Immunoglobulin G4-related immune responses to common food antigens in patients with ulcerative colitis and Crohn's disease

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ABSTRACT

Background/Aims: *It is unclear whether IgG4-related immune responses to food can play a role in the pathogenesis of inflammatory bowel disease (IBD). The aim of the present study was to investigate the serum levels of IgG4 to common food antigens in patients with ulcerative colitis (UC), Crohn's disease (CD), and healthy controls.*

Materials and Methods: *Thirty-six patients with CD (n=12) or UC (n=24) and 36 sex- and age-matched healthy individuals (mean age, 49 years) participated in the study. Serum levels of IgG4 to 90 common food antigens were measured. The number of subjects with positivity, defined by cut-off values ≥0.7 U/mL, was compared.*

Results: *Serum titers of IgG4 to salmon, onion, shrimp, cuttlefish, eel, millet, gluten, soybean, and coconut in patients with IBD were significantly or tended to be higher than those in the control group. Serum levels of IgG4 to salmon, millet, and onion in patients with CD were significantly or tended to be higher than those in the control group. Serum titers of IgG4 to cuttlefish and onion in patients with UC tended to be higher than those in the control group. The number of subjects with positivity to cod, tuna, mackerel, oat, pea, peanut, and coconut was significantly higher in patients with CD than in healthy controls. The number of subjects with positivity to kiwi and cuttlefish was significantly higher in patients with UC than in controls.*

Conclusion: *Patients with IBD shows higher serum levels of IgG4 to diverse food antigens. Patients with CD present IgG4-related immune reactions to more foods than patients with UC.*

Keywords: *Crohn's disease, food, immunoglobulin G4, inflammatory bowel disease, ulcerative colitis*

INTRODUCTION

Inflammatory bowel diseases (IBDs), such as Crohn's disease (CD) and ulcerative colitis (UC), are relatively more common in the West than in the East. However, the incidence of IBD is rapidly increasing, especially in Asia (1). This rapid increase in Asia suggests the importance of environmental factors in the pathogenesis of this disease. Among the environmental factors, diet may play a key role (2). Westernization of dietary habits may be involved in the increased prevalence of IBD in Asia, including South Korea.

Several mechanisms, including direct dietary antigens, changes in the gut microbiome, and effects on gastrointestinal permeability, are possible mechanisms through which food may trigger intestinal inflammation (3). The role of food hypersensitivity, classified as IgE-mediated and non-IgE-mediated reactions, in patients with IBD has been a very controversial subject (4). Food-specific IgE antibodies are easy to recognize through the overt allergic reaction they induce or diagnostic testing for food allergies (5). However, non-IgE-mediated reactions are relatively difficult to recognize. Among the four subclasses of IgG antibodies, IgG4 reactions occur in the gut after repeated exposure to food antigens (6,7). Commercial food hypersensitivity tests evaluating serum IgG4 levels against various food antigens are widely available. Recently, studies regarding IgG-related adverse reactions to food in patients with IBD are increasing. It was reported that serum IgG4 antibodies to common foods are higher in patients with IBD (8). A food-specific IgG4 antibody-guided exclusion diet is known to improve symptoms in patients with IBD (9). Furthermore, approximately 70% of patients with IBD avoid certain foods (10). However, few studies regarding serum IgG4 levels to common food antigens in Asian patients with IBD have been reported.

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The aim of the present study was to investigate the levels of serum food-specific IgG4 to common food antigens in patients with IBD and healthy controls in South Korea.

MATERIALS AND METHODS

Subjects

Patients with IBD who visited the Gastroenterology Department of a teaching hospital were screened for the current study. All subjects were diagnosed with IBD based on the consensus guidelines of the European Crohn's and Colitis Organization (11,12). Clinical data, including medical records, blood tests, colonoscopy with biopsy, and radiologic studies, were comprehensively reviewed. Clinical activity was evaluated using the CD activity index (13) for CD and the Mayo score (14) for UC. Exclusion criteria were (1) patients with severe comorbidities, such as cardiovascular diseases, chronic renal diseases, or chronic liver diseases, among others; (2) patients with mental illnesses or pregnancy; (3) patients who recently underwent (<3 months) gastrointestinal surgery.

The healthy control group included subjects who did not have gastrointestinal diseases or recurrent abdominal symptoms. They were age- and sex-matched with the patient group. They completed the symptom questionnaire, blood tests, and colonoscopy in order to exclude the presence of any recurrent abdominal symptoms and organic diseases. Informed consent was obtained from all participants before participating in the study.

