

## **EVALUTION OF INFLAMMATORY RESPONSE IN PLAQUE PSORIASIS**

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### **Abstract**

**Background:** To evaluate the state of some biochemical markers in sera of plaque psoriatic patients .

**Aim :** The aim of this study is to investigate the levels of inflammatory markers(leptin,adiponectin,CRP,TNF-alpha,IL-6 and IL-10) in plaque psoriatic and control groups and their relationship with the clinical severity of psoriasis.

**Patients and Methods:**The study was conducted on sixty patients with plaque psoriasis and thirty apparently healthy individuals were taken as control group.The sera obtained from the blood were used to determine the level of leptin,adiponectin, TNF-alpha, IL-6,IL-10 and CRP concentrations in both groups by enzyme linked immunosorbant assay (ELISA) method. Also determine the Correlation of the inflammatory markers with The Psoriasis Area and Severity Index (PASI) was determined.

**Results and Discussion:** The results of the present study showed a significant increase( $P < 0.05$ ) in leptin, TNF-alpha, IL-6 and CRP concentration, and a significant decrease ( $P < 0.05$ ) in adiponectin and IL-10 in sera of plaque psoriasis group compared with those of the control group.Also,the results of linear regression analysis showed a significant positive correlation of leptin( $r = 0.81, p < 0.05$ ),TNF-alpha ( $r=0.74, p < 0.05$ ), IL-6 ( $r = 0.75, p < 0.05$  ) and CRP ( $r = 0.79, p < 0.05$ ) . Also ,show a significant decrease in correlation of adiponectin ( $r= - 0.43, p < 0.05$ ) and IL-10 ( $r= -0.74, p < 0.05$ ) with the Psoriasis Area and Severity Index (PASI).

**Conclusion:** There is a significant increase in levels of inflammation markers and significant decrease in markers of anti-inflammation in plaque psoriasis as compared to non psoriatic control group.Also ,we correlated them with the clinical severity of psoriasis.

### **الخلاصة**

**الخلفية :** لمتابعة المتغيرات الكيموحيوية في امصال مرضى الصدفية اللوحية.  
**الهدف:** اجريت الدراسة الحالية لمقارنة تأثير الصدفية اللوحية على علامات الالتهابات وإرتباطهم مع شدة المرض.  
**المرضى وطريقة العمل:**

أجريت الدراسة على ستين مريضا ببدء الصدفية اللوحية و ثلاثون شخص سوي أخذت كمجموعة سيطرة. تم الحصول على عينات الدم من مرضى الصدفية ومجموعة السيطرة في مستشفى الصدر التعليمي مركز الامراض الجلدية. استخدمت المصل التي تم الحصول عليها من الدم لغرض قياس تأثير داء الصدفية على هرمون اللبتين ، الاديونكتين TNFalpha , CRP ,الانترلوكين-10 و ، الانترلوكين-6 وكذلك تم قياس شدة المرض من خلال حساب (PASI score).

**النتائج ومناقشتها:** أظهرت نتائج هذه الدراسة زيادة ملحوظة ( $P < 0.05$ ) في تركيز هرمون اللبتين، الانترلوكين-6، TNF-alpha و نقصان ملحوظ ( $P < 0.05$ ) في الاديونكتين والانترلوكين-10 في مجموعة مرضى الصدفية ومقارنتها بمجموعة السيطرة. كما بينت الدراسة الحاليه باستخدام طريقة تحليل الانحراف الخطي أن مقياس علامات الالتهاب تتناسب مع معدل شدة المرض (PASI score) بعلاقه طرديه موجبه معتد بها احصائيا.حيث يتناسب اللبتين ( $r = 0.81, p < 0.05$ ) ، عامل نخر الورم ( $r = 0.74, p < 0.05$ ) ، الانترلوكين-6 ( $r=0.75, p < 0.05$ ) و CRP ( $r = 0.79, p < 0.05$ ) ، الاديونكتين ( $r = - 0.43, P < 0.05$ ) والانترلوكين-10 ( $r = - 0.74, p < 0.05$ ) مع شدة المرض (PASI) .

