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## Role of Interleukin-18, Tumor Necrosis Factor-α, Osteopontin, Paraoxonase and Lipoprotein (a) in Psoriasis Pathogenicity

**Amina Hamed Alobaidi[a] Abdulghani Mohamed Alsamarai[b]**

[a]*Kirkuk University College of Medicine, Kirkuk, Iraq [KUCOM]*

[b]*Tikrit University College of Medicine, Tikrit, Iraq*

**Abstract**

To clarify the role of tumor necrosis factor-α (TNF-α), interleukin-18 (IL-18), osteopontin, lipoprotein (a) and paraoxonase in psoriasis in Iraqi community this study was conducted. Cross-sectional study included 94 subjects with psoriasis vulgaris, with a mean age of 37.5 ± 11.6 year. Serum osteopontin, IL-18 and TNF-α were determined using Enzyme linked immunosorbent assay kits. The mean serum levels of TNF-α, IL-18, osteopontin (OPN), and lipoprotein (a) (LP (a)) were significantly higher in individuals with psoriasis as compared to controls. In contrast, PON 1 mean serum value was significantly lower in psoriasis compared to controls. Odd ratio indicated a significant association between increase in TNF-α, IL-18, OPN and Lp(a) and the decrease in PON1 in our cohort study. Disease severity significantly correlated with serum levels of TNF-α, IL-18 and Lp (a), while inversely correlated with serum levels of PON 1. TNF-α was with high predictivity in monitoring psoriasis severity and response to treatment. The elevation of serum IL-18, OPN, LP(a) and reduction of PON1 indicated that these biomarkers may play a role in psoriasis pathogenesis. The significant correlation of serum levels of TNF-α, IL-18 and LP (a) with PASI and inverse correlation of PON1 with PASI are useful biomarkers for monitoring of disease severity and treatment outcome

***Keywords:*** Psoriasis, TNF-α, IL-18, osteopontin, lipoprotein, paraoxonase.

### Introduction

Psoriasis is a chronic disease with a prevalence rate ranged from 0.51% to 11.43% worldwide [1] and 2.7% in Iraqi community [2]. In the past, psoriasis was thought to be localized skin disease. But recent studies indicated that psoriasis inducted as localized lesion which converted later into a systemic disease [3]. Many factors affecting the prevalence of psoriasis which include: genetic, infectious, environmental, biochemical, immunological, psychological and endocrinological factors. Psoriasis characterized by chronic course with remission and relapse [4].

Psoriasis was started as a dermatologic lesion to establish the induction phase of the disease which characterized by inflammatory and immunological responses [3,5,6, 7]. Subsequently, systemic inflammation, immune responses, metabolic and neurological changes was initiated and contributed to complicated course of the disease [8-13]. Thus psoriasis was a systemic disease and its pathogenesis sequences include inflammatory responses, immunological reactions, and metabolic changes [14-16], which lead to the development of metabolic syndrome [17] and atherosclerosis [8,18].

Previous studies concerning evaluation the role of biomarkers in psoriasis mainly performed on small size study population and was limited to a small number geographical areas [19-70]. Previous studies that investigate systemic inflammation and immunologic responses in psoriasis used different biomarkers and reported conflicting findings [71,72]. The investigated biomarkers in patients with psoriasis include adipokines, cytokines, chemokines, lipoproteins and enzymes. Osteopontin (OPN), a glycoprotein expressed in macrophage and dendritic cells [73,74]. OPN was produced by tumor cells, osteoblast, epithelia tissue, smooth muscle cells and the immune system cells [75]. OPN inhibit T- helper 2 (Th2) cytokine expression and enhance Th1 expression through its interaction with cluster of differentiation (CD 44) and integrins [76]. OPN was expressed in skin biopsies from psoriasis lesions and peripheral blood mononuclear cells [75]. OPN may play a role in pathogenesis of psoriasis as suggested on

*Corresponding author e-mail: galsamarrai@yahoo.com

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the findings of previously reported case-control studies [19-30].

