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Infantile atopic dermatitis: Serum vitamin D, zinc and TARC levels and their relationship with disease phenotype and severity

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Abstract
Background: Several markers that influence the clinical course of atopic dermatitis (AD) have been investigated so far. Thymus and activation regulated chemokine (TARC) - a Th2-related cytokine - increase in various atopic diseases. It has been shown that vitamin D affects Treg cells and immune responses. Zinc as an essential trace element for cell-cell interactions, cellular differentiation, and proliferation. However, the effect of these markers on infantile AD and disease severity are mostly unknown.
Objective: The aim of this study was to investigate the relationship between TARC, vitamin D, zinc levels, and the disease severity in infants with AD.
Method: AD patients (n = 160) with age and sex that matched healthy controls (n = 79) were included in the study. The diagnosis of AD was made based on the Hanifin-Rajka criteria. The objective SCORAD index was used for the assessment of disease severity.
Results: A total of 160 patients (male 71.9%) with AD were included in the study. The median age of onset of symptoms was 2 (1.0-3.5) months. The lesions initially started on face 76.9%, neck 6.9%, extremities 7.5%, and body 8.8%. Nearly 40% of the patients were found to be atopic. Food allergy was found in 39.4%. The median of objective SCORAD index was 27.5 (17.5-40) in the study group. The TARC levels of AD patients were higher than control group [1803 pg/ml (1006-3123) vs 709 pg/ml (504-1147), $p < 0.001$] There was a significant correlation between objective SCORAD scores and TARC values in subjects with AD ($r = 0.363$, $p < 0.001$). As the severity of AD increased, vitamin D levels decreased (p for trend 0.015) and TARC values increased (p for trend < 0.001). Serum zinc levels did not change with the severity of the disease. The presence of atopy did not have an influence on serum TARC, zinc, and vitamin D levels.
Conclusion: In infants with AD, disease severity is positively related with TARC levels; and inversely proportional to vitamin D levels. TARC levels differ between patients and healthy controls. The presence of atopy has not been shown to affect these markers.

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Introduction

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease of childhood which is characterized by itching, dry skin, and eczematous lesions.[1] Clinical presentation depends on the age of the patient and the severity of the disease. AD is a heterogeneous and multifactorial disease that genetic and environmental factors, mainly T-helper 2(Th2) type immunological mechanisms, and epidermal barrier dysfunction and activation of the keratinocytes contribute to the pathogenesis.[2,3]

Increased allergen penetration from the defective skin barrier leads to the release of cytokines like IL-4, IL-5, and IL-13 inducing Th2 polarization. Biomarkers such as thymic stromal lymphopoetin (TSLP), thymus and activation regulated chemokine (TARC/CCL17), periostin, and vitamin D have been the subject of interest in recent studies and serum and plasma biomarkers have been demonstrated to correlate with AD severity and chronicity.[4]

TARC is an intrinsically expressed chemokine in the thymus and is a part of the Th2 chemokine family attracting CC chemokine receptor 4-positive (CCR4) cells. Th2 cells, especially during the acute phase of AD, have been found to play a key role in the pathogenesis.[5] TARC is expressed in epidermal keratinocytes, vascular endothelial cells, and dendritic cells in AD patients.[6,7] Serum TARC level is strongly associated with AD severity[6,8] and TARC has been found to be a useful marker for evaluating the efficacy of treatment in AD. However, its importance in infantile AD remains to be clarified.

Vitamin D has various effects on the skin, varying from keratinocyte proliferation, differentiation, and apoptosis to barrier maintenance and immune regulation.[9] Lack of vitamin and/or signaling would promote a primary Th2 response and increase of IgE. Vitamin D may alter outcomes of allergy through a complex effect on the impaired barrier protection and immune dysregulation.[10] While some studies reported no significant association,[11] most studies observed a negative relationship between severity of AD and vitamin D levels with dose-dependent effects.[12,13] There is still need for evidence for the role of serum vitamin D in modifying disease severity in AD.

