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Treatment of Polycystic Ovary Syndrome with Insulin Sensitizer

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Abstract: Polycystic ovary syndrome (PCOS) is a common disorder of women in reproductive age characterized by clinical and biochemical disorders, and it´s main symptoms might appear from adolescnce. PCOS (polycystic ovary syndrome) is characterized by menstrual disorders (amenorrhea or oligomenorrhea), anovulation, hyperandrogenism and polycystic change of ovaries. Insulin-resistant hyperinsulinism is an important extrinsic factor in the steroidogenic dysregulation of PCOS and lowers the treatment of ovulation. I investigate the relation between hyperinsulinemia and PCOS and the effect of metformin, insulin sensitizer in treatment of PCOS by case-control study of 30 patients with clomiphene citrate-resistant PCOS and 30 women with regular menstrual cycles. Patients with PCOS had hyperinsulinemia compared with control group significantly. The ovulation rate of laparoscopic ovarian drilling plus metformin therapy was 95.5% (21/22).

Keywords: Polycystic Ovary Syndrome, Hyperinsulinemia, Metformin

1. Introduction

Polycystic ovary syndrome (PCOS) is a common disorder of women in reproductive age characterized by clinical and biochemical disorders but the mechanism of anovulation remains uncertain [1], [2]. The typical gross morphology of anovulatory polycystic ovaries is the presence of multiple antral follicles 2–8 mm in diameter, which signifies arrest of follicle development prior to the preovulatory phase. Ovulation can be induced in most cases by treatment which increases serum concentrations of follicle-stimulating hormone (FSH), but while serum levels of FSH are slightly lower than in the early follicular phase of the normal cycle, FSH deficiency is unlikely to be the primary abnormality in PCOS. Although arrested antral follicle growth probably reflects the abnormal endocrine environment in PCOS (and, particularly the effect of hyperinsulinemia), there is increasing evidence of abnormalities of follicle development from the very earliest, gonadotropin-independent stages. The underlying molecular basis of this fundamental ovarian abnormality remains to be determined.

It is conceivable that androgens may also contribute to the disordered folliculogenesis of PCOS. In granulosa cell cultures, androgens augment gonadotropin-induced cAMP production, and it is therefore possible that the hypersecretion of ovarian androgens, which is typical of the polycystic ovary, can by the same common intracellular mechanism, add to the effects of LH (luteinizing hormone) and insulin on follicle maturation. There is direct evidence for premature responsiveness to LH in antral follicles of anovulatory women with polycystic ovaries. Granulosa cells from follicles of normal ovaries (or from polycystic ovaries from ovulatory women) only secrete estradiol in response to LH when the follicle has reached 9–10 mm in diameter. By contrast, in cells derived from anovulatory women with polycystic ovaries, LH stimulated secretion of estradiol and progesterone in granulosa cells from follicles as small as 4 mm.

Furthermore, antral follicles around 6–8 mm in diameter produced levels of estradiol and progesterone that were similar to those found in the normal, preovulatory follicle. The mechanism of this "premature" response to LH remains to be

determined; it could represent an effect of endogenous hyperinsulinemia (with or without the influence of hyperandrogenism) but may also reflect an intrinsic abnormality of the control of follicle development. Inappropriate steroidogenesis by prematurely advanced antral follicles may also help explain the slightly but significantly lower levels of serum FSH in anovulatory women with PCOS. Using mathematical modeling, it can be predicted that enhanced estradiol production by a proportion of small antral follicles in a "cohort" would—by a negative feedback effect—suppress FSH and prevent further development of "healthy" follicles within that cohort. This would also explain why low-dose FSH—presumably by promoting growth of the healthy follicles—leads to normal development of a dominant follicle in women with PCOS.

Insulin acts primarily on its own receptors to induce tyrosine phosphorylation of insulin–receptor substrates that initiate glucose uptake, protein synthesis, and steroidogenesis. As insulin receptors are located on theca cells, surrounding stroma, granulosa cells, and oocytes, insulin acting alone or as a co-gonadotropin stimulates theca cell androgen production and amplifies LH-stimulated granulosa cell E2 and P4 production.

