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Serum Vascular Endothelial Growth Factor, Transforming Growth Factor β1, and Nitric Oxide Levels in Patients With Psoriasis Vulgaris: Their Correlation to Disease Severity

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Background: Vascular endothelial growth factor (VEGF), transforming growth factor β1 (TGF-β1), and nitric oxide (NO) have been reported to be contributory factors to the pathogenesis of psoriasis vulgaris. In the current study, we aimed to investigate the association between the levels of VEGF, TGF-β1, and NO and psoriasis severity (as expressed by psoriasis area severity index, PASI). *Methods:* Fifty-eight patients with psoriasis vulgaris and twenty-two controls were included in the study. The serum levels of VEGF and TGF-β1 were estimated by ELISA technique. The serum levels of NO were determined by colorimetric method. *Results:* The serum levels of VEGF, TGF-β1, and NO were significantly higher in patients than controls. Moreover, the serum levels of the studied biochemical variables in patients with severe disease activity were significantly higher than mild cases. The duration of disease showed significant positive correlations with each VEGF ($r = 0.35$, $P < 0.01$) and TGF-β1 ($r = 0.41$, $P < 0.05$). In addition, the PASI score was significantly positively correlated with VEGF ($r = 0.65$, $P < 0.001$), TGF-β1 ($r = 0.31$, $P < 0.05$), and NO ($r = 0.51$, $P < 0.001$). *Conclusion:* These findings suggest an association between psoriasis disease severity and serum levels of VEGF, TGF-β1, and NO, which can be recognized as markers of the psoriasis severity. The modulation of their production may represent a therapeutic potential strategy for psoriasis. J. Clin. Lab. Anal. 28:496–501, 2014.

Key words: patients; psoriasis vulgaris; VEGF; TGF-β1; NO

INTRODUCTION

Psoriasis is an immune-mediated, multifactorial skin disease with hyperproliferation and altered differentiations of keratinocytes, linking the pathways of angiogenesis and inflammation (1). Vessels' expansion plays an important role in the evolution of psoriatic plaques. The dysregulated angiogenesis has been observed in inflammatory diseases and might underlie chronic cutaneous inflammation in psoriasis (2).

Several growth factors are recognized as pivotal factors responsible for angiogenesis in different tissues. Vascular endothelial growth factor (VEGF) and transforming growth factors (TGFs) α and β demonstrate angiogenic activity (3). VEGF and its high-affinity tyrosine kinase receptors VEGFR-1 (Flt-1) and VEGFR-2 (KDR in humans/Flk-1 in mice) are essentially involved in vascular embryogenesis and adult neovascularization (4). VEGF, first described as vascular permeability factor, represents in its active form a homodimeric glycoprotein of 40–45 kDa (5). VEGFR-1 and VEGFR-2 are primarily expressed by vascular endothelial cells. VEGF binding to either of these receptors leads to receptor activation

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and intracellular signal transduction (6). It is known that VEGF contributes to angiogenesis by both direct and indirect mechanisms. On the one hand, VEGF stimulates the endothelial cells to proliferate, to migrate, and to alter their pattern of gene expression. On the other hand, it renders these endothelial cells hyperpermeable so that they spill plasma proteins into the extravascular space, leading to profound alterations in the extracellular matrix that favor angiogenesis (7).

Overexpression of VEGF can promote new blood vessel formation and account for the chronicity in psoriatic lesion (8). In vitro culture studies revealed that VEGF in the skin is secreted predominantly by keratinocytes and its concentration is enhanced in skin of patients with psoriasis (9). Moreover, constant delivery of VEGF to the skin in the transgenic VEGF mouse results in development of psoriasis-like inflammation (10).

TGF-β1 is a pleiotropic cytokine that is produced by almost all cell types, including activated inflammatory cells and keratinocytes (11). It possesses strong immunoregulatory properties, acts in autocrine and paracrine modes, and controls the differentiation, proliferation, and activation state of immune cells (12). TGF-β1 controls immune responses in a complex and often context-dependent manner (13). Its effects on immune cells depend on the type of cell, state of differentiation of the cell, and environment of the cytokines present (14). TGF-β1 can modulate expression of adhesion molecules, and provide a chemotactic gradient for leucocytes and other cells participating in an inflammatory response (12). TGF-β1 is linked to keratinocyte proliferation, which stimulates fibroblast production in the extracellular matrix and activates angiogenesis (14). Consequently, TGF-β1 may play an important role in the pathogenesis of psoriasis (11).

