Original paper

Selected immunological parameters in clinical evaluation of patients with atopic dermatitis

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Abstract

Introduction: It has been suggested that soluble immune receptors (SIRs) such as sCD25 and sCD30 may serve as potential biomarkers in evaluation of atopic dermatitis (AD). Previous studies clearly indicated that serum levels of interleukin (IL)-13 and total IgE (tIgE) might be potentially useful in the evaluation of patents with AD.
Aim: To evaluate whether serum levels of sCD25 and sCD30 are suitable biomarkers of AD. Moreover, we have decided to estimate the usefulness of tIgE and IL-13 serum level determination in the evaluated population.
Material and methods: A group of 102 AD patients was investigated. Serum concentrations of sCD30, sCD25, IL-13 and tIgE were measured. The clinical phenotype of AD was classified as extrinsic (ADe) or intrinsic (ADi) based on the presence of IgE. Statistical analysis was performed to estimate correlations between obtained results and clinical features of the population such as AD phenotype, age, disease extent and severity.
Results: Extrinsic AD was diagnosed in 71% of patients, while ADi phenotype was observed in 29% of the investigated population. A negative correlation between serum levels of sCD25 and sCD30 and disease severity as well patients' age was established. Serum levels of IL-13 did not reach the cut-off point set by the manufacturer. A positive correlation between serum levels of total IgE and disease severity and patients' age was observed.
Conclusions: This paper shows that serum levels of sCD25 and sCD30 as well as tIgE are age dependent. Determination of serum levels of sCD25, sCD30 and IL-13 is not useful in everyday practice.

Key words: atopic dermatitis, sCD25, sCD30, interleukin-13, IgE.

Introduction

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease with a complex, yet not fully elucidated etiology. The complex pathogenesis of AD includes genetically determined dysfunction of the epidermal barrier and immunological disorders [1, 2]. The cytokine profile of lymphocytes Th1 includes, among others, interleukin 2 (IL-2) and interferon-γ while Th2 pattern is characterized by secretion of interleukins 4, 5, 13 (IL-4, IL-5, IL-13) and CD30 [3, 4]. Interleukin-2 is a fundamental interleukin of the immune system, since it stimulates the activation and proliferation of both T and B cells [3, 5]. Several studies confirmed that serum levels of the soluble form of CD25 (sCD25, sIL2-Rα), a unique marker molecule present on the surface of activated lymphocytes B and macrophages, correlate positively with disease severity in patients with asthma and AD [6, 7]. CD30 is a transmembrane molecule classified among the tumor necrosis factor superfamily. Elevated serum levels of the soluble form of CD30 (sCD30) have been detected in sera from patients with atopic diseases (AD and asthma) [8]. Significantly elevated serum levels of sCD30 have been scored in patients with atopic disorders, in comparison with non-atopic individuals, patients with allergic contact dermatitis or psoriasis [9]. During the onset of AD and the inflammation process, IL-13 is mainly responsible for remodeling of the skin and respiratory tract tissues. Moreover, IL-13 stimulates the eosinophil proliferation, IgE secretion, as well as growth and development of mast cells. In patients with diagnosed eAD, the serum levels of IL-13 were significantly higher than in patients with intrinsic AD (ADi) [10, 11].

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Determination of tIgE and asIgE serum levels is listed among 23 minor criteria of AD. Correlation with disease extent and severity and beneficial effect of the anti-IgE therapy in a number of studies has been emphasized [12, 13], but the usefulness of determination of tIgE levels is often overestimated [14].

Nevertheless, it is still debated whether SIRs are useful in clinical diagnostic approach in patients with AD. Numerous findings regarding the role of IL-2 in the atopic inflammation are based on the studies covering patients with asthma [15], while the number of experiments in the field of AD is not abundant [4, 7], yet results remain contradictory [8, 9]. Currently available evidence studies are based on several previously published results, usually performed with a very limited number of patients and/or with limited age range among the investigated population. Therefore, we decided to assess the usefulness of sCD25 and sCD30 serum levels in a large population of patients with a wide range of age to evaluate the general trend for these biomarkers in the course of chronic atopic skin disease.

