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Serum Lipocalin-2 in Patients with Psoriasis Vulgaris in Relation to Itching and Psoriasis Severity

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ABSTRACT

Background: Psoriasis vulgaris (PV) is a chronic immune-mediated inflammatory skin lesion, which affects approximately 2.5% of the populations. It is featured by erythematous plaques covered with silvery scales, in particular over the extensor surfaces, scalp, and lumbosacral region. Lipocalin-2 (LCN2) is a secreted protein belonging to the lipocalins superfamily. LCN2 stimulates neutrophils to release pro-inflammatory cytokines; IL-6, IL-8, TNF- α, and IL-1 α, via activating the 24p3R receptor on the cell surfaces.

Objective: To assess the possible relation between serum lipocalin-2 levels and the degree of itch in psoriatic cases in relation to psoriasis severity.

Patients and Methods: The current study was a case-control study that included 60 patients with PV and 60 healthy controls (HC) of matched age and sex. The dermatological examination included examinations of site, size, distribution of lesion, assessment of disease severity by Psoriasis Area and Severity Index score. Serum LCN2 concentrations were measured by specific ELISA kits.

Results: The median Psoriasis Area and Severity Index (PASI) score among patients was 25.2 ranging from 5.7 to 56.4. All cases experienced itching. LCN2 was significantly increased among cases compared to the controls. No significant correlation was detected between LCN 2 and body mass index or PASI score. Higher levels of LCN2 were detected in patients experiencing severe itching than those with mild to moderate itching.

Conclusion: The current study concluded that lipocalin-2 was markedly increased among psoriatic cases compared to psoriatic free ones. Also, lipocalin-2 seemed to have a positive correlation with psoriasis degree of itch in cases with PV but not with disease severity by measured PASI score.

Keywords: Psoriasis, Lipocalin-2, Erythematous Plaques, Psoriasis Area and Severity Index.

INTRODUCTION

Psoriasis vulgaris (PV) is considered as a chronic proliferative and inflammatory skin lesion which has incompletely understood etiology [(1)]. It is featured by itching sensation in about 75% of cases [(2)]. Itch has been associated with major distress in psoriatic cases, not only by interfering with life quality but also by worsening exanthema owing to scratching [(3)].

Itching in cases of PV is frequently neglected and isn't considered in disease management. Potential mediators of itch in PV involve histamine, opioids and interleukin-(IL-)31[(4)].

LCN2, a protein secreted primarily by triggered neutrophils, is accompanied by neurodegeneration, overweight, and inflammatory responses [(5)]. Additionally, LCN2 is a secreted glycoprotein member belonging to lipocalins superfamily. [(6)].

LCN2 could participate in PV pathogenesis by modulation of neutrophil activities, such as neutrophil infiltration, migrations, and stimulation, inducing neutrophils to produce pro-inflammatory mediators [(7)]. In addition, LCN2 has been demonstrated to be accompanied by a higher possibility of metabolic syndrome development among cases with PV [(8)]. Moreover, cases with PV were associated with a significant increase in LCN2 value compared to PV free ones [(9)]. As a result, LCN2 could be a possible target in the context of PV management [(10)]. So, our study was done to correlate between serum lipocalin-2 levels and the itch degrees among psoriatic cases in relation to psoriasis severity.

PATIENTS AND METHODS

The current study was a case-control study that included 60 psoriatic cases and 60 healthy controls of matched age and sex. The study was conducted on Egyptian patients attending the outpatient clinic of Dermatology Department, Mansoura University Hospitals, between January 2022 and December 2022.

This study included patients with uncomplicated chronic plaque psoriasis from both genders and aged between 18 to 60 years with or without previous treatment, while the control group included subjects without any prior history of psoriasis lesions and matching with patient group in age and sex. But we excluded cases with associated conditions such as diabetes mellitus (DM), asthma, malignant tumour, or any other diseases were ruled out from the study.

