Biochemical Significance of Proinflammatory Cytokines in Psoriasis vulgaris among Egyptian Patients

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Abstract

Background: Psoriasis has been characterized by hyperproliferation accompanied by acanthosis and aberrant differentiation of keratinocytes. Several growth factors and cytokines, are assumed to be important. Recent studies indicate that various cytokines including tumor necrosis factor - α (TNF - α), IL - 2R and IL - 6 play an essential role in the induction and maintenance of psoriatic lesion.

Objectives: To analyse relevant inflammatory mediators in the serum of patients with active psoriasis (Psoriasis vulgaris) of mild-to-moderate and severe psoriasis compared to healthy controls.

Patients / Methods: Forty psoriasis patients were recruited from the dermatology outpatient clinic of Cairo University Hospital. Patients body mass index (BMI), waist circumference and psoriasis area and severity index (PASI) were recorded. Fasting serum samples were obtained on enrolment. All the patients did not receive any treatment (locally or systemically), for at least four weeks before enrolment. Age, sex and (BMI) matched with forty healthy controls were also recruited. Serum TNF - α, IL - 2R and IL - 6 levels were estimated using an Enzyme-Linked Immunosorbant Assay (ELISA) technique. The patients group were subdivided to two groups according to the diseases severity, PASI , into, mild-to-moderate psoriasis group and severe psoriasis group.

Results: Serum TNF - α, IL - 2R and IL - 6 were all statistically significant elevated in the patients group compared to healthy controls ($p < 0.05$). Also they were all statistically significant increased in severe psoriasis compared to mild-to-moderate psoriasis ($p < 0.05$).

Conclusions: These data support the view that serum TNF - α, IL - 2R and IL - 6 are involved in the pathogenesis of psoriasis, possibly by induction and maintenance of psoriatic lesion. We recommend a use of an array of these cytokines as a useful follow-up marker for monitoring of psoriatic patients and optimizing therapeutic strategies. Also we suggest the study of antisense therapy using the antibody of these cytokines in psoriatic patients.

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Keywords: Psoriasis vulgaris, Cytokines, TNF - α, IL - 2R and IL - 6.

1. Introduction

Psoriasis is relatively common, chronic, inflammatory and hyperproliferative skin disease that may appear at any age and affect any part of the skin. It affects 1.4 % to 2.0 % of the population and comprises 2.6% of skin related visits to primary care physicians, or between 0.3% and 1.6% of all visits to family physicians. It is a very troublesome disease with a high economic impact **(Ulrich and Kristian 2009).** The disease often persists for life, and the patient has an increased risk of cardiovascular diseases and their complications. One out of five patients develops psoriatic arthritis. The clinical picture of psoriasis is highly variable with regard to lesional characteristics and the severity of disease **(Batya *et al*. 2010).**

Psoriasis vulgaris is a multifactorial heritable disease characterized by severe inflammation resulting in poorly differentiated, hyperproliferative keratinocytes. It is including genetic background, environmental factors, and vascular and immune system disturbances. Current research is dominated by the hypothesis that an immunological disorder with inflammatory reaction, mediated through T-lymphocytes, plays a key role in the pathogenesis of psoriasis **(Nograles *et al*. 2010).**

The characteristic histological features of the disease are epidermal hyperproliferation and infiltration of both dermis and epidermis by inflammatory cells including neutrophils, lymphocytes, macrophages and mast cells. Interactions between infiltrating T cells and skin resident cells (keratinocytes, fibroblasts, endothelial cells) are often mediated by the synthesis and release of different proinflammatory cytokines **(Krueger and Ellis 2005).**

Recently, much attention has been directed towards the influence of cytokines in psoriasis, as they play an important role in inflammatory diseases. In addition, a number of studies have suggested that various cytokines released by keratinocytes and inflammatory leucocytes could contribute to the induction or persistence of the inflammatory processes in psoriasis; however, the precise mechanism of their involvement in psoriasis remains unclear. Few studies have been reported on serum cytokine levels that may be expected to alter if they are involved in the pathogenesis of psoriasis **(Kristina and Krueger 2009).**

