



Role of Tristetraprolin in Psoriasis: A Case Control Study

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2022/v34i2231602

Open Peer Review History:

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: <https://www.sdiarticle5.com/review-history/91842>

Original Research Article

Received 14 July 2022

Accepted 20 September 2022

Published 27 September 2022

ABSTRACT

Background: Tristetraprolin (TTP) is RNA-binding protein encoded by Zfp36 gene which regulates the mRNA stability of several important cytokines. Due to its critical role in control of inflammation, TTP deficiency leads to the spontaneous development of a complex inflammatory syndrome. So far, this phenotype has been largely attributed to dysregulated production of TNF and IL23 by myeloid cells, such as macrophages or DCs. The expression of TTP was studied in keratinocytes and explored its role in the imiquimod-induced psoriasis model.

Objective: To study the possible role of Tristetraprolin in the pathogenesis of psoriasis.

Methods: The study included 32 patients who were randomly assigned to two groups, group 1 included 22 patients with psoriasis and group 2 included 10 apparently healthy individual as a control group. Skin specimens were obtained by punch biopsy (3mm) from the skin lesion of the patients and normal skin of controls. Skin tissue from each case was homogenized in phosphate buffer saline (pH 7.4). The crude homogenate was centrifuged, and the resultant supernatant was removed and used for the measurement of Tristetraprolin level by ELISA.

Results: Regarding to Tristetraprolin (ng/m protein) level, there was a significant difference between cases and control group regarding skin tissue TTP level. TTP was significantly lower in psoriasis patient when compared to controls (P value < 0.001). As regard relation between the

level of TTP and the disease severity represented as PASI score; there was significant difference in TTP level between different grades (P value 0.001) with the lowest level in cases with severe psoriasis.

Conclusions: Tristetraprolin may play a role in pathogenesis of psoriasis and may provide important clues to assist in the development of new therapeutic strategies for psoriatic patients.

Keywords: Psoriasis; tristetraprolin; psoriasis; RNA-binding protein; ELISA.

1. INTRODUCTION

“Psoriasis is a chronic disease with a complex etiology that affects skin and joints in 1%–3% of the general population. It is characterized by inflamed and scaly skin lesions. It arises in genetically susceptible hosts in response to ill-defined environmental triggers” [1,2]. “Although psoriasis may be asymptomatic, up to 70% of patients complain that it is itchy or sore, particularly when their psoriasis is going through an active phase” [3].

“While psoriasis was previously considered as an autoimmune disease, the current pathogenic model emphasizes the central role of innate immune populations, including plasmacytoid and inflammatory myeloid dendritic cells (DCs)” [4,5]. “Dysregulated production of tumor necrosis factor (TNF), Interleukin 23 (IL), and other inflammatory cytokines was shown to promote IL-17 and IL-22 expression by multiple lymphoid subpopulations” [6].

“Tristetraprolin (TTP) regulates the mRNA stability of several important cytokines. Due to the critical role of this RNA-binding protein in the control of inflammation, TTP deficiency leads to the spontaneous development of a complex inflammatory syndrome” [7].

“Studies were done in mice with conditional deletion of TTP in keratinocytes. TTP-deficient mice spontaneously develop a complex TNF and IL-23 dependent inflammatory syndrome” [8].

2. PATIENTS AND METHODS

2.1 Patients

This study included 22 adult patients with psoriasis (Group 1) in addition to 10 healthy individuals of matched age and sex who served as a control group (Group 2). The duration of the study was from February 2020 to end of July 2020. The cases were collected from the Outpatient Clinic of Dermatology and Venereology Department, Tanta University

Hospitals. Patients with concurrent dermatological or other systemic diseases, immunosuppressive diseases, concomitant intake of immunosuppressive drugs, pregnancy, lactation were excluded from the study.

