Assessment of Serum Level of Paraoxonase-1 in Patients with Psoriasis Vulgaris

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ABSTRACT

Background: Psoriasis is a chronic inflammatory dermatological disease with a strong genetic predisposition and autoimmune pathogenic traits. The hallmark of psoriasis is sustained inflammation that leads to uncontrolled keratinocyte proliferation and dysfunctional differentiation. **Objective:** The aim of this study was to evaluate serum level of paraoxonase-1 in psoriasis patients compared to control group. **Patients and methods:** This research included 50 psoriasis patients and 40 healthy controls that were comparable in age and sex to the cases category. They were chosen at random from the Outpatient Clinic of Dermatology Department, Mansoura University Hospitals.

Results: Psoriasis group showed significantly lower level of paraoxonase-1 when compared to control group (median=35.6 versus 54.5; $p < 0.001$). Additionally, median paraoxonase-1 level decreased gradually with increased psoriasis grades ($p < 0.001$). No significant associations were found regarding paraoxonase-1 level according to gender, smoking, and FH in psoriasis group ($p > 0.05$ for each). Paraoxonase-1 level showed significant negative correlation with PASI score ($p < 0.001$), but not with age, onset, or duration ($p > 0.05$ for each). Lower paraoxonase-1 level was considered as independent predictor of psoriasis development. Lower paraoxonase-1 level was considered as independent predictor of psoriasis severity ($p < 0.001$).

Conclusion: Paraoxonase-1 level in psoriasis patients had substantially lower levels than healthy controls. Paraoxonase-1 level showed significant negative correlations with PASI score. Lower baseline paraoxonase-1 level was suggested to be independent risk predictor for psoriasis occurrence and severity.

Keywords: Paraoxonase-1 level, PASI score, Psoriasis vulgaris.

INTRODUCTION

Psoriasis is a multifactorial disease in which certain environmental variables acting on those who have a genetic predisposition leading to immunologic dysregulation and disordered keratinization, resulting in development of characteristic skin lesions [(1)]. Psoriasis is a genetically based chronic inflammatory disease affecting the skin. It is characterized by epidermal hyper proliferation, aberrant differentiation of keratinocytes, T-cell infiltration, and enhanced cytokine production resulting in appearance of inflamed plaques [(2)]. Histologically, psoriasis is characterized by epidermal hyper-proliferation, abnormal differentiation of keratinocytes, dermal infiltration by inflammatory cells, as well as enhanced vascularity [(3)]. Several studies have shown that pharmacological therapies reduce inflammatory process, lipid peroxidation, along with recovery of high density lipoprotein (HDL) activities in adults with psoriasis. This reveals an association between psoriasis, oxidative stress, inflammatory response, and altered lipoprotein functions [(4)].

PON1 (paraoxonase-1) is a multifunctional protein found on the surface of HDL that has been found to protect against oxidative stress-associated illnesses [(5)]. In fact, PON1 protects biological membranes, HDL, and low density lipoprotein (LDL) from lipid peroxidation. This suggests that when PON1 activity is reduced, it becomes unable to protect against oxidation of membranes and LDL, and thus is involved in the enhancement of oxidative stress in psoriatic cases [(5)]. The activity of PON1 is considerably decreased among adult psoriasis patients, and an association with disease activity was also reported [(5, 6)]. The aims of this study was to compare the serum levels of paraoxonase-1 in psoriasis patients to a control group and correlation between paraoxonase-1 level and disease severity based on Psoriasis Area and Severity Index (PASI) score.

PATIENTS AND METHODS

Ninety persons were included in this study. They were chosen from the Outpatient Clinic of Dermatology, Andrology & STDs department, Mansoura University Hospitals from January, 2020 to January, 2021. Patients' group included 50 patients with psoriasis vulgaris and 40 healthy individuals of cross matched age and sex were included as a control group.

Inclusion criteria: Fifty Patients with psoriasis vulgaris and forty apparently healthy people acted as control group underwent evaluation of their serum level of paraoxonase-1.

