REVIEW ARTICLE

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Insulin Resistance, Polycystic Ovary Syndrome and Metformin

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Abstract

Polycystic ovary syndrome (PCOS) is the most common disorder of ovarian function in premenopausal women. PCOS is characterised by chronic anovulation and androgen excess with clinical manifestation of irregular menstrual cycles, hirsutism and/or acne. Insulin resistance with resultant hyperinsulinaemia, irrespective of excess weight or frank obesity, has been reported in patients with PCOS, and, as insulin has a direct effect on ovarian androgen production *in vitro*, insulin resistance may play a crucial role in the physiopathology of PCOS. Although the molecular mechanism(s) of insulin resistance in PCOS is unclear, excessive insulin-independent serine phosphorylation of the β subunit of the insulin receptor, as reported in some patients with PCOS, has been put forward as a new mechanism for insulin resistance.

Insulin-sensitising agents have recently been investigated for their role in the short term treatment of insulin resistance in PCOS. Controlled studies have shown that metformin administration, by promoting bodyweight loss, can decrease fasting and stimulated plasma insulin levels. However, other studies have shown metformin 500mg 3 times daily to decrease insulin secretion and to reduce ovarian production of 17α-hydroxyprogesterone with recovery of spontaneous or clomifene-induced ovulation, independently of weight loss. These findings suggest a new indication for metformin and present insulin-sensitising agents as a novel approach in the treatment of ovarian hyperandrogenism and abnormal ovulation in PCOS. They also suggest that long term administration of metformin might be helpful in treating insulin resistance, thus reducing risks of type 2 (non–insulin-dependent) diabetes and cardiovascular disease in these patients.

1. Background to Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is generally considered to be the most frequent cause of hyperandrogenism and chronic anovulation. Hirsutism, recurrent acne with hyperseborrhoea and/or alopecia, oligomenorrhoea and infertility are the main clinical symptoms, although PCOS shows great variation and heterogeneity of clinical expression. Ultrasound examination generally shows enlarged ovaries with increased numbers of subcapsular follicle cysts and some degree of hyperplasia of the stroma. These criteria form the basis of consensus proposals for the diagnosis of PCOS.[1] According to these criteria, the prevalence of PCOS has been estimated to be as high as 16% within the normal female population.[2] Interestingly, although 20% of patients fulfilling ultrasound criteria for polycystic ovaries maintained

normal ovulation with no evidence of hyperandrogenism, most showed moderate hirsutism and/or acne with some menstrual and ovulatory abnormalities. It is generally believed that the clinical features presented by polycystic ovaries are reversible and represent a syndrome rather than a disease. However, accumulating evidence shows that insulin resistance and hyperinsulinaemia may expose patients with PCOS to an increased risk of type 2 (non–insulin-dependent) diabetes[3] and to the development of premature cardiovascular disease with dyslipidaemia.[4-6]

2. Insulin Resistance in PCOS

Obesity with upper body fat distribution is associated with PCOS in many patients who exhibit hyperinsulinaemia and/or insulin resistance. However, insulin resistance is not restricted to obese patients and can be seen in lean PCOS patients with such upper body fat distribution. Insulin receptors are present on the ovaries, and it has been shown *in vitro* that insulin increases the luteinising hormone (LH)-dependent androgen secretion of thecal cells and that insulin can directly stimulate androgen production by ovarian stroma cells.[7] These findings suggest that hyperinsulinaemia is a key contributor to the complexity of polycystic ovary physiopathology. However, because most women with type 2 diabetes have no clinical history of PCOS, it is unlikely that chronic hyperinsulinaemia *per se* is a prerequisite for developing PCOS. Some other predisposing genetic or environmental feature(s) may be essential for ovarian hyperandrogenism, and such arguments have prompted new research for candidate genes in PCOS family clustering.[7]

2.1 Molecular Mechanism(s) of Insulin Resistance in PCOS

There is evidence that a downstream defect of insulin receptor signalling is responsible for insulin resistance in PCOS.[8] The transduction factors involved in the action of insulin are numerous, but none has been identified as more specifically involved in PCOS-insulin resistance than any others. However, Dunaif et al.[9] reported that 50% of nonobese women with PCOS showed excessive insulin-independent serine phosphorylation of β subunits of insulin receptors. The molecular basis of this newly identified mechanism of insulin resistance has not been clarified to date, but should be congruent with the hypothesis that PCOS might have a genetic component with an autosomal dominant mode of transmission.[10,11]

3. Treatment of PCOS

PCOS treatment has several goals: (i) suppression of hyperandrogenism, with an expected improvement of hirsutism and/or acne; (ii) restoration of normal ovulation when fertility is impaired; and (iii) attenuation of the long term risk of type 2 diabetes and cardiovascular disease. Ovarian androgen suppression can be achieved by administration of estrogens and progestogens. Antiandrogens such as cyproterone acetate and/or spironolactone are useful tools for treating hirsutism and acne. However, androgen suppression does not improve obesity, hyperinsulinaemia and/or insulin resistance.[8] Furthermore, patients experience considerable distress upon recurrence of symptoms if treatment is stopped.

