

Factors that predict disease severity in atopic dermatitis: The role of serum basal tryptase

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ABSTRACT

Background: Increased numbers of mast cells that contain tryptase are found in lesional atopic dermatitis (AD) skin. The association of serum basal tryptase (sBT) with anaphylactic reactions and mast cell diseases has recently been shown in children with venom and food allergy.

Objective: We aimed to identify the risk factors that predict the severity of AD and the association of sBT levels with AD and disease severity.

Method: AD diagnosis was made according to Hanifin and Rajka criteria. Disease severity was scored by the objective scoring atopic dermatitis (SCORAD) index. The sBT levels were measured. Skin-prick testing, total immunoglobulin E, eosinophil percentages and counts, and a questionnaire concerning the history of atopic diseases and the risk factors of AD were applied.

Results: The children, ages 0.5 to 3.0 years, with AD ($n = 85$) were analyzed in two groups according to the presence (AD+/atopy+ [$n = 55$]) or absence (AD+/atopy- [$n = 30$]) of skin-prick test positivity. The comparisons were made with an age- and sex-matched control group ($n = 82$). The median (interquartile range) sBT in the AD+/atopy+, AD+/atopy-, and control groups were 5.01 ng/mL (2.75–6.79 ng/mL), 3.02 ng/mL (1.67–4.44 ng/mL), and 2.63 ng/mL (1.31–4.49 ng/mL), respectively ($p = 0.003$). The median (interquartile range) sBT levels were higher in patients with moderate-severe objective SCORAD index scores compared with the those with mild disease (3.85 ng/mL [2.04–5.91 ng/mL] versus 2.80 ng/mL [1.83–3.48 ng/mL]; $p = 0.038$). Multivariate logistic regression analysis showed that an sBT level of ≥ 3.9 ng/mL (odds ratio 8.77 [95% confidence interval, 1.87–41.18]; $p = 0.006$) was independently associated with an increased risk of moderate-severe AD (objective SCORAD index).

Conclusion: To our knowledge, this was the first study that indicated that sBT levels may be important in the AD disease process and associated with the disease severity and atopy.

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Atopic dermatitis (AD) is a chronic inflammatory disease of the skin that affects up to 20% of children and 3% of adults, with an increasing prevalence in the past 3 decades.^{1,2} Clinical presentations and symptoms vary among patients, and scoring systems have been developed for evaluating the severity of lesions and the extent of involvement. The scoring atopic dermatitis (SCORAD) and objective SCORAD indexes have been the most commonly used scores for this purpose for many years.³ In the pathogenesis of AD, increased infiltration of T cells, dendritic cell (DC)

DC subtypes, macrophages, mast cells, and eosinophils, along with different cytokines and chemokines, can be observed.⁴

Increased numbers of mast cells are found in lesional AD skin, and these mast cells contain abundant tryptase, a neutral serine protease, in their granules.⁵ Immature precursors of α and β tryptase are continuously released into the bloodstream, which reflect an sBT level. Mature β tryptase is stored in mast cells and released under conditions of extensive mast cell degranulation.⁶ Measuring serum tryptase levels is a convenient way to monitor mast cell burden and mast cell activation because very low amounts of tryptases ($<1\%$) are detected in basophils.⁷

Recent studies revealed an association between serum basal tryptase (sBT) levels and the severity of allergic and inflammatory disorders.⁸ In patients with Hymenoptera venom allergy, elevated sBT levels were identified as an increased risk factor for severe systemic reactions.^{9,10} Although the manufacturer validated serum tryptase levels ≥ 11.4 ng/mL as a 95% percentile value, our group found that sBT levels ≥ 4.8

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Table 1 Characteristics of the study population

	Control Group (<i>n</i> = 82)	Atopic Dermatitis Group (<i>n</i> = 85)	<i>p</i>
Age, median (IQR), mo	11.8 (9.0–19.0)	9.0 (7.0–18.0)	NS
Boys/girls	47/35	50/35	NS
IgE, median (IQR), ng/mL	17 (16–41)	22 (17–63)	0.014
Eosinophils, median (IQR), %	2.2 (1.4–3.1)	3.7 (2.2–5.3)	<0.001
Eosinophil count, median (IQR), mm ³	220 (110–322)	390 (232–595)	<0.001
Familial atopy, no. (%)	13 (15.9)	33 (38.8)	0.001
Basal serum tryptase, median (IQR), ng/mL	2.63 (1.31–4.49)	3.40 (2.00–5.43)	0.028