Tumor necrosis factor- α is a proinflammatory mediators that was over expressed in psoriasis [40]. Many cells produced TNF- α which include mast cells, antigen presenting cells in the skin, keratinocytes, monocytes and lymphocytes. TNF- α plays a critical role in the pathogenesis of psoriasis [72,41,34]. TNF- α induced keratinocytes proliferation and enhance immune cell trafficking to the skin [77]. Previous case-control studies and systematic review and meta-analysis all reported that plasma/serum TNF- α level was increased in psoriatic patients compared to controls [31-48, 56,72]. However, there was a conflicting findings regarding the correlation between psoriasis severity and serum/plasma levels of TNF- α [31,33,34,37-41,43,45,47,48]

Interleukin-18 stimulate T- cells, natural killer (NK) cells, innate immunity enhancement and driven the immune response toward Th1 activity [78]. IL-18 produced by monocytes, keratinocytes, and macrophages [79]. Interferon gamma synthesis stimulation by the NK cells is an activity of IL-18 [80]. Previous studies was found that IL-18 elevated in serum of psoriatic patients and there was a significant correlation between disease severity and IL-18 serum levels. However, 6 studies out of the reported 10 studies, the study population sample size is small, i.e. below the sample size accepted in psoriasis studies and 5 of them were from one country [49-55,39,72].

Recent studies suggested that psoriasis and atherosclerosis were an autoimmune diseases and both conditions influenced by Th1 cell response [81]. Many studies reported that lipoprotein (a) [LP (a)] was a risk factor for cardiovascular disease development [82]. In literature, 4 case-control studies found significant increase in serum Lp (a) levels in patients with psoriasis and two of them found significant correlation between serum Lp (a) and disease severity [57-60].

Paraoxonase (OPN-1)(paraoxonase activity EC 3.1.8.1) is a calcium dependent esterase that hydrolyses organophosphates, aromatic carboxylic acid esters and carbonates [83]. PON-1 exerted antioxidant and anti-inflammatory activities against lipid peroxidation and thus may play a role in psoriasis pathogenesis [64]. Previous studies reported metabolic changes in psoriasis (dyslipidemia) [8,16]. Several case-control studies with a sample size of 15 to 52 psoriatic patients reported that PON-1 reduced in serum of patients with psoriasis [61-70]. However, two studies [62,64] not found a significant difference in serum PON-1 levels between patients and controls. Some studies found significant correlation between psoriasis disease severity and serum OPN-1 levels [63,65,70], while others did not find such results [61,68].

As there is limited studies on the biomarkers of psoriasis in Iraqi population and possibility of influence of genetic and environmental factors on the disease course and pathogenicity, thus this study conducted to evaluate the role of TNF-α, IL-18, osteopontin, lipoprotein (a) and paraoxonase in psoriasis in Iraqi community. Additionally, to determine these biomarkers predictivity for monitoring response to treatment and disease severity.

Materials and methods

Sick cases with psoriasis vulgaris recruited from outpatients and private clinics who had not receive topical and systemic treatment for one month were included in the study. Psoriasis diagnosed clinically based on conventional diagnostic criteria of psoriasis. The disease severity assessed using psoriasis area and severity index (PASI) for each patients. None psoriatic apparently healthy individuals were selected as control group. The minimum sample size for research on psoriasis was 41 for patients group. The study included 94 subjects with psoriasis vulgaris, 46 were male and 48 female with a mean age of 37.5 ± 11.6 years old, BMI mean of 26.1 ± 4.5 and 54.1% were with mild disease severity, Table.1. The control group included 54 apparently healthy controls without any metabolic, infections and endocrinological diseases. Of the total 25 were males and 29 were females with mean age of 36.3 ± 13.2 years old and BMI mean of 25.8 ± 3.4. Demographic and clinical characteristics for each patient and control were collected a questionnaire form formulated for this study. Verbal informed consent taken from each individual before their enrolment in the study. The study protocol was approved by the college ethical committee.

**Exclusion criteria**

Patients with pustular psoriasis, erythroderma, psoriatic arthritis, and palmoplantar forms of psoriasis, guttate and flexural psoriasis were excluded. Subjects with histories of Crohn's disease, multiple sclerosis, ulcerative colitis, melanoma, depression, lymphoma, skin cancer, thalassemia, anaemia, diabetes, cardiovascular disease, renal dysfunction, autoimmune disease, liver disease, neoplasms, hyperthyroidism or hypothyroidism were excluded. Patients received drugs such as lipid lowering drugs, antihypertensive drugs, antidiabetic drugs and vitamin supplements, cyclosporine, methotrexate, acitretin, phototherapy and biologic treatment for at least one month before the enrolment were excluded.