Exclusion criteria: Patients receiving systemic therapy for psoriasis during last month, patients receiving topical therapy for psoriasis during last two weeks, pregnant or lactating mothers, patients with any systemic disease such as hepatic and renal impairment, patients with chronic skin diseases such as vitiligo, alopecia areata, children < 18 years old, and erythrodermic or pustular psoriasis.

The following procedures were performed for all patients:

- Detailed history taking regarding age, sex, occupation, marital status, special habits, dietary intake, associated psychological disturbance,

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associated medical or surgical conditions and drug intake.

- Detailed general and dermatological examination which included a clinical assessment of psoriasis using PASI score

PASI assesses severity of lesions and the area affected in a single score ranging from 0 (no disease) to 72 (maximum disease) [7]. The body is subdivided into 4 sections [Head (H) (10%), arms (A) (20%), trunk (T) (30%) and legs (L) (40%)]. Each section is scored by itself, and then the 4 scores were combined to give the overall PASI. For each region, the percentage of area of skin affected was estimated using a scale from 0 to 6: (0) 0% of affected area. (1) < 10% of affected area, (2) 10–29% of affected area, (3) 30–49% of affected area, (4) 50–69% of affected area, (5) 70–89% of affected area and (6) 90–100% of affected area.

Within each skin area, psoriasis severity was assessed based on 3 signs: erythema (red skin), thickness (indurated skin) and desquamation (scaly skin). Severity parameters were described using a scale of 0 to 4, from none to maximal disease. The summation of these 3 parameters was then estimated for each skin section, multiplied by area score for such area and multiplied by weight of this section (0.1 for head, 0.2 for arms, 0.3 for body and 0.4 for legs). All patients underwent laboratory test for their serum level of paraoxonase-1. 3 ml of venous blood were collected from each subject participating in this study, centrifuged at 3000 g for 5 min and serum was separated and preserved at -70°C for subsequent biochemical analysis. Determination of serum Paraoxonase-1 was carried out using ELISA kits Cat. No E2157Hu (Bioassay Technology Laboratory, Cat. No: E2157Hu, Shanghai, China).

Ethical approval:

An approval of the study was obtained from Mansoura Faculty of Medicine's Institutional Review Board (IRB) (MS.19.12.975). Every patient signed an informed written consent for acceptance of 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.

Statistical Analysis

The data were analysed by Statistical package for Social Science (IBM SPSS Statistics for Windows, Version 25.0). Data were expressed and analysed according to the type of data obtained for each parameter. Mean, standard deviation (± SD) for parametric numerical data, while median and range for non-parametric numerical data. Non-numerical data were presented as numbers and percentages. **Student T** Test was utilized to evaluate statistical significance of the difference between 2 groups. To compare between the three groups, **one way** analysis of variance (**ANOVA**) was utilized.

Mann Whitney Test (U test) was utilized to assess the statistical significance of the difference of a non-parametric variable between two study groups. **The Kruskal-Wallis** test was utilized to evaluate statistical significance of the difference between > 2 groups with non-parametric variables. **Chi-Square test** was utilized to evaluate the correlation between 2 qualitative variables. **Fisher's exact test** was utilized to examine correlation between 2 qualitative variables when the expected count is < 5 in > 20% of cells **(Fischer *et al.*, 2004).**

Correlation analysis: To evaluate the strength of relationship between 2 quantitative variables. **The ROC Curve (receiver operating characteristic)** evaluates the sensitivity and specificity for quantitative measures, which categorize cases into one of 2 groups. The cut off was defined as that which maximized the AUC value. AUC with an area > 0.9 indicates high accuracy, while 0.7–0.9 has moderate accuracy, 0.5–0.7, low accuracy and 0.5 a chance result. A p value is considered significant if ≤ 0.05 at confidence interval 95%.

RESULTS

The present study included 50 psoriasis, and 40 healthy control subjects. The mean age of psoriasis group was 43.2 years. They were 30 males (60%) and 20 females (40%). In addition, 40 healthy control group, of matched age and gender (p > 0.05 for each).

Psoriasis cases were significantly associated with higher frequency of smokers (p = 0.040). There was no significant differences were found regarding family history among studied groups. Psoriasis group showed significantly lower level of paraoxonase-1 when compared to control group (median = 35.6 versus 54.5; p < 0.001) (Table 1).

