INTRODUCTION

Acne vulgaris is a common skin problem of the pilosebaceous unit affecting usually adolescents and young adults producing inflammatory and noninflammatory lesions which may heal leaving postacne scars. It has been characterized by excessive sebum production, follicular epithelial hyperkeratosis, and rupture of follicular epithelium, resulting in an increased release of inflammatory-mediating agents. Tumor necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK) belongs to the TNF superfamily. It has an important role in the regulation of cell growth, apoptosis, angiogenesis, and immune reactions. TWEAK exerts its role via binding to its main receptor, Fn14. It was found to be involved in the pathogenic events of many chronic inflammatory conditions, and targeting this molecule may be a promising therapeutic option for those patients.

Despite the chronic inflammatory nature of acne vulgaris, the role of TWEAK in this condition has not been assessed.

The current study was carried out to evaluate the serum levels of TWEAK in acne vulgaris patients.
individuals as controls (Group 2). The enrolled acne patients were divided into two groups (Group 1A included 25 patients with moderate acne and Group 1B included 25 severe acne patients). The study was conducted during the period from November 2016 to December 2017. The local ethics committee on research involving human subjects of Faculty of Medicine approved the study. All enrolled subjects signed an informed consent after explanation of the aim of this research.

Acne vulgaris patients were excluded from this study if they were suffering from concurrent significant medical conditions such as malignancy, diabetes mellitus, hepatic, renal, or cardiovascular diseases, undergone treatment with any systemic antiacne therapy within 1 month, or application of topical antiacne therapy within 2 weeks prior to the study initiation. Pregnant or breastfeeding female patients were also excluded from the study.

### 2.2 Methods

All patients in this study were subjected to full history taking and complete cutaneous examination, to evaluate the clinical type and severity of acne using the Global Acne Grading System (GAGS) and to assess the presence of postacne hyperpigmentation or scarring. Serum TWEAK levels were measured in all participants using ELISA kits.

#### 2.2.1 Sampling

Under complete aseptic conditions, 5 mL of venous blood was drawn. One milliliter was mixed gently with EDTA in a vacutainer to be used in measuring the complete blood count via automated hematology system (Sysmex XE 5000; Sysmex America, Inc.), and the remaining 4 mL was allowed to clot for 30 minutes at room temperature in plain test tubes without anticoagulant. The samples were then centrifuged for 15 minutes at 1000 \( \times g \). The serum was removed, aliquoted, and stored at \(-20^\circ\text{C}\) until assayed. The separated serum was used for the following assays:

- Biochemical tests using Biosystem A15 autoanalyzer (Biosystems SA) by appropriate chemical principles. These tests included the following:
  - Fasting blood glucose level.
  - Liver function tests: serum albumin, total and direct bilirubin, liver enzymes including aspartate aminotransferase (AST) and alanine aminotransferase (ALT).
  - Kidney function tests: serum creatinine and urea.
- Serum TWEAK levels were measured using human ELISA (sandwich technique) kits provided by SuRed, biotechnology, (Cat. No. 201-12-1821) with assay range (15-4200 ng/mL)

### 2.2.2 Statistical analyses

The patients’ data were tabulated and analyzed using STATA/SE version 11.2 for Windows (STATA Corporation). For quantitative data, the mean and standard deviation (SD) were calculated, while frequency and percentage were calculated for qualitative data. Fisher’s exact test (FET) and chi-square test (\( \chi^2 \)) were used to compare differences between proportions. Student’s \( t \) test (\( t \)) and the Mann-Whitney test were used to compare parametric and nonparametric data, respectively, between two groups. The one-way analysis of variance (ANOVA; \( F \)) and the Kruskal-Wallis test were used to compare more than two groups as appropriate, followed by post hoc test using the Bonferroni method to detect differences in pairs. Spearman’s correlation coefficient was used to test for the correlation between serum TWEAK levels and studied parameters.

Receiver operating characteristic (ROC) curve analysis was used to detect the cutoff point of TWEAK levels between patients and controls and between moderate and severe acne. \( P \) value was considered significant when it is <0.05.

### 3 RESULTS

The enrolled patients and control subjects were matching regarding sex (32 vs 34 female patients), age (20.08 ± 4.13 vs 20.64 ± 3.24 years old), and BMI (19.98 ± 1.42 vs 20.22 ± 1.62 kg/m\(^2\)), respectively.

The mean age of onset of acne was 17.01 ± 3.5 years old, and the mean disease duration was 3.07 ± 2.67 years. Fifty percent of our patients had moderate acne, and the other 50% suffered from severe acne. Postacne hyperpigmentation was noticed in 84% of the studied patients, and postacne scarring was detected in 68% of patients.
Serum levels of TWEAK in the patients were significantly higher than those of the control subjects (794.54 ± 621.54 vs 425.40 ± 130.39, respectively; \( P < 0.001 \)).

There was no statistically significant difference in serum levels of TWEAK in patients regarding sex, disease grade, postacne scar, and hyperpigmentation (\( P \) value = 0.43, 0.37, 0.80, 0.67, respectively; Table 1).

There was a significant negative correlation between TWEAK serum levels and the disease duration in Group 1B (\( r = -0.42, \ P = 0.03 \)), while the correlation between serum TWEAK levels and other studied variables such as patient age, age of disease onset, and body mass index were not significant (Table 2 and Figure 1).

