

CLINICAL RESEARCH

## Food intolerance and skin prick test in treated and untreated irritable bowel syndrome

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### Abstract

**AIM:** To correlate the clinical features of treated and untreated patients with irritable bowel syndrome (IBS) to the results of skin prick test (SPT) for food and inhalant allergens.

**METHODS:** We recruited 105 subjects to form three different target groups: treated group ( $n=44$ ) undergoing treatment for IBS, untreated group ( $n=31$ ) meeting the Rome II criteria without treatment for IBS, control group ( $n=30$ ) with no IBS symptoms.

**RESULTS:** SPT results were different among the three groups in which SPT was positive in 17 (38.6%) treated patients, in 5 (16.1%) untreated patients and in 1 (3.3%) control ( $P<0.01$ ). The number of positive SPTs was greater in the IBS group than in the control group ( $P<0.001$ ). The number of positive food SPTs was higher in the treated IBS group than in the untreated IBS group ( $P=0.03$ ).

**CONCLUSION:** Positive food SPT is higher in IBS patients than in controls.

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**Key words:** Irritable bowel syndrome; Skin prick test; Food allergy

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### INTRODUCTION

Irritable bowel syndrome (IBS) is common. Depending on the studies, the prevalence (using Rome II criteria) varies between 9%-22% among Caucasians<sup>[1-3]</sup>. In Korea, the prevalence of IBS has been reported to be 6.6% and there is no difference in the prevalence between men and women<sup>[4]</sup>.

In patients with IBS, postprandial worsening of symptoms as well as food-related reactions to one or more foods is very common<sup>[5]</sup>. In published data, speculation of an immunological reaction to foods in IBS has been reported<sup>[6,7]</sup>. Data from dietary elimination and food challenge studies support the role of diet in the pathogenesis of IBS<sup>[8-10]</sup>. This hypothesis is supported by the response to disodium cromoglycate in such patients<sup>[11,12]</sup>. Although well designed randomized controlled studies are scarce, milk, wheat, egg and foods high in salicylates or amines are consistently a problem among the studies<sup>[13,14]</sup>. Recently, Dainese *et al*<sup>[7]</sup> have indicated discrepancies between reported food intolerance and skin prick test (SPT) findings in IBS patients, suggesting that the SPT used to identify food sensitization mediated by the IgE mechanism is inappropriate. IBS is a heterogeneous disease having various symptoms and severity. So in our study, IBS patients were divided into treatment and untreated groups. Moreover, to clarify the possible role of food hypersensitivity in IBS, we used both common food and inhalant antigens. The results of SPT for food allergens were compared to the SPT for inhalant allergens.

The aim of this study was to correlate the clinical features of treated and untreated IBS patients to the results of the skin prick test for food and inhalant allergens, total IgE level, and radio-allergo-sorbent test (RAST)

### MATERIALS AND METHODS

#### Subjects

The study protocol was approved by the Institutional Review Board of the Hanyang University. Among the 480 medical students, 35 meeting the Rome II but not treated

Table 1 Characteristics of studied subjects, *n* (%)

	Treated ( <i>n</i> = 44)	Untreated ( <i>n</i> = 31)	Control ( <i>n</i> = 30)
Age (years)	37.9±13.2	27.2±1.9	25.8±1.7
Gender			
Male	19 (43.2)	16 (51.6)	22 (73.3)
Female	25 (56.8)	15 (48.4)	8 (26.7)
IBS subgroups			
C-IBS	10 (22.7)	12 (38.7)	-
D-IBS	15 (34.1)	9 (29.0)	-
A-IBS	19 (43.2)	10 (32.3)	-
Type of initial health care system			
Tertiary center	13 (29.5)	-	-
Primary care	25 (56.8)	-	-
OB/Gyn <sup>3</sup>	1 (2.3)	-	-
Oriental-medicine	5 (11.4)	-	-
Reason for seeking for health care			
Abdominal pain	17 (38.7)	-	-
Discomfort, bloating	14 (31.8)	-	-
Altered stool pattern	13 (29.5)	-	-