## **Introduction**

Psoriasis represents a complex, chronic, systemic, T-cell immune-mediated inflammatory dermatopathy characterized by skin and joint manifestations, and presenting commonly with erythematous, scaly plaques on various surfaces of the body<sup>(1,2)</sup>. Its definition by Ferdinand von Hebra as a distinct entity dates back only to the year 1841 and estimates of its prevalence around 2-3% of the general population, and is characterized by an exaggerated proliferation of keratinocytes secondary to an activated immune system.<sup>(3)</sup>

Lesions are typically distributed symmetrically on the scalp, elbows, knees, joints, nails, and essentially any part of the body. It is a disease with an unpredictable course, prone for flare-ups and remissions<sup>(4)</sup>.

It can afflict both men and women, and usually begins in early adulthood, although it has been reported at birth. There is a bimodal distribution in the age of onset. Type I or early onset psoriasis typically appears in individuals between ages 15 to 20 years and shows a tendency to disseminate, greater number of relapses, and higher frequency of familiar history of psoriasis when compared with Type II or late onset psoriasis during or after the fifth decade of life<sup>(5, 6, 7)</sup>.

In clinical studies, a wide variety of assessment tools are used to evaluate the severity of psoriasis, but there is a lack of standardization<sup>(8)</sup>. The introduction of quality of life (QoL) instruments has improved psoriasis evaluation, but there is a need for consensus in order to make valid comparisons between studies<sup>(9)</sup>. The Psoriasis Area and Severity Index (PASI) is the most commonly used method to describe severity of psoriasis, and the Dermatology Life Quality Index (DLQI) is the most common method for measuring QoL in randomized controlled trials<sup>(10)</sup>. The visual analogue scale (VAS) is an often-used tool to measure subjective phenomena, which has shown good reliability and validity in terms of assessment of pain<sup>(11)</sup>.

### **Aim**

The aim of this study is to investigate the levels of inflammatory markers in psoriatic and control groups and their relationship with the clinical severity of psoriasis.

## **Materials and Methods**

### **Materials**

#### **Subjects**

The study was conducted over a period of eleven months from October 2012 till August 2013. Samples were collected from the clinic of dermatology in Al-Sader Teaching Hospital in Najaf City. The laboratory work was performed at the department of biochemistry in College of Medicine / University of kufa.

This study included sixty plaque psoriatic patients and thirty healthy individuals taken as a control group. The diagnosis was mainly clinical and done by specialist dermatologist. A questionnaire was designed to obtain the information from psoriasis patients and control group. It included the name, age, weight, height, gender, duration of disease, drugs allergy and smoking. Exclusion criteria were those suffering from other disease (e.g. hypertension, diabetes mellitus, asthma etc.), those who take medication (e.g. methotrexate, diuretics, steroid, etc.) for at least one month before the history, alcoholics, smokers and pregnant women.

The psoriasis group comprised sixty adults (33 men and 27 women) and their aged mean  $\pm$  SD of  $36.16 \pm 12.89$  year.

The control group includes thirty apparently healthy individuals (17 men and 13 women) and their aged mean  $\pm$  SD of  $35.56 \pm 11.8$  year.

### **Blood Sampling:**

Venous blood samples were drawn from psoriasis and control subjects by using disposable syringes (5mL) in the sitting position. Five ml of blood were obtained from each subject by vein puncture and pushed slowly into plain disposable tubes. Blood was allowed to clot at 37°C for 10-

15 minutes and then centrifuged at 1789 x g for approximately 10-15 minutes, then the sera were obtained and stored at -20°C until analysis .

**Methods**

Markers of inflammation levels (CRP,IL-6,TNF-alpha,IL-10,leptin and adiponectin) were estimated by enzyme linked immunosorbant assay (ELISA) method.

The PASI score is calculated according to an appropriate formula. A PASI score below 10 defines psoriasis as mild, between 10 and 20 as moderate, and above 20 as severe <sup>(12)</sup> . see figure(1).

