The Egyptian Journal of Hospital Medicine (July 2023) Vol. 92, Page 6553- 6560

Lipocalin-2 as a Significant Biomarker in Psoriasis

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ABSTRACT

Background: Psoriasis (Ps) is a chronic inflammatory skin disease characterized by well-defined erythematous plaques with silvery scales and now it is considered a systemic disease. Lipocalin-2 (LCN2) is a protein stored in the specific granules of neutrophils, acting as a pro-inflammatory mediator that enhances the release of many cytokines, including IL-6, IL-8, and CXCL10, which results in aggravation of the disease.

Objective: The present study aimed at determination of the serum lipocalin-2 concentration and its correlation with degrees of itch, psoriatic arthritis (PsA) and body mass index (BMI) in psoriatic patients. Also, to correlate between level of lipocalin-2 and Ps severity using the Psoriasis Area and Severity Index (PASI) score.

Methods: This study included 2 groups; healthy subjects as control group and psoriatic patients' group and each group included 45 patients. The clinical assessment of Ps was done by using PASI score. Serum LCN2 was measured and correlated with manifestations and severity of psoriasis.

Results: Psoriatic patients demonstrated a statistically significantly higher LCN2 concentration, in comparison with control group. There was a significantly higher LCN2 in psoriatic arthritis than in non-psoriatic arthritis. Serum LCN2 showed excellent accuracy. Best cut-off level of 17.9, sensitivity was 86.7%, specificity was 91.1%. This study showed that serum LCN2 showed fair accuracy AUC (AUC=0.745) for prediction of psoriatic arthritis

Conclusion: High serum LCN2 concentrations in psoriatic patients are correlated with severity and particularly indicate disease activity.

Keywords: Psoriasis, Lipocalin-2, Psoriasis Area and Severity Index (PASI) score.

INTRODUCTION

Psoriasis is a chronic inflammatory skin disease characterized by well-defined, scaly, erythematous plaques [(1)]. The etiology of psoriasis is complex, and is affected by genetic and environmental factors. The incidence and prevalence of Ps also significantly differ according to region and ethnicity [(2)]. Its incidence rate is 2.8% worldwide. In Egypt its prevalence is from 0.6 to 4.8% in general population [(3)]. Psoriasis has a genetic basis and is characterized by an enhanced release of cytokines, resulting in erythematous plaques [(4)].

The histological features of psoriasis include hyperproliferation of the epidermis, disordered differentiation of keratinocytes, T-lymphocyte infiltration and high vascularity [(5)]. Comorbidity is a common feature of psoriasis, and mainly includes rheumatoid arthritis [(6)], inflammatory bowel disease, and multiple sclerosis [(7)].

LCN2 is a member of the lipocalin family of proteins [(8,9)]. It is expressed in several tissues such as liver, lungs, kidneys, adipocytes, macrophage, and epithelial cells [(10)]. LCN2 is a pro-inflammatory marker which enhances the release of many cytokines including IL-6, IL-8, and CXCL10, which results in aggravation of some diseases [(11)].

Moreover, LCN2 is an antimicrobial protein which has a role in the innate immunity response to bacterial infections [(12)], and it modulates cellular immune response and inflammatory process. Therefore, the function of LCN2 extends beyond being an antimicrobial, and it has a role in the progression of many diseases such as infectious diseases, cardiovascular diseases, kidney diseases, tumour metastases, and chronic pain [(13)].

LCN2 also may have a role in the pathomechanism of Ps through modulation of the function of neutrophils and increasing T-h 17 expression [(14)]. Furthermore, high serum LCN2 has been found in psoriatic patients compared to control subjects [(15)]. LCN2 may increase the tendency of psoriatic patients to develop metabolic syndrome [(12)].

This study aimed at determination of serum lipocalin-2 concentration and its correlation with degrees of itch, psoriatic arthritis and body mass index in psoriatic patients and to correlate between level of lipocalin-2 and severity of psoriasis by PASI score.

