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Research Article

The Combination of Serum Total IgE and Blood Eosinophil Levels as a Predictor of Response to Phototherapy Treatment in Patients with Atopic Dermatitis

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Atopic dermatitis (AD) is the most common chronic inflammatory skin disease affecting approximately 25% of all people worldwide at some point during their lifetime. Although total serum immunoglobulin E (IgE) and blood eosinophil levels are not elevated in all patients with AD, they have been shown associated with AD severity. This study aimed to investigate whether IgE and blood eosinophil levels correlate with the response to phototherapy treatment, which is a second-line treatment for moderate-to-severe AD, and therefore could be considered a readily available and reliable biomarker that could guide patient management. Eighty-two patients with AD who received phototherapy at the Sheba Medical Center were retrospectively evaluated for the following: demographic characteristics, serum IgE levels, blood eosinophils count, hospitalization duration, response to phototherapy, and requirement for systemic treatment. Response to phototherapy treatment was assessed by comparing the pre- and post-treatment Investigator's Global Assessment score for each patient in relation to the aforementioned factors. The total IgE and eosinophil levels were found to be significantly higher in patients who did not respond to phototherapy ($p = 0.018$ and $p = 0.002$, accordingly). Serum values of 1780 IU/mL for IgE and 225.0 cells/μL for eosinophils showed maximum sensitivity and specificity as predictive values for treatment response. In conclusion, this study found that high total serum IgE levels and eosinophilia were correlated with a low response to phototherapy. These results suggest that escalating treatment is recommended for patients presenting these clinical features.

1. Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by pruritus and a relapsing course. Its clinical diagnosis is established based on the patient's medical history, the morphology and distribution of the skin lesions, and associated clinical signs [1].

Recent advances in molecular medicine have given us insight into the pathogenesis of the disease, which is now regarded as a complex inflammatory cutaneous disorder driven by interplay of epidermal barrier dysfunction, immune dysregulation, and microbiome alterations. One of the main characteristics of immune dysregulation is the deviation of the immune system toward the T helper 2 pathway

in the initiation phase with a subsequent increase in immunoglobulin E (IgE) production [2, 3].

Hanifin and Rajika developed a diagnostic standard for diagnosing AD, comprising essential and minor features, which is still widely in use today [4]. Currently, disease severity is assessed merely on clinical features [5]. The most commonly used scoring systems are the SCORing Atopic Dermatitis (SCORAD) Index, the Eczema Area and Severity Index, and the Investigator's Global Assessment (IGA). However, because of their complex and time consuming nature, they are primarily used in clinical trials. Moreover, they reflect the patient's state at a certain point in time and thus do not account for the fluctuating characteristics of the disease. Hence, most clinicians use general subjective questions, such as those pertaining to itch, sleep disturbances, impact on activities of daily living, and persistence of the disease, to guide their treatment management strategies for patients with AD [6–8].

The need for an easier, accessible, reliable, and objective biomarker to assess disease severity and guide patient management has prompted for increased research. With the discovery of new T-lymphocyte subgroups, novel cytokines, and chemokines, numerous potential biomarkers have been reported. Relevant studies have investigated serum levels of CD30, macrophage-derived chemoattractant, interleukins 12, 16, 18, and 31, T helper 2 cell cytokines CCL 17, 22, and 27, thymus activation-regulated chemokine (TARC), and filaggrin mutations [9]. Unlike the previously mentioned biomarkers, total serum IgE levels and peripheral blood eosinophils count are readily available indices used in everyday clinical practice. Both eosinophilia and IgE levels are known to be related to AD and to its severity [10]. Yet, their role in predicting the response to various treatments given in AD is less studied [11, 12].

