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Original Article

Serological Evaluation of The Role of Heparinase in Psoriatic Patients

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Abstract

Background: Psoriasis is a chronic inflammatory skin disorder with a complex pathogenesis. While the roles of immune cells and inflammatory mediators have been extensively studied, the involvement of extracellular matrix components, especially heparan sulfate and its degrading enzyme heparinase, has not been fully investigated. Given the enzyme's known functions in other autoimmune conditions, its potential role in psoriasis needs more investigation. This work aimed to assess the serum level of heparinase among psoriasis patients and its relationship with disease severity and activity.

Methods: We carried out a case-control study involving 20 patients with plaque psoriasis and 20 healthy controls at the Dermatology Outpatient Clinic, Zagazig University. Patients underwent clinical assessments, including the Psoriasis Area and Severity Index (PASI), and serum heparinase levels were measured using an enzyme-linked immunosorbent assay (ELISA).

Results: Psoriatic patients had significantly higher heparinase levels than the controls (P<0.001). Heparinase levels had a strong positive correlation with PASI scores (r=0.86, P<0.001). Stratified analysis revealed significantly elevated heparinase levels across severity groups (P<0.001).

Conclusions: Heparinase is markedly upregulated in psoriasis and strongly correlates with disease severity. It could be a promising biomarker for diagnosing and monitoring disease activity. Further studies with larger populations are needed to validate these findings and explore their potential as a therapeutic target.

Key words: Heparinase; Biomarker; Psoriasis; Severity; Activity

.INTRODUCTION

Psoriasis is a prevalent, chronic inflammatory skin disorder with a complex and incompletely understood pathogenesis. Clinically, it presents with sharply defined erythematous plaques, while histologically, it is marked by hyperproliferation of the epidermis, neovascularization within the dermis, and a dense infiltration of immune cells [1,2].

Among the dominant cell types within psoriatic lesions are T lymphocytes, innate immune cells like the macrophages, and dendritic cells [3–5]. The interaction between these immune components and epidermal keratinocytes plays a central role in disease progression, primarily through the sustained production of pro-inflammatory cytokines, chemokines, and growth factors. These molecules stimulate keratinocytes to express major histocompatibility complex class II (MHC II), adhesion molecules, and angiogenic mediators, creating a cycle of persistent inflammation and pathological remodeling [2,5].

Recently, research has been advanced for characterization of the molecular drivers of psoriasis, specifically as regards to the pro-inflammatory cytokines like interleukin (IL)-12, IL-17, and IL-23, tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), as well as their associated signaling pathways involving nuclear factor-kappa B (NF-κB) and signal transducer and activator of transcription (STAT) proteins [5,6]. However, little is understood about the contribution of the extracellular matrix (ECM) and its enzymatic degradation in modulating the immuno-epithelial dialogue central to the disease.

Heparinase cleaves heparan sulfate (HS) for the first time in mammals and is the unique endoglycosidase among mammals. Heparinase is involved in the structure and functional regulation of the ECM and basement membranes [7,8]. The HS, a sulfated glycosaminoglycan generally expressed on cell surfaces and throughout the ECM, contributes to matrix stability and supports tissue architecture by mediating tight interactions between cells and their surrounding matrix [9,10].

Recent studies suggest that HS also modulates inflammatory responses by binding to a range of cytokines, chemokines (e.g., IL-2, IL-8, IL-10), growth factors (e.g., vascular endothelial growth factor [VEGF], fibroblast growth factor [FGF]), and adhesion molecules such as selectins. Disruption of HS integrity through enzymatic degradation by heparinase has been shown to trigger profound effects in various inflammatory processes, including enhanced leukocyte recruitment, ECM remodeling, and the release of bioactive molecules stored within the matrix [11,12].

Elevated heparinase expression has been observed in several autoimmune and inflammatory conditions, including the experimental models of delayed-type hypersensitivity, vascular injury, and colitis, as well as in human diseases like atherosclerosis, rheumatoid arthritis, and inflammatory bowel disease. Despite this evidence, the role of heparinase in the immunopathology of psoriasis remains to be clarified [13:15].