PATIENTS AND METHODS

This study enrolled Egyptian patients who attended the outpatient clinic of Dermatology Department, Mansoura University Hospitals in the period between September, 2020 and September, 2021. Cooperative patients with chronic plaque psoriasis aged 18-50 years who did not receive systemic treatment in the previous 3 months were included, but pregnant or breastfeeding patients, patients with cardiac failure, and liver cirrhosis were excluded.

Methods

Detailed history, which included patient complaint, age, gender, occupation, marital state, any special habit, diet, psychological disease, existing medical diseases, medications and previous surgeries. Thorough general and dermatologic examination,

Received: 06/03/2023
Accepted: 03/05/2023

which included psoriasis assessment by PASI score. Calculation of body mass index for each patient BMI = weight (kg) / [height (m^2)].

Psoriasis was assessed by using the PASI score (Fig. 1). It was used to evaluate the disease and combine the evaluation of lesion severity and the area of skin involved into a single score that ranged between 0 (no disease) and 72 (maximal disease)[16]. The body was divided into 4 parts [head (H) (10% of skin); arms (A) (20%); trunk (T) (30%); legs (L) (40%)]. Each area was scored by itself, and then all scores were combined to represent final PASI. For each body part, the % of area of skin affected, was estimated and then graded from 0 to 6: [0] 0 percent of affected area, [1] < 10 percent of affected area, [2] 10–29 percent of affected area, [3] 30–49 percent of affected area, [4] 50–69 percent of affected area, [5] 70–89 percent of affected area, and [6] 90–100 percent of affected area[16].

Within each skin section, Ps severity was estimated based on 3 parameters: erythema (red skin), induration (thickness) and desquamation (scaly skin). Severity parameters are measured on a scale of 0 (none) to 4 (maximum) [17]. The sum of these three clinical signs was then calculated for each section, multiplied by the area score for that area and multiplied by weight of respective section (0.1 for head, 0.2 for arms, 0.3 for body and 0.4 for legs).

PASI= 1 (Eh+Ih+Dh) Ah+ 3 (Et+It+Dt) At+ 2(Eu+Iu+Du) Au+ 4 (El+ Il+Dl) Al

Where E=erythema, I=infiltration, D=desquamation, A=area; H=head; T= trunk; U=upper and L=lower extremities [18].

Laboratory Investigations

All participants were subjected to measuring serum LCN-2 with ELISA kits (R and D Systems, Minneapolis, MN, US) at the Clinical Pathology Department, Mansoura Faculty of Medicine, Mansoura, Egypt.

Sample Preparation

Peripheral blood samples were obtained from all participants and were left to clot over 30 minutes. Then, samples underwent centrifugation over 15 minutes at 1000×. Sera were collected and kept at ≤−20°C till analysis.

The Psoriasis Area and Severity Index (PASI) is a quantitative rating score for measuring the severity of psoriatic lesions based on area coverage and plaque appearance.

Plaque characteristic	Lesion score	Head	Upper Limbs	Trunk	Lower Limbs
Erythema	0 = None 1 = Slight 2 = Moderate 3 = Severe 4 = Very severe				
Induration/Thickness					
Scaling					
Add together each of the 3 scores for each body region to give 4 separate sums (A).					
Lesion Score Sum (A)					

Percentage area affected	Area score	Head	Upper Limbs	Trunk	Lower Limbs
Area Score (B) *Degree of involvement as a percentage for each body region affected (score each region with score between 0-6)*	0 = 0% 1 = 1% - 9% 2 = 10% - 29% 3 = 30% - 49% 4 = 50% - 69% 5 = 70% - 89% 6 = 90% - 100%				
Multiply Lesion Score Sum (A) by Area Score (B), for each body region, to give 4 individual subtotals (C).					
Subtotals (C)					
Multiply each of the Subtotals (C) by amount of body surface area represented by that region, i.e. x 0.1 for head, x 0.2 for upper body, x 0.3 for trunk, and x 0.4 for lower limbs.					
Body Surface Area		**x 0.1**	**x 0.2**	**x 0.3**	**x 0.4**
Totals (D)					
Add together each of the scores for each body region to give the final PASI Score.					

