

## Serum Tumor Necrosis Factor- $\alpha$ (TNF- $\alpha$ ) with Erectile Dysfunction in Psoriatic Patients

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### ABSTRACT

**Background:** Erectile dysfunction (ED) is a common disorder leading to serious, negative impact on the quality of the patient's life and self-esteem. Its occurrence rate increases with psoriatic patients, as it is a systemic disease intervenes with endothelial dysfunction. A link is described among systemic inflammation and endothelial dysfunction (Psoriasis), and ED.

**Objective:** Estimate of the serum level of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) in erectile dysfunction patients with psoriasis and patients with erectile dysfunction without psoriasis.

**Subjects and Methods:** This study was conducted over a period of one year starting from February 2018 until February 2019. The study was consented by the Ethics Committee of Al-Azhar Faculty of Medicine. A sample of 90 men (30 men psoriatic patients with ED and 30 men with ED complaints and 30 healthy men of matched age as controls) were conscripted from the Dermatology and Andrology Outpatient Clinics at Al-Hussien and Bab Al-Shariah University Hospitals. ED presence and severity were tested by the five-item version of the International Index of Erectile Function questionnaire (IIEF-5). Psoriatic patients were evaluated by PASI score. All subjects had thorough medical history and full physical examination. The serum level of TNF- $\alpha$  was measured for all cases and healthy controls using specific enzyme-linked immunosorbent assay (ELISA) technique. All men volunteered to partake in this study were married and have only one sexual partner.

**Results:** In this study, serum TNF- $\alpha$  levels were indicatively elevated in psoriatic patients with ED compared to ED patients only. In addition, the difference reached highly statistical significance between psoriatic patients with ED and healthy controls. The elevation correlates with duration of the disease, and family history. Levels of TNF- $\alpha$  were further increased when ED was associated with psoriasis advocating a more severe course of ED in these patients.

**Keywords:** Erectile dysfunction, tumor necrosis factor- $\alpha$ , psoriasis.

### INTRODUCTION

Erectile dysfunction (ED) is defined as the incompetency to attain and/or maintain penile erection and it is a multifactorial condition that is estimated to affect more than 150 million men worldwide. It seriously affects the quality of life of patients and their partners. Erectile dysfunction becomes increasingly ubiquitous with age. The presence of chronic disease (e.g., CVD), as well as smoking, alcohol or drug abuse, and sedentary lifestyle are major risk factors for erectile dysfunction <sup>(1)</sup>. Psoriasis is a common, chronic inflammatory disease of the skin affecting 1–3% of the general population and characterized by complex amendments in epidermal growth and differentiation with multiple biochemical, immunological, and vascular abnormalities <sup>(2)</sup>.

Although the accurate etiology of psoriasis remains uncertain, current evidence indicates that it is T-cell driven. Individuals with active skin disease have elevated levels of tumor necrosis factor alpha (TNF- $\alpha$ ) in both blood and skin lesions <sup>(3)</sup>.

Cytokines are protein molecules that comprise *Tumor Necrosis Factor (TNFs)*,

Interleukins (ILs), various Colony Stimulating Factors and Interferons (IFNs) <sup>(4)</sup>.

It is noticeable that diseases associated with high levels of TNF- $\alpha$  such as psoriasis, psoriatic arthritis are associated with erectile dysfunction <sup>(5)</sup>. Endothelial dysfunction is a key event in the pathophysiology of erectile dysfunction and endothelial function is impaired in the presence of increased oxidative stress and inflammatory conditions such as psoriasis <sup>(6)</sup>. TNF- $\alpha$  plays a key role in inducing endothelial dysfunction. Many studies indicated that TNF- $\alpha$  may be the causal agent of endothelial dysfunction such as in erectile dysfunction and psoriasis <sup>(7)</sup>.

### AIM OF THE WORK

The aim of this study was to estimate the serum level of TNF- $\alpha$  in erectile dysfunction patients with psoriasis and patients with erectile dysfunction without psoriasis.

### SUBJECTS AND METHODS

This study was conducted over a period of one year starting from February 2018 until February 2019. **The study was approved by the Ethics**

**Committee of Al-Azhar Faculty of Medicine. Written informed consent was obtained from all of the patients and healthy controls.**

The study included 90 individuals that were divided into 3 groups: Group I: 30 patients with erectile dysfunction and psoriasis. Group II: 30 patients with erectile dysfunction only. Group III: 30 normal individuals (control). The patients were collected from the Dermatology and Andrology Outpatient Clinics at Al-Hussien and Bab Al-Shariah University Hospitals.

