathogenic mechanism. There is a need for well-controlled, large-scale studies to clearly define the clinical relevance of food-specific IgG responses. Until more substantial evidence is provided, clinicians are advised to interpret IgG results cautiously and to consider them within the broader context of each patient's clinical presentation before recommending restrictive dietary changes.

Keywords: allergy; Immunoglobulins; IgG; IgG4; food intolerance; food tolerance

1. Introduction

Research has suggested a potential role for food-specific IgG antibodies in understanding food intolerance [1]. This refers to adverse reactions to foods not mediated by IgE. Investigating this connection may improve our understanding of food intolerances and lead to more effective management strategies [1]. Measuring these food-specific antibodies may serve as an effective strategy for identifying foods to which individuals may exhibit sensitivity, thereby aiding in developing an appropriate dietary plan [2]. A survey by the University of York in the United Kingdom investigated the effects of eliminating foods identified through a food-specific IgG ELISA blood test [3]. Among the patients who adhered strictly to the elimination diet, 75.8 percent reported a significant improvement in their condition [3]. Furthermore, of those who rigorously followed the

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diet and experienced considerable benefits, 92.3 percent noted a relapse of symptoms upon reintroducing the identified offending foods. The survey's authors concluded that employing an elimination diet based on food-specific IgG blood tests can effectively aid in managing the symptoms associated with various chronic medical conditions [3].

In recent decades, the potential role of anti-food IgG antibodies in mediating adverse food reactions has become a subject of considerable debate. Some researchers have suggested that elevated levels of food-specific IgG antibodies may indicate non-IgE-mediated intolerance and could be utilized to inform elimination diets. Initial studies yielded promising outcomes; for example, numerous patients adhering to an IgG-guided dietary regimen reported symptomatic improvement and experienced recurrences upon reintroduction of the implicated foods. However, increasing evidence indicates that food-specific IgG responses may represent a normal immunological reaction from regular dietary protein exposure [4]. In healthy individuals, these antibodies may even signify the development of immune tolerance rather than hypersensitivity [4].

Food-specific IgG and IgA antibodies are often identified in patients and healthy individuals. Yet, their role in food intolerance continues to generate considerable debate among researchers. The production of IgG4 isotype antibodies in response to dietary protein antigens may represent a typical immune reaction at mucosal surfaces [5,6]. Consequently, an increase in specific IgG4 antibodies directed against food antigens is associated with immune tolerance to these dietary components [7]. The presence of serum IgG antibodies does not inherently suggest a predisposition to hypersensitivity reactions; rather, it serves as a marker of immune tolerance, which is linked to the activation of regulatory T cells [7].

This multifaceted picture is further complicated by studies in both pediatric and adult populations, for example. At the same time, elevated IgG levels have been linked with later development of IgE-mediated allergies in children; they are also abundant in asymptomatic individuals. Thus, the clinical utility of food-specific IgG testing remains unresolved. The current body of literature calls for well-controlled, large-scale studies to differentiate between a marker of exposure or immune tolerance and a true mediator of food-induced pathology.

2. Materials and Methods

This review presents an overview of anti-food immunoglobulin G (IgG) through a comprehensive, non-systematic literature search conducted across various databases, including Scopus, EMBASE, PubMed, ISI Web of Science, ScienceDirect, Medline, Cochrane Library Plus, and Google Scholar. The search encompassed publications from inception until March 2025. Only articles with verified abstracts in English, Spanish, German, and French were included in this search. There were no restrictions based on the type of study. Scientific articles were selected from high-impact journals, specifically Q1, Q2, and Q3. The studies referenced in the sections about preclinical and clinical evidence were primarily chosen based on the clarity and reproducibility of their methodologies and their overall scientific quality. In addition, the web pages of the American and European Societies of Allergy and Clinical Immunology and Gastroenterology were assessed.

