

## Association of Inflammatory Metabolic Markers in Psoriasis Patient: A Case-Control Study in Karbala City

Zainab Adil Mohammed<sup>1</sup>, Haneen Hadi Abbas<sup>2</sup>, Dhay Abdul Jaleel Kami<sup>3</sup>, Zahraa Emad Hussein<sup>4</sup>

<sup>1</sup>Basic Sciences, College of Dentistry, University of Al-Ameed, Karbala, Iraq

<sup>2</sup>Al-Zahraa University for Women, College of Health and Medical Technologies Faculty, Department of Radiologic Technology

\*Corresponding Author  
Zainab Adil Mohammed

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**Abstract:** B This case-control study was investigated the systemic inflammatory markers in 70 patients with psoriasis against 30 healthy controls in Karbala teaching hospitals, Iraq. Demographic, hematological and immunological parameters were assessed, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), interleukin (IL)-17, IL-23 and C-reactive protein (CRP). The patients with psoriasis had a high inflammatory marker that were significantly high in comparison to the controls: SII (632.78 vs 377.2,  $p=0.032$ ), SIRI (1.042 vs 0.833,  $p=0.041$ ), and CRP (6.4 mg/L vs 3.8 mg/L,  $p=0.01$ ). The amount of vitamin B12 was significantly reduced among patients (138.5 pg/mL vs 391.5 pg/mL,  $p<0.001$ ). A significant correlation was found between SII and CRP ( $r=0.714$ ,  $p=0.043$ ) and between SII and IL-23 ( $r=0.471$ ,  $p=0.007$ ), and IL-17 demonstrated weaker correlations (SII:  $r=0.136$ ,  $p=0.154$ ). The results suggest that SII/SIRI is useful as a biomarker in the context of resource limitations and indicate the existence of possible metabolic comorbidities in the population. The clinical implication of the deficiency of vitamin B12 and IL-23/IL-17 imbalance in Middle East psoriasis patients should be investigated in further studies

**Keywords:** CRP, Psoriasis, SII, SIRI, IL-17, IL-23

## INTRODUCTION

Psoriasis is a kind of inflammatory immune system disease that may be observed on the skin, nails, and joints. It is chronic and happens in flares with remissions and exacerbation, and is never contagious<sup>1</sup>. It affects 2-4 percent of the population, which is regarded as a severe and disabling disease in most instances<sup>2</sup>. psoriasis comorbidities affecting it may include obesity, metabolic syndrome, psoriatic arthritis, cardiovascular disease, non-alcoholic fatty liver disease, and inflammatory bowel disease<sup>3</sup>. Psoriatic patients have greater susceptibility to obesity and metabolic syndrome than the general population, Obesity may cause metabolic consequences, deteriorating the health of an individual, a close relationship between the psoriasis and obesity condition is associated with the existence of low level of inflammatory condition and the overabundance of cellular oxidation. Adipose tissue can be regarded as an immunometabolism organ that has an autocrine, paracrine, and endocrine activity. The activation of macrophages, which results in unremitting inflammation and secretion of bioactive compounds, including proinflammatory cytokines: C-reactive protein (CRP), growth factor ss (TGF- $\beta$ ), plasminogen activator (PA-1), interleukin (IL) 1ss, IL-6, tumor necrosis factor a (TNF-a), and adipokines (endocrine action) takes place in obesity<sup>4</sup>. These have insulin resistance, atherogenesis and prolonged inflammation; which has systemic consequences (endocrine action) and also on local organs, including lymphocytes in local lymph nodes (paracrine action)<sup>5</sup>.

Psoriasis is typified by an excessive epidermal growth and failed keratinocyte differentiation along with immune activation, as well as many inflammatory and immunological changes, including innate and acquired

immunity<sup>6</sup>. The strong effect of biological agents against tumor necrosis factor alpha (TNF), a pleiotropic mediator of inflammation in multiple organs, and anti-p40 antibodies, which prevent differentiation and proliferation of Th1 and Th17 lymphocytes by IL-23<sup>7</sup>. A recent finding of a subpopulation of T lymphocytes expressing IL-17, the expansion of which is dictated by the action of IL-23 secreted by antigen-presenting and dendritic cells onto naive T precursors<sup>15</sup> has transformed the pathogenesis of psoriasis, a significant proliferation of cytotoxic T lymphocytes or other cells independently expressing IL-17 and IL-22 has also been established in psoriatic epidermis<sup>8</sup>. The expansion of Th1 lymphocytes would feedback this process, by stimulating the synthesis of IL-12 and IL-23 by antigen-presenting cells through the production of IFN  $\gamma$ <sup>9</sup>.

