RESEARCH ARTICLE

Food and Celiac Disease Antibodies in Diarrhea-Predominant Irritable Bowel Syndrome

Authors
Toshimi Chiba[1], Maiko Mori[2], Yuka Ikenoue[3], Kazuyuki Suzuki[4]

Affiliations
[1] Division of Internal Medicine, Department of Oral Medicine, Iwate Medical University, 19-1 Uchimaru, Morioka, Iwate 020-8505, Japan
[2] Ajinomoto Co., Inc., 15-1, Kyobashi 1-chome, Chuo-ku, Tokyo 104-8315, Japan
[3] Research Institute, EA Pharma Co., Ltd., 1-1, Suzuki-cho, Kawasaki-ku, Kawasaki-shi, Kanagawa, 210-8681, Japan
[4] Iwate Medical University, 19-1 Uchimaru, Morioka, Iwate 020-8505, Japan

Correspondence to: Toshimi Chiba, M.D., Ph.D.
Division of Internal Medicine
Department of Oral Medicine
Iwate Medical University
19-1 Uchimaru
Morioka, Iwate 020-8505
Japan
TEL: +81-19-651-5111
FAX: +81-19-654-3281
Email: toschiba@iwate-med.ac.jp

Abbreviations
EMA, endomysial antibody; FGIDs, functional gastrointestinal disorders; HLA, human leukocyte antigen; IBS, irritable bowel syndrome; IBS-D, diarrhea-predominant irritable bowel syndrome; Ig, immunoglobulin; tTG-IgA, tissue transglutaminase-IgA

Abstract

Background: Some foods can exacerbate the symptoms of irritable bowel syndrome (IBS), although the associations between the pathophysiology of IBS and IgG food antibodies levels are not well known. We examined IgG antibodies elicited in response to food and celiac disease in diarrhea-predominant IBS (IBS-D).

Methods: Twenty patients with IBS-D and 20 healthy controls (HC), were enrolled. Serum immunoglobulin (Ig) G antibodies to 88 dietary items were measured and scored in accordance with the rate of antibody positivity. Serum tissue transglutaminase-IgA (tTG-IgA) and IgA endomysial antibody (EMA) were measured as markers of celiac disease. Serum IgE antibodies were also measured.

Results: For the 88-item food-related IgG scores there was no significant difference in the number of dietary items with a ≥ 0.5 IgG score between the IBS and HC groups. Total IgG scores between groups were not significantly different. Scores for wheat, rye, and oats were not significantly different for the IBS versus the HC group. IgG scores for apples were significantly higher in the IBS versus the HC group. Serum tTG-IgA and EMA titers were negative in both groups and not significantly different between groups. Serum IgE was also not significantly different between groups. One patient with high titers for wheat, rye, and oats had duodenal mucosa histology classified as Marsh 1 and was negative for human leukocyte antigen DQ haplotypes *HLA-DQ2/HLA-DQ8*.

Conclusions: We investigated IgG antibodies to food, tTG-IgA, and EMA in patients with IBS-D in whom IgG levels are likely influenced by dietary habits.

Keywords: Food antibodies; Celiac disease antibodies; Celiac disease; Diarrhea-predominant irritable bowel syndrome

Introduction

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder (FGID) characterised by abdominal pain, abdominal distension, and diarrhea or constipation with bowel dysfunction. The reported prevalence of IBS is more than 15%.[1] IBS is one of the most common diseases that gastroenterologists treat and it impacts the quality of life (QOL) of those affected by it.[2] Despite patients with IBS being prescribed anti-diarrheal or anti-constipational agents, antispasmodics, and/or antidepressants, the symptoms can persist to some extent. Food elimination diets are another option that patients with IBS can consider for disease management as food intolerances are generally higher in them compared with healthy controls, and high IgG scores for specific foods have been reported.[3] However, food IgG scores do not always increase in IBS as has been reported in some studies, so the effects of food elimination for IBS remain somewhat controversial.[4,5] Comprehensive investigations of food IgG scores in IBS are still lacking.