C-IBS = Constipation-predominant IBS; D-IBS = Diarrhea-predominant IBS; A-IBS = Alternating constipation and diarrhea IBS.

for IBS and 35 randomly selected healthy undergraduate students were recruited in the study. After giving their informed consent, all volunteers underwent a physical examination and laboratory screening (upper gastrointestinal endoscopy, colonoscopy, routine red and white blood cell count, and biochemical examinations). Subjects receiving any medication (antihistamines, steroids, H<sub>2</sub> receptor antagonist, anti-inflammatory drugs, and herb medications) over a two-week period prior to study and those with current severe allergic disease identified by interview were excluded from the study (*n* = 9). Therefore, out of 70 students, 31 untreated IBS students and 30 healthy students participated in the trial. Forty-four consecutive patients with IBS referred to our institution for evaluation and treatment served as positive controls. Standard workup included upper gastrointestinal endoscopy, laboratory testing and colonoscopy.

The enrolled patients were divided into three groups after clinical evaluation and the application of Rome II criteria. Group I consisted of 44 patients with IBS referred to our institution for evaluation and treatment. All treated patients were selected from a single tertiary outpatient clinic (treatment group). Group II consisted of 31 untreated IBS patients meeting the Rome II criteria but not treated for IBS (untreated group). Group III consisted of 30 healthy undergraduate students (control group).

### Questionnaire and clinical measurements

To assess abdominal symptoms and intensity, all study participants were given a questionnaire. A modified WHOQOL (WHOQOL-BREF) method validated by Min *et al.*<sup>15</sup> was used to measure the quality of life in the IBS and control groups. The questionnaire consisted of 26 items measuring four dimensions of health: physical health, psychological health, social relationships and environmental health. Each item asked the respondents to indicate the extent to which their IBS interfered with their

health during the previous four weeks.

### Skin prick test and RAST

SPT was carried out on all subjects on the upper back involving the application of 70 fresh food extracts using the prick-by-prick method. Some of the fresh food extracts used were saury, mackerel, beef, pork, chicken, milk, egg white, egg yolk, wheat flour, buckwheat, rice, beans, apples, peaches, tomatoes, celery, carrots, onions, peanuts, chocolate, and coffee. A doctor carried out an additional SPT involving the application of inhalant allergens. The 11 commercial allergens tested for D-pteronyssinus, D-farinae, alternaria alternata, grass pollen, tree pollen, mugwort pollen, willow pollen, ragwort, dog hair, cat fur, and cockroaches mix. In both SPTs, one drop of the extract was placed on the skin, and a disposable syringe needle was placed into the drop and then into the skin until a small puncture was visible. A histamine control was employed. SPT was considered positive if the net wheal diameter was significantly greater than the net wheal diameter of the histamine reaction. The reaction to the extract was measured 15-20 min after application. Discomfort and bleeding were not evident.

Serum samples for total IgE and total eosinophil count were collected by trained phlebotomists. Two 10 mL blood samples from an antecubital vein were taken. IgE measurement was determined by the paper radioimmunosorbent test (PRIST, Pharmacia Laboratories, USA) using a Phadebas IgE kit. The total IgE test provided evidence for IgE sensitivity to antigens because the IgE antibody resulted in mast cell activation and release of histamine. Also, total eosinophils were stained with a Hinkelman solution, and the eosinophil count provided immediate hypersensitivity to IgE antibody.

### Statistical analysis

Tables were constructed for frequency and percentage. Categorical data were analyzed using the chi-square test or Fisher's exact test. Continuous data were analyzed using the Student's *t*-test and one-way ANOVA or Scheffe's test. To minimize type I errors, *P* < 0.05 was considered statistically significant. Exact *P*-values are listed in the tables and text. All statistical analyses were performed using the SPSS 11.0 statistical package.

