

Plasma Granzyme B as a Potential Biomarker of Pruritus Severity in Atopic Dermatitis

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ARTICLE INFO

Received: 24 September 2026
Accepted: 27 September 2026
Published Online: 2 October 2026

DOI: 10.5281/zenodo.23105382

Volume: 10, Number: 2, Page: 645-648

e-ISSN: 2789-5912
ISSN: 2617-0817

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ABSTRACT

Background: Atopic dermatitis (AD) is a chronic inflammatory skin disorder, which is marked by recurrent pruritus and epidermal barrier dysfunction. Granzyme B has been involved in inflammatory and tissue-remodeling and could be related to the severity of pruritus in AD. In this study the relationship between pruritus severity and plasma Granzyme B was assessed in AD patients. **Methods & Materials:** A group of 48 subjects was used, including 24 patients with AD and 24 seemingly healthy controls. Diagnosis of AD was made based on the Hanifin and Rajka criteria. The Scoring Atopic Dermatitis (SCORAD) index was used to measure the severity of disease, whereas a visual analogue scale (VAS) was used to measure pruritus severity. The concentration of Plasma Granzyme B was determined using enzyme-linked immunosorbent assay (ELISA). Granzyme B, VAS, and SCORAD scores were correlated with each other. **Results:** Plasma Granzyme B was moderately positively correlated with VAS score ($r = +0.545$) and significant ($p = 0.006$) showing that the higher the Granzyme B levels in plasma, the higher the levels of pruritus. Conversely, the positive relationship between plasma Granzyme B and SCORAD had no statistical significance ($r = +0.398$, $p = 0.054$). There was no significant relationship between age, sex, food allergy or prior personal history of atopy and granzyme B concentrations. **Conclusion:** Plasma Granzyme B had a significant relationship with patient-reported pruritus severity AD but not with overall severity of the clinical disease. This evidence indicates that Granzyme B could be a promising biomarker with regards to itch burden in AD. More longitudinal studies are recommended to confirm this association.

Keywords: Atopic dermatitis; Granzyme B; Pruritus; VAS; SCORAD; Biomarker

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INTRODUCTION

Atopic dermatitis (AD) or atopic eczema is a permanent, flaring skin condition, inflammatory, marked by impaired epidermal barrier functions, immune-mediated and recurrent pruritus. It usually starts in the childhood stage but the disease can be carried up to adolescence and adulthood. Persistent itching, sleep disturbance, discomfort, and frequent skin lesions pose a significant burden to the patients and their families since these conditions may negatively impact activities and the quality of life on a daily basis. Atopic dermatitis is a significant dermatological issue among children in Bangladesh and a high prevalence has been reported among the children (Pedersen CJ)^[1]. Clinical presentation and severity of AD is heterogeneous and thus should be assessed taking into consideration both objective disease activity and patient-reported symptoms. One of the most typical and problematic symptoms of AD is pruritus, which is directly connected with the disease burden. Constant itching encourages a recurrent scratching, which may produce an

additional cutaneous inflammation since it can further disturb the epidermal barrier. The evaluation of pruritus is hence a significant element of assessing the patients with AD. Scoring Atopic Dermatitis (SCORAD) index represents a widely used tool to evaluate the severity of the overall clinical picture, including objective skin examination, and subjective symptoms. Conversely, the visual analogue scale (VAS) is a relatively easy patient-reported scale of perceived intensity of itch, and it has been employed to assess pruritus in dermatological conditions (Reich A)^[2]. Since the severity of objective disease and the intensity of subjective itch might not necessarily be close, biomarkers inherently linked to pruritus could be useful to provide extra data on the symptom burden. The etiology of AD is multi-factorial and constitutes the combination of affected epidermal barrier, immune homeostasis, environmental and skin microbiome changes. Breaches of barrier associated proteins such as filaggrin, in combination with T-helper-cell-mediated inflammatory signaling, are facilitative in disease initiation and maintenance. The microbial

change and enhanced colonization by potentially pathogenic organisms can further enhance the inflammatory responses. Although much research has been conducted on the mechanism of AD, no individual laboratory biomarker is regularly used to determine disease activity or the severity of the symptoms (Wollenberg)^[3]. It has generated an interest in inflammatory mediators, and molecular markers that could indicate particular clinical appearances of the disease. Granzyme B is a serine protease that is known traditionally to mediate cytotoxic lymphocyte-mediated apoptosis. This is primarily contained in cytotoxic granules of natural killer cells and CD8-defensive T lymphocytes. Non-cytotoxic effects of extracellular Granzyme B, however, also mediate through the cleavage of extracellular matrix proteins, adhesion molecules and tissue integrity and inflammatory signalling components (Jung K)^[4]. These extracellular activities have further generated a growing interest in Granzyme B as a mediator of tissue injury and inflammatory events in addition to the

classical role of cytotoxicity of immune-cells.

