

Eosinophilia as a predictor of food allergy in atopic dermatitis

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ABSTRACT

Food allergy plays an important role in atopic dermatitis (AD). Adequate predictors and guidelines for when dietary manipulation is indicated for AD are needed. The clinical significance of eosinophilia as a predictor for food allergy of late eczematous reactions in AD was investigated. Three hundred three patients with AD were studied, using elimination diets and food challenge tests. Food allergy prevalence was compared in groups of eczematoid AD patients with high or normal eosinophil levels. The effects on the blood eosinophil fraction of an elimination diet and milk allergy provocation of late eczematous reactions were evaluated. The prevalence of food allergy was 51.1% (135/264) in patients with eczematoid AD. The major type of food allergy in AD was late eczematous, rather than IgE mediated. Among eczematoid AD patients, 44.9% had high eosinophil levels. In patients with eczematoid AD, the food allergy prevalence was 70.8% (85/120) in the high eosinophil group and 34.7% (50/144) in the normal blood eosinophil group. An elimination diet improved clinical severity and decreased blood eosinophil levels. In milk allergy patients, a milk challenge significantly increased the blood eosinophil level. Skin-prick tests and food-specific IgE tests were useful for diagnosing IgE-mediated food allergy. Eosinophilia appeared to be a significant predictor of food allergy in AD and an indicating factor for diet manipulation, including an elimination diet. Food allergy may be responsible for eosinophilia in AD. Food allergy patterns for AD in Korea were different from those in western countries.

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Key words: Allergy, atopic dermatitis, elimination diet, eosinophilia, food allergy, food challenge test, IgE-mediated, late eczematous reactions, skin-prick test

Food allergy plays an important role in atopic dermatitis (AD).^{1,2} Although IgE-mediated anaphylactic food allergy has been intensively studied, this research focused on food-induced eczema and non-IgE-mediated food allergy in AD patients.³ Sensitization to foods triggers isolated skin symptoms in ~30% of children, and dietary avoidance of highly allergenic foods in infancy may help to prevent allergen sensitization and reduce the severity of AD and food allergies.⁴ However, although the association between AD and food allergy is well established, the role of dietary manipulation in AD remains controversial.⁵ Implementation of proper dietary avoidance can improve symptoms, but inappropriate elimination diets can have significant negative nutritional and social consequences.² Adequate indicators and guidelines for dietary manipulation in AD are needed.

Th1/Th2 imbalance is known to be responsible for AD,⁶ and blood eosinophilia is partially under the control of Th2 cell-derived cytokines, particularly IL-5.⁷ Blood eosinophilia is a characteristic of mild and severe AD and correlates in some studies with disease severity.⁸ Blood eosinophil levels are used as an indicator for classifying and treating AD.⁹

In this study, the relationship between high blood eosinophil level and non-IgE-mediated food allergy in late eczematous reactions of AD was investigated. Dietary manipulation trials were evaluated for their effectiveness in patients with AD with high blood eosinophil.

MATERIALS AND METHODS

Study Design and Subjects

This study included 303 AD patients (152 male and 151 female patients; mean age, 14.3 ± 14.7 years) who participated in the "Atopy-safe school project, Seodaemoo-Office, Korea" from January 2007 to July 2009 and visited the outpatient clinic at the Seoul Allergy Clinic. All subjects met the Hanifin and Rajka criteria¹⁰ and discontinued all oral or systemic medications, including antihistamines and steroids, for at least 7 days before and throughout the study. To exclude possible environmental factors, patients maintained their normal living patterns during the test period.

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Eczematoid AD subjects were divided into a high eosinophil group (eosinophil fraction of $\geq 5\%$) and a normal eosinophil group (eosinophil fraction of $< 5\%$). To evaluate the clinical significance of the blood eosinophil fraction for food allergy, both groups were put on an elimination diet with subsequent food challenges to diagnose food allergies. To determine blood eosinophil levels for group classification, the correlation between blood eosinophil level and absolute blood eosinophil count was evaluated. Noneczematoid AD patients all had IgE-mediated food allergies that were managed by relevant protocols.