2.2 Methods

Skin specimens were obtained by punch biopsy (3mm) from the skin lesion of the patients and normal skin of controls. Skin tissue from each case under the study was homogenized in phosphate buffer saline (pH 7.4) containing 0.1 % triton X100 in a ratio of 1:4 with a Potter-Elvehjem tissue homogenizer. The crude homogenate was centrifuged at 10000 rpm for 15 minutes at 4 C°, and the resultant supernatant was removed, subdivided into aliquots and stored at -80°C till used for assay for the measurement of total skin tissue protein content, and Tristetraprolin (TTP) level.

2.3 Statistical Analysis

Data were collected and analyzed using SPSS (statistical package for social science) version 20. Data were expressed as mean \pm standard deviation (SD) for quantitative variables, while qualitative variables were expressed as number and percentage. Chi-square test (X^2), Kruskal-Wallis test, and Mann-Whitney test were used as appropriate. P-value <0.05 was considered significant.

3. RESULTS

The current study was conducted on a total number of 32 subjects; 22 cases with psoriasis as patient group beside 10 age and sex matched healthy subjects as a control group. The patients were 17 (77.3%) males and 5 (22.7%) females with their ages ranged from 11 to 72 years with 49.0 ± 15.53 as a mean \pm SD value. Control subjects were 6 (60 %) males and 4(40%) females. Their ages ranged from 18 to 45 years with 29.20 ± 8.28 as a mean \pm SD value. Regarding clinical data of the studied cases, the course of the disease was progressive in 10

(45.5%) cases and was stationary in 12 (54.5%) cases. The duration of the disease ranged from 5 to 25 years with a mean of 12.73 ± 5.92 years. Family history of psoriasis was positive in 3 (13.6%) cases and was negative in 19 (86.4%) cases (Table 1).

Regarding distribution of psoriasis, 14 (63.6%) of cases had generalized psoriasis and 8 (36.4%) had localized psoriasis. All cases (100 %) had psoriasis on extremities, 16 (72.7%) on trunk, 9

(40.9 %) on scalp, 3 (13.6 %) had nail psoriasis and 12 (54.5 %) had palmar psoriasis.

Regarding disease severity; 5 patients (22.7 %) had mild PSAI Score ranged from 1 to 9.95 with a mean± SD of 4.84 ± 3.32, six patients (27.3 %) had moderate score ranged from 10.10 to 20 with a mean and SD of 14.05 ± 3.96 and 11 patients (50%) had severe score ranged from 29.80 to 65.2 with a mean ± SD of 43.69 ± 11.51 (Table 2).

Table 1. Demographic and clinical characteristics for the studied subjects

Clinical data and patients	Patient (n= 22)		Control (n= 10)		Test of sig.	P
	No.	%	No.	%		
Age						
Min. – Max.	11.0 – 72.0		18.0 – 45.0		t=4.689*	<0.001*
Mean ± SD.	49.0 ± 15.53		29.20 ± 8.28			
Median (IQR)	48.50(40.0 – 60.0)		29.50(22.0 – 35.0)			
Sex						
Male	17	77.3	6	60.0	χ ² = 1.015	FEp=0.407
Female	5	22.7	4	40.0		
Course						
Progressive	10	45.5	–	–	–	–
Stationary	12	54.5	–	–	–	–
Duration (years)						
Min. – Max.	5.0 – 25.0		–	–	–	–
Mean ± SD.	12.73 ± 5.92		–	–	–	–
Median (IQR)	10.0(10.0 – 20.0)		–	–	–	–
Family history						
No	19	86.4	–	–	–	–
Yes	3	13.6	–	–	–	–

χ²: Chi square test FE: Fisher Exact t: Student t-test
 p: p value for comparing between the studied groups
 *: Statistically significant at p ≤ 0.05

Table 2. PSAI score of the studied cases

PSAI score	Mild	Moderate	Severe
No	5	6	11
%	22.7	27.3	50.0
Range	1.0 – 9.95	10.10 – 20.0	29.80 – 65.20
Mean ± SD.	4.84 ± 3.32	14.05 ± 3.96	43.69 ± 11.51
Median (IQR)	4.0(3.60 – 5.60)	13.10(10.60 – 17.40)	43.20(36.0 – 44.20)

