بسم الله الرحمن الرحيم

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Assessment of the serum high-mobility group box 1 level in vitiligo patients in comparison to healthy subjects and its relation to total oxidant status and disease activity

Thesis

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بسم الله الرحمن الرحيم
قالوا
سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم الحكيم
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List of Abbreviations

Abbr.	Full-term
AD	*Atopic dermatitis*
bFGF	*Basic fibroblast growth factor*
CIs	*Calcineurin inhibitors*
COPD	*.Chronic obstructive pulmonary disease*
CSs	*Corticosteroids*
CRC	*Colorectal cancer*
CTL	*CD8+ T cell*
CTL	*Cytotoxic T lymphocytes*
DCs	*Dendritic cells*
DLQI	*Dermatology Life Quality Index*
DOPA	*Dihydroxyphenylalanine*
ET*-1*	*Endothelin-1*
FDA	*Food and drug administration*
HeNe	*Helium neon*
HLA	*Human leukocyte antigen*
HMB45	*Human Melanoma Black 45*
HMGB1	*High mobility group box1*
HPA	*Hypothalamic-pituitary-adrenal axis*
HSPs	*Heat shock proteins*
IBD	*Inflammatory bowel disease*
IFNγ	*Interferon gamma*
IL*-1α*	*Interleukin-1 beta*
IL*-1*	*Interleukin*
IL*-1α*	*Interleukin-1 alpha*
iNKT	*Invariant natural killer T cells*
KUVA	*Khellin plus UVA light*
LTC*-4*	*Leukotriene C4*
MEL	*Monochromatic Excimer Laser*

MOP ..... *Methoxypsoralen*
NB-UVB ..... *Narrow-band ultraviolet B*
NFκB ..... *nuclear factor kappa-light-chain-enhancer of activated B cells*
NK ..... *Natural killer*
Nrf2 ..... *Nuclear factor E2-related factor 2*
NSV ..... *Non-segmental vitiligo*
OMP ..... *Oral mini pulse therapy*
OSI ..... *Oxidative stress index*
PRRs ..... *Pattern Recognition Receptors*
PUVA ..... *Psoralen UVA*
PV ..... *PsorasisVulgaris*
QOL ..... *Quality of life*
RA ..... *Rheumatoid arthritis*
RAGE ..... *Receptor advanced glycosylation end products*
ROC ..... *Receiver operating characteristic*
ROS ..... *Reactive oxygen species*
SCF ..... *stem cell factor*
SLE ..... *Systemic lupus erythematosus*
SSUV ..... *solar stimulated ultraviolet radiation*
ST2 ..... *Suppressor of tumorigenicity 2*
SV ..... *Segmental vitiligo*
TAS ..... Total antioxidant status
TCR ..... *T cell receptor*
Th ..... *T-helper*
TLR2 ..... *Toll-like receptor 2*
TLR4 ..... *Toll-like receptor 4*
TMP ..... *Trimethylpsoralen*
TNF-α ..... *Tumor necrosis factor alfa*
TOS ..... *Total Oxidant status*

UV..... *Ultraviolet*
UVA..... *Ultraviolet A*
UVB..... *Ultraviolet B*
VASI..... *Vitiligo Area Scoring Index*
VEGF ..... *Vascular endothelial growth factor*
VETF..... *Vitiligo European Task Force*
VETI..... *Vitiligo Extent Tensity Index*
VIDA ..... *Vitiligo disease activity*

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Abstract

Background: Vitiligo is an acquired pigmentary disorder of unknown etiology, affecting approximately 1% of the world population, without predilection for race or sex. High mobility group box 1 (HMGB1) is a nonhistone DNAbinding protein active in the bending of DNA and in its transcription that participates in a number of physiological and pathological processes, including cytokine production, cell proliferation, angiogenesis, cellular differentiation, and cell death**.**

Aim and Objectives: The aim of work was to evaluate the serum level of high-mobility group box 1 in vitiligo patients and its relation to total oxidant status levels and disease activity**.**

Subjects and methods: It is a cross-sectional study which was carried out on 48 patients diagnosed as having vitiligo (24 active patients and 24 and non-active) and 48 health controls. All patients were selected from the dermatology outpatient clinic of vitiligo, Ain-Shams University Hospitals.HMGB1 and Total Oxidant Status (TOS) were measured in cases and controls.