Zinc, which is essential trace element for physiological processes, plays a major role in many enzymes and is implicated in cell–cell interactions, cellular differentiation, and proliferation. Although in multiple inflammatory skin diseases – such as AD and lichen planus – zinc deficiency has been identified,[14,15] there is not enough data to support the use of zinc supplementation in AD care. The link between zinc and AD is, however, less defined.

The aim of this case control study was to investigate the relationship between serum vitamin D, zinc, TARC levels, and the disease severity in infants with AD.

Materials and Methods

Patient population

In this case-control study, the infants younger than 1 year of age with AD who were admitted to Pediatric Allergy and Asthma Division of Hacettepe University, İhsan Dogramaci Children's Hospital between January 2016 and July 2017 were included. AD was diagnosed according to the criteria of Hanifin–Rajka[16] which proposed to diagnose AD when the patient meets at least three of the four items including pruritus, typical morphology and distribution (facial and extensor eruptions in infants and children; flexural lichenification in adults), chronic or chronically relapsing dermatitis, personal or family history of atopy (asthma, allergic rhinitis, AD), and at least three of 23 minor features.

A total of 160 infants with AD and 79 healthy controls were involved in the study.

Initial evaluation on admission comprised a survey including demographic information: age, gender, gestational week, living conditions, atopic diseases, family history for atopic diseases; environmental conditions during pregnancy; and baby's early-life environment and nutritional characteristics. Objective severity scoring of atopic dermatitis (o-SCORAD) index was used to assess the severity of AD at first visit. Patients with a total o-SCORAD score less than 15 were classified as mild, 15–40 as moderate, and above 40 as severe AD.[17]

Blood samples were taken on admission for complete blood count, serum vitamin D, zinc, tryptase, and total IgE. The percentage of blood eosinophils was calculated and serum total IgE was measured with using enzyme linked immunoassay (ELISA) using the ImmunoCAP system. Serum 25-(OH)D_3 levels were determined using an ELISA kit and the zinc was measured by atomic absorption spectroscopy. All children under 1 year of age routinely take 400IU of vitamin D daily in our country. None of the infants was taking zinc before or during the study. Vitamin D and zinc levels are only evaluated in the patient group and not in the control group.

Skin prick test was performed on the child's upper back with common food allergens in Turkey[18] (cow's milk, egg white, egg yolk, soy, peanut, walnut, hazelnut, wheat, sesame, and lentils) and house dust mites (DP, DF) with positive (10 mg/ml of histamine phosphate), and negative (0.9% sterile saline) controls. Skin prick test positivity was accepted as a test induration ≥3 mm that of the negative control[19] and children with at least one positive test were classified as atopic.

Measurement of serum TARC levels

Serum TARC levels were measured in 160 infants with AD and 79 healthy controls. Levels of TARC in serum samples were determined by using Human CCL17/TARC Quantikine ELISA Kit (R&D Systems) according to manufacturer's instructions. Briefly 100 µl assay diluent and 50 µl of serum or standards were added to each well and incubated for 2 h at room temperature (RT). Plates were washed and 200 µl of conjugate were added to each well. After 1 h of incubation, plates were washed and substrate solution (200 µl/well) were added. Plates were incubated for half-an-hour at RT by protecting from light then reactions were stopped by adding 50 µl of 2 N sulfuric acid. Plates were read at 450 nm for the determination of concentrations. Samples were diluted twice in appropriate buffer if necessary.

Our study was completed in accordance with the ethical standards specified in the declaration of Helsinki

and it was approved by the Medical Ethics Committee of Hacettepe University (Hacettepe University, GO 17/654-18). All parents provided informed consent.

Statistical analysis

Statistical analyses were performed using SPSS 22 software program. Descriptive analysis was used to characterize the patients. Pearson's χ^2 test or Fisher's exact test was used for between-group comparisons. Values are shown as median and interquartile range for data not normally distributed. The Mann–Whitney U test or Kruskal–Wallis test was used to compare values. P value for trend analysis was done by Jonckheere-Terpstra test. Logistic regression analysis was performed to predict the associations between clinical and/or laboratory parameters and infantile AD severity. Firstly, univariate analysis was done and the parameters with a p value <0.2 were analyzed with multiple logistic regression analysis. All statistical tests were two-sided and the level of statistical significance was set at $p < 0.05$.