Table 3. Skin tissue Tristetraprolin (TTP) level (ng/m protein) in the patient and control groups

TTP (ng/mg protein)	Patient (n = 22)	Control (n = 10)	U	P
Min. – Max.	38.0 – 180.27	59.73 – 400.0	24.0*	<0.001*
Mean ± SD.	88.63 ± 48.56	230.73 ± 113.49		
Median (IQR)	66.38(44.29 – 139.95)	220.0(180.0 – 320.0)		

U: Mann Whitney test; p: p value for comparing between the studied groups
 *: Statistically significant at p ≤ 0.05

Table 4. Relation between tissue Tristetraprolin (TTP) level (ng/m protein) and severity of psoriasis (PSAI score)

PSAI score	TTP level (ng/mg protein)			Kruskal Wallis test	P
	Min. – Max.	Mean ± SD.	Median (IQR)		
Mild	110.0 – 180.27	151.71 ± 25.87	155.78 (150.61 – 161.91)	13.688*	0.001*
Moderate	44.89 – 147.28	97.15 ± 43.11	93.94 (65.88 – 136.95)		
Severe	38.0 – 97.79	55.31 ± 22.37	44.29 (39.67 – 60.45)		

H: H for Kruskal Wallis test,
 p: p value for association between different categories
 *: Statistically significant at $p \leq 0.05$

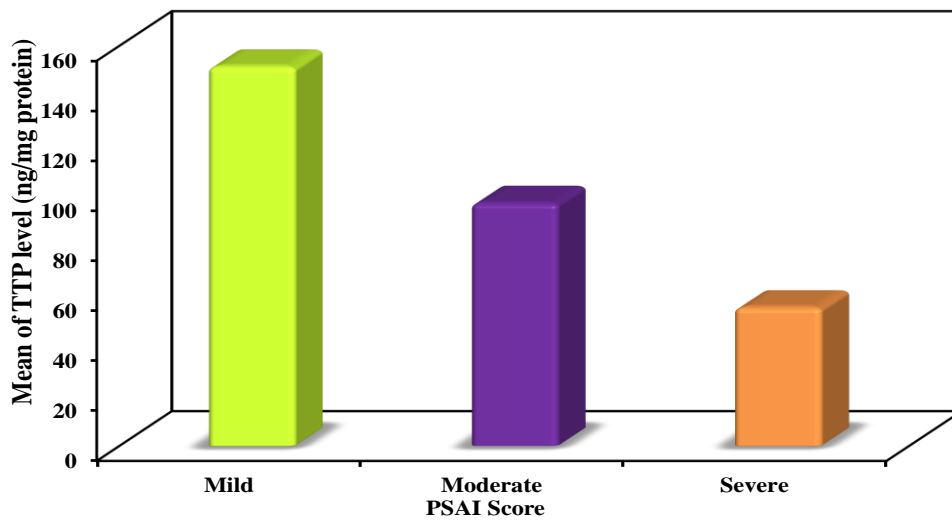


Fig. 1. Relation between tissue Tristetraprolin (TTP) level (ng/m protein) and severity of psoriasis (PSAI Score)

