بسم الله الرحمن الرحيم

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Assessment of the serum paraoxonase1 level and its relation to total oxidant status and disease activity in vitiligo patients

A Thesis

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By

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Haiam Mahmoud Thakeb Yassin

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LIST OF ABBREVIATIONS

Abbr.	Full-term
ARE	**:** Arylesterase
BSA	**:** Body surface area
CAT	**:** Catalase
CHD	**:** Coronary heart disease
DAMPS	**:** Damage-associated molecular pattern
DCS	**:** Dendretic cells
DHC	**:** dihydrocoumarin
DM	**:** Diabetes mellitus
DS	**:** Doner site
ELISA	**:** Enzyme-linked Immunosorbent Assay
ER	**:** Endoplasmic reticulum
GWA	**:** Genome-wide association
HDL	**:** High-density lipoprotein
HSP	: heat-shock proteins
IFN	: Interferon gamma
IL	**:** Interleukin
LDL	**:** Low-density lipoprotein

MBEH : Monobenzyl ether of hydroquinone

MPO : Myeloperoxidase

NB : Narrow band

NCES : Non cultured epidermal suspention

NK : Natural killer

NSV : Non-segmental vitiligo

OMP : Oral mini-pulse corticosteroid therapy

OSI : oxidative stress index

PL : Polypodium leucotomos

PON : Paraoxonase

PON1 : Paraoxonase-1

RA : Rheumatoid artherities

ROS : Reactive oxygen species

RS : Recipient site

SD : Standard deviation

SPSS : Statistical Package for Social Science

SV : Segmental vitiligo

TAC : Total antioxidant capacity

TAS : total antioxidant status

TCS **:** Topical corticosteroids

TOS **:** Total oxidant status

UPR **:** Unfolded protein response

UV **:** Ultra violate

UVB **:** Ultraviolet B

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Assessment of the Serum Paraoxonase1 Level and its Relation to Total Oxidant Status and Disease Activity in Vitiligo Patients

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ABSTRACT

Background: Vitiligo is characterized by white macules and patches, whose size increases over time, due to the loss of melanocytes.It can appear at any time, and it significantly impairs the patients' quality-of-life. Vitiligo is a multifactorial disorder due to genetic and environmental factors. One of the important hypotheses in the pathogenesis of vitiligo is the oxidative stress hypothesis, which is based on the reality of the formation of some toxic metabolites throughout pigment biosynthesis. Human paraoxonase-1 (PON1) is a Ca^{2+} dependent esterase synthesized in the liver. Reduced serum PON1 activity has been reported to be associated with some diseases under oxidative stress and inflammation conditions.

Aim of the Work: The aim of the work was to evaluate the serum level of paraoxonase1 in patients with vitiligo and its relation to total oxidant status and disease activity in vitiligous patients.

Patients and Methods: This is a case control study which included 48 vitiligo patients and 48 age- and sex-matched controls. The patients recruited from the Outpatient Dermatology Clinic at Ain Shams University Hospitals during the period from August 2020 till March 2021. Serum level of paraoxonase1 (PON1) and total oxidant status (TOS) where assessed by ELISA technique.

Results: We observed a statistically significant higher oxidative stress reflected by the high serum TOS levels among the vitiligo compared to controls. This finding supports the aforementioned hypothesis and it also came in accordance with the observations of high oxidative stress state in vitiligo patients which was repeatedly reported in many studies. Furthermore, we also reported the significant inverse relation between PON1 levels and the oxidative stress reflected by the serum TOS levels in vitiligo patients. This reflected the reduced protective antioxidant mechanisms in vitiligo patient making them more vulnerable to oxidative stress

Conclusion: Oxidative stress may play an important role in the pathogenesis of vitiligo. The finding of a PON1 decrease in vitiligo patients emphasises the underlying hypothesis in the progression of the disease, and it can highlight the effect of free radicals and leading oxidative damage in vitiligo disease. However, further, larger studies are necessary to confirm our results.

Keywords: Serum Paraoxonase1 Level; Total Oxidant Status; Vitiligo

1. Introduction

Vitiligo is an acquired pigmentary disorder of unknown etiology, affecting approximately 1 % of the world population, without predilection for race or sex. It is characterized by white macules and patches, whose size increases over time, due to the loss of melanocytes. Vitiligo can appear at any time, and it significantly impairs the patients' quality-of-life ***(Taieb et al., 2013).***

Multiple pathogenetic factors have been proposed to clarify the etiology of vitiligo, including the neural theory, genetic predisposition, impaired anti-oxidative defense and the autoimmune theory ***(Alikhan et al., 2011).***

One of the important hypotheses in the pathogenesis of vitiligo is the oxidative stress hypothesis, which is based on the reality of the formation of some toxic metabolites throughout pigment biosynthesis **(*Yesilova et al., 2012).***

Oxidative stress may play an essential role in activating subsequent autoimmune responses related to vitiligo ***(Xie et al., 2016).*** Reactive oxygen species (ROS) are induced by multi-factors.The stressed melanocytes generate damage-associated molecular patterns (DAMPs) or autoantigens that then initiate innate immunity and adaptive immunity, leading to the

dysfunction and death of melanocytes via an inflammatory cascade ***(Richmond et al., 2013).***

Reactive oxygen species (ROS) can damage key lipid, protein, and enzyme systems involved in melanogenesis, and they also impair protein-repair mechanisms ***(Glassman, 2011).*** Apart from direct or indirect evidence of elevated ROS in vitiligo patients, there is also evidence of deficient antioxidants ***(Sravani et al., 2009).***

Measurement of total oxidant status (TOS), using a recently established method, better reflects the global effects of various oxidants in an organism ***(Esen et al., 2012).***

Paraoxonase (PON1) is an antioxidant enzyme and a member of the PON enzyme family, comprising PON-1, PON-2, and PON-3 that degrade bioactive oxidized lipids and are thus antiatherogenic **(*Levy et al., 2019*).** PON-1, an esterase carried by high-density lipoprotein, is known to exert a protective effect against oxidative damage of cells and lipoproteins playing an anti-inflammatory and antiatherogenic role ***(Mackness and Mackness, 2015).*** PON1 mRNA is restricted to adult kidney, liver, and colon and fetal liver, whereas PON-2 mRNA is more widely distributed in adult human brain, heart, kidney, spleen, liver, colon, lung, small intestine, muscle, stomach, testis, placenta, salivary,

thyroid and adrenal glands, pancreas, skin, and bone marrow **(*Mackness et al., 2010).***

Paroxonase1 (PON1) has two main roles: detoxifying organophosphate compounds, such as paraoxon, and protecting low-density lipoprotein by hydrolysis of lipid peroxides ***(Atasoy et al., 2015).***

Reduced serum PON1 activity has been reported to be associated with some diseases under oxidative stress and inflammation conditions ***(Esen et al., 2015).*** Antioxidants have a protective role in the development of some autoimmune diseases like psoriasis, vitiligo, and alopecia aerate ***(Ramadan et al., 2013).***Paraoxonase 1 can be used as an indicator in determining the existence of oxidative stress in the pathogenesis of vitiligo diseases ***(Yesilova et al., 2012).***In the view of the role of oxidative stress in vitiligo and the role of PON1 as antioxidant,we thought to investigate the total oxidant status(TOS)and (PON1) levels in vitiligo and its relation to disease activity**.**