

Serum TSLP is a potential biomarker of psoriasis vulgaris activity

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Background: The proallergic cytokine, thymic stromal lymphopoietin (TSLP) may synergize with T cell–derived CD40 ligand (CD40L) to allow IL-23 production in patients with psoriasis. IL-23 is a central cytokine that mediates the inappropriate immune reaction in patients with psoriasis.

Objective: The aim of the study was to correlate serum level of TSLP with psoriasis severity.

Methods: The study was carried out on 53 patients with psoriasis. They were divided into mild, moderate, and severe according to PASI score. The patients' ages ranged from 10 to 62 years. The patients included 29 males and 24 females. A total of 53 healthy subjects with matched age and sex served as control group. Blood samples were collected from the venous blood of the patients and control subjects then the serum was separated. The serum samples were immediately frozen at -20°C. Serum TSLP was measured by Sandwich Enzyme-linked Immunosorbant Assay (ELISA).

Results: There was a statistically very highly significant increase ($p < 0.001$) in serum TSLP levels among the case group (1042.7 ± 812.93) compared to the control group (314.21 ± 220.78). There was also a statistically very highly significant increase ($p < 0.001$) in serum TSLP levels with increased psoriasis severity estimated by PASI score.

Conclusion: In this study, we found that serum TSLP is elevated in psoriasis patients and is correlated with disease severity.

Keywords: TSLP, psoriasis vulgaris, serum biomarker

Introduction

Psoriasis vulgaris is a common skin disorder characterized by focal formation of inflamed, raised plaques that constantly shed scales. The cellular changes in the skin include acanthosis, parakeratotic hyperkeratosis, and infiltration of T lymphocytes, neutrophils, and other types of leucocyte in affected skin.¹

Psoriasis vulgaris is caused by inappropriate activation of the immune cells.²

Thymic stromal lymphopoietin (TSLP) is an epithelial-derived cytokine similar to IL-7 and it exerts its biological function through the TSLP-Receptor (TSLP-R). TSLP is expressed primarily by epithelial cells at barrier surfaces such as the skin, gut and lung. TSLP is crucial for the maturation of antigen presenting cells and hematopoietic cells.³

TSLP synergizes with T cell–derived CD40 ligand (CD40L) to promote IL-23 production in patients with psoriasis. IL-23 a heterodimeric cytokine comprising IL-12p40 and IL-23p19, produced by monocytes, macrophages, neutrophils, and dendritic cells (DCs). Moreover, IL-23 induced IL-17– and IL-22–producing T cells, numbers of which have been shown to be increased in psoriatic lesions.⁴

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The clinical efficacy of the anti-IL-12p40 mAb against psoriasis and the association of a single nucleotide polymorphism in the IL-23 receptor gene in patients with psoriasis support the important pathogenic role of IL-23 in these patients.⁵

TSLP is produced by keratinocytes, and DCs (both dermal DCs and myeloid DCs) in patients with psoriasis and TSLP in turn primes for IL-23 production by DCs.⁶

In patients with psoriasis, TSLP could serve as a therapeutic target to reduce DC activation and production of pathogenic IL-23.⁷

In situ, TSLP was strongly expressed by keratinocytes of untreated psoriatic lesions but not in normal skin. Moreover, it was demonstrated that IL-4, an important Th2 cytokine seen in patients with atopic dermatitis (AD), inhibited IL-23 production induced by TSLP and CD40 ligand.⁸

TSLP is a novel player within the complex psoriasis cytokine network. Blocking TSLP in patients with psoriasis might contribute to decreasing DC activation and shutting down the production of IL-23.⁹

Patients and methods

Fifty-three psoriasis vulgaris patients were included in this case-control study. Along with 53 healthy subjects, a control group was selected randomly, matching age and sex as closely as possible. A written informed consent form approved by the institutional review board (IRB) was obtained from every participant over 18 years of age and from a legal guardian of any participant under the age of 18. The work was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion criteria included psoriasis vulgaris patients of any age and both sexes, untreated or no systemic treatment for at least 2 months, or no topical treatment for at least 2 weeks before taking blood sample.

Exclusion criteria included patients with other diseases in which serum TSLP is elevated as graft versus host disease (GVHD), AD, allergic rhinitis and rheumatoid arthritis. Patients with blood diseases and patients on anticoagulant therapy were also excluded.

All patients were subjected to complete history taking, general examination, and examination of psoriatic lesions using the PASI score. Patients were divided according to the severity of psoriasis into three subgroups (mild<10, moderate 10–20, severe>20).¹⁰

Three milliliters of venous blood samples were collected from patients and control subjects by vein puncture

under complete aseptic precautions. Blood was with drawn in to a serum separator tube (SST). The sample was allowed to clot for 30 minutes then the tube was centrifuged for 15 minutes at approximately 1000 rpm and the serum was stored at –20 °C until assay for TSLP.