Although the cytokine mediated response is an essential part of the natural protective mechanism, excessive production of pro-inflammatory cytokines, or production of cytokines in the wrong biological context are associated with the pathology in a wide range of diseases including psoriasis. At the present time, one of the main areas of research in the psoriasis field concerns the role of cytokines in the pathogenesis of this disease. Different cytokines play a part in sustaining the two main characteristics of a psoriatic lesion; keratinocyte hyperproliferation and inflammation **(Stephen and Gelfand 2008).**

Interleukin - 2 (IL – 2), interleukin - 6 (IL – 6), and tumor necrosis factor alpha (TNF - α) are the hallmark cytokines in a psoriatic cytokine network. Several investigators have suggested the possible use of TNF - α , IL - 6, IL - 8 and soluble interleukin - 2 receptor (IL - 2R) as markers of disease severity in psoriasis. The interleukin - 2 receptor (IL - 2R) is a heterotrimeric protein expressed on the surface of certain immune cells, such as lymphocytes, that binds and responds to a cytokine called interleukin 2 **(Hidetoshi *et al.* 2009).**

Recent studies indicate that various cytokines including tumor necrosis factor alpha (TNF – α) play an essential role in the induction and maintenance of psoriatic lesion. TNF - α is a 17 - k D polypeptide that plays a central role in the regulation of innate immune responses. It is involved in stimulating the production of inflammatory cyokines, inducing the expression of cell surface adhesion molecules, enhancing the phagocytic/bactericidal properties of macrophages, and activating apoptotic pathways. TNF - α is produced by a wide variety of cells, ranging from lymphocytes and monocytes, to keratinocytes, mast cells and antigen presenting cells in the skin. It is believed to contribute to the pathogenesis of psoriasis through its ability to both promote immune cell trafficking to the skin and induce keratinocyte proliferation **(Gottlieb *et al.* 2003).**

Overexpression of IL - 6 has been implicated in the pathology of numerous autoimmune and chronic inflammatory diseases, including psoriasis **(Kristina and Krueger 2009).** Cytokine IL - 6 is a multifunctional immunoinflammatory mediator with a MW of 25 to 30 kDa protein **(Kawano *et al.* 1988).** It is produced by a number of different cell types including keratinocytes **(Kupper *et al.* 1989)** and leukocytes **(Baumann *et al.* 1984).** It also stimulates the proliferation of human keratinocytes in culture **(Krueger *et al.* 1991)** and this proliferative effects are suggested to be mediated indirectly via the epidermal growth factor/transforming growth factor alpha receptor **(Elder *et al.* 1992)**. Thus IL - 6 has been speculated to play an important role in the pathogenesis of psoriasis, and in fact, its enhanced expression was demonstrated in the psoriatic lesional skin **(Ohta *et al.* 1991)**, together with the reports of its increased production by monocytes and of its elevated circulating levels **(Neuner *et al.* 1991).** Overexpression of IL - 6 has been implicated in the pathology of numerous autoimmune and chronic inflammatory diseases, including psoriasis **(Wojciech *et al.* 2008).**

2. Aim of the work

This study aimed to evaluate the association of a panel of some proinflammatory cytokines (TNF - α , IL - 6, and soluble interleukin - 2 receptor (IL -2R), in the serum of patients with active psoriasis (Psoriasis vulgaris) and compare them to healthy controls.

Also, to investigate which would be an attractive, patient-independent, and observer-independent marker of disease severity. And, to determine the use of these cytokines as markers of disease severity in patients of mild – to - moderate and severe psoriasis.

3. Material and Methods

3.1. Subjects

This study comprised forty consecutive patients of psoriasis were recruited from the dermatology outpatient clinic of Cairo University Hospital. All the patients were subjected to detailed examination including the elicitation of dermatological and psychiatric complaints. The diagnosis was made clinically, based on the presence of characteristic plaque-type psoriatic lesions. All the patients were asked to provide socio-demographic data, medical history, and family history. Other questions included the duration of disease, age of onset of the disease, any treatment taken and use of psychotropic drugs. Dermatological examination, hairs, mucosal involvement and nail changes were recorded. The patients group were subclassified to two groups according to the diseases severity, severity index (PASI) into, mild-to-moderate psoriasis group and severe psoriasis group. Forty healthy age and sex matched volunteers with no family history of psoriasis were included in the study as a control group. The purpose and nature of the study were explained to all subjects. All included subjects have consented to be enrolled in this study.

