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Does the severity of atopic dermatitis change with allergic sensitization? Is it real or a myth?

Serdar Al^{a*}, Suna Asilsoy^b, Özge Atay^c, Özge Kangallı^b, Nevin Uzuner^b

^aDepartment of Pediatric Allergy and Clinical Immunology, Basaksehir Cam and Sakura City Hospital, Istanbul, Turkey

^bDepartment of Pediatric Allergy and Clinical Immunology, Faculty of Medicine, Dokuz Eylul University, Izmir, Turkey

^cDepartment of Pediatric Allergy and Clinical Immunology, Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital, Izmir, Turkey

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Abstract

Objective: Atopic dermatitis (AD) is a chronic inflammatory skin disease that can occur at any age. This study aimed to evaluate the impact of food allergy on disease severity as well as clinical/laboratory findings in children with AD.

Methods: Clinical and laboratory data of AD patients evaluated for food allergy between January 2021 and December 2022 were examined retrospectively.

Results: Of the 52 patients evaluated, 32 (61.5%) were males, with a median age of 6 months (2-118 months). Among them, 26 (50%) had food allergies (FA) and five (9.6%) had inhalant allergen sensitivity. No significant difference in AD severity was observed between patients with and without FA. However, the FA group showed higher serum lactate dehydrogenase (LDH) levels (343.3 ± 81.5 U/L vs 297.7 ± 77.4 U/L; $P = 0.011$) and lower red cell distribution width (RDW). Inhalant allergen sensitivity was associated with higher AD severity.

Conclusion: While guidelines recommend investigating food allergies in moderate to severe AD, this study found no significant difference in the relationship between AD severity and the presence of FA. However, inhalant allergen sensitivity was linked to increased AD severity. Therefore, a comprehensive patient history should include an evaluation of food allergies in children with AD, regardless of disease severity. Elimination and provocation tests related to suspected food items should be performed, and allergenic foods should be removed from the diet if they are found to contribute to the allergy.

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*Corresponding author: Serdar Al, MD, Department of Pediatric Allergy and Clinical Immunology, Basaksehir Cam and Sakura City Hospital, Istanbul, Turkey. Email address: drserdaral@gmail.com

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Introduction

Atopic dermatitis (AD) is a chronic skin condition characterized by itching, redness, and inflammation and is more common in childhood.¹

Atopic dermatitis is thought to result from genetic predisposition, leading to a defect in skin barrier and impaired immune system response, and complex pathologic exposure to various inducers, such as allergens, irritants, and microorganisms.² The association between food allergy (FA) and AD, especially in children, is confirmed by the fact that symptoms decrease with the elimination of the potential food from the diet but again increase with its reintroduction.³ While the prevalence of FA is generally 5-8% in children in Western societies, FA has shown its presence in one-third of the children with moderate to severe AD.^{4,6} Up to six-fold higher FA has been found in children with AD aged 3 months.⁷ FA is believed to play a less significant role in AD pathogenesis in adults.⁸ Guidelines recommend investigating the presence of FA in moderate to severe AD.

The Eczema Area and Severity Index (EASI), the Patient-Oriented Eczema Measure (POEM), the Children's Dermatology Life Quality Index (CDLQI), and the SCORing Atopic Dermatitis (SCORAD) Index are commonly used to measure the clinical severity of AD. SCORAD is the most widely used method to assess AD severity. The SCORAD index is based on a combination of clinical findings (such as redness, swelling, and itching) and subjective measurements.⁹ Many studies have sought to identify biomarkers of AD severity. These biomarkers may include certain proteins, hormones, and immune system molecules found in the skin.

In our study, we aimed to evaluate whether there are clinical and laboratory differences between AD patients with food allergies and those without food allergies to understand the nature of the disease and to evaluate the factors that may be associated with AD severity. For this purpose, the effect of food sensitivity on disease severity and clinical and laboratory findings were evaluated.

