Research Paper Medical Science

Insulin Resistance in Polycystic Ovary Syndrome

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a common endocrine disease with metabolic, reproductive and psychological consequences effecting reproductive age women. In addition to the clinical features of oligo-anovulation, infertility and hyperandrogenism, PCOS is closely interrelated with insulin resistance (IR) and hyperinsulinemia, with a high prevalence. IR is also suggested to have a role in the pathogenesis of PCOS. Post-receptor defects, as well as genetic susceptibility has been held responsible for underlying mechanisms of IR. Assessment of IR includes tests of fasting insulin and blood glucose levels. In especially obese women with PCOS, oral glucose tolerance tests are recommended for screening. To overcome IR, reducing body fat and weight with a healthy diet is the initial step. Therapeutic approach includes insulin-sensitizing agents. The prevention of long-term consequences of IR in PCOS, like cardiovascular disease, type 2 diabetes and endometrium cancer, through appropriate screening, diagnosis and intervention is highly important.

KEYWORDS Polycystic ovary syndrome,insulin resistance, hyperandrogenemia

Introduction:
Polycystic ovary syndrome (PCOS) is a multi-systemic endocrine disease affecting 4 to 12% of reproductive age women. PCOS is recognized as a common reproductive disorder with cardio-metabolic, and psychological features. Among the significant adverse impacts, insulin resistance (IR) is a central aetiological phenomenon observed in most of the affected women. First report in 1980 (1), documenting the association between PCOS and hyperinsulinemia, was followed by numerous researches about insulin action in PCOS. At the end of 1980s, the direct effects of insulin on ovarian steroidogenesis, other than metabolic aspects were recognized (2). Thereafter, hyperinsulinemia was suspected to play a role in the pathogenesis of the disease (3). Actually, today, whether PCOS is a consequence of a specific defect in insulin action or of adaptive hyperinsulinemia associated with any condition of IR remain unknown (4).

IR is defined as increased circulating levels of insulin with intact pancreatic β-cell function (4). In the presence of IR, the cells fail to respond to normal actions of insulin and decreased peripheral glucose utilization occurs. IR is present in 65-70% of the women with PCOS (5,6). The factors associated with IR are obesity, body fat composition, muscle mass and ethnicity (7). However, even lean women with PCOS have IR (8). Obesity, another associated symptom in PCOS women, is highly prevalent in PCOS (9). IR shows exacerbation by obesity and up to 80% of obese women with PCOS exhibits IR (8). Nevertheless, independent from adiposity, IR in women with PCOS contributes to reproductive and metabolic complications (10). IR is most prevalent and severe in women with the classic NIH PCOS pheno-type involving hyperandrogenism and anovulation. PCOS diagnosed with Rotterdam criteria with regular cycles are metabolically less abnormal (11-13).

The increased prevalence of impaired glucose tolerance (IGT) and type 2 diabetes (T2D) diabetes in PCOS is widely documented (OR 2.48, 95% CI 1.63-3.77 and OR 4.43, 95% CI 4.06-4.82) (14). The prevalence of IGT and T2D is reported as 30% and 10% in obese and 10% and 1.5 % in lean women with PCOS, respectively (15). As a result, in long-term, PCOS quadruples the risk of T2D (16). The reported conversion rate from IR to diabetes is 8.7% per year (17). In addition, PCOS contributes to 40% of T2D in reproductive age women (18). Substantially increased risk of T2D in PCOS highlights the need for prevention and management. Other long-term consequences of IR in PCOS are non-alcoholic fatty liver disease, hypertension, cardiovascular disease, and endometrium cancer (3,19). In this narrative review about PCOS, cellular and molecular defects in insulin action, insulin receptor function, genetic trait of IR, hyperandrogenemia related IR is summarized. The assessment of IR in PCOS is being discussed and the evidence about effective treatments is reviewed, as well.

