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Assessment of Serum Level of Paraoxonase-1 in Patients with Non-Segmental Vitiligo

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ABSTRACT

Background: Vitiligo is a chronic progressive depigmented skin disorder, characterized by extensive melanocytes destruction. The explanation for the skin problem remains unknown. Human paraoxonase-1 (PON1) is a hepatic calcium-dependent esterase. PON1 is related to high-density lipoprotein (HDL). Reduction in serum PON1 activity has been recorded to be accompanied by certain pathological conditions under oxidative stress situations.

Objective: To evaluate the serum PON1 activity as an indicator of oxidative stress in patients with non-segmental vitiligo (NSV).

Patients and Methods: This case-control study included 2 groups, group (A) included 20 patients with NSV and group (B) included 20 age and sex matched healthy controls. The Vitiligo Area Severity Index (VASI) score was used to assess the disease severity. Serum PON1 level was measured using enzyme-linked immunosorbent assay (ELISA).

Results: The mean VASI score was 9.86±15.61. The mean PON1 level demonstrated a statistically significant difference between both groups (p=0.002), suggesting that vitiligo cases may be associated with low PON1 levels. PON1 levels showed a significant negative correlation with the severity score measured by the VASI. Only PON1 was found to be a significant predictor of vitiligo severity.

Conclusion: Vitiligo cases were associated with a reduction in PON1 level, which emphasizes the underlying theory of disease progression and could emphasize the effect of free radicals and leading oxidative damage in vitiligo. Low PON1 was found to be a significant predictor of a higher VASI score.

Keywords: Serum Paraoxonase-1, Non-Segmental Vitiligo, Vitiligo Area Severity Index Score.

INTRODUCTION

Vitiligo is a depigmented skin disease characterized by sharp, demarcated white maculae developing as a result of melanocyte loss. The explanation for the skin problem remains unknown [1]. Vitiligo affects about 1.25% of individuals globally. Ninety five percent of cases usually occur before the age of 40 [2].

Vitiligo can be categorized according to distribution into four primary types: segmental vitiligo (SV), NSV, mixed, and non-classified. The commonest form is NSV, which has a lot of clinical subtypes such as generalized (vitiligo vulgaris), acrofacial, mucosal and universal [3]. The actual pathogenesis of vitiligo is still unknown and complex, involving the interplay of multiple factors [4].

One of the essential hypotheses in terms of vitiligo pathogenesis is the oxidative stress theory. This theory is based on the actual formation of certain toxic agents throughout the process of pigmentation synthesis [5]. The oxidative stress condition occurs as a result of excessive formation of pro-oxidants and the dropping of antioxidant defense mechanisms. It has been demonstrated to be accompanied by cellular injury by damaging its DNA and protein components [6].

PON1 is a hepatic calcium-dependent esterase. PON1 is linked to HDL. PON1 has two primary functions: detoxifying organophosphates, which include paraoxon, and protecting low-density lipoprotein by lipid hydrolysis [7]. A reduction in serum PON1 activity has been recorded to be accompanied by certain pathological conditions under oxidative stress situations [8]. Antioxidant agents protect against the development of certain autoimmune diseases (AIDs) such as psoriasis, vitiligo, and alopecia aerate [9,10].

AIM OF THE WORK

To evaluate the serum PON1 activity as an indicator of oxidative stress in cases with non-segmental vitiligo and to assess the correlation between level of paraoxonase-1 and severity of disease by VASI score.

PATIENTS AND METHODS

This study was a case-control study conducted over one year. The participants of the study were recruited from the dermatology outpatient clinic of the Department of Dermatology of Mansoura University Hospital, Egypt. A total of 40 subjects were involved, including 2 groups, **group (A)** included 20 patients with non-segmental vitiligo and **group (B)** included 20 age and sex matched healthy controls.

