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Insulin Resistance and Polycystic ovary Syndrome: A Review

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ABSTRACT

Polycystic Ovary Syndrome (PCOS) is the most common, yet complex, endocrine disorder affecting women in their reproductive years and is a leading cause of infertility. This disease appears to be multifactorial and polygenic in nature involving multisystem dysfunction, namely reproduction, endocrine and metabolic. Hyperandrogenism and insulin resistance appear to be central cause to the pathophysiology of the disease. The glucose and insulin metabolism pathways have been studied and debated to understand whether Insulin Resistance is due to a defect in insulin action or a primary defect in β-cell function or decreased hepatic clearance of insulin, or a combination of all these factors. Numerous studies have demonstrated that obese, normal weight and thin women with PCOS have a form of insulin resistance that is unique and intrinsic to the disorder. Moreover obese women with PCOS possess an additional burden of insulin resistance resulting from their excess adiposity. Hyperinsulinemia leads to increase in androgen production directly by acting as a co-gonadotropin, augmenting Luteinizing Hormone activity within the ovary, and indirectly by increasing serum LH pulse amplitude. Whereas Androgens may in turn contribute at least partially to the insulin resistance state linked with PCOS. In this review, we will briefly study the role of insulin resistance in polycystic ovary syndrome.

Keywords: Polycystic ovary syndrome, insulin resistance, Hyperandrogenism.

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Introduction

Polycystic Ovary Syndrome (PCOS) is the most common, yet complex, endocrine disorder affecting women in their reproductive years and is a leading cause of infertility [1, 2]. The pathophysiology of PCOS is a highly debated and complex topic. PCOS is manifested clinically by a combination of ovulatory dysfunction, hyper androgenic state and abnormal ovarian morphology. This disease appears to be multifactorial and polygenic in nature involving multisystem dysfunction, namely reproduction, endocrine and metabolic. Hyperandrogenism and insulin resistance appear to be central cause to the pathophysiology of the disease. The incidence of disease with various symptoms also presents various risks like endometrial hyperplasia and endometrial cancer, insulin resistance / type 2 DM, high blood pressure, dyslipidaemia, cardiovascular disease, strokes, weight gain, miscarriages [3].In the clinical scenario, PCOS is conventionally described as "a young lady, probably obese, presenting with manifestations of hirsutism, oligomenorrhea and infertility". But renewed interest in PCOS has led to the realization that it involves far more than just the reproductive system. PCOS presents an early characteristic feature of the metabolic syndrome with a cluster of abnormalities where the combination of insulin resistance and compensatory hyperinsulinemia predisposes individuals to develop a high plasma triglyceride and a low high-density lipoprotein cholesterol concentration, high blood pressure and coronary heart disease [4].Therefore PCOS is sometimes defined as a Metabolic Syndrome (MetS) that includes obesity, dyslipidemia, insulin resistance, diabetes mellitus, hypertension and cardiac diseases [5]. Furthermore, recent studies have focused on association of PCOS with malignancies like cancerous conditions of the Endometrium, Breast and Ovary [6, 7]. Its clinical manifestation includes chronic anovulation, hyperandrogenic symptoms and it can be associated with the metabolic dysfunction in which hyperinsulinemia and peripheral insulin resistance are clinical features. The syndrome is also associated with dyslipidemia and acanthosis nigricans and may increase the risk for cardiovascular disease and hyperestrogen related cancers such as endometrial and breast cancers. During the reproductive years, PCOS is associated with significant reproductive morbidity including infertility, abnormal uterine bleeding, miscarriage and other complications of pregnancy [8].

Insulin Resistance in PCOS

Insulin, a polypeptide hormone secreted by the β - cells of the pancreas, plays a dominant role in maintaining glucose homeostasis. The classic target tissues of insulin include the

liver, muscle and fat. Insulin stimulates peripheral glucose uptake in muscle, fat tissue and induces protein synthesis, cell growth and differentiation. Insulin promotes glycogen storage and inhibits gluconeogenesis and glycogenolysis in the liver. It also inhibits lipolysis. The terms insulin sensitivity and insulin resistance generally refer to the actions of insulin on glucose homeostasis [9]. PCOS is characterized by a metabolic disorder in which hyperinsulinemia and peripheral insulin resistance are central features [10]. The characteristic disturbances of insulin secretion and action are much more prominent in PCOS women with amenorrhea or anovulatory menses than in equally hyperandrogenic women with regular cycles [11]. Measurements of fasting insulin, fasting glucose/fasting insulin ratio area under the curve (AUC) in oral glucose tolerance tests (OGTT), rapid intravenous glucose tolerance test (IVGTT) [12] and the euglycemic hyperinsulinemic clamp studies have explained substantial decreases in peripheral sensitivity to insulin in PCOS. This decrease (approximately 35%to 40%) is of a similar magnitude to that seen in type 2 DM. Obesity, body fat location (upper versus lower body), and muscle mass all have important independent effects on insulin sensitivity. Alterations in any of these parameters could potentially contribute to insulin resistance in PCOS [10]. The characteristic disturbances of insulin secretion and action are much more prominent in PCOS women with amenorrhea or anovulatory menses than in equally hyperandrogenic women with regular cycles [11]. PCOS may occur along with insulin resistance when the cell doors do not respond appropriately to the normal amounts of insulin produced by the body. In other words, insulin 'key' does not fit well into the 'lock' on the cell walls. When this happens extra insulin is produced to increase the chances of getting more glucose into the cells. This results in too much insulin in the body [13]. Since insulin is a growth hormone, too much insulin promotes weight gain, mostly in the midsection above the belly button resembling a 'spare tire'. If there is weight gain without significant changes to diet or exercise, excess insulin could be the culprit. If not well managed, elevated insulin levels may lead to type 2 diabetes as the insulin receptors on the cell walls become more resistant to insulin that results in hyperinsulinemia. Obesity, body fat location and muscle mass all have independent effects on insulin sensitivity. Alterations in any of these parameters could potentially contribute to insulin resistance in PCOS [10].

