

Detection of serum and tissue levels of interleukin 39 in psoriasis: a case control study

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Abstract

Introduction: Psoriasis is a chronic immune-mediated disorder with a genetic component that primarily affects the skin and has potential systemic involvement. Advances in understanding the interaction between the innate and adaptive immune systems have facilitated improved disease management.

Methods: This study included 25 patients with psoriasis and 20 healthy controls of both sexes. All participants underwent detailed medical history-taking and dermatological examination, including assessment of the body surface area and the Psoriasis Area and Severity Index (PASI). Blood samples (3 ml) were collected from all subjects, and 4 mm lesional skin punch biopsies were obtained from psoriatic patients and healthy controls.

Results: Serum and tissue levels of interleukin 39 (IL-39) were significantly elevated in psoriatic patients compared to healthy individuals. Patients with a positive family history of psoriasis showed higher serum IL-39 levels than those without such a history. In addition, psoriatic individuals with diabetes mellitus or hypertension had higher serum IL-39 levels than those without these comorbidities. A statistically significant correlation was found between disease severity and serum IL-39 concentration.

Conclusions: Elevated serum and tissue IL-39 levels in psoriatic patients suggest a potential role for IL-39 in the pathogenesis of psoriasis, highlighting its possible utility as a biomarker or therapeutic target.

Keywords: psoriasis, cytokines, autoimmune disease, IL-39, ELISA

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Introduction

Psoriasis is a chronic inflammatory skin disease characterized by the presence of scaly, well-demarcated papules and plaques that can appear anywhere on the body (1). Although topical treatments may suffice for mild or localized forms of psoriasis, systemic or biological therapies are often required for more severe or widespread cases. Over the past 2 decades, significant advances in understanding the immune-mediated pathophysiology of psoriasis have led to the development of targeted biological agents for systemic treatment (2).

Although the disease's complex pathogenesis is not yet fully understood, recent studies have highlighted the critical role of the interleukin (IL)-23/17 axis, resulting in the emergence of therapies specifically designed to inhibit this pathway (3). Individuals with psoriasis are also known to have a higher risk of major adverse cardiovascular events, a connection that has been recognized for some time (4). Like other chronic inflammatory disorders such as atherosclerosis, psoriasis is thought to be driven by systemic inflammatory mechanisms shared between the two conditions (5, 6).

IL-39 is a heterodimeric cytokine composed of the IL-23p19 and Epstein-Barr virus-induced gene 3 (EBI3) subunits, and it has been implicated in modulating immune responses, particularly through its effects on neutrophil activation and pro-inflammatory signaling (7, 8). However, its specific role in the pathogenesis of psoriasis remains unclear. Assessing both tissue and serum IL-39 levels in patients with psoriasis may offer insights into its potential contribution to disease mechanisms and its possible value as a biomarker for disease severity or therapeutic response (9). In

addition, elevated serum IL-39 levels have been associated with left ventricular systolic dysfunction in individuals with ST-segment elevation myocardial infarction, suggesting a broader role in systemic inflammation (10).

To assess IL-39 expression, several detection methods can be utilized, including enzyme-linked immunosorbent assay (ELISA) for measuring serum levels, and immunohistochemistry (IHC), quantitative PCR (qPCR), and Western blotting for tissue analysis (11, 12). Detecting changes in IL-39 levels may provide new insights into the inflammatory mechanisms underlying psoriasis and potentially reveal novel therapeutic targets (13, 14). This study investigates IL-39 variations in both blood and tissue samples from individuals with psoriasis and evaluates its association with disease severity.

Methods

A prospective case-control study that included a total of 45 subjects classified into two cohorts: patients with psoriasis ($n = 25$) and a healthy control group ($n = 20$) was conducted at the outpatient clinic of the Dermatology Department, Faculty of Medicine, Fayoum University, Fayoum, Egypt. Ethical approval was granted by the Ethics Committee of the Faculty of Medicine, Fayoum University (approval number M-399) on April 14th, 2019. Written informed consent was obtained from each participant prior to enrollment. The study was carried out over a 6-month period, from May 2019 to October 2019.

The study included patients of both sexes, between 20 and 70 years old, all diagnosed with plaque-type psoriasis. Individuals with erythrodermic, pustular, or palmoplantar forms of psoriasis,

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nail psoriasis, or psoriatic arthritis were excluded. In addition, patients that had received systemic treatment for psoriasis within the previous 4 weeks were also excluded.