Symptoms of diarrhea-Predominant Irritable Bowel Syndrome (IBS-D), such as diarrhea, abdominal pain, and bloating, are similar in patients with celiac disease. It is suspected that some cases of celiac disease could be misdiagnosed as IBS because serological examinations or biopsy specimens from the duodenal mucosa that are needed for the diagnosis of celiac disease, are not usually perfomed.

Although some foods may exacerbate symptoms of IBS, the associations between the pathophysiology of IBS and IgG food antibody levels are not well known. This study researched whether foods, or several types of foods, result in high IgG antibody levels in patients with IBS-D. Furthermore, we

examined whether patients with celiac disease are a subgroup of those with IBS-D.
The specific aims of this study were to examine the IgG levels elicited in response to 88 dietary items and to investigate the presence of antibodies in patients with celiac disease who were diagnosed with IBS-D.

Patients and Methods

Patients

Twenty patients with IBS-D under the age of 60 years (7 females, 13 males; mean age 41.3 years) under the Rome III criteria and 20 healthy controls (10 females, 10 males; mean age 33.3 years) were enrolled in this study. There were no significant differences in age or gender distribution between the IBS and control groups.

Methods

Serum IgG antibodies to 88 dietary items (Genova Diagnostics, USA) were measured and scored 0 <lowest>, 0.5, 1, 2, and 3 <highest> commensurate with the rate of antibody positivity (Table 1). Serum tissue transglutaminase-IgA (tTG-IgA) and serum IgA endomysial antibody (EMA) were measured as markers of celiac disease. Serum IgE antibodies were also measured. Seropositivity cutoffs that applied were ≥7 IU/mL for tTG-IgA and ≥20 IU/mL for EMA. The celiac disease-associated human leukocyte antigen (HLA)-DQ haplotypes (*DQ2, DQ8*) were determined in cases with high titers for wheat, rye, and oats.

Table 1: Lists of 88 dietary items by food type for which serum IgG antibodies can be measured.

Dairy products	Fruit	Vegetables	Seafood / meat	Cereals and nuts	Others
casein	apple	alfalfa meal	clam	almond	yeast
cheddar cheese	apricot	asparagus	cod	sunflower seeds	sugar cane
cottage cheese	banana	avocado	crab	walnut	chocolate
milk	blueberry	radish	lobster	quail beans	coffee
goat milk	cranberry	broccoli	oyster	peaks	honey
lactalbumin	grapes	cabbage	red snapper	green beans	
yogurt	grapefruit	carrot	salmon	lentil	
	lemon	celery	sardine	rye beans	
	orange	cucumber	shrimp	peanuts	
	papaya	garlic	flounder	soy	
	peaches	shishi Tang	trout	oats	
	pear	lettuce	tuna	gulten	
	pineapple	mushroom	beef	buckwheat	
	plum	olive	chicken	rice	
	raspberry	onion	egg white	rye	
	strawberry	beans	egg yolk	sesame	
		sweet potato	lamb	cone	
		potato	pork	cone gluten	
		spinach	turkey	wheat	
		green beans			
		tomato			
		zucchini			

IgG, immunoglobulin G

All participants provided written informed consent and the research was carried out in accordance with relevant ethical guidelines and regulations. This study was approved by the Investigation Review Board of the Institution.

Statistical analysis

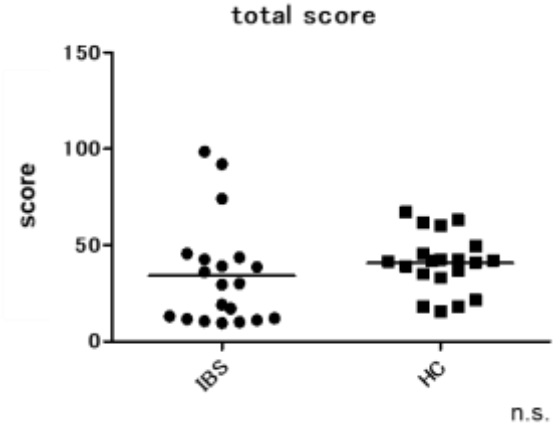
The Mann-Whitney U test was used to compare the median values for age or distribution of gender as well as the median IgG food antibody levels, tTG-IgA, EMA, or serum IgE antibody levels. A p value <0.05 was considered statistically significant.