The possible involvement of Granzyme B in AD is particularly important since one of the main characteristics of the disease is the disruption of the epidermal barrier. The change in the barrier-related proteins can also help to make tissue vulnerable and sustain inflammation. Past reports have shown that plasma levels of Granzyme B are higher in patients with AD than in healthy individuals (Kamata Y) [5]. It has also been experimentally postulated that extracellular Granzyme B could play a role in epidermal barrier pathophysiology by acting on structural proteins, such as filaggrin and other factors of the epithelial integrity [4]. Granzyme B has also been implicated in inflammatory and tissue-remodeling in a variety of inflammatory skin conditions (Hiebert PR, Gleave A) [6,7].

Notably, earlier studies have noted that there is a correlation between the plasma Granzyme B level and pruritus in persons with AD. Direct correlation between the levels of Granzyme B in the plasma and the VAS-measured pruritus, indicating that Granzyme B is perhaps correlated not with the occurrence of any dermatitis, but with the clinical burden of itching [5]. Nevertheless, correlation of Granzyme B plasma with various concentrations of the severity of pruritus is a field that needs to be assessed further, especially among children as well as in the Bangladeshi population.

Thus, the current research was planned to examine the relationship between the plasma Granzyme B level and the severity of pruritus in patients with AD. The research narrowly assessed the relationship between the plasma Granzyme B and VAS score as well as assessed concentrations of the Granzyme B in various pruritus categories of severity. The association between

Granzyme B and SCORAD was also evaluated to show whether it was associated with pruritus with equivalent relationship with overall severity of the clinical disease.

METHODS & MATERIALS

This was a cross-sectional comparative study conducted in the Department of Dermatology and Venereology, Bangladesh Medical University (BMU), Dhaka, Bangladesh. The study was conducted from May 2023 to March 2025. A total of 48 participants were enrolled, comprising 24 clinically diagnosed patients with atopic dermatitis (AD) and 24 apparently healthy individuals without AD who served as controls. Participants were recruited using consecutive sampling.

Inclusion Criteria

Patients with atopic dermatitis diagnosed according to the Hanifin and Rajka criteria, irrespective of age and sex, were included. Apparently healthy individuals without atopic dermatitis were recruited as controls.

Exclusion Criteria

Patients with inflammatory, autoimmune, metabolic, respiratory, or infectious diseases were excluded. Patients who had received topical treatment during the preceding one month were excluded. Patients who had received systemic immunosuppressive therapy or phototherapy within the previous three months were excluded.

Testing of Pruritus and Atopic Dermatitis.

The Scoring Atopic Dermatitis (SCORAD) index was used to measure clinical severity of AD. The SCORAD system takes into account the clinical manifestations of AD and gives a general measure of the severity of the disease. The degree of pruritus was measured on a visual analogue scale (VAS).

The level of pruritus was used to classify the participants based on the VAS score.

Plasma Granzyme B: Measurement.

Blood samples were taken of the study participants, and the plasma concentration of Granzyme B was determined by an enzyme-linked immunosorbent assay (ELISA). The concentration was measured in pg/ml.

Data Collection

A semi-structured questionnaire was used as a pre-designed data collection form to gather data on patients with atopic dermatitis and healthy controls. Demographic and other pertinent clinical data such as age, sex, residence, family and personal history of atopy, and food allergy were noted. Atopic dermatitis diagnosis was made based on Hanifin and Rajka. SCORAD and VAS were used to measure the severity of the disease and pruritus, respectively. Venous blood samples were taken and the levels of plasma Granzyme B were determined by ELISA.

Statistical Analysis

Correlation analysis was done to determine the relationship between plasma Granzyme B level and the VAS score. Comparison of the plasma Granzyme B levels were also made across various categories of VAS severity. The correlation between Granzyme B and SCORAD score was measured individually. A p-value of <0.05 was considered statistically significant.