Figure (1): PASI score [18].

Assay of lipocalin-2

The kit was for estimating LCN-2 concentration in the sample. Microtiter plate was coated with human lipocalin-2 (LCN-2), then lipocalin-2 was added to wells, and lipocalin-2 antibody was combined with labeled HRP to form antibody-antigen complex. After washing, TMB substrate solution was added, TMB substrate becomes bluish in colour at HRP enzyme-catalyzed. Termination of the reaction was done by adding a stop solution and the colour change was measured at a wavelength of 450 nm. The lipocalin-2 levels in samples were then quantified by comparing the O.D. of the samples to the standard curve. All reagents were brought to room temperature, 50 µl standard dilution were pipetted in each tube. Pipette 100 µl standard (9 µg/L) was pipetted in the first tube. 100 µl from the first tube were taken out into the second, 50 µl from the second tube were pipetted to the third tube to produce dilution series, 40 µl were pipetted to testing sample well, then added testing sample 10 µl, the plate was covered with the adhesive strip provided, incubated over 30 minutes at 37℃, wash solution was diluted 30-times with distilled water. The adhesive membrane was removed, liquid discarded, Pipette washing buffer was pipetted to every well, still for 30s then drain and repeated five times. HRP-conjugate reagent 50 µl was added to all wells, except blank well. The plate was incubated again for 30 min at 37℃, then washed again, 50 ul chromogen solution A and chromogen solution B were added to all wells, 50 ul stop solution was added to all wells. The absorbance was read at 450 nm after pipetting then stop solution was added within 15 minutes. The results were calculated automatically.

Ethical Considerations

This study obtained its approval from the Institutional Research Board, Mansoura Faculty of Medicine. Consents were taken from all participants before participation. The steps, purpose, the benefits and hazards of the procedures in the study were told to all participants. Confidentiality of all participants' data was insured. All enrolled subjects were told that they have the right to withdraw at any time. The Helsinki Declaration was followed throughout the study's conduct.

Statistical Analysis

Data were analysed by the Statistical Package for the Social Sciences, software for Windows (v21). The normality of data was tested using one-sample Kolmogorov-Smirnov test. Qualitative data were represented as numbers and percents. Correlation between categorical variables was performed by Chi-square test. Continuous variables were expressed as means ± SDs for parametric data and as median and range in nonparametric data. Student t-test was utilized to compare between 2 groups. Pearson correlation was utilized to correlate continuous data. Sensitivity and specificity at different cut off levels were tested by ROC curve. The significance of a result was set as 5% level (p-value).

RESULTS

Our study was conducted on 2 groups; healthy subjects as control group and psoriatic patients' group and each group included 45 patients. No significant difference existed between patient and control groups regarding age, gender, weight, height, BMI, and systolic and diastolic blood pressure. There was statistically significant increase of smoking and family history (FH) in psoriatic patients as compared to controls (Table 1).

Table (1): Demographics, anthropometric measures, risk factors and blood pressure in patients and controls

		Controls N=45		Psoriatic cases N=45		*P*
Age (years)	**Mean±SD**	37.0	±9.5	39.4	±10.4	0.187
Males	**N, %**	17	37.8%	22	48.9%	0.288
Females	**N, %**	28	62.2%	23	51.1%	
Weight (kg)	**Mean±SD**	79.0	±15.2	86.3	±13.4	0.098
Height (cm)	**Mean±SD**	1.66	±0.1	1.7	±0.1	0.689
BMI (kg/m^2)	**Mean±SD**	29.0	±5.7	29.9	±4.3	0.282
Smoking	**N, %**	2	4.4%	8	17.8%	**0.044**
Family history	**N, %**	1	2.2%	10	22.2%	**0.004**
SBP (mmHg)	**Mean±SD**	118.9	±8.6	120.9	±11.8	0.361
DBP (mmHg)	**Mean±SD**	76.0	±9.1	77.1	±6.6	0.511