Results

88-item dietary-related IgG scores

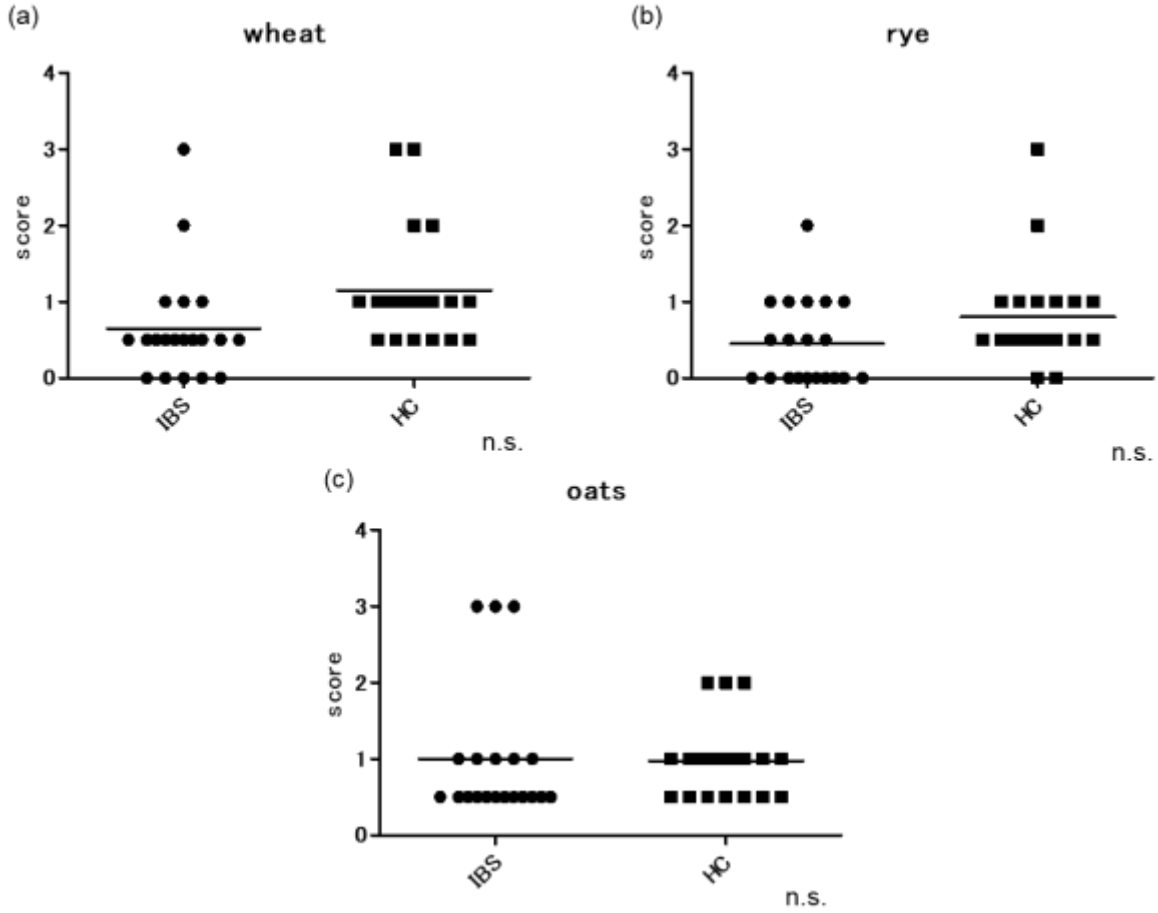
There was no significant difference in the number of dietary items for which the IgG score was ≥0.5 between the IBS and control groups. Total IgG scores were also not significantly different between groups (Figure 1). Additionally, the number of dietary items with IgG scores ≥0.5, ≥1, ≥2 was not significantly different between the IBS and control groups. The IgG scores for wheat, rye, and oats, which are typically associated with celiac disease, were not significantly different between the IBS and control groups (Figure 2). The IgG scores for apples were significantly higher in the IBS group than in the control group (Figure 3). Other dietary items were not significantly different between these groups.