To evaluate the effects of a proper elimination diet on blood eosinophil level, the high eosinophil group was divided into two groups: an intervention group placed on an elimination diet and a control group who received no treatment. Clinical severity scoring and laboratory tests for blood eosinophil were conducted before and after treatment for both groups.

Patients who underwent a double-blind placebo-controlled food challenge (DBPCFC) for milk in the intervention group were classified into positive and negative milk allergy groups. Positive milk allergy patients randomly received either milk or a placebo in a double-blind manner. Negative milk allergy patients were challenged with milk to evaluate the effects on blood eosinophil fraction of allergy provocation in late eczema reactions.

Elimination Diet

The intervention groups of the high and normal eosinophil groups were put on a complete elimination diet for 7 days. A control group from the high eosinophil patients did not receive the elimination diet. Elimination was performed for seven foods (milk, eggs, soybeans, wheat, beef, pork, and chicken), selected according to data from previous reports.¹¹ Patients were also restricted for food(s) for which they had a history of allergy, such as peanuts. Substitutes for the restricted food components were used during the elimination period for balanced nutrition. Patients under the elimination diet were instructed to avoid everything containing the eliminated foods. Diets were supervised by diet diaries, recorded over the entire study period. To confirm the elimination of all foodstuffs identified to be causative allergens and to ensure proper intake of the challenged food, each dietary diary was analyzed by allergy nurses and a dietitian. For patients with noneczematous AD and pure IgE-mediated food allergy, elimination was performed only for known and suspected food allergens before the open food challenge (OFC).

Food Challenge

Conditions for the food challenge were (1) obvious clinical improvement after an elimination diet and sta-

ble clinical status for at least 1 week and (2) complete elimination of allergens to be tested from the diet. Conditions were checked through the monitoring of a dietary diary by an allergy nurse and/or an allergy dietitian.

DBPCFCs were conducted for milk or eggs. OFCs were performed for soybeans, wheat, chicken, pork, beef, or other foods in the average Korean diet for which patients had a history of allergy and that were difficult to test with DBPCFC.¹² Patients consumed the food twice a day at breakfast and dinner.

DBPCFC was performed using a vehicle of 15 g of mixed cereal flour consisting of brown rice flour (5 g), glutinous rice flour (5 g), and barley flour (5 g), all purchased commercially. Placebos contained 6 g of brown rice flour with 15 g of vehicle. For the DBPCFC for milk or eggs, 6 g of freeze-dried egg flour or skim milk powder was added to 15 g of vehicle. Before DBPCFC, patients were confirmed for tolerance of mixed cereal flour with no reactions, including allergic reactions, by challenging with placebo for 5 days. If no symptoms were reported, DBPCFC was conducted. Two challenges, separated by 5 days, were performed, one with placebo only and the other with suspected food antigen in the vehicle. Randomization and challenge preparation were performed by dietitians in the clinical research unit. All reactions were scored for type, time of onset, severity, and duration.

If patients showed positive signs for late eczematous reactions, the test was stopped and a positive food allergy was diagnosed. If patients showed a positive response to the food challenge, the food was eliminated for the rest of the study. If patients showed exacerbation of symptoms and signs, the next challenges were delayed until the patients recovered to the prechallenge state and remained stable for at least 4 days. If patients consumed the food that was to be eliminated, challenge tests were stopped and patients were observed for at least 4 days until they returned to the prechallenge state.

Although blinded challenges are ideal, open challenges can be appropriate in some cases.¹³ In this study, OFCs were conducted for IgE-mediated food allergies that might require emergency care, as well as non-IgE-mediated allergies for foods other than milk and eggs. When patients showed food-specific IgE levels of > 10 kU/L for milk or 5 kU/L for eggs¹⁴ and/or had a convincing history of a severe allergic reaction to foods in addition to milk and eggs, a previously reported protocol was used.¹⁵ A convincing history was defined as an immediate allergic reaction to a food within the previous 2 years that developed after an isolated ingestion of the suspected food and required emergency management by a physician.