3. IgG Antibodies Against Food

A significant correlation has been noted between the titers of food-specific IgG antibodies and biomarkers that indicate intestinal permeability in adults [8]. Elevated levels of specific IgG antibodies against food antigens are frequently documented in conditions that exhibit increased intestinal barrier permeability, particularly in celiac disease, inflammatory bowel disease, and immunoglobulin A deficiency [5,9,10]. On the other hand, a study involving 1003 healthy individuals in Israel showed that many food antigens triggered systemic IgG responses in up to 50% of individuals [11]. Dietary intake of specific food proteins was linked to antibody binding, indicating that diet influences the IgG epitope repertoire. This conclusion agrees with the report of Czaja Bulsa

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et al [12], in which positive IgG against wheat was detected in patients infected with *Helicobacter pylori* who did not have food allergy.

Volpi and Maccary [13] conducted a study on IgG antibodies to 160 different foods within an Italian cohort of 6,879 subjects. Their findings revealed that 44 antigens exhibited an IgG response exceeding 10%, while only 14 foods demonstrated an elevated reactivity surpassing 20%, notably including cow and goat milk, several milk derivatives, eggs, and yeasts [13].

Antico et al [14] studied 73 adult patients with suspected food allergy and clinical manifestations of chronic urticaria or other allergy-suspected skin symptoms (pruritus or rashes). They tested for specific IgG4 against foods and made an open food challenge for all IgG4-positive foods. A double-masked, placebo-controlled food challenge controlled all positive open tests. Forty-five patients (62%) were food IgG4 positive (mainly egg, milk, casein, and wheat). None of the patients with IgG4-positive testing showed adverse reactions, neither immediate nor delayed, to the corresponding food. The authors concluded that testing for specific IgG4 in adult patients lacks clinical utility for diagnosing food allergy or intolerance [14]. Also, in children, there were no differences in ovalbumin-specific IgG, IgG1, and IgG4 between egg-allergic (n=40), egg-resolved (n=22), and control (n=18) [15]

Positive IgG4 to food is prevalent in adults without symptoms associated with food. In 13 healthy laboratory workers, positive results for IgG4 against different foods were found in all samples, and they don´t have any relationship to clinical problems from the intake of these foods [16]. Positive IgG4 tests to foods do not indicate the presence of food allergy but probably reflect prolonged exposure to food components [16].

The European Academy of Allergy and Immunology (EAAI) task force report concluded that food-specific IgG4 does not indicate food allergy or intolerance [16]. The report is supported by the American Academy of Allergy, Asthma, and Immunology [17] and the Canadian Society of Allergy and Clinical Immunology [18].

The food-specific IgG4 would be a physiological response after exposure to food components. Therefore, testing IgG4 for foods is considered irrelevant for laboratory work-ups on food allergy or intolerance and should not be performed in case of food-related complaints [16]. Other scientific associations covering the specialties of allergology (DGAKI, EAACI), internal medicine (DGIM), laboratory medicine (DG-KL), nutritional medicine (DAEM), and ecotrophology (VDOE) consider that the determination of IgG and IgG4 antibodies against food has no diagnostic value [19]. A recent review of non-IgE-mediated food allergy in children does not mention IgG anti-food as a tool for diagnosis [20].

Subsequent sections will address various medical conditions in which measuring anti-food IgG may serve as a valuable diagnostic parameter.

3.1. IgG Against Cow´s Milk Protein

The role of cow´s milk protein-specific IgG in cow´s milk allergy is controversial. Some consider it a normal physiological response to dietary milk proteins [21,22]. Still, others claim that food-specific IgG indicates variants of food allergies. Some longitudinal studies have reported that clinically reactive cow´s milk allergy patients had higher cow´s milk protein-specific IgG levels than in tolerized patients or controls [23,24].

The maintenance of tolerance to cow's milk in individuals, both children and adults, who do not have a cow's milk allergy, is associated with elevated levels of specific IgG4, as demonstrated by Ruiter et al [25]. Additionally, a study on children revealed that tolerance to cow's milk is linked to increased IgG4 levels of beta-lactoglobulin and alpha-casein. Consequently, upon follow-up, children diagnosed with cow's milk allergy exhibit diminished IgG4 levels to beta-lactoglobulin and alpha-casein [26]. Furthermore, in a cohort of children suffering from atopic dermatitis, the mean levels of IgE and IgG4 were found to be higher among those who tested positive in a double-blinded, placebo-controlled food challenge (DBPCFC) compared to those with negative outcomes in the DBPCFC across all food items studied [27].