Table (1): Comparison of demographic data, risk factors and paraoxonase-1 level between studied groups

		Control (N=40)		Psoriasis (N=50)		P
Age (years)	**Mean ± SD**	41.7	±14.3	43.2	±14.8	0.635
Males	**N, %**	27	67.5%	30	60%	0.463
Females	**N, %**	13	32.5%	20	40%	
Smoking	**N, %**	1	2.5%	8	16%	**0.040**
Positive family history (FH)	**N, %**	1	2.5%	3	6%	0.626
Paraoxonas-1	**Median**	54.5		35.6		**<0.001**
	Range	42.2-600		24.5-47.5		

SD, standard deviation; student t test was used for numerical parameters; Chi square test was used for categorical parameters.

Mean age of onset was 34.5 years. Median disease duration was 6, ranged from 1 to 20 years. Median baseline PASI score was 13.1, ranged from 2.2 to 29.1. Disease severity cohorts were categorized based on PASI severity scores into mild: 0 ≤ PASI ≤ 5, moderate:

5 < PASI ≤ 12, severe: 12 < PASI ≤ 20 and very severe: 20 < PASI. The studied cases, 10% had mild, 30% had moderate, 38% had severe and 22% had very severe grades of psoriasis (2).

Table (2): Clinical features in all studied cases

		Psoriasis N=50	
Age of onset (years)	**Mean ± SD**	34.5	±11.2
Disease duration (years)	**Median (range)**	6	1-20
PASI	**Median (range)**	13.1	2.2-29.1
Mild (0:5)	**N, %**	5	10%
Moderate(6:12)	**N, %**	15	30%
Severe (13:20)	**N, %**	19	38%
Very severe > 20	**N, %**	11	22%

Receiver operating characteristic (ROC) curve of paraoxonase-1 levels was conducted for discrimination between psoriasis cases and control groups (diagnosis of psoriasis). Paraoxonase-1 showed high accuracy AUC (AUC = 0.991). At best cut off value of 42, sensitivity was 90%, specificity was 100%, PPV was 90%, NPV was 100%, and accuracy was 94.4% (Table 3).

Table (3): Validity of Paraoxonase-1 level for discrimination between psoriasis cases and control groups

	Paraoxonase-1
AUC	0.991
Cut off	<42
Sensitivity (%)	90
Specificity (%)	100
PPV (%)	90
NPV (%)	100
Accuracy (%)	94.4

AUC, area under ROC, OC, receiver operating curve; PPV, positive predictive value; NPV, negative predictive value.

ROC curve of paraoxonase-1 level was conducted for discrimination between low (mild + moderate) and high (severe + very severe) PASI score psoriasis grades. Paraoxonase-1 showed high accuracy AUC (AUC=0.956). At best cut off value of 37, sensitivity was 93.3%, specificity was 90%, PPV was 93.3%, NPV was 90%, and accuracy was 92% (Table 4).

Table (4): Validity of paraoxonase-1 level for discrimination between (mild + moderate) versus (severe + very severe) psoriasis grades

	Paraoxonase-1
AUC	0.956
Cut off (pg/mL)	< 37
Sensitivity (%)	93.3
Specificity (%)	90
PPV (%)	93.3
NPV (%)	90
Accuracy (%)	92

No significant associations were found regarding paraoxonas-1 level according to gender, smoking, and FH in psoriasis group (p > 0.05 for each). Median paraoxonase-1 level decreased gradually with increased psoriasis grades (p < 0.001) as shown in table (5).

Table (5): Association of paraoxonase-1 level according to gender, smoking, FH and severity grades in psoriasis group

		Psoriasis N=50				
		Paraoxonas-1				P
		N	Median	minimum	maximum	
Gender	Male	30	35	24.5	47.5	0.620
	Female	20	36.45	29.8	47.4	
Smoking	No	42	36.15	24.5	47.5	0.711
	Yes	8	35	29.5	39.6	
FH	Negative	47	36.3	24.5	47.5	0.165
	Positive	3	31	28.6	33.8	
Grades	Mild	5	45.8	42.2	47.5	**<0.001**
	Moderate	15	38.6	34.9	41.8	
	Severe	19	34.5	32.6	39.5	
	Very severe	11	30.7	24.5	31.8	

Logistic regression analysis was conducted for prediction of psoriasis development using smoking, FH and paraoxonase-1 level as confounders. Lower paraoxonase-1 level was considered as independent predictor of psoriasis development (Table 6).