SD: standard deviation

Received: 06/03/2023
Accepted: 03/05/2023

Clinical features of psoriatic patients are shown in table 2. About half of studied cases had psoriatic arthritis. Itching degree was mostly severe. Psoriatic patients showed statistically significantly higher Serum lCN2 concentrations in comparison with control group (Table 3).

Table (2): Clinical features of psoriasis patients

		Psoriatic cases N=45	
Duration of psoriasis (years)	**Median (range)**	5	1-15
PASI	**Median (range)**	21.6	7.5-70.8
Psoriatic arthritis		23	51.1%
Itching degree	**Mild**	5	11.1%
	Moderate	12	26.7%
	Severe	28	62.2%

Table (3): Comparison of LCN2 levels between the study groups

		Controls N=45		Psoriatic cases N=45		*P*
Serum LCN2	**Mean±SD**	13.7	3.3	20.6	2.9	**<0.001**

SD: standard deviation, LCN2: lipocalin-2

ROC curve of LCN2 concentration was constructed to discriminate psoriatic cases from controls. Serum LCN2 displayed very good AUC (0.925). Best cut-off level of 17.9, sensitivity was 86.7%, specificity was 91.1%, PPV was 90.7%, NPV was 87.3%, and accuracy was 88.9% (Figure 2). ROC curve of LCN2 concentration was constructed to predict psoriatic arthritis. Serum LCN2 showed fair AUC (AUC=0.745). Best cut-off level of 20.8, sensitivity was 73.9%, specificity was 68.2%, PPV was 69%, NPV was 73.2%, and accuracy was 71% (Figure 3).

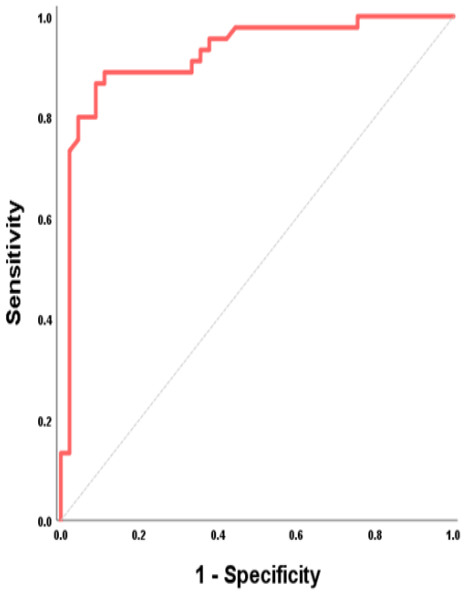

Figure (2): ROC curve of serum LCN2 concentration to discriminate psoriatic patients from controls

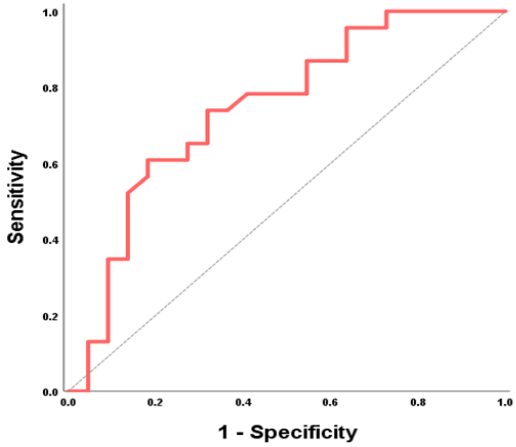

Figure (3): ROC curve of serum LCN2 concentration to predict psoriatic arthritis

No significant associations existed between serum LCN2 concentration and gender, smoking, family history, and BMI. There was significant higher serum LCN2 in psoriatic arthritis as compared with non-psoriatic arthritis. Serum LCN2 showed statistically increasing levels in association with severe itching in comparison to mild and moderate itching (Table 4).