## RESULTS

### Patient population

In the study population, 44 treated IBS patients had a mean age of 38 years (37.9 ± 13.2), 31 untreated IBS patients had a mean age of 27 years (27.2 ± 1.9), and 30 controls had a mean age of 26 years (25.8 ± 1.7). There were no statistically significant differences in gender ratio, height, weight, alcohol and coffee intake, and smoking habits among the three groups (not shown). In the treated group, the number of females (56.8%, *n* = 25) was greater than that of males (43.2%, *n* = 19). In this group, the most subtype IBS was found in 19 patients. The subtype constipation dominant IBS was found in 12 patients of untreated group. Subjects in the treated group mainly sought for a primary care setting as the first visit due to

**Table 2 Symptoms, duration of symptoms, and onset of IBS, n (%)**

	Treated (n = 44)	Untreated (n = 31)	P
Duration of symptom			0.035
Less than 1 h	5 (11.4)	7 (22.6)	
1-24 h	13 (29.5)	15 (48.4)	
More than 1 day	26 (59.1)	9 (29.0)	
Severity of subjective symptoms			0.001
Extremely severe	6 (13.6)	-	
Very	22 (50.0)	5 (15.6)	
Somewhat	14 (31.8)	19 (62.5)	
Not very	1 (2.3)	6 (18.8)	
Not at all severe	1 (2.3)	1 (3.1)	
Onset of IBS symptoms			0.065
Recent 6 mo	3 (6.8)	2 (6.3)	
1 year ago	8 (18.2)	1 (3.1)	
1-2 years ago	6 (13.6)	4 (12.5)	
2-5 years ago	13 (29.5)	12 (40.6)	
5-10 years ago	7 (15.9)	11 (34.4)	
10-20 years ago	5 (11.4)	1 (3.1)	
More than 20 years ago	2 (4.5)	-	

abdominal pain (15 patients), stool pattern change (13 patients) and abdominal bloating (13 patients) (Table 1).

### Subgroup analysis and scores of quality of life (WHOQOL-BREEF)

We utilized a questionnaire to compare and estimate the onset, duration and severity of symptoms between the two IBS groups. More than half of the treated IBS patients (59.1%) reported that the symptoms lasted for more than 24 h, but only 29.0% of untreated IBS patients reported that the symptoms lasted for more than 24 h. Five IBS patients (11.4%) in the treated group complained of abdominal symptoms almost all day for more than one month. Subjective severity score of symptoms was also higher in the treated IBS patients than that of the untreated IBS patients ( $P=0.001$ ). But there was no significant difference in the onset of the disease between the two groups ( $P=0.065$ ) (Table 2).

Modified WHOQOL (WHOQOL-BREEF) questionnaire validated by Min *et al*<sup>[15]</sup> was used. It consisted of 26 items measuring four dimensions of health. All dimensions including overall quality of life scores were significantly lower in IBS patients than in controls (Table 3).

### History of allergies and food intolerance

There was no significant difference in the reported food intolerance among the three groups. However, among the treated and untreated IBS patients, dairy products were reported to cause most of the intolerance. Of the treated and untreated IBS patients, 25 (56.8%) and 21 (67.7%) had an allergic condition and only 9 (30%) of the controls had an allergic condition ( $P=0.008$ ). However, no difference in the number of allergic conditions was found between the treated and untreated IBS patients. Rhinitis was the most common condition, and five patients had a history of asthma in the IBS patients (Table 4).

### Skin prick test and IgE level

Seventy fresh food extract allergens were used to identify

**Table 3 Score of quality of life (mean ± SD)**

Domain	Treated (n = 44)	Untreated (n = 31)	Control (n = 30)	P value <sup>a</sup>	P value <sup>c</sup>
Physical health	52.47±15.06	59.09±13.17	75.74±16.25	0.001	0.001
Psychological health	52.98±17.00	56.06±13.71	68.75±13.79	0.001	0.014
Social relationships	53.77±13.92	59.47±11.59	61.81±16.47	0.067	0.005
Environmental health	48.44±15.19	54.69±11.19	63.15±12.70	0.001	0.005
Overall QOL	5.79± 1.09	6.36± 1.33	8.21± 0.93	0.001	0.002

