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Alterations of Food-Specific Serum IgG4 Titers to Commom Food Antigens in Patients with Irritable Bowel Syndrome

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Hong Sub Lee

- ABSTRACT –

Alterations of Food-Specific Serum IgG4 Titers to Common Food Antigens in Patients with Irritable Bowel Syndrome

The role of dietary factors in the pathogenesis of IBS is still unclear. The aim of this study was to compare IgG4 levels to common food antigens between patients with IBS and healthy controls. Thirty-two patients diagnosed as IBS according to Rome III criteria (12 diarrhea subtype; 20 non-diarrhea subtype) and 32 sex and age-matched healthy controls participated in the study. Serum IgG4 titers to 90 common foods were measured in each subject. The number of subjects with positivity defined as the cut-off value ≥ 0.7 U/mL was compared. Patients with IBS had significantly higher IgG4 titers to wheat, leek, and taro compared to those of controls. Serum IgG4 titers to ginger, cocoa, walnut, white radish, onion, and lettuce in IBS patients tended to be higher than controls. IgG4 titers to wheat, gluten and gliadin in the diarrhea subgroup, and lettuce, leek, and taro in the non-diarrhea subgroup tended to be higher, compared with controls. The number of subjects with positivity to apple, orange, lettuce, and leek was significantly higher in IBS patients than controls. The number of subjects with positivity to apple, orange, gluten, and gliadin in the diarrhea subgroup, and egg white, pineapple, soybean, lettuce, and leek in the non-diarrhea subgroup was significantly higher, compared with controls. Serum IgG4 antibody levels to some common foods are abnormally elevated in IBS patients. The type of foods with abnormally elevated serum IgG4 titers in the diarrhea subgroup may be different from that in the non-diarrhea subgroup.

Keywords: Food, Irritable bowel syndrome, Immunoglobulin G

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I. INTRODUCTION

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder that has been estimated to affect 1.1–29.2% of the global population.[1, 2] The pathophysiology of IBS is not completely known. However, several factors, including dietary factors, have been suggested to play a role in the pathophysiology of IBS. About 50% of patients with IBS report postprandial exacerbations of symptoms.[3] It has been reported that perceived food intolerance is high (70%) in subjects with IBS.[4] In addition, a prevalence rate of perceived food intolerance is greater than 50% among subjects with IBS, which is a rate that is 2-fold greater than that reported by those without IBS.[5]

It is common for IBS patients to avoid some foods, particularly fatty foods, milk products, carbohydrates, caffeine, alcohol, and high protein.[6] Moreover, they want to know information about dietary modifications. However, because there is little evidence for dietary factors in IBS, physicians usually have difficulty in providing appropriate advice for diet. The estimates of food allergy prevalence were reported to be 8% of children and 5% of adults.[7] Several mechanisms including food hypersensitivity, direct stimulation by food chemicals, and luminal distension have been suggested to explain GI symptoms induced by food.[8] Among them, food hypersensitivity, classified in IgE-mediated and non-IgE mediated reactions, has been a very controversial subject.[9] Food-specific IgE antibodies are known to play a role in food allergy.[7] However, the role of non-IgE mediated reaction remains poorly understood.

Among four subclasses of IgG antibodies, IgG4 reactions take place in the gut during repeated exposure to food antigens. Studies have reported raised serum IgG4 levels in patients with atopy.[10, 11] Zar et al. also reported elevated serum IgG4 levels to some foods in IBS patients.[12] In that study, no significant differences in IgE levels were observed between IBS patients and healthy controls. Moreover, it was reported that food elimination based on IgG4 levels improved symptoms in IBS patients.[13] However, the role of IgG4 antibodies against foods is controversial yet.[14] Few studies have evaluated the role of IgG4 reaction to foods in IBS.

In the present study, we aimed to compare food-specific IgG4 levels to common food antigens between patients with IBS and healthy controls.

II. MATERIALS AND METHODS

A. Study Subjects and Design

IBS patients who visited the gastroenterology department of Myongji hospital were screened for the current study. All of the subjects were given the list of symptoms by validated Korean version of the Rome III questionnaire (Rome III-K).[15] In addition, blood tests and colonoscopy were performed in all participants.

Exclusion criteria were (1) Subjects with organic bowel diseases including inflammatory bowel disease and infectious bowel disease; (2) Patients who have functional dyspepsia; (3) Patients who have severe comorbidities such as cardiovascular diseases, chronic renal diseases or chronic liver diseases, etc.; (4) Patients with mental illnesses; (5) History of GI surgery.