Insulin Resistance (IR) and Abnormalities in metabolic pathways

The glucose and insulin metabolism pathways have been studied and debated to understand whether Insulin Resistance is due to a defect in insulin action or a primary defect in β-cell function or decreased hepatic clearance of insulin, or a combination of all these factors. An intrinsic genetic defect in the post-receptor insulin signal transduction has been found in women with PCOS [14]. This may lead to decreased insulin action and a compensatory increased insulin secretion from the pancreatic β-cells. Regarding β-cell function, some investigators have shown a defective glucose-stimulated insulin secretion, indicating a primary defect in β-cell function. Others have found an increased insulin response a possible compensatory mechanism to a peripheral defect in insulin action, and yet others have found unaffected acute insulin secretion. The impact of hyperinsulinemia and insulin resistance was elucidated on reproductive and metabolic aspects of the syndrome. Path breaking studies have shown that the classic PCOS syndrome is determined by a distinct form of insulin resistance; however, this molecular anomaly is not universally present. In PCOS, increased insulin levels are incriminated for direct stimulation of ovarian androgens' production by means of the favourable action of this hormone to 17a-hydroxylase and to 17,20 lyase (cytochrome P450cl 7a) and in cytochrome P450scc [15-17].

The most substantial advance in the field over the past decade has been the realization that many women with PCOS are resistant to insulin. Many women with PCOS have insulin resistance beyond that predicted by their BMI, with 50–70% of these women demonstrating insulin resistance by various measures [18]. Numerous studies have demonstrated that obese, normal weight and thin women with PCOS have a form of insulin resistance that is unique and intrinsic to the disorder. Moreover obese women with PCOS possess an additional burden of insulin resistance resulting from their excess adiposity. The pancreas compensates for insulin resistance in PCOS by increasing insulin release, which allows for the maintenance of normal glucose tolerance during the early stages of the disorder [19, 20].

Hyperinsulinemia, resulting from insulin resistance plays a pathogenic role in PCOS by stimulating ovarian testosterone production, decreasing serum sex hormone binding globulin concentrations, and impending ovulation [21-23]. The molecular mechanisms of insulin resistance involve defects in the insulin-receptor signalling pathway in both adipocytes and well as in skeletal muscle [10]. Further Insulin may act directly in the hypothalamus, the pituitary or both and thereby contribute to abnormal levels of gonadotropin [24]. High insulin can also serve as a co-factor to stimulate ACTH mediated androgen production in the adrenal glands [25]. When serum insulin levels in women with PCOS are decreased, either due to direct suppression of insulin release (Diazoxide) or by enhancement of peripheral insulin sensitivity (Metformin), circulating free testosterone decreases and ovulatory function enhances [26, 27, 19]. Insulin has been shown to stimulate steroidogenesis in both granulosa and theca cells of the human ovary. The stimulation of steroidogenesis by insulin occurs in follicles obtained from both normal and polycystic ovaries and there are no obvious differences in responsiveness between the two types of ovaries.

There is a marked interaction of insulin with gonadotrophins in stimulation of granulosa cell production of estradiol and progesterone. In particular, it has been observed a more than tenfold increase in responsiveness to LH after preincubation of granulosa cells with insulin. Some authors believe that this may be relevant to the mechanism of anovulation in PCOS [19, 23, 28]. Anovulation in PCOS is characterized by a possible arrest of antral follicle development at the 6–10 mm stage and, therefore, a failure to enter the preovulatory phase of the cycle. Follicular fluid steroid levels and in vitro studies of estradiol production by granulosa cells isolated from PCOS clearly demonstrated that, for the most part, these follicles remain steroidogenically active and indeed show evidence of increased aromatase activity when compared with follicles of similar size from ovulatory women. Therefore there is a, marked disparity between follicle growth and steroidogenesis in this condition.

