

The level of total immunoglobulin E as an indicator of disease grade in adults with severe atopic dermatitis

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Atopic dermatitis is one of the most common inflammatory dermatoses in children and adults. The disorder is associated with significant worsening of quality of life. Due to the frequently suggested pathogenetic relationship with atopic dermatitis, immunoglobulin E seems to be an adequate indicator of the disease.

The aim of the study was to assess the association between the total serum immunoglobulin E levels and the grade of skin lesions measured with the SCORAD and oSCORAD scales in the population of adult patients suffering from severe atopic dermatitis.

Material and methods. The study was performed in the group of 31 patients suffering from atopic dermatitis since early childhood (17 women and 14 men) in 2017. Total IgE was measured by the fluoroenzymatic immunoassay. The Spearman's rank correlation coefficient was used to determine the power of the relationship between the concentration of total IgE and atopic dermatitis severity. The Kruskal-Wallis and Mann-Whitney's tests were used to compare the distribution of IgE concentration and the distribution of atopic dermatitis grade.

Results. The statistically significant correlation between SCORAD/oSCORAD and the measured IgE levels was found in the patients with the IgE level above 3500 IU/ml (19 subjects).

Conclusions. The present study demonstrated that in the patients with severe extrinsic atopic dermatitis, the concentration of total IgE was correlated with the severity of the disease. This suggests an opportunity of employing IgE as an atopic dermatitis biomarker.

Key words: atopic dermatitis, immunoglobulin E, SCORAD, oSCORAD

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Stężenie całkowite immunoglobuliny E jako wskaźnika nasilenia choroby u dorosłych chorych na ciężkie atopowe zapalenie skóry

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Atopowe zapalenie skóry (AZS) to jedna z najczęstszych dermatoz zapalnych u dzieci i dorosłych. Zachorowanie wiąże się ze znacznym pogorszeniem jakości życia. Ze względu na wielokrotnie sugerowane związki patogenetyczne z AZS, immunoglobulina E wydaje się być odpowiednim wskaźnikiem choroby.

Celem pracy była ocena korelacji między stężeniem całkowitego IgE w surowicy a stopniem nasilenia zmian skórnych mierzonych przy użyciu skali i oSCORAD w grupie dorosłych chorych na ciężkie AZS.

Materiał i metody. Badanie przeprowadzono w roku 2017 w grupie 31 chorych na AZS od wczesnego dzieciństwa (17 kobiet i 14 mężczyzn). Stężenie IgE było oceniane metodą fluoroimmunoenzymatyczną. Współczynnik korelacji rang Spearmana wykorzystany został do określenia siły związku między stężeniem całkowitego IgE a nasileniem AZS. Za pomocą testów Kruskala-Wallisa oraz Manna-Whitneya porównano rozkłady stężenia całkowitego IgE oraz rozkłady nasilenia AZS.

Wyniki. Wykazano istotną statystycznie zależność między wskaźnikami SCORAD i oSCORAD a badanym wskaźnikiem całkowitego IgE u chorych ze stężeniem całkowitego IgE > 3500 IU/ml (19 osób).

Wnioski. Przeprowadzone badanie wykazało, że u chorych na ciężkie AZS stężenie całkowitego IgE koreluje z nasileniem objawów chorobowych. Sugeruje to możliwość wykorzystania oznaczania stężenia całkowitego IgE jako biomarkera AZS.

Słowa kluczowe: atopowe zapalenie skóry, immunoglobulina E, SCORAD, oSCORAD

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Atopic dermatitis (AD) is a chronic and recurrent inflammatory dermatosis characterized by the presence of eczematous skin lesions (presenting the morphology of either acute or chronic eczema) and typical (depending on patient age) location. In each case, the eruptions are followed by pruritus (being referred to as the "clinical hallmark" of AD) [32]. At present, AD is one of the most prevalent (according to some references, the most prevalent) non-infectious inflammatory skin disorders affecting up to 25% of children and 7-10% of adults in the developed countries [21,32]. According to the estimated data from the Polish Society of Allergology, from 1.5 to 2.5 million of Poles suffer from AD

