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Serum TARC and SCCA2 Levels In Infantile Atopic Dermatitis: Associations with Atopy and Severity

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ABSTRACT

Objective: Atopic dermatitis [AD] is a common chronic inflammatory skin disease. Although numerous indicators have been investigated, reliable biomarkers are still needed to objectively measure the severity of AD. We aimed to evaluate serum thymus and activation regulated chemokine (TARC) and squamous cell carcinoma antigen (SCCA2) levels in infants with AD, and the relationship between these biomarkers and atopy and severity.

Materials and Methods: Forty-two children with AD and 42 healthy controls were included in the study. The severity was evaluated via SCORAD at the baseline, 1 month, and 3 months. Food-specific Ig E (sIgE) and/or skin prick tests were performed to determine food sensitivity in the AD group. Serum TARC and SCCA2, complete blood count parameters, and serum total IgE were measured in the AD group.

Results: Analysis showed that 54.8% of the AD group were mild to moderate and 45.2% were severe. Food sensitivity was present in 42.9% of the patients with AD. There was no difference between AD and control groups in terms of serum TARC and SCCA2 levels ($p>0.05$). Serum TARC levels were higher in the AD group with food sensitivity ($p=0.033$). A high degree of positive correlation was determined between food sIgE values and serum TARC levels in the AD group ($r=0.517$, $p<0.001$). A significant positive correlation was observed between serum TARC and SCCA2 levels in the AD and control groups ($r=0.600$; $p<0.01$, and $r=0.830$, $p<0.001$, respectively).

Conclusion: Serum TARC levels were high in AD patients with food sensitivity. Serum TARC and food sIgE values were positively correlated. Serum TARC levels may be associated with food sensitivity in patients with AD.

Keywords: Atopic dermatitis, serum TARC, serum SCCA2, food sensitivity

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by a complex pathophysiology and various phenotypic characteristics (1). The disease commences in the first six months in 45% of the children, and is generally seen in the first year in up to 60% and in the first five years of age in up to 85% (2). Several factors may be involved in the pathogenesis, including genetic disposition, immunological anomalies, impaired skin barrier function, environmental agents, and infections. An AD severity scale (SCORAD-Scoring Atopic Dermatitis) is used to determine the severity of the disease. However, there is no specific and routine laboratory test available for use in the diagnosis.

The predominance of type 2 cells and cytokines increases in skin with lesions in the acute phase of AD. Thymus and activation-regulated chemokine (TARC) is a member of the type 2 chemokine family. Type 2 dominance in the

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skin of patients with AD is thought to be associated with TARC. Significantly higher serum TARC levels, increasing in line with the severity of the disease, have been reported in patients with AD compared to other inflammatory skin diseases (3). Squamous cell carcinoma antigen 1 (SCCA1/SERPIN B3) and squamous cell carcinoma antigen 2 (SCCA2/SERPIN B4) are members of the ovalbumin-serpin family used as tumor markers specific to various squamous cell carcinomas (4). In addition, SCCA1/2 has been shown to play a role in the pathogenesis of various inflammatory diseases including AD, asthma, and psoriasis (4). The purpose of this study was to measure serum TARC and serum SCCA2 levels in the evaluation of the severity of disease in infants with AD, to compare these with the values in healthy children, and to investigate the relationship between the biomarkers and atopy.

MATERIALS and METHODS

Study Population

Forty-two children aged 3-24 months presenting to the Department of Pediatric Allergy and Immunology Clinic, between December 2018 and January 2020, diagnosed with AD, and with active lesions were included in the study.

Forty-two healthy children presenting to the Hospital's Children's Health and Diseases clinics for routine health examinations, of similar age and sex, and with no developmental retardation, chronic disease, acute or chronic infection, history of prematurity, neurometabolic disease, or atopy, were enrolled as the control group.