Phototherapy is a second-line treatment option for patients with AD who failed to improve with topical treatments, namely, emollients, corticosteroids, and calcineurin inhibitors. Furthermore, the valuable effects of solar exposure in patients with AD have been reported with numerous patients describing a significant improvement of their condition during the summer. Currently, phototherapy modalities used in AD include (BB)-UVB (290–320 nm), (NB)-UVB (311–313 nm), UVA-1 therapy (340–400 nm), UVA-1 therapy with 8-methoxypsoralens (PUVA), excimer laser, and full spectrum light [13–17]. Advances in photoimmunology suggest that phototherapy targets inflammatory cells, alters cytokine production, prompts the apoptosis of infiltrating T cells, and inhibits the antigen-presenting function of Langerhans cells, thereby inducing a positive immunosuppressive effect. Furthermore, UV radiation was shown to have an antibacterial effect; indeed, (NB)-UVB has been proven to decrease the production of superantigens and modify mRNA levels of antimicrobial peptides [18–20]. In a systematic review of randomized controlled trials on phototherapy for AD, it was concluded that both UVA and UVB resulted in a significant reduction in SCORAD scores from baseline following a 12-week treatment. All the patients in the UVB group showed more than a 50% reduction in SCORAD scores, while 93% of patients in the UVA group showed improvement [14]. Moreover, phototherapy is generally considered to be safe and could effectively reduce cutaneous inflammation; systemic side effects have been rarely reported. Since UVA-1 phototherapy is expensive and not widely available, NB-UVB has emerged as an effective alternative. Some of its commonly localized adverse effects are xerosis, erythema, and tenderness. Its limitations include limited availability and low patient compliance to a thrice-weekly program [13, 15]. To prevent patients from experiencing disappointment by the lack of benefit or even worsening of skin symptoms after a lengthy treatment, it would be useful for clinicians to have an objective, measurable, and easily accessible biomarker to predict NB-UVB phototherapy treatment response.

Therefore, the aim of this study is to investigate whether total serum IgE levels and eosinophils count correlate with the response to phototherapy treatment in patients with AD, in an effort to assess their utility as potential biomarkers.

2. Materials and Methods

All patients admitted to the Dermatology Department of the Sheba Medical Center who were diagnosed with AD and received phototherapy treatment between 2011 and 2016 were considered in this study. Data were retrieved using the Electronic Medical Records (Chameleon) at the Sheba Medical Center.

Inclusion criteria included the following: (1) fulfillment of the diagnostic criteria for AD by Hanifin and Rajika; (2) a measurement of serum total IgE levels (international unit per mL) as well as peripheral blood eosinophils count (cells per μL); (3) having undergone any course of phototherapy treatment at our institution; phototherapy was categorized as "full" course (an 8-week course of thrice-weekly attendance) and "partial" course (any course that lasted <8 weeks); and (4) detailed clinician notes available for both admission and follow-up visits, determining the patient's IGA score and enabling comparison of disease severity. The IGA is a five-point scale that provides a global clinical assessment of AD severity ranging 0–4, where 0 indicates clear, 1 indicates almost clear, 2 indicates mild, 3 indicates moderate, and 4 indicates severe AD.

Other patient details obtained from the medical records were demographic data (age and sex), any atopic background (type I allergies, allergic rhinitis, asthma, or other), hospitalization duration, systemic treatments (such as treatments with methotrexate, cyclosporine, mycophenolate mofetil, and azathioprine), and any improvements experienced with respect to pruritus as stated by the patient and recorded by the examining clinician during each visit.

Due to the retrospective nature of this study, only patients with comprehensive clinician records, which enabled evaluation and categorization, were included. This study was approved by the institutional ethical committee.

2.1. Statistical Analysis. Response to phototherapy was evaluated by the examining clinician using the IGA scoring system during the patient's final follow-up visit; the evaluation was based on clinical history and examination findings. Patients who had an improvement of ≥2 points in their IGA score were defined as "responsive," whereas all others were considered as "nonresponsive."

The Mann–Whitney *U* test was applied to compare continuous variables. The chi-square test was employed to compare categorical variables. The results are presented as means ± standard deviation (SD), median with 25^{th} and 75^{th} percentile, and minimum and maximum values for continuous variables and as counts and percentages for categorical variables. A scatter plot model was used to identify the threshold levels of serum IgE and blood eosinophils with maximum sensitivity and specificity for treatment response. The significance level was defined as $\alpha = 0.05$. Analyses were performed using IBM SPSS Statistics for Windows version 24.0.

3. Results and Discussion

3.1. Results. Data of 82 patients (52 males and 30 females) who fulfilled the inclusion criteria as described above were obtained (Tables 1 and 2). Among the 82 patients, 31 were identified as responders and 51 as nonresponders to phototherapy treatment after IGA score evaluation.