Results

The number of patients (male 71.9%) with AD who were included in the study were 160. The median age of the patients was 5.5 (4.2–6.9) months. The median age of onset of symptoms was 2.0 (1.0–3.5) months. Initial symptoms appeared on face in 76.9%, on the neck in 6.9%, in the extremities in 7.5%, and in the body in 8.8% of the patients. Further, 64 out of 160 patients (39.9%) were found to be atopic. Food sensitization was found in 63 (39.3%) patients, sensitization to egg white was found in 78.3% patients, to cow's milk in 46.4%, to egg yolk in 42%, to nuts in 5.8%, and to wheat in 2.9%. House dust mite sensitization was found in one patient (0.6%). Family history of atopy was present in 29.4% of the patients.

The median objective SCORAD index was 27.5 (17.5–40.0) in the study group. Characteristics of the patient and control groups were shown in Table 1. According to the levels of o-SCORAD index, AD patients were classified as having mild 19% (n = 31), moderate 57% (n = 91), and severe 24% (n = 38) AD. The characteristics along with disease severity have been detailed in Table 2.

The TARC levels of AD patients were higher than control group (1803 pg/ml [1006–3123] vs 709 pg/ml [504–1147], $p < 0.001$] (Table 1). Additionally, there was a trend of increase in TARC levels as the disease severity increased (p for trend <0.001), (Figure 1A and 1B).

TARC levels also correlated with the objective SCORAD values and as the values of objective SCORAD increased, the serum levels of TARC also increased ($r = 0.363$, $p < 0.001$), (Figure 2). The strength of the correlation is found to be mild-to-moderate.

The frequency of atopy was higher in patients with severe AD. However, it did not affect the serum levels of TARC, vitamin D, and zinc. There was a significant difference between vitamin D serum levels and AD phenotypes ($p = 0.029$). Vitamin D serum levels decreased as the disease severity increased (p for trend was 0.011), (Figure 1C).

Initial wrist and finger involvement (odds ratio [OR]: 4.847, 95% confidence interval [CI] : 1.662–14.132, $p = 0.004$) was found to be a risk factor predicting the presence of severe AD during infancy when logistic regression analysis was performed, with the adjustment for presence of atopy, serum TARC level, total IgE, and eosinophil number (Table 3).

Discussion

In the present study, characteristics of 160 infants with AD were evaluated and the relationship between TARC and vitamin D levels; and their relationship with disease phenotype and clinical severity were assessed. In infants with AD, disease severity is positively related with TARC levels;

Table 1 Characteristics of the study population.

	Atopic dermatitis n = 160	Control group n = 79	P
Current age (months)*	5.5 (4.2-6.9)	6.0 (4.0-9.0)	0.075
Gender, Male, n (%)	115 (71.9%)	49 (62.0%)	0.123
Total IgE* (kU/L)	21.0 (6.0-71.0)	16.5 (5.0-18.0)	0.048
Eosinophil number (mm^3)*	600 (400-1000)	230 (137-400)	<0.001
Eosinophil %	5.5 (3.7-8.6)	2.2 (1.4-3.9)	<0.001
TARC* pg/mL	1803 (1006-3123)	709 (504-1147)	<0.001
Objective SCORAD index*	27.5 (17.5-40.0)	-	-
Atopy	39.9%		
Distribution of sensitizations	Egg white 78.3% Milk 46.4% Egg yolk 42% Nuts 5.8% Wheat 2.9% House dust mite 0.6%		

*Median (Inter quartile range), **Mean ± standard deviation.
TARC: Thymus and activation regulated chemokine, CCL17.