**Results**

The results of the present study showed a significant increase(P< 0.05) in leptin, TNF-alpha, IL-6 and CRP concentration, and a significant decrease (P< 0.05) in adiponectin and IL-10 in sera of plaque psoriasis group compared with those of the control group. Table (1).

**Table(1): Mean and standard deviation of leptin,adiponectin,TNF-alpha,IL-6,CRP and IL-10 concentration in psoriasis and control groups.**

Subject	No	Parameter	Mean ±SD	P value
Patients	60	Leptin ng/ml	23.03±10.87	P<0.05
Control	30		4.2± 1.83	
Patients	60	Adiponectin ng/ml	10.17± 5.84	P<0.05
Control	30		61.69± 15.32	
Patients	60	TNF-alpha pg/ml	50.65± 27.04	P<0.05
Control	30		7.52 ± 3.05	
Patients	60	IL-6 pg/ml	268.15±82.92	P<0.05
Control	30		81.01± 43.03	
Patients	60	hs-CRP µg/ml	8.52±5.04	P<0.05
Control	30		1.05± 0.74	
Patients	60	IL-10 pg/ml	14.25 ±10.61	P<0.05
Control	30		406.81±189.23	

The results of linear regression analysis show a significant positive correlation of leptin(r = 0.81, p<0.05),TNF-alpha (r=0.74, p<0.05), IL-6 (r = 0.75, p < 0.05 ) and CRP (r = 0.79, p < 0.05) . Also ,show a significant decrease in correlation of adiponectin (r= - 0.43, p<0.05) and IL-10 (r= -0.74, p<0.05) with the Psoriasis Area and Severity Index (PASI). Table (2).

**Table (2): linear regression analysis of PASI score with inflammatory markers in patients with plaque psoriasis.**

Parameter	r	P
<b>Leptin</b>	<b>0.81</b>	<b>&lt;0.05</b>
<b>Adiponectin</b>	<b>- 0.43</b>	<b>&lt;0.05</b>
<b>TNF-alpha</b>	<b>0.74</b>	<b>&lt;0.05</b>
<b>IL-6</b>	<b>0.75</b>	<b>&lt;0.05</b>
<b>CRP</b>	<b>0.79</b>	<b>&lt;0.05</b>
<b>IL-10</b>	<b>- 0.74</b>	<b>&lt;0.05</b>

There was a significant positive significant correlation was found between serum leptin and CRP levels with IL-6 and TNF-alpha. Also The data show a negative correlation between serum of adiponectin and IL-10 with IL-6 and IL-10 in plaque psoriatic patients as show Table (3).

**Table (3): linear regression analysis of leptin,adiponectin, CRP and IL-10 with TNF- $\alpha$ , and IL-6 in plaque psoriasis .**

Parameter	IL-6		TNF-alpha	
	r	P	r	P
Leptin	0.98	0.001	0.96	0.001
Adiponectin	- 0.57	0.001	- 0.61	0.001
CRP	0.97	0.001	0.98	0.001
IL-10	- 0.85	0.001	- 0.76	0.001

Score	0	1	2	3	4	5	6
<b>Erythema</b>							
<b>Induration</b>	none	mild	moderate	severe	very severe	—	—
<b>Desquamation</b>							
<b>True Area (%)</b>	0	1-9	10-29	30-49	50-69	70-89	90-100

Head (H)	Score
Erythema	□
Induration	□
Desquamation	□
<b>Sum</b>	□ □
<b>x Area</b>	□
<b>=</b>	□ □
<b>x 0.1 =</b>	□ . □

Lower Limbs (LL)	Score
Erythema	□
Induration	□
Desquamation	□
<b>Sum</b>	□ □
<b>x Area</b>	□
<b>=</b>	□ □
<b>x 0.4 =</b>	□ . □

Trunk (T)	Score
Erythema	□
Induration	□
Desquamation	□
<b>Sum</b>	□ □
<b>x Area</b>	□
<b>=</b>	□ □
<b>x 0.3 =</b>	□ . □

Upper Limbs (UL)	Score
Erythema	□
Induration	□
Desquamation	□
<b>Sum</b>	□ □
<b>x Area</b>	□
<b>=</b>	□ □
<b>x 0.2 =</b>	□ . □