Method

Patients diagnosed with AD between January 2021 and December 2022 in the pediatric allergy and clinical immunology department of Dokuz Eylul University Faculty of Medicine (DEU) were evaluated. Gender, mode of delivery, allergenic food (milk and products, eggs, fish, and nuts) consumption during pregnancy, nutrition in the first 4 months, history of food allergy, recurrent of wheezing episodes, presence of doctor-diagnosed atopic disease in the family (asthma, allergic rhinitis, AD, or food allergy), findings of allergic diseases other than AD, SCORAD indexes, and treatments recommended were recorded in the data registration forms of the patients with AD findings.

The diagnosis of AD is made by the presence of three major and at least three minor findings based on the Hanifin-Rajka criteria.¹⁰ The AD severity is evaluated through the SCORAD index. Accordingly, AD was considered mild if the SCORAD score was <25, moderate if the SCORAD score of was ≥ 25 and ≤ 50 , and severe if the SCORAD score was >50 .¹¹

Complete blood count, total immunoglobulin E (IgE), C-reactive protein (CRP), erythrocyte sedimentation rate, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and vitamin D (25OHD₃) levels obtained at the time of diagnosis or within the last 3 months were evaluated.

Food provocation tests were conducted to confirm the diagnosis of food allergy in patients with suspected food allergy based on medical history and clinical findings, and with supporting evidences, such as food-specific IgE > 0.35 kU/L or wheal diameter > 3 mm, larger than the negative control in skin prick test. Skin prick tests, prick-to-prick, and provocation tests were applied to patients with food-specific IgE levels, persistent AD, or respiratory findings in their history, inhalant allergen-specific immunoglobulin E (SptIgE) levels, and SptIgE positive cases. Patients with specific IgE ≥ 0.35 kU/L and ≥ 3 -mm induration from negative control for the skin prick and prick-to-prick tests were considered positive. In the food provocation test, low-medium and full-dose graded food challenge test protocols were applied.¹² The diagnosis of food allergy was based on improvement in symptoms with elimination of suspected allergenic food items and reappearance of symptoms with reintroduction of provocation. Patients with confirmed food allergies by elimination and provocation tests were included in the study. This study was approved by the DEU ethics committee (Approval No.: 2022/10-07).

Statistics

Data were analyzed using the IBM SPSS Statistics 22.0 software (IBM Corp., Armonk, New York, USA). Descriptive statistics were expressed as the number of units (n), percentage (%), mean \pm standard deviation ($\bar{x} \pm SD$), median values, and minimum-maximum values. Numerical variables were analyzed by the normality test. For comparisons between groups, the independent two-sample t -test was used for the variables with normal distribution, while the Mann-Whitney U-test was used for the variables not having normal distribution. The logistic regression test was used as a multivariate analysis to calculate odd ratios (ORs) and 95% confidence intervals (95% CIs). Whether the categorical variables were dependent or not was determined by Chi-square, Yates's correction for continuity, and Fisher's exact test. To determine whether there was a relationship between two variables, Pearson correlation analysis was conducted for the variables with normal distribution, while Spearman correlation analysis was conducted for the variables not showing normal distribution. Multiple group comparisons were analyzed using the Kruskal-Wallis test. $P < 0.05$ was considered statistically significant.

Results

In our study, data from 52 patients, 32 (61.5%) of whom were males, with a median age of 6 (2-118) months were analyzed retrospectively. Of the included patients, 35 (67.3%) were born by cesarean section and 51 (98.1%) of them were born at term. No mother followed a special allergy diet during pregnancy. In the first 4 months,

32 (61.5%) of the cases had exclusive breastfeeding and 20 (38.5%) had breastfeeding + infant formula feeding.

There was no case of consanguineous marriage in family histories. There was a history of atopy in 28 (53.8%) family members. While the mother had a history of atopic disease in 20 (38.5%) of the patients, fathers of six (17.7%) patients, and siblings of two (3.8%) patients had a history of atopic disease. More than one family member had atopic disease in six (11.5%) of the patients. The most common atopic diseases in family members were allergic rhinitis in 16 (30.7%) and AD in 15 (28.8%) patients, respectively.