Aim

Our aim was to evaluate whether the serum levels of sCD25 and sCD30 in patients with AD are suitable biomarkers. We have decided to check the usefulness of determination of tIgE and IL-13 serum levels in the evaluated population.

Material and methods

A total number of 102 patients were enrolled into the study, 59 females and 43 males. Patients were recruited from an outpatient clinic in our Department of Dermatology. A written consent form was obtained from AD patients or their parents. A thorough clinical examination by a dermatologist was performed and clinical condition of AD patients was evaluated according to the SCORAD scoring system. Patients qualified for the study had a history of a topical (corticosteroids and calcineurin inhibitors, emollients) and systemic (antihistamines) therapy. Individuals with a history of current or recent (within 2 months) treatment with systemic corticosteroids, cyclosporine or subcutaneous immunotherapy at any time, were not qualified for the study as these factors might significantly influence serum levels of biomarkers. Depending on the presence of asIgE in serum, the investigated group of AD patients was divided into two phenotypes: extrinsic AD (ADe) and ADi. Blood samples were obtained from all AD patients at the first study visit. Serum was separated into 4 aliquots and stored at –80°C. Serum levels of tIgE were determined with the use of fluorescence enzyme immunoassay (FEIA, UniCap, Phadia, Uppsala, Sweden). Antigen-specific IgE levels were determined against food allergens (cow's milk, hen's

egg, peanut, wheat, soy, cod) and skin prick tests (SPT) with airborne allergens were performed (trees I, trees II, weeds, grasses/grains, animal dander, house dust mites, molds). Levels of tIgE and asIgE were measured in protein units labeled as kU/l, with a lower detection limit of 0.35 kU/l. The concentrations of sCD25, sCD30 and IL-13 were determined in serum samples by Quantikine (R&D Systems, Minneapolis, USA) enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's protocols (the absorbance of microwells was measured at 450 nm, all samples were analyzed in duplicates). The studied parameters (SCORAD, tIgE, sCD25, sCD30, IL-13) were described by arithmetic mean, standard deviation (±), as well as maximum and minimum measurements. Additionally, SCORAD, tIgE, sCD25, sCD30 and IL-13 were described by median measurement.

Statistical analysis

The obtained results were considered significant at $p < 0.05$. The statistical analysis was performed using statistical software package Statistica v. 8.0 (StatSoft, Inc., Tulsa, USA).

Results

The mean age of the recruited population of AD patients was 9.7 ±9.1 years. Seventy one percent of the recruited population presented signs of ADe, with a mean age of 11.1 ±9.4 years. In the investigated population, 57% showed sensitization to airborne allergens, while 12% presented signs of sensitization to food allergens. Asthma and allergic rhinitis were diagnosed in 19% and 25%, respectively, of the evaluated AD population (Table 1). In turn, 29% of AD patients were classified as the ADi. The mean age of patients with ADi-phenotype was significantly lower than in the ADe group ($p = 0.017$) (Table 1, Figure 1).

The mean SCORAD value obtained in the investigated population was 42.9 ±24 points, with significantly higher scores ($p < 0.001$) in the group of ADe patients (50.4 ±23.6 points) in comparison with ADi (24.8 ±13.05 points) (Table 1, Figure 1).

Serum levels of IL-13 did not reach the cut-off point set by the manufacturer. Therefore, we decided to lower the threshold level, however statistical analysis did not show any significant difference between evaluated ADe and ADi groups ($p = 1.0$). We also did not observe any significant correlation between serum levels of IL-13 and SCORAD score, both in the entire population of patients with AD ($r_s = -0.039$, $p = 0.695$) as well as in the ADe group ($r_s = -0.340$, $p = 0.114$) and in the ADi group ($r_s = -0.023$, $p = 0.904$). Moreover, we did not observe any significant correlation between patient's age and serum levels of IL-13, both in the entire population of patients with AD ($r_s = 0.053$, $p = 0.134$), as well as in the eAD ($r_s = 0.154$, $p = 1.0$) and ADi group ($r_s = 0.076$, $p = 1.0$).