[18]. The presence of itching and skin lesions leads to essential consequences for the overall health state (e.g. sleep disturbances, reduced self-esteem, difficulties in social relations, increased susceptibility to skin infections and others), what necessitates considering this condition a systemic disease [5]. Even though AD is generally thought to be a skin condition related to childhood, the number of adults with AD invariably increases, what was confirmed by extensive epidemiological analyses conducted in recent years in Europe, the USA, Canada and Japan [3]. Despite the increasing disease incidence and continuously expanded knowledge about its pathophysiology,

there are still no generally acceptable, clinically applicable laboratory tests or histopathological findings (biomarkers) available that would be characteristic solely of AD [30].

The aim of the study was to assess the degree of association between the level of total serum immunoglobulin E (IgE) and deterioration of skin lesions measured with the SCORAD (SCORing Atopic Dermatitis) (0-103 points) and oSCORAD (objective SCORAD) scales (0-83 points) in the group of adult patients suffering from severe AD.

MATERIAL AND METHODS

The investigation was performed after receiving approval from the Bioethical Commission of the Jagiellonian University in the group of 31 patients suffering from AD since early childhood (17 women and 14 men) in 2017. All the participants gave their informed consent to participate in the research. The diagnosis of AD was established by a specialist in dermatology-venereology and a specialist in allergology in keeping with the *Hanifin* and *Rajka's* criteria [12]. The grade of skin abnormalities was assessed referring to the SCORAD and oSCORAD scales, defining severe AD with the score above 50 points in SCORAD [25]. The exclusion criteria were: lack of informed consent to participate, coexistence of another inflammatory skin disease and age below 18 years.

The level of IgE was measured during the routine diagnostic tests employing the fluoroenzymatic immunoassay (FEIA) with a UniCAP 100 unit (ImmunoCAP-System, Phadia AB, Sweden), according to the manufacturer's protocol. The statistical analysis was conducted using Statistica v13.1 (Dell Inc., USA). To describe the results of IgE and AD grade assessment, the authors applied non-parametric measures – the median, minimal value and maximal value. The *Spearman's* rank correlation coefficient was used to determine the power of the relationship between IgE and AD severity. The *Kruskal-Wallis* and *Mann-Whitney's* tests were used to compare the distribution of IgE concentration and the distribution of AD grade. In all the analyses, statistical significance was established as $p < 0.05$.

RESULTS

At the moment of recruitment, all the patients presented with skin lesions qualifying them to the severe AD group. The minimal SCORAD value was 50.4 points, the maximal was 80.4 points

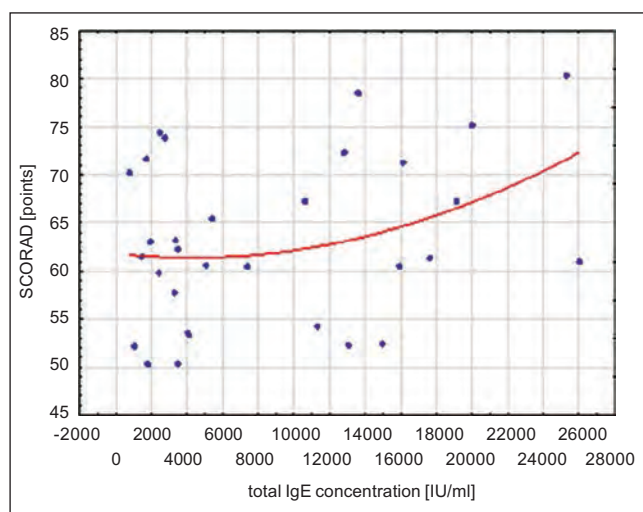


Figure 1. Relationship between skin lesions severity (SCORAD) and blood serum total IgE level in patients with AD and total IgE level >3500 ($p=0.01$)
Rycina 1. Zależność między nasileniem zmian skórnych (skala SCORAD) u chorych na AZS i całkowitym IgE >3500 a stężeniem całkowitego IgE w surowicy ($p=0,01$)

(median: 61.5 points). The patients were additionally analyzed employing the oSCORAD scale. The minimal result was 23.6 points, the maximum was 60.4 (median: 41.5 points). The aforementioned analysis allowed for subdividing the participants into two groups: 10 patients (32.2%) with moderate AD (oSCORAD ≤ 40 points) and 21 patients (67.7%) with severe AD (oSCORAD > 40 points).

