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Serum Elafin Level as a Potential Marker of Psoriasis Severity

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ABSTRACT

Background: Elafin is barely detectable in normal skin and is strongly expressed in inflamed skin. It is highly expressed in epidermis, sputum, and urine of psoriatic patients but is not specific for psoriasis.

Objective: To estimate the serum level of elafin in psoriasis cases and its correlation with the severity of psoriasis.

Patients and methods: This was a case-control study carried out on 45 patients with different clinical types of psoriasis who were newly diagnosed or stopped systemic treatment for at least 3 months before the study. They were recruited from the Outpatient Clinic of Dermatology Department, Mansoura University Hospital. In addition 45 normal healthy subjects with matched age and sex were selected to act as a control group.

Results: The mean onset, duration and psoriasis area severity index (PASI) were 37 ± 9.43, 8.37 ± 8.07 and 23.28 ± 14.53 respectively. Psoriasis group was associated with a significant increase in serum elafin level compared to the control group. Cases with severe psoriasis demonstrated the highest serum elafin level followed by moderate psoriasis and lastly mild psoriasis. ESR, CRP and elafin could be used as reliable biomarkers in terms of the differentiation among psoriasis and the control group with high accuracy, sensitivity and specificity. Elafin level was demonstrated to be significantly correlated with PASI, ESR and CRP.

Conclusion: Elafin level demonstrated significant elevation among psoriatic cases and correlated positively with the disease severity (as revealed by PASI score). Thus, it could be used as a promising predictor for psoriasis diagnosis, which could impact the therapeutic lines in the future.

Keywords: Serum elafin level, CRP, ESR, PASI, Psoriasis.

INTRODUCTION

Psoriasis is a chronic, hyperproliferative inflammatory skin disease with a genetic background, with characteristic erythematous squamous plaques that have specific silver scaly appearance. Its percentage in the general population is 1-3 % [(1)]. Diagnosis of psoriasis is informed by examination of the skin. The classic symptoms of psoriasis vulgaris are highly visible chronic erythematous plaques covered by silvery white scales, forming on the elbows, knees, scalp, umbilicus and lumbar area [(2)]. Additional types of psoriasis comprise approximately 10% of cases. They include pustular, inverse, napkin, guttate, oral, and seborrheic-like forms [(3)]. Pustular psoriasis (PP) is a group of inflammatory skin conditions characterized by infiltration of neutrophil granulocytes in the epidermis to such an extent that clinically visible sterile pustules develop [(4)]. Psoriasis causes functional impairment and emotional distress to patients. The impact of the disease can result in restrictions to social and recreational activities and productive life, in addition to possible harm to these patients' affective and sexual relationships [(5)].

The psoriasis area severity index (PASI), which is used for clinical evaluation, is the most cited and most often used tool due to its high degree of reliability, applicability and reproducibility [(6)].

Lesional skin in psoriasis is characterized by the excessive production of antimicrobial peptides (AMPs), which are known for their role in killing pathogenic microorganisms and modifying host inflammatory responses [(7)].

Elafin is one of natural AMPs [(8)]. It is a serine protease inhibitor produced by epithelial and immune cells with anti-inflammatory properties [(9)]. Elafin's functions are not only restricted to its protease inhibitor action but also extend to involve other molecular properties, influencing cellular proliferation and inflammation [(10)].

Interleukin 1 beta and TNF alpha are released by neutrophils in skin disorders with extensive dermal neutrophil infiltration (as psoriasis), causing over-expression of elafin, which acts as a protective agent against damage of the epidermis by neutrophil elastase [(11)]. The aim of this work was to estimate serum level of elafin in psoriasis cases and its correlation with the severity of psoriasis.

PATIENTS AND METHODS

This is a case control study carried out on 45 patients with different clinical types of psoriasis. They were recruited from the outpatient clinic of Dermatology department of Mansoura University Hospital, from August 2018 to August 2019. In addition 45 normal healthy subjects with matched age and sex were selected to act as a control group.

The subjects were subdivided into two groups: **Group A** (patient group): includes 45 patients with different clinical types of psoriasis, and **Group B**

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(control group): includes 45 healthy persons who match the patient in the same age and sex.