Table 1. Demographic, clinical and laboratory characteristics of the recruited patient population (n = 102)

Parameter	Total population (n = 102)	Extrinsic AD (n = 72)	Intrinsic AD (n = 30)
Age [years]:			
Mean ± SD	9.7 ±9.1	11.07 ±9.42	6.44 ±7.27
Range	0.6–33	1.5–33	0.5–30
SCORAD [points]:			
Mean ± SD	42.9 ±24	50.4 ±23.6	24.8 ±13.05
Range	0–101	0–101	4–60
Median	39.7	47.7	23.9
Gender, n (%):			
Male	59 (58)	43 (60)	16 (53)
Female	43 (42)	29 (40)	14 (47)
Co-morbidity, n (%)			
Food sensitization	12 (12)	12 (17)	0 (0)
Airborne sensitization:	58 (57)	58 (57)	0 (0)
Asthma	20 (19)	19 (26)	1 (3)
Allergic rhinitis	26 (25)	26 (36)	0 (0)
Soluble receptors levels:			
sCD25 [pg/ml]:			
Mean ± SD	1501.7 ±760.5	1382.3 ±711.55	1658 ±570
Range	298–4897	298–4897	639–2204
Median	1362.07	1233.85	1554
sCD30 [ng/ml]:			
Mean ± SD	89.3 ±54.8	84 ±57	102.4 ±47.7
Range	16–270	16–270	21–145
Median	73.9	67.5	89.4
Serum levels of IL-13 [pg/ml]:			
Mean ± SD	16.2 ±13	17.2 ±13	13.8 ±12.9
Range	0–65	0–65	0–40
Median	16	17	10.5
Total IgE [kU/l]:			
Mean ± SD	485.94 ±1182.84	680.8 ±1363.7	18.32 ±15.5
Range	2.63–7865	32–7865	2.63–57
Median	45.65	94.3	12.35

Serum analysis of SIRs revealed highly significant inverse correlations in the entire evaluated AD population between patients' age and serum levels of sCD25 ($r_s = -0.78$, $p < 0.001$) and sCD30 ($r_s = -0.63$, $p < 0.001$) (Table 2, Figure 2). Moreover, a positive correlation was observed between patient's age and serum levels of tIgE ($r_s = 0.36$, $p < 0.001$) in the entire population (Figure 2), and in the ADe group ($r_s = 0.25$, $p = 0.035$) (Table 2). In the ADe group, the correlation of patients' age with serum levels of sCD25 and sCD30 ($p < 0.001$ vs. $p < 0.001$) as well as SCORAD scores and serum levels of tIgE ($p < 0.001$) reached statistical significance (Table 2). In the ADi group, a statistically significant correlation was observed between patients' age and serum levels of sCD25 and sCD30 ($p < 0.001$ vs. $p < 0.001$) (Table 1). An inverse correlation of tIgE with sCD25 and sCD30 was observed in the entire AD population ($p < 0.001$ vs. $p < 0.001$), and between detected tIgE values and sCD30 ($p = 0.004$) in the ADi group (Table 2). Furthermore, an inverse correlation of SCORAD scores and serum levels of sCD25 and sCD30 was noted in the AD population, although comparable correlations were not observed in ADe and ADi groups (Table 2, Figure 3).