Methods

All cases were subjected to full history taking comprising personal history (name, age, Sex, address), history of current illness (onset, course, duration and predisposing factor for the disease), past history (other autoimmune diseases as thyroiditis), medical history (drugs as corticosteroids and immunosuppressives), and family history of similar skin conditions. All patients were subjected to general examination to rule out any chronic diseases, which could interfere with the results. Dermatologic assessment included

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examinations of site, size, distribution of lesion, evaluation of disease degree by PASI score [(11)].

PASI has been considered as the most broadly utilized approach in the context of measurement of PV severity. PASI combines the evaluation of the degree of lesions and the area affected into a single score in the range zero (none) to 72 (maximum disease). Zero means 0% of affected area, one means < 10% of affected area, two means 10–29% of affected area, three means, 30–49% of included area, four means 50–69% of affected area, five means 70–89% of affected area and six means 90–100% of affected area. Also, the degree of itch was evaluated by a visual analog scale (VAS = 0-100) [(12)].

Laboratory Investigation

Serum lipocalin-2 (LCN2) values were measured in all included subjects by utilizing specialized ELISA kits. The lab work was conducted in Clinical Pathology Department, Mansoura Faculty of Medicine, Mansoura, Egypt**.**

Ethical Considerations

The study protocol was approved from Institutional Research Board, Faculty of Medicine, Mansoura University. An informed written consent was obtained from all the participants before taking any data or doing any investigations. The participants were informed with the aim of the study, which was explained in a simple manner to be understood by common people. All data were considered confidential. The Helsinki Declaration was followed throughout the study's conduct.

Statistical analysis

Data analysis was conducted by SPSS software (SPSS Inc., PASW statistics for windows version 18. Chicago, USA). Qualitative data were defined by utilizing number and percent. Chi-Square test was utilized for comparing qualitative data between groups as appropriate. Quantitative data were presented as mean, standard deviation (SD), median, and interquartile range. The Mann Whitney U was utilized for comparing between 2 studied groups, while the Kruskal Wallis test was utilized for comparing among more than 2 studied groups, for nonnormally distributed data. The Student-t test was utilized for comparing 2 independent groups for normally distributed data. The Spearman's correlation was utilized to detect the strength and direction of a linear relationship. ROC curve was utilized for assessing validity of continuous variables with calculation of best cut off point, predictive values and accuracy were assessed using cross tabulation. P value < 0.05 was considered significant.

RESULTS

The present study was a case control study that was conducted on 60 matched psoriatic cases and control group. Table **(1)** demonstrates no statistically significant difference between studied groups concerning age, sex, family history and smoking history. There was statistically significant higher mean ± SD body mass index among cases than control group. Mean lipocalin-2 was statistically significantly higher in cases group than in control group.

Table (1): Comparison of sociodemographic characteristics, body mass index, and lipocalin 2 of the studied groups

	Cases group n=60(%)	**Control group n=60(%)**	**Test of significance**
Age/years mean±SD	41.37±11.64	37.32±11.26	t=1.92 p=0.06
Sex			
Male	28(46.7)	32(53.3)	χ^2=0.533
Female	32(53.3)	28(46.7)	p=0.465
Family history			
-ve	52(86.7)	52(86.7)	χ^2=0.0
+ve	8(13.3)	8(13.3)	p=1.0
Smoking			
-ve	45(75.0)	38(63.3)	χ^2=1.92
+ve	15(25.0)	22(36.7)	p=0.166
BMI (kg/m^2)	29.96±5.20	25.49±4.33	t=5.11 p<0.001*
Lipocalin-2	37.11±8.19	22.90±5.45	t=9.25 p<0.001*

*: Significant

Table **(2)** shows that 53.3% of the studied cases had gradual disease onset, 55% intermittent course, 100% positive grattage, 100% koebnerization, and 26.7% nail affection. The median PASI score was 25.2 ranging from 5.7 to 56.4. The itching severity was 36.6% severe disease.