Insulin sensitivity in PCOS patients, however, is intrinsically impaired from abnormal postreceptor signal transduction. Increased serine, rather than tyrosine, phosphorylation of insulin–receptor substrates in some PCOS patients reduces insulin mediated glucose uptake without affecting steroidogenesis. Consequently, PCOS patients have insulin resistance that is independent of and additive to that of obesity, with combined PCOS and obesity synergistically impairing glucose–insulin homeostasis and contributing to frequent hyperandrogenic symptoms in obese PCOS patients. The resulting hyperinsulinemia promotes ovarian hyperandrogenism by stimulating theca cell 17α-hydroxylase activity, amplifying LH- and IGF-I stimulated androgen production, elevating serum-free T levels through decreased hepatic sex hormone-binding globulin (SHBG) production, and enhancing serum IGF-I bioactivity through suppressed IGF-binding protein production. Acting directly or indirectly through androgens, insulin promotes follicle recruitment in rat organ culture. Hyperinsulinemia from insulin resistance in PCOS patients is positively associated with the degree of multifollicular ovarian development, with hyperinsulinemic PCOS patients undergoing gonadotropin therapy developing a larger number of follicles between 12 and 16 mm in diameter and having a greater risk of ovarian hyperstimulation syndrome than normal insulinemic women.

Moreover, the insulin response to oral glucose tolerance testing in women undergoing gonadotropin therapy is positively correlated with ovarian volume. While still investigational, the insulin sensitizer metformin has been administered to PCOS patients receiving gonadotropin therapy for IVF to determine whether it improves hyperinsulinemia and ovarian hyperandrogenism and if so whether it lowers the risks of exaggerated multifollicular recruitment and ovarian hyperstimulation syndrome. Metformin therapy to PCOS women lowered serum fasting insulin, total and free T as well as E2 levels at oocyte retrieval, enhanced clinical pregnancy and livebirth rates, and diminished the risk of severe ovarian hyperstimulation syndrome.

I investigated the hyperinsulinemia in PCOS and the efficacy of metformin, insulin sensitizer in treatment of PCOS by case-control study of 30 patients with PCOS and 30 women with regular menstrual cycles which was the first attempt in my country.

2. Materials and Method

2.1. Materials

The study group consisted of 30 women with clomiphene citrate-resistant PCOS who presented to Pyongyang maternity hospital with infertility. The control group consisted of 30 healthy volunteer women. The diagnosis of PCOS is based Rotterdam criteria (2003). The Rotterdam criteria define PCOS when two of the three primary features are present: unexplained clinical or biochemical signs of hyperandrogenism, oligo-anovulation, and/or polycystic ovaries. Hyperandrogenism was defined as an elevated serum total testosterone level 80ng/dL (2.4nmol/L). No study patient or control had thyroid dysfunction; galactorrhea; cardiovascular, renal or liver dysfunction, based on clinical examination and routine laboratory findings. The body mass index was calculated in all participants.

2.2. Method

Blood samples from all participants were obtained during days 3 to 7 after spontaneous or progesterone-induced menstruation. All participants underwent a 75g oral glucose tolerance test. After a venous blood sample was obtained for fasting glucose and insulin, 75g of glucose was ingested and further blood samples were obtained 30, 60, 90, and 120 minutes later to measure serum glucose and insulin levels. Plasma glucose was measured by using the glucose oxidase technique (Roche Diagnostics GmbH, Germany). Insulin levels were measured by microparticle enzyme immunoassay (Abbott, Germany). Serum concentration of testosterone was measured by chemiluminescent enzyme immunoassay. Metformin, insulin sensitizer was ingested (starting dose was 500mg and target dose was 1500mg) to patients who did not response to clomiphene and laparoscopic ovarian drilling for 6 months. Follow-up had carried out in all patients.

3. Results and Discussion

3.1. Results

The groups were similar in age, body mass index but women with PCOS had significantly higher serum testosterone than did controls (p=0.001). Table 1 shows age, BMI (body mass index) and serum testosterone in participants.

Table 1. *Age, BMI and serum testosterone in participants. NS (no significant).*

Characteristics	Study group	Control group	P value
age(y)	27.7±6.0	27.5±6.0	*NS*
BMI(kg/m²)	20.7±2.4	20.3±2.7	*NS*
T(ng/mL)	99.0±11.6	58.4±28.5	0.001

Mean serum insulin levels at fasting and at 30, 60, 90, and 120 minutes were significantly higher in the PCOS group than in controls ($p < 0.001$). Table 2 shows mean serum insulin levels at fasting and at 30, 60, 90, and 120 minutes in the PCOS group and controls.

Table 2. *Mean serum insulin levels at fasting and at 30, 60, 90, and 120 minutes in the PCOS group and controls.*

Mean serum insulin levels	Study group	Control group	P value
Fasting(μIU/mL)	13	9	0.01
30min	87	45	0.001
60min	85	39	0.001
90min	90	26	0.001
120min	70	22	0.001

8 of 30 patients with PCOS treated with metformin and the cumulative ovulation rate was 75% (6/8) at 24 months follow-up. 22 patients treated with laparoscopic ovarian drilling and the cumulative ovulation rate was 77.3% (17/22) at 24 months follow-up. 5 patients who did not respond to laparoscopic ovarian drilling treated with metformin and ovulation rate was 80% (4/5) at 24 months follow-up. The ovulation rate of metformin therapy combined with laparoscopic ovarian drilling was 95.5% (21/22).