Table 1. The Studied Study Population Characteristics

| Variable | Patients | Controls | P value |
|---|---|---|---|
| Number | 94 | 54 | NA |
| Male/ Female | 46/ 48 | 25/ 29 | NS |
| Mean age ± SD | 37.5 ± 11.6 | 36.3 ± 13.2 | NS |
| BMI, Mean ± SD | 26.1 ± 4.5 | 25.8 ± 3.4 | NS |
| Mild/ moderate- severe | 33/61 | NA | NA |

**Serum sample**

Venous 5 mil blood collected from controls and patients in vials without anticoagulant. Sera separated and stored at – $70^0$ C until analysed.

Investigations

Serum osteopontin, IL-18 and TNF-α were determined using Boster Biological Technology Co Ltd, Enzyme linked immunosorbent assay kits (ELISA), Fremont. Serum paraoxonase and lipoprotein (a) were measured using ELISA kit, MyBiosource. The procedure performed according to manufacturer instructions.

Statistical analysis

The data presented as mean and standard deviation. The statistical analysis performed using SPSS (version 20). Student t test used to determine the significance of differences between patients and control groups, disease severity, influence of age and gender. Odd ratio (OR) was calculated to clarify if there was an association between biomarkers and disease development. Pearson correlation analysis was used to determine bivariate correlation between disease severity and serum values of tested biomarkers. P value of <0.05 was considered significant.

**Results**

Patients with psoriasis show significant (P=0.001) high mean serum levels of TNF-α (38.89 ± 18.41 pg/ml), IL-18 (267.11 ± 115.31 pg/ml), osteopontin (64.61 ± 22.72 ng/ml), and lipoprotein (a) (370.17 ± 70.07 mg/dl) as compared to controls (TNF-α = 14.72 ± 9.39 pg/ml; IL-18 = 195.64 ± 45.43 pg/ml; osteopontin = 40.81 ± 13.16 ng/ml; and lipoprotein (a)= 117.43 ± 23.45 mg/dl). In contrast, paraoxonase mean serum level was significantly (P=0.001) lower in psoriatic patients (44.21 ± 6.77 mIU/ml) as compared to controls (85.98 ± 16.31 mIU/ml), as shown in Table 2.

Table 2. Mean serum values of variables in psoriatic patients compared to controls

| Variable | Mean [SD] | | P value |
|---|---|---|---|
| | Patients | Controls | |
| TNF α, pg/ml | 38.89 [18/41] | 14.72 [93.99] | 0.001 |
| IL-18, pg/ml | 267.11 [115.31] | 195.64 [45.43] | 0.001 |
| Osteopontin, ng/ml | 64.61 [22.72] | 40.81 [13.16] | 0.001 |
| Paraoxonase, mIU/ml | 44.21 [6.77] | 85.98 [16.31] | 0.001 |
| Lipoprotein (a), mg/dl | 370.17 [70.07] | 117.43 [23.45 ] | 0.001 |

Disease severity significantly (P=0.001) influenced serum levels of TNF-α, IL-18, paraoxonase, and lipoprotein (a) in psoriatic patients as demonstrated using PASI score strata of > 10 or ≥10. However, osteopontin mean serum levels was not show a significant difference (P=0.42) between mild psoriatic cases (60.12 ± 18.26 ng/ml) and moderate to severe psoriasis cases (64.99 ± 23.65 ng/ml), as shown in Table 3.

Table 3. Mean serum values of variables in psoriatic patients according to PASI

| Variable | Mean [SD] | | P value |
|---|---|---|---|
| | PASI < 10<br>No. 33 | PASI ≥ 10<br>No. 61 | |
| TNF α, pg/ml | 23.59 [8.32] | 42.51 [18.30] | 0.001 |
| IL-18, pg/ml | 169.06 [46.81] | 290.32 [32.50] | 0.001 |
| Osteopontin, ng/ml | 60.12 [18.26] | 64.99 [23.65] | 0.42 |
| Paraoxonase, mIU/ml | 46.64 [6.52] | 41.56 [6.07] | 0.001 |
| Lipoprotein (a), mg/dl | 340.16 [65.64] | 402.84 [59.84] | 0.001 |

Age did not show a significant influence on mean serum values of TNF-α, IL-18, osteopontin, paraoxonase and lipoprotein (a) in psoriatic patients when the findings analysed on <25 versus ≥ 25 year and <30 versus ≥ 30 year, as shown in Table 4.