Ethical approval:

This study was approved by the Institutional Review Board, Faculty of Medicine, Mansoura University (IRB code: MS.18.12.413.R1). All patients signed informed consents before participation in the study. This work has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion Criteria: Newly diagnosed patient, patient who stopped systemic treatment for at least 3 months before the study, and cooperative patient.

Exclusion Criteria: Patient with Graft Versus Host Disease (GVHD), celiac disease, myocardial ischemia, pulmonary hypertension, patient receiving systemic treatment, and non-cooperative patient.

All patients and controls were subjected to:

I) Full history taking:

A) **Personal history:** Name, age, sex, occupation, residence, medical problems and special habits of medical importance (smoking).

B) **Present history:** Body mass index (BMI), current treatment, duration of disease

C) **Past history:** Previous medical history (diabetes mellitus, hypertension).

D) **Family history:** Presence of any other family member with psoriasis.

II) Physical and dermatological examination.

All patients were subjected to full clinical examination that included:

A) **General examination:** Examination of the pulse, temperature and blood pressure, were done.

B) **Dermatological examination:** Such examination includes skin, hair and nail evaluation.

C) **Determination of severity of psoriasis vulgaris by PASI score:** Extent and severity of psoriasis was assessed using the psoriasis area and severity index (PASI) that was developed in **1978 by Fredriksson and Pettersson**[12] to evaluate the severity of psoriasis. This index analyzes the four regions of the body (head, trunk, upper and lower limbs) in relation to erythema, induration (thickness), desquamation (scaling) of the plaques, and body surface area (BSA) affected [13]**.**

According PASI score psoriasis vulgaris was classified into [14]:

- **Mild psoriasis,** which means less than 3% of your body is affected. This typically means that, isolated patches on the limbs as well as the scalp. Psoriasis is also considered mild if a skin medication controls it or if it only affects the quality of life a little bit.
- **Moderate psoriasis**, when 3% to 10% of the body has patches. This usually means it affects the arms and legs, torso, and scalp. It's also considered moderate if it can't be controlled using a skin medication or if it has a significant impact on quality of life.
- **Severe psoriasis**, if more than 10% of the body is affected, or if large areas on the face, palms or soles of the feet have patches**.** It can also be deemed severe if it can't be controlled using a skin medication or it has a severe impact on quality of life.

D) Laboratory investigations:

The laboratory work was done in Clinical Immunology Unit, Clinical Pathology Department, Mansoura Faculty of Medicine.

Sampling:

Five milliliters of venous blood was collected by venipuncture under complete aseptic precautions from every subject and divided into two tubes:

I) Determination of Erythrocyte sedimentation rate: In the first tube, 1.6 ml of blood was added to citrated tubes for erythrocyte sedimentation rate (ESR) estimation by Wester Green method.

II) Determination of C-reactive protein (CRP) and serum elafin level: In the second tube, three ml of blood was withdrawn into a plain tube. The sample was allowed to clot for 30 minutes, the tube was centrifuged for 15 minutes at approximately 1000×g, and the serum was divided in two tubes; one used for C-reactive protein (CRP) and the second stored at -20 °C until assay for elafin, using an ELISA technique.

CRP Assay:

Assay of CRP was done using hs-CRP+CRP fast test sit (Immunofluorescence Assay) that is intended for in vitro quantitative determination of C-reactive protein (CRP) in serum, plasma, whole blood, or fingertip blood. Measurement of CRP is useful for the detection and evaluation of infection, tissue injury and inflammatory disorders. Measurement of high sensitivity CRP (hs-CRP), when used in conjunction with traditional clinical laboratory evaluation of acute coronary syndromes (ACS), may be useful as an independent marker of prognosis for recurrent events in patients with stable coronary disease or ACS **(Cat No. MD221 SL, Company Name: MD PACIFIC (TIANJIN) BIOTECHNOLOGY CO., LTD, China).**

Determination of serum elafin level:

Serum Elafin was determined using (Human Peptidase Inhibitor 3, Skin Derived (PI3/elafin) ELISA Kit) (Cat No. 201-12-4511 sunredbio, Shanghai, China).