C-reactive protein (CRP) is a major inflammatory mediator that is increased in psoriasis and is associated with the severity of the disease and systemic inflammation. The elevated levels of CRP are associated with cardiovascular risk and psoriatic arthritis (PsA). CRP is also a biomarker of inflammatory response and treatment response in psoriasis and is driven down by good systemic therapies (e.g., biologics)<sup>10-11</sup>. The study aimed to determine the relationship between some immunological and inflammatory markers in patient with psoriasis in karbala city, Iraq.

## Materials and methods

### Study Design and Participants

A controlled hospital-based case-control study was carried out in order to compare psoriasis patients and healthy controls. Both Alhussein Hospital and Alkafeel Hospital were used to recruit the participants based on

the dermatology departments. Ethical consent was taken before the study was started and a total of 120 participants were recruited, including 70 confirmed cases of psoriasis patients and 50 individuals of the same age and sex without psoriasis (the controls). Several cases were determined by clinical and/or histopathological diagnosis of psoriasis through dermatologist research.

### Inclusion Criteria

Patients who had chronic plaque psoriasis as determined by a dermatologist were included. Those who were aged between 18 years to 65 years were also deemed eligible and informed consent and willingness to allow blood sampling.

### Exclusion Criteria

Other autoimmune disease patients (e.g., rheumatoid arthritis, lupus) were excluded. Active infected people, malignancies as well as recently steroid/immunosuppressed therapy (within the last 3

months) were excluded. The pregnant or lactating women were not included in the study.

### Demographic data

Clinical and demographic data, such as age, sex, BMI, and waist circumference, were obtained through the venous samples of blood under aseptic conditions to analyze the hematological and biochemical and inflammatory markers and the laboratory measurements were carried out using standard protocols in the hospital diagnostic labs, the creatinine, hemoglobin, neutrophil, lymphocyte, monocyte, and platelet counts, HDL cholesterol, CRP, SII, SIRI, IL-23, IL-1.

### Statistical Analysis

Continuous variables were expressed as mean  $\pm$  standard deviation. Independent t-tests or Mann-Whitney U tests were used for group comparisons and A p-value of  $<0.05$  was considered statistically significant.

## RESULTS

Demographic and clinical features of the study patients were compared between healthy control and psoriasis patients. The analysis involved 70 psoriasis and 30 control participants. Mean age of the patients with psoriasis was also determined to be a little more than the control patients, however not significantly different. The number of males and females in each group were found to be close to equal, and no significant difference was found to exist. Significant differences were found between the rates of metabolic parameters of the two groups. Patients of psoriasis were observed to have significantly higher mean BMI than the controls. Likewise, the table of patient showed a significant increase in the waist circumference (1).

**Table 1. Demographic and Clinical Characteristics**

Variable	Psoriasis Patients (n=70)	Controls (n=50)	p-value
Age (years)	45.2 $\pm$ 12.3	42.1 $\pm$ 11.8	0.15
Female, n (%)	40 (57.1%)	18 (60%)	0.90
Male, n (%)	30 (42.9%)	12 (40%)	
BMI (kg/m <sup>2</sup> )	29.4 (24.1–33.2) *	24.8 (21.9–27.1)	$<0.01$
Waist (cm)	101.3 $\pm$ 18.2	92.5 $\pm$ 14.7	0.003

\*Data presented as mean  $\pm$  SD or median (IQR). p-values  $<0.05$  were considered significant. \*

The comparison of neutrophil count between psoriasis patients and healthy controls indicated that the median value of neutrophil count was greater in patients with psoriasis (4.94  $\times 10^3$ /mL, IQR: 4.18–5.75) than in the healthy controls (3.93  $\times 10^3$ /mL, IQR: 3.32–4.63) and this difference was observed to be significant ( $p = 0.0237$ ). The levels of IL 17 were also found to be significantly higher in psoriasis patients with median of 107.91 pg/mL (IQR: 85.59–121.40), and the control group had a median of 57.88 pg/mL (IQR: 46.11–73.58), giving p-value highly significant, 0.0001. Similarly, the levels of interleukin 23 (pg/mL) were significantly different in patients with psoriasis [138.5 (129–149)] and healthy controls [391.5 (292–468)], which is a strong statistical difference with a p-value of less than 0.001. Additionally, the level of C-reactive protein (CRP) (mg/L) was also significantly higher in the psoriasis group [6.4 (2.1–12.6)], compared to the control group [3.8 (2.2–5.0)], the p-value of this was 0.01.