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In a study conducted by Burks and coworkers [28], it was found that IgG specific to milk proteins did not show an increase in patients diagnosed with milk-protein intolerance. Conversely, another investigation indicated that patients with non-IgE-mediated cow's milk allergy exhibited elevated levels of β-lactoglobulin-specific IgG4 compared to both tolerized patients and control groups [29]. This research suggests that IgG4 may play a significant role in the context of delayed, non-IgE-mediated cow's milk allergy [29].

Additionally, a study involving nineteen adult patients experiencing milk intolerance, which resulted in asthma, eczema, or both conditions, revealed high titers of IgG subclass antibodies directed against cow's milk beta-lactoglobulin, alpha-lactalbumin, and alpha-casein [30]. However, it is essential to note that subsequent studies have not corroborated these findings [31,32].

Hochwallner et al [33] evaluated IgG subclass (1,2,3,4), and IgA antibody levels to purified recombinant αS1-casein, αS2-casein, β-casein, κ-casein, α-lactalbumin, and β-lactoglobulin by ELISA and IgE level by ImmunoCAP. They have four patient groups: patients with IgE-mediated cow's milk allergy (n=25), patients with non-IgE-mediated cow's milk protein intolerance (n=19), patients with gastrointestinal symptoms not associated with cow's milk ingestion (n=15), and control persons without gastrointestinal symptoms (n=26) [33]. The highest IgG1 and IgG4 antibody levels to αS1-casein, αS2-casein, β-casein, κ-casein, and α-lactalbumin were seen in cow's milk allergic patients [33]. There were no differences in levels of IgG1, IgG2, IgG3, IgG4, and IgA to purified cow's milk allergens between patients with non-IgE-mediated cow's milk protein intolerance and persons without cow's milk protein intolerance (patients with symptoms not related to cow's milk and controls) [33]. These authors concluded that cow's milk protein-intolerant patients cannot be distinguished from persons without cow's milk protein intolerance based on IgG subclass or IgA reactivity to cow's milk allergens [33]. Lo et al. [34] pointed out that allergy patch testing, IgG testing, or IgG4 testing is not helpful in any cow milk allergy evaluation since clinical assessment is the priority in those individuals.

The controversy of testing anti-food IgG can be clearly understood by examining the medical conditions linked to the presence of antibodies.

3.2. Eosinophilic Esophagitis (EoE)

Serum IgG4 levels to food proteins are elevated in patients with eosinophilic esophagitis (EoE) compared to controls [35–37]. Higher levels of IgG4 specific to milk have been independently associated with milk consumption and IgE sensitivity to milk proteins [37]. Additionally, esophageal biopsies from patients with EoE show significantly higher titers of IgG4 than those from control subjects [35,36]. In children with EoE, increased levels of serum IgG against cow's milk proteins, such as α-lactalbumin, β-lactoglobulin, and caseins, have also been reported [38]. However, dietary interventions based on IgG4 levels have not significantly improved histology or symptoms [39].

While serum milk-specific IgG4 levels have not consistently differed between individuals with and without milk-triggered EoE, the SOFEED (Six Food vs One Food Eosinophilic Esophagitis Elimination Diet) study found that baseline levels predicted dietary response in an EoE population [40]. Higher IgG4 responses to trigger foods than nontrigger foods have been observed in esophageal tissues and secretions. A combined assessment of T-cell proliferation and food-specific IgG4 led to a successful tailored elimination diet in 21% of subjects, with 14 out of 19 showing decreased eosinophil counts [41].

Elevated IgG and IgA subclasses levels, excluding IgG4, have been observed in patients, indicating a complex immune response to food allergens [42]. Despite the presence of these antibodies, allergen-specific B cells were not detected in the peripheral blood [42]. This finding suggests that the B cells within the lesions are primarily responsible for antibody production [42]. IgG4 colocalizes with food proteins in tissues with active EoE, particularly those with milk-triggered EoE [42]. This suggests that IgG4 may form immune complexes with these food proteins, which can penetrate the esophageal mucosa for extended periods during active EoE [42]. The implications of

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these complexes for antigen presentation, potential protective effects, or inflammation are still unclear, indicating that the role of IgG4 in EoE needs further investigation.