Given the parallels between psoriasis and other autoimmune disorders in which heparinase is implicated, this work aimed to assess the serum level of heparinase among psoriasis patients and to assess its relationship with disease severity and activity.

METHODS

Participants

A total of 40 individuals participated in this case-control study over one year, from January 2024 to January 2025, including 20 patients diagnosed with plaque psoriasis (as the case group) and 20 healthy control subjects with matched age and sex. Patients were eligible if they were 18 years or older and had a confirmed diagnosis of plaque psoriasis. To reduce the risk of treatment-related confounding, patients were excluded if they had received systemic therapy (including oral, injectable, or phototherapy) for psoriasis within the preceding two months or topical treatment within the preceding two weeks. Additional exclusion criteria included pregnancy or lactation, and concurrent use of anti-inflammatory, immunosuppressive, or

immunomodulatory medications.
Following approval from the institutional review board (ZU-IRB#166/3-March-2024), all participants provided written informed consent before enrollment. The study adhered to the ethical principles outlined in the Declaration of Helsinki, which is part of the World Medical Association's guidelines for human subject research.
All enrolled participants underwent a structured clinical evaluation starting with a comprehensive medical history, which included personal demographic data (name, age, sex, occupation, and place of residence), clinical details of the current dermatologic condition (onset, progression, duration, and treatment history), use of medications—particularly anticoagulants or immunosuppressants—as well as history of systemic illnesses, associated skin conditions, and relevant family history.
A general physical examination was conducted for all participants to identify any underlying systemic conditions. This was followed by a thorough dermatologic examination assessing the skin, scalp, and nails. Psoriasis severity in affected patients was evaluated using the Psoriasis Area and Severity Index (PASI). According to the European Medicines Agency (EMEA) classification, disease severity was classified as mild (PASI <10), moderate (PASI 10–20), or severe (PASI >20) [16].
As part of the clinical work-up, all patients and controls underwent routine laboratory investigations, involving complete blood count, liver function tests, renal function tests, prothrombin time, and activated partial thromboplastin time. Additionally, the serum level of heparinase enzyme was quantified in both groups using a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) method (Human Heparanase [HPA] ELISA Kit, No.: 201-12-1341; Sunredbio, Shanghai). The manufacturer specified the assay's detection range and sensitivity, ensuring accurate quantification of serum heparinase levels.
Statistical analysis
Data was analyzed using SPSS version 27. Frequency described categorical data, and chi-square tested their differences. Shapiro-Wilk checked data normality. Means (±SD) or medians (IQR) were characterized for quantitative variables based on distribution. We used independent t-tests to compare two groups when the data were normal. Correlations were assessed by Pearson (normal data) or Spearman tests (non-normal data)—one-way ANOVA tests differences among more than two groups, with Bonferroni post-hoc tests identifying specific group differences. Statistical significance was defined as $P<0.05$.

RESULTS

Non-statistically significant variations were found in gender distribution between the psoriasis group and controls, with females representing 65% of the case group and 50% of the controls ($P = 0.327$). Similarly, mean age did not differ significantly between the two groups ($P = 0.089$). Among patients with psoriasis, only about 1/3 of the patients exhibited a progressive disease course. As assessed by the PASI score, disease severity showed that about half of the patients had severe disease. The median PASI score was 17.85 (range: 4.6–36), and the median disease duration was 6 years (range: 1–30 years) **(Table 1)**.
Psoriatic patients had significantly higher heparinase levels than the controls ($P<0.001$) **(Table 2)**. Mean heparinase levels varied significantly across severity groups ($P < 0.001$). Post hoc analysis confirmed significant differences between all severity subgroups (mild vs. moderate, moderate vs. severe, and mild vs. severe; all $P < 0.001$) **(Table 3)**. Heparinase showed strong diagnostic utility in assessing psoriasis severity.

With 100% sensitivity and 80% specificity, achieving 91.7% diagnostic accuracy for moderate psoriasis and 100% sensitivity and 83.3% specificity, resulting in 90% accuracy for severe psoriasis **(Table 4)**.

