The Effect of Narrow Band Ultraviolet B on Tissue Levels of Lipocalin-2 in Psoriatic Patients and Controls.

A Thesis Submitted For Partial Fulfillment of MSc Degree in Dermatology

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كلية الطب
الدراسات العليا والبحوث

محضر
اجتماع لجنة الحكم على الرسالة المقدمة من

الطبيب / محمود مصطفى محمد سليمان
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تحت عنوان باللغة الإنجليزية :

باللغة العربية : مدى تأثير الأشعة الفوق بنفسجية ضيقة المدى على مستوى الإيبوكاليين ٢ في الأنسجة لدى مرضى الصدفية والبهاق

بناء على موافقة الجامعة بتاريخ / / ٢٠٠ تم تشكيل لجنة الفحص والمناقشة للرسالة المذكورة أعلاه على النحو التالي :-

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Abstract

Background: Psoriasis is a chronic inflammatory skin disease characterized by red scaly plaques, which may occur on any site of the body; prevalence is about 2–3% in population. Lipocalin-2 has been recently identified as an adipokine present in the circulation; it is related to insulin resistance, obesity, atherosclerotic diseases and type 2 diabetes. Lipocalin-2 is assumed to be closely associated with the metabolic syndrome in addition to their role in innate immune response to bacterial infection, role in renal injury and in apoptosis. Narrow band ultraviolet B (NBUVB) is a good option in treatment of extensive cases of psoriasis.

Objective: Our aim was to estimate the tissue levels of lipocalin-2 in psoriasis and to find and possible association with metabolic syndrome criteria detected in our patients. The aim of the study was also to estimate the effect of NBUVB on tissue levels (lesional and non-lesional) of lipocalin-2 in psoriatic patients and to compare them with control subjects.

Patients and methods: This study was conducted on 25 psoriatic patients and 25 healthy controls. All patients and controls were subjected to clinical examination in which height, weight, body mass index, waist circumference and blood pressure were measured. Also tissue lipocalin-2 was done by ELISA technique before and after treatment with NBUVB. Lipid profile and fasting blood sugar were measured using regular laboratory methods.

Results: In this study we detected that tissue lipocalin-2 is a good prognostic indicator during treatment of psoriasis. No correlation was detected between tissue lipocalin-2 and disease extent or PASI score. Also there were no correlations between tissue lipocalin-2 and metabolic syndrome and related disorders. NBUVB is a good option in treating extensive cases of psoriasis.

Conclusion: Our patients with psoriasis were found to be at increased risk of metabolic disorders compared to healthy controls. NBUVB is a good treatment option of psoriasis; might be through reduction of tissue lipocalin-2. Tissue lipocalin-2 is related to disturbed differentiation rather than metabolic syndrome criteria in our patients' series.

KEY WORDS:

Psoriasis, lipocalin-2, metabolic syndrome, NBUVB.

List of Abbreviations

ACE	Angiotensin Converting Enzyme
AKI	Acute Kidney Injury
APCs	Antigen Presenting Cells
APP	Acute-Phase Protein
BBUVB	Broad-Band Ultraviolet-B
BCC	Basal Cell Carcinoma
BMI	Body Mass Index
BP	Blood Pressure
CD	Cluster Of Differentiation
CKDs	Chronic Kidney Diseases
CLA	Cutaneous Leukocyte Associated Antigen
DCs	Dendritic Cells
DNA	Deoxyribonucleic Acid
EGF-R	Epidermal Growth Factor Receptor
ELISA	Enzyme-Linked Immunosorbent Assay
FPG	Fasting Plasma Glucose
FPG	Fasting Plasma Glucose
GWAS	Genome-Wide Association Studies
HDL-C	High Density Lipoprotein-Cholesterol
HeLa cells	Henrietta Lacks Cells
HIV	Human Immunodeficiency Virus
HLA-Cw6	Human Leukocyte Antigen-Cw6
HPA-axis	Hypothalamic-Pituitary-Adrenal Axis
HRP	Horseradish Peroxidase
hs-CRP	High-Sensitivity C-Reactive Protein
ICAM-1	Intercellular Adhesion Molecule-1

IDF	International Diabetes Federation
IFN	Interferon
IFN-γ	Interferon- γ
Ig	Immunoglobulin
IGF-1	Insulin-Like Growth Factor 1
IL	Interleukin
IL- R	Interleukin Receptor
JNK	JunN-terminal Kinase
KA	Keratoacanthoma
kDa	Kilo Dalton
KGF	Keratinocyte Growth Factor
LDL-C	Low Density Lipoprotein-Cholesterol
LFA	Lymphocyte Function-Associated Antigen
LPS	Lipopolysaccharide
MED	Minimal Erythema Dose
MHC	Major Histocompatibility Complex
MMP	Matrix Metalloproteinase
mRNA	Messenger Ribonucleic Acid
MS	Metabolic Syndrome
NBUVB	Narrow-Band Ultraviolet-B
NF-kB	Nuclear Factor-Kappa B
NGAL	Neutrophil Gelatinase–Associated Lipocalin
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OA	Osteoarthritis
OD	Optical Density
OGTT	Oral Glucose Tolerance Test
P.acne	Propionibacterium Acnes
PAI-1	Plasminogen Activator Inhibitor-1

