Allergologia et immunopathologia
Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica
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ORIGINAL ARTICLE

OPEN ACCESS

Exploring the association between interleukin-27 and *Dermatophagoides*-specific IgE responses in children with allergic rhinitis and asthma

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Received 18 September 2025; Accepted 17 December 2025
Available online 1 May 2026

KEYWORDS
allergic asthma;
allergic rhinitis;
children;
dermatophagoides pteronyssinus;
house dust mite;
IL-27;
interleukin-27;
pediatric allergy;
specific IgE;
Th2 cytokines

Abstract
Purpose: House dust mite (HDM) allergy is a common cause of allergic rhinitis (AR) and allergic asthma (AA). Interleukin-27 (IL-27) is known to suppress Th2-mediated inflammation, a key driver of these diseases. This study aimed to assess regional sensitization to *Dermatophagoides* subspecies and to investigate the association between HDM-specific IgE responses and serum IL-27 levels.
Methods: Fifty-eight children with HDM allergy were evaluated, of whom 53 were sensitized to D. Pteronyssinus. Serum Der p 1/Der p 2 specific IgE (sIgE) (FEIA) and IL-27, IL-5, and IL-13 levels (ELISA) were measured. Twenty-five healthy children served as controls.
Results: Among patients (43% AR, 57% AA), Der p 1 and Der p 2 sensitization rates were 49% and 55%, respectively. Both Der p 1/Der p 2 sIgE levels were significantly elevated compared to controls ($p < 0.001$). Although IL-27 levels were lower in patients, the difference was not statistically significant ($p = 0.98$). However, IL-27 showed positive correlations with IL-5, IL-13, and Der p 1 sIgE (all $p < 0.05$). IL-27 levels were unexpectedly higher in Der p 1-sensitized patients ($p = 0.006$), particularly in AR ($p = 0.02$; $r = 0.43$), but not in AA.
Conclusions: This is the first clinical study to investigate the relationship between IL-27 and HDM-sIgE in children and to demonstrate a phenotype-specific interaction. IL-27 may act as a context-dependent immunomodulator rather than a simple Th2 suppressor. The positive correlation between IL-27 and Der p 1 sIgE in AR patients may indicate a compensatory feedback mechanism triggered by allergen-specific inflammation.

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https://doi.org/10.15586/aei.v54i3.1564

Introduction

House dust mite (HDM) allergy is one of the most prevalent inhalant allergen-induced allergies worldwide.[1] HDM allergens can cause a spectrum of allergic conditions, including seasonal keratoconjunctivitis, atopic dermatitis, allergic rhinitis (AR), or allergic asthma (AA), through skin contact or inhalation. Early-life exposure to these allergens can significantly impact airway functions. Among the many mite subspecies, the most allergenic and frequently encountered are *Dermatophagoides pteronyssinus* (d1-European HDM) and *Dermatophagoides farinae* (d2-American HDM). Approximately 85% of patients with asthma and allergic symptoms are sensitized to at least one of these two species.[1,2] According to the WHO and the Allergen Nomenclature Subcommittee of the International Union of Immunological Societies, Group 1 (Der p 1, Der f 1), Group 2 (Der p 2, Der f 2), and Der p 23 are considered the major allergenic proteins.[3-5] Approximately 95% of HDM-allergic patients are sensitized to Der p 1 and 78% to Der p 2.[6]

AR and AA are characterized by abnormal type 2 helper T cell (Th2) immune responses and airway inflammation. Bronchial epithelial cells contribute to airway inflammation by releasing Th2 cytokines such as IL-4 and IL-5.[7,8] Inhalant allergens also stimulate innate lymphoid cell 2 (ILC2)-related inflammation in AR and AA, further contributing to the Th2-dominant environment.[9,10] IL-4 contributes to the production of Th2 cytokines by converting naive T cells into Th2 cells, IL-5 stimulates eosinophilia, and IL-13 triggers IgE production.[9]

IL-27, a member of the IL-12 family of cytokines, is mainly produced by activated antigen-presenting cells (APCs), NK cells, endothelial cells, and microglia. Its immunomodulatory role in both innate and adaptive immunity has gained increasing interest due to its regulatory functions in immunopathological pathways contributing to the development of airway allergies.[11,12] IL-27 maintains the Th1 (type 1 helper cell)/Th2 balance by promoting Th1 responses and suppressing Th2 cytokiness.[12] Studies in IL27R-α-deficient mice, characterized by increased allergic inflammation, suggest that IL-27 attenuates Th2-mediated airway inflammation by inhibiting ILC2 cell proliferation and cytokine release.[14]

Since Th2 inflammation predominates in the pathogenesis of AR and AA, IL-27 may play a crucial role in modulating this process. Although preclinical evidence supports its ability to suppress Th2 responses, its clinical association with specific IgE sensitization to different allergen types has not yet been investigated. This study aims to evaluate sensitization to *Dermatophagoides* subspecies and to explore the relationship between HDM sensitization and serum IL-27 in children with AR and AA.

