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Evaluation of Food Specific Immunoglobulin G (IgG)- Guided Exclusion Diet in the Treatment of Irritable Bowel Syndrome and Inflammatory Bowel disease

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Abstract

From the beginning of this century, symptomatic improvements in different disorders with food specific immunoglobulin G (IgG)-guided exclusion diet have been reported. Most of them belong to gastrointestinal tract such as irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD). Although this diet has given a chance of symptomatic improvement as the main treatment in IBS or adjuvant therapy in IBD, it is still a matter of debate. Presence of food specific IgG antibodies also in healthy individuals and the use of IgG4 antibodies, known as protective antibodies against excessive immune responses in some of these studies are the main causes of these controversies. Additionally, there is no definite nomenclature for the reaction mediated by food specific IgG antibodies, the name of food intolerance is often used and it makes confusion by evoking non-immune adverse food reactions. Finally, the underlying mechanisms of these improvements have not been fully elucidated yet. Removal of foods that cause intensive immune responses or non-IgE-mediated allergic reactions or increased mast cell activation through IgG-food antigen complexes are among the suggested mechanisms. The effectiveness of this diet, opposing views and possible mechanisms to explain symptomatic improvements are focused in this manuscript.

Keywords: Inflammatory bowel disease, Irritable bowel syndrome, Food-specific IgGs, Food exclusion.

Abbreviations: IBD-Inflammatory Bowel Disease, IBS- Irritable Bowel Syndrome, CD-Crohn's disease, UC-Ulcerative Colitis, CDAI-Crohn's Disease Activity Index, EEN-Exclusive Enteral Nutrition, IgG- Immunoglobulin G, CRH- Corticotropin Releasing Hormone,

Introduction

Irritable bowel syndrome (IBS) is one of the common gastrointestinal disorders in the world with low-grade inflammation of the intestines [1]. Inflammatory bowel disease (IBD) includes Crohn's disease (CD) and ulcerative colitis (UC) which are chronic idiopathic inflammatory disorders with increasing incidence and prevalence in recent decades [2]. Although IBS is a functional disorder and IBD is an autoimmune one, there are some similarities between them. For instance, their etiopathogeneses are unknown, their therapeutic managements are often unsatisfactory and food-related complaints are frequently observed in these two diseases [2-4].

Adverse food reactions are perceived in up to 65% of IBS patients [3] and many patients with IBD often give histories of food related onset or aggravation of their attacks [2,4]. Some patients with IBS modify their diet by excluding self-identified foods and a few of them have to feed themselves with a very limited number of food. In patients with CD, exclusive enteral nutrition (EEN) usually can induce remission [5], however, relapse commonly occurs when normal diet is reintroduced [4,6]. The role of foods in both IBS and CD was demonstrated by Jones and his colleagues with elimination of symptom-forming foods from the diet [7,8].

These foods were found by adding a single food daily in patients' diet after making them asymptomatic with some applications e.g., TPN treatment as in some CD patients. 51 of 77 CD patients remained well for periods of up to 51 months with diet only [8]. Afterwards, these initial observations, some studies were achieved in IBS [9] and one study in CD [10]. In the largest study of patients with IBS, symptomatic improvements were found in 48% of patients with maintaining for a mean 14.7 months [11]. But in clinical practice, this procedure has not become prevalent because food selection takes time (for at least 3 months), needs more effort and is negatively affected by poor patient compliance [12].

Elimination of foods which have increased specific IgG antibodies seems as another successful diet for both IBS and IBD. Normally, healthy individuals have low levels of IgG antibodies against food antigens [13,14]. In IgG-guided exclusion diet, foods which have increased IgG levels above the cut-off value of healthy individuals are excluded and these foods can be briefly called "IgG-positive". In the year 2000, symptomatic improvements with this diet were first reported in patients having treatment resistant delayed food allergy [15]. Then similar results have been published for different disorders such as IBS [16-20], CD [4,21-23], UC [24], migraine [20,25,26] and



asthma [27]. In three of these studies, increased IgG4 antibody values were used for excluding foods [17,22,23].

