Scientific Validity, IVD tests sIgG$_4$ and sIgG

Purpose of the document

DST and AESKU offer tests for the simultaneous measurement of human specific antibodies of the IgG type against various foods/antigens, with a focus on IgG$_4$ testing but also IgG tests. These tests are intended to allow an estimation of the IgG$_4$/IgG reactivity to various food antigens. The tests are mostly used by our customers for "Food Intolerance/Hypersensitivity Testing" which help qualified personnel to give improved dietary advice by a faster identification of relevant foods. This document will give a short overview of studies and findings on these topics.

Biological and clinical background

Adverse reactions to foods are common. They are often chronic and diminish the patients' quality of life. Some may even be life-threatening, such as anaphylactic reactions to peanuts and nuts. Theses reactions can have various causes, such as deficits in certain digestion enzymes or immunologic reactions. IgE antibodies against food components are a hallmark of food allergies and play a central role in food allergy testing [IgE 1], but can also be found in asymptomatic persons [IgE 2]. Anti-food antibodies of other isotypes, especially IgGs, have also been found in allergic patients and asymptomatic persons. Although their specific role in immunologic reactions to food and other allergens is not really understood so far, in the last decade, it became clear that IgGs, especially IgG$_4$ antibodies, may have a regulatory role in allergy and other IgE-mediated reactions.

IgG$_4$ is the least abundant component of the four human IgG subclasses (about 4% of total IgG) and has unusual structural and functional properties [IgG4 1]. In contrast to IgG$_1$ and IgG$_3$, IgG$_4$ does not drive inflammatory reactions. It is believed to act by blocking the interaction of IgEs with the allergens by binding to allergens in blood before they can interact with cell-bound IgE. Antigen-specific IgG$_4$ is upregulated in specific allergen immunotherapy [IgG4 3] and chronic helminth infections [IgG4 8] and seems to target similar epitopes as the corresponding IgE antibodies [IgG4 2,5]. Compared to IgG$_1$, IgG$_4$ responses are short-lived and probably more likely demonstrate ongoing but chronic immune processes [IgG4 9]. IgG$_4$ was also found to be a marker for chronic inflammatory processes presumably not driven by IgE [IgG4 6].

While there are indications that IgG$_4$ antibodies may dominate the total IgG response to certain allergens and food antigens due to their specialized role and regulation, this has not been analyzed in broad extent. Several studies indicate that while IgG$_1$ has a broader reaction spectrum, e.g. for milk proteins [IgG4 4], IgG$_4$ might be more focused on specific allergen components, resembling an IgE-like response.

Specific adverse reactions to food proteins result in a wide spectrum of symptoms in the gastrointestinal tract, the skin, the respiratory, and the neural systems. The underlying processes are not well understood so far, neither for IgE nor for non-IgE associated reactions. For both, IgE and non-IgE antibody associated adverse reactions, food avoidance of the offending food is the only treatment currently available. In the vast majority of self-reported adverse reactions to foods neither IgE nor skin prick tests will give a positive result, making it very difficult for the physician to identify the provoking food. IgG and IgG$_4$ testing has been described as a tool to accelerate this identification process. As for anti-food IgE testing, also IgG/IgG$_4$ results require confirmation by adjustments of the diet.

Anti-food IgG & IgG$_4$ and "Food Intolerance"

Historically and up to now, most allergy societies do not recommend IgG or IgG$_4$ testing for food allergies or other food related disorders due to the lack of clear-cut evidence [IgE 1].

A high proportion of children develops transient allergic reactions to staple foods such as milk, egg and wheat (PED 1-2). These reactions are usually temporary, leaving an immunologic "scar" of IgG/IgG$_4$ antibodies to these allergens. Antibodies to these allergens can still be found in many asymptomatic adults, while IgGs to other foods are rare (IgG 1,2). Commercial IgG/IgG$_4$ assays are usually optimized to compensate for this effect. As mentioned above, IgEs to various foods are also frequently found in non-allergic donors (IgE 1,2).