The mean severity of AD was 33.9 ± 14.2 if graded with SCORAD in all patients. While 18 (34.6%) of the patients had mild AD, 28 (53.8%) had moderate AD and 6 (11.5%) had severe AD. Eighteen (34.6%) of the patients were treated with the recommended moisturizers, 28 (53.8%) were treated with moisturizers + mild potent topical corticosteroids (TCS), and 6 (11.5%) were treated with moisturizers + moderate potent TCS. All patients with a history of persistent findings or suspected FA risk underwent a food provocation test. Food sensitivity was detected in 26 (50%) patients. FA was found in 6 (33.3%) patients having mild AD findings, 16 (57.1%) patients with moderate AD findings, and 4 (66.7%) patients having severe AD findings. Although the incidence of food allergy increased proportionally with the increasing severity of AD, no significant correlation was found (Fisher's Exact Test $P = 0.225$). While 13 (25%) patients were sensitized to cow's milk, 24 (46.2%) patients were sensitized to egg, and 2 (3.8%) patients were sensitized to wheat. More than one food sensitivity was found in 14 (53.8%) patients with food sensitization. While 9 (17.3%) of the patients with food sensitivity had IgE-mediated food allergy and AD findings, 17 (32.7%) had only AD symptoms. In all, 50 patients were evaluated for inhalant allergen sensitivity, and five (10%) tested positive.

When AD severity was compared in terms of the SCORAD index, no difference was found between the

groups with and without FA ($P = 0.111$). No difference was found between the two groups in terms of age, total IgE, eosinophilia, 25OHD₃, ALT, AST, CRP, and erythrocyte sedimentation levels (statistical data are presented in Table 1). The serum LDH level was higher in children with AD with food allergy (mean \pm SD: 343.3 ± 81.5 U/L, for the food allergy group, and 297.7 ± 77.4 U/L, $P = 0.011$, for the group without food allergy. In patients without food allergies, LDH correlated with SCORAD (rho [ρ]: -0.535 ; $P = 0.006$). The correlation graph is shown in Figure 1.

No correlation was discovered between AD severity (SCORAD) and gender ($P = 0.399$), mode of delivery ($P = 0.961$), time of delivery ($P = 0.231$), feeding with breast milk or breast milk + infant formula for the first 4 months ($P = 0.357$), wheezing episode ($P = 0.187$), family history of atopy ($P = 0.308$), presence of other atopic diseases in the child ($P = 0.516$), and food sensitivity ($P = 0.111$). However, a correlation was discovered between the severity of AD and the potency of the inhalant allergen SptIgE and the TCS used in the treatment. The data are presented in Table 2.

Correlation analysis revealed a weak correlation between inhalant allergen serum SptIgE serum level and SCORAD (rho: 0.327 ; $P = 0.022$) as shown in Figure 2.

In case the patients were evaluated in total, no correlation was found between AD severity (SCORAD) and the number and percentage of leukocytes, neutrophils, lymphocytes, monocytes, basophils, eosinophils, erythrocyte count, hemoglobin, hematocrit, mean corpuscle (cell) volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), RDW, platelet count, mean platelet volume (MPV), CRP, sedimentation, LDH, total IgE, ALT, AST, 25OHD₃ and vitamin levels.

Nine (17.3%) patients had a history of wheezing episodes. Of these, six (11.5%) had a history of more than three wheezing episodes, while three (5.8%) had a history of less than three wheezing episodes. Six (11.5%) patients

Table 1 Comparison of patients with and without food allergy.

