Lipocalin-2 Level in Patients with Polycystic Ovary Syndrome: Association with Insulin Resistance and Metformin Therapy

Thesis

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List of Abbreviations

Abb.	Full term
2, 5-DHBA	*2, 5-dihydroxy benzoic acid*
ADPKD	*Animal model of autosomal polycystic kidney disease*
AKI	*Acute kidney injury*
ALL	*Acute lymphoblastic leukemia*
AML	*Acute myelogenous leukemia*
ATP	*Adenyl transpherase*
BCR-ABL	
BMDMs	*Bone marrow-derived macrophages*
BMI	*Body mass index*
C/EBP	*CCAAT/enhancer binding protein*
CD21 and CD35	*Complement receptors*
CKD	*Chronic kidney disease*
CML	*Chronic myeloid leukemia*
CVD	*Cerebrovascular disease*
CVUs	*Chronic venous ulcers*
DAG	*Dyacylglycerol*
DENND1A	*Domain-containing protein 1A*
EAE	*Experimental autoimmune encephalomyelitis*
ELISA	*Enzyme-linked Immunosorbent Assay*
ER	*Endoplasmic reticulum*
FFA	*Free fatty acids*
FSH	*Follicle-stimulating hormone*
GLUT-4	*Glucose transporter*
GM-CSF	*Granulocyte macrophage colony-stimulating factor*
GP330	*Glycoprotein*

List of Abbreviations (Cont…)

Abb.	Full term
H	*Healing*
H-CVU	*Healing chronic venous ulcers*
HDL-C	*High-density-lipoprotein cholesterol*
HER-2/ErbB2	*Human epidermal growth factor receptor-2*
HFD	*High-fat diet*
HLA-G	*Human leukocyte antigen G*
HNL	*Human neutrophil lipocalin*
HOMA IR	*Homeostasis model assessment _insulin resistance*
HRP	*Horseradish Peroxidase*
IC	*Immune complex*
IDF	*International Diabetes Federation*
IGF-1	*Insulin-like growth factor 1*
IL-1β	*Interleukin-1β*
IL-6	*Interleukin-6*
IR	*Insulin resistance*
IRS	*Insulin responsive substrates*
IUD	*Intrauterine device*
LCN2	*Lipocalin-2*
LDL	*Low-density lipoprotein*
LH	*Luteinizing hormone*
LPS	*Lipopolysaccharides*
MAbs	*Monoclonal antibodies*
MAPK	*Mitogen activated protein kinase*
MBS	*Metabolic syndrome*
MCP-1	*Monocytes chemo-attractant protein-1*
MMP-9	*Matrix metalloproteinase 9*

List of Abbreviations (Cont…)

Abb.	Full term
MSFI	*Migration stimulating factor inhibitor*
NAFLD	*Nonalcoholic fatty liver disease*
NF-κB	*Nuclear factor κB*
NGAL	*Neutrophil gelatinase-associated lipocalin*
NH	*Non-healing*
NH-CVU	*Non-healing chronic venous ulcers*
OA	*Osteoarthritis*
OD value	*Optical density*
PC	*Pancreatic cancer*
PCOM	*Polycystic ovarian morphology*
PCOS	*Polycystic ovary syndrome*
PCT	*Proximal convoluted tubules*
PI 3-kinase	*Phosphatidylinositol 3-kinase*
PI3-K	*Phosphoinositide 3-kinase*
PIPD 1&2	*PI dependent protein kinases1& 2*
PKB	*Protein kinase B*
PKC	*Protein kinase C*
PPARγ	*Peroxisome proliferator-activated receptor-γ*
RA	*Rheumatoid arthritis*
ROS	*Reactive oxygen species*
SD	*Standard deviation*
SH2	*Src-homology-2 domain proteins*
SHBG	*Sex Hormone Binding Globulin*
SHPTP2 or Syp	*Phosphotyrosine phosphatase*
SLC22A17	*Solute carrier family 22 member 17*
SLE	*Systemic lupus erythematosus*
SV-40	*A simian virus*

List of Abbreviations (Cont…)

Abb.	Full term
T2DM	*Type 2 diabetes mellitus*
TERA	*Transitional endoplasmic reticulum ATPase*
tg2	*Tranglutaminase 2*
THADA	*Thyroid adenoma-associated protein*
TMB	*Tetramethylbenzydine*
TNF-α	*Transferase alpha*
Treg	*T regulatory cells*
TZD	*Thiazolidinedione*
U.S	*United States*
WHO	*World Health Organization*
WHR	*Waist hip ratio*

ABSTRACT

Background: PCOS appears to be associated with an increased risk of metabolic aberrations, including insulin resistance and hyperinsulinemia, type 2 diabetes mellitus, dyslipidemia, and cardiovascular disease throughout womens' lifespan. Obesity is a state of chronic low-grade systemic inflammation. This chronic inflammation is characterized by abnormal cytokine production and activation of inflammatory signaling pathways in adipose tissues, which contributes to insulin resistance and its related diseases such as PCOS and metabolic syndrome.