Results: The serum levels of HMGB1 among patients and controls revealed that patients had statistically high significant levels of HMGB1. HMGB1 serum levels in vitiligo patients were significantly positively correlated to TOS serum levels and VIDA.

Conclusion: Serum HMGB1 level is a promising biomarker for monitoring disease activity in patients with vitiligo and it may play a role as a link between oxidative stress and melanocyte damage in vitiligo.

Keywords: High-mobility group box1, Total Oxidant Status, Vitiligo disease activity, 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 ***(Alikhan et al., 2011; Taieb et al., 2013; Lotti et al., 2014).***

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).***

Oxidative stress was first noted in vitiligo from the presence of high levels of H2O2 in affected skin, and disturbed reactive oxygen species (ROS) homeostasis was demonstrated in tissue and blood of patients with vitiligo, especially when the disease was active **(Arican and Kurutas, 2008; Glassman, 2011).** ROS can damage key lipid, protein, and enzyme systems involved in melanogenesis, and they also impair protein-repair mechanism **(Hasse et al., 2004; Glassman, 2011).** Apart from direct or indirect evidence of elevated ROS in vitiligo patients, there is also evidence of deficient antioxidants **(Schallreuter et al., 1999; Beazley et al., 1999; Hasse S et al., 2004; Sravani et al., 2009).**

High-mobility group protein B1 is a nucleoprotein that contributes to the stabilization of genome. HMGB1 can be released from the cells under endogenous or exogenous stress and then acts as a damage associated molecular pattern molecule that triggers inflammatory responses by binding to certain pattern recognition receptors (PRRs), including the receptor for advanced glycosylation end products (RAGE), toll-like receptor 2 (TLR2), and toll-like receptor 4 (TLR4) **(Bangert et al., 2016; Mou et al., 2017).** HMGB1 is involved in the development of many autoimmune skin diseases, including psoriasis **(Zhanget al., 2017)**, atopic dermatitis **(Karuppagounder et al., 2015; Wang et al., 2018),** and lichen planus **(de Carvalhoet al., 2018).** High levels of extracellular HMGB1 in plasma, serum and skin correspond with morbidity from various autoimmune conditions, including systemic lupus erythrematosis (SLE), cutaneous lupus erythrematosis and rheumatoid arthritis **(Abdulahad et al., 2011).**

Kim et al. (2017) reported that HMGB1 was over expressed in both blood samples and lesional specimens from patients with vitiligo, indicating that HMGB1 could be involved in the immune pathogenesis of vitiligo. They demonstrated that secretion of HMGB1 from neighboring keratinocytes influences melanocyte survival and the expression of melanogenesis-related molecules, and thus hypothesized that external stimuli like oxidative stress and

ultraviolet irradiation may trigger HMGB1 release by keratinocytes, thereby induce HMGB1-induced melanocytic apoptosis. It has been shown that keratinocytes and their products are necessary for the function of melanocytes in the epidermis and play a prominent role in the melanocytic death process **(Prignano et al., 2009)**.

In addition to the identified release from keratinocyte affecting the melanocyte in a paracrine pattern, **Cui et al. (2019)** showed that HMGB1 was secreted by melanocytes under oxidative stress, and was able to promote the secretion of chemokines from keratinocytes, which could induce the cutaneous infiltration of CD8 +T cells and the maturation of dendritic cells (DCs). Thus, HMGB1 may play a crucial role in the main pathogenesis of vitiligo, that is, the formation of autoimmunity that targets and undermines melanocytes.

In the view that oxidative stress has been linked to vitiligo pathogenesis and disease activity, HMGB1 was detected to be higher in serum of patients with vitiligo, and it is linked to the mechanism of oxidative stress- induced vitiligo; we thought to investigate the serum level of HMGB1 in vitiligo patients compared to healthy controls and its possible relation to total oxidant status levels and disease activity in vitiligo patients.