Study of the Adipocytokine Visfatin in Patients with Polycystic Ovary Syndrome

Thesis

Submitted for Partial Fulfillment of the Master Degree in Endocrinology

Presented by

Dina Atif Ahmed
(M.B., B.Ch.)

Under Supervision of

Prof. Dr. Salah El-Dein Ahmed Shelbaya
Professor of Internal Medicine and Endocrinology
Faculty of Medicine - Ain Shams University

Prof. Dr. Salwa Sedik Hosny
Professor of Internal Medicine and Endocrinology
Faculty of Medicine - Ain Shams University

Dr. Khaled Mahmoud Makboul
Assistant Professor of Internal Medicine and Endocrinology
Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain Shams University
2012

List of Contents

List of Contents (Cont.)

List of Tables

List of Figures

List of Figures (Cont.)

List of Figures (Cont.)

List of Abbreviations

ADP	Adenosine di-phosphate
ATP	Adenosine tri-phosphate
CRP	C-reactive protein
dextran–FITC	dextran-flurescein isothiocyanate
HNMPA-(AM) $_3$	Hydroxy-2-naphthalenylmethylphosphonic Acid Trisacetoxymethyl Ester
IL-1β	Interleukin-1β
IL6	interleukin-6
IL-8	Interleukin-8
IR	insulin receptor
MCP-1	monocyte chemoattractant protein-1
MMP-9	matrix metalloproteinase-9
mRNA	Messenger ribonucleotide amino acid
NAD$^+$	*Nicotinamide adenine dinucleotide*
Nampt	nicotinamide phosphoribosyltransferase
NAPRTase	Nicotinate phosphoribosyltransferase
NMN	*nicotinamide mononucleotide*
oxLDLs	oxidized low-density lipoproteins
PBEF	pre-B-cell colony-enhancing factor
PRPP	Phosphribosyl pyrophosphate
QAPRTase	Quinolinate phosphoribosyltransferase
SAT	Subcuteneous adipose tissue
SGBS	Simpson Golabi Behmel syndrome
T2DM	Type 2 diabetes mellitus
THP-1 cells	Human acute monocytic leukemia *cell* line
TNF-α	tumour necrosis factor-α
VAT	Visceral adipose tissue

List of Abbreviations (Cont.)

BMI	Body mass index
HOMA	Homeostasis Model Assesment.
PCOS	Polysyctic ovary syndrome
CKD	Chronic kidney disease
WHR	Waist hip ratio
CT	computed tomography
IGT	impaired glucose tolerance
NGT	normal glucose tolerance
SBP	systolic BP
DBP	diastolic BP
T1DM	Type 1 diabetes mellitus
GDM	gestational diabetes mellitus
GH	growth hormone
NEFAs	non-esterified fatty acids; 'free fatty acids'
PPARγ	peroxisome proliferator-activated receptor γ
C/EBPα	CCAAT/enhancer-binding protein
GLUT4	glucose transporter 4
MAPK	mitogen-activated protein kinase
JAK2	Janus kinase 2
PI3K	phosphoinositide 3-kinase
HIF-1α	hypoxia-inducible factor-1α
MCF-7	acronym of Michigan Cancer Foundation - 7
LH	luteinizing hormone
FSH	Follicle Stimulating hormone
SHBG	sex hormone-binding globulin
GnRH	Gonadotrophin releasing hormone
IGF	Insulin growth factor

List of Abbreviations (Cont.)

LOCAH	Late-onset congenital adrenal hyperplasia
VLCD	very low calorie diets
IVF	In vitro fertilization
OCS	Oral contraceptives
HMG	Human menopausal gonadotrophin
LOD	laparoscopic ovarian drilling
IRS	insulin receptor substrates
HDL	High density lipoprotien
LDL	Low density lipoprotein
ELISA	Enzyme linked-Immuno-Sorbent Assay
INS-EASIA	phase Enzyme Amplified Sensitivity Immunoassay
MAbs	monoclonal antibodies
HRP	horseradish peroxidase
EIA	Enzyme immunoassay
SA-HRP	Streptavidin-horseradish peroxides
SPSS	Statistical Package for Special Science version 12
m	mean
SD	Standard deviation
ANOVA	Analysis of variance
NS	Non significant
SIG	significant
HS	Highly significant
Wt	Weight
Ht	Hight
TG	Triglyceride

List of Abbreviations (Cont.)