Exclusion Criteria

Individuals in the AD patient group with skin diseases other than AD or chronic diseases (such as lung, liver, and kidney disease, malignancy, growth development retardation, obesity, history of prematurity, neurometabolic disease, or primary immune deficiency) were excluded from the study. Children with symptoms of acute or chronic infection or receiving any anti-inflammatory therapy or topical or systemic steroids in the previous 15 days were also excluded.

Study Design and Definitions

The definite diagnosis of AD was based on the diagnostic criteria published by Hanifin and Rajka (5). Severity was evaluated using SCORAD scoring, and all data were recorded onto case forms. Using the SCORAD scoring, patients were classified as mild, moderate, or severe, based on objective (size and intensity of lesions) and subjective (itching and sleep disorder) criteria. SCORAD scores <25 were regarded as mild, scores ≥ 25 and <50 as moderate, and scores ≥ 50 as severe AD (6).

Disease severity was re-evaluated at one and three months using SCORAD scoring in order to assess the relationship between short-term prognosis and the biomarkers. The patients continued with their treatments in the light of the guidelines at three-monthly observations (7). The treatments received were recorded.

Serum TARC and SCCA2 Measurement

Serum TARC and parameters were investigated once at the beginning of the study from all members of the patient and control groups. Blood specimens were placed into biochemistry tubes, centrifuged at -85 degrees, and stored. TARC and SCCA2 levels were measured using commercially available ELISA kits (Bioassay Technology Laboratory, China). The TARC test has sensitivity of 5.51 ng/L, a detection range of 10-4000 ng/L, and a repeatability variation coefficient within and between experiments of <10% (intra-CV and inter-CV). For the SCCA2 test, sensitivity was 0.02 ng/ml, the detection range was 0.05-15 ng/ml, and the repeatability variation coefficient within and between experiments of <10%.

Atopy Evaluation

Food-specific IgE [FX5 (milk, egg, wheat, soy, peanut, and fish), egg-specific IgE, and milk-specific IgE] levels were investigated to evaluate atopy in children with AD, and skin prick tests were performed for those granting consent.

Food sIgE (specific Immunoglobulin E) was measured using the ImmunoCAP (PhadiaAB, Uppsala, Sweden) system. Values higher than 0.35 kIU/L were regarded as positive. Food allergens were examined using the skin prick test (SPT) [cow's milk, casein goat (goat's milk casein), casein mucca (cow's milk casein), lactoalbumin, lactoglobulin, egg yolk, egg white, wheat, peanut, hazelnut, walnut, soy, and fish], together with house dust allergens (Dermatophagoides pteronyssinus and Dermatophagoides farinae). An induration diameter on the SPT ≥3 mm greater than the negative control diameter was regarded as positive. Cases with positive food-specific IgE and/or skin prick tests were defined as food-sensitive (8).

Cases with histories of atopy in the mother, father, or any sibling were regarded as high-risk infants (9). Complete blood count parameters were measured in all participants and an eosinophil count >400 µl was regarded as high. Total IgE levels were investigated in the AD group and classified into two groups, elevated and normal, based on reference values according to the patient's age (10).

Ethics Approval

Approval for the study was obtained from the local ethics committee (protocol no. 2018/1442). Written informed consent forms were also obtained from the families agreeing to take part.

Statistical Analysis

Descriptive statistics for variables exhibiting a normal distribution were expressed as mean ± standard deviation (SD), or as median values (25-75th percentiles) for non-normally distributed variables. Normality of distribution of quantitative variables was assessed using the Kolmogorov-Smirnov test. Independent group comparisons were performed using the independent samples t test for normally distributed variables or with the Mann-Whitney U test for non-normally distributed variables. Differences in categorical variables between the groups were determined using the chi-square test. Spearman's correlation test was used to examine relationships between two non-normally distributed quantitative variables. Qualitative variables were expressed as frequency (%) values. P values <0.05 were regarded as statistically significant.

