Orginal Article

Evaluation of Serum Tumor Necrosis Factor-alpha-Induced Adipose-Associated Protein (TIARP/STEAP4) Level and Its Association with Disease Activity in Patients with Psoriasis: A Single-Center Prospective Comparative Study

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Abstract

Aim: Tumor necrosis factor-alpha (TNF-α)-induced adipose-associated protein (TIARP/STEAP4) is a protective metalloreductase against oxidative stress that is induced by various proinflammatory cytokines, including TNF-α and interleukin-17. This study aimed to evaluate whether STEAP4 is elevated in patients with psoriasis and whether it is associated with disease activity.

Materials and Methods: In this prospective cross-sectional single-center study, serum STEAP4 levels measured by the ELISA method in serum samples collected from psoriasis patients and healthy individuals. The association between STEAP4 levels and demographic characteristics and clinical findings in patients with psoriasis was further evaluated.

Results: Forty-one psoriasis patients with a female: male ratio of 1:1 and a median age of 44 years and 40 controls were included in the study. The median STEAP4 level of the patients with psoriasis (9.25) was significantly higher than that of the control group (1.04) ($P < 0.001$). Although STEAP4 levels did not differ significantly in patients with psoriasis regarding sex, joint, and nail involvement, no significant correlation was found with age, age at disease onset, disease duration, and severity.

Conclusion: The high levels of STEAP4 detected in patients with psoriasis might reflect its anti-inflammatory effects on Th-1 and Th-17 responses and on neutrophil and macrophage infiltration. On the other hand, a possible genetic variation or defect at the receptor level for STEAP4 in patients with psoriasis might hamper an adequate anti-inflammatory effect and lead to increased STEAP4 expression as a compensation mechanism. The present study not only indicates that STEAP4 might play a role in the pathogenesis of psoriasis but also suggests potential implications for its role in treatment and follow-up, which offers a promising direction for further investigation.

Keywords: Psoriasis, inflammation, TIARP, STEAP4

Introduction

Psoriasis is a chronic inflammatory disease caused by defective innate and adaptive cutaneous immune responses. The complex interplay between dendritic cells, macrophages, mast cells, neutrophils, and keratinocytes, along with T-cells, plays a role in the basic pathogenesis of the disease. Through various cytokines, such as tumor necrosis factor-alpha

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(TNF-α), these cells induce a chronic inflammatory state and alter epidermal hyperproliferation, differentiation, apoptosis, and neoangiogenesis, producing the cutaneous manifestations observed in psoriasis.[1,2]

TNF-α-induced adipose-associated protein (TIARP), also known as TNF-α induced protein 9 (TNFAIP-9) or STAMP2, belongs to a family of six transmembrane proteins called STAMP or STEAP4, expressed on macrophages, neutrophils, and synoviocytes.[3,4] Previous studies showed that TIARP was a separate but similar cofactor with TNF-α, induced by TNF-α during adipose tissue differentiation.[3-5] Additionally, proinflammatory cytokines such as interleukin-17 (IL-17), IL-6, and IL-1β, which are essential in the pathogenesis of psoriasis, were shown to induce TIARP.[2,5-10]

TIARP/STEAP4 levels were reported to be increased in both mice models of arthritis and patients with rheumatoid arthritis (RA), and their levels were correlated with the severity of arthritis. Furthermore, a significant decline in TIARP/STEAP4 mRNA expression was detected in splenocytes following TNF-α antagonist treatment. Thus, it was proposed as a biomarker that might be used for evaluating the effectiveness of TNF-α antagonists, which are also frequently used in the treatment of psoriasis.[3,6] Additionally, genetic variations in STEAP4 have been associated with numerous metabolic disorders, such as obesity and type 2 diabetes, which are among the comorbid conditions of RA and psoriasis.[7]

Psoriasis is an inflammatory disease similar to RA in terms of pathogenesis and treatment modalities, such as TNF-α antagonists. Moreover, psoriasis is also known to be associated with metabolic disorders.[1] Based on these findings, we hypothesized that plasma STEAP4 levels might be higher in patients with psoriasis than in individuals without a history of psoriasis. We also aimed to evaluate the relationship between STEAP4 and disease activity.

Materials and Methods

This prospective, cross-sectional, single-center study included 50 patients diagnosed with psoriasis who were followed up in the dermatology outpatient clinic of our tertiary referral center as the patient group and 50 age and gender-matched healthy individuals without psoriasis as the control group. Individuals under 18 years of age and those with any other chronic inflammatory conditions [obesity (individuals with a body mass index ≥ 30) and diabetes mellitus], autoimmune disorder, known malignancy, or active acute/chronic infection were excluded from the study. Moreover, in the patient group, generalized or localized pustular psoriasis patients weren't included in this study due to different pathogenic mechanisms. In addition, patients who had problems with serum samples due to laboratory and kit-related problems were also excluded from the study. Written and verbal consent was obtained from participants who agreed to participate voluntarily before starting the study.