Symptomatic improvements with IgG-guided exclusion diets suggest that there may be a relationship between IgG positive foods and these disorders. However it is really difficult to explain how these foods may be at least one of the important pathogenetic factors for different disorders in different systems or even of the same system such as IBS and IBD; one is functional and the other one is autoimmune. Despite the increasing number of these studies, the role of exclusion diet, guided food specific IgG antibody testing in the treatment have been contradictory. Removal of foods causing non-IgE mediated hypersensitivity reactions [3,15,28] or intensive immune responses [4] or increased mast cell activation by IgG-food antigen complexes [29] and stabilizing intestinal flora after EEN [4] have been suggested to be as pathogenetic mechanisms. In this review, the efficacy of this diet, possible mechanisms and opposing views are discussed.

IgG-guided exclusion diet results in patients with IBS and IBD

The therapeutic effects of the elimination diet, based on the food specific IgG antibodies in patients with IBS were first studied by Atkinson and his colleagues [16]. They randomly divided patients into true diet (whose exclude IgG positive foods) and sham diet (whose exclude same number of foods but not IgG positive) groups. After 12 weeks, the true diet group had in a 10-26% reduction in symptom score (related to their compliance) than the sham diet group. They concluded that food elimination based on IgG antibodies might be effective in reducing IBS symptoms and test for IgG antibodies might help select foods for elimination.

In the second study of patients with IBS, exclusion diet was administered according to food specific IgG4 antibody results [17]. Significant improvements were reported in severity and frequency of pain, severity of bloating with satisfaction of bowel habits and increase in rectal compliance. Then, three studies in patients with IBS were reported with elimination diet according to IgG antibody positivity. In the first one, the symptoms relieved completely in 31.4% and remarkably in 34.3% of patients at the end of eight weeks [18]. In the other study, the 12-week diet was evaluated in patients with diarrhea-dominant IBS. They obtained significant improvements in abdominal pain and distension, stool frequency and shape, general feelings of distress and total symptom score as compared with baseline findings of patients [19]. In the last one, the improvements were reported not only in IBS symptoms but also in migraine pain of the patients with both IBS and migraine [20].

The efficacy of this diet was more investigated in CD than UC. In the first study, the daily stool frequency in the patients with CD decreased significantly during a true diet in comparison to sham diet. Their abdominal pain reduced and general well-being improved [21]. In the second one, foods were eliminated according to IgG4 antibody results. At the end of four weeks, symptomatic improvement with a significantly reduction in modified CDAI and decreased ESR were obtained [22]. In a double-blinded randomized sham-controlled study with IgG4 guided four-week exclusion diet, improvement in quality of life and symptoms were shown [23]. In another study, IgG-guided exclusion diet also found to be useful in maintaining remission [4]. Patients in remission after EEN were divided as with or without (control group) diet intervention. Disease relapsed in 12.5% of the exclusion group compared with 25% of the control group. Moreover, more remarkable increasing in CDAI and ESR in the control group than in diet intervention group was obtained [4].

To date, there is only one study, investigating the effect of IgG positive food exclusion diet in patients with UC. Patients were randomly divided into an intervention (whose exclude IgG positive foods) and a control (whose eat healthy diet as normal) groups. At the end of six

months, stool frequency and Mayo score decreased, rectal bleeding, mucosal characteristics, and quality of life improved significantly in the intervention group than in the control group. Moreover, the number of patients with extraintestinal manifestations also decreased in the exclusion diet group [24].

Terminology Complexity

There is no definite nomenclature for the reaction, mediated by increased food specific IgG antibodies. "Food intolerance" is often used term for this reaction [30,31]. In fact, food intolerance includes non-immune-mediated adverse reactions to foods, related to enzyme deficiencies (e.g., lactose intolerance), pharmacologically active constituents of foodstuffs (e.g., tyramine in cheese) and unclear causes, such as certain irritants [3,32,33].