Determination of serum TSLP was done using a double antibody sandwich enzyme linked immunosorbent assay (ELISA). The kit was provided from Sun Red company, catalogue number: 201-12-45.¹¹

Data were analyzed by Statistical Package of Social Science (SPSS) software version 24.0 (SPSS Inc., 2016). Continuous variables were presented as the mean \pm SD and median. Categorical variables were presented by count and percentage. Normality was checked using the Shapiro-Wilk test. Pearson and Spearman correlation analysis was used to evaluate the relationship between variables. A receiver operating characteristic (ROC) curve was used to determine the threshold value for optimal sensitivity and specificity of a test.

Results

The age of the studied case group ranged from 10 to 62 years, with a mean age of 37.38 years While that of the control group ranged from 17 to 58 years, with a mean age of 34.58 years. There were no statistically significant differences between them in age.

Regarding sex, 54.7% were male in the case group, and 49.1% in the control group, with no statistically significant difference in sex distribution.

It was found that the duration of psoriasis among the studied group ranged from 4 days to 22 years, with a mean of 6.47 years. The PASI score ranged from 4 to 38 with mean 14.44. Regarding family history, 26.4% had a positive family history. Also 73.6% of the studied group had itching and 5.7% had arthritis and 60.4% had moderate psoriasis.

According to the PASI scores in our patients, they were divided according to psoriasis severity, 22.6% had mild psoriasis, 60.4% had moderate psoriasis, and 17% had severe psoriasis.

There was a statistically very highly significant increase in serum TSLP levels among cases group compared to control group (mean 1042.7 in cases versus 314.21 in control group) (Table 1).

There was a statistically very highly significant correlation between PASI scores and serum TSLP levels among cases group (Table 2).

Table 1 Comparison of serum thymic stromal lymphopoietin (TSLP) levels in the two studied groups

Variable	Cases (n=53)	Control (n=53)	MW	P
TSLP (pg/ml):	1042.7±812.93	314.21±220.78	8.22	<0.001
Mean ± SD				
Median	810	240		***
Range	325–5192	4–670		

Note: ***Very highly significant ($P \leq 0.001$).

Abbreviations: n = number; SD = standard deviation; MW = Mann Whitney test.

Table 2 Correlation between serum TSLP levels and age, duration and PASI score of the patients group

Variable	TSLP (n=53)	
	r	P
Age (years)	0.18	0.21 NS
Duration (years)	0.10	0.47 NS
PASI score	0.86	<0.001**

Notes: r: Pearson's and Spearman's correlation. **Very highly significant ($P \leq 0.001$). NS = non-significant ($P > 0.05$).

Abbreviations: TSLP, thymic stromal lymphopoietin; PASI, Psoriasis Area and Severity Index.

There was a statistically significant increase in serum TSLP levels among smokers comparing to non-smokers. A statistically highly significant increase in serum TSLP levels was noted in cases having psoriatic arthritis, compared to cases without arthritis (Table 3).

In our study, the sensitivity of serum TSLP in a diagnosis of psoriasis at cut off 595 pg/ml was 88.7%, specificity was 83% and the accuracy was 85.8% (Figure 1).

In this work, the sensitivity of serum TSLP in the diagnosis of active Psoriasis (moderate and severe types by PASI scores) at cut off 755 pg/ml was 82.1%, specificity was 85.7% and the accuracy was 83% (Figure 2).

Discussion

TSLP is mainly produced by epithelial cells mainly in the lungs, skin, and gut, as well as DCs. TSLP signals via a TSLP receptor. The TSLP receptor is widely distributed on

many immune cells, including DCs, T cells, B cells, and mast cells.¹¹

Although TSLP was established as a major proallergic cytokine in AD, recently it has also been proved to contribute to human psoriasis pathogenesis.¹²

TSLP is mainly produced by KCs, while myeloid dendritic cells (mDCs) are the major TSLP-responsive cellular subset in both humans and mice. TSLP induces DC maturation and production of inflammatory cytokines specially IL-23, that may be synergistically enhanced by CD40L. Thus TSLP is becoming a novel player within the complex cytokine network, supporting the IL-23/IL-17 axis.¹³

According to our results, serum TSLP has been found to be higher in psoriatic patients compared to healthy control. There was a statistically significant increase ($p < 0.001$) in serum TSLP levels among the case group (1042.7±812.93) compared to the control group (314.21±220.78). There was also a

Table 3 Relationship between serum TSLP levels and associated arthritis among the patient groups

Variable	Without psoriatic arthritis (n=50)	With psoriatic arthritis (n=3)	MW	P
TSLP (pg/ml)	946.6±579.25	2644.7±2209.4		
Mean ± SD				
Median	805	1492	2.50	0.01
Range	325–4200	1250–5192		**

Note: **Highly significant ($P \leq 0.01$).