FBS	Fasting blood sugar
WHO	World Health Organization
OGTT	Oral glucose tolerance test
FBG	Fasting blood sugar
QUICKI	Quantitative insulin sensitivity check index
G/I ratio	Glucose/Insulin ratio
AUCI	Area Under Curve
NICHD	National Institute of Child Health and Human Development
TNF	Tumor Necrosis Factor
WHR	Waist Hip Ratio
CVD	Cardio vascular disease
LOCAH	Late-onset congenital adrenal hyperplasia

INTRODUCTION

Visfatin, a protein secreted by adipose tissue, is suggested to play a role in the pathogenesis of insulin resistance. In polycystic ovary syndrome (PCOS), insulin resistance might be involved in the development of endocrine and metabolic abnormalities ***(Kowalska et al., 2007).***

Visfatin, a novel adipocytokine is up regulated in visceral fat in parallel with insulin resistance. It activates the insulin signal transduction pathway through binding to the same receptor. Systemic visfatin concentrations are actually regulated by glucose, insulin and elevated in patients with insulin resistance, obesity and diabetes ***(Dominik et al., 2007).***

It was isolated as a secreted factor that synergizes with interleukin-7 and stem cell factors to promote the growth of B cell precursors. It also known as pre-B cell colony-enhancing factor ***(Samal et al., 1994).***

Visfatin gene is expressed in adipocytes, where it is subjected to regulation ***(Kralisch et al., 2005).***

The cause of up regulation of visfatin mRNA in both subcutaneous tissue and omental adipose tissue of women with polycystic ovary syndrome as a pro inflammatory state is of unknown aetiology ***(Tan et al., 2006).***

The increased macrophage population in obese human visceral white adipose tissue might be responsible for the enhanced production of visfatin, which might be considered a pro-inflammatory marker ***(Curat et al.,2006).***

Polycystic ovary syndrome (pcos), is a very common endocrine disorder affecting up to 10% of women of reproductive age, is expressed as chronic anovulation and hyperandrogenism ***(Polson et al., 1998).***

Obesity occurs in about 50% of women with PCOS but is not universal ***(Bernasconi et al., 1996).***

Insulin resistance is found in both lean and obese patients with PCOS, but obesity and PCOS independently may affect insulin resistance ***(Dunaif et al., 1989).***

High serum visfatin is associated with insulin resistance and markers of hyperandrogenism in lean PCOS patients. ***(Kowalska et al., 2007).***

AIM OF THE WORK

- To asses plasma visfatin concentrations in women with polycystic ovary syndrome.
- Correlate serum visfatin with their BMI

VISFATIN

Introduction

Obesity is a rapidly growing disease in industrialized countries that is characterized by an excessive accumulation of adipose tissue ***(Kahn and Flier, 2000).*** Both hyperplasia and hypertrophy of adipocytes are found in this disorder ***(Kahn and Flier, 2000).*** Adipose tissue has been shown to secrete various proteins, so-called adipokines. Over the last few years, it has become obvious that obesity and various components of the metabolic syndrome, such as insulin resistance and hypertension, are strongly linked due to the differential secretory function of adipose tissue. Thus adipokines, including adiponectin, IL (interleukin)-6, leptin, MCP-1 (monocyte chemoattractant protein-1), resistin, TNF-α (tumour necrosis factor-α), vaspin and visfatin, might play an important role in the pathogenesis of insulin resistance and cardiovascular disease. ***Fukuhara et al. (2005)*** isolated visfatin, which is also known as PBEF (pre-B-cell colony-enhancing factor) and Nampt (nicotinamide phosphoribosyltransferase), as a novel adipokine that improved glucose tolerance and might play a role in the development of obesity-associated insulin resistance and T2DM (Type 2 diabetes mellitus). Visfatin/PBEF/Nampt was shown to mimic the effects of insulin by binding to the insulin receptor at a site different from that of insulin