3.3. Irritable Bowel Syndrome (IBS)

Zar et al. [43] conducted a study involving 108 IBS patients and 43 control participants to assess IgG4 and IgE titers in response to 16 commonly consumed food items. The findings revealed that individuals diagnosed with IBS exhibited significantly elevated IgG4 titers to wheat, beef, pork, and lamb compared to the control group [43]. However, no significant differences in antibody titers were observed for potatoes, rice, fish, chicken, yeast, tomatoes, and shrimp [43]. Furthermore, the study indicated no significant differences in IgE titers between the IBS patients and the control participants. Notably, the study reported a lack of correlation between elevated IgG4 antibody titers and the symptomatology experienced by the patients [43].

In a study with IBS patients with functional dyspepsia and titers of IgG and IgE against common foods (beef, chicken, codfish, corn, crab, eggs, mushroom, milk, pork, rice, shrimp, soybean, tomatoes, and wheat), the authors reported titers of IgG against crab, egg, shrimp, soybean, and wheat than the control group [44]. Nevertheless, there were no differences in the percentage of individuals with positive food antigen-specific IgE antibodies between the three groups [44].

Lee and colleagues [45] reported that patients with irritable bowel syndrome who exhibit diarrhea have significantly elevated serum IgG4 titers against wheat, gluten, and gliadin compared to those without diarrhea. Patients without diarrhea had higher, but non-significant, titers against lettuce, leek, and taro than healthy controls [45]. These findings affirm earlier research that identified significant alterations in antibody production within a specific subgroup of patients.

Atkinson et al. [46] assessed the effectiveness of a dietary intervention that involved eliminating all foods to which patients with IBS had elevated IgG antibodies. This intervention was compared to a sham diet that excluded the same number of foods, albeit not those to which the patients had specific antibody responses [46]. The results revealed that the proper dietary intervention led to a 10% greater reduction in symptom scores than the sham diet after 12 weeks ($p = 0.024$) [46]. Moreover, Drisko et al. [47] demonstrated that a diet tailored to IgG responses to food and mold panels significantly improved the symptoms and quality of life for 20 IBS patients who had not benefited from standard medical treatments [46].

An open-label study, which included 73 female patients, compared the effectiveness of three different dietary treatment plans (low FODMAP diet, IgG-based elimination-rotation diet, and control diet recommended by an attending gastroenterologist) in patients with mixed IBS [48]. In the group of IgG-based elimination-rotation diet, IBS symptoms and comorbid symptoms significantly improved or disappeared altogether. This diet was more effective than low FODMAP and control diets [48].

The American College of Gastroenterology does not recommend testing for food allergy or food sensitivities in all patients with IBS unless there are reproducible symptoms concerning a food allergy [49,50].

3.4. Inflammatory Bowel Disease (IBD)

In the study by Frehn et al. [51], no significant differences were observed in antibody levels against food antigens, specifically wheat and milk extracts and purified ovalbumin, between patients suffering from IBD and healthy controls. However, subgroup analysis indicated that patients with Crohn's disease exhibiting severe manifestations, characterized by stricturing and penetrating lesions, possessed slightly elevated levels of anti-food IgA [51]. Conversely, Crohn's disease and ulcerative colitis patients with arthropathy demonstrated reduced levels of anti-food IgG antibodies [51].

Other studies have reported significant differences in serum anti-food IgG antibodies between Crohn's disease patients and healthy controls [52–56]. Notably, in the study by Cai et al. [53], food-specific IgG antibodies were detected in 75.9% (60 out of 79) of Crohn's disease patients and 63.6%

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(21 out of 33) of ulcerative colitis patients, compared to 33.1% (88 out of 266) of healthy controls [53]. A diet designed around these IgG antibodies has been shown to reduce daily stool frequency compared to a control diet [52,54].