Abbreviations: n = number; SD = standard deviation; MW = Mann Whitney test; TSLP, thymic stromal lymphopoietin.

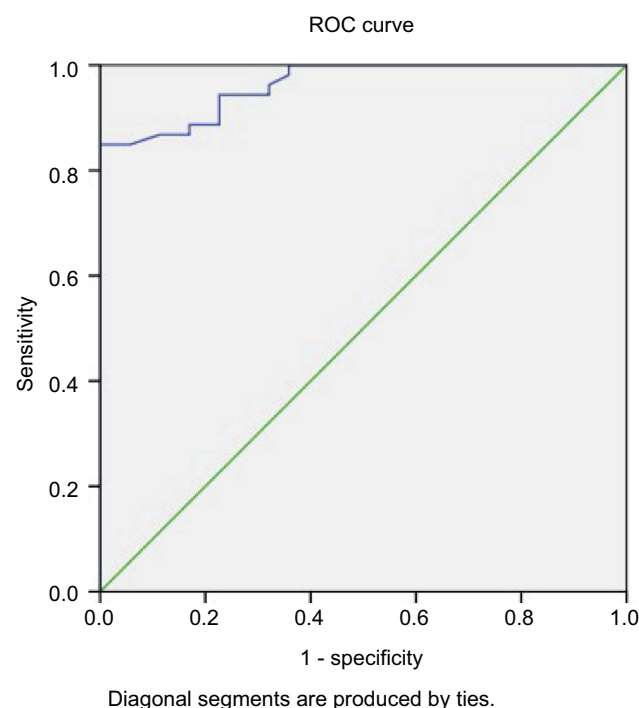


Figure 1 ROC curve of thymic stromal lymphopoietin (TSLP) validity in diagnosis of psoriasis.

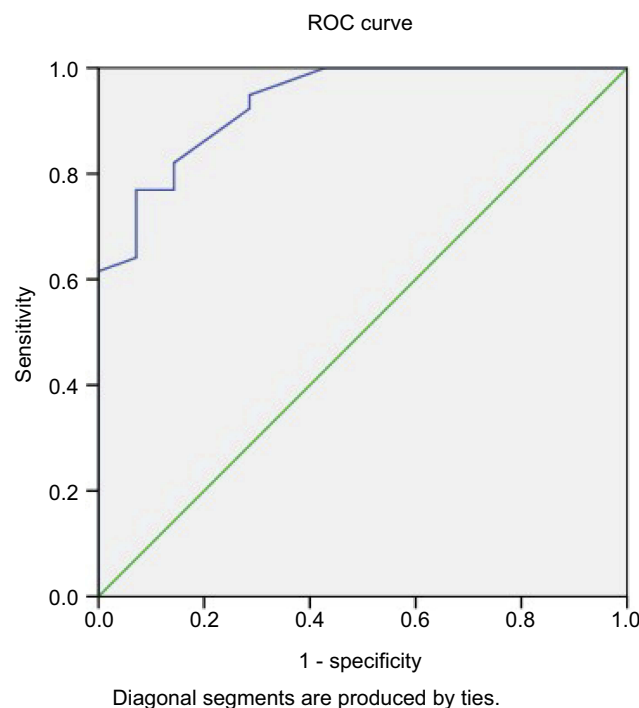


Figure 2 ROC curve of thymic stromal lymphopoietin (TSLP) validity in diagnosis of active psoriasis.

statistically significant increase in serum TSLP levels with increased psoriasis severity. This result was against previous research on serum TSLP which stated that TSLP is a marker of atopic march and not increased in psoriatic patients.

Our results were consistent with the findings of Tsilingiri et al, 2017 who proved that TSLP increased in psoriatic patients compared to normal individuals.¹⁴

Our study is considered the first study to measure the serum level of TSLP among psoriatic patients. In 2014 Volpe et al investigated TSLP level in 10 psoriatic patients by using tissue samples and found that TSLP expression was increased in psoriatic lesions compared to normal and non-lesional skin.

Based on Volpe et al's results we try to investigate TSLP in the serum of 53 patients not receiving treatment and assess the severity using PASI. Results showed that there was a statistically very highly significant increase in serum TSLP levels with increasing severity among case groups with very highly significant differences ($p < 0.001$), where it was the highest in severe cases (2115.4 ± 1541.9) and the lowest in mild cases (609.58 ± 184.84).

In our study, there was a statistically highly significant increase ($P = 0.01$) in serum TSLP levels in cases having psoriatic arthritis compared to cases where arthritis was not present. We recommend further studies on serum TSLP in psoriatic arthritis patients.