Clinical Severity Scoring and Diagnosis of Food Allergy

Clinical severity scores for food allergy in late eczematous reactions were assigned using the SCORing Atopic Dermatitis (SCORAD) index, which is used worldwide to assess the severity of atopic eczema.¹⁶ A diagnosis of food allergy was made if the clinical severity score increased by >10 points in subjects with a basal score <50 points or if the score increased by >20% for those with a basal score $\geq$ 50 points. New skin lesions or itching were regarded as positive reactions for the diagnosis of food allergy by food challenge.

The diagnosis of acute or subacute IgE-mediated food allergy was made based on characteristic symptoms and signs including urticaria/skin rash, angioedema, respiratory symptoms such as dyspnea and/or cough, cardiovascular symptoms and signs such as hypotension, and/or other typical symptoms signs of IgE-mediated food allergy.¹⁷

Blood Tests and Skin-Prick Tests

Both intervention and control groups received blood tests before and after the elimination diets were started. Blood tests were also conducted on the positive and negative milk allergy groups, before and after OFC for milk. Venous blood was drawn from the antecubital vein. Complete blood counts were tested and differential white blood cells counts were conducted to determine the blood eosinophil fraction and total serum IgE levels. Total eosinophils were also counted and milk-specific IgE levels were measured in initial tests with skin-prick tests.

Skin-prick tests were conducted on the left forearm using commercial allergen extracts for milk, *Dermaphagoides pteronyssinus* and *Dermatophagoides farinae* (Bencard, Brentford, England). Histamine hydrochloride (1 mg/mL; Bencard) was used as a positive control. Physiological saline, distilled water, and glycerol were used as negative controls. Reactions were read after 15 minutes and classified as negative (0, no reaction) or positive (+, reaction greater than the control but smaller than one-half the size of the histamine reaction; ++, one-half the size of the histamine reaction; +++, equal to the size of the histamine reaction; and +++, twice the size of the histamine reaction). The minimum size of a positive reaction was 3 mm, and the ratios of allergen to histamine wheal size were also calculated.

Statistical Analysis

Statistical analysis used the Wilcoxon signed-rank test and paired *t*-test to evaluate the effects of the elimination diet and milk challenge for individual groups, using SigmaPlot software (Systat Software,

Inc., San Jose, CA). The χ^2 -tests were performed to determine significant differences in food allergy prevalence between the high eosinophil and normal eosinophil groups. Pearson's product moment correlation and linear regression analyzed the relationship between blood eosinophil level and absolute eosinophil count. The values of $p < 0.05$ were considered significant.

RESULTS

AD and Blood Eosinophil Levels

The mean blood eosinophil level of the eczematoid AD patients was $6.0 \pm 5.0\%$. Among the eczematoid AD patients, 44.9% (136/303; 78 male and 58 female patient; mean age, 13.6 ± 12.4 years) had high eosinophil levels (blood eosinophil fraction of $\geq 5\%$; mean blood eosinophil = $8.9 \pm 5.0\%$), and 55.1% (167/303; 74 male and 93 female patients; mean age, 15.3 ± 16.0 years) showed normal eosinophil levels (blood eosinophil fraction of $< 5\%$; mean blood eosinophil = $2.7 \pm 1.2\%$; Table 1). The clinical severity scores in the high eosinophil group (60.3 ± 18.4) were significantly higher than those in the normal eosinophil group (42.1 ± 11.6 ; $p < 0.001$).

Blood eosinophil levels and absolute eosinophil counts were correlated, with a coefficient of 0.862 and an adjusted $R^2 = 0.741$ ($p < 0.001$). The 5% blood eosinophil level was compatible with 368 counts/ μ L (absolute eosinophil count = $10.9 + 71.5 \times [\text{blood eosinophil}]$ level [%]; Fig. 1).