Table (6): Regression analysis for prediction of psoriasis susceptibility

	p	OR	95% CI	
Smoking	0.422	1.747	0.448	6.815
Positive FH	0.140	3.236	0.858	9.896
Paraoxonas-1	**<0.001**	0.722	0.617	0.845

OR, odds ratio; CI, confidence interval. Logistic regression test was used

Linear regression analysis was conducted for prediction of psoriasis severity (higher PASI score) using age, gender, smoking, FH, onset, duration and paraoxonase-1 level as confounders. Lower (negative charge of β) paraoxonase-1 level was considered as independent predictor of psoriasis severity (p < 0.001) as shown in table (7).

Table (7): Regression analysis for prediction of factors affecting severity of psoriasis (higher PASI score)

	B	P
Age	0.043	0.612
Gender	0.385	0.880
Smoking	-1.126	0.741
Positive FH	2.820	0.135
Onset	-0.021	0.809
Duration	0.493	0.133
Paraoxonase-1	-1.575	**<0.001**

β, linear regression coefficient

DISCUSSION

In our study, the mean age of psoriasis group was 43.2 years, they were 30 males (60%) and 20

females (40%). In addition, 40 healthy control group, their mean age was 41.7 years, they were 27 males (67.5%) and 13 females (32.5%). Cases and control groups had matched age and gender ($p > 0.05$ for each). This mean age is in accordance with **Megna *et al.*** [8] and **El-Hanafy *et al.*** [9]**. Zander *et al.*** [10] found that the mean age at diagnosis of psoriasis was 43.2 ± 10.9 years and 56.5% of subjects were male.

Our result revealed that male was slightly predominant. The male: female ratio in our patient group was 30: 20. Similarly, **Naito & Imafuku** [11] found of the 429 patients, 295 (68.8%) were men and 134 (31.2%) were women (male : female ratio: 2.1). However, reports from Spain and England showed that both sexes were equally affected [6, 12]**.**

In the present study, psoriasis cases were significantly linked to higher frequency of smokers ($p = 0.040$). **Dai *et al.*** [13] revealed that current smoking enhanced psoriasis risk, especially for persons who smoked >25 cigarettes/day and for > 20 pack-years, while alcohol consumption was not significantly associated with psoriasis development. Smoking produces free radicals, which might activate signaling pathways involved in psoriasis including mitogen-activated kinase, nuclear factor kB, and Janus kinase-STAT pathways. Byproducts from smoking, like nicotine and dioxin, activate T lymphocytes to release IL-12, IL-17, and IL-22 [14]**.** This is in contrast to **Praveenkumar *et al.*** [15] study where the proportion of patients and stable controls with a history of smoking did not vary significantly.

Family history of psoriasis existed only in 6 % of our patients similar to published data in **Kamiya *et al.*** [16] in which approximately 4.6% of the patients had a family history of psoriasis.

In our study, the median disease duration was 6 years, ranged from 1 to 20 years this goes hand to hand with the disease's persistence, progressive existence, as shown by **Rendon and Schäkel** [17]**.**

In this study, median baseline PASI score was 13.1, ranging from 2.2 to 29.1. The same in **Iskandar *et al.*** [18] study in which the median baseline PASI score was 13 ranging from 10 to 18.3.

In our study, psoriatic cases were classified according to PASI score into: 5 cases (10%) mild, 15 cases (30%) moderate, 19 cases (38%) severe and 11cases (22%) very severe grades. Conversely, **Khan *et al.*** [19] reported that most (76.3%) patients had mild disease followed by 23.7% had moderate to severe disease.