IQR = Interquartile range; NS = Non-significant; IgE = immunoglobulin E.

ng/L to be a significant risk factor for severe reactions in children with venom allergy.¹¹ In addition, we reported high sBT levels in children with food allergy who experienced anaphylaxis and indicated sBT as a predictor of anaphylaxis in these patients.¹² However, no association was shown between sBT and severe reactions in children with a drug allergy.¹³ Consequently, more research is needed to elucidate the role of sBT in allergic diseases and to confirm the results of current studies.^{11–13} Based on our previous results, we aimed to determine risk factors that predict the severity of AD and the association of sBT levels with AD and disease severity. In addition, we aimed to investigate whether sBT would be a useful marker for the severity of AD.

METHODS

Study Population

The study population was composed of children who were followed up in the outpatient clinic of the general pediatrics department (control group) and of children brought to the pediatric allergy and immunology department with a concern of AD (patient group) between January and March 2014. The sBT and total immunoglobulin E (IgE) levels were measured by using the Immuno-CAP technique (Pharmacia & Upjohn, Uppsala, Sweden) at the Hacettepe University Allergy Laboratories. Blood samples were collected between 8:00 and 11:00 A.M. The sBT levels of 11.4 ng/mL were determined to be above normal (according to the manufacturer's guidelines) and were evaluated in detail for the presence of clonal mast cell disorders. The diagnosis of AD was made according to the Hanifin and Rajka criteria.¹⁴ Disease severity was scored with the objective SCORAD index by the same allergist (UMS) and classified as mild (mean score, <15), moderate (15–40), or severe (>40).³ Skin-prick testing, eosinophil percentages and counts, and a questionnaire concerning the history of atopic diseases and the risk factors of AD were used. None of the children had a documented

history of venom allergy or mast cell-associated clonal disease, which may cause elevated sBT levels. The study protocol was approved by the ethical committee of Erciyes University. Informed consent was obtained from all the parents. U. Murat Sahiner and B. Buyuktiryaki contributed equally to this study. All the authors approved the final version of the manuscript.

Statistical Analysis

The parameters of the study population (sBT level, IgE level, and eosinophil count) were not normally distributed and were given as median and interquartile range. Spearman correlation analysis was used to test the relationship between sBT level and the objective SCORAD index. Non-normally distributed sBT levels were compared by using the Kruskal-Wallis test, and Bonferroni correction was made between the groups. A receiver operating characteristic curve analysis was made to determine a cutoff value of sBT to differentiate between mild and moderate-severe AD. To predict the risk factors for moderate-severe AD, multivariate logistic regression analysis was performed. Familial atopy, IgE levels, eosinophil percentages, atopic sensitization, and tryptase level were included in the analysis. SPSS 18.0 software program (SPSS, Inc., Chicago, IL) was used for all the statistical analysis. A *p* value of <0.05 was considered significant.

RESULTS

A total of 167 children ages 0.5 to 3.0 years, with a median (interquartile range) age of 10 months (8.0–18.0) (boys/girls, 97/70), were included in the study. There were 85 children with AD, and comparisons were made with an age- and sex-matched healthy control group (*n* = 82). Characteristics of the study population are shown in Table 1. Median (interquartile range) sBT levels in AD and control groups were 3.40 ng/mL (2.00–5.43 ng/mL) and 2.63 ng/mL (1.31–4.49 ng/mL), respectively (*p* = 0.028). This significance increased when the children with AD (*n* = 85) were

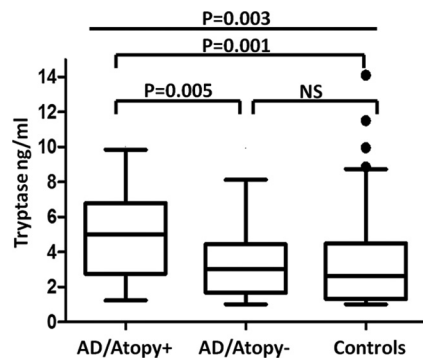


Figure 1. Comparison of serum basal tryptase levels in children with AD+/atopy+, AD+/atopy−, and healthy controls. AD = Atopic dermatitis.