The distinction between ADe and ADi revealed significant differences between the two phenotypes of AD.
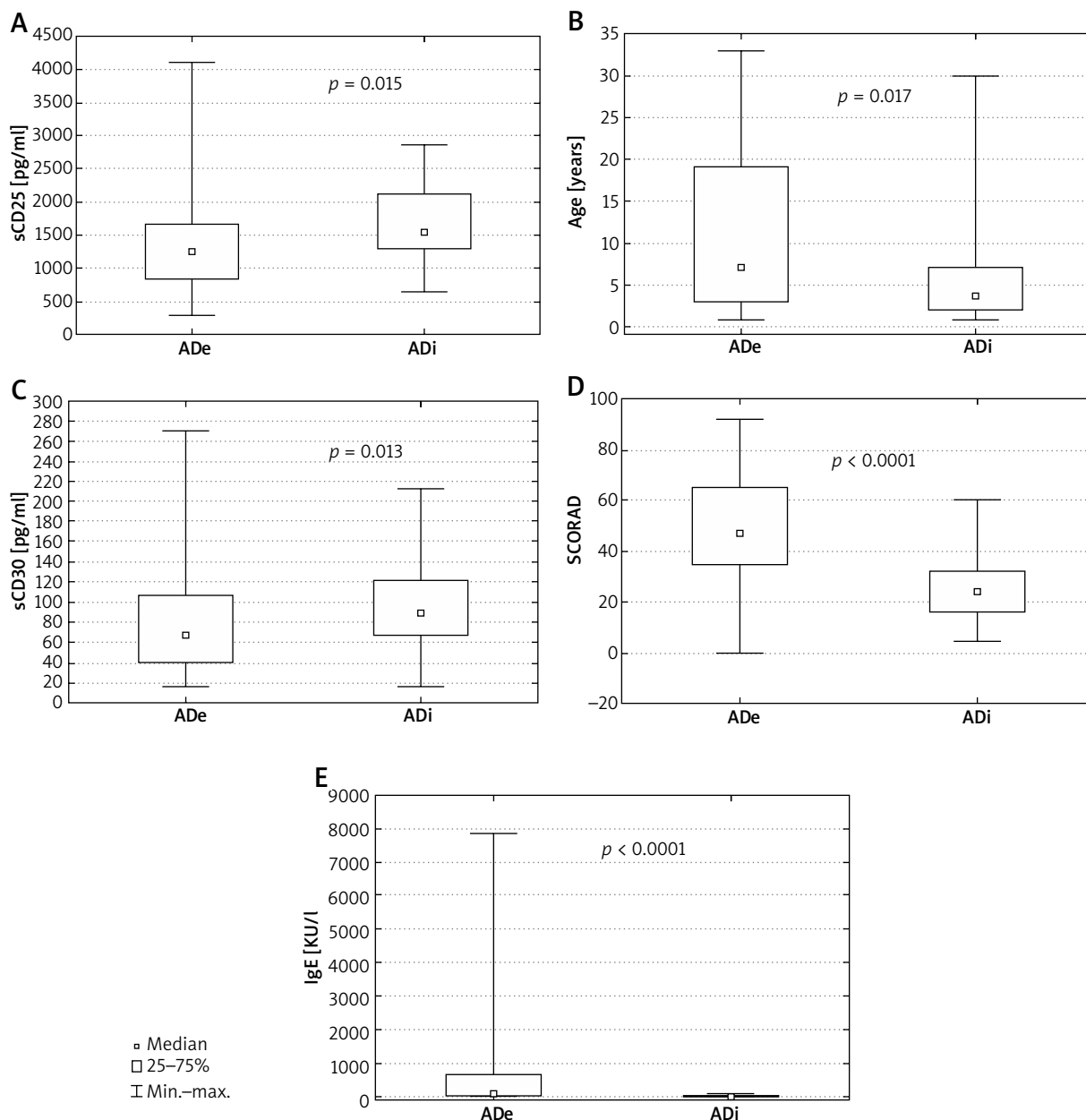
Figure 1. Comparison of serum levels of sCD25, sCD30 and tIgE as well as SCORAD and age between patients with extrinsic and intrinsic AD as evaluated by Mann-Whitney test

Apart from increased serum levels of tIgE in the ADe phenotype ($p < 0.0001$), the difference regarding age ($p = 0.017$), disease severity ($p < 0.0001$), and serum levels of sCD25 ($p = 0.015$) was statistically significant (Figure 1). We found it interesting that serum levels of sCD25 were significantly higher in the ADi group. Moreover, the difference in serum levels of sCD30 between two phenotypes of AD did not reach statistical significance ($p = 0.113$) (Figure 1).