The healthy control group recruited as the same way. The control group included healthy subjects who didn't have organic diseases and recurrent abdominal symptoms. They are age and sex matched with the patient group. They filled up the symptom questionnaire, and undertook blood tests and colonoscopy in order to check the presence of recurrent abdominal symptoms and organic diseases. All participants gave informed consent before they participate in this study.

This study was performed in a prospective, controlled design. The study protocol and informed consent form were approved by the institutional review board of Myongji Hospital according to the guidelines of the Declaration of Helsinki (MJH14-063). This trial was registered in http://cris.nih.go.kr (KCT0001774). All the participants completed the bowel disease symptom questionnaire (Rome III-K). It was a validated Korean questionnaire for Rome III criteria.

B. Measurement of Serum Food Antigen-specific IgG4 Titers

The eligibility of the subjects was determined before the start of experiments. Serum food antigen-specific IgG4 titers were measured with Food Allergy Screening ELISA Kit (Metametrix Clinical Laboratory, 3425

Corporate Way, Duluth, GA 30096, USA). Food allergens are (derived from native foods) immobilized on solid phase (The enzyme-linked immunosorbent assay plate), and IgG4 titers to 90 common foods were measured.

Food groups were classified into 6 categories: (1) dairy/meat/poultry; (2) fruit; (3) fish/shellfish; (4) grains/legumes (5) vegetables (6) nuts/seeds/miscellaneous (Table 1). The antibody titers were expressed as U/mL. The relative degree of IgG4 to each food is ranked in classes of 0 to +5 according to cutoff points established by the manufacturer. The cut-off value in this study was defined as +2 rank of 0.7 U/mL for each food antigen. The number of subjects with positivity defined as cut-off value $\geq$ 0.7 U/mL was compared using Pearson's Chi-square test.

Table 1. The list of 90 common food antigens tested in the current study

Dairy, meat, and poultry antigen	Fruit antigen	Fish and shellfish antigen	Grains and legumes antigen	Vegetables antigen	Nuts, seeds and miscellaneous antigen
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
Yoghurt	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	

C. Sample Size Calculation

In the previous study, the mean IgG4 level to pork in IBS patients and controls was 31.54 U/mL (standard deviation 0.45) and 30.80 U/mL (standard deviation 0.59), respectively.[16] The number of participants in each arm of this study was calculated to obtain results with an α of 0.05 and a power of 0.90. Therefore, we calculated that 54 subjects including 27 subjects and 27 controls were needed. We enrolled 70 subjects in the consideration of 15% drop out rate.

D. Statistical Methods

The statistical comparison between subjects with IBS and healthy control was performed using the Pearson's chi-square test and an independent sample t-test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. A *P*-value < 0.05 was considered significant. SPSS for Windows ver. 11 software (SPSS Inc., Chicago, IL, USA) was used for all analyses.

III. RESULTS

A. Subject Characteristics

From February 2015 through January 2016, 6 participants of the 70 subjects screened were excluded because one had ulcerative colitis and five subjects withdrew the consent. Among them, 32 patients were diagnosed as IBS using a validated Korean questionnaire of Rome III criteria (12 diarrhea subgroup; 20 non-diarrhea subgroup). Thirty-two sex and age-matched healthy individuals (15 women and 17 men; mean age, 56 years) without IBS symptoms and organic diseases participated in the study. The demographic features including age, sex, body mass index, and history of allergic disease were comparable in both study groups (Table2).

Table 2. Demographic features of the study subjects

Characteristics	Patients (n = 32)	Controls (n = 32)	*P*-value
Age (age)	57.4 ± 11.2	56.8 ± 14.9	0.865
Sex (male:female)	17:15	17:15	
History of postprandial exacerbation (%)	71.8	0	
Body mass index (kg/m^2)	24.1 ± 2.2	23.6 ± 3.8	0.463
History of diabetes	5	4	0.719
History of allergic disease	1	1	1.000

Values are presented as mean ± standard deviation or numbers.

B. Serum IgG4 Titers

Patients with IBS had significantly higher IgG4 titers to wheat (4.22 ± 7.67 U/mL vs 1.17 ± 3.06; $P = 0.043$), leek (0.13 ± 0.22 U/mL vs 0.03 ± 0.10; $P = 0.026$), taro (1.00 ± 2.17 U/mL vs 0.11 ± 0.26; $P = 0.029$), compared with healthy controls. Serum IgG4 titers to ginger, cocoa, walnut, white radish, onion, and lettuce in IBS patients tended to be higher than those in controls. IgG4 titers to wheat, gluten, and gliadin in the diarrhea subgroup tended to be higher than those in controls. Patients in the non-diarrhea subgroup tended to have higher IgG4 levels to lettuce, leek, and taro, compared with healthy controls (Table 3).