Table (2): Disease characteristics, disease severity PASI and itching severity of the studied cases.

	N=60	**%**
Onset		
Acute	16	26.7
Chronic	12	20.0
Gradual	32	53.3
Course		
Intermittent	33	55.0
Progressive	27	45.0
Grattage	60	100
Koebnerization	60	100
Nail	16	26.7
Itching Severity		
Mild	19	31.7
Moderate	19	31.7
Severe	22	36.6
PASI		
Median (min-max)	25.2(5.7-56.4)	

Table **(3)** illustrates that there was no statistically significant correlation between lipocalin-2 and BMI and PASI score. A statistically significantly higher median lipocalin was detected among cases with severe itching score than moderate and mild itching score.

Table (3): Correlation between lipocalin-2 and BMI, PASI score and itching severity among studied cases.

	Lipocalin-2	
	r=	p=
BMI (kg/m^2)	-0.079	0.549
PASI	-0.122	0.394
Itching severity **Mild** **Moderate** **Severe**	 34.4(27.1-51.1) 35(25.7-58.4) 3٩.4(28.1-54.6)	 KW=3.70 P=0.02*

r: Spearman correlation coefficient, *: Significant

Table **(4)** shows that there was no statistically significant association between lipocalin-2 and age, sex, family history, smoking, onset, course, systemic treatment, topical treatment and nail affection.

Table (4): Relation between lipocalin-2 and age, sex, medical history, and used treatment among studied cases.

	Lipocalin-2	**Test of significance**
Age/years	r=-0.074	P=0.575
Sex Male Female	 35.35(27.1-58.3) 36.65(25.7-58.4)	 Z=0.674 P=0.500
Family history -ve +ve	 35.8(25.7-58.4) 36.2(27.1-57)	 Z=0.098 P=0.922
Smoking -ve +ve	 35.7(25.7-58.4) 36.7(27.1-54.6)	 Z=0.034 P=0.973
Onset Acute Chronic Gradual	 37(28.1-49.4) 35.55(27.1-51.1) 35.65(25.7-58.4)	 KW=0.105 P=0.949
Course Intermittent Progressive	 35.9(25.7-58.4) 35.1(27.1-54.6)	 Z=0.661 P=0.508
Systemic treatment -VE +VE	 37.2(25.7-58.4) 34.9(27.1-58.3)	 Z=0.23 P=0.818
Topical treatment -VE +VE	 34.9.(27.1-58.3) 37.5(25.7-58.4)	 Z=0.621 P=0.534
Nail -VE +VE	 35.85(25.7-58.3) 35.45(27.1-58.4)	 Z=0.192 P=0.848

Table **(5)** and figure **(1)** demonstrate that area under curve for lipocalin-2 was excellent in differentiating between cases and control (0.884) with the best detected cut off point was 25.85.

Table (5): Validity of lipocalin-2 in differentiating between cases and control groups

	AUC (95% CI)	**P value**	**Cut off point**	**Sensitivity%**	**Specificity%**	**PPV%**	**NPV%**	**Accuracy%**
Lipocalin-2	0.884 (0.824-0.944)	<0.001*	25.85	98.3	65.0	73.8	97.5	81.7