**Table (1): showed relationship between inflammatory parameters in patient and control**

Parameter	Psoriasis (median, IQR)	Control (median, IQR)	P-value (Mann-Whitney U)
Systemic Immune-Inflammation Index SII	632.78 (301.4-713.3)	377.2 (253.6-442.9)	0.0318
Systemic Inflammation Response Index SIRI	1.042 (0.633-1.84)	0.833 (0.221-0.952)	0.041
Interleukin 17	107.91 (85.59–121.40)	57.88 (46.11–73.58)	0.0001
Interleukin 23	65.73 (53.22–73.33)	26.49 (23.54–29.43)	0.0000
Vitamin B12 (pg/mL)	138.5 (119.6–249.7)	391.5 (292.5–468.9)	<0.001
CRP (mg/L)	6.4 (2.1–12.6)	3.8 (2.2–5.2)	0.01

There was a statistically significant positive correlation between the SII and CRP; thus, an increase in the values of the systemic immune-inflammation index is related to an increase in the level of CRP. The correlation between SIRI and CRP was also observed to be moderate and positive, and it was also found to be significant. Both SII and IL-23, and SIRI and IL-23 had significant positive correlations, which indicated the association of the indices with high concentrations of IL-23 in psoriasis patients. Conversely, there were no statistically significant relationships between SII and IL-17 or between SIRI and IL-17, which, however, showed moderate strength of relationships in the case of SIR.

**Table (2): showed correlation inflammatory markers**

Variable	Spearman r	p-value
SII vs CRP	0.714	0.0425
SIRI vs CRP	0.533	0.0375
SII vs IL-23	0.471	0.0074
SIRI vs IL-23	0.43	0.0158
SII vs IL-17	0.136	0.154
SIRI vs IL-17	0.478	0.094

## DISCUSSION

Psoriasis is a condition that needs multidisciplinary treatment. Besides the erythematous plaques on the skin and nails and high rates of comorbidity that it causes, it may lead to psychological disorders that adversely affect self-esteem, confidence, and quality of life, even in the way such patients eat, as the table 1 the present study revealed that body mass index in patient psoraiss was 29.4 higher than control 24.8 which evidences that psoriasis exacerbates such patients, so weight control is required in preventing the subclinical inflammation and oxidative damage 12.

There was also no significant difference in sex between psoriasis patients and healthy controls ( $p = 0.90$ ). Psoriasis patient group consisted of 40 females (57.1) and 30 males (42.9) and the control group comprised 18 females (60%), and 12 males (40%). The seen non-significance of the sex-based differences in the prevalence of psoriasis ( $p = 0.90$ ) is in line with the study by 13, which showed no incidence difference of psoriasis between both sexes in a worldwide systematic review. Similarly, According to 14, the sex distribution in the cohorts of psoriasis among populations of varied origins did not show any dominant sex; this fact supports the

assumption that sex might not play the leading role in determining the susceptibility of the disease.

The circumference of the waist was found to be significantly greater in psoriasis patients (101.3  $\pm$  18.2 cm) than in healthy controls (92.5  $\pm$  14.7 cm;  $p = 0.003$ ). The current observation correlates with the prior literature on the relation between psoriasis and central obesity, such as the meta-analysis that 15 conducted (they have found that patients with psoriasis were more likely to have abdominal adiposity by 1.5 times compared to control groups). The correlation between psoriasis and high waist circumference has been also reinforced by 16, who explained the link by the metabolism dysregulation caused by chronic inflammation.

It was found that the levels of systemic inflammatory markers were significantly higher in patients with psoriasis than in controls. Systemic Immune-Inflammation Index (SII) was significantly elevated in psoriasis patients (median=632.78, IQR=301.4-713.3) when compared to controls (median=377.2, IQR=253.6-442.9;  $p=0.0318$ ). Likewise, Systemic Inflammation Response Index (SIRI) showed a much higher level in the psoriasis group (median=1.042, IQR=0.633-1.84)

compared to the controls (median=0.833, IQR=0.221-0.952;  $p=0.041$ ).

The same findings are in line with past studies that show that psoriasis is a chronic systemic inflammatory condition. The high SII values have already been mentioned by 17 in their study of inflammatory biomarkers in patients with psoriasis, in which SII is found to be a valid measure of disease severity. In the same manner, the fact that the SIRS levels increased is consistent with the research of 18, who discovered that this index was strongly correlated with inflammatory skin conditions. The neutrophil counts are included in the SII and SIRS and have been identified to be increased in psoriasis because of persistent immune stimulation 19. In addition to the inflammatory indices indicate lymphocyte counts that have been identified to change in case of psoriatic inflammation 19.