Figure 1: Total IgG scores of foods.



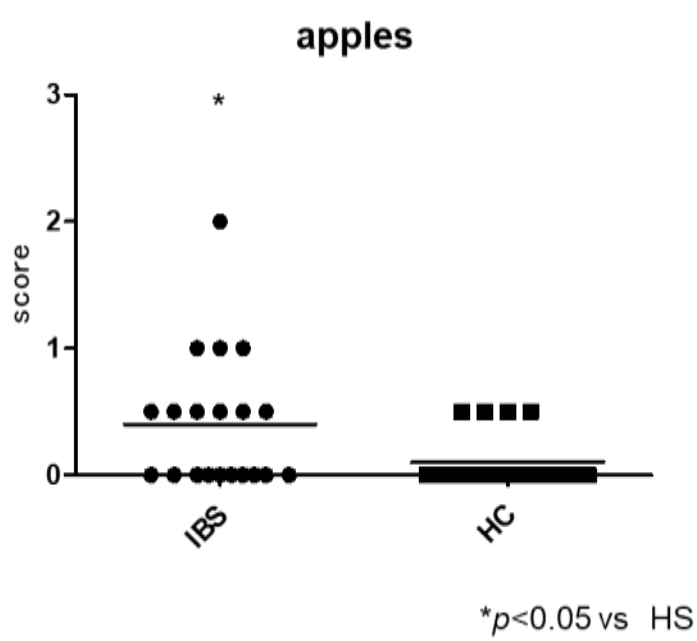
Abbreviations: HC, healthy control; IBS, irritable bowel syndrome; IgG, immunoglobulin G; n.s., no significant difference in total IgG scores between IBS and HC groups.

Figure 2: IgG scores for (a) wheat, (b) rye, and (c) oats.
(a) There was no significant difference in the IgG scores of wheat between IBS and control.
(b) There was no significant difference in the IgG scores of rye between IBS and control.
(c) There was no significant difference in the IgG scores of oats between IBS and control.



Abbreviations: HC, healthy control; IBS, irritable bowel syndrome; IgG, immunoglobulin G; n.s., no significant difference between IBS and HC groups.

Figure 3: IgG scores for apples.
The IgG scores for apples in IBS were significantly higher compared to those in control.
*p<0.05 versus HC.

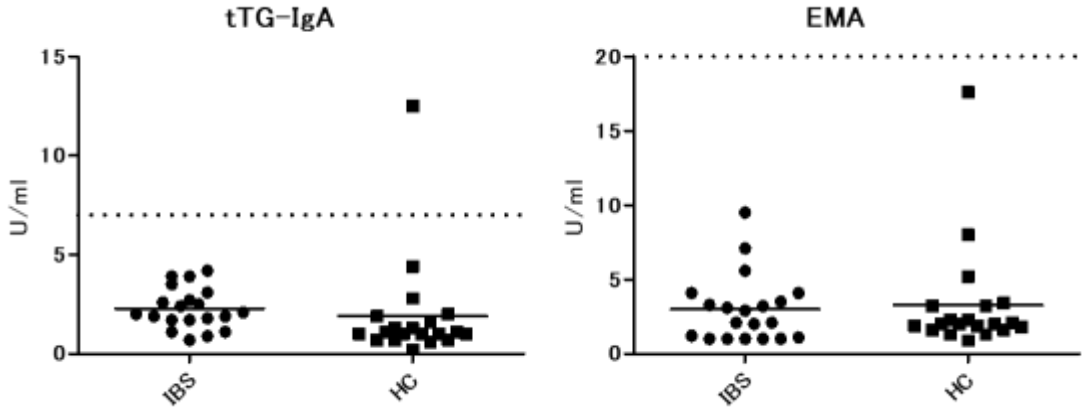


Abbreviations: HC, healthy control; IBS, irritable bowel syndrome; IgG, immunoglobulin G.