3.1 Dietary Weight Loss

In PCOS patients, a low calorie diet resulting in bodyweight loss has been shown by several investigators to decrease fasting insulin levels and to improve hyperandrogenism by increasing sex hormone-binding globulin (SHBG) and decreasing androgen levels.[12-18] Most of these studies have shown that dietary weight loss can also restore ovulation (to the point of allowing conception) even when ideal bodyweight is not attained.[15-19] Decreases in fasting and glucose-stimulated insulin levels can be obtained by dietary manipulation in obese women with and without PCOS. In contrast, data show that dietary weight loss achieved reductions in circulating levels of 17-hydroxyprogesterone in obese women with PCOS but not in obese women with normal ovulation.[20] These findings confirm that ovarian overproduction of

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17-hydroxyprogesterone is a specific feature of PCOS[21] and that ovarian hyperactivity can be reduced through the reduction of insulin secretion.[20]

Results of some studies have shown that dyslipidaemias such as low levels of high density lipoprotein cholesterol and high levels of triglyceride are improved by diet in hyperandrogenic and obese women.[13,16] It is concluded from these studies that weight loss on a long term basis should be encouraged to maintain short and long term health benefits in patients with PCOS.[22]

3.2 Metformin: An Indirect Insulin-Sensitising Agent

The biguanide metformin is commonly used to lower blood glucose levels.[23] Metformin treatment has been reported to decrease fasting insulin levels in women with type 2 diabetes.[24] Although the molecular mechanisms involved in the action of metformin are still incompletely understood, the drug is known to increase peripheral glucose uptake and to lower hepatic glucose output. Several studies have investigated the potential benefit of metformin administration in obese patients with PCOS.[25]

Velazquez et al.[26] were the first to report the effect of metformin 500mg 3 times daily for 8 weeks in 26 moderately obese women [body mass index (BMI) <27 kg/m^2 in 13 patients and >27 kg/m^2 in the other 13]. With metformin, BMI decreased by 1.5%, waist-to-hip ratio by 2.8% and the area under the curve of plasma insulin level *versus* time during oral glucose tolerance testing by 35%. Metformin also significantly reduced plasma levels of LH and androgen and increased levels of follicle-stimulating hormone (FSH) and SHBG. Interestingly, the decrease in the area under the curve of plasma insulin level *versus* time was a significant independent positive determinant of the reduction in testosterone levels. Normal menstrual cycles resumed in all 7 patients who received metformin, and 3 patients became pregnant. The authors also showed that a 6-month course of metformin improved menstrual cycle regularity and fertility in 22 patients with PCOS,[27] and that metformin decreased plasma plasminogen activator inhibitor-1 and lipoprotein (a) levels with a significant association with decreased fasting insulin levels.[28]

However, 2 controlled studies failed to confirm these results. Acbay and Gündogdu,[29] in a single-blind study, compared 10 weeks of metformin 850mg twice daily with 8 weeks of placebo treatment in 16 insulin-resistant patients with PCOS. They reported that, with BMI at steady state, metformin did not decrease insulin sensitivity or fasting plasma levels of insulin, androgens and gonadotropins, or improve lipid profiles. Similar results were published by Ehrmann et al.,[30] who studied 22 obese nondiabetic women with PCOS before and after treatment with metformin 850mg 3 times daily for 12 weeks. They showed that, with weight maintenance, metformin did not improve oral glucose tolerance, insulin sensitivity or the insulin secretory response to glucose administration. In addition, metformin did not affect levels of free testosterone, basal and gonadotropin-releasing hormone (GnRH) agonist-stimulated LH, FSH and 17-hydroxyprogesterone.