QOL: quality of life. <sup>a</sup> $P < 0.05$  by  $\chi^2$ -test; <sup>c</sup> $P < 0.05$  by  $\chi^2$ -test between IBS patients and control.

the cause of food hypersensitivity. SPT results were different among the three groups. SPT was positive in 17 (38.6%) treated IBS patients, in 5 (16.1%) untreated IBS patients, and in 1 (3.3%) control ( $P < 0.01$ ). The number of positive SPTs was greater in the IBS patients than in the controls ( $P < 0.001$ ). The number of positive food SPTs was greater in the treated patients than in the untreated patients ( $P=0.03$ ). The most frequent SPT positive food allergen was saury among the different groups. Five IBS patients had positive SPT for rice (Table 5). Eleven treated and untreated IBS patients and four controls had positive SPT for inhalant allergens. No significant difference in SPT inhalant allergens was noted among the three groups. The most common reactive inhalant allergens were D-farinae and D-pteronyssinus.

There were no significant differences in IgE and total eosinophil counts among the three groups. Also, no significant differences in IgE and total eosinophils were noted between the treated and untreated IBS patients (Table 6).

### Characteristics according to the food SPT in treated and untreated groups

When SPT for food allergen and gender ratio were compared between those with a positive and negative SPT, no difference was noted. Also, there were no significant differences in positive SPT between IBS subtype and current allergy history. However, food intolerance and positive inhalant allergen were much higher in SPT positive food allergens ( $P=0.013$ ,  $P=0.006$ ). Twenty-two IBS patients had one or more skin positive tests. Serum samples were taken for RAST in order to compare the SPT results. Only three treated IBS patients had a positive RAST for beans, pork, and beef (Table 7).

## DISCUSSION

The term "adverse food reaction" or "food-related symptoms" encompasses immunological responses and non-immunological responses to food. Food hypersensitivity/allergy is used to describe conditions in which an immunological mechanism may be demonstrable<sup>[16,17]</sup>. In contrast, food intolerance is a non-immunological response to proteins that may result from particular constituents of foods such as toxins (e.g., food poisoning) or pharmacological agents (e.g., caffeine or tyramine) or from host factors such as lactase deficiency. However, food hypersensitivity

Table 4 History of allergies and food intolerance, *n* (%)

	Treated ( <i>n</i> = 44)	Untreated ( <i>n</i> = 31)	Control ( <i>n</i> = 30)	<i>P</i> value <sup>a</sup>	<i>P</i> value <sup>c</sup>	<i>P</i> value <sup>e</sup>
History of allergies	25 (56.8)	21 (67.7)	9 (30.0)	0.017	NS	0.008
Atrophy	5 (11.4)	5 (16.1)	2 (22.2)			
Asthma	3 (6.8)	2 (6.5)	-			
Rhinitis	10 (22.7)	7 (22.6)	5 (55.6)			
Eczema	4 (9.1)	5 (16.1)	3 (33.3)			
Hives	4 (9.1)	7 (22.6)	-			
Reported food intolerance	36 (81.8)	27 (87.1)	23 (76.7)	NS	NS	NS
Dairy products	24 (54.5)	17 (54.8)	11 (36.7)			
Coffee	13 (29.5)	7 (22.6)	6 (20.0)			
Alcohol	16 (36.4)	15 (48.4)	15 (50.0)			
Cold, raw foods	15 (34.1)	10 (32.3)	8 (26.7)			
Spicy foods	17 (38.6)	6 (19.4)	8 (26.7)			
Others	10 (22.7)	3 (9.7)	1 (3.3)			

<sup>a</sup>*P* < 0.05 by  $\chi^2$ -test; <sup>c</sup>*P* < 0.05 by  $\chi^2$ -test between treated and untreated patients; <sup>e</sup>*P* < 0.05 by  $\chi^2$ -test between IBS patients and controls.