The control cohort consisted of healthy volunteers of both sexes, with no personal or family history of psoriasis, and who were neither diabetic nor hypertensive.

Each participant underwent a series of evaluations. This began with detailed history taking, including the onset, course, and duration of the disease, as well as past, family, and general medical history. A thorough dermatological examination was then conducted, during which the distribution of lesions and severity were assessed using the body surface area method (15), and psoriasis severity was quantified using the Psoriasis Area and Severity Index (PASI) score (16).

For specimen collection, 3 ml of venous blood was drawn from each participant. In addition, a 4 mm lesional skin punch biopsy was obtained from psoriatic patients and matched sites in the controls.

Quantitation of human IL-39

IL-39 levels were measured using an ELISA kit (Bioassay Technology Laboratory, Shanghai, China; cat. no. E7444Hu). The assay is based on a sandwich ELISA principle, in which human IL-39 in the sample binds to antibodies pre-coated on the plate. A biotinylated detection antibody specific to IL-39 is then added, followed by the binding of streptavidin-horseradish peroxidase. After washing to remove unbound components, a substrate solution is added, inducing a color change proportional to the amount of IL-39 present. The reaction is halted with an acidic stop solution, and absorbance is measured at 450 nm.

Statistical analysis

Data were analyzed using SPSS version 17.0 (IBM, New York, USA). Descriptive statistics for qualitative data were expressed as numbers and percentages. For quantitative parametric data, results were expressed as means and standard deviations.

To compare two independent groups with parametric data, an independent Student's *t*-test was used. When comparing more than two independent groups, a one-way ANOVA was performed, followed by Bonferroni post-hoc analysis for significance at *p* < 0.05. For non-parametric quantitative data, comparisons among more than two groups were made using the Kruskal–Wallis test, and the Mann–Whitney *U* test was applied for pairwise comparisons.

To assess relationships between variables in qualitative data, the two-tailed bivariate Pearson correlation test was used. Diagnostic accuracy was evaluated using the receiver operating characteristic (ROC) curve, including sensitivity and specificity assessments. A *p*-value of less than 0.05 was considered statistically significant.

Results

Demographic data and sex distribution

Table 1 summarizes the demographic characteristics. There was no statistically significant difference in age between patients and controls. The mean age was 40.80 ± 12.03 years in the control group and 38.55 ± 11.25 years in the psoriasis group (*p* = 0.525). Patient ages ranged from 21 to 66 years, and control participant ages ranged from 22 to 56 years.

Psoriasis severity, assessed using the PASI score, ranged from 5.60 to 56.80 with a mean of 20.42 ± 11.53. Disease duration had a median of 96 months (range: 8 to 360 months). Based on severity, 18 patients (72%) were classified as moderate, four (16%) as severe, and three (12%) as mild.

Relation between IL-39 levels in serum and tissue between the cohorts

The IL-39 concentration levels were evaluated in both tissue and serum for patients with psoriasis and compared to healthy controls. The IL-39 level in serum was high in the patient cohort compared to the healthy control, with medians of 461.36 ng/l and 148.62 ng/l, respectively. The IL-39 level in tissue also tended to be elevated in the patient cohort compared to the controls, with a median of 353.46 ng/mg versus 176.61 ng/mg. There was a significant difference between both cohorts regarding IL-39 levels in tissue and serum, with *p*-values of 0.001 and 0.0001, respectively (Table 2).

Relation between IL-39 concentration level in serum and various characteristics in the psoriasis cohort

The IL-39 concentration level in serum was evaluated among patients with psoriasis and compared accordingly with the descriptive and clinical data of the patients. The results revealed that there was a significant difference between IL-39 and sex, whereby female patients had higher IL-39 levels than males, with a median of 611.32 ng/l and 187.05 ng/l, respectively, with a *p*-value of 0.05.

There was also a significant difference between IL-39 and family history, at *p* = 0.05. The IL-39 level in serum was elevated in patients with a positive family history of psoriasis in comparison to patients with a negative family history, with medians of 611.34 ng/l and 187.04 ng/l, respectively.

No significance was found for other parameters, including hypertension, diabetes mellitus, and the extent of the disease, at *p* > 0.05 (Table 3).