Materials and Methods

Fifty-eight children diagnosed with HDM-related AA or AR based on clinical history, physical examination, laboratory testing, and positive skin prick test (SPT) results were included. Exclusion criteria were: (1) corticosteroid use in the past three months; (2) respiratory tract infection in the past two weeks; (3) sensitization to any allergen other than d1/d2; and (4) presence of respiratory or autoimmune disease. Demographic and clinical data—age, gender, symptom onset, age at diagnosis, family history, physical examination findings, and laboratory values (d1 and d2 specific immunoglobulin E-sIgE, total IgE, and percentage of eosinophils)—were obtained from the patient files.

SPT (Allergopharma, Reinbek, Germany) panel included common aeroallergens such as *D. pteronyssinus*, *D. farinae*, cat dander, dog dander, winter grass, grass pollens, tree pollens, and molds (*Alternaria*, *Cladosporium*, *Aspergillus*), etc. Polysensitization was defined as a positive response to more than one aeroallergen. Only children with monosensitization to HDM (*D. pteronyssinus* and *D. farinae*) or HDM-predominant sensitization (with all other SPT results negative) were included. A wheal >3 mm larger than the negative control was considered positive. Specific IgE to d1 and d2 was measured by fluorescent enzyme immunoassay (FEIA; Phadia 250, Thermo Fisher, Sweden), and a result >0.35 kUA/L was considered positive.

Of the patients, 53 sensitized to *D. pteronyssinus* were selected as the "d1-sensitized group," which was further categorized into HDM-related AR and AA subgroups. A control group of 25 healthy children with no history of atopy, respiratory, autoimmune, or infectious diseases was also included. Informed consent was obtained from all parents.

All cases were initially evaluated for their responses to Der p 1 and Der p 2, the major allergenic proteins of *D. pteronyssinus*, and serum sIgE concentrations were measured by FEIA (Phadia 250, Thermo Fisher, Sweden). A result >0.35 kUA/L was considered positive.

Serum IL-5, IL-13, and IL-27 concentrations were measured in duplicate using commercial sandwich enzyme-labeled immunoassay (ELISA) kits (SunRed Biotech, Shanghai). Detection ranges for IL-5, IL-13, and IL-27 were 2–32 pg/mL, 4–64 pg/mL, and 7,5–120 pg/mL, respectively, and the analytic sensitivities were 0,158 pg/mL, 0,413 pg/mL, and 0,92 pg/mL, respectively.

Age adjustment could not be performed due to the limited sample size; therefore, age remains a potential confounder.

The study received ethical approval from the Ege University Medical Research Ethics Committee (21-5T/87). The STROBE checklist is supplied (Supplementary file 1).[15]

Statistical analysis

Data analysis was performed using SPSS v22.0. Descriptive statistics and/or frequency distributions were evaluated according to the types of variables. The Mann-Whitney U test or Kruskal-Wallis test was used to compare independent groups for numerical data that did not show a normal distribution based on the Kolmogorov-Smirnov concordance test, and the one-way ANOVA test was used for data with a normal distribution. Correlations were assessed using Spearman's rank correlation. A value of $p < 0.05$ was considered statistically significant.

Results

Among the 58 HDM-allergic children (full results in the appendix), 53 were sensitized to *D. pteronyssinus* and 50 to *D. farinae*. The demographic, clinical, and laboratory characteristics of d1-sensitized patients (40 boys, 13 girls; 10,6 ± 3,97 years old) are given in Table 1. The control group included 16 boys and 9 girls (10,2 ± 3,0 years old).