Table 4. Mean serum values of variables in psoriatic patients according to age

| Variable | Mean [SD] | | P value |
|---|---|---|---|
| | Age in year < 30 [No. 26] | Age in year ≥ 30 [No. 68] | |
| TNF α, pg/ml | 34.66 [14.36] | 39.83 [19.21] | 0.21 |
| IL-18, pg/ml | 282.91 [161.42] | 263.61 [103.22] | 0.50 |
| Osteopontin, ng/ml | 65.44 [25.22] | 63.76 [22.29] | 0.75 |
| Paraoxonase, mIU/ml | 45.57 [8.45] | 43.36 [5.39] | 0.17 |
| Lipoprotein (a), mg/dl | 362.36 [83.75] | 375.02 [60.34] | 0.39 |

Gender influenced significantly (P=0.002) the lipoprotein (a) serum levels in patients with psoriasis. However, gender does not significantly (P>0.05) influenced mean serum values of TNF-α, IL-18, osteopontin and paraoxonase in psoriasis, as shown in Table 5.

Table 5. Mean serum values of variables in psoriatic patients according to gender

| Variable | Mean [SD] | | P value |
|---|---|---|---|
| | Male No. 46 | Female No. 48 | |
| TNF α, pg/ml | 41.79 [21.07] | 35.76 [14.58] | 0.11 |
| IL-18, pg/ml | 258.21 [61.05] | 276.79 [136.98] | 0.42 |
| Osteopontin, ng/ml | 64.15 [24.56] | 63.97 [20.80] | 0.97 |
| Paraoxonase, mIU/ml | 43.44 [6.92] | 44.86 [6.64] | 0.31 |
| Lipoprotein (a), mg/dl | 394.60 [60.32] | 349.57 [71.61] | 0.002 |

Bivariate analysis indicated a significant association between psoriasis and increased serum levels of TNF-α (OR=13.8;P<0.01), IL-18 (OR= 6.71; P<0.01), osteopontin (10.62; P<0.001) and lipoprotein (a)(OR= 49.29; P<0.0001). In contrast, significant association was observed between psoriasis and decrease in serum levels of paraoxonase (OR= 74.4; P<0.0001), as shown in Table 6.

Table 6. Odd ratio and frequency of high serum values in psoriatic patients

| Variable | Percent with high serum value*/ Control | Association | | |
|---|---|---|---|---|
| | | Odd Ratio | Z value | P value |
| TNF α, pg/ml | 73.40/16.67 | 13.8 | 6.056 | <0.01 |
| IL-18, pg/ml | 50/13 | 6.71 | 4.189 | <0.01 |
| Osteopontin, ng/ml | 64.89/14.81 | 10.62 | 5.374 | <0.001 |
| Paraoxonase, mIU/ml | 97.87/11.11 | 74.40 | 6.040 | <0.0001 |
| Lipoprotein (a), mg/dl | 96.81/1.85 | 49.29 | 5.968 | <0.0001 |

Cut off = control mean + SD

Age was significantly inversely correlated with serum values of osteopontin (r= -0.203; P=0.049) and paraoxonase (r=0.217; P=0.035). PASI score was with significant correlation to serum values of TNF-α (r = 0.79; P=0.001) and IL-18 (r = 0.607; P=0.001). However, PASI scores were significantly inversely correlated with paraoxonase (r = -0.565; P=0.000) and lipoprotein (a) (r = -0.565; P=0.000). TNF-α significantly correlated with IL-18 (r = 0.467; P=0.001), osteopontin (r = 0.269; P=0.009) and lipoprotein (a) (r = 0.362; P=0.001). In contrast, TNF-α serum levels were significantly inversely correlated with paraoxonase (r = -0.243; P=0.018). IL-18 serum values were significantly correlated with lipoprotein (a) (r=0.221; P=0.033). Osteopontin serum levels were significantly correlated with paraoxonase serum levels (r =0.362; P=0.035). Lipoprotein (a) serum levels were significantly inversely correlated with paraoxonase serum levels (r = -619; P=0.001), as shown in Table 7.