Initially based on anecdotal evidence, Dixon had suggested that the analysis of IgG responses to foods could be a tool to accelerate the identification of symptom-evoking foods in some cases of adverse reactions to foods by targeted dietary procedures (IBS 1). Several other studies indicated that diets based on such tests can reduce patients' symptoms, most focusing on irritable bowel syndrome (IBS) (IBS 1-6) and inflammatory bowel disorders (IBDs) (IBD 1-4). Studies in this field are often hampered by diffuse clinical definitions of the disorder(s) and response criteria, small patient sample sizes, the multitude of clinical symptoms and the lack of interest by the pharmaceutical industry, as food avoidance is the therapy option of choice. In addition, different IgG or IgG$_4$ tests by multiple vendors and in various test formats have been used in these studies. This limits the comparability.

By now, our understanding of the pathogenic processes involved in IgG-associated "food intolerance" reactions is rather limited. Very recently, findings in eosinophilic esophagitis (EoE), a not-IgE driven inflammatory reaction to food in throat, and related disorders may allow new insights herein. IgG$_4$ expressing B cells where found in lesions of EoE (EOE 1,2). Elimination diets based on anti-food IgG$_4$ reactivity where found to be helpful (EOE 3,4), reducing inflammation, lesions and IgG$_4$ B cells. The esophageal IgG$_4$s could also be detected in patients' sera (EOE 4). IgG$_4^+$ B cell-rich infiltrates were also found in IBDs (EOE 5) and eosinophilic chronic rhinosinusitis (EOE 6). If these findings are transferable to other food induced disorders, such as eosinophilic gastroenteritis, remains to be established.

Summary

Anti-food IgG/IgG$_4$ tests are intended to allow physicians or nutritionists improved dietary advice by a faster identification of relevant foods. Several studies and anecdotal evidence by users worldwide demonstrate their clinical value. However, non-IgE associated adverse reactions to food proteins are still not well understood. New findings indicate a special role of IgG$_4$ in such processes. As both, IgE and IgG against food, are known to exist in symptomatic and asymptomatic donors, the clinical relevance of immunoassay findings requires confirmation by adjustments of the diet. Recent findings on the role of IgG$_4$ in non-IgE dependent adverse food reactions will result in a deeper understanding of pathogenic mechanisms, as well as its diagnostic applications.

Literature

IgE 1: Ansotegui et al – World Allergy Organization Journal 2020 13 100080: "IgE allergy diagnostics and other relevant tests in allergy, a World Allergy Organization position paper".

IgE 2: Haftenberger – Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2013 56 687: „Prevalence of sensitisation to aeroallergens and food allergens: results of the German Health Interview and Examination Survey for Adults (DEGS1)" (in German).

IgG4 1: Aalberse et al – Clin Exp Allergy 2009 39 469: "Immunoglobulin G4: an odd antibody".

IgG4 2: Goldblum et al – Mol Immunol 2018 101 527: „Molecular patterns in the isotype-specific antibody responses to the major cedar aeroallergen Jun a 1".

IgG4 3: Reithofer et al – Clin Exp Allergy 2018 48 741: „Alum-adjuvanted allergoids induce functional IgE-blocking antibodies".

IgG4 4: Hochwallner et al – Allergy 2011 66 1201: "Patients suffering from non-IgE-mediated cow's milk protein intolerance cannot be diagnosed based on IgG subclass or IgA responses to milk allergens".

IgG4 5: Sackensen et al – Pediatr Allergy Immunol 2020 31 158: "IgE and IgG4 binding to lentil epitopes in children with red and green lentil allergy".

IgG4 6: Jackson et al – Am J Transplant 2020 20 513: "IgG4 donor-specific HLA antibody profile is associated with subclinical rejection in stable pediatric liver recipients".

IgG4 8: Caldas et al – Acta Trop 2008 108 109: "Human schistosomiasis mansoni: immune responses during acute and chronic phases of the infection".

IgG4 9: Unger et al – Eur J Immunol 2020: "Divergent chemokine receptor expression and the consequence for human IgG4 B cell responses".