In the current study, psoriasis group showed significantly lower level of paraoxonase-1 when compared to control group (median = 35.6 versus 54.5; $p < 0.001$). This is in accordance with **Ramadan *et al.*** [20]**, Houshang *et al.*** [21] and **Oszukowska *et al.*** [22] **studies.**

The lower PON1 activity observed by **Ferretti *et al.*** [23] in patients affected by psoriasis was because they are more exposed to oxidative damage. PON1 exerts an antioxidant and anti-inflammatory role. **Houshang *et al.*** [21] reported a statistically significant reduction in PON1 concentration from mild to moderate and from moderate to severe psoriasis. Reduced plasma PON1 concentration might play a role in pathophysiology of enhanced LDL oxidation and enhanced vulnerability to oxidative stress in psoriatic cases. Similarly, **Oszukowska *et al.*** [22] found a lower activity of PON-1 ($p < 0.001$) in psoriatic patients as compared to controls. A lower PON-l activity among psoriasis patients might be explained by the chronic inflammation accompanying it.

Receiver operating characteristic (ROC) curve of paraoxonas-1 levels was conducted for discrimination between psoriasis cases and control groups in our study. Paraoxonase-1 showed high accuracy AUC (AUC=0.991). At best cut off value of 42, sensitivity was 90%, specificity was 100%, PPV was 90%, NPV was 100%, and accuracy was 94.4%. We conducted ROC curve of paraoxonas-1 level for discrimination between low (mild-moderate) and high (severe-very severe) PASI score psoriasis grades. Paraoxonas-1 showed high accuracy AUC (AUC=0.956). At best cut off value of 37, sensitivity was 93.3%, specificity was 90%, PPV was 93.3%, NPV was 90%, and accuracy was 92%.To our knowledge no more available studies for comparing our results.

In the present study, median paraoxonase-1 level decreased gradually with increased psoriasis grades ($p < 0.001$). No significant associations were found regarding paraoxonas-1 level according to gender, smoking, and FH in psoriasis group ($p > 0.05$ for each). Paraoxonas-1 level showed significant negative correlation with PASI score ($p < 0.001$), but not with age, onset, nor duration ($p > 0.05$ for each).

Oszukowska *et al.* [22] study demonstrated that PON-1 activity among psoriasis patients did not associate with PASI scores, BMI, abdominal circumference or with any other marked risk factors for atherosclerosis. Furthermore, there was no corrrelation between PON-l activity and dietary habits, smoking or metabolic syndrome. They proved also, however, that a reduced PON-l concentration occurs in psoriasis patients with a positive family history in comparison with patients who do not report any cases of this disease in the family. **Usta *et al.*** [24] proved that a reduced PON-l activity in psoriasis patients was correlated with the increased disease severity. Also, **Ferretti *et al.*** [23] revealed that a lower PON-l activity in the patients with psoriasis was correlated negatively with PASI score. **Houshang *et al.*** [21] also observed the negative association between decreased values of PON1 among psoriatic patients and psoriasis severity. Interestingly, **Toker *et al.*** [25] demonstrated no correlation between PON-l and PASI. **Ramadan *et al.*** [20] described a negative association of PON-l activity with patients' age. They also reported a greater PON-l activity among female patients.

Logistic regression analysis was conducted by us for prediction of psoriasis development using smoking, FH and paraoxonase-1 level as confounders. Lower paraoxonase-1 level was considered as independent predictor of psoriasis development.

We conducted linear regression analysis for prediction of psoriasis severity (higher PASI score) using age, gender, smoking, FH, onset, duration and paraoxonas-1 level as confounders. Lower (negative charge of β) paraoxonase-1 level was considered as independent predictor of psoriasis severity ($p < 0.001$).

Eventually, lipid peroxidation mediated by free radicals is believed to be one of the major causes of cell damage. Increased levels of lipids and lipoproteins (especially TC, LDL, Lp(a) and Apo B) and decreased levels of antioxidants (SOD,CAT, PON1, bilirubin and uric acid) could lead to an accumulation of ox-LDL and ROS in patients with psoriasis, which may have an important role in immune inflammatory events that result in progressive skin cell damage or atherosclerosis in patients with psoriasis.

CONCLUSION

Paraoxonase-1 level in psoriasis patients had substantially lower levels than healthy controls. Paraoxonase-1 level showed significant negative correlation with PASI scores ($p < 0.001$). Lower baseline paraoxonase-1 level was suggested to be independent risk predictor for psoriasis occurrence and severity.

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