

Psoriasis is a systemic disease: A proposed approach for inflammation scale calculation

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ABSTRACT

Background: Psoriasis is a skin disease affecting 2.3% of the Iraqi population and begins as a local disease with subsequent systemic comorbidities. **Aim:** The aim was to clarify whether psoriasis is a local or systemic disease. **Materials and Methods:** A total of 211 subjects with psoriasis and 163 sex- and age-matched controls were included in the study. Serum adiponectin, interleukin-6, interleukin-8, interleukin-10 (IL-10), interleukin-23 (IL-23), interleukin-18 (IL-18), paraoxonase, lipoprotein (a), osteopontin, chemerin, tumor necrosis factor- α (TNF- α), high-sensitivity C-reactive protein (hs-CRP), bilirubin, D-dimer, and creatinine were determined using commercial kits. **Results:** There was no significant difference in the mean age and BMI between psoriasis and the control groups. However, there was significantly higher mean serum values of IL-6, IL-8, IL-10, IL-23, lipoprotein (a), chemerin, TNF- α , hs-CRP, osteopontin, D-dimer, troponin I, creatinine, bilirubin, and platelet counts in psoriatic patients than in the controls. Meanwhile, the serum mean values of adiponectin, paraoxonase, and cortisol were significantly lower in psoriasis subjects than in the controls. The mathematical model was proposed to clarify whether psoriasis is a systemic or local disease. The application of the model to our data of biomarkers indicated the presence of systemic inflammation in psoriasis. **Conclusion:** The present study finding suggests that psoriasis is a systemic disease rather than a local skin disease. However, there is a need for the application of the model in a large-scale study.

Key words: Psoriasis; Interleukin 10; Interleukin 18; Interleukin 23; Paraoxonase; Lipoprotein (a); Osteopontin; chemerin

INTRODUCTION

Psoriasis is a skin disease affecting 2.3% of the Iraqi population [1] and 1–3% globally [2]. The disease is characterized by a chronic natural history characterized by remission, relapse, and acute exacerbation [3]. Although psoriasis has an obscure etiology, previous studies have suggested that genetic, infectious, immunological, and environmental factors play a role in the induction of the disease [4,5]. Psoriasis is induced as a local dermatological disease with subsequent immuno-inflammatory and metabolic changes [6,7].

In the literature, numerous studies have reported systemic changes, such as dyslipidemia, cytokines,

and inflammatory and immunologic biomarker abnormalities [8-27]. Some researchers suggest that psoriasis is a systemic disease rather than a local skin disease [6,7,17,28-35]. An alternative explanation for the biomarker abnormalities is that the disease is a combined local and systemic syndrome or that the local skin changes are a dermatological manifestation of a systemic disease.

Suggestions that psoriasis is a systemic disease depend on findings of increased or decreased serum or plasma levels of immunological, inflammatory, and metabolic biomarkers [6,7,17,28-35]. However, there are conflicting variations in these biomarkers among different studies.

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The diagnosis of systemic inflammation with a mathematical model was previously reported for clinical conditions such as obstetric, acute multiple injuries, heart surgery, and sepsis [36,37]. Thus, this study proposed a mathematical model for the calculation of a scale that may be employed to diagnose the presence of systemic inflammation in psoriasis and to monitor treatment response of the disease.

MATERIALS AND METHODS

Study Population

The present study included 211 subjects with psoriasis attending a dermatology clinic during the period from January 2012 till the end of May 2014.

A total of 163 subjects, sex- and age-matched controls, were included in the study.

The mean age of the patients was 37.85 (± 14.81) years, and that of the control group was 36.76 (± 10.92) years with no significant difference between the two groups. Additionally, the mean BMI was 25.83 (± 6.41) in the patients with psoriasis and 25.90 (± 13.16) in the controls, with a non-significant difference. The gender frequency rate was not significantly different between the patients and controls (Table 1). The study was approved by the ethical committee of Tikrit University College of Medicine and informed consent was taken from each subject included in the study. Individuals with

liver disease, a family history of hyperlipidemia, diabetes, cardiovascular disease, hypertension, smoking, hypothyroidism, renal disease, connective tissue disease, and those using lipid-lowering drugs were excluded from the study.

Determination of Inflammation

Inflammatory responses were determined with an approach by Zotova et al. [37], with some modifications. Step 1 involved systemic cellular stress estimation performed using some cytokines and other inflammatory mediators as indicators of systemic inflammatory responses (SIR). In step 2, the systemic inflammation scale was determined by SIR systemic microthrombogenesis, organ dysfunction, systemic alterations, and distress reactions [38,39]. The calculation sequences are described below.