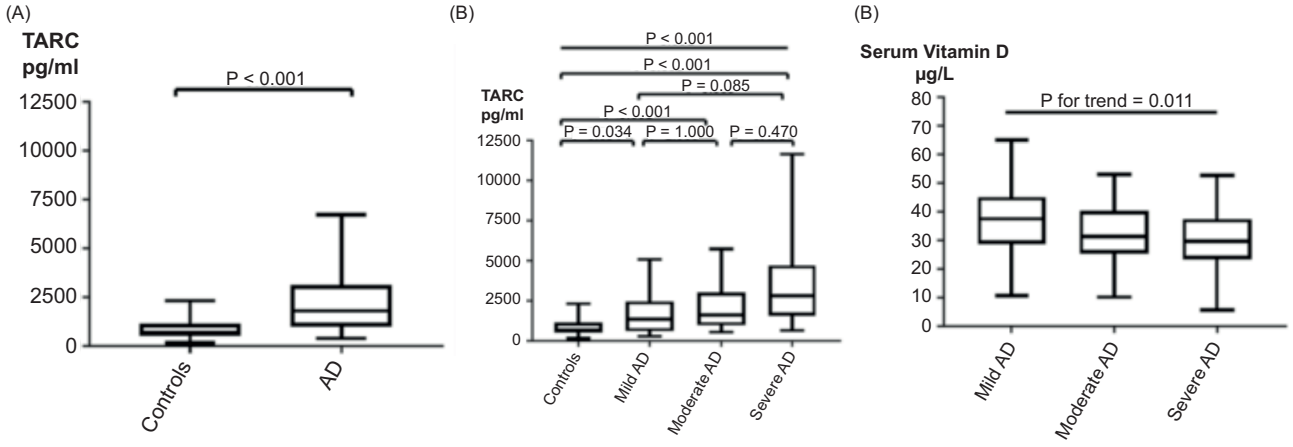

Figure 1 (A) TARC levels in patients and controls. (B) TARC levels in controls and groups formed according to the severity of AD. (C) Levels of Vitamin D in groups formed according to the severity of AD.

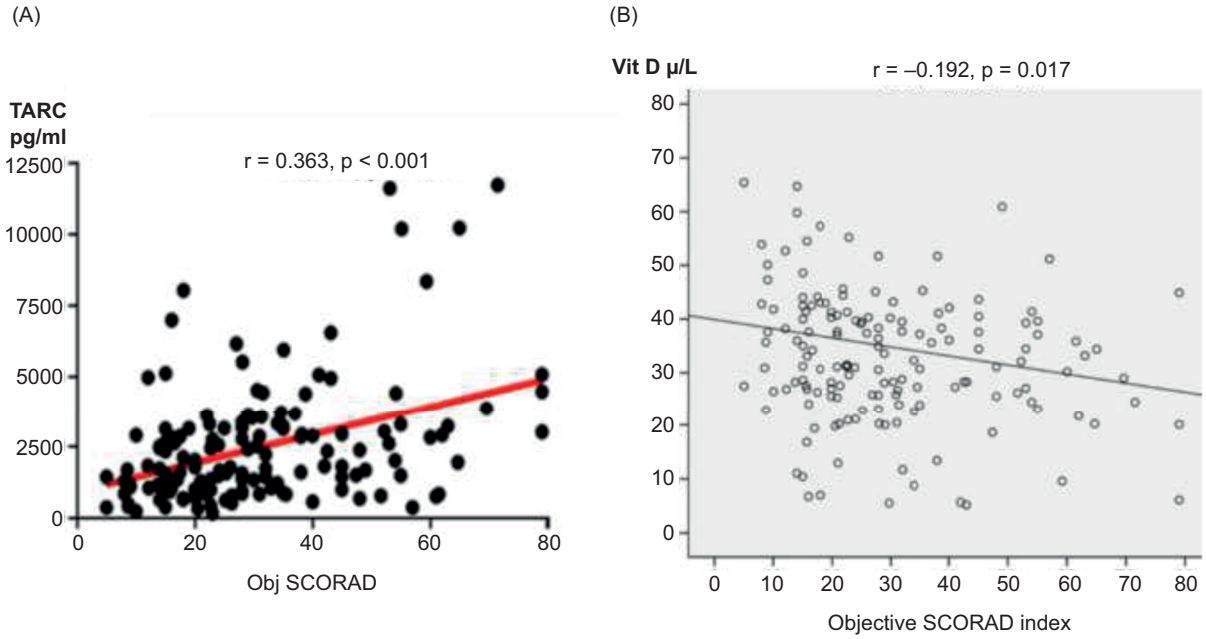

Figure 2 (A) Relation of TARC and o-SCORAD. (B) Relation of vitamin D and o-SCORAD.

and inversely proportional to vitamin D levels. TARC levels differ between patients and healthy controls as a measure of type 2 inflammation. The presence of atopy has not been shown to have a significant effect on these markers.