Statistical analysis

Results were statistically analyzed using statistical package of social sciences (SPSS 22.0, IBM/SPSS Inc., Chicago, IL). Quantitative data were presented as mean and standard deviation or media (range) according to normality by using Kolmogrov-Smirnov test. It included estimates for summarizing the continuous data as mean (X) and standard deviation (SD) for normally distributed data or median (Med) and interquartile range (IQR) for skewed data. Frequency with percentage (%) was used for presenting qualitative data. **Pearson Chi-square (χ2) test** was used to compare between two or more groups regarding one qualitative variable. **Fisher's Exact Test** was used instead of Chi-Square (χ^2) test when the assumption that at least 80% of the expected frequencies are greater than five was violated. **Receiver operating characteristic (ROC) analysis** is graphical plot of sensitivity against one minus the specificity (false positive rate) for different cutoffs. The optimal cutoff value was determined using **Youden index J** that is the farthest point on ROC curve from the diagonal line of equality [maximum (sensitivity + specificity)-1]. P value < 0.05 was considered significant.

RESULTS

There were no statistically significant differences among both groups as regards age, gender, marital status, smoking, weight, length and BMI **(P > 0.05).** There was highly statistically significant increase in ESR, CRP and elafin level in psoriasis group compared to the control group **(P < 0.001) (Table 1).**

Table (1): Analysis of demographic data, anthropometric measures, ESR, CRP and serum elafin level in the two studied groups

		Groups				Test of significance
		Psoriasis group (N=45)		Control group (N=45)		
Age (years)		45.47 ± 14.34		37.53± 7.13		t= 1.869 p =0.0087
Gender	Male	24	53.3%	22	48.8%	χ2= 0.805 P= 0.439
	Female	21	46.7%	23	51.2%	
Marital status	Married	39	86.7%	36	80%	FET= 1.027 P= 0.175
	Single	5	11.1%	9	20 %	
	Widow	1	2.2%	0	33.3%	
Smoking	Yes	14	31.1%	10	22.2%	χ2 = 1.350 P= 0.146
	No	31	68.9%	35	77.8%	
Weight (Kg)		88.65 ± 21		86.72 ± 16.34		t= 1.948 p = 0.124
Length (cm)		169.75 ± 10.22		166.8 ± 9.43		t= 1.341 p = 0.184
BMI (Kg/m^2)		30.69 ± 6.44		29.13 ± 3.86		t= 1.412 p = 0.172
ESR (mm/hr)		13		5		z= -7.520 **p < 0.001***
CRP (mg/L)		4.8		0.99		z= -6.669 **p < 0.001***
Elafin (pg/ml)		1.41		1.19		z= - 4.309 **p < 0.001***

P: probability. Continuous data expressed as mean ± SD. Categorical data expressed as Number (%). T= independent samples t-test χ2= Chi-square test FET: Fischer's exact test *: statistically significant (p < 0.05)

The mean onset, duration and PASI were **37 ± 9.43**, **8.37 ± 8.07** and **23.28 ± 14.53** respectively. In addition, positive family history was demonstrated in 20% of the studied cases only. In terms of psoriasis type, the majority of the studied cases had psoriasis vulgaris (80%), while only 4.4%, 8.9% and 6.7% had erythrodermic psoriasis, guttate psoriasis and pustular psoriasis respectively (Table 2).

Table (2): Analysis of the disease criteria in the psoriasis group

Items		Study cases n=45
Onset of the disease	Mean ± SD	37 ± 9.43
	Median	35
Duration of the disease	Mean ± SD	8.37 ± 8.07
	Median	6
PASI	Mean ± SD	23.28 ± 14,53
	Median	20.1
Family history		
Positive		**9 (20%)**
Negative		**36 (80%)**
Type of psoriasis		
Psoriasis Vulgaris		**36 (80%)**
Erythrodermic psoriasis		**2 (4.4%)**
Guttate psoriasis		**4 (8.9%)**
Pustular psoriasis		**3 (6.7%)**

Continuous data expressed as mean ± SD and median (range) Categorical data expressed as Number (%)

There was statistically significant relation between serum elafin level and smoking, in which smoker cases demonstrated statistically significant increase in serum elafin level compared to non-smokers **(P = 0.015)** (Table 3).