Table (4): Correlation of serum LCN2 concentration with gender, smoking, FH, obesity, psoriatic arthritis, degree of itching in psoriasis group

		Serum LCN2				*P*
		N	**Mean**	**±**	**SD**	
Gender	**Male**	22	21.1	±	2.7	0.248
	Female	23	20.1	±	3.1	
Smoking	**No**	37	20.4	±	3.0	0.280
	Yes	8	21.6	±	2.3	
Family history	**Negative**	35	20.7	±	2.9	0.548
	Positive	10	20.1	±	3.1	
BMI	**<30**	25	20.7	±	3.3	0.810
	≥30	20	20.5	±	2.4	
Arthritis	**No**	22	19.4	±	3.2	0.006
	Yes	23	21.7	±	2.0	
Degree of itching	**Mild**	5	15.0	±	1.8	**<0.001**
	Moderate	12	19.2	±	1.1	
	Severe	28	22.2	±	1.8	

Student t test was utilized for comparisons.

LCN2 levels were positively associated with degree of itching and with psoriatic arthritis. In contrast, no significant relationships were found between serum LCN2 and age, BMI, duration of psoriasis, and PASI score (Table 5).

Table (5): Associations of serum LCN2 concentration with age, BMI, blood pressure, duration, PASI score, psoriatic arthritis and degree of itching in psoriasis group

	Serum LCN2	
	R	***P***
Age	0.080	0.601
BMI	0.034	0.825
SBP	0.015	0.920
DBP	0.035	0.820
Duration	-0.206	0.175
PASI score	0.011	0.943
Psoriatic arthritis	0.403	**0.006**
Itching degree	0.822	**<0.001**

r: correlation coefficient. SBP: systolic blood pressure, DSP: diastolic blood pressure

Logistic regression analysis was carried out to predict Ps development using smoking, FH, obesity, BP, and serum LCN2 concentration as confounders. Positive FH and higher serum LCN2 were proposed to be significant predictors of psoriasis development in uni- and multivariable analyses (Table 6).

Table (6): Regression analysis to predict psoriasis susceptibility.

	Univariable				Multivariable			
	P	**OR**	**95% CI**		***P***	**OR**	**95% CI**	
Smoking	0.152	2.512	0.993	6.352				
Family history	**0.008**	4.324	1.475	12.671	**0.036**	5.813	1.126	30.019
Obesity	0.578	1.162	0.685	1.972				
SBP	0.409	1.011	0.985	1.037				
DBP	0.563	1.010	0.976	1.045				
Serum LCN2	**<0.00**	1.403	1.245	1.582	**<0.00**	1.436	1.247	1.654

OR: odds ratio, CI: confidence interval.

Logistic regression analysis was carried out to predict psoriatic arthritis susceptibility, age, gender, smoking, FH, obesity, BP, Serum LCN2 concentration as confounders. Higher serum LCN2 was found to predict psoriatic arthritis susceptibility. Ordinal regression analysis was carried out to predict factors affecting itching degree in psoriatic patients, using age, gender, smoking, FH, obesity, BP, and serum LCN2 concentration as confounders. Higher serum LCN2 was found to predict higher itching degree (Table 7).