Diagnostic performance of serum TWEAK levels for acne was tested using the ROC curve. The best cutoff point for the diagnosis of cases was 430 ng/mL; the corresponding sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 82%, 43.33%, 70.69%, and 59.09%, respectively; and the area under the curve (AUC) was 0.7567, while the best cutoff point for the diagnosis of severe cases was 799 ng/mL; the corresponding sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 76%, 36%, 54%, and 60%, respectively; and the area under the curve (AUC) was 0.5736 (Figures 2 and 3).

4 | DISCUSSION

It seems that serum levels of TWEAK reflect the inflammatory nature of some diseases including systemic lupus erythematosus,\(^8\) rheumatoid arthritis,\(^9\) bullous pemphigoid,\(^10\) urticarial vasculitis,\(^11\) cutaneous vasculitis,\(^12\) and psoriatic arthritis.\(^13\) In this study, we found that TWEAK serum levels in acne vulgaris patients were significantly elevated when compared to the levels of the control subjects.

Chen et al.\(^14\) did not report significant difference between atopic and seborrheic dermatitis patients and the healthy control subjects regarding serum levels of TWEAK, but they reported altered TWEAK cutaneous expression.

Despite the inflammatory nature of polymyositis and dermatomyositis, it was interesting to detect the lower serum levels of the inflammatory marker TWEAK when compared to the matched healthy control group Peng et al.\(^15\) That team work explained this finding by the high serum levels of CD163 (one of the TWEAK receptors) which can selectively bind and neutralize TWEAK.\(^16\) Moreover,
monocytes/macrophages expressing CD163 can bind and internalize TWEAK.\textsuperscript{17}

Bilgiç et al\textsuperscript{18} reported that serum TWEAK levels were significantly higher in psoriasis patients than in healthy controls. In addition, Alaoui et al\textsuperscript{19} found that the epidermis of psoriasis patients had increased expression of TWEAK and its receptor, Fn14, while Zimmermann et al\textsuperscript{20} did not detect significant differences in the expression of TWEAK in the epidermis obtained from the psoriasis patients and the control subjects.

These different TWEAK profiles in different inflammatory conditions and the discrepancy between the serum levels and the tissue expression of TWEAK recommend further studies to clarify the exact role and behavior of TWEAK in different inflammatory and autoimmune diseases.

Although Turkmen et al,\textsuperscript{21} Kowal-Bielecka et al,\textsuperscript{22} Llaurado et al,\textsuperscript{23} and Xia et al\textsuperscript{13} showed that serum levels of TWEAK in healthy individuals may be affected by age and gender, these factors did not correlate significantly with serum TWEAK levels in the present work or in other studies which evaluate TWEAK in different inflammatory conditions such as acute pancreatitis Koçak et al.\textsuperscript{24}

It seems that the inflammatory response in these inflammatory conditions can ameliorate the age and gender effects on the TWEAK levels.

In the present work, TWEAK serum levels did not correlate with the disease severity as there was no significant difference in serum levels of TWEAK in different acne grades. From all these findings, we can propose that TWEAK may be a player in the pathogenic process of acne vulgaris; however, it cannot reflect the disease severity. In fact, this absence of correlation between serum levels of TWEAK and severity of acne may be related to the nature of the studied groups as we did not include cases with mild acne.

Bilgiç et al\textsuperscript{18} and Chen et al\textsuperscript{14} also did not report a relation between the serum levels of TWEAK and the severity of psoriasis and atopic dermatitis, respectively. This may be because psoriasis is considered as a systemic disease, so serum TWEAK would reflect the affection of skin and other body systems at the same time, not only the severity of the cutaneous lesions. On the other hand, TWEAK serum levels had been found to be a good marker of disease severity in different diseases including psoriatic arthritis\textsuperscript{12} and rheumatoid arthritis.\textsuperscript{9}

In this study, there was a significant negative correlation between the duration of the disease and the serum levels of TWEAK in the severe acne vulgaris patients (Group B).

Kowal-Bielecka et al\textsuperscript{22} and Choe et al\textsuperscript{8} reported a negative correlation between TWEAK levels and the disease duration in systemic sclerosis and SLE patients, respectively. However, TWEAK levels did not correlate significantly with psoriasis duration.\textsuperscript{18} Does TWEAK secretion undergo reduction with prolonged inflammatory process? Does TWEAK act only as a trigger for the initiation of inflammation? More studies should be carried out to clarify this finding.

The relation between TWEAK and liability for fibrosis is not yet clear. Although higher serum levels of TWEAK had been proved to be protective against the development of lung fibrosis in systemic sclerosis via enhancing C-C motif chemokine ligand 5 (CCL5) production in the lung,\textsuperscript{25} and the TWEAK/Fn14 signaling induces renal fibrosis via different mechanisms\textsuperscript{5}, the current work did not find any relation between TWEAK serum levels and the liability for post acne scar formation in acne patients. This might be due to the small study sample.

5 | CONCLUSION

It seems that TWEAK may be involved in different inflammatory cutaneous disorders including acne vulgaris. However, levels of TWEAK in serum and urine as well as its tissue expression in skin diseases have not been studied enough yet. Role and behavior of TWEAK in different skin diseases need to be more investigated to clarify its exact pathogenic role and to start investigating the effect of targeting this molecule therapeutically on these diseases progress.

CONFLICT OF INTEREST

Authors have no conflict of interest to declare.

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