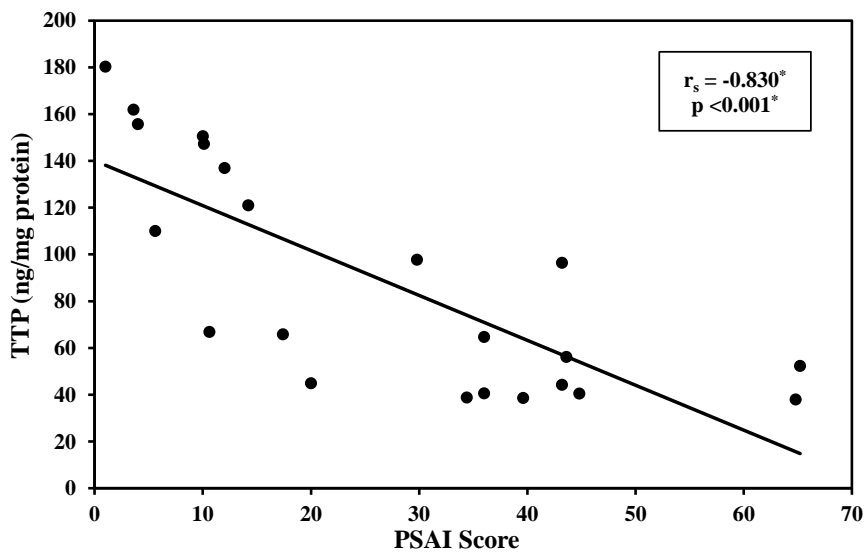


Fig. 2. Correlation between age, disease duration, severity and tissue Tristetraprolin (TTP) level in patient group (n = 22)

Table 5. Correlation between age, disease duration, severity and tissue tristetraproline (TTP) level in patient group (n = 22)

	TTP (ng/mg protein)	
	rs	P
Age	-0.181	0.420
Duration	0.089	0.693
PSAI Score	-0.830	<0.001*

rs: Spearman coefficient

*: Statistically significant at $p \leq 0.05$

Regarding to the level of TTP (ng/m protein) in the studied groups; in the control group, it ranged from 59.73 to 400.0 with a mean and SD of 230.73 ± 113.49 . In the patient group, it ranged from 38.0 to 180.27 with a mean of 88.63 ± 48.56 SD. There was a statically significant difference between patient group and control. TTP was significantly lower in psoriasis patient when compared to controls (P value was < 0.001) (Table 3).

There was non-significant difference between TTP level values and age, sex, duration of disease and distribution of psoriasis. On the other hand, there was significant difference between TTP level and severity of psoriasis (P value 0.001) with the lowest level in cases with severe psoriasis (Table 4), (Fig. 1).

3.1 Correlation between Age, Disease Duration, Severity and Tissue Tristetraproline Level in Patient Group

There was significant correlation between TTP level (ng/m protein) and PSAI Score of patients (P value was < 0.001), but no significant correlation between TTP, age and duration of Psoriasis (P value were 0.420 and 0.693) respectively (Table 5), (Fig. 2).

4. DISCUSSION AND CONCLUSIONS

“Psoriasis is a chronic, immune-mediated, inflammatory condition, which results from rapid proliferation of keratinocytes, forming dusky red erythematous plaques covered by scales. It is characterized by spontaneous remission and relapse and associated with both a physical and a psychological burden” [9].

“Psoriasis affects approximately 2% to 3% of the world’s population” [10]. “It is associated with multiple comorbidities and substantially diminishes patients’ quality of life. Topical

therapies remain the cornerstone for treating mild psoriasis” [11].

“Psoriasis typically affects the skin, but may also affect the joints, and has been associated with a number of diseases. Inflammation is not limited to the psoriatic skin and has been shown to affect different organ systems. Thus, it has been postulated that psoriasis is a systemic entity rather than a solely dermatological disease” [12].

“Tristetraproline (TTP) is RNA-binding protein encoded by Zfp36 gene which regulates the mRNA stability of several important cytokines. Due to the critical role of this RNA-binding protein in the control of inflammation, TTP deficiency leads to the spontaneous development of a complex inflammatory syndrome. So far, this phenotype has been largely attributed to dysregulated production of TNF and IL23 by myeloid cells, such as macrophages or DCs. The expression of TTP was studied in keratinocytes and explored its role in the imiquimod-induced psoriasis model. The authors found that TTP deficiency is associated with systemic inflammation, skin lesions and psoriasis related arthritis” [13].

The aim of the work was to study the possible role of Tristetraproline in the pathogenesis of psoriasis.