In the high eosinophil group, 120 patients were in the intervention group and 16 were in the control group that did not undergo an elimination diet with a food challenge. Among the 167 patients in the normal eosinophil group, 23 were dropped during the study, leaving 139 patients to finish the study. Overall, 264 eczematoid AD patients underwent diet elimination and food challenge, including 144 patients in the normal eosinophil group. All noneczematoid AD patients who had pure IgE-mediated food allergies showed normal blood eosinophil levels.

Food Allergy and Blood Eosinophil Levels in Eczematoid AD

The food allergy prevalence in eczematoid AD patients was 51.1% (135/264); IgE-mediated food allergy with late eczematous reactions was seen in 15.2% (40/264); and all IgE-mediated allergy was overlapped with non-IgE-mediated food allergy (Table 1). The mean age of subjects who had IgE-mediated food allergy was lower (7.0 ± 13.9 years) than the mean age of total subjects (14.3 ± 14.7 years; $p < 0.001$).

In the group with eczematous AD, food allergy prevalence in the high eosinophil group was 70.8% (85/120), which was significantly higher than the 34.7%

Table 1 Food allergy in eczematous atopic dermatitis (AD) with normal blood eosinophils

Type	Eczematoid AD (n = 303)		
Blood eosinophil level	High 136 (44.9%)		Normal 167 (55.1%)
Intervention	Yes	No	Yes
n	120	16	144
Overall food allergy	85 (70.8%)		50 (34.7%)
IgE mediated	24 (20.0%)		16 (11.1%)
Non-IgE mediated	85 (70.8%)		50 (34.7%)
Overlapping	All		All
HDM Sensitization	45/120 (37.5%)		31/144 (21.5%)

HDM = house dust mite.

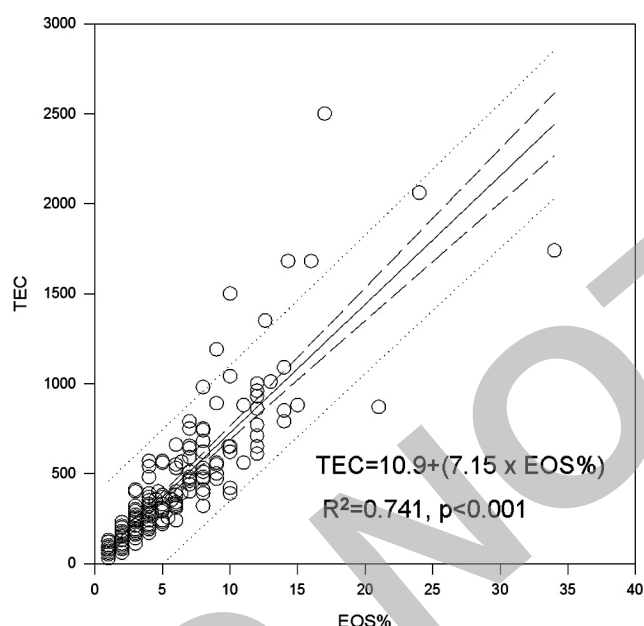


Figure 1. Linear regression for blood eosinophil levels and absolute eosinophil counts. TEC, total eosinophil counts; EOS%, blood eosinophil levels.

(50/144) seen in the normal blood eosinophil group ($p < 0.001$). The prevalence of IgE-mediated food allergy was 20.0% (24/120) in the high eosinophil group and 11.1% (16/144) in the normal eosinophil group. All of the IgE-mediated food allergy patients had non-IgE-mediated food allergy with late eczematous reactions and were in the eczematoid AD group. Pure IgE-mediated food allergy was not seen in the eczematoid AD group.

Of 50 patients with normal blood eosinophil and food allergy, 26.0% (13/50) showed normal serum total IgE and allergy to pork (5 cases) or chicken (8 cases), making up 4.9% (13/264) of the eczematoid AD group. Another 44.0% (22/50) already knew the food responsible for their AD and had avoided the allergen before the study. The remaining 30% (15/50) showed food allergy with normal blood eosinophil levels with no other explanation.