Objective: To evaluate Lipocalin-2 level in a sample of Egyptian females with PCOS and study the effect of metformin therapy on Lipocalin-2 level in patients with PCOS.

Methods: This case control study was conducted on 52 females, collected from the outpatient obstetrics and gynaecology clinics of Ain Shams University Hospitals from June 2018 to March 2019, their age ranged between 17-43 years old. divided into 2 groups: **Group (I):** 32 women with polycystic ovary syndrome According to the Rotterdam diagnostic criteria of PCOS, and **Group (II)** 20 healthy women old with normal ovulatory cycle as a control group. All subjects were subjected to full medical history taking, thorough physical examination including BMI and waist circumference. Fasting plasma glucose, Fasting s.insulin, HOMA-IR, lipocalin-2 level were assessed.

Results: Serum lipocalin-2 levels did not differ between patients with PCOS and BMI-matched healthy controls (P-value 0.193), and there was no significant difference between the 2 studied groups as regard HOMA-IR (p=0.375). Metformin therapy for 3 months in patients with PCOS in the present study, resulted in significant reduction in lipocalin-2 level *(p-value<0.01)*, (mean 54.2±15.3ng/ml before metformin therapy vs 42.9±14.2 ng/ml after metformin therapy). Moreover, metformin therapy in PCOS group resulted in significant reduction in weight, BMI, waist circumference and HOMA-IR. Furthermore, linear regression analysis for the parameters affecting lipocalin level in our study, showed that BMI was the only significant confounder affecting lipocalin level. So, the reduction in lipocalin level following metformin therapy in PCOS group in our study may be due to weight reduction perse.

Conclusion: PCOS per se is not associated with elevated serum lipocalin-2 levels. Metformin therapy induces a significant reduction in serum lipocalin-2 levels, weight, BMI, waist circumference and HOMA-IR in patients with PCOS. Reduction of BMI was the only significant confounder affecting lipocalin level after metformin therapy. So the reduction in lipocalin level following metformin therapy in patients with PCOS in our study may be due to weight reduction perse.

KEYWORDS: LIPOCALIN-2 LEVEL; POLYCYSTIC OVARY SYNDROME; INSULIN RESISTANCE; METFORMIN

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine metabolic disorders worldwide which affects approximately 7–10% of women during their reproductive age and characterized by hyperandrogenism, menstrual disturbance, chronic anovulation, polycystic ovaries, and infertility ***(Kanafchian et al., 2017)***.

According to the diagnostic criteria of Rotterdam in 2003, PCOS women should have at least two of the three criteria such as Oligo or anovulation, clinical hyperandrogenism and show a polycystic ovary on ultrasound ***(Fauser, 2004).***

PCOS appears to be associated with an increased risk of metabolic aberrations, including insulin resistance and hyperinsulinemia, type 2 diabetes mellitus, dyslipidemia, and cardiovascular disease throughout womens' lifespan ***(Teede et al., 2011)*** **.**

Obesity with a preponderance for abdominal fat accumulation is a common feature of PCOS. Anomalies in adipose tissue distribution and function contribute to the metabolic abnormalities such as insulin resistance and the generation of a proatherogenic inflammatory milieu ***(Pazderska and Gibney, 2015).***

Insulin resistance and hyperinsulinemia are key findings in patients with PCOS, whether or not they are obese and about 70% of patients with PCOS are insulin-resistant ***(Kanafchian et al., 2017).***

Recently, Lipocalin-2, also known as Neutrophil Gelatinase-Associated Lipocalin-2 (LCN2 or NGAL) has drawn the attention of many researchers, due to its implication in metabolic alterations and in the regulation of the immune response and cell homeostasis. Lipocalin-2 is a member of the Lipocalin superfamily comprised by small secreted proteins, and it is abundantly expressed in adipose tissue and liver ***(De la Chesnaye et al., 2015).***

Lipocalin-2 is abundantly produced from adipocytes. The expression and secretion of this protein increases sharply after conversion of preadipocytes to mature adipocytes. Its expression can be induced by various inflammatory stimuli, including lipopolysaccharide and IL-1β. This evidence suggests that Lipocalin-2 may participate in inflammation-related disorders ***(Law et al., 2010).*** Lipocalin-2, is associated with obesity, obesity-related inflammatory processes and insulin resistance. Expression of LCN-2 was elevated by agents that promote insulin resistance and reduced by thiazolidinediones that decrease insulin resistance ***(Yan et al., 2007).***