Der p 1 and Der p 2 spIgE concentrations were significantly higher in d1-sensitized patients than in controls, as expected (p < 0.001) (Table 2). The mean IL-27 levels were lower in patients, but the difference was not statistically significant (p = 0.98). However, IL-27 was well correlated with IL-5 (p < 0.001; r = 0.67), IL-13 (p < 0.001; r = 0.69), and Der p 1 spIgE (p = 0.03; r = 0.29) in patients. In terms of Th2 response, IL-5 levels were higher than in controls, but the difference was not statistically significant (p = 0.33). IL-13 levels were almost similar in both groups (p = 0.53) and showed a good correlation with IL-5 in patients (p < 0.001; r = 0.57).

Among the 53 d1-sensitized patients, 23 (43%) had AR and 30 (57%) had AA. All demographic, clinical, and laboratory data of the d1-sensitized AR and AA patient and control groups are summarized in Table 3. Asthmatic children were younger at symptom onset (p < 0.001) and at diagnosis (p = 0.002).

HDM sensitization data, IL-27, and Th2 cytokines in the study groups are summarized in Table 4. Der p 1 and Der p 2 sIgE levels were strongly correlated with each other in both patient groups (p < 0.001; r = 0.82). No significant difference was observed in Der p 1 (p = 0.62) or Der p 2 (p = 0.63) sIgE levels between the AR and AA groups, despite slightly higher levels in AA. As expected, Der p 1 (p < 0.001) and Der p 2 (p < 0.001) sIgE levels differed significantly between the control and patient groups, respectively.

IL-27 levels were lower in the patient groups than in controls but showed no significant difference among all groups (p = 0.98) (Table 4). IL-27 correlated well with IL-5 (p < 0.001; r = 0.76 and p < 0.001; r = 0.61) and IL-13 (p < 0.001; r = 0.80 and p < 0.001; r = 0.57) in the AR and AA groups, respectively.

IL-27 levels were significantly higher in Der p 1-sensitized patients (23,07 ± 6,30 pg/mL) than in non-sensitized patients (19,4 ± 9,11 pg/mL) (p = 0,006) and correlated well with Der p 1 sensitization (p = 0,02; r = 0,43) in AR but not in AA (p = 0,35; r = 0,17). However, IL-27 levels did not show any difference in terms of sensitization to Der p 2 (p = 0,38), although concentrations were higher in sensitized patients (21,5 ± 6,92 pg/mL) than in non-sensitized patients (20,8 ± 9,27 pg/mL).

While IL-5 levels did not show any difference between the study groups (p = 0.52), they were negatively correlated with the mean age in AA patients (p = 0.02; r = −0.42). IL-13 showed higher concentrations in AR patients, but there was no significant difference between the groups (p = 0.76).

Table 1 Demographic, clinical, and initial laboratory characteristics of children sensitized to *Dermatophagoides pteronyssinus*.

	D. pteronyssinus-sensitized patients
Gender**	
boys	40 (75)
girls	13 (25)
Age at the study, years*	10,6 ± 3,97
Age of onset of symptoms, years	5,71 (4,61-6,81)
Age at admission, years	8,97 (7,76-10,1)
Age at diagnosis, years	8,47 (7,27-9,66)
Diagnosis**	
Allergic rhinitis	23 (43)
Allergic asthma	30 (56)
Consanguinity**	7 (13)
Atopy**	20 (38)
Family history of allergy**	31 (59)
D. pteronyssinus spesific IgE, kUA/L	17,8 (8,97-26,7)

Descriptive statistics and/or frequency distributions were evaluated according to the types of variables. Values are presented as: mean (%95 confidence interval), *: mean± standard deviation and **: n (%). Sample size: *D. pteronyssinus*-sensitized patients (n = 53). Units: specific IgE (kUA/L); frequency distributions [n (%)].

Discussion

This study provides new insights into HDM-related allergic diseases in children by exploring the association between

Table 2 Sensitization to major *Dermatophagoides pteronyssinus* allergenic components and Th1/Th2 cytokine levels in sensitized patients and healthy controls.

	D. pteronyssinus-sensitized patients	Healthy controls	p value
Der p 1 spesific IgE	10,4 (4,64-16,3)	0,001 (0,000-0,003)	<0,001
Der p 2 spesific IgE	15,1 (8,21-22,0)	0,005 (0,002-0,009)	<0,001
IL-27	21,2 (19,0-23,4)	23,8 (18,5-29,0)	0,84
IL-5	7,45 (6,29-8,61)	6,57 (5,26-7,88)	0,33
IL-13	11,4 (9,63-13,2)	11,5 (9,30-13,8)	0,53

Values are expressed as mean (%95 confidence interval). Group comparisons were performed using the Mann-Whitney U test for non-normally distributed variables and one-way ANOVA for normally distributed variables. Sample sizes: *D. pteronyssinus*-sensitized patients (n = 53) and healthy controls (n = 25). Units: specific IgE (kUA/L); cytokines (pg/mL).