3.2. Exclusion Criteria

Obese subjects with history of acute or chronic infections, liver disease, renal disease, recent history of cardiovascular disorder, hypertension, neurological disease, or diabetes mellitus were excluded from the study. Moreover, patients who had received oral or topical antipsoriatic therapy within four weeks were not included in the study.

3.3 Methods

3.3.1. Clinical Assessment

Disease severity was monitored by assessing the psoriasis area and severity index (PASI). It includes assessment and recording of erythema, infiltration, desquamation and extent of the disease (area %) by using numerical rating of 0 - 4 for each of the parameter:

0 for absent; 1 for slight (light pink, rare scales, no elevation with area involvement < 10 %) ; 2 for moderate (light red, poorly defined scales, slight elevation with area involvement 10 - 30 %); 3 for severe (red, defined scales, moderate elevation with area involvement 30 – 50 %); and 4 for very severe (very red, heavy scales, marked elevation with area involvement 50 – 70 %). Accordingly, mild-moderate psoriasis and severe psoriasis were defined as PASI < 15 and PASI >15, respectively.

3.3.2. Blood Sampling

Blood samples (10 ml) were collected from patients and control subjects in serum separator vacutainers (BD Vacutainer Systems, Plymouth, UK). Sera were separated and immediately stored at − 80° C until analysis.

3.3.3. Laboratory Investigations

Major laboratory parameters, including blood sedimentation rate, liver and renal function tests, blood cell counts; random blood sugar, were evaluated at the same time points for all participants to exclude any organic disease or inflammation.

3.3.4. Serum Cytokines Measurements

The quantitative determination of TNF - α, IL - 2R and IL - 6 levels were conducted by an Enzyme-Linked Immunosorbant Assay (ELISA) technique, using a commercial available kit, Every sample was run in duplicate, measurements differed by less than 10 %, and the mean value was calculated and used for statistical analysis.

Assessment of plasma TNF-alpha : Analysis was performed by TNF- alpha ELISA Kit, Diaclone research, (URS) - France (Catalog Number 850.090.096) .

Assessment of human sIL-2R: Human sIL-2R levels were measured using commercially available kit (ELISA) based on the sandwich principle, manufactured by T-Cell diagnostics (Endogen Inc., Cambridge, CA). The human sIL-2R concentrations were determined from the standard curve after being run concurrently with the standards **.**

Assessment of plasma IL-6: Analysis was performed using commercially available kit (IL-6 ELISA Kit), Diaclone Research, (URS), - France (Catalog Number 850. 030 .096).

The minimum detectable dose of IL-6 is less than 2pg/ml. Intra and Inter - Assay coefficients of variation of the assay were 0.83-3.86% and 1.89-5.84%.

3.3.5. Statistical analysis

All data were coded and entered using the program statistical package for social sciences (SPSS) version 15 under windows XP. Descriptive data was summarized using mean, standard deviation (SD). Linear regression analysis was done to test for significant predictors for psoriasis severity as measured by PASI score. P values < 0.05 were considered statistically significant.

4. Results

4. 1. Clinical Data

Forty patients with psoriasis vulgaris were included in this study. Twenty of the patients had mild to moderate psoriasis (PASI <15), while the other twenty had severe psoriasis (PASI > 15). Of the forty patients, 26 were females (65%) and 14 were males (35%). Their age ranged between 18 – 62 years. The mean age and standard deviation (SD) was 38.50 ± 12.83 years. The duration of the disease ranged between 4 months to 180 months, with a mean ± SD 57.05 ± 54.08. The PASI score for clinical assessment ranged between 3.5 - 28.5, the mean ± SD was 14.61 ± 6.6. The control group included 29 females (74.5%) and 11 males (25.5%). Their age ranged between 18 - 54 years with mean ± SD 35.70 ± 9.09. Controls were age and sex matched.