Chen et al. reported that 81.3% (78 out of 96) of Crohn's disease patients tested positive for at least one food-specific IgG [56]. Notably, patients with minor bowel inflammation exhibited a higher prevalence of food IgG antibodies than their counterparts without inflammation [56]. Furthermore, Wang et al. [55] demonstrated a positive rate of food-specific IgG for a panel of 14 foods reaching 90.72% in Crohn's disease patients, in contrast to 57.5% in ulcerative colitis patients and 42% in healthy controls. While significant differences emerged between Crohn's disease patients and controls, no such differences were found between ulcerative colitis patients and controls. However, both Crohn's disease and ulcerative colitis patients exhibited a greater number of IgG-positive food items compared to controls.

In Crohn's disease patients, the most prevalent food resulting in positive serum IgG included tomato (80.68%), corn (69.32%), egg (63.64%), rice (61.36%), soybean (46.59%), milk (19.32%), wheat (17.65%), codfish (13.64%), and mushroom (3.4%). In contrast, the prevalent allergens in healthy controls were egg (66.7%), milk (28.6%), corn (19%), soybean (14.3%), mushroom (14.3%), rice (4.8%), and tomato (4.8%) [53]. This study found no association between disease activity and the prevalence of IgG against food [53]. Additionally, Xiao et al. [57] identified significantly higher levels of food-specific IgG in Crohn's disease patients (201) compared to ulcerative colitis patients (100) and healthy controls (178) against various antigens, including corn, codfish, soybean, milk, rice, wheat, egg, and tomato. Conversely, ulcerative colitis patients did not exhibit significant differences in food-specific IgG levels against 14 dietary antigens compared to healthy controls [57].

Research conducted in pediatric populations indicated that IgG antibodies against cow's milk proteins, including bovine serum albumin and beta-lactoglobulin A/B, were elevated in patients with Crohn's disease compared to those with ulcerative colitis and healthy controls [58]. Higher IgG anti-bovine serum albumin titers were observed in Crohn's patients with greater disease activity scores [58].

Quite the reverse, in the study of Jansen et al, anti-food IgG subclass levels were not different between inflammatory bowel disease patients and controls and did not correlate with food intolerance [59]. In contrast to anti-microbial Abs, food-specific IgG responses were predominantly of the IgG4 isotype, and all food-specific IgG subclass levels correlated negatively with age [59]. More research is required in this area.

3.5. Food-Specific IgG in Dermatitis

In a cohort of twenty-one children diagnosed with atopic dermatitis, the levels of IgG specific to ovalbumin and IgA specific to α-lactalbumin were significantly elevated compared to a control group of fifteen healthy children [60]. Furthermore, a study by Liu et al. [61] revealed that food-specific IgG favorable rates were 91.4% in the eczema group (n = 140) and 93.4% in the allergy group (n = 76). These rates were significantly higher than those observed in the control group of healthy children [61]. Patients with atopic dermatitis exhibiting elevated IgE Radio allergosorbent Test (RAST) scores demonstrated increased levels of IgG antibodies specific to wheat proteins [62].

In a study involving thirty children diagnosed with atopic dermatitis, researchers evaluated the presence of specific IgG and IgA for ninety-six food items [63]. The findings indicated no correlations between the levels of IgG or IgA against food items and various clinical parameters, including disease severity as measured by the SCORAD index, quality of life, skin hydration, or trans epidermal water loss [63]. Furthermore, dietary avoidance based on IgG or IgA levels exhibited minimal clinical effects on these parameters [63].

Moreover, children with eczema who initially tested positive for egg and/or milk through skin prick testing and were able to consume the offending foods at four and a half years of age demonstrated elevated levels of IgG4 antibodies specific to both β-lactoglobulin (cow's milk) and

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ovalbumin (hen's egg) upon inclusion in the study [64]. This suggests that elevated IgG4 antibodies to particular foods during infancy may indicate subsequent tolerance to those foods later in life [64].

3.6. IgG Antibodies to Foods in Children Who Subsequently Develop IgE Antibodies to Inhalant or Food Allergens or Allergic Diseases

In a study involving 96 children followed prospectively, it was observed that levels of IgG subclass antibodies to beta-lactoglobulin peaked during early childhood and subsequently declined until the age of 8 years [65]. Notably, children exhibiting atopic symptoms and sensitivity to allergens frequently displayed elevated IgG4 antibody levels to beta-lactoglobulin at age 8 [65]. Additionally, a correlation was identified between atopic dermatitis and heightened levels of IgG subclass antibodies to beta-lactoglobulin in early childhood [65].