Table (7): Regression analysis to predict the susceptibility of psoriatic arthritis and prediction of factors affecting itching degree

	p	**OR**	**95% CI**	
Susceptibility of Psoriatic Arthritis				
Age	0.149	1.028	0.990	1.067
Gender	0.458	1.321	0.633	2.755
Smoking	0.945	0.967	0.371	2.519
Family history	0.426	0.697	0.286	1.696
Obesity	0.286	1.498	0.713	3.150
SBP	0.439	0.987	0.957	1.019
DBP	0.536	0.982	0.929	1.039
Duration	0.963	0.998	0.907	1.098
PASI	0.130	0.974	0.950	1.298
Serum LCN2	**0.009**	1.232	1.053	1.441
Factors Affecting Itching Degree				
Age	0.911	1.002	0.969	1.036
Gender	0.434	0.754	0.371	1.53
Smoking	0.086	2.801	0.864	9.077
Family history	0.618	1.249	0.522	2.991
Obesity	0.894	0.953	0.471	1.931
SBP	0.943	1.001	0.971	1.032
DBP	0.516	1.018	0.964	1.076
Duration	0.430	0.964	0.881	1.055
PASI	0.875	0.998	0.978	1.019
Serum LCN2	**<0.001**	2.080	1.938	8.587

Linear regression analysis was carried out to predict factors affecting severity of psoriasis using age, sex, smoking, FH, obesity, BP, Serum LCN2 level as confounders. None was associated with severity of psoriasis (Table 8).

Table (8): Regression analysis to predict factors that affect psoriasis severity (Higher PASI score)

	Univariable	
	β	***P***
Age	0.011	0.138
Sex	0.111	0.455
Smoking	0.014	0.945
FH	0.143	0.422
Obesity	0.160	0.280
SBP	-0.005	0.435
DBP	-0.007	0.535
Duration	-0.001	0.963
Serum LCN2	0.064	0.941

B, linear regression coefficient; linear regression analysis was used.

DISCUSSION

Psoriasis influences about 2-3% of the populations. It is characterized by well-defined, scaly, erythematous plaques, mainly on the lumbosacral region, scalp and extensor surfaces [(19)].

The pathomechanism of Ps involves skin infiltration by activated T lymphocytes which induce keratinocyte proliferation [(20)]. This results in formation of thick plaques. Other pathologic features include

epidermal hyperplasia and parakeratosis. Also, the epidermal cells fail to secrete lipids resulting in the characteristics scaly skin sign of Ps [21].

Lipocalin-2 is a multifunctional protein belonging to the lipocalin superfamily and involved in many pathological processes, such as inflammation, acute kidney injury and bone physiopathology [22]. There is evidence linking TNF- α – IL-23 – Th17 – IL- 17 axis to the pathogenetic process of Ps [23]. LCN2 has gained attention due to its role in the pathogenetic process of Ps. LCN2 induces neutrophils to produce IL-6, IL-8, TNF- α, and IL-1 α, via 24p3R receptor on the cell surface [24].

Our study aimed at determination of LCN2 concentration in the serum and its correlation with degrees of itch, psoriatic arthritis and body mass index in psoriatic cases. Also, to correlate between level of lipocalin-2 and Ps severity by using PASI score.

The current study included 22 male (48.9%) and 23 female (51.1%) with psoriasis. Their mean age was 39.4±10.4. Controls were 17 male (37.8%) and female (62.2%). Their mean age was 37.0±9.5. As regards age and gender, no significant difference existed among patient and control groups.

The current study showed that psoriatic patients had higher incidence of smoking more than that in the control group, as well as FH of psoriasis, which is a risk factor for psoriasis, was present in about 51.1% of our patients. Our results agreed with **El-Komy *et al.*** [25] who examined 2534 patients with psoriasis and found that 26.9% were smokers. The mean duration of psoriasis was 106.6 ± 60.0 months. The mean PASI score was 8.7 (range= 0.1- 60.4). Positive FH was found in 23.1% which is lower than our results. This may be due to different sample size.

Our study found that half of patients (51.1%) had psoriatic arthritis. This disagreed with **Rech *et al.*** [26]**,** who studied 5291 patients diagnosed with psoriasis and found that 4390 (8.3%) patients had PsA with 178 of them had severe subtype, arthritis mutilans.

