Estimation of osteopontin level in plasma of psoriatic patients as a marker of cardiovascular diseases.

Thesis

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ABSTRACT

Background: Psoriasis is a chronic inflammatory skin disease. Genetic and immunologic mechanisms have been proposed in the aetiology of psoriasis. Psoriasis is associated with an increased risk of cardiovascular (CV) complications and the pathogenic mechanisms involved appear to be complex and multifactorial. Traditional and nontraditional risk factors possibly contributing to the increased risk. Studies showed that the osteopontin (OPN) may be an unfavorable cardiovascular risk factor in psoriatic patients. Our study was undertaken to assess whether psoriatic patients in Egypt have an increased level of OPN or not and its possible role in the pathogenesis of cardiovascular diseases associated with psoriasis

Patients and Methods: This study included 41 patients with chronic plaque psoriasis with variable extent of lesions, as well as 40 control subjects. All cases were subjected to complete history taking, clinical examination including Psoriasis Area and Severity Index (PASI) score. Blood samples were collected from all cases for estimation of plasma osteopontin level by ELISA method. Serum lipids level, blood pressure, body mass index (BMI) and serum glucose level will be also estimated as assessment of dyslipidemia, blood pressure, obesity and diabetes mellitus (DM) which may be associated with psoriasis.

Results: Our results showed statistically significant increase of plasma osteopontin (P value= 0.026), systolic blood pressure (P value= 0.0015), diastolic blood pressure (P value= 0.0015) and body mass index (P value= 0.0115) in psoriatic patients compared to controls. There was statistically significant increase of plasma osteopontin in hypertensive psoriatic patients (p value= 0.001) compared

to non-hypertensive psoriatic patients. Also we found statistically significant decrease of cholesterol (P value= 0.002) and triglycerides (P value= 0.000) in psoriatic patients than in controls.

There was statistically insignificant decrease of HDL (P value= 0.1915) and statistically insignificant increase of FBS (P value= 0.145) in psoriatic patients compared to controls.

In our study we found a significant weak negative correlation between plasma OPN and cholesterol but we found insignificant weak positive correlations between OPN and SBP, DBP, BMI and FBS while we found insignificant weak negative correlations between OPN and triglycerides & HDL in psoriatic patients. Also in our study we found an insignificant weak positive Correlation between PASI and BMI while we found insignificant weak negative correlations between PASI and OPN, FBS, cholesterol, triglyceride and HDL in psoriatic patients.

Conclusion: Our study demonstrated significant increase in plasma level of OPN in psoriatic patients in comparison to the controls which may be related to development of cardiovascular disease in patients with psoriasis. Other significant risk factors of hypertension, obesity, dyslipidemia proved to be involved in the pathogenesis of cardiovascular diseases in psoriasis.

Key words: psoriasis, cardiovascular disease, osteopontin, obesity, diabetes mellitus, hypertension, body mass index, serum lipids.

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AII	Angiotensin II
AA	Arachidonic acid
ABCA1	ATP-binding cassette A1
AIDS	Acquired immune deficiency syndrome
AJC	American Joint Committee
APC	Antigen-presenting cell
APL	Acute promyelocytic leukemia
ATP III	Adult Treatment Panel III
ATRA	All trans retinoic acid
BP	Blood pressure
BMI	Body mass index
CAD	Coronary artery disease
C. albicans	Candida albicans
CAMP	Cyclic adenosine monophosphate
CLA	Cutaneous lymphocyte antigen
CRP	C-reactive protein
CsA	Cyclosporine A
CV	Cardiovascular
CVD	Cardiovascular disease
DCs	Dendritic cells
DHEA	Dehydroepiandrosterone
DLQI	Dermatology Life Quality Index
DM	Diabetes mellitus
ELISA	Enzyme-linked immunosorbent assays
EGF	Epidermal growth factor
EGF-R	Epidermal growth factor receptor
ENaC	Epithelial sodium channel
EPA	Especially eicosapentaenoic acid
ET	Essential hypertension
F	Female
FA	Fatty acid
FBS	Fasting blood sugar
FMD	Flow-mediated dilatation
GM-CSF	Granulocyte-macrophage colony stimulating factor
GP	Guttate psoriasis
HDL	High density lipoprotein

HDL-C	High-density lipoprotein cholesterol
HERVs	Human endogenous retroviruses
HIV	Human immunodeficiency virus
HLA	Human leucocytic antigen
HPVs	Human papilloma viruses
hsCRP	High-sensitivity C-reactive protein
ICAM	Intercellular adhesion molecule
IFN	Interferon
IL	Interleuken
KC	Keratinocyte
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LFA	Lymphocyte functional antigen
M	Male
MetS	Metabolic syndromes
MI	Myocardial infarction
MTX	Methotrexate
NCEP	National Cholesterol Education Program
NGF	Nerve growth factor
NKT	Natural killer T
NSAIDS	Nonsteroidal anti-inflammatory drugs
OPN	Osteopontin
PAI-1	Plasminogen activator inhibitor type 1
PASI	Psoriasis Area and Severity Index
PBMC	Peripheral blood mononuclear cells
PDCs	Plasmacytoid DCs
PGA	Physician Global Assessment
PLE	Polymorphous light eruption
PPARγ	Peroxisome proliferator – activated receptor gamma
PsA	Psoriatic arthritis
PUVA	Psoralen ultra violet A
RAAS	Renin angiotensin aldosterone system
RH	Rheumatoid arthrities
S. aureus	Staphylococcus aureus
SEA	Staphylococcal enterotoxin A
SEB	Staphylococcal enterotoxin B
SEC	Staphylococcal enterotoxin C
SED	Staphylococcal enterotoxin D
SLE	Systemic lupus erythematosus