Table 5 Skin prick test results using food allergens and inhalant allergens, *n* (%)

	Treated ( <i>n</i> = 44)	Untreated ( <i>n</i> = 31)	Control ( <i>n</i> = 30)	<i>P</i> value <sup>a</sup>	<i>P</i> value <sup>c</sup>	<i>P</i> value <sup>e</sup>
Positive food SPT	17/44(38.6)	5/31 (16.1)	1/30 (3.3)	<0.001	0.03	<0.001
Saury	13 (76.5)	2 (40.0)	1 (100.0)			
Mackerel	3 (17.6)	-	-			
Beef	1 (5.9)	2 (40.0)	-			
Pork	2 (11.8)	1 (20.0)	-			
Buckwheat	3 (17.6)	-	-			
Rice	4 (23.5)	1 (20.0)	-			
Arrowroot	3 (17.6)	-	-			
Sweet potatoes	3 (17.6)	-	-			
Beans	2 (11.8)	1 (20.0)	-			
Cabbages	3 (17.6)	-	-			
Celery	3 (17.6)	-	-			
Onions	3 (17.6)	-	-			
Peach	1 (5.9)	1 (20.0)	-			
Tomato	1 (5.9)	-	-			
Melon	2 (11.8)	-	-			
Squid	1 (5.9)	1 (20.0)	-			
Trumpet shell	3 (17.6)	-	-			
Curry	2 (11.8)	-	-			
Positive inhalant SPT	11 (25.0)	11 (35.5)	13.3 (4)	NS	NS	NS
D-farinae	7 (63.6)	7 (63.6)	50.0 (2)			
D-pterynyssinus	5 (45.5)	8 (72.7)	50.0 (2)			
Alternaria alternate	2 (18.2)	-	25.0 (1)			
Grass pollen	27.3 (3)	1 (9.1)	-			
Tree pollen	36.4 (4)	1 (9.1)	1 (25.0)			
Mugwort pollen	-	2 (18.2)	-			
Willow pollen	9.1 (1)	-	-			
Ragweed	36.4 (4)	3 (27.3)	-			
Dog hair	45.5 (5)	1 (9.1)	1 (25.0)			
Cat fur	18.2 (2)	-	-			
Cockroach mix	9.1 (1)	-	-			

<sup>a</sup>*P* < 0.05 by  $\chi^2$ -test; <sup>c</sup>*P* < 0.05 by  $\chi^2$ -test between treated and untreated patients; <sup>e</sup>*P* < 0.05 by  $\chi^2$ -test between IBS patients and controls.

resulting in food intolerance in the cause of gastrointestinal problems is much harder. Niec *et al.*<sup>[18]</sup> reported that milk, wheat, eggs, potatoes, and celery are the most commonly identified factors causing gastrointestinal symptoms. Locke *et al.*<sup>[19]</sup> reported that beans and legumes, chocolate, dairy products, and nuts are the most common foods

causing hypersensitivity. It was reported that patients with IBS reveal intolerance to foods such as milk, bread, pizza, apple, hazelnut, tomato, egg, peach, and greens<sup>[7]</sup>. In our study, dairy products, coffee, alcohol, raw food, and spicy food were the most common foods causing problems. However, SPT was positive for saury, rice, mackerel, buck-

Table 6 IgE and total eosinophil count (mean  $\pm$  SD)

	Treated (n = 44)	Untreated (n = 31)	Control (n = 30)	P value
IgE (IU/mL)	252.36 $\pm$ 558.94	402.34 $\pm$ 765.00	320.53 $\pm$ 659.07	NS
Eosinophil (/ $\mu$ L)	153.74 $\pm$ 149.68	181.72 $\pm$ 126.04	166.42 $\pm$ 139.10	NS

Table 7 Characteristics of treated and untreated patients with IBS, n (%)

Characteristics	Positive food SPT (n = 22)	Negative food SPT (n = 53)	P value
Gender			NS
Male	7 (31.8)	28 (52.8)	
Female	15 (68.2)	25 (47.2)	
Subtypes			NS
A-IBS	8 (36.4)	21 (39.6)	
C-IBS	9 (40.9)	13 (24.5)	
D-IBS	5 (22.7)	19 (35.8)	
Current history of allergies	13 (59.1)	33 (62.3)	NS
Reported food intolerance	9 (40.9)	7 (13.2)	0.013
Inhalant positive SPT	11 (50.0)	11 (20.8)	0.006
Positive RAST	3 (13.6)	-	

wheat, sweet potatoes, celery, onions, and trumpet shell. The results of different studies are inconsistent, which poses the question of the population specificity of such studies.