Age, sex, and atopic background did not display any significant relationship with the response to phototherapy (Table 1). Hospitalization duration was also not significantly different between responders and nonresponders. As expected from the therapeutic ladder for AD, systemic treatment use was significantly higher in nonresponsive patients than in responsive patients ($p < 0.001$). Moreover, improvement with respect to the symptom of pruritus was significantly higher among the group of patients who responded to phototherapy than in those who did not ($p < 0.001$).

While phototherapy course duration showed a borderline significant effect on response ($p = 0.081$), completion of a full phototherapy course, as defined in the Materials and Methods, was not found to be significantly correlated with treatment response; only 51.6% of the responders received a minimum of 8 weeks of treatment. Further analysis of the "full" and "partial" phototherapy subgroups showed that none of the additional defined variables had any correlation to response. Specifically, there were no significant differences in the subjects of these subgroups with respect to age, gender, or any atopic background. Furthermore, no significant difference was found when comparing the IgE values of the patients in the two subgroups, while a borderline significant difference ($p = 0.07$) showing higher eosinophil levels within the "full course" patients was observed.

Total serum IgE levels were found to be significantly higher in nonresponders than in responders ($p = 0.018$). Eosinophils count was also found to be significantly higher in this subgroup ($p = 0.002$).

Although an atopic background was not found significantly related to treatment response, IgE levels were significantly higher in patients with an extrinsic atopic background than in those without (intrinsic AD) ($p = 0.015$; Table 3).

By applying a scatter plot model (Figure 1), a threshold value of total serum IgE levels of 1780 IU/ml in relation to phototherapy response was identified. Thus, in our cohort, patients with serum IgE levels higher than the suggested cutoff value were unlikely to respond to phototherapy treatment.

A different scatter plot model (Figure 2) found a threshold value of blood eosinophil levels of 225.0 cells/μL with respect to response. Thus, in our cohort, patients with eosinophil levels higher than the suggested cutoff value were unlikely to respond to phototherapy treatment.

IgE and eosinophil levels within the same subject did not show any correlation, with no ascending linearity. However, more responders had lower levels of both IgE and eosinophil levels, whereas nonresponders presented a range of higher values (Figure 3).

We also applied the scatter plot model to assess a minimum number of weeks to achieve optimal course duration of phototherapy. In our cohort, the recommended threshold was 8.5 weeks for response to phototherapy treatment (Figure 4).

3.2. Discussion. Our results showed that IgE and blood eosinophil levels were significantly higher in patients who did not respond to phototherapy than in those who did. Based on our statistical evaluation, the cutoff IgE level is 1780 IU/mL, while the cutoff eosinophil level is 225.0 cells/μL; the positive predictive value for the suggested IgE cutoff is 72% and that for the suggested eosinophil cutoff is 52%. When both values are combined, the positive predictive value is raised to 74%. Despite the fact that the present study did not demonstrate a direct linear correlation between serum IgE and eosinophil levels, the results showing that both of these parameters were independently and significantly higher in patients with AD who did not respond to phototherapy than in those who did still indicate a utility in their use as predictive variables for treatment response. A direct correlation of the serum IgE level with AD severity has been extensively studied. Stone et al. evaluated 58 patients with a clinical diagnosis of AD in 1973 and showed a statistically significant relationship between serum IgE levels and the extent of skin involvement [21]. Gurevitch et al. assessed the serum IgE levels in 147 patients with AD and other skin disorders; they reported a correlation of serum IgE levels with AD severity and demonstrated that IgE levels are significantly higher in patients with AD than in the nonatopic "control" patients [22]. A similar relationship was shown by Wüthrich in 1978 after studying 116 adult patients with AD, in which severe chronic cases showed the highest IgE values; however, among the patients with moderate or mild forms of AD, those with bronchial asthma or allergic rhinitis had higher IgE levels than those solely diagnosed with AD did [23]. Acknowledging the requirement to

Table 1: Comparison of demographics, clinical characteristics, and duration of phototherapy between AD patients who responded to treatment and those who did not respond.