Study design, approval, and determination of the sample size

This was a prospective, controlled design study. The institutional review board of the hospital according to the ethical guidelines of the Declaration of Helsinki approved the study protocol and informed consent form (MJH15-004). This trial was registered at http://cris.nih.go.kr (KCT0001779). Serum titers of serum IgG4 against 90 common foods were measured. The eligibility of the subjects was determined before the start of the study.

Table 1. List of the 90 common food antigens tested in the study

Dairy, meat, and poultry antigens	Fruit antigen	Fish and shellfish antigens	Grain and legume antigens	Vegetable antigen	Nut, seed, and miscellaneous antigens
Cow's milk	Apple	Cod	Rice	White radish	Almond
Casein	Banana	Salmon	Wheat	Cabbage	Coconut
Chicken	Grape	Shrimp	Corn	Carrot	Sesame
Egg white	Grapefruit	Tuna	Oat	Celery	Walnut
Egg yolk	Lemon	Clam	Millet	Cucumber	Cashew nut
Lamb	Orange	Crab	Barley	Garlic	Sunflower
Pork	Peach	Lobster	Buckwheat	Mushroom	Pepper
Beef	Pear	Mackerel	Gluten	Mustard seed	Coffee
Yogurt	Pineapple	Oyster	Gliadin	Olive	Tea
Duck	Strawberry	Abalone	Pea	Onion	Baker's yeast
Cheese	Blueberry	Scallop	Soy bean	Green pepper	Ginger
	Watermelon	Cuttlefish	Peanut	Potato	Brewer's yeast
	Plum	Eel	Kidney bean	Spinach	Cocoa
	Kiwi			Tomato	Honey
	Mango			Broccoli	Aspergillus
				Lettuce	Kelp
				Sweet potato	
				Leek	
				Taro	
				Bamboo shoots	
				Eggplant	
				Mugwort	

In a previous study (8), IgG4 positivity in patients with IBD and controls was reported to be 72.3% (81/112) and 33.1% (88/266), respectively. The number of participants to be included in each arm of this study was estimated in order to obtain satisfactory results with an α of 0.05 and a power of 0.90. A total of 64 subjects, with 32 subjects and 32 controls, were determined for the appropriate sample size. We planned to enroll 72 subjects in the consideration of a drop-out rate of 15%.

Measurement of serum food antigen-specific IgG4

Serum food antigen-specific IgG4 levels were measured using the Food Allergy Screening ELISA Kit (Metametrix Clinical Laboratory, Duluth, GA, USA). Food allergens, derived from native foods, were immobilized on solid phase (ELISA plate), and titers of IgG4 against 90 common foods were measured. Food groups were classified into six categories: (1) diary/meat/poultry, (2) fruit, (3) fish/shellfish, (4) grains/legumes, (5) vegetables, and (6) nuts/seeds/miscellaneous (Table 1). The antibody titers were expressed as U/mL. The levels of IgG4 to each food were ranked in classes of 0 to +5 according to cut-off points established by the manufacturer. The cut-off value for +2 was 0.7 U/mL, which was considered positivity for the food antigen. All participants were asked to complete the symptoms questionnaire regarding the presence of abdominal symptoms after eating each of the 90 common foods.

Statistical analysis

Statistical analysis between subjects with IBD and healthy controls was performed using the Pearson's chi-square test and an independent sample *t*-test. Odds ratios and 95% confidence intervals were calculated. The number of subjects with positivity, defined as a cut-off value ≥0.7 U/mL, was compared using the Pearson's chi-square test. A p-value <0.05 was considered statistically significant. The Statistical Package for Social Sciences software for Windows version 11 (SPSS Inc.; Chicago, IL, USA) was used for all analyses.

Table 2. Demographic features of the study subjects

Characteristics	Patients (N=36)	Controls (N=36)	p[a]	Patients with CD (N=12)	Patients with UC (N=24)	p[b]
Age (year)	48.03±16.88	49.75±10.75	0.601	41.08±19.28	49.67±16.35	0.171
BMI (kg/m2)	22.58±3.15	24.03±2.33	0.030*	22.71±3.31	22.51±3.14	0.860
Hypertension	6	7	0.759	1	6	0.343
Diabetes	1	3	0.303	1	0	0.473
Myocardial disease	0	3	0.077	0	0	-
Allergic disease	1	0	0.314	1	0	0.473
Intestinal surgery	5	2	0.233	1	4	0.017*
Disease duration						0.700
—<5				13	8	
—5-10				7	2	
—>10				4	2	
Disease activity						-
—Remission				11	21	
—Mild-to-moderate				1	3	
—Severe				0	0	
Location						
—L1 or E1				5	17	
—L2 or E2				1	5	
—L3 or E3				6	2	
Anti-TNF treatment				3	1	0.002*