Food tolerance is the specific suppression of immune responses to food antigens and considered to play a central role in immune homeostasis. This physiological mechanism prevents unnecessary immune reactions to innocuous dietary antigens [34]. Food intolerance term may be preferred to explain the breakdown of this mechanism for some foods. "IgG-based food intolerance" or "IgG-mediated food intolerance" are the other terms, given for this reaction [24,35,36].

On the other hand, immunologically mediated adverse food reactions are known as food allergy/hypersensitivity [3,32,33]. Food allergy is classified as IgE-mediated (type I or immediate) and non-IgE-mediated (delayed) immune reactions [3,33]. Non-IgE-mediated reactions were postulated as to be type III hypersensitivity (IgG or IgM immune complex reactions) or type IV hypersensitivity (delayed-type or cell-mediated reactions) [33].

40-50% of children who are allergic to cow's milk have non-IgE-mediated e.g., delayed-type immune reactions may be caused by effector T cells or IgG antibodies [33]. "IgG-mediated food hypersensitivity" is another name, preferred for this reaction [3]. Although the general acceptance takes time, this term seems to be the most suitable one for this reaction. For now, it seems more appropriate to use one of the initial names, food sensitivity [16,37], instead of food intolerance.

Possible mechanisms of improvements with IgG-based food exclusion diet

There are some laboratory findings as an objective marker that suggest the relationship between IgG positive foods and CD. While decreased ESR was reported in two studies with elimination diet [4,22], we demonstrated significantly increased highly sensitive CRP levels and white blood cells counts with IgG positive food (6 days) and additive (added last 3 days) provocations in a pilot study [38]. Moreover, the increased fecal calprotectin levels in most of the patients on the following day of first provocation suggested the relationship between intestinal inflammation and IgG positive foods. The development of intestinal inflammation due to food antigens was shown in an experimental study, using a mouse model of colitis [39]. In this study, the inflammation via CD4(+) T cell hyperactivation was induced by food antigens associated with high serum IgG levels. Additionally this inflammation ameliorated by the elimination of food antigens.

On the other hand, clinical improvements in CD patients with decreased CDAIs [4,22,23] and the lower endoscopic score in the food exclusion group compared with the sham diet group of patients with UC [24] are the other objective findings that support the relationship between IgG positive foods and IBD.

The exact mechanism of IgG-mediated food reaction has not been fully elucidated yet. In the definition of food specific IgG test kits, it is suggested that IgG positive food exclusion diet prevents type III hypersensitivity reaction. Prevention of food allergy with IgG positive



food elimination also has been considered by some authors [3,15,28].

Some authors have suggested that the existence of intensive immune responses to food antigens in patients with CD and explained these improvements by excluding the moderately and strongly immunoreactive foods [4]. They observed longer remission periods in CD patients with IgG positive food restriction and have also explained this condition due to stabilizing the decreased microbial diversity, provided by prior EEN treatment [4]. Reduction in microbial diversity with EEN was reported in some studies [40,41]. Besides, it was shown that elimination of the food antigens ameliorated the inflammation in mice without altering the composition of their intestinal microbiota [39].

Another explanation for the improvements with IgG-guided exclusion diet has been based on decreased mast cell activation [29,42]. Although mast cells have long been recognized as only central players in IgE-mediated allergic reactions, recently it has been understood that they are multifunctional immune cells which are effective in several health and disease status [43,44]. Between several activating factors of mast cells, there are IgG-antigen immune complexes [45-48]. Food and food additive antigens often stimulate mast cells mediated by IgG antibodies [49]. While mast cells involve in physiological processes of the intestine such as regulating permeability, secretion, peristalsis and host defence to pathogens [43,44], increased mast cell activation have been suggested as a common feature in the pathogenesis of IBS [1,50,51] and IBD [52-54]. The relationship between increased mast cell mediators and pathophysiologic factors of IBS such as increased excitability of senso-secreto-motor neurons and visceral hypersensitivity [55,56], disturbed motility [57], and increased permeability [58,59] were shown in several studies. Increased IgG-food antigen complexes due to increased food specific IgG antibodies can cause more mast cell activation. Elimination of their specific antigens from diet may reduce mast cell activation by decreasing immune complexes because of lack of the food antigen part of them [29].