The sociodemographic characteristics and medical history of the participants were recorded. Disease severity was measured using the psoriasis area severity index (PASI), age at disease onset, duration of disease, presence of joint and nail involvement, and current treatment methods were also noted.

Serum samples were collected from the venous blood of patients and control subjects. The samples were subjected to ELISA using a STEAP4 kit (BT LAB, Bioassay Technology Laboratory, Shanghai, China). The test results were statistically compared between the two groups. The STEAP4 levels of the patient group were further evaluated in terms of demographic features, clinical findings, and current treatments used for psoriasis.

This study was approved by Çanakkale Onsekiz Mart University Clinical Research Ethical Committee (approval number: 2021-08, date: 03.11.2021). The Çanakkale Onsekiz Mart University Scientific Research Projects Unit provided the financial source of the study (project number THD-2022-3941).

Statistical analysis

SPSS for Windows version 26.0 (SPSS Inc., Chicago, IL, USA) was used for statistical evaluation. Descriptive statistics were calculated as mean ± standard deviation and median (minimum-maximum) values for continuous variables and as frequency and percentage for categorical variables. The chi-square test was used to evaluate the difference in the distribution of categorical variables between the two independent groups. Shapiro-Wilk test was used to assess the normality of the variable distribution. The Student's t-test and Mann-Whitney U test were used to compare two normally and non-normally distributed groups, respectively. Welch ANOVA test was used to compare whether two or more parameters were significantly different. P value < 0.05 was considered statistically significant.

Results

According to the exclusion criteria, 41 psoriasis patients with a female: male ratio of 1:1 and a median age of 44 years, and 40 healthy individuals were included as the patient and control groups, respectively. Table 1 summarizes the sociodemographic characteristics of the patients and controls, while the clinical characteristics of the psoriasis patients are shown in Table 2.

The median STEAP4 level of patients with psoriasis (9.25) was significantly higher than that of the control group (1.04) ($p<0.001$) (Figure 1).

STEAP4 levels did not differ significantly in psoriasis patients regarding sex or between those with and without joint or nail involvement (Table 3). There was also no significant difference in STEAP4 levels between the patients according to the currently used treatment method (Table 4). The STEAP4 level of patients with psoriasis was not significantly correlated with any parameters, including age, age at disease onset, disease duration, and disease severity (PASI).

Discussion

The present study demonstrated significantly high levels of STEAP4 in psoriasis patients regardless of demographic features, clinical findings, and treatment agents used. This result, which is consistent with the induction of TIARP/STEAP4 through cytokines involved in the pathogenesis of psoriasis, underscores the role of STEAP4 in the increased inflammatory environment.

Inoue et al.[11] reported that TIARP suppressed IL-6 production, STAT-3, and nuclear factor kappa B signaling and caused increased apoptosis in macrophages, thereby demonstrating a robust protective role against arthritis. This finding instills confidence in the potential of TIARP as a therapeutic target. The authors also observed increased autoreactive T-helper-1 (Th-1) and Th-17 responses in TIARP-deficient (TIARP-/-) mice, along with significant neutrophil-macrophage infiltration in the joints and spontaneous synovitis and enthesitis.[11] Inoue et al.[12], in another study, demonstrated that TIARP independently downregulated IL-6 production and the expression of chemokine receptors (CXCR1 and CXCR2) on neutrophils, ultimately reducing neutrophil migration to arthritic joints.

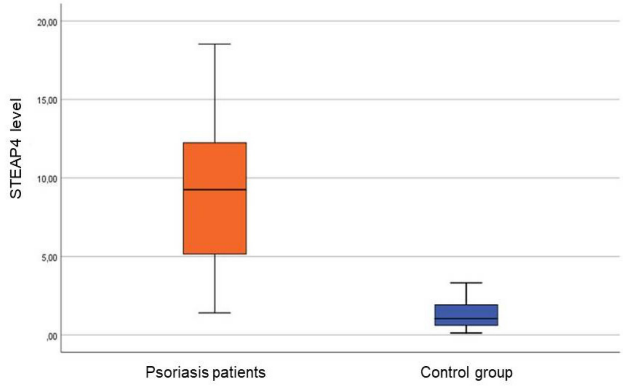

Figure 1. Comparison of STEAP4 levels among patient group (psoriasis patients) and control group