	With FA (n = 26)	Without FA (n = 26)	P
Age (median [min-max]) months	6.5 (2-120)	5 (3-36)	0.562
Gender (male) n (%)	15 (57.7)	17 (65.4)	0.776
Mode of delivery (NSD)	11 (42.3%)	6 (23%)	0.237
With a family history of atopy	14 (53.8%)	14 (53.8%)	1
Exclusive breastfeeding for the first 4 months	18 (69.2%)	14 (53.8%)	0.393
With recurrent wheezing	5 (19.2%)	4 (15.4%)	1
With signs of other allergic diseases	5 (19.2%)	5 (19.2%)	1
SCORAD, median (min-max)	26.2 (12.3-53.6)	33.6 (18-67)	0.111
Eosinophil, mm ³ mean (%)	565 (5.6)	500 (4.8)	0.93
Total IgE, median (min-max), IU/mL	22.6 (1-802)	35 (1-686)	0.401
25OHD ₃ , median (min-max), ng/mL	18.4 (4-44)	22 (9-66)	0.288
Sedimentation, median (min-max), mm/h	3 (1-50)	2 (2-26)	0.329
CRP, median (min-max), mg/L	0.5 (0.2-69)	0.2 (0.2-21.8)	0.51
LDH, median (min-max), U/L	279 (180-580)	317 (246-570)	0.011
RDW, median (min-max), %	14.1 (12-17)	13.5 (12-26)	0.037
ALT, median (min-max), U/L	20 (8-76)	21 (14-58)	0.165
AST, median (min-max), U/L	40 (20-118)	43 (27-109)	0.89

FA: food allergies; CRP: C-reactive protein; SCORAD: SCORing Atopic Dermatitis; ALT: alanine aminotransferase; AST: aspartate aminotransferase; RDW: red cell distribution width; LDH: lactate dehydrogenase; IgE: immunoglobulin E; NSD: normal spontaneous delivery.

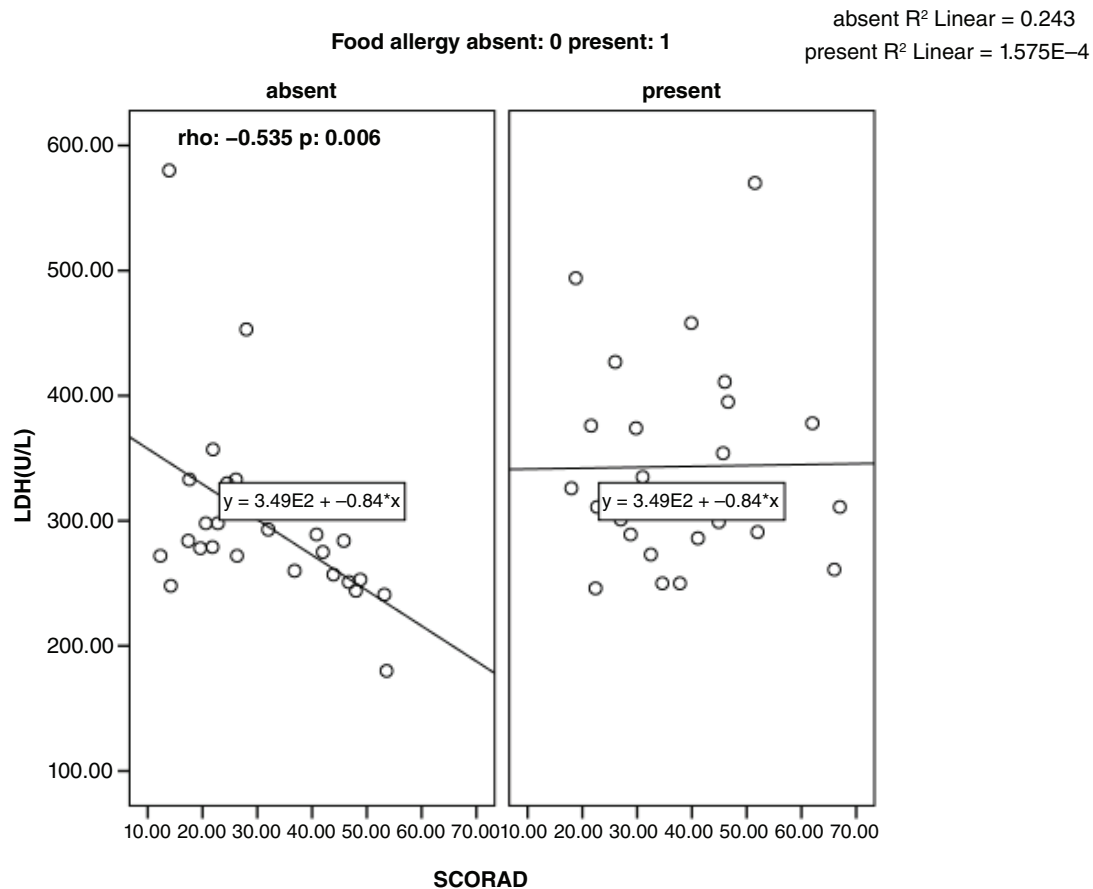


Figure 1 Graph of LDH-SCORAD in the group with and without food sensitization.