Table 3. Food antigens showing differences in IgG4 titers (U/mL) between patients and controls (Only the variables which have *P* < 0.1 was shown in the table).

Variable	Patients (n=32)	Controls (n=32)	*P*-value	Subtype			
				Diarrhea	*P*-value	Non-Diarrhea	*P*-value
Wheat (U/mL)	4.22 ± 7.67	1.17 ± 3.06	0.043*	5.45 ± 7.58	0.081	3.48 ± 7.81	0.219
Gluten (U/mL)	1.23 ± 2.78	0.47 ± 1.41	0.173	2.00 ± 2.64	0.079	0.77 ± 2.82	0.608
Glaidin (U/mL)	1.33 ± 3.12	0.36 ± 1.18	0.111	2.15 ± 2.76	0.050	0.83 ± 3.29	0.546
White radish (U/mL)	0.34 ± 0.83	0.04 ± 0.14	0.052	0.47 ± 1.16	0.234	0.27 ± 0.58	0.100
Onion (U/mL)	0.76 ± 1.90	0.08 ± 0.28	0.053	0.62 ± 1.49	0.237	0.84 ± 2.14	0.128
Lettuce (U/mL)	0.44 ± 1.10	0.07 ± 0.16	0.064	0.12 ± 0.22	0.396	0.64 ± 1.35	0.076
Leek (U/mL)	1.00 ± 2.17	0.11 ± 0.26	0.029*	0.86 ± 2.38	0.302	1.08 ± 2.10	0.054
Taro (U/mL)	0.13 ± 0.22	0.03 ± 0.10	0.026*	0.12 ± 0.23	0.218	0.13 ± 0.22	0.055
Wallnut (U/mL)	0.16 ± 0.21	0.07 ± 0.16	0.064	0.16 ± 0.21	0.203	0.16 ± 0.21	0.124
Ginger (U/mL)	7.19 ± 21.61	0.59 ± 1.57	0.095	3.62 ± 10.69	0.349	9.33 ± 26.13	0.151

Values are mean ± standard deviation unless otherwise stated.

*Statistically significant

C. The number of subjects with positivity for serum food IgG4 titers

The number of subjects with positivity for serum food IgG4 titers to apple, orange, lettuce, and leek was significantly higher in IBS patients than that in healthy controls. The number of subjects with positivity to apple, orange, gluten, and gliadin in the diarrhea subgroup, and egg white, pineapple, soybean, lettuce, and leek in the non-diarrhea subgroup was significantly higher, compared with controls (Table 4).

Table 4. The number of subjects with a positive antigen defined as its IgG4 titer ≥ 0.7 U/mL in IBS patients and healthy controls (Only the variables which have *P* < 0.1 was shown in the table).

Variable	Patient	Control	OR (95% CI)	*P*-value	Subtype			
					Diarrhea	*P*-value	Non-Diarrhea	*P*-value
Egg white	11	5	2.829 (0.851 -9.402)	0.083	3	0.473	8	0.048*
Apple	4	0		0.039*	3	0.003*	1	0.202
Orange	4	0		0.039*	2	0.018*	2	0.068
Pineapple	13	7	2.444 (0.817 -7.308)	0.106	3	0.826	10	0.035*
Gluten	7	4	1.960 (0.512 -7.498)	0.320	5	0.033*	2	0.784
Gliadin	6	3	2.231 (0.506 -9.835)	0.281	5	0.013*	1	0.565
Soy bean	3	0		0.076	0		3	0.024*
White radish	3	0		0.076	1	0.099	2	0.068
Onion	5	1	5.741 (0.631 -52.234)	0.086	2	0.112	3	0.118
Lettuce	4	0		0.039*	0		4	0.008*
Leek	7	1	8.680 (1.001 -75.304)	0.023*	2	0.112	5	0.016*
Eggpant	4	1	4.429 (0.467 -42.021)	0.162	0	0.536	4	0.045*

Values are presented as numbers unless otherwise stated.