PCOS is characterized by hypersecretion of LH and insulin. The synergistic enhancement by insulin of LH induced steroidogenesis by granulosa cells could account for the arrest of follicle growth but enhancement of estradiol production [19]. The outcome of the recent studies of the effects of LH on granulosa cells of normal and PCOS ovaries provide some support for this hypothesis. Granulosa cells from follicles of normal ovaries respond to LH only when the follicles have reached about 10 mm in diameter but, in contrast, in cells obtained from follicles as small as 4.5 mm in diameter from women with anovulatory PCOS respond to LH. Exposure to hyperinsulinemia in vivo could account for

this premature responsiveness to LH [29].Moreover hyperinsulinemia also results in elevated levels of free IGF-1 and further human theca cells express IGF-1 receptor genes (as well as insulin receptor genes), which is another way in which androgen production is stimulated [30]. In addition, free IGF-1 is a potent growth factor that can activate proliferation of ovarian cells [31].

Association of androgens and insulin resistance

The disorders of extreme insulin resistance are commonly linked with hyperandrogenism when they exist in premenopausal women. It has been hypothesized that hyperinsulinemia causes hyperandrogenism because insulin has a variety of direct actions on steroidogenesis in humans. It is suggested that if insulin is to produce ovarian hyperandrogenism, polycystic ovarian changes must be present which predispose the ovaries to secrete excess androgens. Insulin does not seem in vivo to have any acute effects on ovarian function in normal women under physiologic circumstances. In a recently reported case report, surgical removal of insulinoma from a 24 year old woman resulted in resolution of the clinical and biochemical features of PCOS after 4 months, but small change was seen in the ovarian ultrasound scans. It was suggested that obesity and associated hyperinsulinemia could be implicated in the development of PCOS [32]. Studies, in which insulin levels have been lowered with agents that either decrease insulin secretion (diazoxide, somatostatin) or improve insulin sensitivity (metformin, troglitazone), demonstrate decreased androgen levels as well in PCOS women. Abnormalities in apparent 17, 20-lyase activity have improved after metformin treatment in parallel with reduced circulating insulin levels, consistent with an insulin-mediated stimulation of this enzyme [33]. Inverse associations between concentrations of sex hormone binding globulin (SHBG) and insulin are almost consistently found. Insulin has a major role in regulating hepatic production of SHBG and it increases the biological availability of potent steroids, mainly testosterone, through the suppression of SHBG synthesis. Insulin seems to increase adrenal sensitivity to ACTH in hyperandrogenic women [25]. LH may act as an intermediary in insulin augmented hyperandrogenism. Insulin has a direct action on the pituitary enhancing GnRH-stimulated LH release, the consequent hyperandrogenism resulting from an increase in LH secretion. As mentioned previously, insulin acts alone or synergistically with LH to increase androgen production in the ovary. It has also been shown in severely overweight infertility patients that weight reduction with a very low calorie diet results in a decrease in LH concentrations, a reduction in the LH/FSH ratio, and FSH predominance favoring folliculogenesis. The decrease in LH concentrations was inversely related to the severity of insulin resistance [34]. Androgens may produce a mild insulin resistance by increasing the number of less insulin-sensitive type IIb skeletal muscle fibers and by inhibiting muscle glycogen synthase activity. The mild insulin resistance due to androgen administration is not at the same magnitude as that seen in PCOS. There were no significant changes in peripheral or hepatic insulin action after prolonged androgen suppression by the GnRHa. Modest improvements in insulin sensitivity have been reported with anti androgen therapy in less insulin resistant, less obese or non obese PCOS women. It has been suggested that testosterone may indirectly contribute to insulin resistance through facilitating FFA release from the abdominal fat [35].

Conclusion

Hyperinsulinemia leads to increase in androgen production directly by acting as a co-gonadotropin, augmenting LH activity within the ovary, and indirectly by increasing serum LH pulse amplitude. Whereas Androgens may in turn contribute at least partially to the insulin resistance state linked with PCOS. In view of the similarity between the insulin growth factor-1 (IGF-1) and insulin receptor, insulin cross-activity was proposed as a mechanism for hyper androgenism. Stimulation of IGF-1 receptors on ovarian theca cells augments LH mediated androgen production by these cells. Insulin causes modulation of steroidogenesis via its own receptors present on both granulosa and theca cells. More peripherally, by inhibitions of hepatic synthesis, insulin decreases serum sex hormones-binding globulin (SHBG) favoring free circulating androgens, and decreases insulin like growth factor binding protin-1 (IGFBP-1) allowing more IGF-1 to be freely available both locally and peripherally. Elevated levels of androgens in the circulation, especially testosterone, inhibit production of hepatic sex hormone-binding globulin (SHBG). With decreased SHBG in circulation, more androgens are left free or unbound and therefore produce a enhanced clinical response in terms of hirsutism and other manifestation of excess androgen, which are central to PCOS. Hence insulin resistance is an important contributing factor both directly as well as indirectly in PCOS.

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