Nitric oxide (NO) is an active molecule generated in many cells including fibroblasts and endothelial cells, participating in psoriatic inflammatory processes. In context of dermal vascular dilatation and increased blood flow, characteristic features of psoriasis, the contribution of NO deserves special attention; however literature data on NO production in psoriasis are inconsistent (15).

In the current study, we aimed to investigate the association between the serum levels of VEGF, TGF-β1, and NO in patients with psoriasis vulgaris and disease severity.

PATIENTS AND METHODS

Fifty-eight patients with psoriasis vulgaris (36 males and 22 females) were enrolled in this study. The study was conducted at the Dermatology Clinics of a hospital affiliated to Qassim University, Buraydah, Saudi Arabia, between January 2011 and January 2012. The patients' age was (mean ± SE) 30.17 ± 1.406 years. The control group consisted of 22 age- and sex-matched healthy subjects. Their age was (mean ± SE) 29.36 ± 1.882 years. They included 11 males and 11 females. The patients did not receive topical treatment for 1 week or systemic treatment for 1 month such as steroids, methotraxate, Psoralen-Ultraviolet A (PUVA), retenoids, or cyclosporin. All patients were free of infections. Exclusion criteria were hypertension; obesity; diabetes mellitus; connective tissue diseases; and disorders of thyroid, kidney, and liver functions. In order to assess the severity of psoriasis, estimation of psoriasis area severity index (PASI) was done according to Fredrikson and Petterson (16). According to PASI score, the patients were classified into mild (PASI 0–3; $n = 23$), moderate (PASI >3–15; $n = 24$), and severe (PASI >15; $n = 11$) cases.

All patients were subjected to the following: thorough history-taking and clinical examination, full blood picture, hemoglobin concentration, erythrocytic sedimentation rate (ESR), leukocytic count, liver and kidney function tests, ECG, and abdominal sonography. After approval by the ethics committee of the College of Medicine, Qassim University, an informed consent was obtained from each subject enrolled in the study.

Ten milliliters of venous blood was collected from all patients and controls and allowed to clot at room temperature. After centrifugation, serum was collected and stored at −80°C until biochemical analyses. The serum levels of VEGF were determined using enzyme-linked immunosorbant assay (ELISA) kit (DRG International Inc., East Mountainside, NJ, USA). The serum levels of TGF-β1 were also detected using the ELISA kit (DRG International Inc., East Mountainside, NJ, USA). As NO is an unstable molecule, it is rapidly converted to nitrates and nitrites in the body; hence their concentration is parallel to NO levels. Total nitrite was quantified by the Griess reaction after reduction of nitrate to nitrite using *Escherichia coli* nitrate reductase (17, 18). The results were given as micromole per liter.

Statistical Analysis

The statistical analysis was performed using Prism Statistical Package, version 5.0 (Graphpad, San Diego, CA). Data comparisons were performed by Student's *t*-test and ANOVA with Bonferroni's post multiple comparisons test, and the correlations among the clinical and biochemical parameters were performed using Spearman's rank correlation coefficient. The levels of significance were accepted with $P < 0.05$ and the results were presented in tables as mean ± SEM.

RESULTS

The clinical characteristics of patients with psoriasis vulgaris and controls are shown in Table 1. The routine laboratory investigations for patients (mean ± SEM)

TABLE 1. Clinical Characteristics of Controls and Patients With Psoriasis Vulgaris

Variables	Controls ($n = 22$)	Patients ($n = 58$)
Age (years)	29.36 ± 1.882	30.17 ± 1.406
Male/Female	11/11	36/22
BMI (Kg/m^2)	29.58 ± 1.235	28.89 ± 0.7813
Illness duration (years)		10.34 ± 0.879

TABLE 2. Serum Levels of VEGF, TGF-β1, and NO in Patients With Psoriasis Vulgaris Comparing With Controls

Variables	Controls ($n = 22$)	Patients ($n = 58$)
VEGF (pg/ml)	229.3 ± 16.82	357.5 ± 15.04**
TGF-β1 (ng/ml)	25.44 ± 2.289	34.81 ± 2.719*
NO (μmol/l)	46.74 ± 3.539	132.1 ± 10.68**

Values are means ± SE.
*$P < 0.05$ and **$P < 0.001$, respectively, for comparison between patients and controls.

were the following: hemoglobin (13.44 ± 0.25 mg/dl), leukocyte count (7.88 ± 1.58 mm^3), and ESR (19.71 ± 3.13 mm/hr for first hour and 37.25 ± 5.06 mm/hr for second hour). The levels of aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase were in the normal range.