SP	Substance P
TC	Total cholesterol
TCR	T cell receptor
TG	Triglyceride
TGF-α	Transforming growth factor alpha
TGF-β	Transforming growth factor beta
TLC	Therapeutic lifestyle changes
TNF-α	Tumor necrosis factor alpha
T -regs	T regulatory cell
TSST-1	Toxic shock syndrome toxin–1
UVB	Ultra violet B
VCAM	vascular cell adhesion molecule
VEGF	Vascular endothelial growth factor
VLDL	Very low-density-lipoprotein

INTRODUCTION

Psoriasis is a chronic inflammatory disease that occurs in about 0.1% - 3% of the population **(Park and Lee, 2010)** although psoriasis is a disease of unsettled etiology and pathogenesis yet many factors are involved (**Krueger, 2002**). It is characterized by an immune-related pathogenesis, a genetic background which may be triggered by several environmental factors including smoking and infections **(Mercuri and Naldi, 2010)** and T cell-mediated cytokine production that drives hyperproliferation and abnormal differentiation of keratinocytes **(Park and Lee, 2010).**

Occurrence rates of occlusive vascular events, including ischemic heart disease and cerebral infarction, are significantly higher in patients with psoriasis than in the general population. It was reported that psoriasis associated with obesity, hypertension, cardiovascular diseases, DM, and metabolic syndrome (MetS) and also psoriasis has been proposed to be an independent risk factor for myocardial infarction (**Poikolainen et al., 1999**).

Osteopontin (OPN) is a multifunctional glycophosphoprotein secreted by many cell types, including osteoblasts, lymphocytes, macrophages, epithelial cells and vascular smooth muscle cells. It has been implicated in numerous physiologic and pathologic events including cell survival, cell mediated immunity and inflammation (**Chen et al., 2009**). It has been demonstrated that OPN modulates inflammatory processes involved in the psoriasis which is the most prevalent T-cell mediated inflammatory disease in humans through its action as chemotactic factor, supporting the adhesion and modulating the function of T cells and monocytes/macrophages

(Elisabetta Bummino et al., 2009). Although OPN acts as a mediator involved mainly in inflammation and tissue remodeling, it has become apparent that OPN may exert important cardiovascular effect as well. High circulating OPN levels have been reported in several inflammatory diseases, including multiple sclerosis, lupus erythematosis, rheumatoid arthritis and recently in psoriasis (**Chen et al., 2009**).

AIM OF THE WORK

This study is carried out to detect plasma osteopontin level in psoriatic patients and its possible relation to cardiovascular risk factors associated with psoriasis as hypertension, obesity, dyslipidemia and diabetes mellitus.

PSORIASIS

Psoriasis is a chronic, immunologically based, inflammatory skin disease which, regardless of extent, can affect patients' quality of life **(Ibbotson et al., 2004 and Naldi and Griffiths, 2005).** A survey by the National Psoriasis Foundation found that 75% of patients with psoriasis reported a moderate to large negative impact of the disease on the quality of their life, with an alteration of everyday activities **(Bhosle et al., 2006)**. It's characterized clinically by erythematous scaly lesions and pathologically by increased cell proliferation and abnormal patterns of keratinocyte differentiation **(Ghoreschi et al., 2003 and Wolters, 2005)**. The hallmark features of a psoriatic plaque include hyperproliferation of epidermal keratinocytes with resulting hyperkeratosis, infiltration of lymphocytes, and angiogenesis. Mitotic activity of basal keratinocytes is increased several-folds in psoriatic skin, so that keratinocytes need only 3 to 5 days in order to move from basal layer to cornified layer instead of the normal 28 to 30 days. This dramatically shortened maturation time is accompanied by altered differentiation, reflected by the focal absence of the granular layer of the epidermis and parakeratosis, ie, presence of nuclei in the thickened cornified layer. The incompletely differentiated keratinocytes release few of the extracellular lipids used commonly in the adhesion of the keratinocytes, resulting in a poorly adherent stratum corneum **(Mercuri and Naldi, 2010).**

Epidemiology:

a) Incidence:

The estimated worldwide prevalence ranges from 0.6% and 4.8% of the population **(Ruceviae et al., 2003)**. Caucasians are more commonly affected than other ethnic groups (**Lebwohl, 2003)**.

b) Age & sex:

Psoriasis can begin at any age & seems to be genetically determined. Men and women are equally affected. A quarter of patients develop the disease before the age of 20 years. Another peak in incidence is recorded in the fifth and sixth decades **(Lebwohl, 2003 and Burd, 2006)**. Psoriasis that starts in childhood has high family incidence and the earlier the onset, the worse the prognosis **(Romiti et al., 2009)**. It represents a rare dermatosis in childhood and corresponds to about 4% of all dermatosis observed in patients below the age of 16 years **(Hogan, 2003)**.

The risk of developing psoriasis is greater when one of the parents is affected. Among the patients who develop psoriasis in childhood, 49% have affected first degree relatives in comparison to patients who have late onset, 37% have affected first degree relatives. Studies with twins have shown affection of monozygotic twins up to 75% **(Benoit and Hamm, 2007)**.