		Nonresponders	Responders	Total	p value
Age (years)	Valid N	51	31	82	0.174
	Mean (SD)	44.4 (25.2)	36.0 (19.8)	41.2 (23.6)	
	Median [IQR]	44.0 [20.0–65.0]	30.0 [19.0–53.0]	32.5 [20.0–62.0]	
	[Min–Max]	[6.0–91.0]	[16.0–83.0]	[6.0–91.0]	
Sex	Male	34 (66.7%)	18 (58.1%)	52 (63.4%)	0.433
	Female	17 (33.3%)	13 (41.9%)	30 (36.6%)	
Improvement in pruritus	Yes	14 (27.5%)	30 (96.8%)	44 (53.7%)	**<0.001**
	No	37 (72.5%)	1 (3.2%)	38 (46.3%)	
Hospitalization (days)	Valid N	51	31	82	0.217
	Mean (SD)	9.3 (5.5)	7.6 (3.9)	8.7 (5.0)	
	Median [IQR]	8.0 [5.0–12.0]	7.0 [5.0–9.0]	7.5 [5.0–11.0]	
	[Min–Max]	[2.0–24.0]	[2.0–18.0]	[2.0–24.0]	
Phototherapy course duration (weeks)	Valid N	51	31	82	0.081
	Mean (SD)	12.3 (10.1)	8.7 (8.0)	10.9 (9.4)	
	Median [IQR]	10.0 [5.0–14.0]	7.0 [3.0–12.0]	8.5 [4.0–12.0]	
	[Min–Max]	[1.0–52.0]	[1.0–40.0]	[1.0–52.0]	
Full/partial course	Full	32 (62.7%)	16 (51.6%)	48 (58.5%)	0.321
	Partial	19 (37.3%)	15 (48.4%)	34 (41.5%)	
Systemic treatment	No	28 (54.9%)	29 (93.5%)	57 (69.5%)	**<0.001**
	Yes	23 (45.1%)	2 (6.5%)	25 (30.5%)	
Atopic background	No	21 (41.2%)	9 (29.0%)	30 (36.6%)	0.268
	Yes	30 (58.8%)	22 (71.0%)	52 (63.4%)	

SD, standard deviation; IQR, interquartile range; Min, minimum; Max, maximum. P value <0.05 is considered significant.

Table 2: Comparison of IgE levels, eosinophils count, and phototherapy treatment response between AD patients who responded to treatment and those who did not.

		Nonresponders	Responders	Total	p value
IgE (IU/ml)	Valid N	51	31	82	**0.018**
	Mean (SD)	5090.4 (7776.7)	1585.7 (2495.0)	3765.4 (6523.8)	
	Median [IQR]	2070.0 [314.0–7120.0]	740.0 [94.0–1630.0]	1065.0 [254.0–4790.0]	
	[Min–Max]	[7.8–46500.0]	[4.0–9940.0]	[4.0–46500.0]	
Eosinophils count (cells/μL)	Valid N	51	31	82	**0.002**
	Mean (SD)	566.3 (501.8)	227.1 (222.9)	438.0 (448.6)	
	Median [IQR]	360.0 [190.0–1000.0]	160.0 [30.0–380.0]	280.0 [110.0–610.0]	
	[Min–Max]	[0.0–1970.0]	[0.0–910.0]	[0.0–1970.0]	
Post-treatment IGA	Valid N	51	31	82	**<0.001**
	Mean (SD)	3.1 (0.6)	1.1 (0.7)	2.4 (1.1)	
	Median [IQR]	3.0 [3.0–3.0]	1.0 [1.0–2.0]	3.0 [1.0–3.0]	
	[Min–Max]	[2.0–4.0]	[0.0–2.0]	[0.0–4.0]	
Pretreatment IGA	Valid N	51	31	82	0.207
	Mean (SD)	3.4 (0.6)	3.6 (0.5)	3.5 (0.5)	
	Median [IQR]	3.0 [3.0–4.0]	4.0 [3.0–4.0]	3.5 [3.0–4.0]	
	[Min–Max]	[2.0–4.0]	[3.0–4.0]	[2.0–4.0]	
Delta IGA	Valid N	51	31	82	**<0.001**
	Mean (SD)	0.3 (0.5)	2.5 (0.6)	1.1 (1.2)	
	Median [IQR]	0.0 [0.0–1.0]	2.0 [2.0–3.0]	1.0 [0.0–2.0]	
	[Min–Max]	[0.0–1.0]	[2.0–4.0]	[0.0–4.0]	

P value <0.05 is considered significant.

conventionally recognize the association between IgE levels and AD severity, Laske and Niggemann assessed for its presence in 345 children. Using the SCORAD system to assess AD severity, they found a significant correlation between SCORAD and serum IgE levels [11]. Elevation of total serum IgE levels thus remains a major hallmark of AD, and anti-IgE-treatment approaches in patients with severe therapy-refractory AD have become increasingly recommended [24]. Zink et al. studied the combination of extracorporeal immunoadsorption and the anti-IgE antibody

Table 3: IGE levels in relation to the atopic background.