Eight foods gave a positive ratio equal to or $>20\%$, including milk (34.6%), eggs (36.7%), soybeans (24.4%), wheat (29.3%), chicken (30.1%), pork (34.5%), beef (22.4%), and mackerel (23.6%). We observed the peanut allergy prevalence in our Korean patients of 16.7%.

Effects of Diet Elimination on Clinical Severity, Blood Eosinophil, and Serum Total IgE

AD patients with high eosinophil fractions were treated by eliminating seven major allergenic foods from the diet (milk, eggs, soybeans, wheat, beef, pork, and chicken), along with food(s) to which individual patients had a history of adverse reaction. Clinical severity scores decreased from 52.9 ± 14.3 points to 38.1 ± 16.5 points ($p < 0.001$) in the intervention group and were unchanged in the control group, starting at 48.5 ± 13.0 and ending at 52.1 ± 13.8 points ($p = 0.824$). Blood eosinophil in the intervention group was significantly reduced from $10.0 \pm 4.4\%$ to $6.5 \pm 3.7\%$ ($p < 0.001$) and was not significantly changed in the control group from $9.8 \pm 3.3\%$ to $9.6 \pm 3.2\%$ ($p = 0.791$; Fig 2). No significant change was seen in serum total IgE levels (data not shown).

Milk Allergy Provocation of Late Eczematous Reactions and Blood Eosinophil Levels

Among 120 patients who underwent DBPCFC for milk in the intervention group, 37 (23.6%) showed positive milk allergy reactions. Among these 37 positive milk allergy patients with late eczematous reactions, 20 were challenged with milk and 17 were challenged with placebo in random, double-blind tests. In addition, 25 negative milk reaction patients were challenged.

In the positive milk allergy group, the blood eosinophil fraction increased significantly from $6.4 \pm 1.4\%$ to $8.0 \pm 1.7\%$ ($n = 20$; $p < 0.001$) after the milk challenge. However, changes were not significant in the placebo challenge, beginning at $5.8 \pm 1.2\%$ and ending at $5.5 \pm 1.2\%$ ($n = 17$; $p = 0.295$). In the negative milk

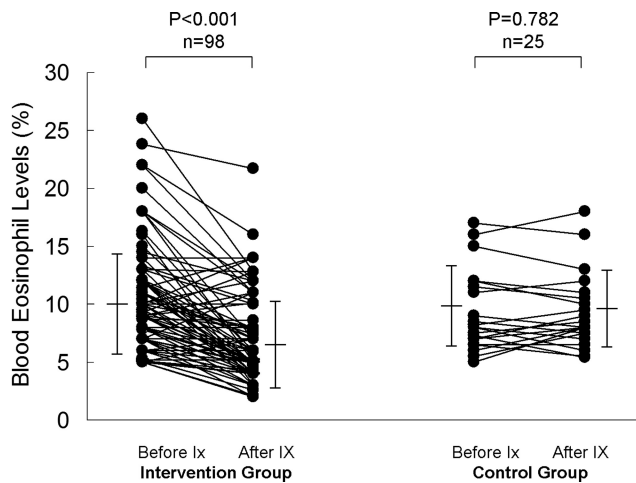


Figure 2. Effects of elimination diet on blood eosinophil level in the high eosinophil group of atopic dermatitis (AD). Before Tx, before the elimination diet; After Tx, after the elimination diet.

allergy group, blood eosinophil went from $5.8 \pm 1.4\%$ to $5.8 \pm 1.5\%$ ($n = 25$; $p = 0.912$) with the milk challenge (Fig. 3). Serum total IgE levels did not changed significantly (data not shown).

D. *pteronysinus*/*D. farinae* Sensitization

Sensitization to house-dust mites was analyzed. The prevalence of sensitization to *D. pteronyssinus*/*D. farinae* in eczematoid AD patients was 28.8% (76/264) compared with 16.7 (1/6) in noneczematoid AD patients. Sensitization was 37.5% (45/120) in the high eosinophil group of eczematoid AD patients and 21.5% (31/144) in the normal eosinophil group. No significant difference was observed in *D. pteronyssinus*/*D. farinae* sensitization, with or without food allergy.