RESULTS

Participant Characteristics

The demographic characteristics of the AD and healthy control groups are shown in Table I. Analysis showed that 64.3% of the patient group and 19% of the control group consisted of high-risk infants, the difference being statistically significant (p<0.001).

The clinical characteristics of the children with AD are shown in Table II. Based on SCORAD scoring at the initial examination, 23 (54.8%) patients were classified as mild-moderate (SCORAD<50) and 19 (45.2%) as severe (SCORAD ≥50).

Laboratory Parameters

The laboratory parameters of the children in the AD and healthy control groups are shown in Table I. Eosinophil counts were significantly higher in the AD group than in the control group (p=0.014). Median total IgE levels were 20.5 (8.75-45.25) IU/ml in the AD group. Median serum TARC and SCCA2 values were not different between the patient and control groups (p>0.05) (Table I). Median serum TARC values were 759.6 (562.67-1521.51) ng/L in the patient group and 986.49 (721.74-1995.57) ng/L in the control group, and the difference was not statistically significant (p>0.05). Median serum SCCA2 values were 2.11 (1.22-3.28) ng/ml and 2.10 (1.24-3.00) ng/ml respectively (Table I).

Table I: A comparison of the demographic and laboratory characteristics of the participants comprising the atopic dermatitis and control groups (n=84).

	Atopic dermatitis (n=42)	Healthy control (n=42)	p
Age (months), [median (25%-75%)]	9.00 (6.00-15.00)	8.50 (6.00-14.00)	0.676
Sex	Male: 22 (52.4%) Female: 20 (47.6%)	Male: 24 (57.1%) Female: 18 (42.9%)	0.661
Weight (kg), [median (25%-75%)]	8.55 (8.00-10.50)	8.60 (7.40-10.50)	0.537
Length (cm), [median (25%-75%)]	71.00 (67.00-80.00)	71.50 (67.00-79.00)	0.720
High-risk infants, n (%)	27 (64.3%)	8 (19%)	<0.001
Eosinophil (/µl) [median (25%-75%)]	560.00 (280.00-861.00)	340.00 (200.00-480.00)	0.014
TARC(ng/L)	759.6 (562.67-1521.51)	986.49 (721.74-1995.57)	0.062
SCCA2(ng/ml)	2.11 (1.22-3.28)	2.10 (1.24-3.00)	0.886

TARC: Thymus and activation regulated chemokine, **SCCA2:** Squamous cell carcinoma antigen 2

Table II: Clinical characteristics of the atopic dermatitis group.

	Patient
Age at onset of eczema symptoms (months) (n=42) [median (25%-75%)]	3.50 (2.00-6.00)
Duration of eczema (months) (n=42) [median (%25-%75)]	3.50 (2.00-8.00)
SCORAD month 0 (n=42) [mean±SD]	49.40±14.22
SCORAD month 1 (n=42) [mean±SD]	26.32±11.68
SCORAD month 3 (n=42) [median (25%-75%)]	15.30 (10.80-22.10)
Time to onset of symptoms following discontinuation of topical corticosteroids before presentation (days) (n=31) [median (25%-75%)]	3.00 (2.00-7.00)
Milk and/or egg elimination without tests before presentation	21 (50%)
Food eliminated before presentation	
None	17 (40.5%)
Egg	8 (19%)
Milk	6 (14.3%)
Milk and egg	11 (26.2%)
Moisturizer cream use before presentation;	34 (81%)
Potency of topical corticosteroids used before presentation *	
Low	13 (31%)
Moderate	12 (28.6%)
High	17 (47.5%)
Length of topical corticosteroid use in the three month after presentation	
Less than 10 days	18 (42.9%)
More than 10 days	24 (57.1%)

*Patients using topical corticosteroids before the previous two weeks were excluded. **SCORAD:** Scoring Atopic Dermatitis

Table III: A comparison of laboratory characteristic in the groups with and without food sensitivity (n=42).