$\text{PASI} = (\text{H}) \square . \square + (\text{T}) \square . \square + (\text{UL}) \square . \square + (\text{LL}) \square . \square = \square . \square$
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**Figure(1): Psoriasis Area and Severity Index (PASI) score assessment (H, head; LL, lower limbs; T, trunk; UL, upper limbs) <sup>(12)</sup>**

## **Discussion**

Leptin has an vital role in inflammation and in immunoregulation. It activates monocyte/macrophage cells and potentiates production of the proinflammatory cytokines, tumor necrosis factor-alpha (TNF-alpha), IL- 6, and direct T cell differentiation to Th1 phenotype<sup>(13)</sup>.

The results of the present study were in agreement with Amira et al.<sup>(14)</sup>, who found that a group with psoriasis have higher levels of the obesity-associated hormone (leptin) than those without psoriasis. The results of the present work disagree with Takahashi et al.<sup>(15)</sup>, who found that no significant relationship between serum leptin concentration and PASI. They also disagree with Aktan et al.<sup>(16)</sup>, who found that there was no significant difference between serum leptin levels of psoriatic patients and control group.

In most studies, leptin is correlated with Psoriasis Area Severity Index (PASI) score, representing, therefore, a biomarker of psoriasis severity and chronicity<sup>(17)</sup>. Considering that inflammation mediated by Th1 lymphocytes is one of the factors leading to the development of atherosclerosis and coronary disease<sup>(18)</sup>.

Adiponectin is an anti-inflammatory adipokine that is richly present in blood stream<sup>(19)</sup>. Adiponectin improves insulin sensitivity and has anti-atherogenic effects, and anti-inflammatory action, including inhibition effect on TNF-alpha, IL-6, and macrophage phagocytic activity. pro-inflammatory factors, such as IL-6 and TNF-alpha, are known to suppress adiponectin production by adipose tissue and thus the elevation observed in IL-6 and TNF-alpha in psoriatic patients might explain a decrease in the production of adiponectin<sup>(20)</sup>. Researchers have determined that adiponectin concentration levels are negatively connected with psoriasis severity calculated by PASI (Psoriasis Area and Severity Index)<sup>(21,22)</sup>. The present study results confirm and extend the results of previous studies that adiponectin concentration levels are negatively connected with psoriasis severity calculated by PASI (Psoriasis Area and Severity Index).

In addition to that, the results are in agreement with Shibata et al.<sup>(23)</sup> who found that adiponectin levels were significantly lower in psoriasis patients than those without psoriasis (control group) and disagree with Corbetta<sup>(24)</sup> who found that serum levels of adiponectin in psoriatic patients had not significantly different from controls.

Studies have also shown that hypo adiponectinemia is associated with elevation of circulating CRP levels<sup>(25)</sup>. In addition, it has been shown that CRP is also produced in adipose tissues and that a significant negative relationship is found between CRP and adiponectin mRNA levels in adipose tissues<sup>(26)</sup>.

TNF-alpha (1) modulates cell growth, differentiation (2) leads to cachexia by inhibiting stimulation of liver lipogenesis and stimulating lipolysis (3) initiates apoptosis of degenerated cells, neoplastic cells or virus-infected cells, and (4) produces inflammation<sup>(27)</sup>.

Monocytes and macrophages are the main cells related to the production of TNF- $\alpha$ , but other immune cells are also capable of synthesizing it such as , basophils, eosinophils, neutrophils and T and B lymphocytes<sup>(28)</sup>. Tumor necrosis factor is a pleiotropic cytokine that has multiple proinflammatory and costimulatory effects on a broad range of cell types<sup>(29)</sup>. Activated T cells, monocytes, and pro-inflammatory cytokines, most notably TNF-alpha, have all been shown play pivotal roles in the pathogenesis of psoriasis<sup>(30)</sup>.

The results of the present study are in agreement with Mizutani et al.<sup>(55)</sup> and Bonifati et al.<sup>(31)</sup>, who found that a positive correlation between serum TNF-alpha levels and PASI score was demonstrated. The results of the present study were disagree with Ozer Arican et al.<sup>(32)</sup>, who found that high serum levels of TNF- $\alpha$  had no correlation with PASI scores in patients with psoriasis.