**Inclusion Criteria:** Patients with erectile dysfunction and psoriatic patients with erectile dysfunction. Ages ranged from 20 to 50 years old. Sexually active (married). Patients had to break off the systemic therapy for psoriasis at least one month before the study.

**Exclusion criteria:** Patients with other autoimmune disease, as Graves' disease, rheumatoid arthritis, thyroid dysfunction etc. Patients with former skin cancer or premalignant skin lesions or taking immunosuppressive drugs such as methotrexate.

**All patients were subjected to:**

Detailed personal, medical, psychological and sexual history. **Personal history:** Age and special habits. **Medical history:** Chronic systemic disease; medication use. History of surgery or trauma. History of previous therapy and response to this therapy. **Sexual history:** Onset, course, and duration of ED. Morning erection. Difficulty in attaining or maintaining erection. Other causes of sexual dysfunction (loss of desire, ejaculation disorder). The health status of the wife, investigating possible sexual disturbances. **Psychological history:** Relational factors (chronic conflicts, disparity of income, loss of sex plead). Intrapsychic environment (performance anxiety, depression, professional stress). **International Index of Erectile Function (IIEF)-5:** To diagnose the existence and assess the severity of ED. Items in the IIEF-5 are phrased to reference the prior six-month period, which conforms with the NIH's current reference period for establishing a diagnosis of ED.

**Physical examination:**

**All patients had a full physical examination including cardiovascular system:** measurement of heart rate, blood pressure, heart sounds, and peripheral pulses. **Neurological examination:** to appraise possible underlying neurological conditions. **Secondary sexual characteristics and the existence of gynecomastia.**

**Genital examination:** Penis: size, scars, hypospadias, plaque or others. Testis: site, volume and consistency. Scrotum: color, rugae or others.

**Dermatological examination:** For assessment of severity of psoriasis by using (PASI score)

**Investigations:** Furthermore, investigations were directed by clinical findings (serum testosterone, serum prolactin, serum prostatic specific antigen, lipid profile, fasting blood sugar, liver and kidney functions). Penile duplex (for ED patients and psoriatic patients with ED). Measurement of serum TNF- $\alpha$ : Venous blood samples were taken from patients and controls under sterile conditions between 08:00 - 10:00 am. All venous samples were centrifuged within 30 minutes at 3000 rpm for 15 min, and serum was separated into multiple aliquots and stored at  $-80^{\circ}\text{C}$  until assayed. The serum level of TNF- $\alpha$  was measured for the three groups using ELISA technique according to the manufacturer's instructions using kits provided by Sunred Biological technology Co., Ltd; Shanghai.

**Statistical analysis**

Data were analyzed using Statistical Program for Social Science (SPSS) version 15.0. Quantitative data were expressed as mean  $\pm$  standard deviation (SD). Qualitative data were expressed as frequency and percentage.

**The following tests were done:**  
**Independent-samples t-test of significance:** was used when comparing between two means. **Chi-square test:** was used when comparing between non-parametric data. **A one-way analysis of variance (ANOVA):** when comparing between more than two means. **Post Hoc test:** was used for multiple comparisons between different variables. **Probability (P-value):** P-value  $< 0.05$  was considered significant. P-value  $< 0.001$  was considered as highly significant. P-value  $> 0.05$  was considered insignificant.

## RESULTS

**Table (1):** Comparison between studied groups as regard age.

Variables		Group I (N = 30)	Group II (N = 30)	Group II (N = 30)	P-value
Age (years)	Mean	31.77	30.60	32.53	0.6
	$\pm$ SD	7.04	6.50	7.98	

This table shows no statistical significant difference (**p-value**  $> 0.05$ ) between studied groups as regard age.

**Table (2):** Comparison between group I and group II as regard duration of erectile dysfunction.

Variables		Group I (N = 30)	Group II (N = 30)	P-value
Duration of erectile dysfunction (months)	Mean	23.83	11.70	< 0.001*
	± SD	8.47	5.23	

\*: p-value < 0.001 is considered highly significant.

This table shows highly statistical significant difference (**p-value < 0.001**) between group I and group II as regard duration of the disease.

**Table (3):** Description of PASI score in group I.

Variables		Group I (N = 30)
PASI score	Mean	7.40
	± SD	3.64
	Min	3.3
	Max	15

This table shows description of PASI in group I. The mean PASI was  $7.4 \pm 3.64$  with minimum PASI of 3.3 and maximum PASI of 15.