1. Calculation of the reactivity index scale (0–6) with the indices shown in Table 2 for IL-6, IL-8, IL-10, IL-18, IL-23, TNF- α , hs-CRP, chemerin, lipoprotein (a), paraoxonase, and adiponectin.
2. Calculation of the coefficient of reactivity (CR) [0–36] with the data extracted from Table 2. The sum of 7 (60%) largest RISs from the 11 factors used gave the CR scale.
3. Transformation of the CR scale (0–36) into the reactivity level scale (RLS) with 0–5 points (40) as shown in Table 3.
4. The Sequential Organ Failure Assessment (SOFA) scale was calculated with the serum level of bilirubin, creatinine, osteopontin, the platelet count, and the presence of sepsis and erythroderma. The SOFA scale was within the range of (0–4) (Table 4).
5. The last step was the calculation of the Systemic Inflammation (SI) scale using the phenomenon described in Table 5.

Investigations

Serum adiponectin, interleukin-6, interleukin-8, interleukin-10, interleukin-18, interleukin-23, paraoxonase enzyme, lipoprotein (a), TNF- α , osteopontin, chemerin, and high sensitivity CRP levels were measured by the enzyme-linked immunosorbent assay. The procedure was performed according to manufacturer instructions.

Statistical Analysis

Variable values were presented as a mean \pm standard deviation [SD]. The Student's *t*-test was used to

Table 1: Biomarkers in the subjects with psoriasis in comparison to the controls

Biomarker	Mean (SD)		t	P
	Psoriasis	Controls		
Adiponectin ng/ml	7.23 (3.42)	8.28 (5.14)		
IL-6 pg/ml	41.85 (13.27)	4.31 (1.87)		
IL-8 pg/ml	47.61 (19.77)	7.68 (2.32)		
IL-10 pg/ml	8.78 (4.81)	5.31 (3.73)		
IL-18 pg/ml	601.7 (247.46)	45.8 (23.11)		
IL-23 pg/ml	73.48 (29.91)	5.98 (6.71)		
Paraoxonase mIU/ml	38.96 (4.15)	91.65 (16.73)		
Lipoprotein (a) mg/dl	376.60 (35.8)	21.85 (13.62)		
Chemerin ng/ml	214.88 (80.5)	34.31 (17.62)		
TNF- α pg/ml	277.93 (150.3)	146.60 (90.9)		
hs-CRP mg/dl	3.75 (0.74)	1.37 (0.39)		
D-dimer ng/ml	374.82 (261.9)	249.61 (217.80)		
Cortisol nmol/L	195.60 (37.8)	289.00 (53.11)		
Troponin I ng/ml	0.27 (0.31)	0.04 (0.09)		
Platelets $10^3/mm^3$	287 (99.7)	256 (113)		
Bilirubin mg/dl	1.91 (0.17)	0.78 (0.09)		
Creatinine mg/dl	1.23 (0.87)	0.71 (0.19)		
Osteopontin pg/ml	638.34 (225.80)	45.78 (18.95)		

Table 2: Indices for the calculation of the reactivity index scale (0–6)

Biomarker	UMN	Reactivity Index						
		0	1	2	3	4	5	6
IL-6	6.18 pg/ml	≤ 3	≤ 6	≤ 12	≤ 25	≤ 50	≤ 100	>100
IL-8	10 pg/ml	≤ 5	≤ 10	≤ 20	≤ 40	≤ 80	≤ 160	>160
IL-10	9.04 pg/ml	≤ 1	≤ 2	≤ 5	≤ 10	≤ 20	≤ 100	>100
IL-18	68.91 pg/ml	≤ 35	≤ 70	≤ 140	≤ 280	≤ 560	≤ 1120	>1120
IL-23	12.69 pg/ml	≤ 5	≤ 10	≤ 25	≤ 50	≤ 100	≤ 200	>200
TNF – α	8.01 pg/ml	≤ 5	≤ 25	≤ 50	≤ 100	≤ 200	≤ 400	>400
hs-CRP	2.76 mg/dl	≤ 1	≤ 2	≤ 3	≤ 4	≤ 5	≤ 10	>10
Chemerin	51.90 ng/ml	≤ 25	≤ 50	≤ 100	≤ 200	≤ 400	≤ 800	>800
Lipoprotein(a)	35.45 mg/dl	≤ 20	≤ 40	≤ 80	≤ 160	≤ 320	≤ 640	>640
Paraoxonase	108.4mlU/ml	> 200	≤ 200	≤ 100	≤ 50	≤ 25	≤ 10	≤ 5
Adiponectin	13.42 ng/ml	>32	≤ 32	≤ 16	≤ 8	≤ 4	≤ 2	≤ 1

Table 3: Transformation of CR into RL

RL Scale	CR Scale	Inflammation Level
0	0–6	Normal physiology.
1	7–12	Classical inflammation but no systemic inflammation.
2	13–18	Typical classical with the possibility of the depressive phase of systemic inflammation.
3	19–24	Zone of uncertainty.
4	25–30	Typical for the hyperergic option of systemic inflammation with a low possibility of classical inflammation.
5	31–36	Confirms the presence of systemic inflammation.