Serum tTG-IgA and EMA

tTG-IgA and EMA titers were negative in patients with IBS. The titers of tTG-IgA and EMA were not significantly different between the IBS and control groups (Figure 4).

Figure 4: Serum tTG-IgA and EMA.
(a) The tTG-IgA titers were negative in IBS and control. There was no significant difference in the titers of tTG-IgA between IBS and control.
(b) The EMA titers were negative in IBS and control. There was no significant difference in the titers of EMA between IBS and control.



Abbreviations: EMA, endomysial antibody; HC, healthy control; IBS, irritable bowel syndrome; n.s., no significant difference between IBS and HC groups; tTG-IgA, tissue transglutaminase-IgA.

Serum IgE antibodies

Serum IgE antibodies in patients with IBS were 178.2 ±311.5 IU/mL, and in the control group they were 168.3 ±201.9 IU/mL. There was no significant difference in serum IgE antibodies between the IBS and control groups.

A case with a high IgG Score for wheat

A patient with high IgG scores of 2, 1, and 3 for wheat, rye and oats, respectively, had duodenal mucosa histology classified as Marsh 1. Furthermore, the HLA-DNA typing of this patient was negative for *HLA-DQ2/HLA-DQ8.*

Discussion

In this study, dietary items with an IgG score of ≥0.5 were detected in patients with IBS; however, there were no significant differences in the numbers of dietary items that scored an IgG ≥0.5 or total IgG scores between the IBS and control groups. Correlations between IBS and food allergies have been reported; a food allergy has been indicated in 20-65% of people with FGIDs, including in patients with IBS.[6-8] The diagnosis of a food allergy is perfomed using a standardized skin prick test or radioallergosorbent test (RAST) which can induce an IgE-mediated immune response to specific foods.[9-10] An IgE-mediated immune response in patients with IBS can be considered rare, and it might be associated with the onset of some IBS symptomology.[6-11] In contrast, an IgG-mediated immune response elicited after exposure to a certain food might be associated with a worsening of postprandial abdominal symptoms in patients with IBS.[12-18] Certain foods can induce IBS symptoms and strategic food elimination approaches can improve IBS symptoms. Serum IgG antibodies for dietary items have been useful to diagnose food allergies or to determine the effects of eliminating certain foods in patients with IBS.[19-23] Zuo et al. reported on the significantly higher serum IgG levels of 5 types of food including crab, egg, shrimp, soybeans, and wheat in patients with IBS compared with healthy controls. [22] Zar et al. reported on IgG levels in response to beef, pork, lamb, and wheat foods, which were significantly higher in patients with IBS compared with healthy controls.[23] Guo and Drisko report that the serum IgG levels of certain foods were higher in patients with IBS compared with healthy controls, and showed that the elimination of these certain foods improved IBS symptoms.[4,21] In contrast, Lagaarden et al. reported no significant differences between IBS and non-IBS patients in terms of serum-specific IgG and IgG4 antibodies in response to 10 dietary items.[24] In that study, the IgG levels in response to milk and wheat were significantly decreased in patients with IBS compared with those without IBS. Furthermore, the lower IgG scores in response to eggs and beef were associated with abdominal symptoms in patients with IBS consistent with other findings that egg and beef appear to be tended to exacerbate symptoms in patients with IBS.[25,26] High food-specific IgG levels might reflect the intake of these specific foods; in fact, IgG levels elicited in response to foods in patients with IBS could be correlated with habitual dietary intake.[27]

High IgG levels in response to certain foods differ according to each report; regional differences in dietary habits between Chinese and western populations for example can be involved.[22,23] IgG levels in response to foods in patients with IBS can also be influenced by personal dietary habits. In our study, the serum IgG scores for apples in patients with IBS were significantly higher than the IgG scores in the control group, although other dietary items were not significantly different between the two groups. High IgG levels pertaining to exposures to certain foods in patients with IBS have been observed, and it is inherently difficult to implement an elimination diet addrressing the high IgG levels with certain foods.[22,23] Because no significant correlations between high IgG levels of foods and IBS symptoms have been reported.[5,28-30] IBS symptoms could be induced by certain foods, and we believe a food elimination diet can improve those symptoms. In order to determine if an elimination diet of high serum food IgG

levels can improve IBS symptoms, it is necessary to examine food intake records. Only then we can clarify the methodology employed in the elimination diet to better manage IBS.