**Table (4):** Comparison between group I and group II as regard penile duplex for ED.

Variables		Group I (N = 30)	Group II (N = 30)	P-value
visual grading of ED	E0	1 (3.3%)	2 (6.7%)	0.6
	E1	12 (40%)	10 (33.2%)	
	E2	5 (16.7%)	8 (26.7%)	
	E3	6 (20%)	5 (16.7%)	
	E4	1 (3.3%)	3 (10%)	
Diagnosis	E5	5 (16.7%)	2 (6.7%)	0.2
	Normal	14 (46.6%)	12 (40%)	
	Arterial insufficiency	12 (40%)	9 (30%)	
	Venous insufficiency	2 (6.7%)	1 (3.3%)	
	Intermediate	2 (6.7%)	8 (26.7%)	

This table shows no statistical significant difference (**p-value > 0.05**) between group I and group II as regard penile duplex for ED.

**Table (5):** Comparison between studied groups as regard TNF- $\alpha$ .

Variables		Group I (N = 30)	Group II (N = 30)	Group II (N = 30)	P-value
TNF- $\alpha$ (pg/ml)	Mean	7.33	6.32	3.09	< 0.001*
	± SD	2.12	1.85	1.18	

\*: p-value < 0.001 is considered highly significant.

This table shows highly statistical significant difference (**p-value < 0.001**) between studied groups as regard TNF- $\alpha$ .

**Table (6):** Post-Hoc test for Comparison between studied groups as regard TNF- $\alpha$ .

Groups Variables		I vs II	I vs III	II vs III
TNF- $\alpha$	LSD	1.001	4.2	3.2
	p-value	<b>0.03*</b>	<b>&lt; 0.001**</b>	<b>&lt; 0.001**</b>

\*: p-value < 0.05 is considered significant.

\*\*: p-value < 0.001 is considered highly significant.

#### This table shows:

- Highly statistically significant difference (**p-value < 0.001**) between group I and group III as regard TNF- $\alpha$ .
- Highly statistically significant difference (**p-value < 0.001**) between group II and group III as regard TNF- $\alpha$ .
- Statistically significant difference (**p-value < 0.05**) between group I and group II as regard TNF- $\alpha$ .

## RESULTS

Thirty psoriatic patients with ED, their ages ranged between 20 and 50 years old (Mean =  $31.77 \pm 7.04$ ) and PASI score (Mean =  $7.40 \pm 3.64$ ). Thirty patients with ED, their ages ranged between 20 and 50 years old (Mean =  $30.60 \pm 6.50$ ). Thirty normal individuals (control), their ages ranged between 20 and 50 years old (Mean =  $32.53 \pm 7.98$ ).

Our study shows no statistical significant difference (p-value > 0.05) between studied groups as regard age (table 1). In addition, our study showed highly statistical significant difference (p-value < 0.001) between group I and group II as regard duration of ED. ( $23.83 \pm 8.47$  vs.  $11.70 \pm 5.23$ ) (table 2). Table (6) showed description of PASI in group I.

The mean PASI was  $7.4 \pm 3.64$  with minimum PASI of 3.3 and maximum PASI of 15.

Our study showed also no statistical significant difference (p-value > 0.05) between group I and group II as regard penile duplex for ED (table 3 and 4).

In our study, serum TNF- $\alpha$  levels were elevated in group 1 (psoriatic patients with ED), Serum TNF- $\alpha$  levels were elevated too in group 2 (ED patients only) and were normal in group 3 (control group). TNF- $\alpha$  were significantly elevated in psoriatic patients with ED compared to ED patients only. And the difference reached highly statistical significance between psoriatic patients with ED and healthy controls.

## DISCUSSION

Erectile dysfunction (ED) is a major public health problem, which becomes increasingly ubiquitous with age, and seriously affects the quality of life and self-esteem of patients and their partners<sup>(8)</sup>. A low-grade inflammatory process is an important

pathophysiologic constituent of HTN, DM, CVD, and ED and high levels of inflammatory mediators are independent risk factors that can anticipate the advancement of these conditions<sup>(9)</sup>.

ED and its comorbid conditions share common risk factors such as endothelial dysfunction, atherosclerosis and metabolic abnormalities. Out of all these risk factors, inflammation, especially TNF- $\alpha$ , has been suggested to play a part in the ED occurrence<sup>(10)</sup>.

Endothelial function, a key event in the pathophysiology of ED, is impaired in the existence of increased oxidative stress and inflammatory conditions<sup>(6)</sup>. TNF- $\alpha$  has the ability to increase arterial reactive oxygen species (ROS) generation, which probably accounts for some of the diminishment in NO levels. In addition to its effects on endothelial function. TNF- $\alpha$  was demonstrated to have a substantial proatherogenic role<sup>(11)</sup>.