OR, odds ratio; CI, confidence interval

*Statistically significant

IV. DISCUSSION

In the present study, we demonstrated that serum IgG4 antibody levels to some foods were abnormally elevated in IBS patients. Furthermore, the type of foods with abnormally elevated IgG4 titers compared to normal controls in the diarrhea subgroup was different from that in the non-diarrhea subgroup. Those findings suggest the possibility that the IgG4-related immune reaction to some foods is involved in the pathogenesis of IBS symptoms.

The previous studies showed that serum IgG4 antibodies to common foods are elevated in IBS patients.[16, 17] Like atopic conditions, those observations suggest the possibility of a role of IgG4-related immune reaction in the pathophysiology of IBS. In a study from UK, IBS patients had significantly higher IgG4 titers to wheat, beef, pork, and lamb compared to controls.[17] In contrast, a study from China showed that IBS patients had significantly higher levels of IgG antibody to crab, egg, shrimp, soybean, and wheat than controls.[16] In that study, patients with functional dyspepsia also had significantly higher titers of IgG antibody to egg and soybean, compared with controls. Those studies suggest that symptoms associated with IBS or functional dyspepsia may be related to food hypersensitivity. In the present study, IBS patients overlapped with functional dyspepsia were excluded, because we aimed to investigate the relationship of IgG4-related immune reaction to food antigens with IBS symptoms. We demonstrated that IBS patients had significantly higher IgG4 titers to wheat, leek, taro compared to controls. Moreover, serum IgG4 titers to ginger, cocoa, walnut, white radish, onion, and lettuce in IBS patients tended to be higher than controls. Although higher levels of IgG4 to wheat antigen were also observed in previous studies, the type of foods showing higher IgG4 titers in IBS patients in the present study was mostly different from that in other previous studies. This difference might be related to the difference in ethnicity or the type of favorite food among countries, that warrants further investigation.

The level of IgG4 antibodies against foods may just reflect the intake of the food. However, certain foods have frequently been reported to generate or exacerbate IBS symptoms. These foods include wheat, milk products, egg, peanut, soy, sesame, tree nuts, shellfish, spicy foods, coffee, vegetables, fatty foods, and alcohol.[7, 16, 17] Actually, IBS patients tend to think that specific foods are triggers.[18] Although many IBS patients mention that

they avoid certain foods, this does not seem to significantly affect their intake of nutrients. According to a dietary survey, the real food intake in IBS patients was not significantly different from that in healthy controls.[19] The observed minor differences showed a tendency toward higher intake of fruit and vegetables and a lower intake of meat and dairy products in IBS patients. Therefore, elevation of serum IgG4 titers to some food antigens is more likely to be involved in the pathogenesis or pathophysiology of IBS rather than just reflecting the intake of the food. In the present study, the type of foods with abnormally elevated IgG4 titers compared to normal controls in the diarrhea subgroup was different from that in the non-diarrhea subgroup. This difference might be related to the involvement of IgG4-related immune reaction to specific food antigens in the generation of specific IBS symptoms. This speculation needs to be verified further.

Studies have shown the inflammatory components of IBS.[20] The difference in the immune reaction to food antigens between individuals may be associated with different permeability to macromolecules in the gut. Actually, increased intestinal mucosal permeability has been reported to be an important pathophysiologic factor in IBS.[21] Increased intestinal mucosal permeability is associated with visceral and thermal hypersensitivity in a subset of IBS patients.[21, 22] Likewise, food hypersensitivity observed in IBS patients may be associated with increased intestinal mucosal permeability. Certain food antigens and specific IgG antibodies may form immune complexes that could cause an inflammatory cascade.[23] Similarly, high levels of the IgG4 food antibodies are also observed in patients with inflammatory bowel disease, where intestinal mucosal permeability is known to be increased.[24, 25]

Some studies have demonstrated that food-specific IgG4 antibody-guided exclusion diet may be effective in alleviating IBS symptoms.[26, 27] The IgG4 antibody-guided exclusion diet affects various symptoms including abdominal pain or discomfort, stool shape, diarrhea frequency, and general feelings of distress. A previous systemic review of clinical trials regarding exclusion diet based on IgG4 showed a 15% - 71% response rate.[28] Immunological adverse reactions by IgG appear to induce mucosal damage and further increase of mucosal permeability, that might be reversed by exclusion diet. The positive effect of the IgG4 antibody-guided exclusion diet suggests that the IgG4-related immune reaction to some foods is involved in the genesis of IBS symptoms.

