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Review Article

Role of insulin resistance and insulin action in polycystic ovary syndrome: a concept review

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a highly prevalent endocrine-metabolic illness that has alarmingly high rates of infertility and other significant effects on the health of women. This review study highlighted that Insulin appears to damage every part of the hypothalamus-hypophysis-ovary axis, and insulin resistance in ovarian tissue leads to impaired metabolic signalling but intact mitogenic and steroidogenic activity, favouring hyperandrogenemia, which is thought to be the primary cause of the clinical symptoms of PCOS. This review also enumerates and briefly summarize the research methods related to effects of insulin resistance in PCOS, including molecular mechanism of action of insulin and anabolic processes that stimulate cell growth and differentiation; increase protein and fat storage; and the binding between α, β dimers and receptors on cell surface that results in alteration in gene expression, metabolism and growth.

Keywords: PCOS, Insulin, Infertility, Women, Reproductive

INTRODUCTION

The endocrine-metabolic disorder polycystic ovarian syndrome (PCOS) is characterized by various hormonal imbalances, reflecting on a clinical presentation dominated by signs of hyperandrogenism, which have both immediate and long-term effects on the health of women.[1]

The effects of PCOS extend beyond the gynecological field; in comparison to women without the condition, those with PCOS have higher prevalence of a number of co-morbid conditions, such as obesity, dyslipidemia, hypertension, metabolic syndrome (MS), and type 2 diabetes mellitus (DM2). These characteristics contribute to the higher risk of developing cardiovascular disease and all-cause mortality seen in these people, coupled with other changes such endothelial dysfunction and a persistent low- grade inflammatory state.[2]

The pancreatic peptide hormone insulin, made by beta cells of the islets of Langerhans, is crucial for controlling the metabolism of carbohydrates, fats, and proteins. The identification of ovarian type I and type II IGF receptors, and the identification of the ovarian production of binding proteins for these two growth factors IGF-binding proteins (IGFBPs)-all contributed to the future development of this discipline. Thus, a role for the structurally related IGFs in ovarian function has been acknowledged in addition to insulin. The role of insulin and IGFs in the ovary at the molecular, cellular, and clinical levels in a range of normal and pathological states has received a lot of attention over the past ten years. Consequently, there is a need for a thorough analysis of what we refer to as the insulin-related ovarian regulatory system.[3]

There is a significant health burden associated with PCOS, which affects 8-13% of women of reproductive

age and has significant metabolic (increased type 2 diabetes mellitus and cardiovascular risk factors), reproductive (leading cause of anovulatory infertility), and psychological (anxiety and depression) effects.[4] The cause of PCOS and the best treatments are still unknown, despite the condition's high frequency. Hyperandrogenism and clinical characteristics are both primarily influenced by insulin resistance. Despite the 4.4-fold higher risk of T2D in PCOS, which accounts for 23% of T2D in young women, the underlying mechanisms of insulin resistance in PCOS are still poorly understood. Medical treatment for PCOS (metformin) and weight control through diet and exercise reduce but do not reverse insulin resistance in PCOS.[5-7]

PCOS is a complex genetic disorder. Numerous genetic susceptibility loci for PCOS have been identified and confirmed. Chinese and European PCOS populations share some of the same susceptibility genes, which may indicate that PCOS is an old condition. Insulin modulates ovarian steroidogenesis by acting as a co-gonadotropin through the appropriate receptor. Insulin transmission in the brain has been genetically disrupted, and this system is crucial for controlling ovulation and body weight, according to the research. These discoveries have been immediately used to a novel PCOS treatment using insulin-sensitizing medications. Androgens also play a role in PCOS's insulin resistance. PCOS may potentially have developmental roots because it was exposed to androgen during vulnerable times or because of intrauterine growth restriction. First-degree relatives who have PCOS have reproductive and metabolic characteristics. According to a study conducted by Burghen et al PCOS in women was associated with elevated insulin responses during oral glucose tolerance testing that could not be explained by obesity. Additionally, acanthosis nigricans in women with typical PCOS suggests that they may be insulin resistant, similar to people with uncommon disorders of high insulin resistance. These findings gave rise to a brand-new area of research on the factors that cause insulin resistance and PCOS.[1,8-10]

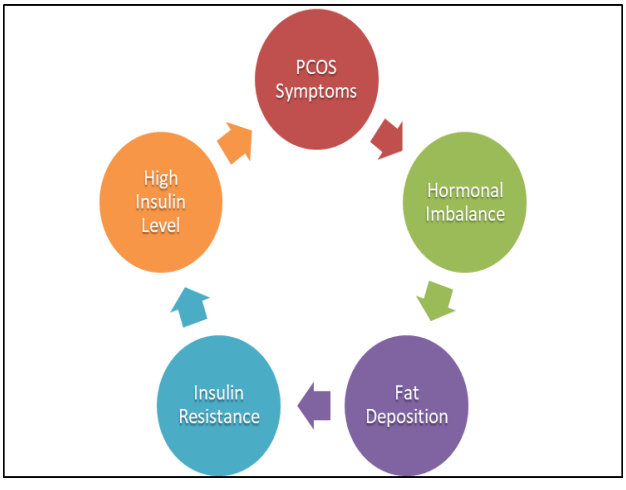

Figure 1: PCOS and insulin resistance cycle.