A strong positive correlation was observed between heparinase levels and PASI scores (r = 0.86; $P < 0.001$) **(Fig.1)**. However, no statistically significant relationship was revealed between heparinase levels and other variables (age, gender, disease course, and duration) **(Table 5).**

Table (1) Demographic & clinical characteristics of the studied group:

	Case group n=20 (%)	**Control group n=20 (%)**	χ^2	***P***
Gender **Female** **Male**	 13 (65%) 7 (35%)	 10 (50%) 10 (50%)	0.921	0.327
	Mean ± SD	**Mean ± SD**	**T**	***P***
Age (year)	49.3 ± 11.66	41.95 ± 14.79	1.745	0.089
Course **Progressive** **Stationary**	 7 (35%) 13 (65%)	 -		
Severity **Mild** **Moderate** **Severe**	 5 (25%) 7 (35%) 8 (40%)			
	Median (range)			
PASI	17.85(4.6 – 36)			
Disease duration (duration)	6(1 – 30)			

χ^2Chi square test t independent sample t test

Table (2) Heparinase enzyme levels in the studied groups:

Heparinase level (Pg/ml)	**Case group [n=20]**	**Control group [n=20]**	**T**	***P***
Mean ± SD	1396.8 ± 349.59	74.41 ± 26.18	16.844	<0.001*

t independent sample t test *P<0.05 is statistically significant

Table (3): Relation between heparinase enzyme levels and grade of psoriasis severity**:**

	Mild	**Moderate**	**Severe**	**F**	***P***
Heparinase level (Pg/ml) *Mean ± SD*	955.23 ± 43.97	1292.38 ± 132.14	1764.14 ± 106.04	94.718	<0.001*
Posthoc	P_1 <0.001*, P_2 <0.001*, P_3 <0.001*				

F One way ANOVA *P*1 difference between mild and moderate *P*2 difference between moderate and severe *P*3 difference between mild and severe *P<0.05 is statistically significant

Table (4) Performance of heparinase enzyme levels in diagnosis of psoriasis severity:

	Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy
Moderate	**≥995.96**	1	1000%	80%	87.5%	100%	91.7%
Severe	**≥1310.1**	1	100%	83.3%	80%	100%	90%

AUC area under curve PPV positive predictive value NPV negative predictive value

Table (5) Relation between heparinase levels and disease-specific data of the studied patients:

Variable	**Sex**		**t**	***P***
	female (*N*=13)	**male (*N*=7)**		
Heparinase (*Pg*/ml) *Mean ± SD*	**1335.7 ± 346.59**	**1510.27 ± 351.62**	**-1.069**	**0.299**
Variable	**Course**		**t**	***P***
	Progressive (N=7)	**Stationary (N=13)**		
Heparinase (*Pg*/ml) *Mean ± SD*	**1427.2 ± 349.54**	**1380.43 ± 362.74**	**0.278**	**0.784**
Variable	**r**	***P***		
Disease duration (year)	**0.324**	**0.164**		
PASI score	**0.86**	**<0.001****		