IgG-guided exclusion diet has also been suggested to help restoration and maintenance of gut barrier by decreasing the local inflammation [4]. On the other hand, mast cell tryptase has been considered as a key factor, disrupting the intestinal barrier in patients with IBS [1,50]. The reduced junctional adhesion molecule-A expression due to mast cell tryptase in patients with IBS was shown [59]. Increased intestinal permeability may be due to increased mast cell activation, mediated by IgG-food antigen complexes, as well. Removal of IgG positive food antigens has been considered to reduce intestinal permeability and bacteria, food and additive antigen absorption by decreasing mast cell activation [29].

Possible causes of food-related IgG antibody elevation

The reasons why IgG antibodies for some foods are elevated have not been exactly known. Increased intestinal permeability related more easily food antigen presentation to the gut immune system is one of the suggested opinions [24]. But this could not be explained by increased generalized intestinal permeability; in this case, IgG antibodies would be expected to rise against all eaten foods [60,61]. Differential permeability of the gut mucosa to different foods may be the other thought [60,61]. Different antigenicity of various foods [28,60], the impact of protein structure modifications during digestive processes [28], disturbance of the process concerning antigen load presented to the immune cells [28] are the other hypotheses, proposed. It has been also thought that different foods may lead to different modification of the gut immune responses [28,61]. However, some authors have suggested that hereditary and immunological factors might be effective [24].

Elevated IgG levels for some foods may also be related to breakdown of oral tolerance to them [28,34,62]. Antibiotic treatment induced

bacterial dysbiosis may affect oral tolerance [34,62]. Other suggested factors that might cause disrupted oral tolerance are injury, shock, trauma, surgery, drugs, blood transfusion and environmental triggers [62]. Mast cell activation related suppression of regulatory T (Treg) cell functions [63-65] may be another factor. Treg cells play a central role in oral tolerance [34]. Xenoestrogens activate mast cells [66] and excess xenoestrogen exposure as pesticide residues may be the common factors influencing oral tolerance because of their wide existence in the environment.

Opinions against IgG test

The first opposing point of view has been related to the presence of IgG antibodies against to food antigens in both normal adults and children. Some authors have considered that they might be the result of physiological response of the immune system, thereby reflecting exposure or tolerance to foods without a pathologic condition [37,67,68]. Actually, food specific IgG antibodies in healthy individuals usually exist but the levels are rather low [13,14] and mainly in IgG4 subclass [14]. Low levels of food specific IgG antibodies may be result of food tolerance. However increased levels for some foods may be due to the loss of tolerance to them and recognizing these food antigens as foreign ones with occurrence of B cell responses [28,34,62]. In addition, small amounts of immune complexes generate from low-level IgG antibodies and their food antigens may be one of the factors, stimulating mast cells for physiological functions in healthy individuals [29].

The second one has focused on food specific IgG4 antibody testing [32,67]. Two different IgG antibody tests were used in these studies. IgG4 test measures only the amount of IgG4, a subclass of IgG antibody. IgG test measures the sum of the amount of four subclasses of IgG antibodies including IgG1, IgG2, IgG3, and IgG4. IgG4 antibodies are usually accepted as "blocking antibodies" especially in the context of allergies [69,70]. They can usually prevent excessive immune responses against sterile antigens and may compete with IgE for allergen binding [69,70]. Immunotherapy studies also support the protective role of food-specific IgG4 antibodies in patients with food allergy [71]. Nevertheless, there were three studies which chose excluded foods to the IgG4 positivity and all obtained good results in patients with IBS [17] and Crohn's disease [22,23]. This situation may be explained by co-elevation of IgG and IgG4 antibodies for same foods especially in frequently consumed ones such as gluten, yeast, chicken egg, cow's milk and products. Elimination of IgG4 positive foods may decrease symptoms because of also elimination the IgG positive ones [29].