In this study, tTG-IgA and EMA were measured to investigate whether IBS-D included celiac disease, and both tTG-IgA and EMA were negative. A case with a high IgG score for wheat in this study had a duodenal mucosa Marsh score of 1 and the HLA-DNA typing of this patient was negative for *HLA-DQ2 / HLA-DQ8*; therefore, celiac disease was not diagnosed in this case. IBS-D patients in this study are unlikely to include patients with celiac disease. However, reports of 3-5% of patients with celiac disease being included amongst patients with IBS-D exist.[31,32] IBS symptoms, such as diarrhea, abdominal pain, and bloating are similar to the symptoms experienced with celiac disease. A serologic examination or a duodenal biposy is usually not performed for the diagnosis of celiac disease, and therefore, it is feasible that some cases of IBS-D might include cases of celiac disease.

It has been reported that the proportion of patients with celiac disease among those patients with IBS is low when a definitive diagnosis is made via a duodenal mucosal biopsy.[33,34] When positive serological markers for celiac disease, such as tTG-IgA and EMA in IBS-D, were 4.8%, the rate of diagnosis of celiac disease was 0.41% as determined via a duodenal mucosal biopsy; this was similar to the rate of non-IBS (0.44%).[34] In order to determine whether patients with celiac disease are among those with IBS, further tests using serological markers in addition to duodenal mucosal biopsies will be necessary. Although reports have shown that some patients with IBS were negative for both serological markers and histological findings for celiac disease, some patients with gluten sensitivities experienced an improvement in their IBS symptoms when they consumed a gluten-free diet. It has been suggested that a gluten-free diet for patients with IBS, but not celiac disease, is effective for improving their IBS symptoms.[35,36]

The diagnosis of celiac disease relies on specific serological testing, histological evaluation of duodenal biopsies, and improvement after the introduction of a gluten-free diet. The strongest and best-characterized genetic susceptibilities in celiac disease are HLA class II genes known as *HLA-DQ2* and *DQ8*.[37] Recently, non-celiac gluten sensitivity (NCGS) related to the wheat and the gluten intolerance has been advocated after excluding celiac disease by serology, HLA typing and duodenal biopsy. However, the borderline between IBS, food intolerance, NCGS and celiac disease is not always clearly distinguishable.[38] The diagnosis and treatment of these patients should need to be further consideration.[39]

There are some limitations associated with this study. First, our investigation was a pilot study with a relatively small number of patients; therefore, we are unable to draw strong conclusions regarding the roles of the IgG scores linked to foods, tTG-IgA, and EMA in patients with IBS-D and celiac disease. Second, since we did not investigate correlations between the IgG scores of foods and symptoms, we should clarify the changes in dietary IgG levels with elimination diets in IBS-D patients. These issues warrant further investigation in a future study.

Conclusion

We investigated IgG food antibodies, tTG-IgA, and EMA in patients with IBS-D. IgG levels associated with exposure to certain foods in patients with IBS are likely influenced by dietary habits. It will be important to diagnose those patients with IBS who do not have celiac disease in order to provide them with appropriate treatment.

Declarations

Authors' contributions

TC, MM conceptualized and designed the study, analyzed and the data and drafted, edited, and approved the manuscript. All authors reviewed and approved the final

manuscript and agree to be accountable for all aspects of the work.

Acknowledgements
A portion of this manuscript was presented at the Japan Digestive Disease Week in 2012.

Conflict of Interest
The authors have no conflicts of interest to declare. M.M. is an employee of Ajinomoto Co., Inc., and Y.I. is an employee of EA Pharma Co., Ltd.

Ethical Considerations
The study proposal was reviewed and approved by the Human Ethics Review Committee of Iwate Medical University. Written informed consent was obtained from each patient prior to enrollment.

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