	Atopic background			
	No	Yes	Total	*p* value
Valid *N*	30	52	82	0.015
Mean IgE (SD)	1884.1 (2983.7)	4034.1 (5006.2)	3237.8 (4470.2)	
Median IgE [IQR]	640.5 [98.0–2070.0]	1630.0 [392.0–6680.0]	1020.0 [254.0–4650.0]	
IgE [Min–Max]	[4.0–9940.0]	[7.8–18300.0]	[4.0–18300.0]	

IgE, immunoglobulin E; SD, standard deviation; IQR, interquartile range; Min, minimum; Max, maximum.

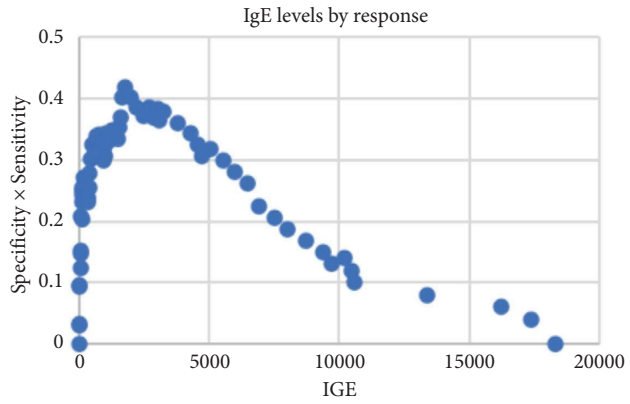

Figure 1: Sensitivity × specificity of IgE by response to treatment. The recommended threshold IgE level with maximum sensitivity × specificity for predicting overall response to phototherapy is 1780 IU/mL. IgE, immunoglobulin E.

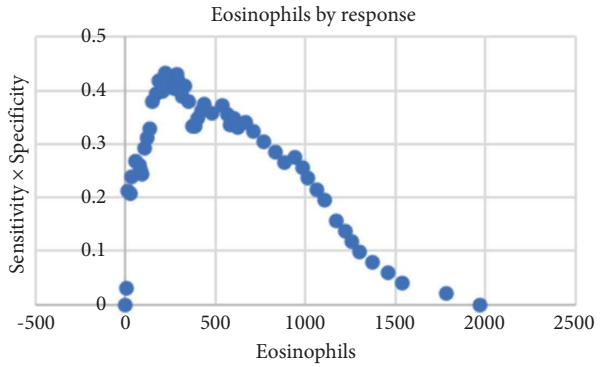

Figure 2: Sensitivity × specificity of blood eosinophils by response to treatment. The recommended threshold eosinophil level with maximum sensitivity × specificity for predicting overall response to phototherapy is 225.0 cells/μL.

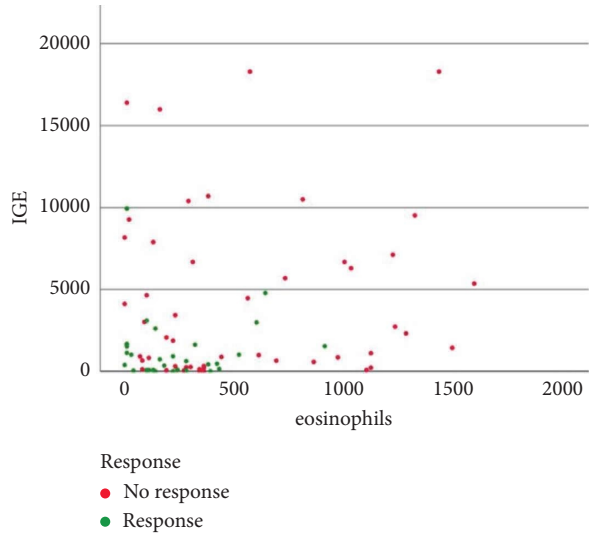

Figure 3: IgE × eosinophils by response to treatment. There is no correlation between IgE and eosinophils irrespective of response. IgE, immunoglobulin E.