As is known, AD affects different areas of the body in different age groups. Infants appear to develop lesions mostly on their cheeks and scalp. Patients with severe AD may have lesions almost everywhere in the body, particularly in the hands, feet, and trunk.[5] When the severity of AD was assessed by areas affected in the body, it was found to be more severe in those with hand eczema.[20,21] This is consistent with our data on the association of severe disease, wrist, and finger eczema.

In the present study, TARC levels were significantly higher in AD patients compared with healthy controls. Additionally, there was a trend of increase in TARC levels as the disease severity increased. Also TARC levels were found to correlate with the objective SCORAD values and has been found to be a useful marker for evaluating the efficacy of treatment in AD. However, in a study evaluating the correlation of SCORAD with TARC in patients with AD, the correlation has been detected weaker in children than in adults, so it was stated that this method may be more suitable for use in adults.[22] In a meta-analysis concerning the biomarkers in AD, serum TARC levels were detected to be the most reliable biomarker; however, due to the considerable heterogeneity of the disease and presence of different clinical phenotypes, the authors suggested that a biomarker panel may be more functional and beneficial.[4]

In the presented study, food sensitization was present in 39.3% of the cases; egg white was the most common sensitized food. In a study evaluating 44 children with AD who

Table 2 Descriptive and laboratory characteristics of AD patients according to disease severity.

	Whole group n = 160	Mild AD n = 31	Moderate AD n = 91	Severe AD n = 38	P*
Age at symptom onset, months	2.0 (1.0-3.5)	2.5 (1.0-3.0)	2.0 (1.0-4.0)	1.8 (1.0-3.6)	0.776
Current age, months	5.5 (4.2-6.9)	5.5 (3.5-6.0)	5.5 (4.2-7.3)	5.8 (4.4-6.0)	0.850
Gender, Male %	71.9%	80.6%	69.2%	71.1%	0.471
Atopy (%)	39.9%	36.7%	34.1%	56.8%	0.055
Family history of atopy	29.4%	22.6%	30.8%	31.6%	0.649
Pet exposure at home	6.9%	6.7%	7.7%	5.3%	0.883
Initial wrist and finger involvement	11.9%	3.2%	5.5%	31.6%	<0.001
Initial eyelid involvement	13.1%	6.5%	9.9%	26.3%	0.020
Initial nipple involvement	11.9%	6.5%	11.0%	21.1%	0.069
TARC (pg/mL)	1803 (1006-3123)	1537(856-2444)	1614(979-3029)	2829(1592-4718)	0.004
Vitamin D µg/L	32.1 (25.8-40.5)	37.5 (28.8-45.2)	31.3 (25.5-40.3)	29.6 (23.5-37.5)	0.029
Zinc µg/dL	96 ± 33	98 ± 33	95 ± 36	96 ± 27	0.904
Eosinophil number (mm^3)	600 (400-1000)	500 (300-750)	600 (300-975)	700 (500-1450)	0.011
Eosinophil %	5.5 (3.7-8.6)	4.2 (3.2-6.7)	5.5 (3.6-8.3)	7.9 (4.2-12.5)	0.005
Total IgE kU/L	21 (6-71)	9 (4-38)	14 (6-52)	45 (21-206)	<0.001

*Zinc analyzed by one way ANOVA, other parameters by Kruskal-Wallis, and non-parametric parameters by Chi Square test.

Table 3 Risk factors to predict the presence of severe atopic dermatitis during infancy.