Table (3): Relation between serum elafin level and smoking

	Psoriasis cases		Test of significance
	Smoker (N=14)	Non-smoker (N=31)	
Elafin (pg/ml)	1.6	1.04	z= - 2.514 **p = 0.015***

P: probability. Continuous data expressed as median (range) z= Mann-Whitney U test *: statistically significant (p< 0.05)

There was highly statistically significant relation between serum elafin level and family history, in which cases with positive family history demonstrated highly statistically significant increase in serum elafin level compared to the negative ones **(P < 0.001)** (Table 4).

Table (4): Relation between serum elafin level and family history

	Psoriasis cases		Test of significance
	Positive family history (N=9)	Negative family history (N=36)	
Elafin (pg/ml)	3.12	1.52	z= - 3.603 **p = 0.001***

P: probability. Continuous data expressed as median (range) z= Mann-Whitney U test *: statistically significant ($p < 0.05$)

There was highly statistically significant differences in serum elafin level among psoriasis types, in which erythrodermic psoriasis demonstrated the highest level followed by pustular psoriasis, then guttate psoriasis and lastly psoriasis vulgaris **(P<0.001)** (Table 5).

Table (5): Analysis of serum elafin level according to the type of psoriasis

	Type of psoriasis				Test of significance
	Psoriasis Vulgaris (N=36)	Guttate psoriasis (N=4)	Pustular psoriasis (N=3)	Erythrodermic psoriasis (N=2)	
Elafin (pg/ml)	1.37	1.83	5.1	9.39	KW= 16.349 **p < 0.001***

P: probability. Continuous data expressed as median (range) KW= Kruskal Wallis test *:statistically significant ($p < 0.05$)

There was highly statistically significant differences in serum elafin level among various grades of psoriasis, in which severe psoriasis demonstrated the highest level followed by moderate psoriasis and lastly mild psoriasis **(P < 0.001)** (Table 6).

Table (6): Analysis of serum elafin level according to the severity of psoriasis (PASI score)

	Severity of psoriasis			Test of significance
	Mild (N=9)	Moderate (N=4)	Severe (N=23)	
Elafin (pg/ml)	1.05	1.19	1.46	KW= 22.465 **p < 0.001***

P: probability. Continuous data expressed as median (range) KW= Kruskal Wallis test *: statistically significant ($p < 0.05$)

The three parameters (ESR, CRP and elafin) demonstrated statistically significant differences in the differentiation among psoriasis and the control groups. At cut off **> 7.5** (AUC=0.959), ESR demonstrated 100% sensitivity, 78% specificity, 72% NPV, 87% PPV, and 90% accuracy in terms of the differentiation among psoriasis and the control groups. At cut off **> 2.41** (AUC=0.910), CRP demonstrated 85% sensitivity, 91% specificity, 80% NPV, 92% PPV, and 84% accuracy in terms of the differentiation among psoriasis and the control groups. At cut off **> 1.34** (AUC=0.764), **elafin** demonstrated 64% sensitivity, 82% specificity, 66% NPV, 80% PPV, and 72% accuracy in terms of the differentiation among psoriasis and the control group (Table 7).

Table (7): Analysis of diagnostic criteria of ESR, CRP and elafin in differentiating psoriasis from control cases

	ESR	CRP	Elafin
AUC	0.959	0.910	0.764
Cut off point	> 7.5	> 2.41	> 1.34
Sensitivity	100%	85%	64%
Specificity	78%	91%	82%
NPV	72%	80%	66%
PPV	87%	92%	80%
Accuracy	90%	84%	72%
P	**<0.001***	**<0.001***	**<0.001***

AUC: Area under curve, PPV: positive predictive value, NPV: Negative predictive value

There were no statically significant correlations among elafin and demographic parameters (age, weight, height and BMI) **(P < 0.05),** while elafin level demonstrated highly statistically significant correlations with PASI, ESR and CRP **(P < 0.001)** (Table 8).