Table. 7. PASI correlation with TNF, IL-18, osteopontin (OPN), Paraoxonase, Lipoprotein (a) in patients with Psoriasis

| Variable | | Age | PASI | TNF-α | IL18 | OPN | Para |
|---|---|---|---|---|---|---|---|
| Age | r | 1 | .148 | .088 | .045 | -.203* | -.217* |
| | P | | .154 | .398 | .665 | .049 | .035 |
| PASI | r | .148 | 1 | .792** | .607** | .199 | -.565** |
| | P | .154 | | .001 | .001 | .054 | .001 |
| TNF α | r | .088 | .792** | 1 | .467** | .269** | -.243* |
| | P | .398 | .001 | | .001 | .009 | .018 |
| IL-18 | r | .045 | .607** | .467** | 1 | .164 | .362 |
| | P | .665 | .001 | .001 | | .115 | .345 |
| OPN | r | -.203* | .199 | .269** | .164 | 1 | .362 |
| | P | .049 | .054 | .009 | .115 | | .001 |
| PARA | r | -.217* | -.565** | -.243* | -.098 | .362** | 1 |
| | P | .035 | .001 | .018 | .345 | .001 | |
| LPA | r | .114 | .656** | .362** | .221* | .077 | -.619** |
| | P | .274 | .001 | .001 | .033 | .461 | .001 |

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

**Discussion**

The present study shows that OPN was increased significantly in individuals with psoriasis and the value was higher that apparently healthy controls in Iraqi community. To my knowledge, this is the 3rd study that was performed in Iraq which reported a higher serum OPN in psoriasis compared to controls [39,84]. Global previous studies indicated an increase in plasma/serum levels in individuals with psoriasis [20-30]. However, the reported studies (A case-control studies with one cross-sectional, one systematic review and meta-analysis) were performed on variable study population sizes which range from 12 to 117 psoriatic patients (Supplementary file). Kyriakou et al [19] in systematic review and meta-analysis reported that OPN was involved in psoriasis pathogenesis.

OPN elevation may lead to reduction in secretion of IL-17 and subsequently modulated Th17 response [20]. Buback et al [85] suggested that Th1 immune response was activated by OPN and there was a relationship between OPN and Th17 and Th1 responses and inhibit Th2 responses [86]. OPN interacts with CD44 and integrins leading to enhancement of Th1 responses and inhibit Th2 cytokines expression [26]. As response to bacterial antigens or injury, the antigen-presenting cells was stimulated by OPN [85]. In addition, leukocyte migration crucially influenced by OPN [87,88] and thus OPN plays a key role in psoriasis pathophysiology [25].

This study shows non-significant correlation between disease severity (PASI score) and serum OPN levels. This finding was in agreement with that reported by others [19,21,22,24,26]. However, one study reported high correlation between PASI score and OPN levels [28]. Additionally, two studies did not confirmed a positive correlation between PASI score and histochemical expression of OPN [89,90].

This study did not indicated the influence of age and gender on OPN serum levels as there was no significant differences between patients and control groups. However, age-dependent variation of plasma OPN was reported in the age from birth to 18 years old irrespective of gender [91]. OPN serum values were with marginal significance with age. Odd ratio calculation indicated a highly significant association of serum OPN with psoriasis disease. Gender not demonstrate a significant influence on serum OPN levels in psoriasis.

The present study shows that the mean serum value of TNF-α was significantly higher in psoriatic patients as compared to matched controls. This finding was consistent with a previously reported studies ( case-control studies with study population range of 30-200 subjects) from different geographical areas [31-48]. However, two studies reported that TNF-α serum levels was not with significant differences between controls and psoriatic patients [56,92]. Dawlatshahi et al [41] in a systematic review and meta-analysis of 87 studies containing 2852 patients found that pooled levels of TNF-α were higher in psoriasis patients than in controls. Bai et al [72] in a systematic review and meta-analysis of 63 studies containing 2876 individuals with psoriasis and 2237 subjects as controls found that pooled serum levels of TNF-α were higher in psoriatic patients in comparison to healthy controls.