By the end of our work, we revealed that the sensitivity of the serum TSLP level in diagnosis of psoriasis at cut off was 595 pg/ml was 88.7%, specificity was 83%, and accuracy was 85.8%. Therefore, the estimation of the serum TSLP level, as a diagnostic indicator, can be used for early detection of psoriatic patients. We also found that the sensitivity of serum TSLP in diagnosis of active Psoriasis (moderate and severe types by PASI scores) at cut off 755 pg/ml was 82.1%, specificity was 85.7% and the accuracy was 83%.

Conclusions

1. In this study, serum TSLP is elevated in psoriasis patients and is correlated with disease severity.
2. Serum TSLP is elevated in patients associated with psoriatic arthritis. It may serve as a serum biomarker of psoriatic arthritis activity.
3. TSLP acts through CD40 L that leads to an increase in IL12/IL-23p40 with an increase in IL-23 and the predominance of Th17 cytokines as in psoriasis patients.
4. The long isoform of TSLP is biased to CD40 L with an increase in IL-23 and the development of psoriasis.
5. TSLP may be a novel target in treating psoriasis vulgaris patients.

Ethics

This study was approved by the Institutional Review Board of the Faculty of Medicine, Zagazig University on June 24, 2017 (approval number 3865).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Bowcock AM, Krueger JG. Getting under the skin: the immunogenetics of psoriasis. *Nat Rev Immunol*. 2005;5(9):699–711. doi:10.1038/nri1689
2. Johnson MA, Armstrong AW. Clinical and histologic diagnostic guidelines for psoriasis: a critical review. *Clin Rev Allergy Immunol*. 2013;44(2):166–172. doi:10.1007/s12016-012-8305-3
3. Soumelis V, Liu YJ. Human thymic stromal lymphopoietin: a novel epithelial cell-derived cytokine and a potential key player in the induction of allergic inflammation. *Springer Semin Immunopathol*. 2004;25(3–4):325–333. doi:10.1007/s00281-003-0152-0
4. Volpe E, Servant N, Zollinger R, et al. A critical function for transforming growth factor-beta, interleukin 23 and proinflammatory cytokines in driving and modulating human T(H)-17 responses. *Nat Immunol*. 2008;9:650–657. doi:10.1038/ni.1613
5. Zheng Y, Danilenko DM, Valdez P, et al. Interleukin-22, a T (H) 17 cytokine, mediates IL-23-induced dermal inflammation and acanthosis. *Nature*. 2007;445:648–651. doi:10.1038/nature05505
6. Sato-Deguchi E, Imafuku S, Chou B, et al. Topical vitamin D (3) analogues induce thymic stromal lymphopoietin and cathelicidin in psoriatic skin lesions. *Br J Dermatol*. 2012;167:77–84. doi:10.1111/j.1365-2133.2012.11130.x
7. Cargill M, Schrodi S, Chang M, et al. A large-scale genetic association study confirms IL12B and leads to the identification of IL23R as psoriasis-risk genes. *Am J Hum Genet*. 2007;80:273–290. doi:10.1086/511051
8. Eckhart L, Fisher H, Tschachler E. Mechanisms and emerging functions of DNA degradation in the epidermis. *Front Biosci*. 2012;17:2461–2575. doi:10.2741/4065
9. Mudigonda P, Mudigonda T, Feneran AN. Interleukin-23 and interleukin-17: importance in pathogenesis and therapy of psoriasis. *Dermatol Online J*. 2012;18(10):1.
10. Faria J, Aarao A, Jimenez L, et al. Inter-rater concordance study of the PASI (Psoriasis Area and Severity Index). *An Bras Dermatol*. 2010;85:625–629. doi:10.1590/s0365-05962010000500005
11. Taylor BC, Zaph C, Troy AE, et al. TSLP regulates intestinal immunity and inflammation in mouse models of helminth infection and colitis. *J Exp Med*. 2009;206:655–667. doi:10.1084/jem.20081499
12. Volpe E, Pattarini L, Martinez-cingolani C, et al. Thymic stromal lymphopoietin links keratinocytes and dendritic cell-derived IL-23 in patients with psoriasis. *J Allergy Clin Immunol*. 2014;134(2):373–381. doi:10.1016/j.jaci.2014.04.022
13. Zhou B, Comeau MR, Smedt TD, et al. Thymic stromal lymphopoietin as a key initiator of allergic airway inflammation in mice. *Nat Immunol*. 2005;6:1047–1053. doi:10.1038/ni1247
14. Tsilingiri K, Fornasa G, Rescigno M. Thymic stromal lymphopoietin: to cut a long story short. *Abstr Image CMGH Awards*. 2017;3(2):174–182.

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