Molecular and Cellular Defects, Insulin Receptor and Signaling Pathways: Insulin as a glucose regulating hormone, acts by stimulating glucose uptake in adipocytes, skeletal and cardiac muscle and decreasing hepatic glucose production. It also inhibits lipolysis and decreases free fatty acid levels in blood (20). To understand the defects in insulin action in PCOS, normal mechanisms on molecular levels should be thoroughly understood. Insulin acts through its receptor (IR), a heterotetramer made of two dimers. It consists of an extracellular ligand binding domain, an α and β subunit spanning the membrane with intrinsic tyrosine kinase activity. Binding of a ligand results in activation of tyrosine kinase and auto phosphorylation of tyrosine residues. Signal transduction to intracytoplasmic region occurs via transmitters designated as insulin receptor substrates (IRS 1-4), src homolog and collagen homolog (shc), and APS (Adaptor protein with PH and SH2 domain). Two pathways are initiated upon insulin receptor binding. One pathway moves through IRS-1/2, acting on glucose metabolism, antilipolysis and protein synthesis (21). The other pathway concludes with mitogenic and other gene-regulatory actions of insulin. Increased glucose utilization and decreased hepatic glucose production are the final effects. Serine phosphorylation of the insulin receptor and IRS inhibits signal transduction in addition to the tyrosine phosphatase action terminates insulin effects.

In women with PCOS, decreased insulin sensitivity in adipocytes with decreased auto phosphorylation after binding to the receptor was previously documented (22). In PCOS, the post-receptor defect has been confirmed also in cultured skin fibroblasts and in skeletal muscle (23). Other than decreased phosphorylation, altered glucose transporter molecules (GLUT4) were also suggested for lower efficacy of insulin in PCOS. An additional defect in remaining fibroblasts without post-receptor defect was downstream insulin signaling (24). Mutations of genes related with insulin receptor and associated molecules are blamed for decreased insulin receptor binding or phosphorylation especially in adipocytes (4). These changes explain the complexity of the disease. Defective mitochondrial oxidative metabolism is another pathogenic mechanism related to IR (25). In PCOS, resistance to metabolic effects of insulin is selective. In PCOS, while IRS1-2 pathway has been suppressed, activation of mitogenic signaling pathways in skeletal muscle has been documented (26). As a result, PCOS is characterized by decreased ability of insulin to mediate metabolic effects. In PCOS, if pancreatic reserve is intact, increased insulin levels are observed to achieve glucose hemostasis. In case of insufficient insulin secretion from pancreatic beta cells, IGT and T2D will develop subsequently. In PCOS, decreased hepatic insulin extraction contributes to hyperinsulinemia, as well. Additionally, catecholamine-stimulated lipolysis increases in PCOS and increased free fatty acids contribute to hepatic IR(4). In vivo insulin action is profoundly decreased in skeletal muscle secondary to signaling defects, but hepatic insulin resistance is present only in obese women with PCOS (27).

Genetic Trait of IR in PCOS:Suggestion of genetic susceptibility of PCOS and IR depends on several observations. Familial aggregation, phenotypic similarity between PCOS and the syndromes associated with IR, persistence of insulin dysfunction in cultured cells and insufficiency in explaining pathogenesis of PCOS are the findings suggesting genetic basis of disease. Clear evidence suggests that PCOS has genetic basis in etiology (28)and genetic variations in a complex trait has been observed. Insulin gene is located in 11p15.5, between the genes for tyrosine hydroxylase and the insulin-like growth factor II. Preliminary studies suggest a candidate locus on chromosome 19p13.2, near to the insulin receptor gene (29). From small sample size studies, an association between variable numbers of tandem repeats (VNTR) locus on insulin gene with disease suggests an inherited risk for developing T2D (30). However, studies in large populations are required to confirm the definitive relationship (31). The low strength of these studies and heterogeneity of diagnosis contribute to the fact that suggesting a strong association between IR in PCOS and any of the known genes related to insulin signaling and glucose hemostasis is difficult (32).

Hyperandrogenemia and IR in PCOS:Hyperandrogenemia is the one of the main features of PCOS. Signs of hyperandrogenemia are hirsutism, acne, alopecia and seborrhea. In PCOS, the incidence of hirsutism is about 60% (33). Androgenic alopecia is characterised by temporal balding and may be seen in severe cases of hyperandrogenism. Acanthosisnigricans, brown to black hyperpigmentation of the skin is found to be associated with endocrine syndromes like IR and hyperandrogenism seen in PCOS.