	Without food sensitivity (n=24)	With food sensitivity (n=18)	p
Total IgE elevation, n (%)	7 (29.2)	14 (77.8)	0.002
Eosinophil elevation, n (%)	15(62.5)	11 (61.1)	0.927
TARC (ng/L) [median (25%-75%)]	622.59 (538.20-1004.04)	1184.96 (735.38-1907.44)	0.033
SCCA2 (ng/ml) [median (25%-75%)]	1.52 (1.03-3.28)	2.41 (1.68-3.71)	0.208

TARC: Thymus and activation regulated chemokine, **SCCA2:** squamous cell carcinoma antigen 2

A Comparison of Patients' Clinical and Laboratory Characteristics in Terms of Food Sensitivity

Food sensitivity was detected in 18 of 42 patients (42.9%) by the skin prick test and/or food-specific IgE. The skin prick test was performed on 28 children and 35.7% (n=10) were found positive. The foods that showed a positive skin prick test results were egg (n=6), cow's milk (n=4), peanut (n=2), and hazelnut (n=2). Multiple food sensitivities were detected in 3 patients. None of the patients who underwent skin prick test were found to be positive for house dust mites. Food-specific IgE was found to be positive in 33.3% (n=14) of the patients who had a food-specific IgE test. Topical corticosteroid (TCS) use in the previous three months, total IgE elevation, and serum TARC levels were different between the groups with and without food sensitivity (Table III). TCS use in the previous three months exceeded 10 days in 77.8% of the patients in the group with food sensitivity and in 41.7% of the patients in the group with no food sensitivity (p=0.019).

Total IgE elevation was present in 21 (50%) patients. The number of patients with total IgE elevation without food sensitivity was 7, within 24 (29%). Serum TARC levels were 1184.96 (735.38-1907.44) ng/L in the group with food sensitivity and 622.59 (538.20-1004.04) ng/L in the group without food sensitivity. Serum TARC levels were

higher in the group with food sensitivity than in the group with no sensitivity (p=0.033).

Correlation Analysis

Moderate positive correlation was determined between serum SCCA2 and serum TARC levels in the patient group (r=0.600; p<0.01). Strong, positive correlation was observed between serum TARC and SCCA2 levels in the control group (r=0.830; p<0.001).

No correlation was found between SCORAD indices and serum TARC or SCCA2 levels. Moderate positive correlation was determined between SCORAD indices calculated at initial examination (SCORAD month 0) and those calculated at months 1 and 3 (r=0.581; p<0.001 and r=0.348; p=0.024, respectively). Decreases in SCORAD scores compared to presentation values at follow-up of the mild-moderate and severe groups are given in Table IV.

A high degree of positive correlation was observed in the patient group between specific IgE values and serum TARC levels (r=0.517; p<0.001) (Figure 1). No correlation was determined between specific IgE values and serum SCCA2 levels.

No correlation was observed in any group between age and serum TARC or SCCA2 levels. When patients were divided into two groups on the basis of age, a greater improvement in SCORAD indices was observed as serum TARC levels increased in patients older than six months (r=-.414, p=0.023).

DISCUSSION

Although no association between serum TARC and SCCA2 levels and the disease and its severity was found in the children with AD in the present study, serum TARC levels being significantly higher in the cases with food sensitivity and being correlated with food-specific IgE levels show that there is a powerful association between atopy and serum TARC levels. A recent study reported higher serum TARC levels in cases of AD with accompanying food allergy compared to cases with no accompanying food allergy (11). In addition, higher serum TARC levels have been observed in patients with food-induced enterocolitis syndrome compared to cases of gastroenteritis (12). A recent case report involving three patients reported higher serum TARC levels in cases with cow's milk allergy, and these decreased with the development of tolerance (13). In the light of these studies and reports and of our

Table IV: Decreases in SCORAD scores compared to presentation values at follow-up of the mild-moderate and severe groups.

