Evaluation of Adipokines (Adiponectin, Resistin and Ghrelin) in Women with Polycystic Ovary Syndrome

Thesis

Submitted for partial fulfillment of the Master degree in

Obstetrics &Gynecology

By

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2017

Acknowledgement

*First and foremost, I owe my deepest gratitude to **ALLAH** the most merciful for his grace and mercy for giving me the effort to complete this work.*

*Words do fail me to express my sincere gratitude to **Prof. Mohamed Alaa Mohei El-Din Elghannam**, Professor of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, for his attentivness, follow up and the equipment with all facilities possible to complete this work. Without his corteous assistance and kind patience, this work would never had come to light.*

*I would also like to convey my deep appreciation and most gratefulness for **Prof. Mohamed Elmandooh Mohamed,** Professor of Obstetrics and Gynecology, Ain Shams University, for his constant guidance, experienced advice and great encouragement which have been of the most important.*

*A great appreciation and most gratefulness for **Dr/ Ahmed Mohamed El-Kotb**, Lecturer in Obstetrics and Gynecology, Ain Shams University. The door to **Dr.Kotb** office was always open whenever I ran into a trouble spot or had a question about my research or writing. He consistently allowed this study to be my own work, but steered me in the right direction whenever he thought I needed it.*

*I shall always be indebted to my brother **Khaled Afifi**.This achievement would never had been possible without him.*

*Finally, I must express my profound gratitude to my **parents and fiancée** for providing me with unfailing support and continuous encouragement throughout my years of study and the process of researching and writing the thesis.*

Thanks for all your encouragement!

Mohamed Mokhtar

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List of Abbreviations

Abbr.	Full Term
AdipoR1	Adiponectin receptor
AMH	Ante Mullerian hormone
AMPK	AMP activated protein kinase
ASRM	American Society of Reproductive Medicine
BMI	Body mass index
CAH	Congenital adrenal hyperplasia
CRP	C-Reactive protein
DM	Diabetes mellitus
FSH	Follicle stimulating hormone
FSIVGTT	Frequently sampled intravenous glucose tolerance test
GHS	Growth hormone secretagogue
GnRH	Gonadotrophin releasing hormone
GTT	Glucose tolerance test
HMW	High molecular weight
HOMA	Homeostasis model assessment
IL-6	Inter- leukin 6
IR	Insulin resistance
IRS	Insulin receptor substrate
IVF	In vitro fertilization

LH	luteinizing hormone
NGF	Nerve growth factor
NIH	National Institute of Health
PAI	Plasminogen activator inhibitor
PPAR-α	Peroxisome proliferator-activated receptor- α
QOL	Quality of life
QUICKI	Quantitative insulin sensitivity check index
RELM	Resistin-like molecule
SHBG	Sex hormone binding globulin
SNPs	Single nucleotide polymorphisms
TGF	Tumor growth factor
TNF	Tumor necrosis factor
TZDs	Thiazolidinediones
VEGF	Vascular endothelial growth factor
WBISI	Whole-body insulin sensitivity
WHO	World health Organization

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Introduction

Polycystic ovary syndrome (PCOS) is a common heterogeneous, heritable endocrine disorder characterized by irregular menstruation, hyperandrogenism and polycystic ovaries. According to Rotterdam ESHRE/ASRM, 2003 criteria, two out of three are enough to diagnose PCOS including oligo-ovulation or anovulation, biochemical and/or clinical hyperandrogenism, polycystic ovaries by ultrasound and diagnosis should be done after exclusion of other causes that mimic the clinical features of PCOS as thyroid diseases, hyperprolactinemia and congenital adrenal hyperplasia, ***(Rotterdam, 2004).***