Furthermore, in a cohort comprising 45 children with atopic or asthmatic parents, those with chronic eczema demonstrated increased ovalbumin IgG levels at 6 months, 1 year, and 5 years of age, along with elevated ovalbumin IgG4 levels at birth, 6 months, and 5 years of age [66]. In contrast, children with asthma exhibited higher concentrations of plasma ovalbumin IgG1 at birth, 1 year, and 5 years of age compared to their healthy counterparts [66].

Calkhoven PG et al. [67] studied 106 children at an increased risk of developing IgE-mediated allergy. High-risk children with a high IgG1 anti-food score more often developed inhalant-specific IgE antibodies than high-risk children with low IgG1 titers. Seventy-three percent of children with high anti-food IgG titers develop IgE anti-house dust mite antibodies, compared with 19% in the group with low titers of IgG [67].

Children at the age of 1 year who had increased levels of IgA or IgG antibodies against cow's milk β-lactoglobulin had a significantly increased risk of being sensitized to at least one of the allergens and food allergens at 6 years [68]. In the same way, children who had increased levels of IgG antibodies against gliadin at the age of 1 year had a significantly increased risk of being sensitized to at least one of the allergens, inhalant allergens, and food allergens at the age of 6 years [68].

In a retrospective study, all children and adolescents (n = 75) with allergic disorders (atopic dermatitis, food allergy, allergic rhinitis, and asthma) had food-specific IgG positive [69]. Dairy, gluten, and eggs were the most detected foods in specific IgG tests [69]. More studies are required to determine the mechanism involved and to ascertain the role of diet and microbiota, especially in the pediatric population.

3.7. IgG Anti-Food in Autism

In children with autism spectrum disorder, 89.89% (80/89 children) had at least one positive anti-food IgG [70]. Eggs, milk, and wheat were the top three food positives. The average concentration of specific IgG antibodies positively correlated with the high-level stereotyped behavior score on the ADI-R scale [70]. The study didn´t compare IgG levels with healthy children [70]. In another study, 162 children with autism spectrum disorders had higher titers of IgG against gliadin, deamidated-gliadin-peptide, and casein compared to controls (n = 44) [71]. However, the relevance of the presence of antibodies against these antigens in autism is still controversial since the same antibodies are found in other diseases.

3.8. Migraine

Zhao et al [72] investigated the differences in headache and comorbidity symptoms between 129 migraine patients with negative and positive food-specific IgG antibodies. Migraine patients who had positive food-specific IgG antibodies had significantly worse headaches, gastrointestinal, and anxiety symptoms, compared to the patients with negative IgG antibodies [72]. The most common positive foods were egg, milk, shrimp, codfish, crab, corn, and chicken [72]. On the other hand, in the Alpay et al [73] study (randomized, double blind, crossover), diet restriction based on IgG antibodies

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against 266 food antigens was an effective strategy in reducing the frequency of migraine attacks and decreasing mean total medication intake [73].

Rees et al [74] showed that 60 of 61 migraine patients (98.4%) had a positive IgG to a total of 48 different foods, with an average of 5.3 (range 0–17) reactions per patient. After two months of exclusion of positive foods, 38.2% of patients reported considerable benefit [74]. Similarly, Arroyave Hernández et al [75] evaluated the IgG against 108 foods in 56 patients with migraine refractory to traditional treatment. The number of positives for food IgG was significantly higher in patients with migraine compared to 56 controls [75]. IgG-based elimination diets control migraines without medications [75]. However, Mitchell et al [76] didn´t encounter any significant difference in the reduction of migraines in the true (according to IgG levels) and sham diet groups at 12 weeks.

Aydinlar et al. [77] evaluated the therapeutic potential of the IgG-based elimination diet in patients with IBS and migraine. In a double-masked, randomized, controlled, crossover clinical trial, they determined IgG antibody tests against 270 foods in 21 patients [77]. The elimination diet was associated with significant reductions in migraine attack count, maximum attack duration, mean attack duration, maximum attack severity, number of attacks with acute medication, and pain-bloating severity [77].