Discussion

Current evidence on the usefulness of evaluation of immune parameters in sera of patients with AD remain a matter of debate. Although it has been emphasized that serum levels of SIRS (sCD25, sCD30) or IL-13 are significantly higher in patients with atopic diseases in comparison with healthy controls, there is still a lack of evidence that would confirm its suitability for clinical evaluation of AD patients. Studies focusing on the practi-

Table 2. Evaluated correlations of serum levels of biomarkers and tIgE with clinical parameters in the investigated groups of AD patients

Variable	sCD30		sCD25		tIgE	
	r_s	P-value	r_s	P-value	r_s	P-value
Total population ($n = 102$)						
Clinical parameters:						
Age	−0.78	< 0.001	−0.63	< 0.001	0.36	< 0.001
SCORAD	−0.26	0.009	−0.20	0.048	0.65	< 0.001
Total IgE	−0.32	0.001	−0.32	0.001		
sCD25	0.68	< 0.001				
ADe group ($n = 72$)						
Clinical parameters:						
Age	−0.78	< 0.001	−0.55	< 0.001	0.25	0.035
SCORAD	−0.16	0.18	−0.05	0.69	0.55	< 0.001
Total IgE	−0.17	0.16	−0.11	0.37		
sCD25	0.63	< 0.001				
ADi group						
Clinical parameters:						
Age	−0.70	< 0.001	−0.68	< 0.001	0.35	0.062
SCORAD	−0.09	0.62	0.12	0.51	0.05	0.77
Total IgE	−0.51	0.004	−0.33	0.07		
sCD25	0.62	< 0.001				

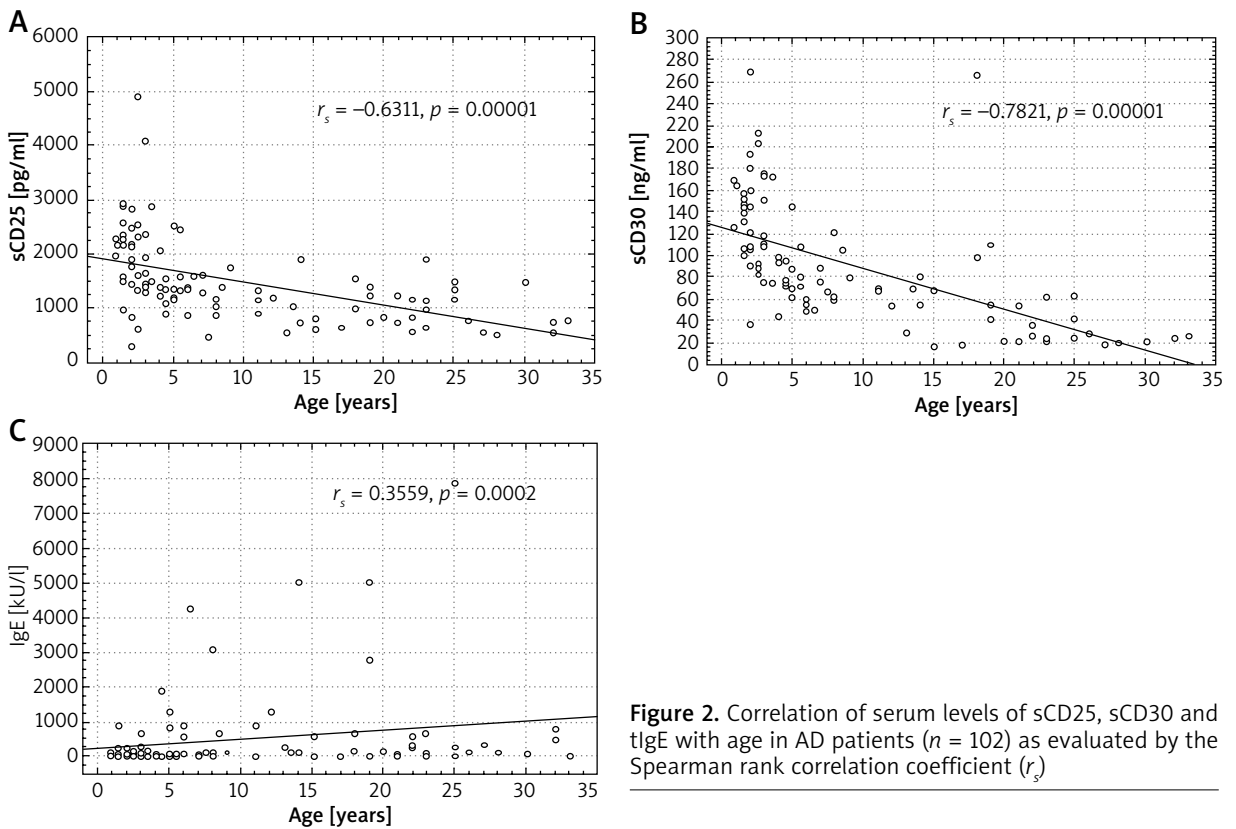*P < 0.05 was considered statistically significant, r_s – Spearman rank correlation coefficient.*