The prevalence of PCOS is about 15%–20% when the ESHRE/ ASRM criteria are used. Clinical manifestations include oligomenorrhea or amenorrhea, hirsutism, and frequently infertility. Risk factors for PCOS in adults includes type 1 diabetes, type 2 diabetes, and gestational diabetes. Insulin resistance affects 50%–70% of women with PCOS leading to a number of comorbidities including metabolic syndrome (MetS) that include (central obesity, dyslipidemia, impaired glucose metabolism, and elevated blood pressure), hypertension, dyslipidemia, glucose intolerance, obesity and diabetes. Mental health problems as depression, bipolar disorder, anxiety, and eating disorders are also recorded **(Sirmans and Pate, 2014).**

PCOS originates in multiple genetic and environmental factors and its further development involves interaction of diverse organs or tissues **(Harwood, 2012).**

Adipose tissue is a versatile organ, crucial for maintaining homeostasis by storing and dispersing energy, producing and releasing adipokines and cytokines and free fatty acids and hormones, with the ability to influence other cells of the body in autocrine, paracrine and endocrine fashion. This highly metabolically active tissue is distributed throughout the body in discrete depots, and its development, expansion and energy balance are regulated by an integrated network of genetic, environmental, epigenetic and pharmacological factors (**Diedrich et al., 2015).**

Adipose tissue dysfunction as in obesity and PCOS leads to development of cardio-metabolic diseases including the metabolic syndrome, type 2 diabetes, inflammatory disorders, and vascular disorders that ultimately lead to coronary heart disease altering secretion pattern of its adipokines as adeponectin, leptin, and resistin ***(Harwood, 2012; Akbarzadeh et al., 2012)***.

Though considered a low grade chronic inflammatory process ***(Duleba et al., 2012)***, it needs to be fully evaluated that whether inflammatory cytokines also mediate the development of PCOS. Several investigations have shown that obesity is not necessarily present in women with PCOS

(Wang and Zhu, 2012).

Many studies demonstrated that some adipokines have multiple biological effects, however, it is still uncertain whether metabolic status could be associated with a peculiar inflammatory pattern in PCOS patients. Adiponectin is one of the most studied adipokines which is considered a protein hormone responsible for regulating multiple metabolic processes (**Diedrich et al., 2015).**

Many other proteins have been proposed as potential new markers of Insulin resistance in PCOS, such as resistin, leptin, RBP4, kisspetin and ghrelin, but their role is still controversial **(Polak et al., 2016).**

Resistin is an adipose-derived peptide hormone discovered in 2001 that potentially links obesity and diabetes mellitus **(Polak et al., 2016)**.

Ghrelin is a multifunctional peptide hormone secreted principally in the stomach. It stimulates several biological functions including food intake, glucose release, cell proliferation and reproduction **(Polak et al., 2016)**.

Insulin has a broad range of metabolic and mitogenic actions in many tissues ***(Kahn 1985)***. It is important to specify the biological action of insulin being measured as well as the tissue being considered, because its action is regulated not only by changes in its concentration but also through changes in the sensitivity of target tissues to

hormone action ***(Kahn 1985).*** Insulin resistance has been defined as a state (of a cell, tissue, or organism) in which a greater than normal amount of insulin is required to elicit the appropriate response ***(Mantzoros 1995).*** Increased insulin secretion by β-cells is the normal response and compensatory hyperinsulinemia follows. As long as hyperinsulinemia overcomes insulin resistance, glucose levels remain normal; if β-cells compensatory response declines; relative or absolute insulin insufficiency develops, with metabolic consequences, i.e., IGT and DM2. The WHO describes insulin resistance as a glucose uptake below the lowest quartile under hyperinsulinemic euglycemic conditions for the background population. Reaven originally identified 25% of the general population as insulin resistant **(*World Health Organization (WHO) Expert Committee on Diabetes Mellitus Second Report 1980*).**

Although several tests exist to assess insulin resistance, the availability of new markers is highly needed in the aim to achieve a more reliable assessment of insulin metabolism. To date, a number of new proteins have been proposed as surrogate markers for the assessment of insulin resistance.

The present study will be carried out to assess the association between adipokines, insulin resistance and obesity in women with PCOS, and its clinical significance.