	SCORAD		p
	Mild+Moderate (n=23)	Severe (n=19)	
SCORAD (month 1-0)	-18.09±9.76	-29.12±12.04	0.002
SCORAD (month 3-0)	-24.97±10.77	-41.73±11.95	<0.001

SCORAD: Scoring Atopic Dermatitis

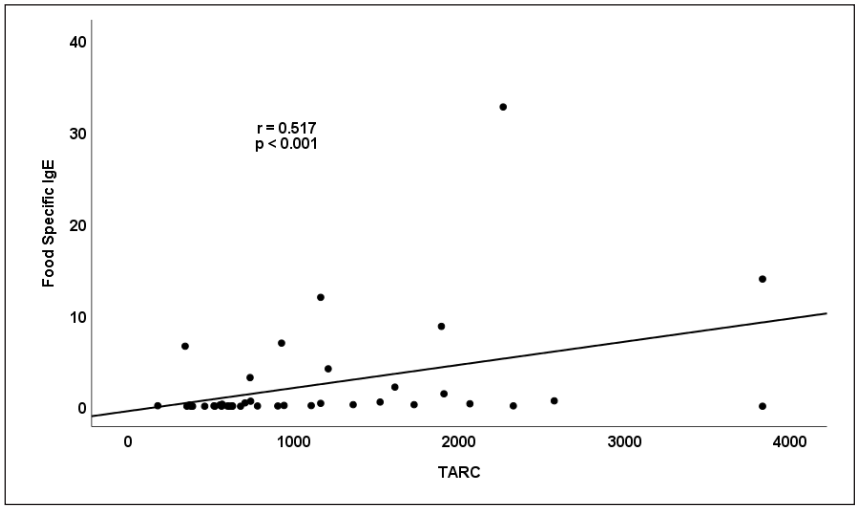

Figure 1. Correlation between food specific IgE values and serum TARC levels in the patient group.

own findings, we think that serum TARC levels may be associated with food sensitivity in cases of AD and that further research is needed on this subject.

Food sensitivity has been shown in 20-30% of cases with moderate-severe AD (14). Knox et al. detected sensitization with eggs (60.7%) and peanuts (60.7%), followed by milk (37.9%) in AD cases under the age of two years in the USA (15). Kahveci et al. investigated 1140 patients with AD under two years and reported egg white as the most frequent food allergy, at 49.7%, followed by cow's milk at 29.9% (16). All the patients in the present study were tested for food sensitivity, and this was detected in 42.9%. Consistent with the previous literature, egg sensitivity was most commonly observed.

Serum TARC levels were significantly high in the group with food sensitivity in this study. A positive correlation was also observed between sIgE levels and serum TARC levels in the patient group. Few studies have investigated the relationship between food sensitivity and serum TARC levels. Higher serum TARC levels have been reported in patients with AD and accompanying food allergy compared to those with no food allergy (11). Another study determined significantly higher serum TARC levels in children with AD with egg allergy compared to those without egg allergy (17). Ahrens et al. reported a significant correlation between serum TARC levels and severity of AD in infants sensitive to food or respiratory allergens (18). Serum TARC levels have been shown to decrease after hydrolyzed formula in infants with cow's milk allergy with high serum TARC levels and milk sIgE, suggesting that serum TARC elevation may be associated with gastrointestinal food allergies (19). The correlation determined between sIgE and serum TARC levels in the present study was not observed between sIgE and serum SCCA2. Few studies have investigated the relationship between food allergy and serum SCCA2 in patients with AD. One study showed higher serum SCCA2 values in infants with AD with food allergies (20). The AD severity scale most widely used in children with the condition is known as SCORAD. The mean SCORAD score of the patients in this study was 49.40±14.22, with 23 (54.8%) cases being evaluated as mild-moderate and 19 (45.2%) as severe. The patients' SCORAD values decreased with treatment during follow-up. A positive correlation was observed between SCORAD scores at the first examination and scores at the second and third examination. Nagao et al. reported a significant decrease in SCCA2 and TARC levels in addition to an improvement in SCORAD scores with treatment (21). No correlation was determined in the present study between SCORAD at time of presentation and serum TARC or SCCA2.