Values are presented as mean±standard deviation or numbers
*Statistically significant; p[a] between patients and controls; p[b] between CD and UC
CD: Crohn's disease; UC: ulcerative colitis; BMI: body mass index; L1, L2, L3 and E1, E2, E3: disease localization according to the Montreal classification; TNF: tumor necrosis factor

RESULTS

Subject characteristics

From March 2016 through October 2016, thirty-six patients diagnosed with CD (n=12, mean age, 41.1 years) or UC (n=24, mean age, 49.7 years) and 36 sex- and age-matched healthy individuals (21 men and 15 women; mean age, 49 years) were included in the study.

Demographic features, including age, comorbidities, and history of allergic diseases, were comparable in both study groups. Body mass index was significantly lower in patients with IBD than in healthy controls (22.6±3.2 kg/m^2 vs. 24.0±2.3; p=0.030). Most of the patients with CD or UC were in remission status, except for four patients with mild-to-moderate disease activity (Table 2). There are no patients using corticosteroid at the time of the study. The number of patients treated with biological agent was significantly higher in patients with CD than in those with UC (3 vs. 1; p=0.002).

Serum IgG4 titers to food antigens

Patients with IBD had significantly higher titers of IgG4 to salmon (0.07±0.18 U/mL vs. 0; p=0.025) and onion (0.27±0.41 U/mL vs. 0.08±0.29; p=0.024) than controls (Table 3). Serum titers of IgG4 to shrimp, cuttlefish, eel, millet, gluten, soybean, and coconut in patients with IBD tended to be higher than those in controls. Serum levels of IgG4 to salmon, millet, and onion in patients with CD were significantly or tended to be higher than those in controls. Serum titers of IgG4 to cuttlefish and onion in patients with UC tended to be higher than those in controls (Table 4).

Table 3. Food antigens showing differences in IgG4 titers (U/mL) between patients and controls

Food antigens	Patients (N=36)	Controls (N=36)	p[a]
Egg white	3.08±7.17	3.58±8.20	0.787
Lemon	0.01±0.07	0.03±0.13	0.300
Mango	0.01±0.07	0.03±0.11	0.319
Salmon	0.07±0.18	0	0.025*
Shrimp	0.10±0.30	0.01±0.09	0.094
Cuttlefish	0.21±0.63	0.01±0.06	0.067
Eel	0.18±0.59	0.01±0.06	0.089
Millet	0.09±0.19	0.02±0.09	0.057
Gluten	5.95±18.30	0.64±1.85	0.092
Soy bean	0.18±0.60	0	0.077
Onion	0.27±0.41	0.08±0.29	0.024*
Coconut	0.51±1.52	0	0.052
Ginger	0.25±0.81	0.87±2.13	0.115

Values are presented as mean (U/mL)±standard deviation, unless otherwise stated
[a]Only food antigens with p<0.1 are shown
*Statistically significant

Table 4. Food antigens showing differences in IgG4 titers (U/mL) between patients with CD or UC and controls

Food antigens	Controls (N=36)	CD (N=12)	p[a]	UC (N=24)	p[a]
Egg white	3.58±8.20	7.26±11.06	0.224	0.99±2.45	0.083
Lemon	0.03±0.13	0.03±0.12	0.954	0	0.093
Mango	0.03±0.11	0.03±0.12	0.989	0	0.085
Salmon	0	0.17±0.26	0.042*	0.02±0.11	0.328
Shrimp	0.01±0.09	0.20±0.46	0.195	0.05±0.16	0.262
Cuttlefish	0.01±0.06	0.03±0.11	0.427	0.30±0.76	0.075
Eel	0.01±0.06	0.14±0.25	0.111	0.20±0.70	0.189
Millet	0.02±0.09	0.20±0.25	0.036*	0.03±0.12	0.602
Gluten	0.64±1.85	13.23	0.165	2.31±7.61	0.301
Soy bean	0	0.25±0.58	0.161	0.15±0.63	0.253
Onion	0.08±0.29	0.26±0.29	0.066	0.28±0.47	0.070
Coconut	0	0.88±2.12	0.177	0.32±1.13	0.174
Ginger	0.87±2.13	0.40±1.27	0.480	0.18±0.47	0.070