Several studies have shown that TIARP/STEAP4 protects cells against inflammation-induced oxidative stress. Thus, high levels of TIARP/STEAP4 might indicate increased inflammation and oxidative stress.[6-13] The present study revealed higher STEAP4 levels in patients with psoriasis, a disease characterized by inflammation, supporting the previous literature. This might be attributed to the increased inflammatory burden in the setting of psoriasis and suggests that STEAP4 levels might be elevated to suppress Th-1 and Th-17 responses, which play crucial roles in the pathogenesis of psoriasis, and to reduce neutrophil and macrophage infiltration. On the other hand, there might be a possible genetic variation or defect at the receptor level for STEAP4 in patients with psoriasis, preventing sufficient anti-inflammatory effects and causing increased STEAP4 expression due to a compensation mechanism.

Low-grade chronic inflammation is also present in obesity and type 2 diabetes, which are components of metabolic syndrome and might accompany both RA and psoriasis. However, interestingly, in patients with diabetes and obesity, unlike those with RA and psoriasis, TIARP levels were reported to decrease. Various inflammatory cytokines, hormones, and adipokine regulate TIARP expression. TIARP was reported to be a novel anti-obesity gene that was significantly downregulated in the adipose tissue of obese patients. Furthermore, overexpression of TIARP might improve glucose uptake and mitochondrial function by increasing insulin sensitivity.[10,11,14] In line with these findings, Wellen et al.[4] showed increased inflammation in the visceral adipose tissue of STAMP2 (TIARP) -/- mice and the development of spontaneous metabolic disease manifested by insulin resistance, glucose intolerance, mild

Table 1. Sociodemographic characteristics of patient group (psoriasis patients) and control group

	Psoriasis patients, (n=41)	Control group, (n=40)	p-value
Sex, n (%)			
Female	19 (46.3)	30 (75)	0.008[a]
Age, years, median (range)	44 (24-72)	24.5 (18-60)	0.001[b]
Smoking frequency, n (%)	20 (48.8)	18 (45.0)	0.733[a]
Alcohol intake, n (%)	7 (17.1)	14 (35.0)	0.066[a]

Alcohol intake: Individuals who consumed alcohol in the last 12 months. [a]Chi-square test, [b]Mann-Whitney U test

Table 2. Clinical characteristics of patients with psoriasis

Clinical characteristics of psoriasis patients (n=41)	
Psoriasis type, n (%)	
Plaque	35 (85.4)
Guttate	4 (9.8)
Palmoplantar	1 (2.4)
Inverse	1 (2.4)
Family history of psoriasis, n (%)	14 (34.1)
Age at disease onset, years, median (range)	25 (6-62)
Disease duration: years, median (range)	16 (1-53)
PASI, median (range)	3.4 (1-11.9)
Nail involvement, n (%)	24 (58.5)
Joint involvement, n (%)	8 (19.5)
Current treatment, n (%)	
Topical treatment only	12 (29.3)
Phototherapy (NB-UVB)	5 (12.2)
Acitretin	4 (9.8)
Methotrexate	4 (9.8)
Biological agent	16 (39.0)
Comorbidities, n (%)	
Hypertension	5 (12.2)
Psychiatric disorder	4 (9.8)

PASI: Psoriasis area severity index, NB-UVB: Narrow-band ultraviolet B

Table 3. Evaluation of STEAP4 levels in patients with psoriasis regarding sex, joint, and nail involvement

	STEAP4 levels, (mean ± SD)	p-value
Sex		
Female	8.6±5.2	0.392[a]
Male	9.9±4.5	
Joint involvement		
Yes	7.0±3.9	0.134[a]
No	9.8±4.9	
Nail involvement		
Yes	9.0±4.9	0.706[a]
No	9.6±4.8	

SD: Standard deviation, [a]Student's t-test

Table 4. Evaluation of STEAP4 levels in patients with psoriasis according to treatment method in the last 3 months

	STEAP4 levels Median (range)	p-value
Topical treatment*	11.01(1.46-17.85)	[a]0.157
Phototherapy (NB-UVB)	5.41 (1.40-7.37)	
Conventional agents**	9.92 (3.27-18.53)	
Biological treatment***	9.98 (3.66-18.23)	

*Corticosteroid, calcipotriol, **Methotrexate, acitretin, ***Adalimumab, ustekinumab, secukinumab, ixekizumab, guselkumab, risankizumab, NB-UVB: Narrow-band ultraviolet B, [a]Welch ANOVA test

hyperglycemia, dyslipidemia, and fatty liver. Gordon et al.[7] reported that TIARP expression was downregulated by chronic obesity and hyperglycemia. The authors speculated that obesity indirectly augments the destructive effect of inflammation by downregulating TIARP, which has a protective role against cellular stress.[7] These results might explain why obesity is a risk factor for the development of psoriasis.