t independent sample t test r Pearson correlation coefficient

FIGURES

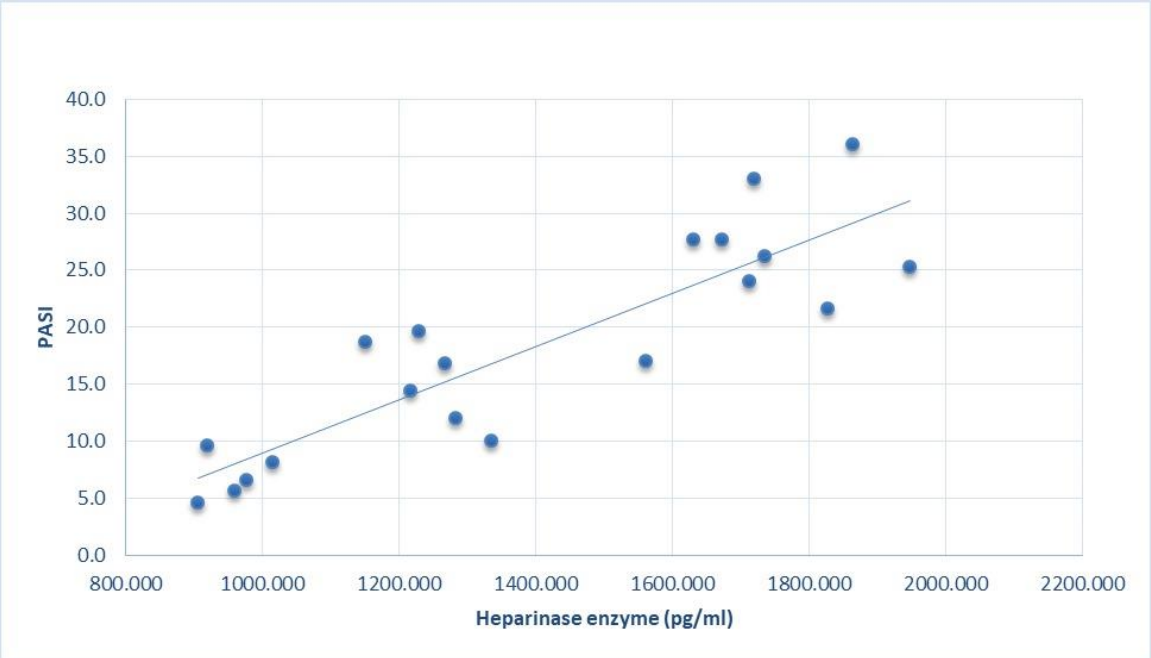

Fig.1: Scatter dot plot: showing significant statistical positive correlation between heparinase enzyme and PASI score.

DISCUSSION

Recent studies suggest that the enzyme *heparinase* may serve as a promising biomarker for assessing the severity and activity of psoriasis. Heparinase breaks down heparan sulfate in the ECM, a process that appears to be amplified in psoriatic skin, potentially contributing to inflammation and immune cell recruitment. Elevated levels of this enzyme have been linked to more extensive skin involvement and active disease states, highlighting its potential role in the disease mechanism and in monitoring disease progression and treatment response [17,18].

Furthermore, heparinase has been implicated in modulating immune responses within psoriatic lesions. It promotes the activation of macrophages and enhances NF-κB signaling, leading to increased production of pro-inflammatory cytokines such as TNF-α. These cytokines further exacerbate the inflammatory milieu characteristic of psoriasis [19].

In the current research, non-significant variation was found between the two groups regarding gender. This aligns with several studies indicating that psoriasis affects both genders relatively equally. However, some research suggests variations in disease severity and treatment patterns between genders. A study reported that men tend to have more severe psoriasis and are more frequently prescribed systemic therapies compared to women. Conversely, certain studies have found a higher prevalence of psoriasis among women, particularly in specific subtypes such as psoriatic arthritis, where the female-to-male ratio varies between 1.2 and 2. These discrepancies may be attributed to hormonal influences, genetic predispositions, or environmental factors that differentially affect disease expression and progression in men and women [20,21].

Psoriasis can manifest at any age, but it commonly presents in two peak periods: between 20 and 30 years and 50 and 60 years. Our findings are consistent with this bimodal distribution, suggesting that while psoriasis can occur early in life, a substantial number of cases also emerge later, possibly influenced by age-related changes in immune function or cumulative environmental exposures [22,23].

Regarding disease course, 35% of our psoriasis patients exhibited a progressive disease course, while 65% had a stationary course. This distribution is comparable to findings from other studies. Research conducted in Egypt reported that 68% of psoriasis patients experienced a progressive course, and 32% had a stationary course [24]. Variations in disease progression among patients may be influenced by factors such as genetic predisposition, adherence to treatment, lifestyle factors, and the presence of comorbid conditions. These observations underscore the multifaceted nature of psoriasis that contributes to its epidemiology and clinical presentation.

Our study observed a significant elevation in serum heparinase levels among psoriasis patients compared to healthy controls. This finding aligns with research indicating increased expression of heparinase in psoriatic lesions. A study demonstrated a significant up-regulation of heparinase 1 and heparinase 2 at both protein and mRNA levels in psoriatic plaques compared to non-affected skin [19].