Hyperinsulinemia in PCOS not only has affects on carbohydrate mechanism, but also have direct effects on ovarian steroidogenesis in vitro, stimulating theca cells to synthesize androgens (2). Insulin like growth factors (IGF-1) and insulin share similar mechanisms both of which have similar tyrosine kinase receptors and signal through IRSs (34). IGF-1 and insulin receptors are both present in ovaries, with direct effects on steroidogenesis. Because resistance to insulin is selective, ovarian insulin action is preserved. At supraphysiological levels of insulin, 17-alpha-hydroxylase is induced in theca cells resulting in increased androgen synthesis. Furthermore, theca cells of PCOS women are more sensitive to the androgen stimulating actions of insulin (35). Moreover, hyperinsulinemia also plays role in augmenting the effect of increased LH stimulus in PCOS (35). It also decreases sex hormone-binding globulin synthesis in the liver, which causes increased free androgen levels (36). In addition, high insulin levels stimulate adrenal ACTH-induced androgen synthesis. So,hyperinsulinemia plays a pivotal role in hyperandrogenemia and PCOS. On the other hand, androgens can directly alter insulin action in target tissues like skeletal muscle and adipocytes (4). Androgens reduce insulin-sensitizing adiponectin (4) and hyperandrogenemia can produce IR itself by altering adipokine secretion and by increasing visceral adipocity. As a result, androgen effects on insulin action contribute to IR in PCOS. However, the starting point of this vicious cycle about androgens and IR has not been clearly defined yet.

Assessment of IR in PCOS:Although not all organizations recommend routine IR screening for women with PCOS, IR screening is of potential benefit to guide diagnostic and therapeutic management. Up today, several methods were developed for diagnosing IR. However, the gold standard method is Euglycemic hyperinsulinemic glucose clamp technique' described by DeFronzo et al. in 1979 (37). This technique involves continuous insulin infusion with continuous glucose administration to maintain steady glucose levels (37). The amount of glucose that is infused is equal to the levels taken up by the tissues and can be used as a measure of peripheral sensitivity to insulin (37). The cut-off for the diagnosis IR is 4.45 mg/kg/min in euglycemic-hyperinsulinemic clamp technique (37). As this method is somehow grueling, it is only used in clinical experiments. Due to the need of simple and inexpensive methods for assessment of insulin sensitivity, measurements based on fasting glucose and insulin levels have been defined. In women with PCOS, fasting glucose/fasting insulin ratiohas predictive value for IR,if the ratio is <4.5 (38). This is a safe, easy, highly sensitive and specific way for daily practice. The homeostatic model assessment of insulin resistance (HOMA-IR) (insulin/glycemia in µmol/L/22.5)(39) and quantitative insulin sensitivity check index (QUICKI) (1/log insulin + log glycemia in mg/dL)(40) are other measures calculated by fasting insulin and glucose levels.IR was defined as HOMA-IR > 2.1 and QUICKI <0.357 (41). Among the methods for detecting IR, the accuracy of HOMA has been verified using the hyperinsulinemic-euglycemic clamp test (42).

The above-mentioned IR indexes are not useful in individuals with severely IGT or diabetes. For instance, screening with fasting plasma glucose, fail to identify 41% of pre-DM and 20% of DM subjects (43).Therefore, biochemical screening in the form of an oral glucose tolerance test (OGTT) is recommended to evaluate any IGT and T2D (27). As obese PCOS (BMI >30 kg/m2, or >25 in Asian populations) patients are at higher risk for IGT and T2D, screening with 75 gr OGTTis indicated (27). Screening should be performed in the following conditions as well: hyperandrogenism with anovulation, acanthosis nigricans, and in women with a family history of T2D or gestational diabetes mellitus (27).Many international specialist societies recommend an OGTT test every 2 years in all women with PCOS and every year in those with additional risks (age, parenteral history of diabetes, physical inactivity, smoking, oral contraceptive pill use)(44).

Treatment and Follow-up of Women with IR and PCOS:Lifestyle modification should be the first approach to all of the women with PCOS as well as the patients with IR. Considering the implications of excess weight on reproductive and metabolic consequences of PCOS and IR, obese or overweight PCOS patients should be firstly encouraged about weight loss and exercise (45) with a healthy diet including less fat and regular exercise. Lifestyle change with a >5% weight loss in overweight women with PCOS reduces T2D risk by approximately 50-60% (44) and a weight loss about 7% significantly improves hyperandrogenemia. Understanding the importance of these modifications is the mainstay for treatment and prevention of unpleasant long-term consequences of the syndrome.

Metformin: Insulin sensitizers improve insulin action by increasing insulin sensitivity. Metformin is the most common insulin sensitizer used for glucose intolerance both in T2D and PCOS (45). Today, none of the anti-diabetic agents have US Food and Drug Administration (FDA) approval for the treatment of PCOS. However, metformin is the preferred agent due to safest risk-benefit ratio (46). Metformin is a biguanide-used as first-line pharmacologic therapy. It acts by reducing gluconeogenesis and glycogenolysis in the liver, in addition by increasing peripheral glucose uptake by skeletal muscle and adipose tissue (47).