In the present study, IgG4 titers to wheat, gluten and gliadin tended to be higher in the diarrhea subgroup, whereas those to lettuce, leek and taro in the non-diarrhea subgroup, compared with controls. The number of subjects with positivity to apple, orange, gluten, and gliadin in the diarrhea subgroup, and eggwhite, pineapple, soybean, lettuce, and leek in the non-diarrhea subgroup was significantly higher, compared with controls. Those findings indicate that the diarrhea subtype of IBS may be more associated with wheat and gluten sensitivity than the non-diarrhea subtype of IBS. The spectrum of gluten-related disorders includes celiac disease, non-celiac gluten sensitivity (NCGS), and wheat allergy.[29, 30] NCGS is actually known to be characterized by intestinal symptoms, such as diarrhea, abdominal discomfort or pain, bloating, and flatulence, or extra-intestinal symptoms such as headache, lethargy, attention-deficit/hyperactivity, skin manifestations, or recurrent oral ulceration.[31, 32] A dramatic relief in abdominal pain and chronic diarrhea on gluten-free diet and reappearance of symptoms upon resumption of a gluten-containing diet has been reported.[33, 34] Gluten influences intestinal barrier functions in IBS patients with diarrhea, and those patients may benefit from a gluten-free diet.[34] Therefore, the antibody to wheat or gluten seems to play a pathophysiological role in IBS. A different response to food antigens between IBS subgroups needs to be verified in a larger sample of IBS patients. Furthermore, the underlying mechanism related to the association of higher IgG4 levels to lettuce, leek, taro, egg white, pineapple, and soybean with the non-diarrhea subgroup requires further investigation.

The present study has several limitations. First, the number of subjects who participated in this study might not be enough. Larger sample size is required to confirm the results of the present study. Second, there may be a risk of selection bias, because the study population included only the subjects who visited hospital. Third, the dietary patterns were not checked in the current study. Further studies in the consideration of the dietary patterns are warranted.

V. CONCLUSIONS

Based on our observations, serum IgG4 levels to some common foods are abnormally elevated in IBS patients. The type of foods with abnormally elevated IgG4 titers compared to normal controls in the diarrhea subgroup of IBS patients may be different from that in the non-diarrhea subgroup of IBS patients. The role of food hypersensitivity in the pathogenesis of IBS needs further investigation.

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- 국문요약 -

과민성 장 증후군 환자에서 일반 식품 항원에 대한 식품 특이적 혈청 IgG4 역가의 차이

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과민성 장 증후군의 발병 기전에서 식이 요소의 역할은 여전히 불분명하다. 이 연구의 목적은 과민성 장 증후군 환자와 건강한 대조군 간 일반적인 음식 항원에 대한 IgG4 역가를 비교하는 것이다. 로마 III 기준 에 따라 과민성 장 증후군으로 진단 된 32 명의 환자(12 명의 설사 아형 환자, 20 명의 비 설사 아형 환자)와 32 명의 성별 및 연령이 일치하는 건강한 대조군이 이 연구에 참여했다. 90 개의 일반 식품에 대한 혈청 IgG4 역가를 각 대상에서 측정했다. 0.7 U / mL 이상의 cut-off value 로 정의된 양성의 피험자 수도 환자 군과 대조 군의 차이를 비교하였다. 과민성 장 증후군 환자에서는 대조군에 비해 밀, 부추, 토란에 대한 IgG4 역가가 유의하게 높았다. 과민성 장 증후군 환자의 생강, 코코아, 호두, 흰 무, 양파, 상추에 대한 혈청 IgG4 역가는 대조군보다 높았다. 설사형 과민성 장 증후군 환자들에게서 밀, 글루텐(gluten), 글리아딘(gliadin)에 대한 IgG4 역가가 대조군에 비해 높았다. 비 설사 군에서는 상추, 부추, 토란에 대한 역가가 대조군에 비해 높았다. 사과, 오렌지, 상추, 부추에 양성 반응을 보인 환자의 수는 대조군보다 과민성 장 증후군 환자에서 유의하게 높았다. 설사 하부 군에서 사과, 오렌지, 글루텐, 글리아딘에 양성 반응을 보인 피험자와 비 설사 군에서 계란 흰자, 파인애플, 콩, 상추, 부추가 대조군에 비해 유의하게 높았다. 일부 일반 식품에 대한

혈청 IgG4 항체 수치는 과민성 장 증후군 환자에서 비정상적으로 상승되어 있다. 설사 하위 그룹에서 비정상적으로 상승 된 혈청 IgG4 역가를 갖는 식품의 유형은 비 설사 하위 그룹과 다를 수 있다.

핵심어: 음식, 과민성 장 증후군, 면역 글로불린 G