3.9. Obesity and Cardiovascular Disorders

Wilders-Truschnig et al [78] evaluated the level of IgG anti-food in 30 obese juveniles and compared it with non- obese juveniles. They found that obese juveniles showed a highly significant increase in the thickness of the intima media layer of the carotid arteries, elevated C-reactive protein values, and anti-food IgG antibody concentrations compared to normal weight juveniles. Also, anti-food IgG correlated with C-reactive protein and the thickness of the intima media layer [78].

A general conception that people with obesity have higher titers of IgG anti-food antibody is guided by the fact that a restricted diet ameliorates their condition. However, since there is a dietary restriction in the process, the decrease in body weight can be due to the exclusion diet and not to the specific IgG. The role of microbiota may be crucial in this process and needs to be studied.

A prospective study analyzing a pro-inflammatory diet in an extensive study from Northern Sweden showed that the inflammatory diet has repercussions in the incidence of myocardial infarctions, but only in males [79]. These results generate a question concerning the importance of gender and anti-food IgG. There are no studies concerning this topic.

3.10. IgG Anti-Food in Autoimmune Diseases

In 93 arthritis rheumatoid patients, 53 had raised levels of IgG antibodies to one or both dietary proteins (milk or wheat) [80]. In another study, elevated antibody levels against one or more nutritional antigens were found in all rheumatoid arthritis patients [81]. Still, these measurements could not predict which food would aggravate the symptoms. The authors indicated that a systemic humoral immune response against food is probably not involved in the pathogenesis of rheumatoid arthritis [81].

In a study conducted by Coucke [82], 100 patients with autoimmune diseases were compared with 25 controls without autoimmunity. IgG levels for specific food antibodies were significantly higher in the patient group than in the control group. The most reactive foods were casein, cow milk, wheat, gliadin, white eggs, and rice. The author suggested that a diet based on IgG results could be helpful for this kind of patient [82].

Patients with immune thrombocytopenic purpura didn´t show differences with controls in the results of IgG against 200 foods [83]. On the contrary, patients with rheumatoid arthritis were randomized to a gluten-free vegan diet in a clinical trial. After one year, levels of IgG against gliadin and β-lactoglobulin were reduced significantly in the responder group (according to the criteria of the American College of Rheumatology 20, ACR 20) in comparison with non-responders or patients on a well-balanced non-vegan diet [84]. This study's authors suggest that a vegan diet's positive effect

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in a subgroup of rheumatoid arthritis patients may be due to a diminished immune response to exogenous food antigens [84].

In 153 Hashimoto´s thyroiditis patients, the positive food-specific IgG antibody rate was 64.05% [85]. In another study, in 85 patients with Hashimoto´s thyroiditis, this rate was 97.65% against 90 food items, with an average of 15.76 ± 10.61 types of food intolerances, compared with 95.40%, with an average of 9.57 ± 8.90 types of food intolerances, in 87 healthy controls [85]. In the group of patients, the most common intolerances were eggs (75.29%), bok choy (71.76%), and milk (65.88%) [85]. In 74 Hashimoto´s thyroiditis patients, another group found positivity in twelve foods of a 125 food antigens panel, like in controls. Only anti-plum IgG was higher in patients than in the control group. There were no associations between IgG positivity and symptoms, thyroid hormone, autoantibodies, or food consumption [86].

In patients with active Behçet's disease, a significantly higher level of anti-beta-casein and anti-beta-lactoglobulin IgG and IgA antibodies was described [87].

Thus, patients with autoimmune diseases are more likely to have IgG levels against food circulating in the plasma, and this increase may be due to the condition and not related to an allergic reaction.

3.11. Food-Specific Serum IgG Reactivity in Psychiatric Disorders

Serum IgG levels against 39 selected food antigens were determined in patients with major depressive disorder (n = 22). IgG food hyperreactivity was detected in 64% of the patients compared to 19% of healthy controls (n = 21) [88]. However, in another study in 34 depressed patients and 29 controls, there was no significant difference in mean IgG concentration against 44 food antigens between patients and controls [89]. Significantly higher serum food antigen-specific IgG favorable rates were found in 186 adolescent patients with depressive disorders compared to the same number of healthy controls [90]. Individuals with bipolar disorder had increased levels of IgG antibodies to gliadin compared with controls [91].