This case control study included a total number of 32 cases with exclusion of patients who had any other dermatological or systemic diseases and pregnant or lactating women. Patients were subdivided into 2 groups: group I were 22 patients with Psoriasis and group II were 10 healthy individuals (control group).

Skin specimens were obtained by punch biopsy from lesional skin of the patients and also from the controls. Tristetraproline level was made for skin specimens by ELISA.

Regarding to TTP level, there was a significant difference between cases and control group regarding skin tissue TTP level. TTP was significantly lower in psoriasis patient when compared to controls (P value < 0.001). As regard relation between the level of TTP and the disease severity represented as PASI score; there was significant difference in TTP level between different grades (P value 0.001) with the lowest level in cases with severe psoriasis.

Although the studies in the role of Tristetraproline in the pathogenesis of psoriasis are few, some

studies discuss the effect of TTP in other autoimmune diseases.

A recent study by Yang et al. [14] was “the first study to prove that TTP dysregulation might be related to the pathogenesis and development of Rheumatoid arthritis (RA), and the polymorphism of the TTP gene may be protective of RA in a Chinese population. They suggested that TTP might be involved in the regulation of autoimmune diseases”.

Tristetraprolin as a RNA-binding protein was expressed widely in mammalian cells [15]. “TTP-deficient mice exhibited systemic autoimmune inflammatory symptoms consisting of erosive arthritis, cachexia, conjunctivitis, dermatitis and glomerular mesangial thickening, the symptoms can be avoided in TTP-deficient mice by injecting with antibodies to tumor necrosis factor- α (TNF- α), suggesting that the inflammatory symptoms are caused by TNF- α elevation” [16].

Haneklaus et al. [17] was “the first to study TTP in psoriatic patients. They reported that TTP is downregulated in fibroblasts derived from the skin of psoriasis patients compared to those obtained from healthy individuals; these cells display higher inflammasome activity than their normal counterpart and show that TTP restoration determines a decrease in inflammasome activation that depends on the ability to directly target for degradation of mRNA. The inflammasomes are multiprotein complexes formed and activated after exposure to pathogenic microbes and host danger signals. Their activation is an essential component of the innate immune response and is critical for the clearance of pathogens and damaged cells by maturation and secretion of IL-18 and IL-1 β ”.

In agreement with our study, Bertesi et al. [18] studied “the mechanism of TTP action in reducing psoriasis inflammation. The study included a total number of 54 cases, 33 patients had psoriasis and 21 healthy donors. The expression of TTP and inflammasome main components in fibroblasts derived from psoriatic donors or healthy individuals was studied and the results showed that TTP was significantly downregulated at the protein level in psoriatic fibroblasts compared to fibroblasts derived from the healthy donors”.

Chiara et al. [19] showed that “dermal fibroblasts from lesional psoriasis skin are important producers of inflammatory mediators, including

IL6, CXCL8 and CXCL2. This increased cytokine production was found to be regulated by ZFP36 family members ZFP36, ZFP36L1 and ZFP36L2, RNA-binding proteins with mRNA-degrading properties”.

In agreement with our study, Chiara et al. [19] found that “the expression of ZFP36L1 and ZFP36L2 was downregulated in psoriasis normal skin, when compared to healthy skin. Additionally, the expression of ZFP36 family proteins was found reduced in chronic inflammatory conditions that mimic psoriatic lesional skin. To gain more insights into the specific involvement of ZFP36 members in different inflammatory skin diseases, the authors compared psoriasis and atopic dermatitis (AD) skin transcriptomes. They observed that all ZFP36 members were downregulated in psoriasis lesional skin when compared to AD lesional skin, and in psoriasis normal skin versus AD normal. These results indicate that these proteins could contribute to the pre-inflammatory phase in psoriasis development”.

Of interest, this is the first study to measure TTP in skin homogenate of psoriasis and not only in fibroblast, as TTP was found to be expressed not only in fibroblast but also in keratinocytes, macrophages and DCs.