On the other hand, some foods with increased IgG antibody levels may not cause symptoms [68,72] and this may be the subject of discussion. This situation can be explained by the binding of some IgG-antigen complexes to the inhibitory receptors of mast cells [29]. Inhibitory receptors FcγRIIB do not trigger any intracellular signal and even trigger negative signals when they are co-aggregated with activating receptors by immune complexes [46]. Provocation for each IgG positive food after the patient becomes symptomless with elimination diet, may be necessary to rule out this possibility [42]. Additionally IgG positivity detected for some foods which not even been tasted beforehand. This may be due to antigenic similarity.

How the ideal IgG testing should be?

An ideal food specific IgG testing contains as much as food antigens based on the dietary characteristics of each country. In addition, it may contain antigens for alternative foods against the possibility of positivity of the ones frequently eaten. It is better to add the antigens such as maize, rice, buckwheat, quinoa or egg white, yolk and quail egg for gluten and chicken egg positivities. Some applications, related preparing milk and products e.g., boiling or fermentation will alter the antigenic structures. Hence boiled milk, yoghurt, cheese, and kefir



antigens should be checked separately. In addition, bread and brewer's yeast must be examined.

The type of test is especially important. Qualitative testing with fingertip blood cannot measure the level of antibodies, so cannot detect the antibodies very close to the upper limit. This is important in IBD patients who are under the immunosuppressive treatment. Even, anti-TNF therapy was shown to reduce the amount of IgG antibodies to food [28]. It is better to choose a quantitative testing.

What are the other additional factors to be considered in application of the IgG antibody-guided exclusion diet?

According to my personal data, most of the food additives especially thickening ones also cause elevation of IgG antibodies against themselves. It is not possible to examine all of them because of their large number. To get good results when applying IgG-guided exclusion diet, adding an empirically additive free diet seems to be logic.

Additionally, to reduce symptoms due to mast cell mediators may increase the success of the diet. Xenooestrogens such as pesticides and bisphenol A are common triggers for mast cells. The frequent sources of pesticides are contaminated water and foods [66]. To decrease their entrance into the body, spring waters instead of tap water should be used both for drinking and cooking. Bisphenol A, a polymer that can be released by polycarbonated plastics and by the linings of metal cans that are used for food and beverages. Therefore, avoiding storage of foods in these cans, plastic boxes and bottles will decrease bisphenol A contamination.

Moreover, one of the mast cell stimuli is the corticotropin-releasing hormone (CRH) induced by psychological stress [73]. Even, stress-induced mast cell degranulation was shown experimentally [58]. It will be beneficial for patients to get away from stressful life.

My another personal experience is that genetically modified crops can affect the success of IgG-guided exclusion diet. These foods contain new antigens and toxins. For example, transgenic plants, resisting insects contain significant amounts of Cry toxins (Cry proteins e.g., Cry1Ab, Cry1Ac) of *Bacillus thuringiensis* [74,75]. While Cry1Ab protein was shown in human sera [75], high immunogenicity of Cry1Ac with inducing antibody responses, including IgG was shown experimentally [74] e.g., food specific IgG antibodies. Therefore, it is better to use organic foods in which IgG-guided exclusion diet is not successful.

Conclusion and Future Expectations

Increased food specific IgG antibodies can be considered as a reliable indicator in finding most of the foods for exclusion and also management of IBS and IBD. In many of the patients with IBS, IgG based exclusion diet gives a treatment chance. In patients with IBD it will increase the success of medical treatment, shorten the course of active disease and prolongation of remission with reducing the economic burden of these diseases.

In the near future, after solving the IgG-IgG4 complexity, quantitative testing with allergen panels, prepared with the participation of as many but necessary foods as possible, seems to be more promising treatment results.

Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this paper.

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