Values are presented as mean (U/mL)±standard deviation, unless otherwise stated
[a]Only food antigens with p<0.1 are shown
*Statistically significant
CD: Crohn's disease; UC: ulcerative colitis

Table 5. The number of subjects with food-specific IgG4 titers ≥0.7 U/mL

Food antigens	Patients (N=36)	Controls (N=36)	p[a]	Subtypes CD (N=12)	p[a]	UC (N=24)	p[a]
Pineapple	16	8	0.046*	5	0.189	11	0.054
Kiwi	9	4	0.126	1	0.785	8	0.035*
Cod	3	0	0.077	3	0.002*	0	-
Tuna	5	1	0.088	3	0.016*	2	0.333
Mackerel	2	0	0.151	2	0.012*	0	-
Cuttlefish	3	0	0.077	0	-	3	0.030*
Oat	12	3	0.009*	6	0.001*	6	0.077
Pea	2	0	0.151	2	0.012*	0	-
Peanut	10	3	0.032*	6	0.001*	4	0.325
Coconut	4	0	0.040*	2	0.012*	2	0.078

p is calculated by Pearson's chi-square test
[a]Only food antigens with p<0.05 are shown
*Statistically significant

Number of subjects with positivity for serum food-specific IgG4

The number of subjects with positivity to pineapple (16/36 vs. 8/36; p=0.046), oat (12/36 vs. 3/36; p=0.009), peanut (10/36 vs. 3/36; p=0.032), and coconut (4/36 vs. 0/36; p=0.040) was significantly greater in the IBD group than in controls. The number of subjects with positivity to cod, tuna, and cuttlefish tended to be greater in patients with IBD than in controls (Table 5).

The number of subjects with positivity to cod (3/12 vs. 0/36; p=0.002), tuna (3/12 vs. 1/36; p=0.016), mackerel (2/12 vs. 0/36; p=0.012), oat (6/12 vs. 3/36; p=0.001), pea (2/12 vs. 0/36; p=0.012), peanut (6/12 vs. 3/36; p=0.001), and coconut (2/12 vs. 0/36; p=0.012) was significantly higher in patients with CD than in healthy controls. The number of subjects with positivity to kiwi (8/24 vs. 4/36; p=0.001) and cuttlefish (3/24 vs. 0/36; p=0.030) was significantly higher in patients with UC than in controls (Table 5).

DISCUSSION

Patients with IBD have a tendency to avoid specific foods because their symptoms tend to be induced or aggravated by their consumption (15). Moreover, dietary recommendations and food restrictions for the management of IBD have been suggested (16). However, dietary factors in IBD are still controversial. Identification of foods that might initiate or exacerbate CD or UC is very difficult. In the present study, levels of serum IgG4 to some food antigens were significantly higher in patients with IBD than in healthy controls. This could be observed more frequently in patients with CD than in patients with UC, which might be related to the extent of the disease. Significantly higher levels of IgG4 to food antigens may indicate increased antigen exposure to the mucosal immune system, probably due to increased mucosal permeability, which may be associated with the development or exacerbation of IBD.

IgG4-guided exclusion diet improves symptoms and reduces the levels of inflammation in patients with CD.(17) Similarly, nutritional intervention based on the serum levels of food IgG was reported to significantly lower stool frequency and abdominal pain in patients with CD than in a sham diet (18). Immunological adverse reactions mediated by IgG appear to facilitate damage and increase permeability further, which might be reversed by an exclusion diet. The relationship between serum IgG levels related to excluded foods and disease activity needs to be further studied.

Some researchers insist that a higher serum antibody level to a food antigen is merely a physiological response present in healthy individuals (19). Although IgG-mediated reactions may be considered to be natural immune reactions to infiltrating food antigens, enhanced IgG reactions are likely to be associated with impaired mucosal permeability. Strong IgG responses to some food antigens may represent increased immune response leading to inflammation or symptoms. Our findings that patients with IBD, particularly in patients with CD, showed increased IgG4-related responses to diverse food antigens suggest the role of dietary factors in the pathogenesis of IBD. The main mechanism underlying increased serum IgG levels to some common foods in patients with IBD is more likely to involve impaired mucosal permeability rather than increased exposure to such food antigens. As a matter of fact, some food antigens have been reported to induce gut inflammation in patients with CD (20). Therefore, higher levels of serum IgG4 against some food antigens are likely to be involved in the induction or exacerbation of inflammation in patients with IBD. Whether food-specific IgG4 plays a crucial role in the induction of immunological response to food antigens needs to be further investigated.