Lower vitamin B12 levels were significantly lower in psoriasis patients (median=138.5 pg/mL, IQR=119.6-249.7) compared to controls (median=391.5 pg/mL, IQR=292.5-468.9;  $p<0.001$ ). The present vitamin B12 deficiency in patients with psoriasis is consistent with those by 20 who found that patients with psoriasis had significantly lower levels of vitamin B12 as compared to healthy participants in their cross-sectional study involving 150 participants ( $p<0.001$ ). This correlation has been linked to various possible mechanisms that could be Chronic inflammation-induced malabsorption 21, Increased use of B12 in inflammatory processes 20 and altered gut microbiome that impacts on B12 metabolism 22. Concurrently, higher CRP levels were detected in the psoriasis group (median=6.4 mg/L, IQR=2.1-12.6) versus controls (median=3.8 mg/L, IQR=2.2-5.2;  $p=0.01$ ).

Psoriasis patient has a high level of CRP, which confirms the long-standing correlation between psoriasis and systemic inflammation, as 23 ( $n=5,438$ ) found in their population-based study. Nonetheless, our results are not similar to those of 24 who reported that CRP increase were less predictable in the studies that accounted for the confounding factors ( $b=0.24$ , 95% CI -0.03 to 0.51) indicating that markers of inflammation could be affected by other factors. 25 have already investigated the inverse correlation of vitamin B12 and inflammatory markers in psoriasis and suggested that B12 deficiency could contribute to the enhancement of inflammatory responses by disrupting the homocysteine pathway. The low B12 and high CRP levels that we obtained simultaneously support this hypothesis.

There were high positive relationships between systemic inflammatory indices and CRP levels. Systemic Immune-Inflammation Index (SII) was significantly correlated with CRP ( $r=0.714$ ,  $p=0.0425$ ), whereas the Systemic Inflammation Response Index (SIRS) was not ( $r=0.533$ ,  $p=0.0375$ ). This association is physically possible because SII (including neutrophil, lymphocyte,

and platelet counts) and CRP both indicate acute-phase inflammatory events, which are naturally high in the pathogenesis of psoriasis 24. The weak positive SIRS-CRP result ( $r=0.533$ ) corresponds to the study by 12 who determined SIRS a useful measure of subclinical inflammation in chronic inflammatory diseases. But our effect size was also somewhat smaller than that which they reported ( $r=0.61$ ) possibly because of the difference in disease severity distribution and SII may be better than SIRS to measure systemic inflammation in psoriasis as indicated by stronger CRP correlations 22.

Our study found IL-23 References (Strong SII/SIRS correlation, the significant positive correlations observed between systemic inflammatory indices (SII and SIRS) and interleukin-23 (IL-23) are consistent with previous research demonstrating the central role of IL-23 in driving psoriatic inflammation. The stronger association with SII ( $r=0.471$ ) compared to SIRS ( $r=0.43$ ) may reflect the preferential activation of neutrophil and platelet pathways by IL-23-mediated immune responses, as described in recent immunological studies. These findings support the current understanding of IL-23 as a key upstream regulator of systemic inflammation in psoriasis, particularly through its effects on myeloid cell populations that contribute to SII calculation 26.

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TThese patterns of differential correlation between the two interleukins and the systemic indicators of inflammation can have significant clinical implications. This closer relationship between IL-23 and the SII and SIRS indicates the therapeutic potential of IL-23 inhibitors in individuals who have a high systemic inflammation biomarker profile. In its turn, the lower correlation of interleukin-17 (IL-17) with these indices is intriguing since it indicates that the blockage of interleukin-17 (IL-17) may be especially effective in patients with local and not systemic inflammatory markers. While IL-17 is recognized as a crucial effector cytokine in psoriasis pathogenesis, its dissociation from systemic inflammatory markers in this study suggests potential compartmentalization of IL-17 effects to local tissue inflammation rather than systemic circulation. This observation aligns with emerging evidence that IL-17 activity may be more tissue-specific, with limited direct impact on peripheral blood inflammatory indices. The modest correlation trend observed for SIRS and IL-17 ( $r=0.478$ ,  $p=0.094$ ) could indicate some monocyte-mediated IL-17 effects that warrant further investigation 27.

The difference in correlation that exists between the two interleukins and the systemic markers of inflammation could have significant implications in the clinical field. The significance of IL-23 in terms of SII and SIRS is stronger, which underlies the therapy principle of IL-23 inhibitors in patients with the increase of systemic inflammation indicators. On the contrary, the lower relationship between IL-17 and these indices may indicate that IL-17 blockade may be especially effective



with patients whose inflammatory processes are more local and less systemic. The findings will help to accumulate the existing body of knowledge of individual treatment against the background of specific inflammatory profiles in patients with psoriasis.

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