Table 2 Factors associated with the severity of AD.

	SCORAD (min-max)	P
SplgE inhalant (+) n: 5	46.7 (34.6-67)	0.020 ^a
SplgE inhalant (-) n: 45	28.8 (12.3-66)	-
Treatment step		
Moisturizer (n: 18)	22.75 (12.3-53.2)	0.003 ^b
Moisturizer + mild TCS (n: 28)	32.25 (13.9-66)	-
Moisturizer + moderate TCS (n: 6)	49.35 (31-67)	-

^aMann-Whitney U-test (U: 42.000); ^bcalculated using the Kruskal-Wallis test.

SplgE: specific immunoglobulin E; TCS: topical corticosteroids.

were diagnosed with allergic rhinitis, five (9.6%) with asthma, and one (1.9%) with allergic conjunctivitis.

Discussion

In our study, it was found that food sensitization increased proportionally with increase in AD severity (SCORAD), but the presence of FA did not affect the clinical severity of AD. In those with food allergies, LDH was high and RDW was low. Meanwhile, in those without food allergies, LDH was negatively correlated with SCORAD. A correlation

was found between AD severity and inhalant allergen sensitization.

Genetic predisposition, lifestyle, cesarean section, use of antibiotics at an early age, microbial colonization on mucosal and cutaneous surfaces, viral infections, Western-type eating habits, and obesity have been found effective in the development of allergic diseases.¹³

The best-known risk factor for atopic diseases is family history.¹⁴ Most patients (65.4%) had a family history of atopic disease, most commonly in their mothers. Families most commonly had allergic rhinitis and AD. The presence of an atopic disease in the family was not a factor affecting food allergy in our patients. One of the questions we sought to answer and expected to find positive response before conducting the study was whether atopic family history is related to the development of food allergies in AD patients. However, we found that family history was not a factor associated with food allergy in AD.

Cesarean section, gender, exclusive breastfeeding, or supplemental cow's milk formula in the first 4 months of life had no effect on the incidence of food allergy.

Dietary avoidance of allergenic foods during pregnancy has not been found to prevent allergic diseases.¹⁵ In all of our patients, their mothers did not follow any avoidance diet during pregnancy.

Atopic dermatitis children with allergy to cow's milk in infancy are more likely to develop other allergic diseases in adolescence.¹⁶ In half of our patients, food allergy was