Table (8): Correlation between elafin with other variables in the control group

Variable	Elafin	
	r	p
Age (Years)	-0.073	0.634
Weight (kg/hL)	0.009	0.957
Height	0.021	0.899
BMI (kg/m^2)	0.001	0.994
PASI	0.957	**<0.001***
ESR (mm/hr)	0.581	**<0.001***
CRP (mg/L)	0.803	**<0.001***

r: Pearson's correlation. *: statistically significant ($p< 0.05$).

DISCUSSION

Concerning the demographic characteristics (age and sex, marital status and smoking) in the current study, both groups demonstrated insignificant differences ($P > 0.05$). Such results indicated that both groups were comparable and the demographic characteristics were not interfering with the net results of the study. This is in agreement with **Alghonemy *et al.*** [15] who conducted a case–control study that included 90 subjects classified into group I, which included 60 patients with moderate to severe psoriasis according to PASI, and group II, which included 30 apparent healthy age- and sex-matched participants as a control group. They demonstrated that the mean age of psoriatic cases was 41.75 ± 12.53 with a range from 12.0 to 66.0 years vs a mean value of 40.20 ± 15.72 with a range of 13.0–67.0 years, in the control group. Most cases were males

(66.6%) in both groups. There was no significant difference between both groups in age and sex distribution, with P=1 and 0.640 respectively.

The current study revealed that, the mean onset, duration and PASI were 37 ± 9.43, 8.37 ± 8.07 and 23.28 ± 14.53 respectively. In addition, positive family history was demonstrated to be in 20% of the studied cases only. In terms of psoriasis type, the majority of the studied cases had psoriasis vulgaris (80%), while only 4.4%, 8.9% and 6.7% had erythrodermic psoriasis, guttate psoriasis and pustular psoriasis respectively. **Alghonemy *et al.*** [15] demonstrated that, the mean value of PASI was 14.37 ± 9.83, with a range of 3.60–42.20, and the median duration of disease was 9.57 ± 6.21, with a range from 1 to 21 years. No dermatological diseases other than psoriasis were noticed in the patient group. In only 5% of cases, there was a positive family history of psoriasis, without significant difference between both groups (P = 0.548).

The current study demonstrated that there was highly statistically significant increase in serum elafin level in psoriasis group compared to the control group being significantly increased among psoriatic cases **(P < 0.001).** This comes in agreement with **Alghonemy *et al.*** [15] who demonstrated that, the mean serum elafin level in the psoriatic group was 6.09 ± 8.91, which was significantly higher than the level in the control group (0.40 ± 0.35) (P<0.001). Comparable results were also recorded by **Elgharib *et al.*** [16]**,** who conducted a case-control study on 26 psoriatic cases along with 26 healthy controls. They reported highly significant difference (P < 0.001) between the psoriatic patients (2.47 ± 1.64) and the controls (0.61 ± 0.49) in terms of serum elafin levels.

In terms of the correlation between elafin level and psoriasis severity, the current study demonstrated that, there was a highly statistically significant correlation between elafin level and psoriasis severity in which mild psoriasis was associated with low elafin level, while severe psoriasis was associated with high elafin level (PASI score) (P<0.001). Additionally, there was a highly statistically significant correlation between elafin level and PASI score. This comes in agreement with **Alghonemy *et al.*** [15], who demonstrated that, there was a positive significant correlation between elafin level and PASI in the case group (r=0.467 and P<0.001). The positive association (r=0.76) between serum elafin level and psoriasis severity with very large differences (P<0.001) is consistent with the findings of **Alkemade *et al.*** [17] and **Tanaka *et al.*** [18], which suggested that elafin levels were well associated with the clinical status of psoriasis represented by the PASI score and its serum measurement in patients with psoriasis. Similarly, circulating elafin levels are positively correlated with disease severity in patients with adaptive immune diseases (psoriasis and graft-vs-host disease) according to **Elgharib *et al.*** [16] and **Paczesny *et al.*** [19]**.** This correlation could be explained by the psoriasis worsening, which is linked to an imbalance between elastase, proteinase-3, and their inhibitors such as elafin. High levels of elafin associated with the clinical condition help elafin act as a protective agent against epidermal damage caused by neutrophil enzymes [20]. This was reinforced by the findings of **Alkemade *et al.*** [17], who recorded a higher mean level of serum elafin in psoriatic patients in comparison with the controls and the decrease of serum elafin, which correlated with a decrease in PASI score after cyclosporine therapy, proves its usefulness as a tool for monitoring of disease activity.