Figure 2. Correlation of serum levels of sCD25, sCD30 and tIgE with age in AD patients ($n = 102$) as evaluated by the Spearman rank correlation coefficient (r_s)
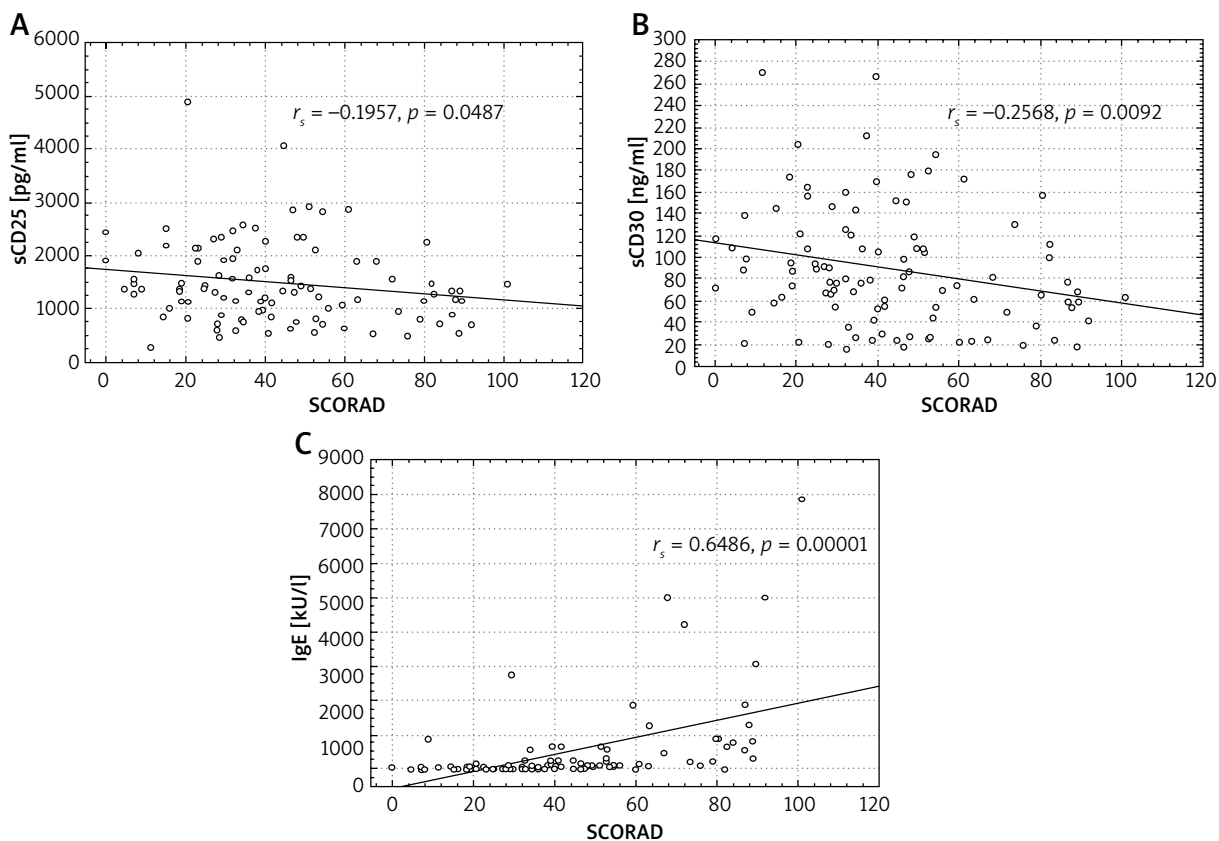
Figure 3. Correlation of serum levels of tIgE and sCD30 with SCORAD in AD patients ($n = 102$) as evaluated by the Spearman rank correlation coefficient (r_s)