Itching was the commonest symptom. Itching was mild in 11.1%, moderate in 26.7% and severe in 62.2% of cases. This is in line with **Bahali *et al.*** [27]**,** who found that itching was more prominent in their psoriatic patients.

Our study revealed that psoriatic patients had statistically significant higher level of serum LCN2, in comparison with control group (mean=20.6 versus 13.7 respectively). Also this came in accordance with **Nguyen and Nguyen** [28] who found that LCN2 concentrations were significantly high among psoriasis cases in comparison with controls. They also reported that subjects with acute psoriasis (psoriatic erythroderma and pustular psoriasis), had significantly higher serum LCN2 concentrations compared with patients with the chronic plaque type. **El-Hadidi *et al*.** [29] oppose our result , found that estimation of serum LCN2 levels revealed no significant difference between psoriatic cases and controls.

Our study revealed no significant correlations regarding serum LCN2 level with obesity (BMI >30 kg/m^2) in psoriasis group in comparison with overweight (BMI <30 kg/m^2). This agrees with **Kamata *et al.*** [8] study, which found that LCN2 concentrations among psoriatic cases were significantly higher than control subjects, however no significant association was found between LCN2 level and BMI.

Our study showed no statistically significant correlations regarding LCN2 level and male gender, age, smoking, positive family history, disease duration and PASI scores. This agrees with **Baran *et al.*** [30] study which revealed that LCN2 concentrations were significantly higher among psoriatic cases than in control subjects. Also, no significant associations with smoking, positive family history, disease duration, nor BMI or PASI were noted. This is in agreement with some studies that showed that LCN2 level is not correlated with BMI and disease activity in psoriasis/PsA cases [10,31]. Furthermore, conflicting results do exist concerning the positive association between LCN2 level and PASI [12].

The current study showed a statistically significant higher serum LCN2 in psoriatic arthritis in comparison to non-psoriatic arthritis (mean = 21.7 versus 19.4). In addition, serum LCN2 showed statistically increasing levels in association with severe itching in comparison to mild, moderate, and severe itching (mean=22.2 versus 19.2 versus 15 respectively). Consistent with our result, the meta-analysis by **Wang and co-workers**[32] revealed that LCN2 values were significantly higher among psoriasis/PsA cases compared with control subjects. LCN2 concentration might serve as a potential risk factor or marker for psoriasis/PsA.

The current study showed that higher serum LCN2 was suggested to be a predictor for higher itching degree. This agrees with **Aizawa *et al.*** [9] study, which reported significantly higher LCN2 levels in psoriatic cases in comparison with controls. Also, LCN2 concentrations were associated with the degree of itching in psoriatic cases, signifying that LCN2 levels might serve as a potential clinical marker for itching.

To discriminate psoriatic patients from controls in the current study, serum LCN2 had excellent accuracy. Best cut off level of 17.9, sensitivity was 86.7%, specificity was 91.1%, PPV was 90.7%, NPV was 87.3%, and accuracy was 88.9%.

The current study showed that serum LCN2 showed fair AUC (AUC=0.745) for prediction of psoriatic arthritis. At best cut off level of 20.8, sensitivity was 73.9%, specificity was 68.2%, PPV was 69%, NPV was 73.2%, and accuracy was 71%.

LIMITATIONS

Our study has limitations. We substituted serum LCN2 values instead of their expression within the

involved tissue. Further studies with a large number of patients are required for validation of the potential contributions and underlying mechanisms of various immunological pathways in the pathogenetic process of psoriasis.

CONCLUSION

Our study revealed that serum LCN2 levels were higher among psoriatic cases compared with control group, as well as psoriatic arthritis. High serum LCN2 concentrations in psoriatic cases are correlated with severity and particularly indicate disease activity. We supposed that LCN2 can have an important role in the pathogenetic process of acute psoriasis and can act as a useful clinical marker of disease severity.

Conflict of interest: None.
Sources of funding: This research didn't receive any specialized grant from funding agencies.

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