IgG 1: Volpi & Maccari – J Immunoassay Immunochem 2008 30 51: „Serum IgG Responses to Food Antigens in the Italian Population Evaluated by Highly Sensitive and Specific ELISA Test".

IgG 2: Piuri et al – Nutrients 2019 11 1096: "Blind Analysis of Food-Related IgG Identifies Five Possible Nutritional Clusters for the Italian Population: Future Implications for Pregnancy and Lactation".

PED 1: Schwarz et al – J Allergy Clin Immunology 2016 138 1426: „IgG and IgG4 to 91 allergenic molecules in early childhood by route of exposure and current and future IgE sensitization: Results from the Multicentre Allergy Study birth cohort".

PED 2: Wilson et al – J Allergy Clin Immunol 2018 141 419: „Allergen sensitization in a birth cohort at mid-childhood: focus on food component IgE and IgG4 responses".

IBS 1: Dixon – Otolaryngol Head Neck Surg 2000 123 48: "Treatment of Delayed Food Allergy Based on Specific Immunoglobulin G Rast Testing".

IBS 2: Zar et al – Am J Gastroenterol 2005 100 1550: "Food-specific Serum IgG4 and IgE Titers to Common Food Allergens in Irritable Bowel Syndrome".

IBS 3: Atkinson et al – Gut 2004 52 1453: "Food elimination based on IgG antibodies in irritable bowel syndrome: a randomised controlled trial".

IBS 4: Drisko et al – J Am Coll Nutr 2006 25 514: "Treating irritable bowel syndrome with a food elimination diet followed by food challenge and probiotics".

IBS 5: Lee and Lee – J Neurogastroenterol Motil 2017 23 578: "Alterations of Food-specific Serum IgG4 Titers to Common Food Antigens in Patients With Irritable Bowel Syndrome".

IBS 6: Xiao et al – Intern Med 2018 57 2787: "Food-specific IgGs Are Highly Increased in the Sera of Patients with Inflammatory Bowel Disease and Are Clinically Relevant to the Pathogenesis".

IBD 1: Bentz et al – Digestion 2010 81 252: "Clinical relevance of IgG antibodies against food antigens in Crohn's disease: a double-blind cross-over diet intervention study".

IBD 2: Rajendran und Kumar – Colorectal Disease 2011 13 1009: "Food-specific IgG4-guided exclusion diets improve symptoms in Crohn's disease: a pilot study".

IBD 3: Gunasekeera et al – Digestive Diseases Sci 2016 61 1148: "Treatment of Crohn's Disease with an IgG4-Guided Exclusion Diet: A Randomized Controlled Trial".

IBD 4: Jian et al – Inflam Bowel Dis 2018 24 1918: "Food Exclusion Based on IgG Antibodies Alleviates Symptoms in Ulcerative Colitis: A Prospective Study".

EOE 1: Mohammad et al – J Pediatr Gastroenterol Nutr 2018 67 204: "Pediatric Eosinophilic Esophagitis Is Associated With Increased Lamina Propria Immunoglobulin G4-Positive Plasma Cells".

EOE 2: Schuyler et al – J Allergy Clin Immunol 2018 142 139: "Specific IgG4 antibodies to cow's milk proteins in pediatric patients with eosinophilic esophagitis".

EOE 3: Dellon et al – Clin Transl Gastroenterol 2019 10 e00099: "A Novel Allergen-Specific Immune Signature-Directed Approach to Dietary Elimination in Eosinophilic Esophagitis".

EOE 4: Wright et al – J Allergy Clin Immunol 2016 138 1190: "Food-specific IgG4 is associated with eosinophilic esophagitis".

EOE 5: Wang et al – Sci Rep 2018 8 10018: "High level of IgG4 as a biomarker for a new subset of inflammatory bowel disease".

EOE 6: Koyama et al – Allergology International 2019 68 216: "Significance of IgG4-positive cells in severe eosinophilic chronic rhinosinusitis".