The importance of insulin resistance in polycystic ovary syndrome

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The most widely accepted criteria for the diagnosis of polycystic ovary syndrome (PCOS) are hyperandrogenism and/or hyperandrogenemia and oligo-ovulation, with the exclusion of other hyperandrogenic disorders (1). Thus, androgen elevation defines the syndrome. This definition permits a wide range of presentations and clinical appearances, that is, a continuum of patients with PCOS. Androgen excess, of ovarian and often also adrenal origin, underlies the symptoms of hirsutism, acne, alopecia, and seborrhea, and treatment with anti-androgens is the most effective method of reducing these complaints. Hyperandrogenemia may also be responsible for the weight gain present in about 50% of cases.

What has been increasingly recognized is that PCOS is associated with insulin resistance and compensatory hyperinsulinemia. While not required for the diagnosis of PCOS, insulin resistance appears to cause or exacerbate hyperandrogenemia in many patients, as evidenced by the reduction in ovarian and adrenal androgen levels with insulin-sensitizing therapy (2–6). More importantly, insulin resistance leads to hypertension, diabetes, and cardiovascular disease, the most significant complications of PCOS.

Detection of Insulin Resistance in PCOS

Exactly what proportion of women with PCOS actually have insulin resistance depends on the method of measurement. The gold standard, the euglycemic clamp technique, is invasive and used only as a research tool. Other methods, such as the frequently sampled IV glucose tolerance test, are also impractical. Most popular in clinical settings is the fasting glucose-to-insulin ratio (7). Unfortunately, this only gives information about one moment in time and may fail to detect insulin-resistant subjects. In addition, the ratio is not valid if beta cell function has deteriorated and glucose intolerance is already present (8). We have found the homeostasis model assessment equation (9) to be a useful tool; however, this is also based on a single fasting measurement of glucose and insulin.

A recent study suggested that oral glucose tolerance testing is more sensitive than the glucose-to-insulin ratio in the detection of impaired glucose tolerance in adolescents with PCOS (10). The oral glucose tolerance test may be the test that gives the most information with the least patient burden. In any case, estimates of the prevalence of insulin resistance in PCOS range from a minority to the vast majority, with higher detection rates when using more sensitive methods (11–14). Also, a woman with PCOS may test negative for insulin resistance when young and thin but develop it with time. Hyperinsulinemia appears to worsen spontaneously with age in adult women with PCOS without worsening of hyperandrogenemia (15). Obesity, when present, also leads to insulin resistance; however, PCOS confers a risk of insulin resistance beyond that caused by obesity (16, 17).

Insulin Resistance and Increased Risk of Atherosclerosis

Much more important than how many patients with PCOS have insulin resistance is the fact that these women are at increased risk of having the metabolic syndrome (syndrome X). This is characterized by dyslipidemia, central obesity, hypercoagulability, impaired fibrinolysis, and an increased risk of development of hypertension, type 2 diabetes mellitus, and cor-
onary artery disease. Hyperinsulinemia has been found to correlate with a profile of increased cardiovascular risk factors in PCOS (18). Older women with PCOS have been found to have a greater burden of atherosclerosis than normal women as measured by carotid intima-media thickness on ultrasound (19). Adolescents with PCOS and impaired glucose tolerance lack the normal nocturnal decline in blood pressure (20). As women with PCOS reach their fourth and fifth decades, the risk of hypertension is increased three-fold and of myocardial infarction up to seven-fold (21, 22). By their fifth and sixth decades, women with and without PCOS appear to have similar cardiovascular risk factor profiles, but those with PCOS have a higher prevalence of diabetes and coronary artery disease (23), suggesting that they developed adverse risk factors at an earlier age, leading to increased long-term risk.

Chronic inflammation, a predisposing factor to coronary heart disease, is increased in PCOS, as evidenced by elevated C-reactive protein levels that correlate with insulin resistance and obesity, not androgen levels (24). PCOS has also been associated with impaired fibrinolysis (25) and elevated homocysteine levels (26). Elevated levels of plasminogen activator inhibitor-1 (PAI-1), which inhibits fibrinolysis, were found in women with PCOS and were correlated with insulin levels (27). Endothelin-1, a marker of abnormal endothelial function, has also been found to be elevated in PCOS; treatment of insulin resistance reduced these levels (28).

Lipid abnormalities characteristic of the metabolic syndrome, depressed HDL cholesterol levels and elevated triglyceride levels, as well as elevated LDL cholesterol levels, have also been found in women with PCOS (29–34). Insulin resistance/hyperinsulinemia, as opposed to hyperandrogenemia, often appears to be the main predictor of these lipid abnormalities as well as elevated levels of atherogenic small, dense LDL cholesterol in PCOS (31–34).