Table 3 Demographic, clinical, and initial laboratory characteristics of *Dermatophagoides pteronyssinus*-sensitized children with allergic rhinitis and allergic asthma.

	D. pteronyssinus-sensitized patients		p value
	Allergic rhinitis	Allergic asthma	
Gender**			
boys	16 (70)	24 (80)	-
girls	7 (30)	6 (20)	
Age at the study, years*	12,2 ± 4,09	9,38 ± 3,45	0,006
Age of onset of symptoms, years	7,82 (6,08-9,56)	4,10 (2,91-5,28)	<0,001
Age at admission, years	10,9 (9,09-12,7)	7,48 (6,00-8,95)	0,002
Age at diagnosis, years	10,6 (8,90-12,3)	6,80 (5,35-8,24)	0,002
Consanguinity**	3 (11)	4 (13)	0,97
Atopy**	11 (41)	9 (29)	0,18
Family history of allergy**	15 (56)	20 (65)	0,37
Total IgE	265 (113 - 418)	628 (105 - 1362)	0,39
Eosinophils**	4,66 (3,22 - 6,10)	4,21 (2,28 - 6,15)	0,34
D. pteronyssinus spesific IgE	11,7 (5,35 - 18,1)	22,8 (7,21 - 38,4)	0,34

Values are expressed as mean (%95 confidence interval), *: mean ± standard deviation and **: n (%). Group comparisons were performed using the Mann-Whitney U test for non-normally distributed variables and one-way ANOVA for normally distributed variables. Sample sizes: Allergic rhinitis (n = 23) and Allergic asthma patients (n = 30). Units: specific IgE (kUA/L); cytokines (pg/mL), total IgE (KU/L), eosinophils (%), frequency distributions [n (%)].

Table 4 Sensitization to major *Dermatophagoides pteronyssinus* allergenic components and Th1/Th2 cytokine levels in sensitized children with allergic rhinitis, allergic asthma, and healthy controls.

	D. pteronyssinus-sensitized patients			Healthy controls	p value
	Allergic rhinitis	Allergic asthma	p value		
Der p 1 spesific IgE	4,93 (1,71-8,16)	14,7 (4,72-24,7)	0,62	0,001 (0,000-0,003)	<0,001*
Der p 2 spesific IgE	13,1 (4,28-22,0)	16,6 (6,04-27,2)	0,63	0,005 (0,002-0,009)	<0,001**
IL-27	21,1 (17,9-24,2)	21,3 (18,0-24,5)	0,52	23,8 (18,5-29,0)	0,98**
IL-5	7,78 (5,91-9,64)	7,20 (5,63-8,76)	0,51	6,57 (5,26-7,88)	0,52*
IL-13	12,0 (8,90-15,1)	11,0 (8,70-13,3)	0,87	11,5 (9,30-13,8)	0,76*

Values are expressed as mean (%95 confidence interval). Group comparisons were performed using the Mann-Whitney U test/ Kruskal Wallis test* for non-normally distributed variables and one-way ANOVA** for normally distributed variables. Sample sizes: Allergic rhinitis (n = 23) and Allergic asthma patients (n = 30) and healthy controls (n = 25). Units: specific IgE (kUA/L); cytokines (pg/mL).

major allergenic components and IL-27. In a limited number of regional studies in our country, HDM sensitization in children was reported to range between 48% and 72%.[15,16] This study reveals higher sensitization rates to *D. pteronyssinus* (87,9%) and *D. farinae* (84,5%). d1-sensitized children developed symptoms at older ages and were diagnosed later.

In allergic diseases characterized by abnormal Th2 responses to specific allergens and inflammatory changes in the airways, it is well known that Th2 cytokines modulate airway inflammatory changes, airway hyperreactivity, and tissue fibrosis.[7,8,17] In this study, elevated IL-5 levels in patients and their correlation with IL-13 reflected an increased Th2 response.