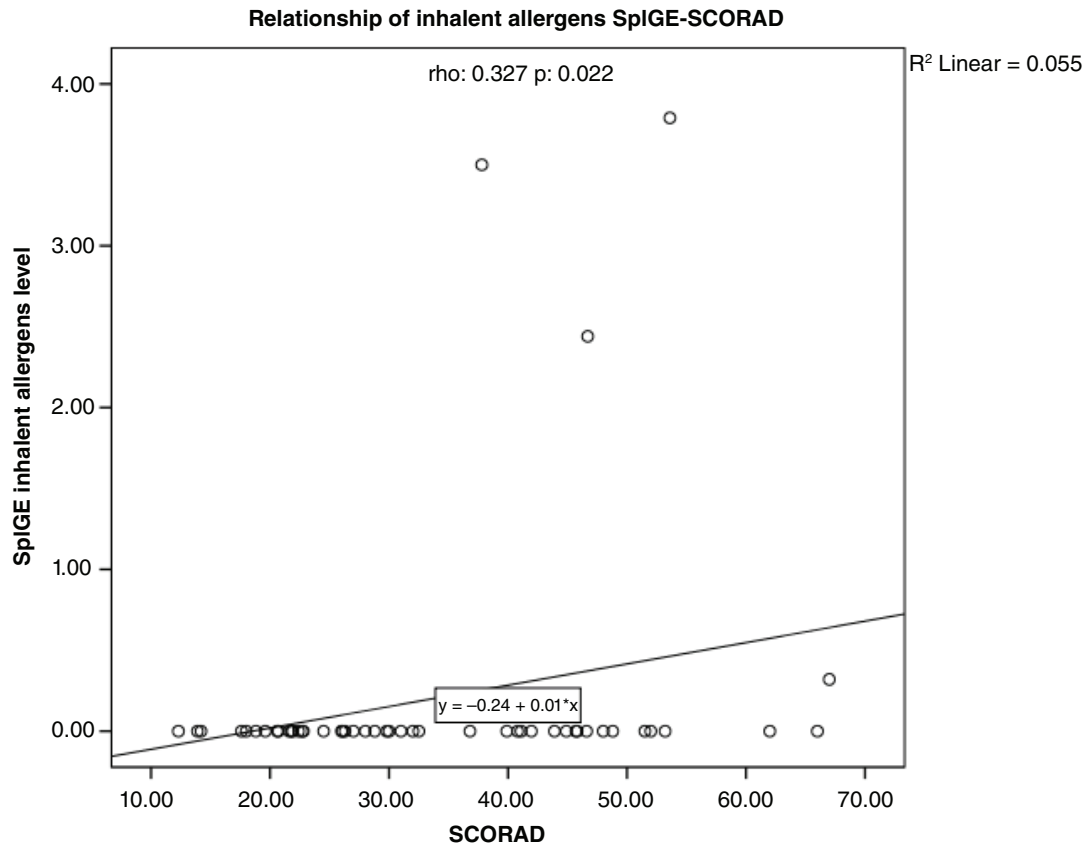


Figure 2 Correlation graph between inhalent allergen serum SpiGE and SCORAD.

present with AD findings. There was a significant difference between the LDH and RDW of patients with food allergies and those without food allergies. LDH is an enzyme involved in carbohydrate metabolism found in many cells. It shows tissue destruction in many diseases. It is important to note that there was no difference in SCORAD, which indicated the severity of AD, but a higher LDH could indicate that inflammation and tissue destruction could be more severe in children with AD who had food allergies, even though there was no clinical evidence to support this. A relationship was determined between LDH elevation and AD severity.¹⁷⁻¹⁹

Although the number of patients with inhalant allergen sensitization was small in our study because of the small age group, the severity of AD (SCORAD) was higher in these children. It is well established that there is a strong relationship between AD and inhalant allergens. Inhalant allergens can lead to weakening of skin barrier and allergic reactions in patients with AD. These allergens include house dust mites, pollen, animal dander, and mold fungi. It has also been shown that exposure to these allergens may increase inflammation in the skin barrier and lead to exacerbation of symptoms in patients with AD.²⁰

In our study, in accordance with the guidelines, in addition to moisturizing and skin care recommendations, higher-potency TCS were used for treatment in all patients with severe findings.

Conclusion

In this study, we aimed to investigate the relationship between food allergy and AD severity in pediatric patients. The study included 52 patients, and established that 50% of them had food allergies, with cow's milk and egg being the most common allergens. No significant correlation was found between the incidence of food allergy and AD severity. No significant differences were determined between the two groups in terms of age, IgE, eosinophilia, 25OHD3, ALT, AST, blood count parameters, CRP, and sedimentation. However, serum LDH levels were higher in children with AD and food allergy, and LDH correlated with SCORAD in the group without food allergy. The clinical severity of AD was found higher in patients with inhaled allergen sensitization. This study had limitations, such as a small sample size and lack of a control group. Thus, further research is required to understand in a better manner the relationship between food allergy and AD severity.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Serdar Al, Özge Atay, Özge Kangallı, Suna Asilsoy and Nevin Uzuner. The first draft of the manuscript

was written by Serdar Al, Suna Asilsoy and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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