*: Significant

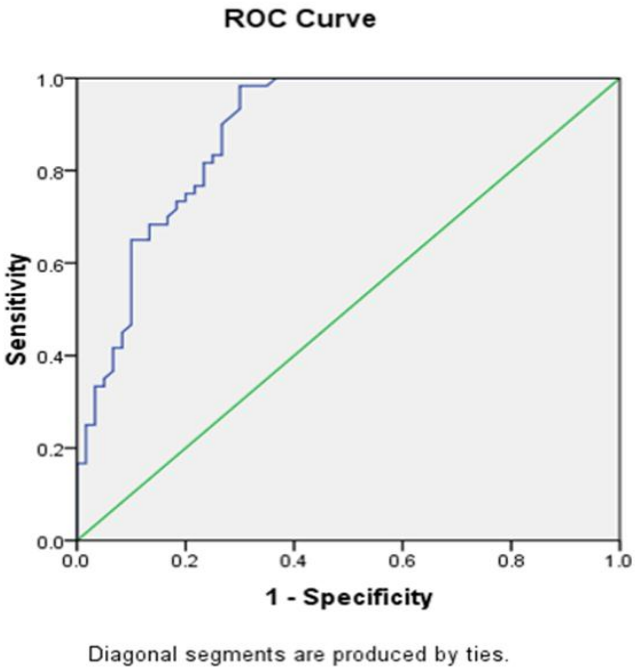

Figure (1): ROC curve of lipocalin-2 in differentiating between cases and control groups.

DISCUSSION

Psoriasis is a common immune-mediated skin lesion which affects about 2.5% of the population. It is featured by erythematous plaques covered with silvery scales, in particular over the extensor surfaces, scalp, and lumbosacral area [(13)]. Pathophysiology of psoriasis is a complex genetic disorder that is stimulated by different predisposing factors. The hallmark of PV is sustained inflammation inducing uncontrolled keratinocyte proliferation [(14)]**.** Impaired regulation of keratinocyte turnover has been demonstrated to be associated with thick plaque formation. Additional accompanying characteristics involve epidermal hyperplasia and parakeratosis [(15)]**.**

Lipocalin-2 (LCN2) is a secreted glycoprotein member belonging to lipocalins superfamily. LCN2's altered expression is assigned to critical roles in a lot of pathologic conditions, such as hepatic injury and steatosis, kidney dysfunction, cerebral injury, cardiomyopathy, musculoskeletal diseases, pneumonia, and malignant tumour in multiple organs [(16)].

Shao *et al.* [(7)] revealed that keratinocytes and neutrophils were the sources of LCN2 in the affected area of psoriatic cases. They recommend that LCN2 is comprised in the PV pathogenesis via modulation of neutrophil functions, and that it may act as a possible target in the context of PV management**.** LCN2 triggers neutrophils to discharge pro-inflammatory cytokines; IL-6, IL-8, TNF- α, and IL-1 α, via activating the 24p3R receptor on the cell surfaces [(17)]**.**

We aimed to assess the possible relation between serum lipocalin-2 (LCN2) levels and the degree of itch in psoriatic cases in relation to psoriasis severity and the validity of utilization of lipocalin-2 as a biomarker of activity and severity of this disease. The present study included 28 males (46.7%) and 32 females (53.3%) in cases group. Their mean age was 41.37±11.64. Controls were 32 males (53.3%) and 28 females (46.7%). Their mean age was 37.32±11.26. There were no significant differences between cases and controls concerning all demographic characteristics.

Our study revealed female predominance (53.3%). Similarly, **Egeberg *et al.*** [(18)] found that 54% were females. On the contrary, **Kavanaugh *et al.*** [(19)] had examined 12,090 cases with psoriasis and revealed that 50.8% of cases were men with a mean age of about fifty years which disagreed with our results regarding age and sex predominance.

Among our patients 13.3% were with positive family history and 25% were smokers, versus 13.3% positive family history, 36.7% smokers for control group, with no statistically significant difference between cases and controls. Smoking was recorded to be an independent predisposing factor for PV development, and smoking incidence was reported to be doubled among psoriatic cases compared to the overall healthy population [(20)]. On the other hand **Rifaioglu and Ozarmagan** [(21)] displayed a rate of 42.3% which disagreed with our results.

The present study displayed that psoriatic group had greater body mass index than controls which was statistically significant (29.96 ± 5.20 versus 25.49 ± 4.33, respectively) in agreement with **Akbulut *et al.*** [(22)] who examined total of 618 psoriatic cases, as regard BMI revealed a median BMI of 27 kg/m^2.