IL-27 is reported to inhibit Th2 cell differentiation and cytokine production both in vivo and in vitro.[13,14] Studies have shown that IL-27 deficiency in IL27R-α–deficient mice is associated with increased mucosal ILC2 and that cytokine production is significantly reduced with IL-27 treatment.[13] It has also been shown that IL-27 inhibits ILC2 proliferation and function in individuals sensitized to *Dermatophagoides* species, and IL-5 production is suppressed after dose-dependent IL-27 stimulation.[14]

The increased IL-5 levels observed in d1-sensitized patients may suggest enhanced type 2 inflammation; however, without direct cellular phenotyping, the specific contribution of ILC2 cells cannot be determined.

IL-27 levels were not significantly different between the control and patient groups, but mean levels were lower in patients. The contradictory positive correlation between IL-27 and IL-5/IL-13 levels in the patient groups cannot be explained by establishing a causal relationship. IL-27 may play a compensatory or modulatory role in the

allergic response rather than acting as a simple inhibitor of Th2 inflammation. IL-27 has been reported to exhibit context-dependent immunomodulatory effects in preclinical studies. In our study, serum IL-27 levels correlated with Th2 cytokines, but the precise cellular mechanisms underlying this association remain unclear.

Understanding *Dermatophagoides* species-specific IgE sensitization is particularly important in designing effective treatment protocols for HDM allergy.[1] Based on this approach, when responses to the two major allergens were examined, 49% of d1-sensitized cases had Der p 1 sIgE sensitization and 55% had Der p 2 sIgE sensitization. The prevalence of sensitization varies between 44–94% for Der p 1 and between 53–97% for Der p 2 in similar studies conducted in different countries.[4,20-25] This similarity indicates a common reactivity pattern across different geographic regions and ethnic groups. Der p 2 sensitization is reported to be more common in Europe, as in our study.[20-25] While it is stated that HDM sensitization in children varies depending on the regions of our country, it is reported that the frequency of Der p in adults is similar to studies conducted in countries in the same climate zone (France 38,1%, Greece 32,7%, Italy 38,9%, and Portugal 22,2%).[26]

While some studies have shown that Der p 1/Der p 2 sIgE levels are higher in AA than in AR,[21-23] Bronnert et al.[5] found no association between the prevalence of IgE reactivity to HDM components and the type of allergic disease. In contrast to the study by Zou et al.,.[6] in our study, Der p 1 sIgE levels were higher in asthmatic children, but there was no significant difference between the two groups in terms of Der p 1/Der p 2 sensitization.

Although there was no significant difference between the AR and AA groups, higher IL-5 levels and a positive correlation with IL-13 once again reflected increased Th2 inflammation.

IL-27 is reduced in AR and AA through activation of different signaling pathways.[27-29] There was no significant difference between our groups, but IL-27 levels were lower and correlated with Th2 cytokines and Der p 1 in the AR group. The correlation between mite allergy and IL-27 does not directly explain whether mite allergy sensitization induces or antagonizes IL-27 or whether another condition resulting in elevated IL-27 may induce mite sensitization. However, similar findings have been obtained in other studies. Ouyang et al.[30] also showed that IL-27 levels decreased in AR and that IL-27 was effective by suppressing Th17 responses. However, our study did not measure Th17-associated markers; therefore, these pathways cannot be directly assessed. Furthermore, it has been highlighted that ILC2 cells may play different roles in HDM-related AR and that immunotherapy increases IL-27 levels.[31,32] It has also been shown that Der p 1 sIgE levels, nasal ILC2 cells, and type 2 cytokines decrease after IL-27 administration in a mouse model.[18] Similarly, IL-27 deficiency was associated with increased ILC2 mucosal infiltration in an inflammatory lung disease model, and IL-27 treatment inhibited cytokine production.[13,14] Gan et al.[33] also showed that decreased IL-27 expression correlated with Th2 responses and IL-5/IL-13 levels in AR. These findings align with ours and may support the concept of IL-27 as a context-dependent regulator rather than a universal suppressor of allergic inflammation. The phenotype-specific correlation may suggest that IL-27 exerts different immunological effects depending on the clinical presentation of the allergy, possibly due to differences in local tissue responses (nasal vs. bronchial mucosa) or immune cell composition.

Der p 1 is a cysteine protease that disrupts epithelial tight junctions and increases antigen penetration. This epithelial barrier dysfunction may facilitate the activation of local antigen-presenting cells, trigger IL-27 production at the mucosal level, and partially account for the higher IL-27 levels observed in children sensitized to Der p 1. However, it remains unclear whether this increase reflects a suppressive effect or a feedback response to ongoing Th2 inflammation. Enhanced type 2 activity may induce IL-27 as a homeostatic counter-regulatory mechanism; nevertheless, serum IL-27 levels may not accurately reflect mucosal cytokine activity. Therefore, assessment of IL-27 in nasal or bronchial samples is needed to clarify the biological significance of this association.