The relation between ED and increasing serum level of TNF- $\alpha$  was proved by many studies. They found that diseases associated with high levels of TNF- $\alpha$  such as psoriasis, psoriatic arthritis<sup>(12)</sup>, ankylosing spondylitis<sup>(13)</sup> and chronic obstructive pulmonary disease are also bound with ED in men<sup>(14)</sup>. Overexpression of TNF- $\alpha$  in a mouse model decreased induced erections, mounting behavior and number of intromissions<sup>(15)</sup>. Conversely, TNF- $\alpha$  in KO mice showed increased number of spontaneous erections<sup>(16)</sup>. Administration of TNF- $\alpha$  in vivo decreased the release of NO and induced impairment of endothelium-dependent vasorelaxation in a variety of vascular beds<sup>(17)</sup>.

Isolated corpora cavernosa from TNF- $\alpha$ -infused mice displayed decreased NANC-dependent relaxation and increased sympathetic-mediated contractions, which could favor penile detumescence to occur<sup>(18)</sup>.

Furthermore, TNF- $\alpha$  suppresses eNOS and nNOS expression by inhibiting the gene promoter activity in endothelial cells <sup>(18)</sup>.

The aim of the present study was to appraise whether the inflammatory cytokine TNF- $\alpha$  is associated with ED compared to psoriatic patients with erectile dysfunction and the matched controls with normal sexual function. Also, whether it could be used as a marker to diagnose ED, and act as an early warning signal for the blossoming of more serious conditions. Such a marker may also act as a non-subjective measure of the degree of ED, and lead to more suitable dosage treatment routines. The rationale for assaying inflammatory factors for ED is that they have been shown to promote endothelial dysfunction, which is an important determinant of erectile function <sup>(19)</sup>.

Subjects were comprehensively evaluated and asked to answer the five-item version of International Index of Erectile Function (IIEF-5) questionnaire as a method to diagnose and classify ED. All Psoriatic patients were evaluated by (PASI) score.

*There are different studies support our study:* (Vlachopoulos *et al.*) <sup>(9)</sup> demonstrated an increase in the levels of inflammatory markers such as TNF- $\alpha$  in patients with ED, suggesting that low-grade systemic inflammation is present in these subjects. Moreover, other investigators reported that ED was associated with increased levels of TNF- $\alpha$ , which increased progressively with the severity of penile vascular disease, augmenting the role of these markers in the pathophysiology of ED <sup>(10)</sup>. In another study, which is contradictory to our results reported reduced levels of adiponectin, an anti-inflammatory cytokine that attenuates endothelial cell adhesion molecules, and the levels of inflammatory cytokines, such as TNF- $\alpha$ , IL-8, and IL-6, were observed in patients with ED <sup>(20)</sup>. Moreover, preclinical studies demonstrated that the administration of TNF- $\alpha$  in vivo decreases the release of NO, and induces impairment of endothelium-dependent vasorelaxation in a variety of vascular beds <sup>(17)</sup>.

Furthermore, TNF- $\alpha$  suppresses eNOS and nNOS expression by inhibiting the gene promoter activity in endothelial cells <sup>(18)</sup>. TNF- $\alpha$  was acutely decreased after sildenafil administration in men with vasculogenic ED <sup>(21)</sup>.

Although the underlying pathogenesis of ED is still unknown, endothelial dysfunction, induced by inflammatory cytokines has been proposed as a possible mechanism. Collected data strongly suggest that group 1 which pointing to psoriatic patients with

ED have the most elevated TNF- $\alpha$  serum level than the other two groups. The coexistence of ED and Psoriasis is linked with higher levels of this marker on top of ED alone. These findings supports the possibility that this factor could be a general inflammatory marker of endothelial damage, and emphasize the pathophysiological involvement of TNF $\alpha$  and endothelial dysfunction in the pathogenesis of ED. Men consulting for ED may benefit from measurement of such cytokines for better disease assessment and determination of the risks that it confers.

## CONCLUSION

The results of this study showed that TNF- $\alpha$  plays a detrimental role in erectile function, and indicates that it could be implicated in the pathogenic process of ED, and could be used as a marker for screening the disease severity and progress. The coexistence of ED and psoriasis is associated with higher levels of this marker on top of ED alone. These findings supports that this factor could be a general inflammatory marker of endothelial damage, and emphasize the pathophysiological involvement of TNF $\alpha$  and endothelial dysfunction in the pathogenesis of ED.

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