The serum levels of VEGF, TGF-β1, and NO were significantly higher in patients than the corresponding levels in controls (Table 2). The serum levels of the studied biochemical variables, VEGF, TGF-β1, and NO, in patients with severe disease activity were significantly increased in comparison with mild cases ($P < 0.001$, $P < 0.05$, and $P < 0.001$, respectively; Figs. 1–3). In addition, the levels of VEGF and TGF-β1 did not show any significant differences in the moderate cases in comparison with mild cases.

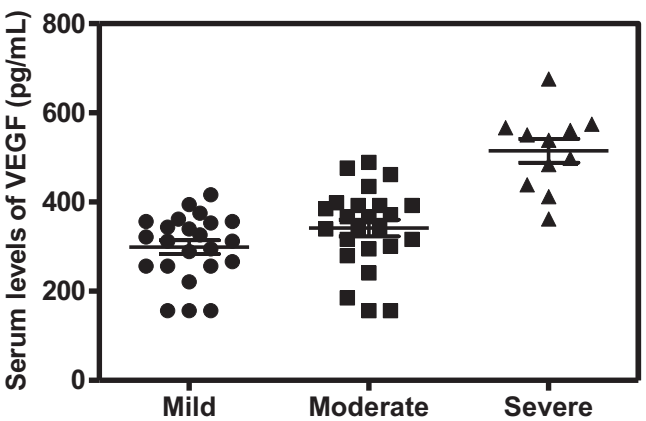

Fig. 1. Serum levels of VEGF were significantly higher in patients with severe psoriasis activity than in mild ones ($P < 0.001$).

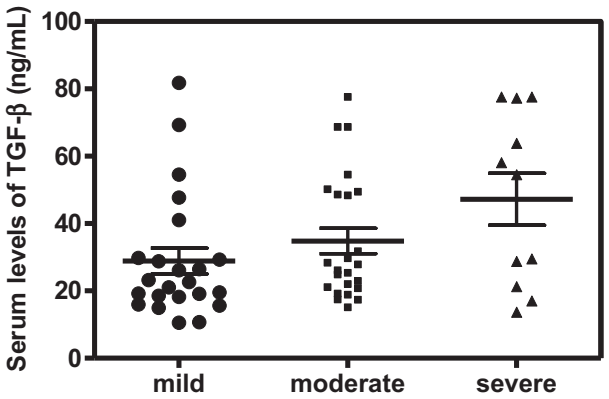

Fig. 2. Serum levels of TGF-β1 were significantly higher in patients with severe psoriasis activity than in mild ones ($P < 0.05$).

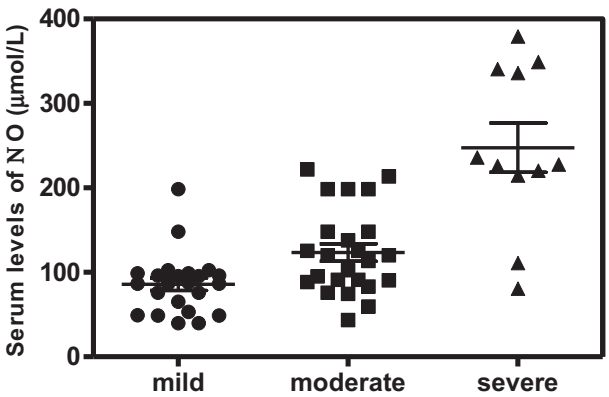

Fig. 3. Serum levels of NO were significantly higher in patients with moderate and severe psoriasis activities than in mild ones ($P < 0.01$ and $P < 0.001$, respectively).