This study included patients with non-segmental "active" vitiligo (have recent onset lesions or advancement of pre-existing lesions) within previous 3 months, but we excluded patients with chronic diseases such as kidney dysfunction, hepatic diseases, coronary artery disease concomitant and diabetes mellitus, with inflammatory disease and AID, with tumours, with recent major surgical approach and patients with segmental vitiligo patients.

METHODS

All participants were subjected to detailed history taking, especially age, sex, occupation, marital status, special habits, past history of medical or surgical

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problems, drug intake, family history of vitiligo or any other AID and duration of vitiligo.

General examination was conducted to rule out systemic or autoimmune disease. Thorough dermatologic assessment included skin, hair, nail, oral and genital mucosa to exclude any accompanying disease. Description of vitiligo included site, symmetry, localization, type, activity, and stability. VASI score is the percentage of vitiligo affection was measured as regards hand units. One hand unit is about one per cent of the total body surface area (TBSA), one hundred percent - full depigmentation, ninety percent – presence of specks of pigmentation, seventy five percent - depigmented region extends beyond the pigmented region, fifty percent - pigmented and depigmented regions are identical, twenty five percent - pigmented area extends beyond the depigmented region, and ten percent - only specks of depigmentation present [11].

Three ml of venous blood were withdrawn and sent for centrifugation at 3000r.p.m to measure serum PON1 level using ELISA kits Cat. NoDLR-PON1-Hu. (Ireland) at Clinical Pathology Unit, Faculty of Medicine, Mansoura University.

Ethical Consideration:

Mansoura University Ethical Committee granted clearance for the study. Written informed permission was acquired from each participant. Throughout the examination, adherence to the Helsinki Declaration was maintained.

Statistical analysis

The collected data were analyzed using SPSS Version 25.0. Quantitative data were presented as mean, standard deviation (SD), median, and range. Qualitative data were presented as frequency and percentage. The Shapiro test assessed the normality of the data distribution. The Student T test compared the means between two study groups. One-way ANOVA test compared the means among more than 2 study groups. The Mann-Whitney test compared non-parametric variables between two study groups. The Kruskal-Wallis test compared non-parametric variables among more than two study groups. The Chi-Square test assessed the relation between 2 qualitative variables. P value: If < 0.05, it was deemed significant.

RESULTS

Table **(1)** shows that there was significant difference between the vitiligo and control groups regarding age and gender. The vitiligo group had a significantly higher proportion of participants reporting a positive history of stress compared to the control group. Such outcomes recommend a potential association between stress and the development of vitiligo.

Table (1): Comparison of demographic data and history of stress among studied groups

	Vitiligo n = 20		**Control n =20**		**Test**	**p**
	No.	**%**	**No.**	**%**		
Gender						
Male	8	40%	9	45%	X^2= 0.102	0.749
Female	12	60%	11	55%		
Age (years)						
Mean ± SD.	35 ± 18.71		32.25 ± 9.04		t= 0.592	0.558
Median	34.50		33.50			
Min. – Max.	12 – 70		18 – 47			
History of stress						
Negative	4	20%	20	100 %	X^2= 26.67	<0.001 *
Positive	16	80%	0	0%		

SD: Standard deviation, Min.: Minimum, Max.: Maximum, t: independent t student test; X^2: Chi square test.

Table **(2)** shows that none of the participants in either group had a family history of other AIDs. Regarding Koebner phenomenon, the difference was significant between the 2 studied groups.

Table (2): Comparison of family history and Koebner phenomenon of among studied groups

Family history of	**Vitiligo n = 20**		**Control n =20**		**Test**	**p**
	No.	**%**	**No.**	**%**		
Vitiligo						
Negative	17	85%	20	100 %	X^2=3.243	0.072
Positive	3	15%	0	0%		
Other autoimmune diseases						
Negative	20	100 %	20	100 %	-	-
Positive	0	0%	0	0%		
Koebner phenomenon						
Negative	16	80%	20	100 %	X^2=4.444	0.035 *
Positive	4	20%	0	0%		

X^2= Chi square test, *: Significant.