Yasukochi et al. observed a more rapid decrease in serum TARC levels with treatment in patients from a severe AD group compared to a moderate AD group (22). In the present study, the improvement in the SCORAD index was higher in patients with AD older than six months with high serum TARC levels at three-month follow-up. A greater decrease in SCORAD index scores was observed in patients with severe AD compared to those with mild-moderate AD at both the first and third months. This was potentially attributed to the skin barrier being more impaired in patients with severe AD, and to better TCS absorbance through the skin (23).

Serum TARC levels have been shown to be almost three times higher in babies compared to adults (24). Studies have also shown higher serum SCCA2 and TARC levels in children with AD compared to healthy children (20,21). A study has reported that serum TARC and SCCA2 levels increased in line with the severity of AD (21). That study also showed that serum SCCA2 levels were superior to serum TARC levels both in determining the clinical severity of AD and in evaluating the response to treatment. Similarly, Ohta et al. showed a positive correlation between serum SCCA2 levels and disease severity (20). In the study conducted by Koizumi et al. in 35 patients aged 6 months, significant correlations were observed between SCORAD scores and serum TARC levels (25). In the study conducted by Esenboga et al. on 160 children with AD, there was a significant correlation between the objective SCORAD scores and TARC values in cases with AD (26). In contrast to those studies, there was no significant difference between the patient and control groups in terms of serum SCCA2 or TARC levels in the present study, and no correlation was determined between the clinical severity of AD and serum TARC or SCCA2 levels. This may be associated with the low patient number in our study and the low age group since serum TARC levels are known to be higher even in healthy children in the young age group, and also to the high rate of potent TCS use before 15 days prior to presentation. In addition, although the majority of our patients were severe AD cases, TARC and SCCA2 may not be as sufficient as predicted for determining the disease and its severity in children aged 3-24 months.

A significant positive correlation was determined between serum TARC and SCCA2 in both healthy children and those with AD in this study. Okawa et al. determined a positive correlation between serum SCCA2 levels and serum TARC levels in adult patients with AD (27). Izuhara et al. also reported a correlation between serum SCCA2 and serum TARC levels in children with AD (28). The present study is thus consistent with the previous literature from that perspective.

The correlation between serum TARC and SCCA2 levels in the control group may be due to both markers of inflammation. In the study by Hirayama et al., the serum TARC, SCCA1, and SCCA2 decreased during treatment in severe AD patients. Serum levels of SCCAs in healthy children were similar across different age groups. Serum levels of SCCAs were similar between healthy volunteers and those with asthma or allergic rhinitis (29). In the study of Nagao et al., SCCA2 was correlated with TARC (21).

The strengths of this study are the prospective design and the evaluation of all patients in terms of food sensitivity. The principal limitations are the low patient number, the fact that biomarkers were not investigated during follow-up, and that it cannot be generalized to the entire population. In this study, skin testing was not performed in healthy children due to the inclusion of infants and the invasive nature of the procedure. However, it should be noted that there may be sensitized individuals among healthy children. Therefore, our data should be carefully considered and evaluated in this context.

In conclusion, this research is valuable in terms of AD patients aged 3-24 months being evaluated prospectively, and in terms of its investigating the relationships between disease severity, three-month prognosis, and atopy. We think that this study will add to the existing literature due to our observation of higher serum TARC levels in cases with food sensitivity and the high degree of positive correlation found between food sIgE values and serum TARC levels. There are currently no biomarkers used routinely worldwide to predict the diagnosis, severity, and prognosis of AD, and studies with much larger patient numbers are now needed.

Conflict of Interest
The authors have no conflicts of interest to declare.

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Author Contributions
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