Our study found that the median PASI score was 25.2 ranging from 5.7 to 56.4, with most cases had gradual onset with intermittent course. The present study revealed that all cases had positive grattage and

koebnerization and 26.7% had nail affection. The most common symptom we recorded was itching. All cases experienced itching (36.6% had severe symptoms, 31.7% had moderate and 31.7% had mild symptoms). On the contrary to our results, another study reported that the median PASI score was 8.1. Most of the studied cases (58.5%) had PASI score < 10, while 41.5% of them had PASI score >10. The PV onset was sudden in 56.2% of cases, while gradual onset was reported in 43.8% of them. The PV course was progressive in 46.4% of cases, remission and exacerbations were recorded in 37%, and regressive course was recorded in 16.7% [22].

In addition, **Meena *et al.*,** [23] found that mild PV was detected in 132 cases while 68 cases had moderate to severe PV. In agreement with our results, itch was recorded in 172 (86%) out of 200 cases. Of which, 161 (93.60%) patients had itch restricted to psoriatic plaques, the remaining cases (6.39%) developed itch on both diseased and normal skin. It has been demonstrated that there was a diurnal variation of itch in 27.32% of cases with deteriorating manifestations at night. The etiology of nocturnal worsening could be a lower itch threshold as a result of the patient's increased attention to itch in the absence of different activities.

The present study displayed that the mean LCN2 was higher in psoriasis patients than control group (37.11 ng/ml for cases versus 22.9 ng/ml for control group) with statistically significant difference between them. These results are in agreement with the data obtained by **Wang *et al.*** [24] who demonstrated that serum LCN2 levels were substantially greater in psoriatic cases compared to HC in their study on the correlation between serum LCN2 values and PV. In disagreement to our results, **El-Hadidi *et al.*** [25] found a significant difference in tissue levels of LCN2 between psoriatic patients and controls.

Our study displayed no statistically significant correlation between LCN 2 and body mass index or PASI score. These results agreed with the results of **El-Hadidi *et al.*** [25] who concluded that LCN2 has no role in determining severity of psoriasis**.**

Baran *et al.* [26] reported that there were no significant correlations between LCN2 and BMI or PASI. Following topical therapy, serum LCN2 value didn't significantly change, and still remaining greater compared to the controls, in spite of clinical improvement.

The current study revealed higher values of LCN2 in cases experiencing severe itching than those with mild to moderate itching. Thus, lipocalin-2 was suggested to be a predictor for higher itching degree. This is in line with **Aizawa *et al.*** [5] who revealed that serum LCN2 value were significantly higher in psoriatic cases than HC. Also serum LCN 2 level is accompanied by higher itching severity in psoriasis patients, recommending that serum LCN2 could be utilized as a helpful marker for itch.

In agreement with our results **Tominaga *et al.*** [27] **and Basha *et al.*** [28] recorded that serum LCN2 concentrations were significantly greater in psoriatic cases who had itching than those who didn't. LCN2 levels were demonstrated to have a significant correlation with VAS but not with PASI.

The relationship between LCN2 value and degree of itching among psoriatic cases explains its association with itching pathogenesis in PV and that serum LCN2 level could be used as a promising marker for itch among psoriatic cases.

In terms of differentiation between psoriatic cases and normal controls in the present study, serum LCN2 revealed excellent accuracy. Excellent area under curve (0.884), with the best detected cut off point of 25.85 yielded sensitivity of 98.3%, specificity of 65%, PPV was73.8, NPV was 97.5, and total accuracy was 81.7%.

CONCLUSION

The current study concluded that lipocalin-2 was markedly increased among psoriatic cases compared to psoriatic free ones. Also, lipocalin-2 seemed to have a positive correlation with PV degree of itch in cases with PV but not with disease severity by PASI score. In addition, lipocalin-2 could be used as a promising predictor in discrimination between psoriatic cases and normal subjects with a higher sensitivity and accuracy.

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