PASI score	Psoriasis Area and Severity Index score
PCOS	Polycystic Ovary Syndrome
PCR	Polymerase Chain Reaction
PPAR-c	Peroxisome Proliferator-Activated Receptor-c
PPARγ	Peroxisome Proliferator-Activated Receptor- γ
PSORS	Psoriasis Susceptibility Loci
RBP-4	Retinol-Binding Protein-4
RT	Reverse Transcriptase
SCC	Squamous Cell Carcinoma
SD	Standard Deviation
SPSS	Statistical Package For The Social Sciences
TGF	Transforming Growth Factor
Th1	T Helper 1
Th17	T Helper 17
TIR	Toll/IL-1 Receptor
TMB	Tetramethylbenzidine
TNF-α	Tumor Necrosis Factor α
TP	Thymidine Phosphorylase
UV	Ultraviolet
UVR	Ultraviolet Rays
VEGF	Vascular Endothelial Growth Factor
WAT	White Adipose Tissue
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
WC	Waist Circumference

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Introduction

Psoriasis is a chronic skin disease that affects about 1.5% of the Caucasian population. It is a disease that affects the skin, mucous membranes, nails and joints. It is characterized by typical macroscopic and microscopic skin alterations ***(Sabat et al., 2007a).*** Psoriatic lesions are sharply demarcated, red and slightly raised lesions with silvery-white scales (the most common presentation), it can also be presented as pustular lesions of varying extent. Occasionally, the entire skin can become involved, leading to erythroderma or exfoliative dermatitis ***(Bos and De Rie, 1999).***

The pathogenesis of psoriasis is diverse; it includes cellular alterations in the skin with marked hyperplasia of the epidermis, altered keratinocytes differentiation and angiogenesis. The infiltrate is composed of skin-infiltrating CD4+ memory T-cells predominantly showing a T helper 1 (Th1) phenotype, neutrophils, macrophages, and increased numbers of dendritic cells ***(Chamian et al., 2005).***

Although the precise pathomechanism of psoriasis remains unknown, various cytokines and growth factors are involved in this disease (***Griffiths and Barker 2007).***

Lipocalin-2, or neutrophil gelatinase–associated lipocalin (NGAL) ***(Kjeldsen et al., 1993)***, is a 25-kDa secretory glycoprotein that was originally identified in mouse kidney cells and human neutrophil granules. In addition to neutrophils, lipocalin-2 is expressed in several other tissues, including liver, lung, kidney, adipocytes, and macrophages ***(Meheus et al., 1993).***

Several inflammatory stimuli, such as lipopolysaccharides and interleukin (IL) 1b, can markedly induce lipocalin-2 expression and secretion in these cells ***(Jayaraman et al., 2005)***.

Although lipocalin-2 was identified more than a decade ago, the physiologic functions of this protein remain poorly understood. Previous studies have focused on the role of this protein in the innate immune response to bacterial infection and in apoptosis ***(Flo et al., 2004).*** Previous reports suggested that lipocalin-2 might be a sensitive biomarker for early renal injury, also both clinical and experimental evidence demonstrated that circulating lipocalin-2 is a marker for obesity and its associated pathologies ***(Mishra et al., 2005)***..

Adipose tissue is now considered an endocrine organ secreting different cytokines known as adipocytokines including IL6, IL8, tumor necrosis factor (TNF)-α, as obesity is a state of chronic inflammation ***(Engström et al., 2003)***. Thus, lipocalin-2 plays a role in inflammatory processes**.** It is assumed that aberrant secretion of adipocytokines induces metabolic syndrome, which is a strong predictor of cardiovascular disease, diabetes mellitus and coronary heart disease ***(Eckel et al., 2005).***

Previous studies also reported higher tissue and serum levels of lipocalin-2 in psoriatic patients compared to healthy control subjects ***(El-Hadidi et al., 2014).***

Narrow-band ultraviolet-B (NBUVB) phototherapy is an effective treatment for psoriasis through downregulation of Th17 pathway in psoriatic epidermis and strong inhibition of type 1 and type ll interferon (IFN) signaling pathways which are critical in the pathogenesis of psoriasis ***(Rácz et al., 2011)***