In the high eosinophil group with eczematoid AD, the subjects with food allergy showed significantly higher sensitization (25.8%, 31/120) than subjects who did not have food allergy (11.7%, 14/120). This was different from the normal eosinophil groups.

Skin-Prick Test and Specific IgE for Milk

No significant difference was seen in skin-prick responses to milk between the positive (wheal size ratio for allergen to histamine = 0.5 ± 0.4 ; $n = 30$) and negative (wheal size ratio for allergen to histamine = 0.3 ± 0.4 ; $n = 50$) groups for milk allergy with late eczematous reactions ($p > 0.05$). However, skin-prick test results were significantly different for patients with IgE-mediated food allergy (wheal size ratio for allergen to histamine = 2.2 ± 1.0 ; $n = 12$) when compared with those with positive or negative milk allergy with late eczematous reactions ($p < 0.001$).

Milk-specific IgE levels were similar to skin-prick test results for milk, but were not significantly different between the positive (2.1 ± 4.3 kU/L; $n = 30$) and

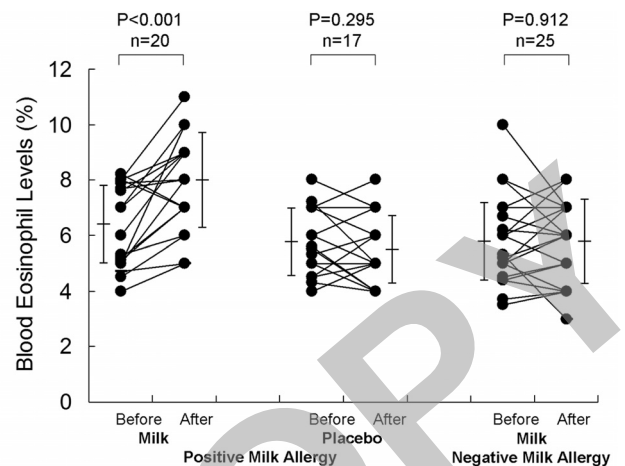


Figure 3. Changes in blood eosinophil fraction after milk allergy provocation. Before, before challenge; After, after challenge; Milk, milk challenge; Placebo, placebo challenge; Positive milk allergy, positive milk allergy patients in the high eosinophil group after double-blind placebo-controlled food challenge (DBPCFC); Negative milk allergy, negative milk allergy patients in the high eosinophil group.

negative (0.5 ± 1.3 kU/L; $n = 50$) milk allergy patients with late eczematous reactions ($p > 0.05$). Milk-specific IgE levels were markedly high in patients with IgE-mediated milk allergy, however (58.3 ± 76.4 kU/L, $n = 12$), when compared with patients with positive or negative milk allergy and late eczematous reactions ($p < 0.001$). IgE-mediated milk allergy and non-IgE-mediated milk allergy with late eczematous reactions could be differentiated by skin-prick tests for milk and milk-specific IgE levels.

DISCUSSION

We found that for patients with AD, 7 days of a proper elimination diet decreased blood eosinophil levels (Fig. 2), but levels were elevated by allergy provocation of late eczematous reactions (Fig. 3). The mean intramedullary maturation and storage time of an eosinophil is <5 days, and the half-life of eosinophils in circulation is <1 day.^{18,19} In addition, 5 days are sufficient to elevate blood eosinophil levels by allergy provocation through oral challenge. Therefore, an elimination diet for 7 days was expected to lower blood eosinophil levels sufficiently if further allergy provocation was prevented.

Eosinophilia, an important laboratory indicator for AD, is a diagnostic parameter for differentiating allergic and nonallergic AD.²⁰ Infants with cow milk allergy show marked eosinophilia.²¹ Our results suggest that food allergy should be considered in cases of eczematoid AD with eosinophilia. This is easily confirmed by a normalization or decrease in blood eosinophil levels after a proper elimination diet, regardless of whether food allergy is the main cause of the eczematous AD.