Table 4: Sequential Organ Failure Assessment (SOFA) scale calculation parameters

Biomarker	Scale (0–4)				
	0	1	2	3	4
Bilirubin mg/dl	< 1.2	1.2–1.9	2–5.9	6–11.9	≥ 12
Creatinine mg/dl	< 1.2	1.2–1.9	2–3.4	3.5–4.9	≥ 5
Platelets 10 ³ /mm ³	> 150	< 150	< 100	< 50	< 20
Osteopontin pg/ml	≤ 65	≤ 130	≤ 260	≤ 520	> 520
Sepsis	Negative	Negative	Negative	Positive < 12 hrs.	Positive > 12 hrs.
Erythroderma	Negative	Negative	Negative	Positive < 24 hrs.	Positive > 24 hrs.

Table 5: Parameters for the calculation of the Systemic Inflammation (SI) scale

Phenomenon	Criteria	Points
Systemic Inflammatory Response (SIR)	Levels RL-scale (0–5)	2–5
Microthrombogenesis	D-dimer (≥ 500 ng/ml)	1
Distress Response	Cortisol (≥ 1380 or <100 nmol/L)	1
Systemic alteration	Troponin I (≥ 0.2 ng/mL) Myoglobin (≥ 800 ng/ml)	1
Multiple Organ Dysfunction (MOD)	SOFA scale and/or other MOD criteria	1

determine the significant differences between the groups. A P value of less than 0.05 was regarded as significant.

RESULTS

There was no significant difference in the mean age and BMI between the psoriatic and control groups. However, there was a significantly higher mean serum value of IL-6, IL-8, IL-10, IL-23, lipoprotein (a), chemerin, TNF-α, hs-CRP, osteopontin, D-dimer, troponin I, creatinine, bilirubin, and the platelet count in the psoriatic patients than in the controls. Meanwhile, the serum mean values of adiponectin, paraoxonase, and cortisol were significantly lower in the psoriatic subjects than in the controls (Table 1).

DISCUSSION

The above biomarkers were selected to determine the levels of inflammation based on the reported association between psoriasis and these biomarkers [41]. Previous studies showed an increase in serum levels of IL-6, IL-8, IL-10, IL-23, lipoprotein (a), chemerin, TNF-α, hs-CRP, osteopontin, D-dimer, Troponin I, creatinine, bilirubin, creatinine, and the platelet count in patients with psoriasis, and a decrease in the serum levels of adiponectin, paraoxonase, and cortisol [21,32,41-64]. Serum osteopontin was selected as a biomarker for the calculation of the SOFA scale depending on its role as the bridging of adaptive and innate immunity in autoimmune diseases, including psoriasis [65].

Table 6 shows the data of the RI scale calculated as described in Table 2 with the information in Table 5. Then, CR was calculated by the sum of the 7 [60%] largest values of RIS and, thus, the CR value for the psoriatic patients was 32. According to the criteria presented in Table 3, the CR scale value was

Table 6: Coefficient Reactivity, the SOFA scale, and the SI scale in patients with psoriasis

A. Coefficient Reactivity (CR) calculation (-36)	
Biomarker	CR points
IL-6	4
IL-8	4
IL-10	3
IL-18	5
IL-23	4
TNF - α	5
hs-CRP	5
Chemerin	5
Lipoprotein(a)	4
Paraoxonase	3
Adiponectin	3
B. SOFA scale	
Biomarker	Point s
Bilirubin	1
Creatinine	1
Platelets	0
Osteopontin	4
Sepsis	0
Erythroderma	0
SUM	6
B. SI scale	
Phenomenon	Points
Systemic Inflammatory Response (SIR)	5
Microthrombogenesis	0
Distress Response	0
Systemic Alteration	1
Multiple Organ Dysfunction (MOD)	1
SUM	7
Scale value indicating systemic inflammation	≥ 5

transformed into the RL scale and, thus, for our study cohort, the RL scale was 5 (Table 3).

Table 6, shows the SOFA scale calculated according to the criteria presented in Table 4 and, thus, the SOFA scale value for the psoriatic patients was 6. The systemic inflammation scale (SI) was determined with the criteria presented in Table 5 and, for the psoriatic patients, the SI scale was 7. The scale cut-off value that indicated systemic inflammation was equal to or above 5 points.

The mathematical model for the diagnosis of systemic inflammation was used previously in other clinical conditions, such as in obstetric, acute multiple injuries, heart surgery, and sepsis [36,37].

CONCLUSION

The mathematic model presented here is of predictive value in the determination of systemic inflammation and the discrimination between local and systemic inflammation.

Statement of Human and Animal Rights

All the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 2008 revision of the Declaration of Helsinki of 1975.

Statement of Informed Consent

Informed consent for participation in this study was obtained from all patients.

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