Relation between IL-39 concentration level in patients' serum and disease severity

After evaluating the IL-39 concentration level in serum in relation to disease severity based on the PASI score, the results showed that patients classified as mild had a median IL-39 concentration

Table 1 | Demographic data of patients.

Parameters	Psoriasis (n = 25)	Control (n = 20)	<i>p</i> -value
Age (years), mean ± SD	40.80 ± 12.03	38.55 ± 11.25	0.525 ^a
Sex, n (%)	Female	6 (30)	0.497 ^b
	Male	14 (70)	
Family history, n (%)	6 (24)	0 (0)	0.009*
Hypertension, n (%)	5 (20)	0 (0)	0.003*
Diabetes mellitus, n (%)	4 (16)	0 (0)	0.001*

^aOne-way ANOVA, ^bchi-squared test, *significant at *p* < 0.05. SD = standard deviation.

Table 2 | Interleukin-39 concentration levels in serum and tissue between patient and healthy control cohort.

Biomarkers	Psoriasis	Control	<i>p</i> -value
IL-39 serum (pg/ml)	461.36	148.62	0.0001*
	(56.64–2000.00)	(63.02–206.70)	
IL-39 tissue (pg/mg)	353.46	176.61	0.001*
	(191.41–741.62)	(122.45–232.54)	

Data are shown as median (range). A chi-squared test was used, and the Mann–Whitney *U* test for significance. *Significant at *p* < 0.05.

IL = interleukin.

Table 3 | Interleukin-39 concentration level in serum by patient cohort parameters.

Parameters	IL-39 (pg/ml) in serum	
	Psoriasis patients (n = 25)	p-value
Sex		
Female (n = 10)	611.32 (56.64–1528.50)	0.05*
Male (n = 15)	187.05 (105.09–2,000.00)	
Family history		
Negative (n = 19)	187.04 (56.64–2,000.00)	0.05*
Positive (n = 6)	611.34 (403.94–719.36)	
Hypertension		
Negative (n = 20)	286.10 (56.64–2,000.00)	0.080
Positive (n = 5)	611.34 (403.94–719.36)	
Diabetes mellitus		
Negative (n = 21)	385.17 (56.64–2,000.00)	0.114
Positive (n = 4)	665.35 (611.32–719.36)	
Extent		
< 20% (n = 8)	611.34 (56.64–1,528.50)	0.722
> 20% (n = 17)	403.94 (129.44–2,000.00)	

Data are shown as median (range). A chi-squared test was used, and the Mann-Whitney *U* test for significance. *Significant at $p < 0.05$. IL = interleukin.

level of 719.36 ng/l. In contrast, in moderate and severe patients the median IL-39 level tended to be lower, at 438.00 ng/l and 154.90 ng/l, respectively. There was a remarkable difference between the mild patients and moderate patients with regard to the IL-39 level, with a *p*-value of 0.020, as well as between severe and mild patients, with a *p*-value of 0.04.

Relation between IL-39 concentration level in tissue and various characteristics in the psoriasis cohort

The IL-39 concentration level was assessed, and the results showed that there was no significant relation between IL-39 level and other parameters, including sex, family history, hypertension, diabetes mellitus, or even the extent of the disease, at $p > 0.05$.

Relation between IL-39 concentration level in patients' tissue and disease severity

Based on the PASI score, the results showed that the IL-39 level tended to decrease with the severity of psoriasis. Patients diagnosed with mild psoriasis had an IL-39 concentration level of 379.43 ng/mg as the median. For patients with moderate and severe psoriasis, the median IL-39 levels were 366.66 ng/mg and 260.94 ng/mg, respectively. There was no significant variation between patient cohorts regarding the IL-39 level in tissue, at $p > 0.05$.

Correlation between serum and tissue IL-39 concentration levels and descriptive/clinical data

After assessing the bivariate correlation utilizing Pearson's *r* between the IL-39 serum biomarker and descriptive and clinical data among patients with psoriasis, the findings showed that there were no correlations between age ($r = 0.065$, $p = 0.758$), disease duration ($r = -0.043$, $p = 0.837$), extent of the disease ($r = -0.223$, $p = 0.284$), or PASI score ($r = -0.241$, $p = 0.245$) and the IL-39 concentration level in serum.