	Univariate			Multivariate		
	OR	95% CI	p	OR	95% CI	p
Initial wrist and finger involvement	5.600	2.107-14.883	<0.001	4.847	1.662-14.132	0.004
Initial eyelid involvement	2.915	1.185-7.168	0.020			
Initial nipple involvement	2.217	0.874-5.625	0.094			
Presence of atopy	2.469	1.166-5.228	0.018			
Serum TARC level	1.000	1.000-1.001	<0.001	1.000	1.000-1.000	0.011
Serum vitamin D level (µg/L)	0.975	0.944-1.006	0.115			
Total IgE (kU/L)	1.002	1.000-1.003	0.071	1.001	1.000-1.003	0.086
Eosinophil number(/mm^3)	1.001	1.000-1.001	0.007			

were younger than 12 months, the food sensitization rate was found to be 61%; and the most frequent food sensitization was due to eggs.[23] In a study from Turkey including 501 children with AD (median 15 months of age), food sensitization was detected as 30.9% like the presented study.[24]

In our study, we did not find any relationship between atopy status and the biomarkers that the authors evaluated. One of the reasons for this may be the young age of our patients and the inadequacy of the time interval between atopy development and the elevation of these markers. In a study of Uysal P et al., 60 children with AD and 31 healthy controls were included; TARC and TSLP was shown to predict severe AD; and periostin was found to be a useful biomarker for predicting atopy and chronic course.[25]

The serum total IgE levels were also found to be similar in disease group and healthy controls. Park et al. did not find a significant association between SCORAD and serum IgE in patients under the age of 2 years.[26] As mentioned in Park et al. report, this finding may be attributed to the immature development of the cytokine system in young children. In recent studies, it has been shown that total IgE increases with age and that a time period is needed to increase IgE after sensitization.[27,28]

We observed lower levels of vitamin D as the severity of AD increased. Vitamin D, which is a liposoluble hormone, has a wide variety of effects on innate and adaptive immune system and skin barrier functions including filaggrin expression, epidermal differentiation, cathelicidin production, increase in tolerogenic dendritic cells and regulatory T cells, and decrease in IgE production, Th2 cytokines and B cells.[12,29] Vitamin D levels have been investigated in various allergic diseases including AD. Previous publications reported that vitamin D levels negatively correlated with AD severity. On the other hand, there is still no sufficient data on the recovery of AD with vitamin D supplementation.[30]

Zinc is an essential trace element, which has many effects on the skin including tissue repair, wound healing, and immune response. In the present study, we could not show a relationship between the severity of AD and serum zinc levels. However, erythrocyte and hair zinc levels could also be used for the assessment of zinc status in the body

as well. Given the low-level and moderate-level quality of the studies included, lower levels of serum, hair, and erythrocyte zinc levels were correlated with AD based on the systemic review of zinc and AD, prepared by Gray NA et al. However, they argued that the relationship between low zinc levels and AD should be confirmed in higher quality studies and the need for zinc support in the treatment and prevention of AD should be assessed in randomized controlled trials.[31]

Although we have evaluated different biomarkers, as a result of the logistic regression analysis to evaluate risk factors determining disease severity, we found a single risk factor which is a clinical finding in fact: initial wrist and finger involvement. Although it is a minor criteria of Hanifin-Rajka,[16] recent studies have shown that minor criteria are also important factors for determination of disease severity and chronicity.[32]

There are potential limitations of the present study. Firstly, the vitamin D levels have not been assessed in the control group. Secondly, this is a case-control study and it may not reflect the disease progress which develops by the time. Nonetheless, the present study has some superior aspects as well. The study includes a quite good number of infants younger than 12 months of age and evaluates biomarkers including TARC, zinc, and vitamin D at the same time. The number of studies evaluating the relationship between multiple biomarkers and severity of AD in young infants are very limited.

Conclusion

In conclusion, we found that TARC levels are positively related and vitamin D levels are inversely related with AD severity in infants. We did not find a significant relation between the TARC or vitamin D levels and the atopy status. It is observed in a clinical finding that initial wrist and finger involvement were the only risk factors related with the severity of the AD. Further investigations are warranted to assess the variability of potential biomarkers of AD during infancy. The clinical correlation of biomarkers involved in pathogenesis of AD and their differences in age groups should be shown for the development of targeted therapy strategies.

Conflicts of Interest

The authors declare no conflict of interest. Hacettepe University Scientific Research Projects Coordination Unit provided financial support to this study and TARC kit was received with this financial support.

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