The VEGF and TGF-β1 showed significant positive correlation with the duration of disease. The significant positive correlations between PASI score and each VEGF ($P \leq 0.001$, $r = 0.65$), TGF-β1 ($P \leq 0.05$, $r = 0.31$), and NO ($P \leq 0.001$, $r = 0.51$) are shown in Table 3. Moreover, a significant positive correlation between VEGF and NO was shown ($P \leq 0.05$, $r = 0.28$). The other clinical variables

TABLE 3. Correlation Coefficients Between the Measured Biochemical Variables and Clinical Parameters in Patients With Psoriasis Vulgaris

Variables	VEGF	TGF-β1	NO
PASI	$r = 0.65$ $P < 0.001$	$r = 0.31$ $P < 0.05$	$r = 0.51$ $P < 0.001$
Illness duration	$r = 0.35$ $P < 0.01$	$r = 0.42$ $P < 0.05$	$r = -0.08$ $P > 0.773$

Pearson's rank correlation analysis was conducted to investigate the relationship between variables. Data are presented as correlation coefficient (r) and the level of statistically significance (P).

such as ESR, leukocyte count, and age of the patient were not significantly correlated to the serum levels of VEGF, TGF-β1, and NO.

DISCUSSION

Psoriasis is a common inflammatory skin disease seen in dermatological clinics around the world. It is very common in Saudi Arabia, and Saudi psoriatic patients are expected to have an etiological base on both environmental and genetic factors (19). The most frequently seen form of psoriasis is psoriasis vulgaris, occurring in 90% of cases. It is rarely life-threatening; however, it has a severe negative impact on the patient's quality of life and can be an economic burden. Psoriasis vulgaris is characterized by scaly papulosquemous plaque lesions (20). It has a complex pathogenesis involving inflammation, hyperproliferation of keratinocytes, and enhanced angiogenesis. Angiogenic activity is driven by several growth factors including VEGF and TGF-β1. The most active is VEGF, which induces vascular hyperpermeability resulting in enhanced migration of inflammatory cells from blood vessels into psoriatic lesions (21).

Our results revealed that the levels of VEGF in patients were significantly higher than the corresponding levels in controls. In addition, a significant positive correlation between PASI score and VEGF was shown. There is increasing evidence that VEGF is the primary angiogenic factor involved in the pathogenesis of psoriasis (22). Similarly, many investigators (23) found that baseline mean serum levels of VEGF were significantly higher in patients than in healthy controls. Also, the authors demonstrated a significant correlation between VEGF and PASI score. Previous studies (24, 25) confirmed the significant elevations of VEGF in psoriatic patients and its significant correlation with PASI score. The elevated levels of VEGF in the sera of psoriatic patients may reflect overproduction, either in the skin with overflow into the circulation (9) or as a result of distinct genetic polymorphism (26). Conversely, some investigators (27) have found nonsignificant difference in the mean serum levels of VEGF between patients and controls, and insignificant correlation between serum levels of VEGF and PASI scores. They believed that VEGF plasma levels could not be a useful monitor of psoriasis severity. Another study did not confirm association between VEGF plasma concentration and severity of the disease (28).

The precise role of VEGF in the evolution of psoriatic lesions is not fully explained. It promotes vascular permeability that enhances leucocyte traffic into the dermis of psoriatic lesions (29), induces capillary dilatation that helps to nourish the hyperplasic epidermis (30), alters the dermal capillaries to express leucocyte chemoattractant molecules such as intercellular adhesion molecule 1 (31), and mediates high endothelial venules formation that may be important for T-lymphocyte extravasation and trafficking (32). The previous findings suggest that VEGF is likely a key factor in the link between inflammation and angiogenesis in psoriasis (1).

TGF-β1 is a member of a family of dimeric polypeptide growth factors and directly stimulates angiogenesis (33). Previous study (34) showed a relationship regarding TGF-β1 plasma levels, which was linked to keratinocytes proliferation and differentiation, as well as to skin inflammation associated with psoriasis activity.

Our results revealed that the levels of TGF-β1 were significantly higher in patients than the corresponding levels in controls. In addition, a significant positive correlation between PASI score and TGF-β1 was shown. Several investigators found higher levels of TGF-β1 in patients with psoriasis than controls (35, 36). Unlikely, other investigators (37) found that TGF-β1 levels are higher in serum of psoriatic patients in comparison to controls but insignificant. Flisiak et al. (38) found that in patients with chronic psoriasis vulgaris, baseline TGF-β1 plasma concentrations were significantly higher in only severe cases than control values. In the previous study (39), patients with severe active psoriasis vulgaris showed increased serum concentrations of TGF-β1 and a positive correlation between serum TGF-β1 levels and the intensity of psoriatic lesions.