For the serum IgE concentration values, the median was 5090 IU/ml (minimal = 813 IU/ml; maximal = 26 000 IU/ml). Its level strongly correlated with the severity of skin lesions. A statistically significant correlation between the SCORAD/oSCORAD scores and the measured IgE value was found ($p = 0.01$ and $p = 0.02$, respectively) for the patients with the IgE level above 3500 IU/ml (19 subjects). The results are shown in fig. 1 and 2.

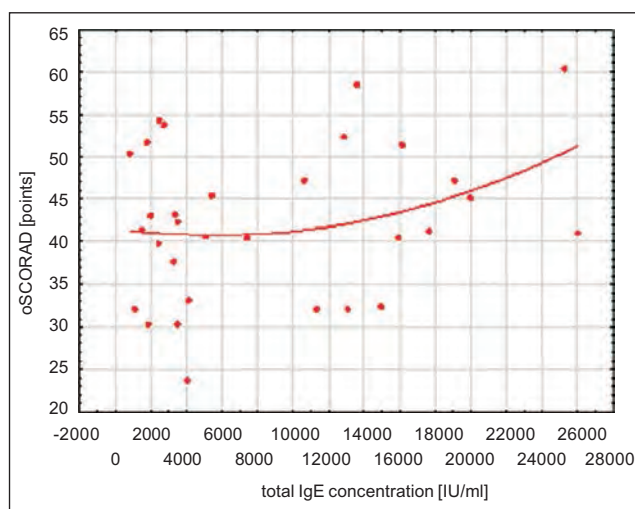


Figure 2. Relationship between skin lesions severity (oSCORAD) and blood serum total IgE level in patients with AD and total IgE level > 3500 ($p=0.02$)
Rycina 2. Zależność między nasileniem zmian skórnych (skala oSCORAD) u chorych na AZS i całkowitym IgE > 3500 a stężeniem całkowitego IgE w surowicy ($p=0,02$)

DISCUSSION

Over the years, numerous attempts have been made to correlate the levels of serum and plasma parameters (cytokines, chemokines, adhesion factors, growth factors) with the severity of symptoms in the course of AD. Moreover, the establishment of an AD biomarker – or the objectively measurable biological indicator(s) capable of revealing the presence of the disease, its exacerbation or remission – could be used to control the organism's response to any employed therapy [30]. The requirement of finding AD biomarkers results from the discrepancies in the clinical picture of this condition and is a part of the attempt at phenotyping the disease on the basis of determination of its subtypes [6, 14]. In the extensive meta-analysis by *Thijs et al.* [30], among 30 AD biomarkers which are presently tested in laboratories, the particular significance was ascribed to TARC (Thymus and Activation Regulated Chemokine; CCL17), IgE, ECP (Eosinophilic Cationic Protein) and E-selectin (CD62E). TARC chemokine is considered to be the most crucial AD biomarker, the concentration of which correlates with both the disease severity and its remission period, what might become useful for the purpose of patient education (for example, an elevated TARC level should convince the patient to introduce proactive therapy, even in spite there are no flaring-up skin lesions) [16].

