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Tumor Necrosis Factor like weak inducer of apoptosis (TWEAK) in serum and tissue of patients with psoriasis vulgaris

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Abstract:

Introduction: Variable in severity, psoriasis is a prevalent chronic inflammatory skin disorder that impacts two to three percent of the populace. The fibroblast growth factor inducible fourteen (Fn14) receptor serves as the sole receptor for tumor necrosis factor-like weak inducer of apoptosis (TWEAK), which regulates multiple proinflammatory cytokines. In order to maintain tissue homeostasis and regulate cell function, TWEAK/Fn14 signals are crucial. Local tissues or resident cells exhibit low levels of TWEAK and Fn14 expression. TWEAK and Fn14 expression can, nevertheless, be increased by inflammatory responses as well as tissue damage. Cell fate, including proliferation and apoptosis, is regulated by TWEAK/Fn14 activation, which also recruits inflammatory cells (macrophages, T-, and B-cells). TWEAK/Fn14 signals are assumed to be involved in the progression of psoriasis vulgaris.

Aim of the study: To investigate the TWEAK levels in serum and tissue of patients with psoriasis vulgaris.

Subjects and Methods: This case-control research was done on 50 subjects (25 psoriasis vulgaris individuals and 25 apparently healthy subjects as controls). Serum and tissue TWEAK levels were measured by the ELISA method. The PASI score was computed for each individual following a comprehensive review of their medical history and a local and general clinical examination.

Results: According to our study, tissue and serum TWEAK were significantly higher in patients than controls. Tissue TWEAK was significantly greater than serum TWEAK. No correlation was detected between tissue and serum TWEAK levels with any of the demographic data, clinical data, PASI score, or severity of the disease. ROC analysis revealed that TWEAK shows 100% sensitivity and 92% specificity regarding serum TWEAK, compared to 96% specificity of tissue TWEAK in diagnosing psoriasis vulgaris.

Conclusions: TWEAK contributes significantly to the pathogenesis of psoriasis vulgaris & could be a possible target in disease therapy.

Keywords: TWEAK; Psoriasis vulgaris; PASI score.
1. Introduction

Psoriasis is particularly prevalent problem observed in the outpatient dermatology clinic. It occurs in approximately 3% of the world population, and there are about 125 million patients around the world, according to the National Psoriasis Foundation of the United States [1]. It's a chronic inflammatory condition caused by T cells and characterized by a cytokine balance between Th1 and Th17. It is known to be a systemic disease that primarily affects skin and joints. Presented on the skin by heavily scaled plaques, incomplete differentiation of epidermal keratinocytes, hyperproliferation, and dense infiltrates of T cells, macrophages, and dendritic cells [2].

It has been demonstrated that pro-inflammatory cytokines, particularly TNF-α, activated T cells, and monocytes, all have crucial functions in the pathogenesis of psoriasis. Activated T cells secrete cytokines like TNF-α, IFN-γ, IL-6, and IL-1b, among others. These cytokines stimulate a diverse array of responses, involving vasodilation leading to erythema, which is a distinctive feature of psoriatic lesions, as well as leukocyte migration towards inflammatory regions [3].

By binding to its sole receptor, the fibroblast-inducible factor 14 receptor (Fn14), TWEAK significantly regulates the activity of numerous proinflammatory cytokines. In order to maintain tissue homeostasis and regulate cell function, TWEAK/Fn14 signals are crucial. Local tissues or resident cells exhibit low levels of TWEAK & Fn14 expression. Nevertheless, TWEAK & Fn14 expression may be increased by inflammatory responses as well as tissue damage [4].

Depending on the cellular environment, their interaction initiates a series of intracellular signal transduction cascades that result in cell survival, proliferation, mortality, or migration. Activation of TWEAK/Fn14 controls cell fate, whether it be apoptosis or proliferation, recruits inflammatory cells (macrophages, T & B cells), and stimulates cytokine production [5]. In the development of a number of skin illnesses, including cutaneous lupus erythematosus, TWEAK/Fn14 signals play a role [6], systemic sclerosis [7], and psoriasis [8].