Table **(3)** shows that among the vitiligo group, the average duration of new lesions was 1.69 ± 0.78 months. The average duration of illness was 6.24 ± 7.6 years. The average VASI score was 9.86 ± 15.61. The commonest type of NSV was vulgaris (40%).

Table (3): Duration of new lesions, duration of illness, severity of vitiligo and types of vitiligo among vitiligo group

		Vitiligo (n = 20)	
Duration of new lesions (months)	Mean ± SD.	1.69 ± 0.78	
	Median	1.75	
	Min. – Max.	0.5 – 3	
Duration of illness (years)	Mean ± SD.	6.24 ± 7.6	
	Median	3.00	
	Min. – Max.	0.25 – 28	
Severity of vitiligo	Mean ± SD.	9.86 ± 15.61	
	Median	2.03	
	Min. – Max.	0.06 – 49.5	
Types of vitiligo	Focal	3	15%
	Acrofacial	6	30%
	Vulgaris	8	40%
	Universal	3	15%

SD: Standard deviation, Min.: Minimum, Max.: Maximum.

Table **(4)** demonstrates that PON1 level was significantly lower in vitiligo group compared to control group.

Table (4): Comparison pf PON1 level among studied groups

	Vitiligo (n = 20)	Control (n = 20)	Test	p
PON1 (ng/ml), Man ± SD.	97.68 ± 24.24	122.56 ± 21.89	t=3.285	0.002*

SD: Standard deviation, T: independent t student test; *: Significant.

Table **(5)** shows than in the vitiligo group there was no significant difference in PON1 level regarding gender, history of stress, associated psychological disturbances, family history of vitiligo, and Koebner phenomenon. The results demonstrated a significant difference in PON1 levels among the different vitiligo subtypes.

Table (5): Association between PON1 and gender, history of stress, associated psychological disturbances, family history of vitiligo, Koebner phenomenon and types of vitiligo among vitiligo group

	PON1 (ng/ml)			Test	P
	Mean ± SD.	Median	Min. – Max.		
Gender					
Male, n=8	102.08 ± 14.92	103.38	76.62 – 123.7	t=0.612	0.548
Female, n=12	94.75 ± 31.44	101.68	47.5 – 166.2		
History of stress					
Negative, n=4	83.69 ± 28.08	88.04	47.5 – 111.2	t=1.226	0.236
Positive, n=16	101.18 ± 24.96	104.15	50.35 – 166.2		
Associated psychological disturbances					
Negative, n=19	96.31 ± 25.8	99.66	47.5 – 166.2	t=1.035	0.314
Positive, n=1	123.7 ± 0	123.70	123.7 – 123.7		
Family history of vitiligo					
Negative, n=17	96.66 ± 27.59	99.66	47.5 – 166.2	t=0.412	0.685
Positive, n=3	103.48 ± 14.07	109.30	87.43 – 113.7		
Koebner Phenomenon					
Negative, n=16	97.13 ± 28.78	101.58	47.5 – 166.2	t=0.185	0.856
Positive, n=4	99.87 ± 8.95	102.13	87.43 – 107.8		
Types					
Focal, n=3	110.73 ± 3.23	111.20	107.3 – 113.7	F=5.221	0.011*
Acrofacial, n=6	109.68 ± 31.5	99.56	77.46 – 166.2		
Vulgaris, n=8	98.93 ± 11.98	104.15	76.62 – 109.3		
Universal, n=3	57.31 ± 14.59	50.35	47.5 – 74.07		

SD: Standard deviation, Min.: Minimum, Max.: Maximum, t: independent student t test; F: One way ANOVA test; *: Significant.

Table **(6)** presents logistic regression analysis for predicting vitiligo susceptibility, using age, gender, stress, family history and PON1. In the univariable analysis, presence of stress and low PON1 levels were found to be significant predictors of vitiligo susceptibility. In the multivariable analysis, after adjusting for other variables, PON1 levels remained a significant predictor, with a lower odds ratio (OR) indicating a protective effect against vitiligo development.