While our study is among the first to report on serum heparinase levels in psoriasis patients, it, in conjunction with existing literature on other biomarkers, underscores the complex interplay of inflammatory mediators in psoriasis and highlights the potential of heparinase as a novel biomarker for assessing disease severity [25].

According to the study conducted by Solak et al. [25], systemic inflammatory markers were assessed in psoriasis patients. They discovered that systemic

immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) were significantly raised in severe psoriasis cases (PASI >10) relative to mild/moderate disease states (PASI ≤10). These markers also correlated with PASI scores, indicating their potential utility in evaluating psoriasis severity.

The lack of significant difference in heparinase levels between progressive and stationary disease courses suggests that the clinical trajectory of psoriasis may not directly influence heparinase expression. This finding is consistent with the understanding that psoriasis progression is multifactorial. While heparinase plays a role in extracellular matrix remodeling and inflammation, its expression may not vary significantly with the disease course [18].

The research findings corroborate reports that point out similar prevalence rates in both genders for psoriasis; however, the severity of the disease and the body regions affected may differ. For instance, some studies have shown that men have psoriasis more severely than women, with higher PASI scores. However, the absence of a marked difference between the genders concerning heparinase levels in our study implies that heparinase is neither gender-dependent nor gender-dependent concerning psoriasis pathology [26].

In our study, the absence of a strong correlation between heparinase levels and age agrees with the view that psoriasis may occur at any age, with peak onset periods in young and late adulthood. Hence, the expression of heparinase does not seem to depend on age in psoriasis [26].

Serum heparinase levels correlated positively with PASI scores in our study ($P < 0.001$); that is, higher concentrations of heparinase mean higher severity of the disease, and this observation corroborates other studies detailing the role of heparinase in the pathogenesis of psoriasis. Zhu et al. [18] showed that heparinase was up-regulated in psoriatic lesions and that the enzyme contributed to the progression of the disease through interactions with the IL-17 signaling pathway. They showed that IL-17 promotes heparinase expression, resulting in enhanced differentiation of Th17 cells in a feedback loop that worsens inflammation. This indicates that heparinase in high amounts could have a role in directly influencing the severity of psoriatic lesions.

The strong correlation between heparinase levels, PASI scores, and disease severity in our findings supports the view that it could be considered a biomarker for the grading of psoriatic severity, further substantiating a direct link between rising levels of heparinase and escalating severity of psoriatic disease. Further possibilities exist for the research required to clarify the mechanism by which heparinase impacts psoriasis progression and evaluate it as a therapeutic target [18].

While earlier studies have pointed to enhanced expression of heparinase in psoriatic lesions and its role in the pathogenesis of the disease, ours is specifically focused on the quantitative measurement of heparinase concentration and its correlation with clinical severity measures of the disease, such as PASI.

This study offers a novel insight into the role of heparinase in psoriasis pathogenesis, highlighting its significant elevation in affected patients and its strong correlation with disease severity, independent of disease course, gender, and age, so that it can be used as a non-invasive biomarker for disease monitoring. A key strength lies in using well-matched control subjects and objective clinical metrics, such as the PASI score, to stratify disease severity. The study also utilized a reliable ELISA-based quantification method, which enhances the accuracy of heparinase measurement and supports the clinical relevance of the findings.

However, the study's limitations must be considered. The sample was relatively small, which can affect the extendability of results to wider populations. Due to the

nature of the cross-sectional design, it is impossible to evaluate causality or the variation in heparinase levels over time or with treatment. Larger studies with long-term follow-up will be required to validate these findings and consider the targeting of heparinase in psoriasis as a potential therapy.

Conflict of Interest or financial disclosure: No potential conflict of interest to be reported by the authors.

CONCLUSIONS

Heparinase is markedly regulated in psoriasis and strongly correlates with disease severity, so it could be a promising biomarker for diagnosing and monitoring disease activity. Further studies with larger populations are needed to validate these findings and explore their potential as a therapeutic target.

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Figure Legends

Fig.1: Scatter dot plot: showing significant statistical positive correlation between heparinase enzyme and PASI score.

Citation

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