Regarding the IL-39 concentration level in tissue, the results showed that there was also no correlation between IL-39 and age ($r = 0.262$, $p = 0.206$), disease duration ($r = -0.178$, $p = 0.395$), ex-

tent of the disease ($r = -0.46$, $p = 0.29$), or PASI score ($r = -0.037$, $p = 0.862$).

Sensitivity and specificity of IL-39 biomarker in the patient cohort

Based on the calculation of IL-39 levels in serum and tissue samples from patients with psoriasis, the applied values of IL-39 were determined as indicators for psoriasis diagnosis. ROC curves were utilized for analysis. The results show that the area under the curve (AUC) and the cutoff value of IL-39 in serum were 0.84 and 403.94 pg/ml with specificity and sensitivity of 72% and 97.5%, respectively, at $p < 0.0001$. For the IL-39 level in tissue, AUC was 0.98 at the cutoff value of 294.43 pg/mg with sensitivity and specificity of 98.0% and 98.5%, respectively, at $p < 0.0001$.

Relation between serum and tissue IL-39 concentration levels in psoriasis

To measure the relationship between the IL-39 concentration level in both serum and tissue, a model was conducted for which IL-39 was the dependent variable. Based on linear regression analysis, the unstandardized coefficient was -0.423 with a standard error of 0.792. For the standardized coefficient, the beta value was -0.111 , *t*-value = -0.535 , and *p*-value = 0.036. Thus, IL-39 in serum is considered a dependent variable for psoriasis with IL-39 in tissue in the diagnosis of the disease.

Discussion

Psoriasis is characterized by an overactive immune system and uncontrolled keratinocyte proliferation, both central features of its pathophysiology. Immune dysregulation plays a key role in disease development. For moderate to severe cases, biological therapies targeting cytokines such as tumor necrosis factor (TNF)- α , IL-12/IL-23, IL-17, and IL-23/IL-39 have been approved. The cytokine-driven molecular mechanisms underlying psoriasis are closely linked to its clinical manifestations (17).

In this study, IL-39 concentration levels were assessed in both serum and tissue samples of psoriatic patients. The results showed significant elevation of IL-39 levels in both compared to healthy controls. Although age and sex distributions did not show statistically significant differences between the groups, the majority of patients were male.

IL-39 shares structural and functional features with other members of the IL-12 cytokine family, including IL-12, IL-23, IL-27, and IL-35. These cytokines commonly influence T-cell differentiation and immune cell activation. For example, IL-23 supports the differentiation and maintenance of Th17 cells, which are pivotal in autoimmune inflammation. Although IL-39's exact mechanism of action remains unclear, it may exert complementary or antagonistic effects within this cytokine network (18).

Some research suggests that IL-39 can induce proinflammatory cytokines such as IL-6 and IL-8, indicating potential interplay with inflammatory signaling pathways. However, one study evaluating IL-39's effect on human neutrophils reported that exposure to IL-39 did not significantly alter mRNA expression levels of IL-6 or IL-8. This finding suggests that IL-39 may not directly induce these cytokines in neutrophils, at least under the conditions studied (11).

Conversely, in murine models, IL-39 has been implicated in

promoting inflammatory responses. Research has shown that IL-39 can induce the differentiation and expansion of neutrophils, which are key players in inflammation. These neutrophils, in turn, can secrete various proinflammatory mediators, potentially including IL-6 and IL-8, although direct measurements of these cytokines in response to IL-39 were not reported in the study (19).

To the best of our knowledge, the IL-39 concentration level was not previously measured in psoriasis. However, IL-12, which shares structural and functional similarities with IL-39, was reported to be higher in the lesions of psoriatic patients than non-lesional control skin, showing a significant difference between lesions of psoriatic patients and healthy controls (20). A study of thirty patients and ten healthy controls concluded that IL-12 may play a vital role in the development of active psoriatic lesions (20).

Another study that examined the levels of IL-17A, IL-10, IL-23A, IL-17RA, and IL-23R expressions in the skin of sixty psoriatic patients showed that the levels of interleukins tended to be higher in lesions of psoriatic patients when compared to healthy controls, with a significant difference between both cohorts (21). Mouse models with psoriasis generally showed that cytokines (IL-23 and IL-12) that were released from inflammatory myeloid dendritic cells activate IL-17-producing T cells, Th1 cells, and Th22 cells, and it was concluded that these cytokines mediate impacts on keratinocytes to increase psoriatic inflammation (22).