4. 2. Estimation of serum cytokines levels by ELISA technique

The demographic, clinical and biochemical data of the studied subjects are showed in Table (1, 2).

In this study we compare the serum levels of TNF - α, IL - 2R and IL - 6 between forty psoriasis patients and forty age- and sex-matched healthy controls from the Egyptian population. All the patients were untreated, both locally and systemically, for at least four weeks before enrolment. It was also ensured that control subjects had no medication during the 4 weeks before blood sampling.

The mean value (mean ± SD) of serum TNF - α level estimated in patients with mild to moderate psoriasis was (121.24 ± 59.35 pg/ml) and controls (30.85 ± 25.45 pg / ml). A statistically significant difference was found in the serum TNF- α level between patients and controls (P < 0.05). However, when patients were evaluated according to disease severity, serum TNF - α level was significantly higher in patients with severe psoriasis (173.23 ± 70. 45 pg/ml) than patients with mild to moderate psoriasis and controls (p < 0.05) (fig.1).

The mean value (mean ± SD) of serum s IL - 2R level estimated in patients with mild to moderate psoriasis was (355.32 ± 104.21 pg/ml) and controls (144.65 ± 69.44 pg / ml). A statistically significant difference was found in the serum s IL - 2R level between patients and controls (P < 0.05). However,

when patients were evaluated according to disease severity, serum s IL - 2R level was significantly higher in patients with severe psoriasis (475.45 ± 111.45 pg/ml) than patients with mild to moderate psoriasis and controls ($p < 0.05$) (fig.2).

The mean value (mean ± SD) of serum IL - 6 level estimated in patients with mild to moderate psoriasis was (15.24 ± 8.58 pg/ml) and controls (5.99±1.34pg/ml). A statistically significant difference was found in the serum IL - 6 levels between patients and controls ($P < 0.05$). However, when patients were evaluated according to disease severity, serum IL - 6 level was significantly higher in patients with severe psoriasis (33.76 ± 11.34 pg/ml) than patients with mild to moderate psoriasis and controls ($p < 0.05$) (fig.3).

Table (1): The demographic data of the studied subjects

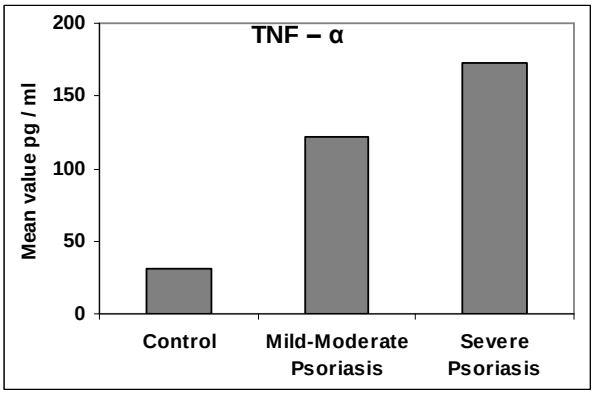
	Control	**Psoriasis patients**
Number	40	40
Age (years) **Range** **mean ± SD**	 18 – 54 35.7 ± 9.09	 18 – 62 38.5 ± 12.83
Sex **Male** **Female**	 11 (25.5 %) 29 (74.5 %)	 14 (35 %) 26 (65 %)
Duration of illness (months) **mean duration** ± SD		4 – 180 57.05 ± 54.08
PASI **Range** **Mean** ± SD		 3.5 – 28.5 14.61 ± 6.6

(Table 2): Serum levels of the studied cytokines in patients with Psoriasis vulgaris compared to healthy controls (mean ± SD)