3.2. Discussion

The presence of polycystic ovaries presents the possibility for a hyperandrogenic state and the expression of the PCOS in a facilitative environment, for example when stimulated by endogenous or exogenous gonadotropins or insulin. A counter argument may propose that the PCO is a secondary effect, whereby it is the exposure of a normal ovary to androgens (stimulated through insulin or LH) that makes it polycystic—although against this proposition is the observation that normalization of endocrinology does not appear to correct ovarian morphology. There are likely to be many routes to the development of the PCOS, including a genetic predisposition, environmental factors, and disturbances of a number of endocrine pathways (e.g., the hypothalamic–pituitary–ovarian axis, feedback loops, hyperinsulinemia, and the metabolic syndrome). In some, the ovary may change as a secondary effect, whereas in others there may be an inherent defect originating in the ovary. Polycystic ovaries are detected in about 27% of the general population, of whom approximately 80% have symptoms of PCOS, albeit usually mild. Thus, approximately 20% of women with polycystic ovaries are symptom free.

The presence of polycystic ovaries, however, may be a marker for increased reproductive and metabolic risk. The presence of polycystic ovaries also appears to be associated with an increased ovarian reserve and a reduced rate of ovarian aging. Ovarian dysfunction is expressed when the ovaries of women with polycystic ovaries alone are stressed, by either a gain in weight and rise in circulating insulin levels or stimulation with FSH for assisted conception treatments. Longitudinal studies are required to better explore the evolution of signs and symptoms of the syndrome over time in women with polycystic ovaries and by comparison with those with normal ovaries.

Metformin, a biguanide, increases insulin sensitivity in the liver to reduce gluconeogenesis and hyperinsulinemia. Clinical studies have shown that administration of metformin to PCOS women resulted in decreased androgen levels, increased rates of spontaneous ovulation, and enhanced ovulatory responses to clomiphene. Recent studies have shown that metformin may have direct effects on ovarian steroidogenesis independent of insulin action. Incubation of human ovarian theca-like tumor cells with metformin inhibited the mRNA expression of steroidogenic regulatory protein and 17α-hydroxylase, whereas no effect was detected for 3β-hydroxysteroid dehydrogenase (3β-HSD) or cholesterol side chain cleavage. In contrast, metformin was not associated with changes in 17α-hydroxylase or 3β-HSD in studies of yeast cells. The disparity between results may reflect differences in the cell systems employed. Side effects of metformin include gastrointestinal symptoms that are dose-related and tend to resolve after several weeks. In addition, precautionary temporal withdrawal of metformin is advised in patients undergoing radiological procedures involving intravascular iodinated contrast materials and surgery. These data demonstrates that patients with PCOS have significant hyperinsulinemia than healthy women with normal menstrual cycles. The pathophysiology of PCOS has not been fully characterized. Many have evidence of abnormal LH secretion (increased LH pulse amplitude and frequency), and a significant percentage of women with PCOS display insulin resistance [3].

The combination of insulin resistance and increased LH secretion appears to stimulate ovarian androgen production. In addition, elevated insulin levels inhibit hepatic synthesis of sex hormone binding globulin. These changes result in increased bioavailability of free androgens. Dysregulation of local follicle regulatory systems by androgens and other factors impedes normal follicular growth, resulting in follicular arrest at the 4 to 8 mm diameter size. A dominant follicle (i.e., 18 to 25 mm in diameter) does not develop, and therefore ovulation does not occur. Thus, the combination of elevated LH, hyperinsulinemia, ovarian androgen overproduction, and disruption of follicle growth produces the PCOS phenotype of oligoovulation and hyperandrogenism [4]. Metformin's major effect is to decrease hepatic glucose production thus reducing the need for insulin secretion; it also decreases intestinal absorption of glucose and modestly improves insulin sensitivity (increases peripheral glucose uptake and utilization). Metformin also has an antilipolytic effect that lowers fatty acid concentrations, thus reducing gluconeogenesis.

These results show the efficacy of metformin in treatment

of clomiphene citrate-resistant and laparoscopic surgery-resistant PCOS patients. Combination of metformin and laparoscopic ovarian drilling increases the ovulation rate in PCOS patients. There is a need to investigate PCOS patients in adolescent women for the possible cause of the disease of future infertility.

4. Conclusion

Within this reseach, patients with PCOS have significant hyperinsulinemia.

Metformin can be a reasonable option for clomiphen-resistant patients with PCOS and combination of metformin and laparoscopic ovarian drilling increases the ovulation rate in PCOS patients (95.5%).

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