cal use of the obtained results of SIRS in patients with AD often present contradictory results [16–20].

Since many factors may influence IL-2 synthesis, augmented serum levels of soluble receptors seem to have an irrelevant diagnostic value. It has been proved however that the serum levels of sCD25 may correlate with disease severity and progression in numerous disorders, including atopic diseases [3–6, 21]. Studies of Ott *et al.* [22] in a large population of children with AD provided evidence that sCD23, sCD25 and sCD30 were not useful in the clinical evaluation of patients with AD, yet were highly age dependent. Nevertheless, serological parameters like tIgE and eosinophilic cationic protein (ECP), correlated positively with age of the investigated population. In opposition to many previous reports usually covering a highly limited number of patients or focusing on populations with a narrow age range, the study presented in this paper focused on a large population of AD individuals with a wide age spectrum, in order to assess the general trend in serum levels of biomarkers and serological parameters. Although we have examined a large population of patients with AD, evaluation of serum levels of IL-13 was not proven useful. As IL-13 stimulates IgE synthesis, we were expecting to find elevated levels of IL-13 in the examined ADe population. In our opinion, evalua-

tion of IL-13 serum levels proves itself more useful in assessing the severity of inflammation in patients with AD.

Age relation with SIRs and tIgE

We have proved that sCD25 and sCD30 correlate with the age of patients with AD in a very significant manner. This inverse correlation was observed both in the entire investigated population, as well as in ADe and ADi phenotypes, which is in conformity with results published earlier [22]. Contrary to these findings, some reports showed positive correlations between disease extent and severity and serum levels of sCD30 in patients with AD, suggesting even the use of this parameter to monitor disease severity [16–18]. The decline in serum levels of sCD25 and sCD30 with progressing age presented in our AD population, confirms former observations of gradual maturation of the immune system. It has been proved that the cytokine profile in the childhood with Th2 predominance switches gradually towards Th1 response pattern. In contrast, in the investigated AD population serum levels of tIgE showed a direct proportional correlation with age of AD patients in the entire investigated population ($r_s = 0.35$, $p < 0.001$), as well as in the ADe phenotype ($r_s = 0.25$, $p = 0.035$), whilst in ADi patients no significant correlation was observed ($r_s = 0.34$, $p = 0.062$)

(Table 2). Prior studies confirmed that dynamic variations of serum levels of tIgE are observed in the population of children below 10 years of age, even without a known record of atopic diseases [23]. On the other hand, in ADe phenotype, IgE-dependent sensitization to external antigens occurs with progression of time, leading to elevation of serum levels of asIgE and tIgE. According to SCORAD values, our population consisted of 35% of patients with mild, 40% with moderate and 25% with severe AD. However, we observed sensitization to airborne allergens in 57% of the investigated population, which points out that they play an important role in the development of atopic inflammation at the level of the skin in AD patients.

Furthermore, we have demonstrated that serum levels of sCD25 and sCD30 significantly correlated with each other, both in the entire evaluated population (r_s = 0.68, p < 0.001) as well as in the ADe and ADi phenotype (r_s = 0.63, p < 0.001 vs. r_s = 0.62, p < 0.001) (Table 2). These correlations imply the synergistic effect of sCD25 and sCD30, even in individuals with a disturbed balance of the cytokine profile in the course of AD. On the other hand, it has been emphasized that serum levels of sCD25 in healthy children are higher compared to adults, and are dropping gradually afterwards to the typical adult levels by the age of 10. Several studies have also confirmed a gradual decrease in sCD30 serum levels related with age, emphasizing a minor diagnostic value of these measurements in children [24]. Since 75.5% of the examined population were of children under 10 years of age, a directly proportional correlation between sCD25 and sCD30 observed in the evaluated population seems more evident.