We also examined the prevalence of food allergy in AD to determine whether proper diet therapy is indicated for AD with eosinophilia. The food allergy prevalence in eczematoid AD cases was 51.1%, and 70.8% of the high eosinophil group showed a food allergy. Consequently, food allergy was considered responsible for the cause of AD, particularly eczematoid AD with eosinophilia. These results were consistent with our previous report that food allergy control is necessary for successful interferon γ therapy for AD patients.¹¹ Sensitization to certain foods triggers isolated skin symptoms in ~30% of children.⁴ Clinical studies have revealed that >50% of all children with AD have a non-IgE-mediated food allergy that can lead to a reaction with either immediate symptoms or a worsening of skin eczema.³

The observed patterns of food allergy with eczematoid AD were different from those seen in western countries. In Korean patients with eczematoid AD, food allergy with late eczematous reaction (51.1%) was more common than IgE-mediated food allergy (15.2%). This is quite different from western countries where not only the prevalence of food allergy was less (estimated at 30%), the prevalence of isolate IgE-mediated food allergy was 43%, and isolated eczematous reactions were seen in 12% of positive challenge.³ The prevalence of peanut allergy, which is the main food allergy in western countries, was not so high in this study (16.7%).

Not only was the prevalence of IgE-mediated peanut allergy lower than in western countries, but meat (beef, chicken, and pork) was a common cause of food allergy with late eczematous reaction in Korean patients, although IgE-mediated meat allergy was not observed. Genetic factors are important for determining the etiology of AD²² and this discrepancy in food allergy patterns between Korean and western patients might be caused by genetic differences.

Interestingly, no patients with only IgE-mediated food allergy were found to have eczematoid AD in this study. However, noneczematous AD patients were found who had only pure IgE-mediated food allergy without both non-IgE-mediated food allergy and late eczematous reactions. From these results, we concluded that non-IgE-mediated food allergy with late eczematous reaction was responsible for eczematoid AD, regardless of the role of IgE-mediated food allergy.

Diagnosis of food-induced eczema requires a thorough diagnostic procedure.^{3,23} In particular, the diagnosis of food allergy with late eczematous reaction can not be made without a food challenge test.²⁴ We found that food allergy with late eczematous reaction was easily detected by the appearance or aggravation of skin eczema after DBPCFC with milk within 6 hours and for as long as 24 hours.

Our analysis also indicated that AD patients without eosinophilia had food allergies, requiring that Besnier's prurigo type AD may be considered. We found a prevalence of nearly 5% for this type of AD, consistent with a previous study.⁹ Patients who had already identified the food(s) that caused their allergy were avoiding them.

Other allergens, including house dust mites, may provoke late eczematous reactions. Sensitization to *D. pteronyssinus*/*D. farinae* was higher in the high eosinophil group than in the normal eosinophil group. In a previous report, we excluded food allergies with supplementary laboratory tests including specific IgE tests and skin-prick tests for house-dust mites.²⁵ Eosinophilia might be helpful for detecting allergy provocation by allergens including house-dust mites when food allergy is not detected.

Strong IgE-mediated reactions are typical for AD.²⁶ However, 10–30% of patients do not show a detectable, specific IgE sensitization. In this study, the results of skin-prick tests and milk-specific IgE tests were not significantly different between the positive and negative milk allergy groups, especially in case of late eczematous reactions. However, skin-prick tests and milk-specific IgE tests definitely discriminated IgE-mediated milk allergy from milk allergy with late eczematous reaction and from a negative milk allergy. Thus, a differential diagnosis of IgE-mediated food allergy and non-IgE-mediated food allergy could be reached with a skin-prick test and food-specific IgE with the presence of characteristic symptoms and signs for IgE-mediated food allergy.

In conclusion, we found that food allergy was, to a large extent, responsible for eczematoid AD, and that a proper elimination diet is indicated for eczematoid AD with eosinophilia. In this study, food allergy with late eczematous reaction was predominant over IgE-mediated acute/subacute food allergy with eczematoid AD. The causes and patterns of food allergy AD in Korea were different from those seen in western countries.

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