Table (6): Logistic regression analysis for prediction of vitiligo susceptibility

	Univariable		Multivariable	
	P	**OR (95% CI)**	**P**	**OR (95% CI)**
Age	0			
Gender	0			
Stress	0.001*	Unidentified	0.076	Unidentified
Family history	0	(		
PON1	0	0	0	0

OR: Odd ratio; CI: Confidence interval. *: Significant, Unidentified: as in the control group, no subjects had stress.

Table **(7)** presents the correlation between PON1 levels and different parameters among patients with vitiligo. PON1 levels showed a significant negative correlation with the severity score measured by the VASI, indicating that higher PON1 levels were associated with lower disease severity. On the other hand, there were no significant associations between PON1 levels and age, duration of occurrence of new lesions, or duration of illness.

Table (7): Correlation between PON1 and different parameters among patients with vitiligo

	PON1	
	Correlation Coefficient	**p**
Age	-0.135	0.569
New lesions occurrence	0.367	0.111
Duration of illness	-0.315	0.176
VASI (Severity score)	-0.760	<0.001*

*: Significant.

DISCUSSION

Vitiligo is a chronic, progressive depigmented macules and patches with a worldwide prevalence of 1.5% [3]. It affects all age groups, and there are two primary forms, SV and NSV. Despite being asymptomatic, it affects the person's beauty, making them anxious about their bad appearance [12].

The actual cause of vitiligo isn't well-identified; on the other hand, the pathogenesis includes loss of melanocyte function with subsequent loss of melanin pigmentation. Genetic background and the role of autoimmunity are concerned with etiology. Additionally, the release of free radicals is believed to have a main role in vitiligo pathogenesis [13].

Treatment for vitiligo has proven to be extremely difficult, and there are several therapeutic modalities that could give partial improvement, such as phototherapy, local steroids, calcineurin inhibitors, and different surgical techniques [14]. Based on the fact that there is an increased value of H_2O_2 in the affected area and there is a disturbance in the oxidant/antioxidant balance among cases of vitiligo, oxidative stress is believed to have an essential role in terms of vitiligo etiopathogenesis [15].

The PON family of antioxidant enzymes could degrade oxidized phospholipids and is reported to be diminished in a lot of pathological conditions. For example, polymorphism of the PON gene is accompanied by the development of metabolic syndrome [16]. It was found that the mean value of serum PON1 was significantly lower in active generalized vitiligo patient group compared with controls [17]. **Akcilar and Namdar** [18] outcomes denote that Q192R polymorphism in the PON-1 gene could be accompanied by vitiligo.

The aim of this study was to assess the serum PON1 activity as an indicator of oxidative stress in patients with NSV and correlation between level of PON-1 and severity of disease by VASI score. This research included 20 vitiligo patients from the outpatient clinic of Mansoura University Hospital's Dermatology Department and matched-age and sex 20 healthy controls.

Regarding the demographic data, our study demonstrated that the mean age of vitiligo cases was 35 ± 18.71 years. The age range varied from 12 to 70 years in the vitiligo group and from 18 to 47 years in the controls. This came in accordance with a study conducted by **Chinthaamani,** [19] which recorded that the mean age of vitiligo is 36.10 years. Another research study denoted that the commonest age group affected by active vitiligo is 16–25 years [20]. On the other hand, the study was hospital based and included a smaller number of patients.

In this study, there was female predominance among patients with vitiligo (60%). This was in accordance with **Kadry *et al.*** [21], **Afify *et al.*** [22], and **Saudi *et al.*** [23] who demonstrated that vitiligo was predominant among females, as they were more worried about their upsetting appearance compared to males, leading to earlier presentations to dermatology clinics. Additionally, the female gender is more susceptible to AIDs. This was in disagreement with **Gopal *et al.*** [24] and **Shankar *et al.*** [25] studies who found that males were more affected than females.