RESULTS

Most patients with atopic dermatitis had a positive family history of atopy and a positive personal history of atopy, each occurring in 18 (75.0%) patients. A history of food allergy was reported in 15 (62.5%) patients, whereas 9 (37.5%) had no reported food allergy (Table I).

Table I
Distribution of Patients with Atopic Dermatitis According to Atopic Characteristics (n=24).

Clinical/Atopic characteristic	Frequency	Percentage (%)
Family history of atopy	18	75.0
No family history of atopy	6	25.0
Personal history of atopy	18	75.0
No personal history of atopy	6	25.0
History of food allergy	15	62.5
No history of food allergy	9	37.5

Plasma Granzyme B concentrations were broadly similar across the three age groups. The highest mean concentration was observed among children aged up to 2 years (47.5±26.2 pg/ml), followed by those aged >10 years (45.9±26.0 pg/ml) and 2–10 years (44.2±22.8 pg/ml). The difference was not statistically significant (p=0.959) (Table II).

Table II
Plasma Granzyme B Concentration According to Age Group in Patients with Atopic Dermatitis (n=24).

Age group	n	Plasma Granzyme B (pg/ml), Mean±SD	Median	Range (min–max)	p-value
Up to 2 years	6	47.5±26.2	41.5	22.9–93.2	0.959
2–10 years	14	44.2±22.8	44.1	17.1–93.1	
>10 years	4	45.9±26.0	44.1	29.1–84.3	

The mean plasma Granzyme B concentration was 46.8±28.3 pg/ml among male patients and 45.7±17.51 pg/ml among female patients. No statistically significant difference was observed between the two groups (p=0.932) (*Table III*).

Table III
Plasma Granzyme B Concentration According to Sex in Patients with Atopic Dermatitis (n=24).

Sex	n	Plasma Granzyme B (pg/ml), Mean±SD	Median	Range (min–max)	p-value
Male	15	46.8±28.3	38.3	17.1–93.2	0.932
Female	9	45.7±17.51	42.9	22.4–82.7	

The mean plasma Granzyme B concentration was identical in patients with and without a history of food allergy (45.3±21.8 vs 45.3±26.4 pg/ml). No statistically significant difference was observed (p=0.988) (*Table IV*).

Table IV
Plasma Granzyme B Concentration According to History of Food Allergy in Patients with Atopic Dermatitis (n=24).

Food allergy	n	Plasma Granzyme B (pg/ml), Mean±SD	Median	Range (min–max)	p-value
Present	15	45.3±21.8	46.5	17.1–93.2	0.988
Absent	9	45.3±26.4	30.8	22.4–93.1	

Patients with a personal history of atopy had a mean plasma Granzyme B concentration of 44.9±23.8 pg/ml, compared with 46.5±22.9 pg/ml among those without such a history. The difference was not statistically significant (p=0.871) (*Table V*).

Table V
Plasma Granzyme B Concentration According to Personal History of Atopy in Patients with Atopic Dermatitis (n=24).

Personal history of atopy	n	Plasma Granzyme B (pg/ml), Mean±SD	Median	Range (min–max)	p-value
Present	18	44.9±23.8	37.1	17.1–93.2	0.871
Absent	6	46.5±22.9	46.0	22.4–82.7	

Spearman correlation analysis demonstrated a moderate positive correlation between plasma Granzyme B concentration and VAS score (r=+0.545), and this association was statistically significant (p=0.006). Thus, higher plasma Granzyme B concentrations were associated with greater patient-reported pruritus severity (*Table VI*).

Table VI
Relationship between plasma Granzyme B concentration and pruritus severity assessed by VAS.

Variables	Correlation coefficient (r)	p-value
Plasma Granzyme B vs VAS score	+0.545	0.006

There was a moderate positive correlation between plasma Granzyme B concentration and SCORAD score (r=+0.398); however, the association did not reach statistical significance (p=0.054) (*Table VII*).

Table VII
Relationship between plasma Granzyme B concentration and overall AD severity assessed by SCORAD.