A simultaneous performance of several laboratory tests results in an even more pronounced ability of predicting AD severity. The correlation coefficient for combinatory testing of TARC, IL-22 and sIL-2R equals 0.84, providing a more precise prognosis of the disease course as compared to determination of TARC level alone [29]. The idea of biomarkers panel proposed by *Thijs et al.* facilitated the selection of four AD

“endotypes”, specified by dominating cytokines clusters. The particular ‘endotypes’ were strictly related to the clinical and immunological phenotype of the disease, and by the same token, with the fundamental factors as far as the planning of the therapeutic procedures was concerned [31]. The recently developed research direction lies in searching for biomarkers associated with distinct signs and symptoms of AD (for example, the level of IL-31 clearly correlates with pruritus) [19]. An effective and frequently selected laboratory test (also as a component of the biomarkers panel) is immunoglobulin E determination.

The discovery of IgE, despite the fact that it shows the lowest prevalence among all the classes of immunoglobulins, revolutionized modern allergology. The generally accepted role of IgE in pathogenesis of atopic diseases [20] underlines the necessity to comprehensively investigate the place of this immunoglobulin in AD pathophysiology. Although its increased level is considered a facultative criterion for the diagnosis of AD, there is observed no increment of tIgE in about 20% of all cases [35]. It is theorized that an elevated level of tIgE could be detected only in a strictly defined subgroup of patients with AD – referred to as suffering from extrinsic atopic dermatitis (eAD), while intrinsic atopic dermatitis (iAD) is characterized by normal tIgE values [20,26]. In view of reports indicating that AD demonstrates the most potent association with IgE among all the skin diseases [7], the perspective of employing IgE as the biomarker of AD (particularly its extrinsic type) seems critically important.

The majority of studies emphasize the correlation between tIgE and AD severity [1,2,8,22,33,34]. It is worthwhile to note that the median value of tIgE level in these studies is approximately 280 IU/ml [1,2,34], whereas among publications claiming no statistically significant association [23], attention is focused on the low level of tIgE in the entire group of patients (median of tIgE below 100 IU/ml). It suggests that the results might have been confounded by iAD patient population. It seems that sometimes the evaluation of the degree of correlation between tIgE and AD severity is restricted by inadequate research methodology, which limits the possibility of interpreting the results of some studies [15,20,28].

Our study determines the correlation between the severity of eAD and the level of tIgE and, according to the best of our knowledge, no similar paper has been published to date. Due to the low levels of tIgE in iAD, it is reasonable to consider the discussed indicator to be the biomarker relevant only for eAD. The obtained results show a pronounced, monotonic dependency between tIgE and the SCORAD/oSCORAD grade for tIgE concentrations higher than 3500 IU/ml. Contrariwise, the average score values for both the scales for tIgE = 800 IU/ml and tIgE = 3500 IU/ml differ one from another by less than 1 unit. This suggests that the severity of AD in the above-mentioned range of concentrations does not depend on tIgE. The given cut-off point for tIgE level emerges as an adequate response for the repetitively conflicting results of previous studies. Expecting a correlation of AD severity with all tIgE levels exceeding the upper limit of normal values, one will receive an unreliable outcome. Meanwhile, tIgE levels above 150-200 IU/ml precisely fit into the characteristics of eAD. The hypothesis that exclusively high concentrations of tIgE (possibly exactly close to 3500 IU/ml) are able to reach the threshold value for eAD exacerbation seems to explain the discussed observations in a feasible way.

The non-linear characteristics of the presented relations indicates a clinically essential fact that the higher levels of tIgE are followed by continuous deterioration of the clinical condition (measured as the SCORAD/oSCORAD grade), even stronger than resulting from directly proportional relationship. This demonstrates the urgency to take particular care while managing AD patients showing high levels of tIgE, because they might be in a group of exceptional risk of rapid worsening of the disease.