If diet and exercise fails as an initial treatment approach in PCOS, metformin is the choice for pharmacologic therapy (48). On the other hand, metformin can be used for prevention of T2D in women with PCOS and IGT, and management of obesity (49).In women with PCOS, metformin has weight reducing effects compared to placebo (50). Metformin, for the above-mentioned indications, is readily available and low cost drug. For the metabolic problems associated with PCOS, metformin improves hyperinsulinemia, altered lipid profile and hypertension (51,52). Although, the use of metformin to treat IR alone without IGT is theoretically useful, the studies supporting clinical outcomes does not support this (53). Long-term effects of metformin on clinical and endocrine features were investigated andthe most striking advance of metformin was on observed in menstrual irregularities (54). At the same time, the insulin lowering effects of metformin can decrease circulating androgen levels (55). Treatment with metformin for 6 months reduces free testosterone and 17-OH progesterone levels in response to GnRH-agonist testing (54).However, the effects of metformin on acne and hirsutism need sufficiently powered studies. Recent data shows that metformin is less effective than the oral contraceptive pill when used for acne and hirsutism(49).

*Thiazolidinediones:*Thiazolidinediones (TZDs) are Peroxisome Proliferator Activator Receptor (PPAR) γ agonists. TZDs are insulin sensitizers acting by increasing fatty acid uptake into adipose tissue and by decreasing the expression of 11γ-hydroxysteroid-dehydrogenase type 1 (56). The TZDs, rosiglitazone, pioglitazone and troglitazone differ in their chemical structures and binding affinities for PPAR γ. The studies concerning troglitazone in PCOS patients showed decreased levels of circulating androgen and insulin (3,57). Additionally, in obese women with PCOS, troglitazone improves ovulation and hirsutismus (58).However, after it became clear that troglitazone treatment is associated with severe liver toxicity, troglitazone was withdrawn from the market.The other TZDs, pioglitazone and rosiglitazone, are the only insulin sensitizing agents available for clinical use, approved by FDA for use in T2D. These agents reduce circulating androgen levels and improve IR and glucose tolerance (59). Although TZDs are effective;weight gain, increased coronary artery disease, and myocardial infarction are practical limitations associated with pioglitazone and rosiglitazone(59,60).

In conclusion, the currently available data does not favor long-term use of insulin sensitizing agents, either metformin or TZDs, to improve cardiovascular morbidity, mortality, or to decrease the incidence of endometrial cancer or psychological disorders (61). In women with PCOS, the use of insulin sensitizing agents should be under the treatment guidelines for IGT or T2D (61).

Myo-inositol and D-Chiro-inositol: In the insulin pathway inositolphosphoglycans (IPGs) are second messengers(62,63). When insulin binds to its receptor, IPGs are generated by hydrolysis of glycosylphosphatidyl inositol lipids located at the outer leaflet of the cell membrane(64).Epimerization of the six hydroxyl-groups of inositol leads to the formation of up to nine stereoisomers, including myo-inositol (MI) and D-chiro-inositol (DCI). MI and DCI are both insulin mimetic when administered in vivo enhancing the physiological insulin-receptor activity and reducing glucose levels in serum (65). An epimerase converts MYO into DCI, in insulin dependent manner by with each tissue having its own particular conversion rate (66,67). In T2D, epimerase activity is reduced where less DCI is synthesized and the DCI/ MI ratio is reduced (68-71). In women with PCOS, a defect in tissue availability or altered metabolism of inositol or IPGs mediators has been suggested as possible contributing factor to IR(72). Both MI and DCI have been used in the treatment of IR in PCOS (73,74). In a systematic review of randomized controlled trials evaluating the effects of MI in women with PCOS, MI decreased insulin plasma levels, glucose/insulin, HOMA index as well as other hormonal parameters(75).According to the results from randomized controlled trials the authors concluded that MI supplementation induces the reduction of insulin levels probably by inducing an increase of IPG levels; therefore, higher IPG levels could be able to amplify insulin signal(75). Regarding the favorable effects of MI through the reduction of insulin plasma levels, MI seem to be an alternative and safe treatment for IR in women with PCOS.

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