Insulin Resistance and Increased Risk of Diabetes

PCOS is a powerful risk factor for impaired glucose tolerance and type 2 diabetes mellitus. In one model of the pathogenesis of type 2 diabetes, insulin resistance is the primary defect and diabetes occurs once the pancreatic beta cells become unable to compensate (35). Insulin-resistant patients with PCOS maintain normal glucose levels by insulin hypersecretion. These patients are likely to be at an increased risk of beta cell exhaustion and development of type 2 diabetes mellitus (36).

In a study of 254 women with PCOS (17), 31% had impaired glucose tolerance, and 7.5% had type 2 diabetes. This represents a huge increase over population expectations. In the nonobese patients with PCOS, 10.3% had impaired glucose tolerance and 1.5% had diabetes, rates almost three times that of normal women. Up to 40% of patients with PCOS have diabetes or impaired glucose tolerance, often with a family history of diabetes (37). Untreated, impaired glucose tolerance progresses to diabetes at a rate of 11% per year (38). In the Nurses’ Health Study, the risk of development of diabetes was increased two-fold among women with long or irregular menstrual cycles, including the nonobese women (39).

Insulin Sensitization Therapy in PCOS

Since the complications associated with insulin resistance, particularly development of diabetes and atherosclerosis, are potentially deadly, in our patient care we emphasize the detection and treatment of insulin resistance. The most studied agent to treat insulin resistance in PCOS is metformin. Metformin has repeatedly been found to lower T levels, increase sex hormone–binding globulin (thus reducing bioavailable T levels), improve menstrual frequency, decrease weight, and facilitate pregnancy (3, 4, 40, 41). One long-term study found that metformin-induced improvements lasted up to 26 months (40). Metformin treatment is also associated with increased HDL cholesterol, decreased LDL cholesterol, and decreased triglycerides (42) as well as improved endothelial function (43). In women with PCOS, treatment with metformin has also decreased PAI-1 and Lp(a) levels (44).

The most commonly studied and used target doses in PCOS are 500 mg three times a day or 850 mg twice a day. The main drawback of metformin use is gastrointestinal intolerance, which often can be avoided by starting with a low dose and titrating to the goal dose over a few weeks. An overview of several trials involving the use of metformin in PCOS (over 360 patients in total) revealed no cases of lactic acidosis in these young women with normal renal function (41).

Most experience with thiazolidinedione insulin sensitizers used troglitazone (2), which has been removed from the market because of hepatotoxicity. Since thiazolidinediones tend to cause weight gain and fluid retention and have been studied less in PCOS, metformin is the insulin sensitizer of choice at this time.

Regarding the long-term effects of treating insulin resistance in PCOS, studies are needed to demonstrate the reduction in rates of diabetes and coronary artery disease with insulin-sensitizing therapy. Large trials in other populations, however, suggest that long-term insulin sensitization may be beneficial. In the Diabetes Prevention Program, subjects with impaired glucose tolerance who were treated with metformin (850 mg twice daily) experienced a 31% reduction in the incidence of diabetes (38). Of note, in this trial, an intensive program of diet and exercise, also expected to ameliorate insulin resistance, reduced the incidence of diabetes by 58%. In the United Kingdom Prospective Diabetes Study, overweight type 2 diabetics treated with metformin experienced a decreased myocardial infarction and stroke rate compared
with those on conventional therapy and a decreased all-cause mortality, total diabetes-related endpoints, and incidence of stroke compared with those treated with insulin or sulfonylurea therapy (45).

Until proven by randomized, controlled trials of metformin use in PCOS, we assume that the prevention of diabetes and cardiovascular events and improved survival attributed to metformin in these studies will apply to women with PCOS. Given the increased risk of atherosclerosis in women with PCOS, blood pressure control, smoking cessation, lipid lowering, diet modification, and exercise are needed in addition to insulin sensitization.

Metformin restores ovulation in a significant proportion of patients with PCOS and has resulted in pregnancy (4, 40, 46). Metformin also increases the efficacy of clomiphene in clomiphene-resistant patients (47, 48). Recent small studies also suggest that metformin continued during pregnancy reduces the high rates of gestational diabetes and first-trimester spontaneous abortion characteristic of PCOS (49–51). No teratogenic effects were observed; further trials with similar results will result in an increased use of metformin during pregnancy in women with PCOS.

The Importance of Insulin Resistance in PCOS

While it is true that not all women with insulin resistance have PCOS, those who do have PCOS are more likely to come to the attention of the medical community. This opportunity to diagnose and treat insulin resistance and possibly reduce long-term morbidity and mortality in these women is critical and must not be overlooked while attention is being focused on their fertility and cosmetic problems. While hyperandrogenemia and concomitant hirsutism, acne, or infertility are certainly troublesome to a woman, an increased risk of developing diabetes and atherosclerosis has the potential to shorten her lifespan. Thus, we recommend an investigation to detect insulin resistance in every hirsute woman. Treating insulin resistance, when present, with metformin may improve fertility, facilitate weight loss, improve the lipid profile, reduce the incidence of diabetes, and prevent atherosclerosis, myocardial infarction, and stroke. Clinical trials verifying these benefits in patients with PCOS are urgently needed.

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