The current study aimed to compare the TWEAK levels in serum and tissue of patients with psoriasis vulgaris.
2. Subjects and Methods

2.1. Subjects

This case-control research was conducted in the Dermatology, STD, and Andrology Department at the school of medicine, Fayoum University, from February 2019 to February 2020.

Inclusion criteria

- Both sexes.
- Individuals with Psoriasis Vulgaris

Exclusion criteria

- Pregnancy and lactation.
- Autoimmune diseases, cancer or any known cause affecting level of TWEAK e.g. cardiovascular disease, viral hepatitis, inflammatory bowel disease.
- Instances involving biological therapeutics, systemic treatment (such as cyclosporine, methotrexate, or systemic retinoids) in the last three months prior to study or Patient who are on acitretin for the last two years.
- Patient with chronic systemic diseases (e.g. diabetes mellitus, anemia, debilitating disease, infections, liver or kidney diseases).

2.2. Information Sources

We conducted a database search using PubMed, Scopus, Web of Science. as well as Cochrane CENTRAL for articles that met our inclusion criteria until February 2020.

Patient evaluation

Full history was obtained from all patients included in this work including personal present, past history and full clinical examination.

Dermatological examination

An assessment was conducted on the patient's cuticles, epidermis, hair, mucous membranes, and skin, as well as the severity of psoriasis was determined using the PASI score.

The body was dispersed into 4 sections, which are head, trunk, lower limbs and upper limbs, each of these sections is scored by itself. PASI provides a weighted of scoring the erythema (redness), infiltration (induration) and desquamation (scaling) of the psoriasis plaques at each section multiplied by scored body surface area (BSA) of section affected, then multiplied by following: (head x 0.1), (trunk x 0.3), (upper limbs x 0.2) and (lower limbs x 0.4); the four scores were combined in to the final PASI.

PASI was computed in accordance with Thompson as well as Frutren's (1997) standardization of the principles proposed by Fredriksson and Petersson in 1978 (Table 1) [9].
Table 1: PASI score.

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>Non</td>
<td>Slight</td>
<td>Moderate</td>
<td>Severe</td>
<td>Very severe</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Infiltration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desquamation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Area percent</td>
<td>0</td>
<td>&lt;10</td>
<td>10&lt;30</td>
<td>30&lt;50</td>
<td>50&lt;70</td>
<td>70&lt;90</td>
<td>90&lt;100</td>
</tr>
</tbody>
</table>

Patients were categorized based on their PASI score.

• Mild psoriasis: PASI below 10.
• Moderate psoriasis: PASI (10 – 15).
• Severe psoriasis: PASI > 15.

2.3. Specimen Collection

Serum collection

40 peripheral venous blood samples were withdrawn from the two groups, group (1) psoriasis vulgaris patients 20 samples and group (2) the control group 20 samples. 3 mL of venous blood were obtained through vein puncture while maintaining strict aseptic precautions.

Skin biopsy

Following written consent, punch skin specimens measuring 2.5 mm were obtained from the psoriatic scaly plaque lesion. Following this, the lesion was disinfected as well as 0.5 ml of local anesthetic was injected. The skin specimens were preserved at -20oC in an empty Eppendorf for ELISA analysis of tissue TWEAK.

2.4. Assay procedure

1. The standard working solution was introduced into the initial two columns, with each concentration of the solution being applied in triplicate to a single well positioned adjacent to the other (100 uL per well). One hundred microliters of the samples were introduced into every other well. After ninety minutes of incubation at 37°C, solutions were introduced to the well at the bottom of the micro ELISA plate.

2. Following the removal of the liquid from each well, 100 L of Biotinylated Detection Ab working solution was promptly introduced into every well. The wells were then covered with the plate sealer and gently mixed. Incubated at 37°C for one hour.

3. Following that, 350 uL of wash buffer was added to every well into which the solution had been aspirated. The solutions were aspirated from each well after soaking for 1~2 minutes and dried on clean absorbent
paper. Three times, this cleansing was performed.

4. In each well, 100 μL of HRP Conjugate working solution was introduced. The plate was coated with a sealant and incubated at 37°C for thirty minutes.