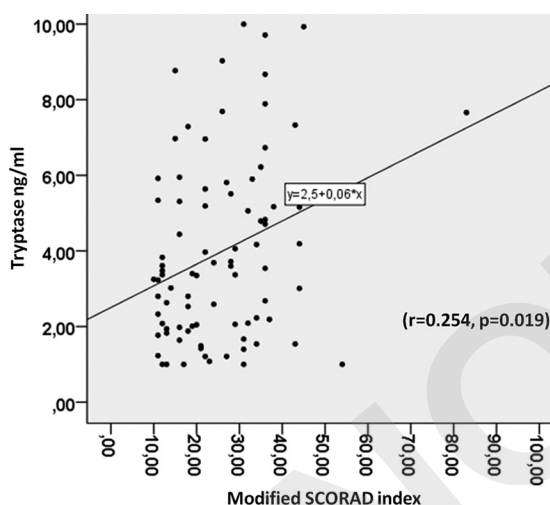


Figure 2. Correlation of serum basal tryptase with objective scoring atopic dermatitis (SCORAD) index.

divided into two groups according to the presence (AD+/atopy+ [$n = 55$]) or the absence of skin-prick test positivity (AD+/atopy− [$n = 30$]).

The median (interquartile range) sBT measurements in the AD+/atopy+, AD+/atopy−, and control groups were 5.01 ng/mL (2.75–6.79 ng/mL), 3.02 ng/mL (1.67–4.44 ng/mL), and 2.63 ng/mL (1.31–4.49 ng/mL), respectively ($p = 0.003$). The differences among AD+/atopy+ and the control group and AD+/atopy− remained significant after Bonferroni correction ($p = 0.001$ and $p = 0.005$, respectively) (Fig. 1). The median (interquartile range) sBT levels were higher in the patients with moderate-severe objective SCORAD index scores compared with those with mild disease (3.85 [2.04–5.91] versus 2.80 [1.83–3.48]; $p = 0.038$). There was a weak but statistically significant correlation between the sBT levels and the objective SCORAD index scores ($r = 0.254$, $p = 0.019$) (Fig. 2). Several other factors tested did not correlate with the sBT levels, including total serum IgE levels, eosinophil counts, and eosinophil percentages.

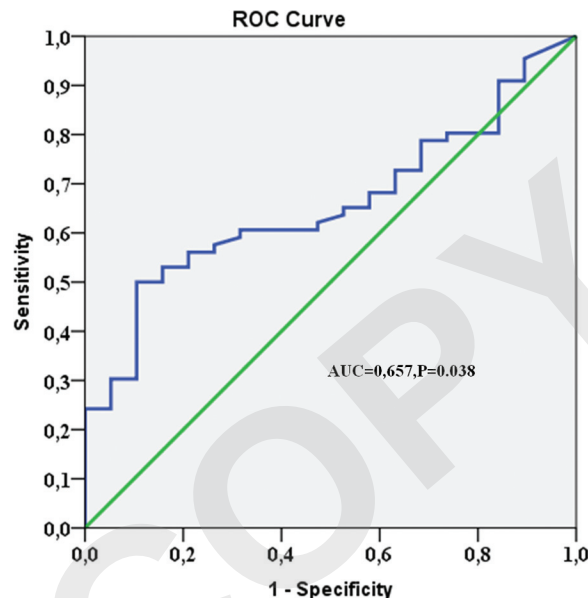


Figure 3. Receiver operating characteristic (ROC) curve predicting moderate-severe atopic dermatitis. AUC = Area under the curve.

A receiver operating characteristic curve analysis to differentiate between mild and moderate-severe AD indicated an sBT level of 3.9 ng/mL (area under the curve, 0.657 ng/mL; $p = 0.038$) (Fig. 3). To predict the risk factors for moderate-severe AD, multivariate logistic regression analysis was performed. Familial atopy, IgE levels, eosinophil percentages, atopic sensitization, and a tryptase value of ≥ 3.9 ng/mL were included in the analysis. An sBT level of ≥ 3.9 ng/mL (odds ratio 8.77 [95% confidence interval, 1.87–41.18]; $p = 0.006$) was associated with an increased risk of moderate-severe AD (objective SCORAD index) (Table 2).