The subsequent, not less fascinating, observation refers to the evident discrepancy between disease severity assessed by the SCORAD and oSCORAD scales (all the patients presented severe AD according to SCORAD, while oSCORAD

indicated 32.2% cases as moderate). The basic qualitative difference between these scales lies in taking into consideration the subjective aspects of the disease (namely pruritus and sleep disturbance) in the SCORAD scale. Therefore, it might be indicated that the “switch” of scales may be interpreted as the expression of particular aggravation of subjective AD symptoms in the analyzed population of patients presenting high levels of tIgE (for the sake of comparison, it should be noted that the maximal tIgE observed in some studies was equal to the median of tIgE in the discussed group [23,33]). The undeniable confirmation of the discussed associations requires additional research, however, compelling mechanistical evidence supports their existence. Cells isolated from skin lesions in AD show an elevated number of FcεRI. In patients with elevated tIgE, there are observed high levels of IL-13 [22], which is a cytokine that inhibits expression of filaggrin (10). It results in dysfunction of the skin barrier and exposition to the excess of antigens. Possibly, IgE is bound to a hypothetical skin autoantigens. In AD, they might be, among others, Mn-SOD (manganese superoxide dismutase), thioredoxin, keratin 6A, actin α2 or tubulin αA1 [10]. Degranulation of mastocytes mediated by the excess of IgE would lead to the troublesome pruritus in this way.

The distinct premise suggestive of the pathogenic role of IgE in AD is supported by data about the (off-label) AD therapy with omalizumab. Omalizumab is a humanized immunoglobulin IgG, class, κ type directed against the Fc domain of IgE and, what is remarkably important here, capable of displacing an immunoglobulin from its complex with FcεRI on the mastocyte surface [4]. A systematic review published in 2016 by *Holm et al.* proved that omalizumab was effective in 74.1% cases of refractory AD. It must be emphasized that clinical deterioration took place only in cases of using small doses of the medicament (one application of 150 mg per 2 weeks) [13]. Corresponding results were received after treatment with AIGT (Autologous Immunoglobulin Therapy), which lowered the level of tIgE [24]. The successful effects of anti-IgE therapy seem to prove the impact of IgE on the clinical course of AD. Presently, a report is awaiting publication that describes the results of an IV phase clinical study determining the effectiveness of omalizumab in AD treatment (NCT02300701).

There have appeared concepts linking the severity of AD not as much with tIgE, but rather with specific immunoglobulins from this class. The most commonly investigated in this respect were immunoglobulins specific to various species of *Malassezia* spp., as their thioredoxin and SOD show similar antigenic structures to the human ones (which, as it was mentioned above, might result in a cross-antibody response) [36]. *Glatz et al.* proved that despite specific antibodies against *Malassezia* indeed presenting some correlation with AD severity (according to SCORAD), tIgE was a more sensitive predictor of the disease course ($r = 0.34$ and $r = 0.55$, respectively) [11]. In our study, we cannot exclude without any doubt the confounding role of some distinct, explicit fraction of IgE in predicting the severity of AD. However, the increment in tIgE level is routinely followed by the parallel accumulation of various antigenic determinants, against which IgE are directed. For tIgE from 41 to 80 IU/ml, their number usually equals about 20 [27]. Therefore, for concentrations ranging from 10^2 to 10^4 IU/ml, the participation of a strongly heterogenous group of IgE is more likely [9].

The results of the presented study have some limitations. Due to the relatively short serum half-life time (about 2-3 days) [17], the concentration of immunoglobulin E is determined by the intensiveness of their ongoing production and removal. Therefore, a single measurement of tIgE is not capable of fully reflecting its possible fluctuations in the future. Regardless of the fact that we have proven the association between the tIgE concentration and the current clinical condition of the patient, the determination whether a tIgE level change allows for predicting a change in disease severity (sufficiently in advance, for example, to implement proactive therapy) requires prospective cohort studies. Moreover, in the studied group, all the patients

suffered from severe AD according to the SCORAD scale, what might have theoretically, despite the statistical model used, led to overstating the correlation level between tlgE and SCORAD.

CONCLUSIONS

The present study demonstrated that in patients with severe eAD, the concentration of tlgE correlated with the severity of the disease. This suggests an opportunity to employ tlgE as an AD biomarker. Also, the unique relationship of tlgE with subjective symptoms was signalized. The confirmation of the significance of the observed relations demands further, prospective trials in a larger population of patients.

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