It was reported that STAMP2 controlled macrophage inflammation through nicotinamide adenine dinucleotide phosphate homeostasis in atherosclerosis, another component of metabolic syndrome and comorbidity associated with psoriasis, and its deficiency accelerated atherosclerosis.[15] Moreover, STAMP2 was found to reduce cardiac dysfunction, insulin resistance, and atherosclerosis in diabetic cardiomyopathy.[16] The cardioprotective effect of metformin, an oxidative stress-reducing agent frequently used in patients with diabetes, was shown to be reduced in an environment in which STEAP4 was disabled.[17] In this context, TIARP/STEAP4 might play an important role in the relationship between psoriasis and metabolic syndrome. Therefore, STEAP4 levels should be measured during the follow-up of patients with psoriasis accompanied by metabolic syndrome.

TNF-α antagonists are the best-known and oldest biological agents for psoriasis patients. It is particularly preferred in patients with joint involvement and accompanying rheumatological disorders.[1,2] However, their contraindications and side effects might limit their use, and more reliable agents with similar effects are needed. Tanaka et al.[6] reported that STEAP4 was expressed on monocytes and neutrophils in the peripheral blood, regulated cell migration, and was downregulated by infliximab, a TNF-α antagonist, and thus may be a possible predictor of response to TNF-α antagonists. Priorly, Inoue et al.[3] also demonstrated a significant decrease in TIARP mRNA expression in splenocytes following TNF-α antagonist treatment. However, since only two patients were using TNF-α inhibitors, TNF-α inhibitors could not be evaluated separately in this study. Evaluation of STEAP4 levels before and after treatment in patients with psoriasis using TNF-α inhibitors may be the subject of a new study. If the demonstration of a decrease in STEAP4 levels following TNF-α antagonist treatment is supported, it may be considered that STEAP4 can be used as a predictor of TNF-α antagonist response in patients with psoriasis, similar to other studies.

TIARP/STEAP4 was investigated in only one study in the dermatological literature. Liang et al.[18] evaluated the levels of STEAP1 along with STEAP4 in generalized pustular psoriasis (GPP), palmoplantar pustulosis, and acute generalized exanthematous pustulosis, which are pustular diseases in which neutrophil chemotaxis is increased. The authors demonstrated increased expression of STEAP proteins (STEAP1 and

STEAP4) in lesion skin. They also reported that STEAP1 and STEAP4 were clustered and positively correlated with IL-1, IL-36, and CXCL1/8 around neutrophilic pustules.[18] Conversely, patients with localized or GPP were not included in our study.

Study Limitations

The main limitation of our study was the relatively small number of patients, which may have affected our results. More comprehensive studies could show that STEAP4 levels may vary depending on disease activity (PASI) and treatment methods. Another limitation was that the patient and control groups could not be matched in terms of age and gender because of the exclusion of individuals from the study due to laboratory-related problems. However, the fact that STEAP4 levels were not correlated with age and sex in our patient group might indicate that STEAP4 is a parameter that is not affected by age and sex. In addition, the currently used treatments for psoriasis might have affected the STEAP4 levels in this patient group. However, STEAP4 levels did not show a statistically significant difference between the patients using different treatment methods in our study. Despite the lowering effect of anti-inflammatory treatments on STEAP4 levels in previous studies, the high STEAP4 levels detected in our psoriasis patients who were actively undergoing these treatments show that our results are even more meaningful.

Conclusion

STEAP4 is a potential marker for the diagnosis, treatment, and follow-up of psoriasis in daily clinical practice. New treatment modalities for psoriasis are constantly being developed, and there is a trend toward targeted therapies. Our results should be supported by more comprehensive studies.

Ethics

Ethics Committee Approval: This study was approved by Çanakkale Onsekiz Mart University Clinical Research Ethical Committee (approval number: 2021-08, date: 03.11.2021).

Informed Consent: Written and verbal consent was obtained from participants who agreed to participate voluntarily before starting the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ö.K., Z.K., M.H.Ş., S.I.M., S.O.K., Concept: Ö.K., Z.K., M.H.Ş., S.I.M., S.O.K., Design: Ö.K., Z.K., M.H.Ş., S.I.M., Data Collection or Processing: Ö.K., M.H.Ş., S.I.M., S.O.K., Analysis or Interpretation: Ö.K., Z.K., M.H.Ş., S.O.K., Literature Search: Ö.K., Z.K., Writing: Ö.K., Z.K., M.H.Ş., S.I.M., S.O.K.

Conflict of Interest: The authors declared that they have no conflict of interest.

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