The IL-12 family is important in the development and maintenance of autoimmune responses, and so IL-39 could be implicated in other skin autoimmune diseases, such as psoriasis. The proinflammatory effects of IL-39 have been previously identified, in which macrophages, dendritic cells, and B cells are the producing cells, and neutrophils are the immune cells responding. It is linked to systemic lupus erythematosus in lupus-prone mice (23).

Currently, no specific IL-39 inhibitors are approved for clinical use, and research on therapeutic targeting of IL-39 remains in the preclinical stage. However, the inhibition of IL-39, either directly or indirectly, could be a potential therapeutic strategy in inflammatory diseases, particularly if further studies confirm its role in promoting proinflammatory cytokines and neutrophil activation. Experimental models suggest that blocking IL-39 signaling could potentially reduce inflammatory responses, making it a promising candidate for future drug development (24, 25).

To date, there are limited specific data on the relationship between IL-39 and nail or joint involvement in psoriatic disease. Most studies have focused on cutaneous manifestations or systemic inflammatory responses. However, given that IL-39 may contribute to the recruitment and activation of neutrophils and other immune cells implicated in psoriatic arthritis and nail psoriasis, it is plausible that IL-39 also plays a role in these disease domains. Future studies focusing on IL-39 levels in patients with psoriatic nail disease or psoriatic arthritis are needed to clarify this potential association. Including assessments of IL-39 in these subtypes could expand the understanding of its broader relevance in the psoriatic disease spectrum (26, 27).

There is currently a lack of direct evidence on how methotrexate or narrowband ultraviolet B (NB-UVB) phototherapy specifically influence IL-39 levels. However, both treatments are known to downregulate systemic inflammation and reduce the expression of various proinflammatory cytokines such as IL-6, IL-17, and TNF- α . Given IL-39's presumed role in amplifying inflammation via neutrophilic activation and cytokine induction, it is plausible that effective anti-inflammatory therapies such as methotrexate and NB-UVB may also reduce IL-39 levels (28).

Contradicting our findings, the IL-39 level was measured in autoimmune thyroid disease in serum, and the results revealed that the IL-39 concentration level tended to be lower in patients than in healthy controls. Among patients with Hashimoto's thyroiditis and Graves' disease, the IL-39 level was slightly lower than in the control cohort, with a statistically significant difference between cohorts (29).

In this study, the PASI score was calculated for all patients, and the majority of the patient cohort was diagnosed as moderately psoriatic. There was a high statistically significant difference between disease severity in the serum IL-39 concentration level.

In agreement with our findings, several studies have demonstrated that serum IL-39 levels tend to rise with increasing severity of various inflammatory and autoimmune conditions, including neuromyelitis optica spectrum disorder (30), hepatitis / liver injury (31), type 2 diabetes mellitus (8), rheumatoid arthritis (32), and lupus (24).

IL-39 shares the p19 subunit with IL-23. In a study investigating IL-23A- and/or EBI3-containing cytokines in psoriatic patients, the authors observed that IL-23 was significantly upregulated in psoriatic skin lesions. They concluded that therapies targeting the IL-23Ap19 subunit, such as anti-IL-23Ap19 antibodies, are highly effective in managing psoriasis (33). Another study involving 39 psoriatic patients and 30 healthy controls found that elevated levels of IL-23, along with TNF- α , interferon (IFN)- γ , IL-6, IL-1 β , IL-18, and IL-17A, were associated with higher PASI scores (29).

This study found no significant differences in the IL-39 level in the tissue of psoriatic patients regarding disease severity. However, the IL-39 level tended to increase as the disease severity worsened. No statistically significant correlations were detected between serum or tissue IL-39 and PASI score, nor between IL-39 and the extent of the lesion in psoriatic patients or the duration of the disease. Studies on IL-39 are limited, and more research is needed to determine its levels in tissues of various skin conditions.

The small sample size of the participants and their heterogeneity regarding the severity of the disease are the major limitations of this study.

Conclusions

The detection of serum and tissue IL-39 levels in psoriasis provides valuable insights into its potential role in the disease's pathogenesis.

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