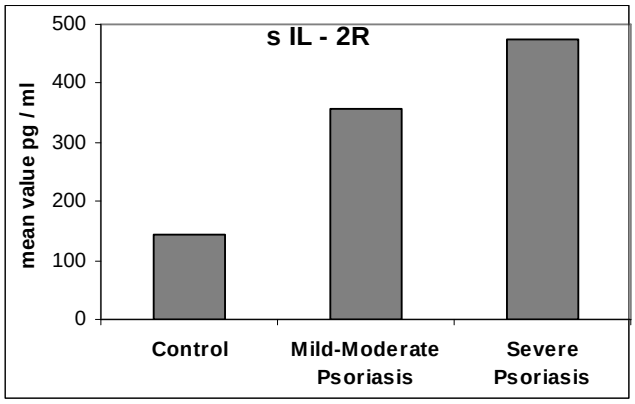
Cytokines	**Mild to Moderate Psoriasis (n = 20)**	**Severe Psoriasis (n = 20)**	**Control (n = 40)**
TNF – α (pg / ml) **P value**	121.24 ± 59.35 * **	173.23 ± 70. 45 * **	30.85 ± 25.45
s IL - 2R (pg / ml) **P value**	355.32 ± 104.21 * **	475.45 ± 111.45 * **	144.65 ± 69.44
IL - 6 (pg / ml) **P value**	15.24 ± 8.58 * **	33.76 ± 11.34 * **	5.99 ± 1.34

Values are mean ± SD (pg/ml of serum).
*P: compared to control
**P: comparison between mild to moderate psoriasis and severe Psoriasis significant ($P < 0.05$) (t - test).

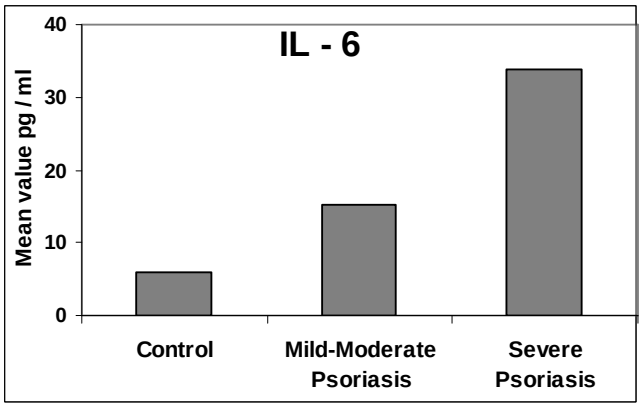
(Fig. 1) : Serum levels of TNF – α in patients with psoriasis vulgaris compared to healthy controls



(Fig. 2) : Serum levels of s IL - 2R in patients with psoriasis vulgaris compared to healthy controls



(Fig. 3) : Serum levels of IL - 6 in patients with psoriasis vulgaris compared to healthy controls



5. Discussion

Psoriasis is a common inflammatory disease of the skin and joints. Its aetiology remains unknown, however, it has been linked to complex interactions between predisposing genes and the environment. The pathophysiology of psoriasis is characterized by epidermal hyperproliferation, enhanced antigen presentation, T helper (Th -1) cytokine production, T cell expansion, and angiogenesis. Tremendous advances in understanding of this disorder has led to the development of novel therapeutics and the FDA approval of more systemic agents for its treatment in the last 5 years than in the previous 50 years combined. Improved understanding of the pathogenesis of psoriasis has led to epidemiologic studies that have contributed towards further characterizing its natural history **(Stephen and Gelfand 2008).** In this study we focused on the impact of serum levels of proinflammatory cytokines (TNF- α, IL - 2R and IL - 6) in psoriasis vulgaris In Egyptian patients which are of major clinical relevance to the clinician.

Sagawa *et al.* (1993) pointed out that TNF - α in combination with other cytokines like IL-6 may be highly injurious due to complex interactions between these cytokines, suggesting a rationale for monitoring of multiple cytokines in the sera of psoriatic patients. Moreover, the cytokine assay results may vary due to the clinical stage and type of disease, methods used for cytokines detection and their sensitivities, lesion activity, interferences due to different drugs used, demographic differences in the patient groups, and the effect of concomitant pathologies.

We evaluated the association of serum levels of some proinflammatory cytokines in vivo and their correlation with severity of psoriasis. The serum levels of cytokines levels were determined with the use of the ELISA method. All mean values of patients were significantly higher than those of controls. There was a significant relation between serum levels of TNF - α, IL - 2R and IL - 6 and the severity of the disease.