Cutaneous antigen stimulation contribute to initiation of inflammation with subsequent induction of TNF-α by keratinocytes, macrophages, T17 cells, Th22 cells, Th1 cells, and BACA-1 dendritic cells that play a role in the inflammatory responses in psoriasis [93]. TNF-α regulated OPN indicating that both play a

crucial role in psoriasis pathogenesis [26]. Langerhan's cells migration were stimulated by TNF-α through lowering the level of e-cadherin. Also TNF-α involved in the NF-kB mediated inflammation pathway, which lead to proliferation, cell survival and transcription of antiapoptotic factors [94]. In addition, C- reactive protein, IL-18 and IL-6 expression enhanced by TNF-α which lead to subsequent mediation of T cell activation, provide signal for neutrophil concentration and mediate acute phase inflammation response [95].

The serum TNF-α levels in psoriatic patients were highly significantly correlated with PASI and this finding was in agreement with that reported by others [33,37,40,41,43,45,48]. However, other studies did not confirm a significant correlation between PASI and TNF-α serum levels [31,34,38,39,47]. Although there are controversial findings of different studies regarding the correlation between PASI and serum/plasma TNF-α values, however, our study indicated a highly significant correlation. Additionally, the role of TNF-α in psoriasis pathogenesis confirmed by the high significant odd ratio.

Age and gender have no significant influence on serum TNF-α values in the present study cohort, while disease severity (PASI) had a significant influence. Dawlatshahi et al [41] reported a significant effect of age on circulating TNF-α levels in a meta-analysis study. Additionally, Bai et al [72] in systematic review and meta-analysis study found that there was a difference in plasma/serum TNF-α between patients and controls independent of gender, age, PASI and study quality.

The correlation between serum TNF-α levels in psoriatic patients and disease severity confirm the beneficial efficacy of the usage of TNF-α blockade as treatment approach for psoriasis. The studies disagreement of the correlation between TNF-α serum/plasma levels and disease severity which is assessed by PASI may be due to many factors that include: study design ,study population, inclusion and exclusion criteria [34]. In addition, changes that happened in blood may be not entirely reflected in the skin and vice versa [72]. Cytokines including TNF-α serum concentrations may be affected by several in vivo process such as tissue deposition, production, elimination and degradation [31].

Psoriasis is a disease with variable clinical forms extend from simple dermatologic lesions to multiple system involvement. These clinical variation may contribute to variation in circulating cytokines including TNF-α and the variations are not reflected on PASI. In addition, PASI calculation in being complex, low in accuracy and a non-linear scale [96,97]. Thus PASI scale improvement did not reflect psoriasis improvement [98]. However, PASI score is the recommended tool for the clinical evaluation of psoriasis [96].

In the present study the mean serum value of IL-18 was significantly higher in psoriasis patients than in controls. This finding was consistent with reported by others [49-55, 31,39]. IL-18 receptor and IL-18 concentration increased in non-lesional and lesional skin in psoriasis patients which indicate its role in psoriasis pathogenicity [79,99]. The increased serum levels of IL-18 in this study and previous studies that reported elevation of IL-18 in plasma/serum of psoriatic patients suggest a systemic activation of IL-18 production.

IL-18 exerted activity on innate immunity and Th1 and Th2 immune responses [100]. The synthesis of interferon gamma by NK cells, T-cytotoxic and T-helper cells was triggered by the synergistic activity of IL-18 and IL-12. Thus interferon gamma synthesis lead to increase in Th1 responses and reduction in Th2 responses [101]. In addition, Nakanishi et al [100] reported that NK cells, mast cells, T-cells, and basophils produced IL-13 and IL-4 as an induction activity of IL-18.

In adipose tissue, macrophages and adipocytes synthesize IL-18 [102,103]. Psoriasis was an inflammatory disease that was associated with dyslipidemia and subsequent atherosclerosis [8]. IL-18 produced in the atherosclerotic plaque [104] and contribute to atherosclerotic plaque instability [105]. The IL-18 activity role in psoriasis pathophysiology may be responsible for subsequent development of atherosclerosis in individuals with psoriasis. Blankenberg et al [106,107] suggested that IL-18 plasma levels was independent predictor of coronary disease in future. IL-18 systemic activation which has been found in this study indicated overproduction of adhesion molecule, neutrophil activation, ICAM-1, VCAM and E-selectin were an outcome of IL-18 systemic activation [108].