In individuals with recent-onset psychosis (n=95) and long-term schizophrenia (n=103), Severance et al. [92] found elevated IgG to casein in comparison to non-psychiatric controls (n=65). Moreover, Kinnell et al. [93] studied 98 schizophrenic patients and 90 unaffected close blood relatives. They measured IgG to oats, wheat, gluten, chicken, calf, and milk protein. Only in a minority of patients were antibodies to food detected [93].

There is not enough data to establish a connection between anti-food IgG and psychiatric syndromes.

3.12. Chronic Inflammatory Breast Disease

In 32 patients with idiopathic granulomatous mastitis (chronic inflammatory breast disease), the prevalence of positive IgG to lentils and curry was significantly higher than in controls (32) [94]. Still, IgG against egg white was more prevalent in controls [94]. It is too early to determine the relevance of this food allergy in breast disease.

4. Suggested Approach to the Diagnosis of Food Allergy

Several suggestions have been made for laboratory tests to define food allergy and the importance of anti-food IgG. Onyimba and coworkers [95] described the available tests for food allergy in a simple table. We have adapted the Table into two Tables to highlight the critical points of the testing from the immunological point of view, taking into account the information represented here.

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Table 1. Recommended Food Allergy Testing.

Test	General description	Pros	Cons
• Oral food challenge	Conduct an oral challenge by gradually increasing the dose of the allergen until a response is observed.	A double-blind study is essential to define the specific trigger.	Potential severe allergic reaction. It may be expensive and inconvenient, especially in pediatric patients.
• Elimination diet (Should be supervised by the nutritionist and the medical doctor)	Exclusion diet of the most allergenic foods: cow's milk, wheat, eggs, soy, nuts, seafood.	Can be therapeutic and serve for diagnostics in celiac disease, EoS, IBS, and IBD.	Nutritional deficiencies can occur in the long term.
• Skin Prick test	Subcutaneous challenge to detect the effect of IgE, activating mast cells and generating a papule. The physician analyzes the papular reaction.	Highly sensitive. It is performed in a short time, and it is less expensive than allergy-specific IgE.	Low positive predictive value and low specificity. Antihistamines and anti-inflammatory drugs may alter results.
• Allergen specific IgE.	Enzyme-labelled antibody assay measuring specific IgE.	The results may be correlated with patient clinical symptoms.	The results from different commercial assays may differ significantly. It is expensive.

Table 2. Not Recommended Food Allergy Testing.

Test	General description	Pros	Cons
• Allergen-specific IgG	Detects IgG, which can be tolerogenic or a marker of exposure.	None available.	Highly unspecific. Difficulty distinguishing between tolerogenic and pathogenic IgG. It may not be elevated in patients with IgE allergy.

5. Conclusions

The evidence surrounding food-specific IgG antibodies illustrates a complex and unresolved scenario. On one hand, several studies indicate that elimination diets based on IgG profiles can lead to symptom relief in selected conditions such as irritable bowel syndrome, migraine, and some autoimmune disorders. On the other hand, the widespread presence of these antibodies in healthy

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individuals, especially in the context of IgG4's role in promoting tolerance, raises serious concerns about their specificity as markers of food intolerance.

Current guidelines from professional organizations in allergy and immunology caution against the routine use of IgG antibody measurements for diagnosing food allergies or intolerances, suggesting that the observed antibody responses may be more of an epiphenomenon associated with exposure and underlying inflammation. Moving forward, future research must focus on disentangling these complex immune responses. Extensive, controlled studies are needed to clarify whether elevated IgG antibodies represent a pathogenic mechanism or a natural immune adaptation to dietary antigens. Until stronger evidence emerges, clinicians should interpret food-specific IgG results cautiously and rely on a broader clinical context before recommending restrictive nutritional interventions.

These revisions not only streamline the narrative for better clarity and impact but also encourage a balanced view that recognizes both the potential and the pitfalls of using IgG antibodies as diagnostic tools in food sensitivity and related disorders.

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