The relationship between IL-27 levels and the clinical features of asthma remains unclear. It has been suggested that IL-27 expression could potentially serve as a biomarker to determine the heterogeneity of asthma phenotypes, and, as shown in our study, lower IL-27 levels were observed in untreated asthma patients. IL-27 levels correlated with IL-5/IL-13. Furthermore, as suggested by Qin et al.,[34] the combination of IL-27 levels and the presence of Th2 inflammation may help predict lung function. Conversely, it has also been reported that IL-27 levels may be increased in the lungs of some patients with severe asthma.[35] It has been shown that IL-27 can reduce allergic inflammation and symptoms in a mouse asthma model and inhibit Th2 cell differentiation. It can reduce airway inflammation and hypersensitivity, regulate Th1 and Treg cell subgroups in lung tissue, and reduce Th2 cytokines.[36] However, the mechanisms and effects of these therapeutic applications have not yet been elucidated.

This study has several limitations. The patient groups differed in terms of age and disease onset, and the study was conducted with a small sample size, which limited statistical power, particularly in subgroup analyses. Future studies with larger patient groups, along with statistical power analysis, will enhance the validity of our findings. The cross-sectional nature of the study and the lack of control for variables such as age, gender, seasonality, etc., are major shortcomings. In particular, differences in age and time to diagnosis between the AR and AA groups are potential confounders and may have influenced the results. The AA group developed symptoms and was diagnosed at an earlier age than the AR group. This age difference complicated the interpretation of cytokine differences between the groups, particularly because it might have affected Th2 cytokine levels. The lack of age-adjusted statistical analysis limited the ability to determine whether the observed differences were independent of age. Future studies will allow for more accurate and reliable assessment of the relationships between IL-27 and Th2 cytokines by analyzing the effects of age. Furthermore, considering age-related cytokine changes will enhance understanding of the phenotypic behavior of IL-27 in AR and AA. Our findings are correlational, and further studies are needed to establish a causal relationship. IL-27 was assessed only at the serum level, which may not reflect its local mucosal activity, and

immune cell phenotyping was not performed. In future studies, cytokine and immune cell analyses in nasal lavage, sputum, or tissue samples will provide a better understanding of the local immune microenvironment. Another important limitation is that the possible effects of IL-27 administration could not be examined. Future larger, multicenter cohort studies and longitudinal designs assessing IL-27 levels before and after allergen exposure or immunotherapy will further help to clarify causality and regulatory roles.

In this study, IL-27 concentrations did not differ significantly between groups; however, they demonstrated consistent correlations with IL-5, IL-13, and Der p 1 sensitization—particularly in children with AR—suggesting a possible phenotype-dependent immunological pattern. This may be the first clinical study to report an association between serum IL-27 and HDM-specific IgE in children; however, given the cross-sectional design and the absence of cellular or mechanistic analyses, these correlations do not establish causality. Whether IL-27 plays an active role in disease pathogenesis or merely reflects ongoing type 2 inflammation remains unclear, underscoring the need for longitudinal studies to clarify its potential as a biomarker or therapeutic target in HDM-related allergic diseases.

Ethics Statement

The study involving human participants was performed in accordance with the Declaration of Helsinki and was approved by the Ege University Medical Research Ethics Committee (21-5T/87).

Consent to Participate

Informed consent was obtained from all individual participants and their parents included in the study.

Mandatory Disclosure on Use of Artificial Intelligence

The authors declare that no AI-assisted tools were used in the preparation of this manuscript. All references have been manually verified for accuracy and relevance.

Acknowledgements

All authors would like to thank Ege University.

Author's Contributions

EA conceived the design. HS, ET, FG, ED were responsible for clinical follow-up. EA, HS, ET performed the primary data analysis and contributed to the study design, interpreted the data, and wrote the manuscript. All authors contributed equally to the manuscript and read and approved the final version of the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

Funding

This study was performed at the Ege University Faculty of Medicine. This research was funded by the Ege University Scientific Research Projects Coordination Unit with Project number TGA-2021-23065. The authors report no involvement in the research by the sponsor that could have influenced the outcome of this work.

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