In two children in the control group, the sBT levels were higher than normal (11.50 ng/mL and 14.10 ng/mL). They were evaluated in detail by an experienced pediatric hematologist for the presence of dermatologic mastocytosis and clonal mast cell disorders (physical examination, abdominal ultrasonography, and peripheral blood smears). In addition, an evaluation for other confounding factors (serum rheumatoid factor and serum IgA levels) was performed. There were no risk factors or signs of mastocytosis for these children who presently remain under observation for the development of any disease. Moreover, clinical conditions that can present with elevated tryptase levels, including end stage renal disease, chronic myelogenous leukemia, and familial tryptasemia, were also excluded in these children.

DISCUSSION

Our study demonstrated that sBT levels were higher in children with AD than in the healthy controls. In

Table 2 Logistic regression analysis for the risk of moderate-severe atopic dermatitis

	Univariate		Multivariate	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Familial atopy	2.838 (0.849–9.491)	0.090		
IgE levels	1.002 (0.998–1.007)	0.324		
Eosinophils percentage	1.117 (0.932–1.339)	0.230		
Atopic sensitization	1.238 (0.416–3.681)	0.701		
Tryptase value of 3.9 ng/mL	8.500 (1.818–39.751)	0.007	8.774 (1.869–41.182)	0.006

OR = Odds ratio; CI = confidence interval; IgE = immunoglobulin E.

addition, high levels were more prominent in the children with atopy than in the patients without atopy. The sBT levels may differentiate patients with moderate-severe AD from mild cases and correlated significantly with objective SCORAD index. In addition, a cutoff value of sBT level of 3.9 ng/mL was found to be a risk factor for moderate-severe AD in logistic regression analysis. To our knowledge, this was the first study that indicated that sBT may be used as a marker for disease severity and that it was associated with atopic sensitization in children with AD.

Mast cells have long been acknowledged as the primary effector cells of allergy.¹⁵ Previous studies revealed increased numbers of mast cells in lesional skin in AD.⁵ Therefore, mast cells are widely considered to contribute to skin inflammation. Because it is highly specific for mast cells, measuring the tryptase level provides information regarding mast cell distribution, numbers, and activation status, and the sBT level in the absence of an allergic reaction is assumed to be an indicator of mast cell load.^{16,17} Nevertheless, studies concerning an association of sBT with AD exclusively in children are scarce. Hence, we investigated the association between sBT levels and AD in children in the current study and observed that children with AD had significantly higher sBT levels than did the healthy controls. Our study supported the results of an adult study in which patients with AD had higher tryptase levels than those of healthy subjects.¹⁸

In contrast, in a pediatric study, serum eosinophil cationic protein, myeloperoxidase, and tryptase levels were measured in children with asthma and AD, and compared with healthy controls.¹⁹ Eosinophil cationic protein was found to be a good marker of ongoing asthma or AD.¹⁹ Myeloperoxidase levels were increased in children with mild asthma and without anti-inflammatory treatment but were found to be normal in children with AD.¹⁹ However, tryptase levels were not detectable in children with asthma, children with AD, or healthy controls.¹⁹ Different from our study, the sample size of the study was small, which included 14 children with mild-moderate AD, excluding severe cases, allergic sensitization of the children was not

documented, the median age of the patients was higher than our patients, and the tryptase levels were measured with a different technique.¹⁹ Of note, the investigators explained these nondetectable levels by rapid turnover of the tryptase in circulation and insufficiently sensitive assays would be a reason.¹⁹

In recent years, many molecules have been investigated to assess the activity of AD. Current evidence indicates that some biomarkers, including cytokines, chemokines, adhesion molecules, and growth factors, may be useful for determining the severity of the disease but none of these markers have been proven to be successful.^{20–23} A meta-analysis investigated the correlation between the severity of AD and various biomarkers that were published in the past decade.²⁴ The total IgE value was the most commonly studied marker but was not found to be appropriate for follow-up of disease severity. Among the 30 biomarkers in the meta-analysis, the serum thymus and activation-regulated chemokine levels were found to correlate significantly with disease severity in AD.²⁴ In line with these findings, we did not find a correlation between disease severity and total IgE value. In addition, eosinophil numbers were not associated with disease severity. As a contribution, we observed that tryptase might also be used as a marker for activity of AD by virtue of discriminating patients with moderate-severe disease from mild cases. Furthermore, we established a predictive cutoff value for the development of moderate-severe AD. This cutoff value was also found to be a risk factor for moderate-severe AD in logistic regression analysis and would be useful in a daily clinical setting to determine children at high risk.