Parallel to the findings of many studies (35, 40), we observed that serum TGF-β1 was correlated significantly and positively with PASI score. The possible reason for the increased circulating TGF-β1 with respect to the disease severity can be inflammation (40) or vascular expansion associated with activation of endothelial cells and fibroblasts that are important sources of TGF-β1 (41). In this respect, serum levels of TGF-β1 are also increased in other inflammatory diseases, such as rheumatoid arthritis and systemic lupus erythematosus, and thus are not specific for psoriasis (42). It is also not clear why serum TGF-β1 levels are correlated with psoriasis severity as measured by PASI, as shown in this study and other studies (35, 38).

Dysregulation of TGF-β1 signaling has been reported in human psoriasis (43). The mechanism for increased serum levels of TGF-β1 in patients with psoriasis remains unclear. Increased TGF-β1 in the epidermis and the serum has been found in psoriatic patients (40) and the TGF-β1 serum level was closely correlated with disease severity (34, 35). In contrast, TGF-β1 is barely detectable in normal skin epidermis because of its short half-life time (43, 44). The increased TGF-β1 could come from activated endothelial cells, fibroblasts, or inflammatory cells in psoriasis patients; all of which can produce more TGF-β1 (34). However, based on clinical data, it is difficult to determine if increased TGF-β1 plays a causal

role in psoriasis, or it is simply a consequence of psoriasis pathogenesis.

NO has been shown to play an important role in the pathogenesis of psoriasis. Previous studies have demonstrated raised levels of NO in psoriatic plaques, which may be attributed to its effect on keratinocytes, local cyclic guanosine monophosphate (cGMP) levels, or its ability to induce angiogenesis (45). Our results revealed that the levels of NO were significantly higher in patients than the corresponding levels in controls. In addition, a significant positive correlation between PASI score and NO was shown. Similarly, several investigators found the same findings (46). This is clearly indicating that the patients with psoriasis were under severe oxidative stress. This may also be indicating that oxidative stress plays an important role in the pathogenesis of psoriasis (46). Moreover, several investigators (45) found that NO levels were significantly increased in patients with psoriasis and these levels showed a positive correlation with severity and duration in the chronic plaque-type group.

Cals-Gierson and Ormerod (47) have stated that NO can stimulate epithelial cells to produce and release chemokines and other growth mediators, such as VEGF, that appear to be important for keratinocyte proliferation and angiogenesis. NO is also found to increase the level of cGMP, which may act as a secondary mediator and bring about proliferation of keratinocytes. Ormerod (48) also demonstrated decreased NO production in psoriatic plaque after application of iNOS inhibitor, NG monomethyl L-arginine. In the current study, the VEGF and NO were shown significantly positively correlated. In this respect, many investigators (49) provide more evidence that NO plays a critical role in angiogenesis. Cooke and Lsordo (50) reported that angiogenesis is attenuated when NO bioactivity is reduced. The mechanisms by which NO promotes angiogenesis are not fully elucidated. NO is an endothelial survival factor, inhibiting apoptosis and enhancing endothelial cell proliferation, perhaps in part by increasing the expression of VEGF or fibroblast growth factor (50). NO may suppress the production of angiostatin, an endogenous antagonist of angiogenesis (49).

CONCLUSIONS

The elevated serum levels of VEGF, TGF-β1, and NO in our psoriatic patients and their significant correlation with psoriasis severity (PASI score) strongly support the proposed role of these bio-indices in the pathogenesis of psoriasis. Accordingly, the serum levels of VEGF, TGF-β1, and NO might be recognized as indicators for clinical evaluation of disease severity. It has been assumed that direct targeting of angiogenesis, particularly the main player VEGF, may help to develop new strategies to treat psoriasis by influencing the angiogenesis required for the inflammatory disease. Further studies must take place to clarify the exact role of these studied growth factors and NO in psoriasis and their possible usefulness from a therapeutic standpoint.

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CONFLICT OF INTEREST

None declared.

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