IL-18 serum levels were significantly correlated to disease severity as measured by PASI. This result confirmed the previously reported significant correlation between PASI and serum/plasma levels of IL-18 [31,39,50,52,53,54]. Bai et al [72] in a meta-analysis suggest that IL-18 tissue levels was correlated to its serum levels. Thus IL-18 may be considered as novel biomarker in psoriasis disease monitoring [72]. This suggestion confirmed by the present study high significant association between serum levels of IL-18 and psoriasis as odd ratio calculation indicated. Age and gender did not influenced serum IL-18 levels in this cohort study. Bai et al [72] found that differences in the analysed studies were overall independent of gender and age.

This study shows that mean serum lipoprotein (a) value was significantly higher in psoriasis as compared to controls. Previous studies from other

geographical areas reported elevation of serum LP (a) in psoriasis [57-60]. Cardiovascular atherosclerotic diseases are common in psoriasis [109-111]. Psoriasis is beyond a skin disease as the previous studies indicated [3,112-115]. Thus the increase in levels of LP(a) in psoriasis is a risk factor for vascular occlusion [116]. Previous studies indicated that LP(a) was the most prevalent and powerful independent risk factor for cardiovascular diseases [117,118].

Serum levels of LP (a) were significantly correlated with PASI as indicator of disease severity. Pietrzak et al [57] and Wadhwa et al [60] reported significant correlation between serum levels of LP (a) and psoriasis severity. Odd ratio confirmed a highly significant positive association between LP (a) and psoriasis development. Age not shows an influence on serum level of LP (a) in patients with psoriasis. However, gender was with influence on LP (a) serum levels in psoriasis. Lipoprotein (a) mean serum level was significantly higher in male as compared to female in our cohort study. However, Habib et al [119], found non-significant difference in serum LP (a) between male and female.

The present study indicated a significant reduction in serum paraoxonase 1 (PON1) in psoriasis patients compared to healthy controls. Significant lower PON1 was reported in psoriatic patients than that in healthy matched controls [63,65,66,69,70]. However, other studies reported increased PON1 levels [61], while other did not find a significant difference [62] or no change following UVB phototherapy [64] in serum PON1 levels. In addition, gender and age did not demonstrate a significant influence on serum PON1 in psoriasis. PON1 serum levels in psoriasis were significantly correlated to disease severity as measured using PASI. This inverse correlation was also reported by others [61,63,67,68], however, one study did not support the inverse correlation between PASI and PON1 serum levels in psoriasis patients [64]. Additionally, Toker et al [61] found no significant association between PON1 serum levels and skin lesion percentage. PON1 is an enzyme with antioxidant and anti-inflammatory defence activities and prevent lipid peroxidation and protect LDL from oxidative stress related peroxidation [120]. The PON1 reduction may be induced by the chronic inflammatory responses accompanied psoriasis [69]. This hypothesis was confirmed by the elevation of serum PON1 level following anti-psoriasis treatment [121]. However, Pektas et al,2013 [64] reported that PON1 activity was not changed following UVA phototherapy. In addition, psoriasis treatment with methotrixate for 8 weeks did not induce an increase in PON1 activity [122]. While Holzer et al [123] reported that anti-psoriasis therapy increased paraoxonase activity.

The present study confirmed a highly significant association between reduction in PON1 serum levels and psoriasis as determined by odd ratio calculation. Thus PON1 activity in psoriatic patients was a reflection of anti-inflammatory, antioxidant and anti-atherogenic capacity. TNF-α serum levels in psoriasis were significantly correlated with serum levels of IL-18, OPN, and PON1. White IL-18 serum values were not significantly correlated with serum levels of OPN and PON1. Lipoprotein (a) serum levels were not significantly correlated to serum levels of OPN.

Conclusion

The present study correlation scenario suggest that TNF-α was a biomarker with high predictivity in monitoring psoriasis severity and response to treatment. Additionally, the elevation of serum IL-18, OPN, LP(a) and reduction of PON1 indicated that these biomarkers may play a role in psoriasis pathogenesis. The significant correlation of serum levels of TNF-α, IL-18 and LP (a) with PASI and inverse correlation of PON1 with PASI are useful biomarkers for monitoring of disease severity and treatment outcome.

**ETHICAL APPROVAL:** Kirkuk University College of Medicine Ethical Committee.

**CONSENT TO PARTICIPATE:** The informed consent was taken from each subject before their enrollment in the study

**HUMAN AND ANIMAL RIGHTS**

The study conducted in adherence with Helsinki Ethical standards.

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**CONFLICT OF INTEREST**

The authors declare no conflict of interest, financial or otherwise.

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