With regard to the relation between serum elafin level and smoking, the current study demonstrated that, there was statistically significant relation between serum elafin level and smoking, in which smoker cases demonstrated statistically significant increase in serum elafin level compared to non-smokers (P=0.015). This is in accordance with **Elgharib *et al.*** [16] who demonstrated that, there was a significant association between the increase of serum elafin level and positive cases of smoking (P = 0.018). Elafin and SLPI are characterized as alarm molecules involved in the regulation of early events in the inflammatory process, therefore, the overexpression of these inhibitors would benefit in combating the inflammatory consequences of smoking [21].

Regarding the relation between serum elafin level and family history, the current study reported that, there was highly statistically significant relation between serum elafin level and family history, in which cases with positive family history demonstrated highly statistically significant increase in serum elafin level compared to the negative ones (P < 0.001). This is in harmony with the study of **Elgharib *et al.*** [16]**,** which revealed that family history of psoriasis was positively correlated with serum elafin levels with significant differences (P < 0.05). Comparable results are also recorded by **Oestreicher *et al.*** [22] who found in psoriasis-related gene mapping an increase in gene expression of elafin in skin lesions. Genes such as PI3 (elafin), S100A2, MTX, and GNA15 all localized to psoriasis susceptibility loci. Sequence analysis of these genes in families with a history of psoriasis may help to identify specific affected alleles at susceptibility loci.

Regarding the correlation among elafin with other variables, the current study demonstrated that there were no statistically significant correlations among elafin and demographic parameters (age, weight, height and BMI) **(P < 0.05),** while elafin level demonstrated highly statistically significant correlations with ESR and CRP **(P < 0.001).** This is in accordance with **Alghonemy *et al.*** [15] who demonstrated that ESR and CRP were significantly higher in cases than in control, with P less than 0.001.

There are inflammatory markers that represent the inflammatory condition in the skin and were documented in psoriasis, irrespective of psoriatic arthritis. CRP and ESR are nonspecific markers that are released for any tissue damage or infection. Conversely, the elafin content of patients in sera may be considered to reflect the clearance rate of psoriatic elafin tissue [15].

In the same line, **Elgharib *et al.* [16]** revealed that, ESR and CRP were measured for both psoriatic patients and controls, and results showed that the ESR (first hour) of the psoriatic group ranged from 6 to 37 with a mean of 25.69 ± 8.25, while that in the control group ranged from 2 to 8 with a mean of 5.08 ± 1.83. CRP ranged from 5.1 to 9.2 with a mean of 6.97 ± 1.24 in the patient group and 2.8–4.8 with a mean of 3.78 ± 0.58 in the control group. Both showed a highly significant difference between the studied patients and the control group ($P < 0.001$).

There was a statistically significant correlation between serum elafin and ESR, CRP, and PASI in patients ($r = 0.59$ and $P < 0.001$), ($r = 0.66$ and $P < 0.001$), and ($r = 0.76$ and $P < 0.001$) [16]. To the best of our knowledge, CRP and ESR are nonspecific markers released in response to any tissue damage or infection. On the contrary, the elafin content in sera of patients may be considered to reflect the clearance rate of psoriatic tissue elafin. The significant correlation between CRP, ESR, and elafin potentiates the role of elafin in acting as a mirror reflecting the inflammatory condition in the psoriatic patients but with more specificity than CRP and ESR [16].

CONCLUSION

The elafin level demonstrated significant elevation among psoriatic cases and correlated positively with the disease severity (as revealed by PASI score). Thus, it could be used as a promising predictor for psoriasis diagnosis, which could impact the therapeutic lines in the future.

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