The clinical severity and activity of psoriasis, and those measurements of serum levels of these cytokines may be objective parameters for the disease severity.

In an earlier studies that was performed by **Ameglio *et al.*, in 1994,** they shown that there was an observed significant reduction in IL - 6, IL - 8, IL - 2R and TNF - α levels following effective therapies in psoriasis patients. Also, **Deeva *et al.* in 2010** had investigated in their study patients affected by very severe forms of psoriasis and they were characterized by increased plasma levels of IL - 4, IL - 6, MCP -1, VEGF. Also, in mild to moderate psoriasis patients, they had showed higher levels of IL - 4, IL - 6, IL - 10, and IL - 13 when compared to healthy controls.

In our results the increment of the investigated cytokines, showed a significant increase in severe psoriasis than in mild-to-moderate ones which are not in agreement to the results obtained by **Deeva *et al.* in 2010** who found that there is no correlation between psoriasis severity assessed by PASI (Psoriasis Area and Severity Index) and levels of these mediators.

Our results are in agreement with earlier studies demonstrated by **Mohammad in 2005,** who showed a significant increase in levels of serum IL-6, IL-8, IL-2R and TNF- α in Saudi psoriasis patients as compared with healthy controls. And he has been suggested that proinflammatory cytokines not only play a fundamental role in the worsening of the disease or activating its pathogenetic mechanisms, but are also directly related to the clinical symptoms and disease evolution after effective therapy.

Eiko *et al.* in 2006 had shown that psoriatic lesions showed elevated mRNA expression for type 1 cytokines (IFN - gamma, IL - 2, and TNF- α), compared with lesion-free psoriatic skin and normal skin, without a significant component of type 2 cytokines (IL - 4, IL - 5, and IL -10) which confirm our results in the increment of the studied serum cytokines .

Also, similar to our results **Ozer *et al.* in 2005** have demonstrated that, serum TNF -[alpha], IFN -[gamma], IL - 6, IL - 8, IL - 12, and IL - 18 levels were significantly higher in active psoriatic patients than in controls. Furthermore, high levels of these parameters have been correlated with the clinical severity and activity of psoriasis, and they concluded that measurements of serum levels of these cytokines may be objective parameters for the disease severity.

in Japanese patients with psoriasis, **Takahashi *et al.* in 2009** have shown that serum levels of tumour necrosis factor (TNF)-alpha, interferon (IFN) - gamma, interleukin IL-2, IL - 6, IL - 7, IL - 8, IL - 12, IL - 17, IL - 18 and vascular endothelial growth factor (VEGF) were significantly increased in patients with psoriasis compared with those of healthy controls. And, increased serum levels of these cytokines were correlated with PASI. Furthermore, these cytokine levels were decreased after psoriasis treatment.

As we gain further insight into the immunopathogenesis of psoriasis, we hope it will provide the basis for the development of safer, more efficacious, and more durable therapeutics in the future. Given its enormous toll on patient health and quality of life, steps should be taken to prevent or decrease the risk of psoriasis associated co-morbidities.

6. Conclusion

Psoriasis is a common chronic relapsing and remitting papulosquamous skin disease that may appear at any age and affect any part of the skin. The systemic overexpression of a variety of proinflammatory cytokines such as TNF - α, IL - 2 and IL - 6 have been evaluated in this study. We found that these cytokines are significantly elevated in patients suffering from psoriasis when compared to control. With increase of the severity of the disease, these cytokines are significantly elevated in severe psoriasis patients than in mild to moderate one which is attributed to the role of these cytokines in the pathogenesis and progress of psoriasis and their elevation is responsible for the development, maintenance and resolution of psoriatic lesions.

We suggest that, a use of an array of these cytokines may be considered as a useful follow-up marker for monitoring of psoriatic patients and optimizing therapeutic strategies. However, detailed time-course studies on sequential analysis of these cytokines in relation to disease severity and / or treatment modalities are warranted to ascertain its real application.

Finally, we recommend the study of the effectiveness of use of antisense therapy using the antibody of these cytokines in psoriatic patients, in particular anti - TNF therapy.

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