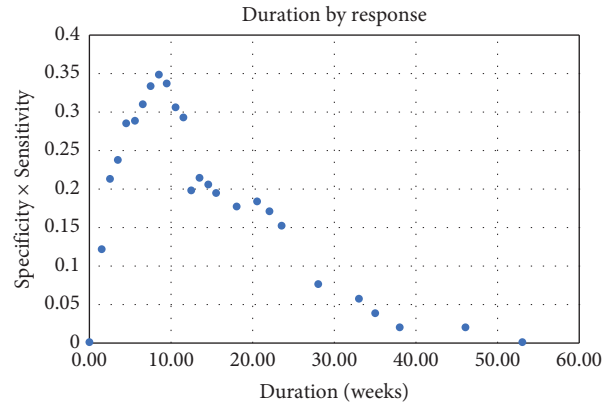

Figure 4: Sensitivity × specificity of duration by response to treatment. The recommended threshold for duration with maximum sensitivity × specificity is 8.5 weeks.

omalizumab in 10 patients. They noted a decrease in IgE with clinical improvement during the treatment, and a reversal of this trend was observed at the 6-month follow-up after treatment was ceased [25]. This suggests that severe cases of AD are unlikely to respond to phototherapy treatments, and their treatment should be quickly escalated to immunosuppressive or biological treatment.

Eosinophilia is not present in all patients with AD and may also be caused by allergic processes; therefore, its diagnostic utility in AD remains unclear [26, 27]. However, the assessment of peripheral blood eosinophils count in combination with IgE levels has been suggested to be useful for the diagnosis of AD [27, 28]. IgE is a sparse serum immunoglobulin. Elevated levels of total serum IgE are strongly associated with atopic disease. B cells produce IgE after contacting an allergen. The nose and lungs are the important

sites of IgE production in patients with allergies. While IgE-mediated allergic rhinoconjunctivitis and bronchial asthma have a well-established pathophysiology, the role of IgE in AD remains controversial [29, 30]. Since IgE has been a known marker for AD severity, it is expected that it may also serve as a biomarker for the response to therapy, specifically phototherapy, for the disease. The relationship between serum IgE levels and the severity of cutaneous involvement in patients with AD with coexisting atopic respiratory disease was directly recognized in previous studies [23, 31]. However, establishing a link between IgE levels and cutaneous involvement has been proven to be more challenging [22, 32–34].

Furthermore, in our cohort, 52 of 82 patients had atopic background comorbidities. IgE levels were found to be significantly higher in this subset of patients ($p = 0.015$), with a median of 1630 IU/mL; those without an atopic background had a median IgE level of 640 IU/mL. However, no significant difference was found between patients with and without an atopic background in terms of their response to treatment, suggesting that atopic background comorbidities do not influence patients' response to phototherapy.

It is widely accepted that a complete course of phototherapy for AD is a thrice weekly regime of 6–8 weeks [17, 18]. The results of our cohort indicated that a threshold of maximal sensitivity and specificity for response to phototherapy is 8.5 weeks. The fact that completing an 8-week course did not demonstrate a statistically significant role in response to treatment, with some patients demonstrating response after as little as 1 week of phototherapy, could be attributed to the use of targeted topical treatments. Indeed, the patients included in this study begun phototherapy treatment during their hospitalization. It is possible that the use of topical treatments, which were initiated during hospitalization, may have influenced the improvement timeline for some of the participants included in this study who began phototherapy treatment during their hospital stay and could be considered a limitation of the study.

Another limitation of the present study is its retrospective nature and the small group of patients included. A larger, prospective study should therefore be conducted in the future to provide stronger data on the topic. To our knowledge, this is the first study to investigate a direct correlation between AD patients' total serum IgE and eosinophils levels and their response to phototherapy.

4. Conclusions

In summary, we have demonstrated the significance of serum IgE and blood eosinophil levels as readily available biomarkers that could be used to evaluate patients with AD before selecting their treatment. The presented cutoff values of IgE and eosinophil levels may assist clinicians in determining the appropriate course of treatment for their AD patients, including the decision to initiate phototherapy or escalate their treatment to systemic options. Further investigations are required to confirm the utility of total serum IgE levels, particularly in combination with eosinophils count, as potential biomarkers for phototherapy treatment response in patients with AD.

Data Availability

The data used in this study are available upon request to the corresponding author.

Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this paper.

Authors' Contributions

Aviv Barzilai and Theodoulos Drousiotis contributed equally to this work.

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