5. Following the aspiration of the solution from each well, the cleanse procedure was iterated five times in the same manner as described in step 3.

6. In each well, 90 μL of substrate reactant was added. Adhered to with a fresh plate sealant. It was incubated at 37°C for approximately fifteen minutes and shielded from light for 30 minutes.

7. Each well received 50 μL of Stop Solution added in the same sequence as the substrate solution.

8. At 450 nanometers, the optical density of every well was simultaneously defined utilizing a microplate reader.

2.5. Statistical methods

By utilizing SPSS version 19, all data were gathered, organized, and subjected to statistical analysis. The standard deviation (SD) and range (mean) were used to denote continuous quantitative variables. The frequencies absolute (number) and relative (percentage) of qualitative categorical variables were denoted. Shapiro-Wilk analysis was utilized to assess the normality of continuous data. Extraneous both groups of normally distributed data were contrasted utilizing one-way ANOVA (F test). Beyond two categories of non-normally distributed data, the Kruskall-Wallis test was applied. Two collections of non-normally distributed data were contrasted utilizing the Mann-Whitney test. Chi-squared test (χ²) was employed to contrast the categorical data. The coefficient correlation (r: Pearson's correlation) was utilized to determine degree of relationship among two numeric variables. Each exam had double sides. A p-value less than 0.001 was deemed highly statistically significant (HS), a value less than 0.05 was deemed statistically significant (S), as well as a value greater than 0.05 was deemed statistically insignificant (NS). The efficacy of the screening assays (IL, TWEAK) was evaluated by considering their sensitivity, specificity, positive and negative predictive values, as well as their accuracy.
3. Results

The study outcomes are shown in Figure 1.

![Figure 1: The study outcomes. Age in the whole population (A) and the classified groups (B). Sex in the whole population (C) and the classified groups (D).](image)

The current investigation indicated statistically significant disparity in the levels of Tweak in both serum and tissue of patients diagnosed with psoriasis vulgaris when compared to the control group (Figure 2). There is a highly statistically significant relation among Serum Tweak level and tissue Tweak level in patient group with a p-value of <0.001 as shown in (Figure 2 C).

To differentiate psoriatic patients from healthy controls, a receiver operating characteristic curve was computed for serum and tissue TWEAK levels. Highly specificity and sensitivity characterized the diagnostic performance of serum and tissue TWEAK.
4. Discussion

Psoriasis is one of the most common problems observed in outpatient dermatology clinics. It occurs in approximately 3% of the world population and in about 125 million patients around the world, according to the National Psoriasis Foundation of the United States [10]. It is a T cell-mediated, chronic inflammatory disease with a mixed Th1/Th17 cytokine environment that primarily affects skin and is presented on skin by heavily scaled plaques containing dense infiltrates of T cells, macrophages, and DCs, hyperproliferation, and incomplete differentiation of epidermal keratinocytes [2]. It has been demonstrated that pro-inflammatory cytokines, particularly TNF-α, activated T cells, and monocytes, all have crucial functions in pathogenesis of psoriasis. Activated T cells secrete cytokines such as TNF-α, IFN-γ, IL-6, and IL-1b, among others. These cytokines stimulate a diverse array of responses, including vasodilation leading to erythema, which is a distinctive feature of psoriatic lesions, as well as leukocyte migration towards inflammatory regions [3]. TWEAK exerts a significant regulatory effect on numerous proinflammatory cytokines by means of its exclusive receptor interaction, Fn14. TWEAK/Fn14 signals are essential for tissue homeostasis and the regulation of cellular function [11]. Keratinocytes, fibroblasts, kidney cells, human umbilical vein endothelial cells, and other cell types are among those in which this complex phosphorylates the inhibitor Kb-a (1Kba), thereby stimulating the transcription factor NF-Kb. RANTES, a chemotactic cytokine expressed and secreted by normal T-
cells, is generated in response to this process. It serves as a pivotal molecule in the psoriatic epidermis and is regulated upon activation [12]. Resistance to apoptosis protein 2 (survivin) was increased in lesioned keratinocytes in response to TWEAK stimulation. Subsequently, in the presence of psoriatic inflammation, the TWEAK/Fn14 interaction favors keratinocyte proliferation over apoptosis. For keratinocytes undergoing psoriatic inflammation, this novel principle may be attributed to the upregulation of TNF receptors as well as the activation of nuclear factor-Kb signaling-dependent anti-apoptotic proteins [12].