PCOS METABOLIC TRAITS

One of the most prevalent endocrinopathies affecting women of reproductive age is polycystic ovarian syndrome (PCOS), which has detrimental effects on the reproductive, metabolic, and psychological systems. It's complicated pathophysiology necessitates a multidisciplinary clinical strategy. There is still a dearth of literature that summarises the broad clinical consequences of PCOS, which would help clinicians manage the condition.[11]

The Achard-Thiers syndrome, also known as diabetes of the bearded ladies, was first described by Achard and Thiers in 1921. It is characterised by the combination of diabetes mellitus with clinical symptoms of androgen excess in a postmenopausal woman. In order to describe the abdominal fat accumulation, which is the typical male pattern of body fat distribution, Jean Vague of the University of Marseille coined the term android obesity and began to investigate the idea that this type of body adiposity was linked to an increased risk of diabetes and cardiovascular disease. Research proved that obese women with an upper body have insulin resistance. Additionally, the testosterone production rates in these women were higher.[12]

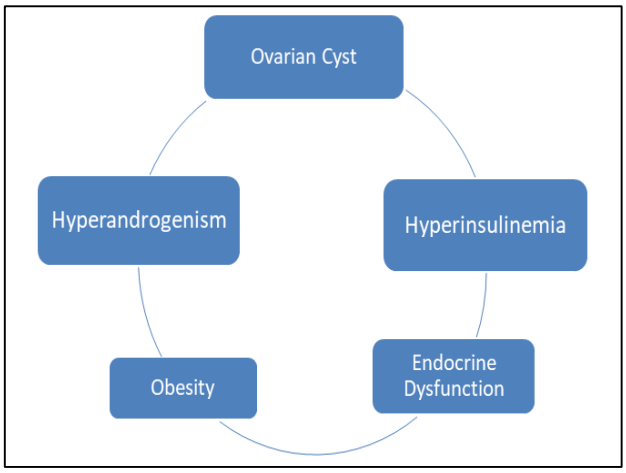

Figure 2: Clinical features of PCOS.

MOLECULAR MECHANISM OF INSULIN ACTION

Beyond controlling the intake of glucose, insulin is involved in a variety of cellular processes. It also has additional anabolic actions that boost protein and fat storage and support cell growth and differentiation. By attaching to its receptor on the cell surface, insulin affects cells. A heterotetramer composed of two α, β dimers connected by disulfide bonds makes up the insulin receptor. One gene result in each α, β dimer. The ligand-binding domain and the subunit's intrinsic kinase activity are both extracellular, and the latter suppresses the former. The subunit traverses the membrane, and the intrinsic protein tyrosine kinase activity seen in the

cytoplasm is further stimulated by ligand-mediated autophosphorylation. IGF-I, the insulin-related receptor, and the insulin receptor are structurally very similar to one another. In order to create hybrid receptors, the insulin receptor's α, β dimer can combine with analogous dimers of the IGF-I receptor or insulin-related receptor.[13-15]

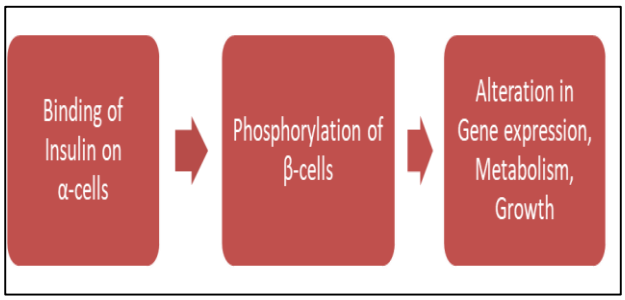

Figure 3: Molecular mechanism of insulin action.

INSULIN ACTION DURING PCOS IN FEMALES

In addition to increasing glucose absorption by adipocytes, skeletal and cardiac muscle, and other insulin-responsive target tissues, insulin also controls the synthesis of hepatic glucose. Insulin also suppresses lipolysis, resulting in a decrease in circulating free fatty acid levels. This might operate as a mediator between insulin and hepatic glucose synthesis. The classic definition of insulin resistance is a diminished ability of insulin to mediate these metabolic activities on glucose uptake, glucose generation, and/or lipolysis, necessitating the need of higher insulin doses to achieve a specific metabolic action.[16-18]

The hyper-insulinemic, euglycemic glucose clamp method is considered to be the gold standard for evaluating metabolic insulin resistance in vivo. By administering a desired dose of insulin and maintaining euglycemia with a variable glucose infusion, where the rate is adjusted based on frequent arterialized blood glucose determinations and a negative feedback principle, this technique quantitatively evaluates the effect of insulin on whole-body glucose uptake. At steady state, the amount of glucose infused equals the amount of glucose absorbed by the peripheral tissues. This is known as insulin-mediated glucose disposal (IMGD) and can be used as a gauge of the peripheral tissues' sensitivity to insulin. Skeletal muscle makes up around 85% of IMGD in lean, healthy people. A greater percentage of IMGD is accounted for when fat mass rises. The infusion of isotopically labelled glucose at baseline and throughout the euglycemic clamp can be used to measure endogenous glucose production, which reflects both hepatic and renal glucose synthesis. The reduction in endogenous glucose production in response to insulin can be used to measure the suppression of hepatic glucose production. Using the frequently sampled intravenous glucose tolerance test (FSIGT), whole-body insulin sensitivity can also be precisely assessed in patients without diabetes with the least amount of model analysis. Insulin sensitivity (sensitivity index), which indicates insulin action to promote glucose uptake and to inhibit glucose synthesis, is determined by the minimum model.[19,20]

CONCLUSION

Infertility in women is primarily caused by PCOS, a complex reproductive issue. Around 50 to 70% of PCOS patients have insulin resistance, which may promote oxidative stress by producing reactive oxygen species. However, hyperinsulinemia and insulin resistance are exclusively present in obese women with PCOS, putting these women at a higher risk of developing cardiovascular illnesses and low-grade inflammation.

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