In contrast, Nestler and Jakubowicz[31] performed a placebo-controlled study in 24 obese women (mean BMI 34.1 kg/m^2) and reported that metformin 500mg 3 times daily decreased the area under the plasma insulin level *versus* time curve after oral glucose administration, increased SHBG levels, decreased LH and free testosterone levels and significantly reduced basal and leuprolide-stimulated 17-hydroxyprogesterone levels. These parameters remained unchanged in the placebo-treated group. These authors extended their investigation to lean patients with PCOS (mean BMI 21.7 kg/m^2) with significantly higher basal and GnRH-stimulated 17-hydroxyprogesterone levels than ovulating lean women.[32] Furthermore, randomised administration of metformin 500mg 3 times daily or placebo clearly showed that metformin decreased the area under the curve of plasma insulin level *versus* time and basal and GnRH-stimulated 17-hydroxyprogesterone levels after oral glucose administration, whereas placebo

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had no such effect. These results confirm increased ovarian cytochrome P450c17α activity as a specific endocrine ovarian disorder in both non-obese[32] and obese patients with PCOS.[31] They also support the concept that increased ovarian cytochrome P450c17α activity is linked to hyperinsulinaemia and suggest that metformin is useful in improving both insulin and ovarian androgen excess in lean women with PCOS, independently of weight loss.

The effect of metformin on glucose utilisation rate, measured during a 2-step euglycaemic hyperinsulinaemic clamp, has been investigated by Diamantis-Kandarakis et al.[33] in a noncomparative study. They reported that metformin did not reduce fasting or glucose-stimulated plasma insulin levels but induced an increase in glucose utilisation rate that was independent of weight loss.

3.3 The Role of Metformin in Restoring Ovulation in Patients with PCOS

Since the early study by Velazquez et al.,[26] it has been shown that metformin treatment can restore regular menstrual cycles with eventual pregnancy in patients with PCOS. Morin-Papunen et al.[34] treated 22 obese patients with PCOS by giving metformin 500mg 3 times daily for 4 to 6 months; they reported that 11 women experienced more regular cycles with no changes in BMI, lipid profile or hirsutism but with significant decreases in circulating levels of testosterone. They later reported that leptin concentration was decreased during the first 2 months of metformin administration (with unchanged BMI), but that it was slightly increased after 4 to 6 months.[35]

The most impressive demonstration of the benefit of metformin in the restoration of ovulation was reported by Nestler et al.[36] These investigators studied 61 obese women with PCOS who failed to ovulate during treatment with clomifene 50mg daily for 5 days and confirmed that metformin 500mg 3 times daily reduced insulin secretion, whereas placebo had no effect. Spontaneous ovulation was restored in 12 (34%) of the 31 patients during metformin administration. Furthermore, in patients who failed to ovulate spontaneously, clomifene treatment resulted in ovulation in 21 (90%) who received metformin compared with only 8% of those who received placebo.[36]

3.4 Dietary Weight Loss and Metformin

Crave and co-workers[37] compared the effect of a low calorie diet (1500 Kcal/day) in hirsute obese (mean BMI 34 ± 1 kg/m^2) patients who were randomised to either metformin 850mg twice daily or placebo for 4 months. Dietary restriction resulted in significant decreases in BMI and fasting insulin, androstenedione and non–SHBG-bound testosterone levels, but no additional benefit of metformin over diet alone was reported. However, although all the patients were obese and hirsute, the mean BMI of the control group was lower and the mean plasma androstenedione level higher than those of the metformin group, indicating some heterogeneity between patients.

4. Discussion

Review of the available data on use of the insulin-sensitising agent metformin strongly supports the concept that ovarian androgen excess is linked to insulin secretion in patients with PCOS. In studies showing reduced insulin secretion after metformin administration, significant increases in SHBG and decreases in testosterone, androstenedione and basal and GnRH-stimulated 17-hydroxyprogesterone levels were also reported. The mechanism(s) of this effect of metformin remains to be clarified. It is agreed that decreases in BMI and/or in upper body fat distribution bring rapid and real improvements in insulin sensitivity, and consequently reduce androgen excess in obese PCOS patients. Results after metformin administration in lean patients with PCOS[32] confirm that metformin has a specific molecular effect on insulin sensitivity and/or on the insulin transduction signal.

Because metformin has not been shown to have any teratogenic effects,[38] it can be considered to be a new means of restoring ovulation in many PCOS patients. In addition, and more importantly, the benefits of metformin administration for meta-

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bolic and lipid profiles have opened a new field of application of insulin-sensitising agents in the primary prevention of type 2 diabetes and reduction of cardiovascular risk in patients with PCOS.[3-6] Further randomised clinical trials are now required to facilitate the development of a novel treatment strategy for bodyweight control in patients with PCOS.

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