No correlation between SPT and patient's intolerance to certain foods was noted. There are several explanations for the discrepancies between reported food intolerance and SPT results. First, SPT is generally considered the most convenient and least expensive screening method for detecting allergic reactions in most patients. However, until the diagnostic efficacy of SPT is fully established with standardized allergens and methods, a positive skin test alone cannot confirm a definite clinical sensitivity to an allergen. Second, clinicians consider cross-reactions among various plants and animal allergens<sup>[20, 21]</sup>. The conservation of these proteins across biologic substances affects cross-reactivity in several ways. Certain foods (e.g., peanut) are able to sensitize and elicit reactions after oral exposure (type 1 allergy) and can trigger responses to related foods (e.g. legumes). Other foods (e.g., apples) containing labile proteins are not strong oral sensitizers. Helbling *et al*<sup>[22]</sup> have reported the clinical cross-reactivity to most fish species and several *in vitro* studies have demonstrated the existence of common allergens between different fish species<sup>[23-26]</sup>. The third explanation is that food allergies are localized at the intestinal mucosa and specific IgEs are primarily present in intestinal mucosa but not systemically. For this reason, Andre *et al*<sup>[27]</sup> have indicated the importance of stool IgE rather than serum IgE. Bischoff *et al*<sup>[28]</sup> have also stressed the importance of stool eosinophil counts and mast cell mediators.

Both SPT and RAST are for IgE-mediated disease, but there is no correlation between the two methods. How-

ever, RAST is not as sensitive as the skin test. As a result, in patients with a history of reactions to foods, insect stings, drugs, or latex, skin testing is still required because of its higher sensitivity even if the RAST is negative. The primary advantage of RAST over SPT is safety with the results not influenced by skin disease or medication<sup>[29]</sup>.

In our study, the IBS patients showed much higher positive SPT rates than the controls ( $P < 0.001$ ). The treated IBS patients were more likely to have a positive SPT than the untreated IBS patients ( $P = 0.03$ ). The untreated IBS patients defined by fulfillment of the Rome IBS criteria complained of severe symptoms ( $P < 0.05$ ) (Table 2), suggesting a possible relationship exists between IBS and allergic diathesis. Further studies are needed to explore this relationship. In addition, we also used common inhalant allergens to compare with the food allergens and did not find any difference in positive SPT between inhalant allergens among the three groups (25%, 35% and 13% respectively). White *et al*<sup>[30]</sup> reported that increased airway responsiveness to inhaled methacholine can be demonstrated in irritable bowel syndrome patients with no clinical evidence for atopic disease<sup>[31]</sup>. These findings are in contrast to the previous hypothesis that IBS is a generalized immune hypersensitivity state. These findings also suggest that food allergens may play a certain role in IBS patients. However, well designed dietary elimination and food challenge studies are needed to document the food hypersensitivity in IBS patients.

In this study, the untreated IBS patients were older than the treated patients ( $P = 0.005$ ). Because age could affect SPT, it may confound our results. But the number and size of prick skin reactions increase throughout childhood until twenty years of age and then gradually decline until age fifty<sup>[32]</sup>. Even if age is considered, more treated patients were positive for SPT in our study.

In conclusion, more IBS patients are positive for SPT and food allergens than healthy controls. However, the IBS patients present more severe symptoms, lower overall quality of life, and higher positive SPT compared to the untreated IBS patients even though the history of allergies is not different.

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