The Study of Serum Chemerin in patients with Polycystic Ovaries Syndrome (PCOS) and its relation to insulin resistance

Thesis

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By

Bahaa Mahmoud Mohamed Taha
Master degree of internal medicine

Supervised of

Doctor/ Mohamed Reda Halawa
Professor of Internal medicine and Endocrinology
Faculty of Medicine – Ain Shams University

Doctor/ Rania Sayed Abd El Baky
Professor of Internal Medicine and Endocrinology
Faculty of Medicine - Ain Shams University

Doctor/ Yara Mohamed Eid
Professor of Internal Medicine and Endocrinology
Faculty of Medicine - Ain Shams University

Doctor/ Merihan Samy Nasr
Associate professor of Internal Medicine and Endocrinology
Faculty of Medicine - Ain Shams University

Doctor/ Laila Mahmoud Hendawy
Associate professor of Internal Medicine and Endocrinology
Faculty of Medicine – Ain Shams University

Faculty of Medicine
Ain Shams University
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List of Abbreviations

Abb.	Full term
A-FABP	ADIPOCYTE fatty-acid-binding protein
AHA	American Heart Association
BMI	Body mass index
CCNB2	Cyclin B2
CCRL2	Chemokine (C-C motif) receptor-like 2
CHD	Coronary heart disease
CMKLR1	Chemokine receptor like 1
CVD	Cardiovascular disease
DCs	Dendritic cells
ER	Endoplasmic reticulum
ERK	Extracellular signal-regulated kinases
FFA	Free fatty acids
GPR1	G protein-coupled receptor
HDL	High-density lipoprotein
HTR2B	Hydroxytryptamine receptor 2B
IL13RA2	Interleukin-13 receptor alpha2
IL-6	Interleukin-6
IR	Insulin resistance
LA-ratio	Leptin / adiponectin levels
LDL	Low-density lipoprotein
LH	Luteinizing hormone
MAPK	Mitogen-activated protein kinase
MCP-1	Monocytes chemo-attractant protein-1
MS	Metabolic syndrome
NHLBI	National Heart, Lung and Blood Institute
PAH	Pulmonary arterial hypertension
PCI	Percutaneous coronary intervention

List of Abbreviations (Cont.)

Abb.	Full term
PCOS	Polycystic ovary syndrome
PI3K	Phosphatidylinositol 3 kinase
PVAT	Perivascular adipose tissue
RAAS	Renin-angiotensin-aldosterone system
RARRES2	Retinoic acid receptor responder 2
RBP4	Retinol binding protein 4
SAT	Subcutaneous adipose tissue
SLC16A	Solute linked carrier 16A
SNS	Sympathetic nervous system
SNS	Sympathetic nervous system
SSC	Squamous cell carcinoma
STEMI	ST segment elevation

INTRODUCTION

Polycystic ovary syndrome (PCOS) is an endocrine-metabolic disorder characterized by multiple hormonal imbalances, reflecting on a clinical presentation dominated by manifestations of hyperandrogenism, which generate short and long term consequences on female health ***(Teede et al., 2010).***

The manifestations of PCOS are not confined to the gynecological sphere; women afflicted by this disease show an increased prevalence of several comorbidities, including obesity dyslipidemia, hypertension, metabolic syndrome (MS) and type 2 diabetes mellitus (DM2) in comparison with women without PCOS ***(Wild, 2002).***

Several studies have pinpointed insulin resistance (IR) as the fundamental link associating PCOS and obesity ***(Reaven, 2011)*** though IR may be present in PCOS independently of obesity ***(Toprak et al., 2001)***. IR,defined as a metabolic state characterized by a decrease in cellular ability to respond to insulin signaling, appears to be an essential pathophysiologic mechanism in the development of all metabolic complications of PCOS ***(Apridonidze e al., 2005)***.

Adipose tissue represent an active endocrine organ that release a large number of bioactive mediators (adipokines) that signal to organs of metabolic importance including brain, liver, skeletal muscle and immune sysem thereby modulating

homeostasis, blood pressure, lipid, glucose metabolism, inflammation and atherosclerosis ***(Rabe et al., 2008)***.