IL-6 is a pleiotropic cytokine. Its typical actions are the regulation of the expression of other cytokines, cell proliferation and differentiation and inhibition of tumor growth, as well as stimulation of acute-phase proteins in the inflammatory reaction. IL-6 is present in normal human skin and is immunologically detected in basal keratinocytes, endothelial cells, fibroblasts and mononuclear cells<sup>(33)</sup>.

The difference between IL-6 levels in cases and controls was significant ( $P < 0.05$ ). This was in agreement with other studies by Abanmi et al.<sup>(34)</sup> who found increased levels of IL-6 in their patients but different results were reported by Jacob et al.<sup>(35)</sup> who found no difference in serum IL-6 levels. IL-6 mediates T-cell activation, stimulates proliferation of keratinocytes and, at the start of acute inflammation, mediates the acute phase responses<sup>(36)</sup>. Goodman et al. observed increased IL-6 levels in psoriatic lesions, compared to the common skin of healthy group<sup>(37)</sup>.

The results of the present study are in agreement with Coimbra et al.<sup>(38)</sup> found that a positive correlation between high IL-6 levels and PASI has also been recorded. So the raised IL-6 levels in psoriatics are therefore consistent with the significant role it plays in the pathogenesis of this disease.

C-reactive protein (CRP), a positive acute phase protein, is released in response to increased levels of cytokines, such as IL-6 and TNF- $\alpha$ , and patients with elevated levels of CRP seem to exhibit an increased risk for adverse cardiovascular outcome<sup>(39)</sup>. Furthermore, the levels of IL-6 and CRP have been reported to be raised in psoriatic patients and seem to correlate with psoriasis severity<sup>(40,41)</sup>.

C-reactive protein (CRP), although non-specific, is known as the most sensitive indicator of inflammation. The new high-resolution CRP assays, allowed clinicians to explore its potential role in predicting and diagnosing low-grade inflammatory conditions<sup>(42)</sup> and the magnitude of its increase seems to be related to the extent of tissue injury and inflammation severity. In the active stage of psoriasis, highly increased CRP levels were found; where as at remission, they present a decrease<sup>(43,44)</sup>. Many studies have reported a correlation between increased levels of CRP and PASI<sup>(45,46)</sup>.

Relative deficiency of IL-10 in psoriatic patients (cutaneous expression and serum levels) appears to be chief in the development of the disease. IL-10 controls inflammatory processes by suppressing the production of pro-inflammatory cytokines, chemokines and antigen-presenting and co-stimulatory molecules on the immune system cells. Various cell populations, including macrophages, T-helper 2 cells, monocytes, B-cells, eosinophils and mast cells, can produce IL-10<sup>(47,48)</sup>. The data showed a negative significant correlation with severity of disease (PASI score). See table(2). and this disagree with Deeva et al.<sup>(49)</sup> had reported elevated level of serum IL-10 in mild to moderate psoriasis when compared to healthy controls.

This was in agreement with other studies by Jacob et al.<sup>(50)</sup> who found that a significant decrease in serum of IL-10 level in psoriatic patients compared to controls. IL-10 mostly produced by monocytes, macrophages, B and T cells, IL-10 is a multifunctional cytokine with diverse effects on most hematopoietic cells. It inhibits the antigen presentation capacity of macrophages and dendritic cells(DC) and the proliferation of CD4 T cells. IL-10 powerfully inhibits cytokine production such as IL-2 synthesis by T-cells and the synthesis of the pro-inflammatory cytokines IL-6 and tumor necrosis factor -alpha<sup>(51)</sup>.

## **Conclusion**

There is an association between the inflammatory markers and the severity of plaque psoriasis.

## **Recommendations**

1. Evaluation of other adipokines such as Resistin and Ghrelin in sera of psoriasis patients and study the correlation of its concentration with disease severity.
5. Determination of insulin in sera of psoriasis patients and study the correlation of its concentration with leptin concentration.

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