The present study showed that strong IgG4-mediated reactions were more frequently observed in patients with CD than in patients with UC. This suggests that food might play an important role in the inflammatory process in CD. Indeed, studies have demonstrated that the use of exclusion diets can improve symptoms and produce a marked reduction in intestinal inflammation in patients with CD (21). Diet may influence intestinal inflammation through immune reactions to dietary antigens and alterations of the gut microbiome (16). The bowel lumen is exposed to numerous food antigens and microbial organisms, and enhanced mucosal permeability may lead to immune reactions to food antigens or microbial organisms. Enhanced immune responses to food antigens may result in hypersensitivity to such foods (22). On the other hand, foods modulate the composition of the gut microbiota, affecting intestinal mucosal permeability (23,24). Increased mucosal permeability may be a consequence of dysbiosis or a primary pathophysiologic mechanism of IBD. Conversely, immune reactions to food antigens may increase mucosal permeability to macromolecules in the gut.

Certain food antigens and specific IgG can form immune complexes that cause an inflammatory cascade (25). In the present study, the increase of serum IgG4

against some food antigens in patients with IBD is likely to be associated with increased intestinal permeability that is an important feature of IBD. This immune reaction can induce or aggravate inflammation in patients with IBD (26). In keeping with our observations, previous studies have demonstrated that serum food-specific antibody levels are higher in patients with IBD (8,27).

In the present study, the number of foods to which serum IgG4 titers were abnormally higher appears to be more in patients with CD than in patients with UC. Although this observation is difficult to definitely explain, the involvement of the small intestine and the extent of inflammation may contribute to the differences between CD and UC. Our results suggest that patients with CD have an increased IgG4-related response to diverse food antigens compared with healthy subjects. A defective mucosal barrier that is known to be an important pathophysiologic mechanism of CD increases exposure to food antigens to the immune system. Defects in this barrier may induce hypersensitivity reactions to foods (22). Similarly, non-celiac gluten hypersensitivity can be associated with IBD (28). CD with small bowel involvement seems to be more associated with food hypersensitivity than UC.

The types of foods showing higher serum IgG4 titers in patients with IBD usually vary across different studies. A study from China showed higher serum IgG levels to eggs, shrimp, and milk in active patients with UC (29). In the USA, eggs, milk, beef, and pork are recommended to be excluded from diets in patients with CD (9). In the present study, serum IgG4 titers against salmon and millet in patients with CD were significantly higher than those in controls. Serum IgG4 titers against 90 common food antigens were not significantly different between patients with UC and controls. Serum titers of IgG4 to cuttlefish and onion in patients with UC tended to be higher than those in controls. Differences in the types of food antigens showing increased serum levels of food-specific IgG4 between the West and the East might be attributed to differences in diet or genetic factors. Food additives, including refined sugar and emulsifiers, can increase intestinal permeability by disrupting tight junctions (30). In previous studies evaluating food-specific IgG4 levels, major antigens showing higher titers included fatty foods and animal fats, including eggs, dairy foods, and red meat (8,16-18). The role of IgG4-mediated responses to fatty foods or food additives in IBD needs to be further investigated.

In the present study, the results failed to show any differences in the prevalence of abdominal symptoms between patients with or without IgG4-associated food hypersensitivity (data not shown). This observation may be attributed to the fact that symptoms in patients with IBD are caused by inflammation of the intestine. IgG4-mediated immune responses appear to play a role in the genesis of inflammatory responses. Similarly, there was no correlation between higher serum IgG4 titers and patient's symptoms in irritable bowel syndrome (31).

The present study has several limitations. First, there may be a risk of selection bias because the study population consisted of subjects who visited the hospital. Second, dietary challenge using foods showing high serum IgG4 titers was not performed. In addition, we did not obtain additional information regarding patient's dietary patterns. Third, there were no follow-up data using food elimination according to the results of serum IgG4 levels. Finally, most of the enrolled subjects were in remission status. Further studies on the effect of food elimination diets in patients with IBD, including active and remission status, warrant further investigation.

In conclusion, patients with IBD show higher serum levels of IgG4 to diverse food antigens. Patients with CD present IgG4-related immune reactions to more foods than patients with UC. The role of IgG4-mediated immune responses to food antigens in the pathogenesis of IBD, particularly in CD, needs to be further investigated.

Ethics Committee Approval: Ethics committee approval was received for this study from Institutional Review Board of the Myongji Hospital (Decision No: MJH15-004).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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