Differences between extrinsic and intrinsic AD phenotype

The ratio between ADe and ADi in the investigated population was comparable to previous reports [25]. As expected, a significant difference was found between serum levels of tIgE in ADe and ADi phenotype (p < 0.001) (Figure 1). Moreover, the difference between patients' age as well as disease severity between the two phenotypes of AD was statistically significant (p = 0.017 vs. p < 0.001) (Figure 1). The clinical and serological differences were partially reflected by detected SIRs levels. Statistically higher serum levels of sCD25 were observed in ADi patients, while no significant correlations were found in regard to sCD30 (p = 0.113). Our data are contrary with previously published results [14]. Ott *et al.* [22] in a study of a population of 100 children, did not prove any significant differences in disease severity, tIgE or SIRs levels (sCD25, sCD30, sCD14) between the two phenotypes of AD. Kagi *et al.* [21] have presented comparable results, although performed on a minor number of patients.

SIRs and IgE levels and disease severity

The number of studies covering the role of IL-2 in the field of AD is not abundant [4, 7] and performed on populations varying in number of subjects, thus obtained results remain often inconsistent and difficult to compare.

For instance, Yoshizawa *et al.* [4] showed a significantly inverse correlation of serum levels of sCD25 and IgE in the evaluated AD population, which is consent with our results. It was suggested that IgE synthesis may be inhibited by IL-2 in AD patients, which may explain significantly higher serum levels of sCD25 in the ADi phenotype, observed during our study. In contrast, results presented by Yamashiro *et al.* [7] showed statistically higher levels of sCD25 in ADe individuals in comparison with the ADi phenotype. However, it should be stressed that these results were based on a study on a small number of subjects with AD, while in our study 102 patients were included.

As for disease severity, we have observed an inverse correlation between SCORAD values and serum sCD25 levels (Table 2), which is in contrast to currently available reports [4, 21]. Other studies performed on both minor and large populations of pediatric patients with AD [22], did not confirm positive correlations between disease extent and severity and sCD25 levels.

Soluble CD30 was expected to be a useful diagnostic indicator in AD patients. Soluble CD30 was suggested to be a marker of disease activity or even a prognostic parameter of the course of AD [17]. Katoh *et al.* [19] examined a group of AD patients, comparable with our evaluated population (age, number of patients) and showed a significant correlation between sCD30 levels and SCORAD values [20]. Our study did not confirm the aforementioned reports, as an inverse correlation, in the entire investigated population as well as in ADe and ADi phenotypes was observed.

Although serum levels of IgE are elevated in the majority of AD patients, the correlation of tIgE serum levels with disease severity is not always reported. In our study, a positive correlation was observed, between disease severity and tIgE serum levels in the entire AD group (r_s = 0.65, p < 0.001) as well as in ADe phenotype (r_s = 0.55, p < 0.001) (Table 2, Figure 2). Total IgE levels were increasing with progressing age and disease duration, confirming the results of previous studies on the usefulness of this parameter in a daily diagnostic approach [26]. Elevated levels of tIgE reflect sensitization to environmental allergens resulting in increased SCORAD, observed in our study.

Conclusions

We have provided further evidence that sCD25 and sCD30 are highly age dependent. As serum concentrations of SIRs decline with progressing age, which is also observed in healthy individuals, a negative correlation

of sCD25 and sCD30 with disease severity in the investigated population with AD is not clinically useful. The available reports on the usefulness of biomarkers in the clinical evaluation of patients with AD are contradictory and require more uniform studies. Thus, investigated biomarkers may not be considered as clinically applicable in clinical evaluation of patients with AD.

Acknowledgments

Conflict of interest

The authors declare no conflict of interest.

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