In our study, we found a significant correlation between the level of TTP, and the severity of psoriasis represented as PASI score. There was significant difference in TTP level between different grades (P value 0.001) with the lowest level in cases with severe psoriasis. This could be attributed to the ability of TTP in the regulatory production of inflammatory cytokines.

Regarding sensitivity of TTP in diagnosis of psoriasis in our study, it was 95.45 %, with specificity 80 %. This indicates that TTP may have an important role as diagnostic and prognostic marker in psoriasis.

In an attempt to clarify the mechanism of TTP in psoriasis, Carballo and colleagues found that TTP directly binds to the adenine/uridine-rich elements (AREs) of TNF- α mRNA and degrades it rapidly [7]. Later, TTP was identified to bind the AREs and regulate other pro-inflammatory cytokines [20,21]. Moreover, TTP could physically interact with histone deacetylases (HDACs) and act as a common suppressor of NF- κ B-dependent transcription [22]. Therefore, TTP not only contribute to regulate the

expression of pro-inflammatory gene through its mRNA-decay function, but also participate in the regulation of inflammatory signal transduction.

Under physiological conditions, the mRNA of pro-inflammatory genes is constantly degraded by AU-rich element binding proteins (AREBPs), which allows a rapid control of gene expression. About 5% of the human transcriptome contains AREs in their mRNA [23,24]. In psoriasis, it was showed that 87.5% of differentially expressed genes (DEGs) common in psoriatic lesional skin and TNF- α -stimulated fibroblasts contain different types of AU-rich elements, highlighting the importance of such regulatory elements in psoriasis manifestations.

Keratinocyte-specific knockout of ZFP36 was previously found to aggravate psoriasis manifestations in mice, and ZFP36 mRNA was found reduced in the epidermis of psoriatic patients, as compared to healthy individuals [13]. These observations, combined with our results, indicate that ZFP36 plays an important role in keratinocytes and fibroblasts.

Early research also demonstrated that TTP was involved in regulating the production of multiple inflammatory cytokines, thereby affecting the immune response, including TNF- α , interleukins (ILs) and interferons (IFNs) [25]. The macrophages from TTP-deficient mice exhibit an apparent primary tendency to excess TNF- α production, which indicates the role of TTP in the biosynthesis and/or release of TNF- α in this cell type [26]. IL-12 is one of the ILs families and regulates immune response. Previous study showed that TTP down-regulates IL-12 at transcriptional level through the NF- κ B pathway [27]. IFN- γ plays a vital role in the immune regulation and enhances antiviral ability. TTP mediates the degradation of IFN- γ by binding to the functionally ARE of IFN- γ mRNA. It implied that TTP mediates IFN- γ mRNA decay [28]. Modification after translation, especially phosphorylation, has a great influence on the anti-inflammatory effect of TTP [29]. Replacing TTP phosphorylation sites conferred significantly protect mice from inflammatory arthritis. It can be used in treatment of inflammatory diseases by changing the degree of phosphorylation [30].

This may give us a signal: immune and inflammatory diseases can be treated by stimulating the expression of TTP.

Reduced ZFP36 expression in the skin was suggested to be a consequence of recurrent

inflammation [13]. As such, reduced ZFP36 family expression in non-lesional skin may represent a first-hit molecular event, which prepares the skin to inflammatory lesional manifestations upon second-hit events (such as after köebnerization) [31]. Furthermore, as ZFP36 selective depletion in the epidermis was shown to initiate not only psoriasis but also arthritis development [13]. It is possible that initial ZFP36 family alterations in the skin could contribute to psoriatic arthritis (PsA), one of the most severe complications in psoriasis [32]. Nonetheless, the development of compounds able to modulate the activity of ZFP36, already shown successful in a clinical trial on psoriatic patients [33] holds potential for further pre-clinical investigations in psoriasis and other inflammatory diseases.

CONSENT AND ETHICAL APPROVAL

Written informed consent was taken from each patient before enrollment into the study that had been approved by the institutional review board at Faculty of Medicine, Tanta University, Egypt.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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