Variables	Correlation coefficient (r)	p-value
Plasma Granzyme B vs SCORAD score	+0.398	0.054

DISCUSSION

Pruritus is surely one of the clearest and most unpleasant symptoms of atopic dermatitis (AD), and its intensity can significantly influence sleep, day-to-day activities, psychological health and quality of life. Despite the fact that pruritus is a significant element of AD, subjective itch intensity may not always be well-related to the total values of the visible disease. The current paper particularly examined the correlation between the plasma Granzyme B and the severity of pruritus in AD patients. The most important result was that the

positive correlation between plasma Granzyme B and the severity of pruritus measured with the visual analogue scale (VAS) was significant, but the positive correlation between plasma Granzyme B and the severity of the overall clinical disease measured with the SCORAD was not significant. This observation brings up the hypothesis that circulating Granzyme B is more closely related to the pruritic aspect of AD as compared to global clinical disease activity. The number of the participants with an atopic background was significant. Sixty-

two percent of patients had a family history of atopy, 75.0% had a personal history of atopy and 62.5% had food allergy. The abundance of these features is consistent with multifactorial pathogenesis of AD, where genetic predisposition, immune system disorder, disruption of the epidermal barrier, and environmental influences interact to contribute to the development of the clinical phenotype [8]. The plasma Granzyme B levels were also fairly similar in the various age groups. The median of concentration was 47.5±26.2 pg/ml in patients who were aged up to 2

years, 44.2 ± 22.8 pg/ml in those aged 2-10 years, and 45.9 ± 26.0 pg/ml in patients who were aged more than 10 years. No statistically significant difference was found ($p=0.959$). These results suggest that age difference was not likely to be a significant factor affecting circulating Granzyme B levels in this group^[9]. The current findings do not indicate any significant age-specific difference in plasma Granzyme B, although AD can have varying clinical features at varying ages and the natural history of the disease might depend on the age of onset and the length of the disease^[8,10].

The same trend happened in regard to sex. The levels of Plasma Granzyme B did not differ between male and female patients, with a mean value of 46.8 ± 28.3 pg/ml and 45.7 ± 17.51 pg/ml in male and female, respectively, and the difference was not statistically significant ($p=0.932$). This observation implies that the apparent correlation between Granzyme B and pruritus could not be explained blatantly by sex-based differences in circulating Granzyme B^[11].

Food allergy did not also seem to affect plasma Granzyme B concentration. There was no significant difference between the mean concentration of 45.3 ± 21.8 pg/ml of the patients that were allergic to foods and those that were not ($p=0.988$). Similarly, the mean Granzyme B level in patients with a personal history of atopy (44.9 ± 23.8 pg/ml) was also similar to patients without a personal history of atopy (46.522 pg/ml) and this was not significant ($p=0.871$)^[12]. In spite of the role of allergic sensitization and barrier dysfunction in the pathogenesis of AD, circulating biomarkers do not always depend on all clinical or atopic traits of the individual^[4,13].

The most clinically important result of the current study was that the positive correlation was significant between the plasma Granzyme B and the VAS score. It had a correlation coefficient of $r=+0.545$ and a $p=0.006$ which portrays a moderate positive relationship. Therefore, patients with more intense pruritus were more likely to have an increased plasma Granzyme B level. This finding is in line with earlier studies among individuals with AD whereby plasma Granzyme B was linked with severity of pruritus^[14,15]. Kamata et al. also found Granzyme B and the itch severity measured by VAS positively correlated, which confirms that Granzyme B could be involved in biological mechanisms that underlie persistent pruritus in AD^[5].

The connection between Granzyme B and the general severity of AD was relatively less strong. Plasma Granzyme B had a moderate positive correlation with SCORAD ($r=+0.398$) although this was not a significant correlation ($p=0.054$). This finding is contrary to that of Kamata et al. who showed a statistically significant association between plasma Granzyme B and SCORAD in patients with AD^[5].

In general, the current results show that the plasma Granzyme B did not show significant age, sex, food allergy, or personal history of atopy, with significant positive correlation with patient-reported severity of pruritus. The results thus justify the need to study more on plasma Granzyme B as a potential biomarker with respect to itch burden in AD.

CONCLUSION

Granzyme B plasma showed a strong positive correlation with the severity of pruritus in atopic dermatitis patients, indicated by a VAS. Conversely, there was a positive, though not statistically significant relationship with overall clinical disease severity based on SCORAD. There were no significant relationships between plasma Granzyme B levels and age, sex, food allergy, or personal history of atopy. The results of these findings are that circulating Granzyme B may be more significantly linked to subjective burden of pruritus than with overall disease severity. More extensive and longitudinal research is needed to confirm its possible use as a biomarker of the severity of pruritus in atopic dermatitis.

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