Additional proinflammatory cytokines, involving interleukin-1 (IL-1), interleukin-6 (IL-15), and interleukin-18 (IL-18), matrix metalloproteinase-9 (MMP-9), MMP-1, as well as prostaglandin E2, are also induced by TWEAK. These cytokines are synthesized by Th-17 cells and contribute to the host's immune response against allergic-specific immune responses, autoimmune diseases, and infections [6].

Expression levels of TWEAK and Fn14 are minimal in local tissues and resident cells. Nevertheless, tissue damage and inflammatory responses can increase TWEAK as well as Fn14 expression [4]. The involvement of TWEAK/Fn14 signals in the progression of numerous skin diseases, including cutaneous lupus erythematosus [6], systemic sclerosis [7], and psoriasis [8],

Upon review of the literature, there were limited studies on the effect of TWEAK on various skin diseases, especially psoriasis, and there were no previous attempts to study the level of both serum and tissue TWEAK in the same setting as an important cytokine in the pathogenesis of psoriasis vulgaris and its correlation with the PASI score and disease severity. This research objective is to measure the serum and tissue levels of TWEAK in cases of psoriasis vulgaris, assessing its possible role in the pathogenesis of the disease and its correlation with the PASI score and disease severity.

In the current study, estimation of TWEAK levels in a sample of Egyptian psoriatic cases and healthy controls revealed that serum and tissue TWEAK levels happened to be highly statistically significant (p-value less than 0.01: highly significant) between patients and controls. To the best of our knowledge, this is the first work to measure TWEAK levels in both serum and skin tissues in psoriasis vulgaris patients quantitatively by ELISA and its correlation to PASI score and disease severity. The current work declared a significantly greater tissue TWEAK in contrast with serum in
Psoriatic cases with a statistically highly significant variance (p-value< 0.01: highly significant). Psoriatic skin harbors plenty of inflammatory cells involving monocytes, dendritic cells, and natural killer cells, and macrophages and monocytes are one of the major sources of TWEAK in inflammatory tissue [6]. They might be condemned for such an increase in lesioned skin.

Additionally, Sidler et al. (2017) demonstrated that administering TWEAK subcutaneously to animals resulted in localized skin inflammation exhibiting molecular and histological characteristics consistent with psoriasis as well as atopic dermatitis [8].

Cheng et al. (2016) stated that elevated levels of TWEAK/Fn14 expression were associated with heightened keratinocyte proliferation and inflammation [12]. In line with our findings, Bilgic et al. (2016) demonstrated that psoriasis patients had significantly elevated serum TWEAK levels compared to healthy controls [2]. Furthermore, they identified a significant relationship between serum TWEAK levels and serum IL-23 levels. However, no significant correlations were found among serum cytokine levels as well as psoriasis severity, illness duration, or IL-23 levels. Additionally, Alaoui et al. (2012) demonstrated that the TWEAK/Fn14 complex, which is present in the healthy epidermis and skin appendices of humans, induced keratinocyte cell death. Psoriasis and other malignant and benign lesions exhibited elevated epidermal TWEAK/Fn14 expression [13].

Contrary to the results of Bilgic et al. (2016), which stated no statistically significant correlations among serum TWEAK levels and the severity or period of psoriasis [2], our findings recommend that serum TWEAK levels might be associated with the pathogenesis of the disease, irrespective of its severity.

Conclusion

It seems that TWEAK levels particularly tissue levels are more significantly associated with pathogenesis of psoriasis.

Ethical consideration and patient consent: The study was approved by the Faculty of Medicine, Fayoum University Research Ethical Committee. Approval and consent to participate were gained by obtaining informed written consent from individuals who were invited to take part in the research.
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**Conflicts of Interest:** All authors declare they have no conflicts of interest.

**References**