So far, serum tryptase levels in terms of atopy status have been investigated in only a few studies. In an adult study, the difference in sBT levels between patients with allergic rhinitis and healthy controls was not significant, and the investigators concluded that local mast cell activation was not necessarily reflected in the circulation.²⁵ Komarow *et al.*²⁶ compared sBT levels between children who were atopic and children who were not atopic, and reported no difference, similar to the adult study. In contrast, we observed signif-

icantly higher sBT levels in children with atopy compared with children who were not atopic. In agreement with our results, Belhocine *et al.*⁷ evaluated sBT levels in infants and observed that patients who were atopic had higher sBT levels than patients who were not atopic. Although the discrepancy in these studies may stem from differences in the study groups, it also points to the need for future studies in this direction.

Taken together, these limited number of studies revealed high sBT levels in patients who were atopic; however, they did not address the causal relationship. Type 2 inflammation is predominant in AD pathogenesis, and we continue to gain insight into the underlying immunologic mechanisms through new ongoing studies. Recently, a relationship between mucosal mast cells and type 2 innate lymphoid cells, which are identified as one of the important key cells in allergic inflammation, was shown.²⁷ Given that mast cell activation may increase in patients who are atopic, we may have found high tryptase values as an indirect indicator of mast cell activation in these patients.

Determining disease severity in AD is of paramount importance with regard to making decisions on the treatment and the follow-up of patients. The SCORAD index is a validated instrument for assessing the clinical signs of AD, but it is time consuming and complicated for routine clinical use, and may be influenced by intra- and interobserver variation.²⁸ Therefore, tryptase may be used as an outcome measure to evaluate disease severity. With concern of this issue, Amon *et al.*²⁹ evaluated 117 hospitalized patients with AD at admission and at discharge but could not find a correlation between the SCORAD index scores and tryptase levels. The atopy status of the patients was not reported, and the age range was between 1 and 80 years in the study.²⁹

Another adult study assessed the correlation between serum tryptase level and disease severity at admission and at discharge in 71 patients with AD and 72 controls.³⁰ Serum levels of tryptase were not different between the patients with AD and the healthy controls, and the results showed no association of the SCORAD index score with tryptase levels.³⁰ In the present study, we did not measure tryptase levels before and after treatment, but this may be the subject of a further study, which we could also perform in this younger age group.^{29,30} However, unlike the above-mentioned two studies, we evaluated our patients by using an objective SCORAD index that excludes subjective parameters (pruritus, loss of sleep) and showed higher tryptase values in moderate-severe cases. In view of these findings, it seems that more research is needed to confirm whether tryptase would be a useful marker in evaluating the severity of AD.

Patients with AD frequently have pruritus as a characteristic feature of the disease. However, the patho-

genesis of pruritus in AD is complex and not adequately understood. Apart from histamine, other mediators from inflammatory effector cells are also involved in pruritic mechanisms.³¹ Recently, tryptase has been shown to induce itch *via* activating protease activated receptor 2 in mice with AD-like dermatitis.³² In this context, it seemed reasonable to speculate that new drug molecules that target the blockade of tryptase may provide improvement in symptoms and disease severity, particularly in patients with high sBT levels and with AD. As a possible limitation, our study group was composed of patients who were admitted to a tertiary care hospital and may not reflect the general population. However, it included children with AD, along with a control group, and the heterogeneity of the patients provided us the opportunity to make comparisons according to the degree of severity and atopic condition. Moreover, the association between sBT and disease severity and a cutoff value for sBT were determined for the first time in AD in this age group.

CONCLUSION

The sBT value may be a predictor of moderate-severe AD and a cutoff of 3.9 ng/mL may be useful in identifying patients at high risk in clinical practice. Importantly, this is the first study that evaluated the association of sBT with disease severity and atopic sensitization in children <3 years of age with AD. However, our results need to be confirmed in future research with different cultures and age groups to better clarify the role of tryptase in AD.

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