Chemerin is an adipokine that has been associated with autocrine /paracrine signaling for adipocytes differentiation and maturation, in addition, it can regulate glucose uptake and stimulate lipolysis via phosphorylation of some intermadiates in human adipocytes which are involved in mediating lipolysis and insulin signaling pahway ***(Goralski et al., 2007).***

Several studies suggested that it could induce insulin resistance in skeletal muscle cells. Thereby it is thought to be elevated in adipose tissue of type 2 diabeic patients. Furthermore, chemerin levels have been reported to be associated with components of the metabolic syndrome, including elevated levels of body mass index, plasma triglycerides and blood pressure ***(Bozaoglu et al., 2007).***

Aim of the Work

To determine serum chemerin level and its relation to insulin resistance in patients with polycystic ovary syndrome.

Chapter 1

POLYCYSTIC OVARIAN SYNDROME

The polycystic ovary syndrome (PCOS) is a disorder that is characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphologic features. As defined by the diagnostic criteria of the National Institutes of Health (i.e., hyperandrogenism plus ovulatory dysfunction), "classic" polycystic ovary syndrome affects 6 to 10% of women of reproductive age, but the prevalence may be twice as high under the broader Rotterdam criteria ***(Dumesic et al., 2015).***

This complex polygenic disorder has environmental influences (e.g., those that contribute to obesity) ***(Dumesic et al., 2015).***

Many studies suggest that inherent abnormalities of ovarian steroidogenesis and follicular development play a role in the polycystic ovary syndrome. The syndrome is also associated with persistently rapid gonadotropin-releasing hormone pulses, an excess of luteinizing hormone, and insufficient follicle-stimulating hormone (FSH) secretion, which contribute to excessive ovarian androgen production and ovulatory dysfunction. In addition, many women with the polycystic ovary syndrome have insulin resistance, and compensatory hyperinsulinemia enhances ovarian (and adrenal) androgen production and increases androgen bioavailability

through reduced levels of sex hormone–binding globulin. Genomewide association studies implicate many genes, including those for gonadotropin receptors, the beta subunit of FSH, insulin receptor, differentially expressed in normal and neoplastic cells domain-containing protein 1A (*DENND1A*), and thyroid adenoma-associated protein (*THADA*). "Developmental programming" through environmental or hormonal imprinting may also contribute to the development of the polycystic ovary syndrome. Various pathophysiological factors may play different relative roles in individual patients ***(Dumesic et al., 2015).***

PCOS and cardiometabolic effects

The polycystic ovary syndrome is associated with cardiometabolic abnormalities and possibly an increased risk of cardiovascular disease ***(Wild et al., 2010).*** Among women with this syndrome, 50 to 80% are obese ***(Dumesic et al., 2015).*** Impaired glucose tolerance is reported in 30 to 35% of U.S. women with classic polycystic ovary syndrome, and type 2 diabetes mellitus is reported in 8 to 10%; the risk of these conditions is influenced by age, adiposity, and a family history of diabetes ***(Ehrmann et al., 1999)***. Women with the polycystic ovary syndrome have lower high-density lipoprotein cholesterol and higher triglyceride and low-density lipoprotein (LDL) cholesterol levels than women without the syndrome. Differences in LDL cholesterol levels are at least partly independent of differences in BMI ***(Wild et al., 2011).***

PCOS and insulin resistance

Fasting insulin level was found to be elevated even in PCOS women without evident metabolic syndrome (MS) and it was suggested that the elevated insulin contributes to the elevated androgen production by the ovaries and other complications. Several studies indicated that as much as 60-95% of PCOS women show insulin resistance (IR), which becomes aggravated if accompanied by increased abdominal fat ***(Stepto et al., 2013).*** However, IR in PCOS women cannot be completely explained by abdominal adiposity and several other factors such as defective glucose, lipid and steroid metabolism, dysregulated insulin signaling and altered adipokine secretion also likely contribute to IR ***(Dumesic et al., 2015).*** IR and elevated circulating insulin were found to stimulate the theca cells of ovaries to produce and secrete androgens and also to enhance the responsiveness of ovaries to luteinizing hormone (LH) to produce androgens ***(Polak et al., 2017)***. In fact, it has been noted that even in the absence of overt obesity, there can be preferential deposition of fat intra-abdominally in PCOS women with normal body weight. This intra-abdominal fat leads to elevated number of small subcutaneous abdominal adipocytes, which contribute to impaired insulin action and thus functional IR and hyperandrogenism ***(Dumesic et al., 2016).*** Decreased ability of intra-abdominal subcutaneous adipocytes to store and sequester fat in normal weight PCOS women leads to ectopic fat deposition in other tissues such as muscle and