In our study, 55% of all vitiligo cases were married similarly, 77.5% were married in **Abd El-Nady *et al.*** [26] study. On other hand, this result was contradicted with **Kiprono *et al.*** [27] who found that more than two thirds of the patients were single. This could be due to the appearance of vitiligo lesions in visible sites of the body

that affect the persons' beauty and hence impair marriage.

It has been demonstrated that many cases of vitiligo prefer isolation and avoid communication with people due to the negative attitude of the community towards them [28]. In the instant study, the median disease duration was 3 years, with a range from 0.25 to 28 years. This result was similar with the results of **Mahajan *et al.*** [29] and **Tsadik *et al.*** [30] who recorded that median disease duration was 5.1 and 3.5 years respectively. This corroborates its slow progression and asymptomatic nature.

Our study displayed that the mean PON1 level in the vitiligo group was 97.68 ng/ml, while it was higher in the control group (122.56 ng/ml). There was a significant difference between both groups (p=0.002), suggesting that vitiligo cases may be associated with low PON1 levels.

Similarly, **El-Farargy *et al.*** [17] demonstrated that the mean value of serum PON1 was significantly lower in the active generalized vitiligo patient group compared with controls. Also, **Yesilova *et al.*** [31] reported a reduced serum PON1 level in cases with active generalized vitiligo in comparison with controls.

Our study was in agreement with a preceding study that assessed the levels of vitamin E and PON1 in three AIDs, such as vitiligo. There was a significant reduction in both substances in vitiligo cases [32]. It was reported that oxidative stress is likely to be included in vitiligo etiopathogenesis. Moreover, this finding indicates a strong association between oxidative stress and vitiligo pathogenesis [20]. Reduction of oxidative stress, therefore, may be a related treatment option, and it could be helpful to propose further medications with antioxidant actions in management [32].

Akcilar and Namdar [18] conducted their study in Turkey to assess whether the PON1 gene Q192R polymorphism is a predisposing factor for vitiligo or not. They displayed a significant increase in the prevalence of the PON1 QR genotype (GT) among vitiligo cases compared to healthy controls. Such outcomes suggest that Q192R polymorphisms in the PON1 gene could have a positive correlation with vitiligo in the studied Turkish subjects. The PON1 QR GT could be considered a main genetic predisposing factor for vitiligo susceptibility and advancement.

Our study revealed that PON1 levels showed a significant negative correlation with the severity score measured by the VASI ($p < 0.001$), indicating that higher PON1 levels were associated with lower disease severity. Likewise, **El-Farargy *et al.*** [17] study showed significant association between serum PON1 and VASI score ($r = -0.780$, $P < 0.001$). This agreed with another study which reported that the reduction in PON1 among cases with vitiligo emphasizes the oxidative stress theory in disease progression, and it could highlight the effects of free radicals, leading to oxidative damage in vitiligo. There was a significant association between serum PON1 and VASI score. This may point to the value of serum PON1 as prognostic marker for evaluating the disease activity. This is an area that requires additional research [31].

CONCLUSIONS

The reduction in PON1 among vitiligo cases emphasizes the underlying theory in disease advancement and could draw attention to the role that free radicals and consequent oxidative damage play in vitiligo. PON1 levels showed a significant negative correlation with the severity score measured by the VASI ($p < 0.001$), indicating that higher PON1 levels were associated with lower disease severity. PON1 levels remained a significant predictor ($p = 0.028$), with a lower odds ratio (OR) indicating a protective effect against vitiligo development. Low PON1 was found to be a significant predictor of higher VASI score.

RECOMMENDATIONS

Additional large-scale studies comprising a higher number of cases with a wider age group are needed to validate the current results and analyze the pathological mechanisms underlying the relationship between vitiligo development and PON1 values. Additional studies are needed to assess PON1 values in various forms of vitiligo with a higher VASI score. Additional studies have to be conducted following treatment with vitiligo to assess the effect of therapy on serum PON1 values.

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