The effect of administration of metformin on lipid profile changes and insulin resistance in patients with polycystic ovary syndrome

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ABSTRACT

Objective: Polycystic ovary syndrome (PCOS) is one of the most common metabolism and endocrine disorders among women. The aim of the present study was to evaluate the effects of metformin on lipid profile changes, insulin resistance, body mass index (BMI), Ovulation and pregnancy rates in patients affected by PCO syndrome.

Materials and Methods: In this randomized controlled study, 200 women aged 20-35 years with PCOS were selected. Diagnostic criteria were based on the diagnostic criteria of PCO syndrome in Noterdam meeting in 2003. Samples of fasting peripheral blood were taken from all patients to test cholesterol, LDL, HDL, TG, FBS and Insulin before treatment. Patients were then divided randomly into two groups. In case group (n=100), metformin was prescribed three times a day (1500 mg daily) and in control group (n=100), placebo was administered in the same way. After three months, sample of blood was taken again in order to test the variance of the above mentioned parameters to compare with these amounts before test. Also, BMI was compared before and after treatment in both groups.

Results: BMI was 28.81±3.18 and 29.49 ± 4.7 Kg/m2 before treatment in case and control groups respectively. This ratio changed after treatment to 28.45 ± 2.8 and 29.29 ± 4.8 Kg/m2 in case and control groups respectively (P-value>0.05). FSH/insulin ratio was 4.67±0.9 and 5.03±1.3 in case and control group respectively, while it changed after treatment to 6.07 ± 1.4 and 5.05 ±1.3 and this difference was significant in case group (P-value=0.0001), but it was no difference in control group. In case group, HDL level increased after treatment from 26.65±9.9 to 33.19± 9.9 MMoL/L (P-value=0.0001), and Triglyceride level decreased after treatment from 208.96±58.9 to 191.54±55.4 MMoL/L (P-value=0.004); whereas there was no change in control group. LDL and cholesterol levels did not change in both groups. Ovulation rate and pregnancy rate were significantly higher in case group than in control group (86% vs. 20%) (P-value=0.003) and (40% vs. 11%) (P=0.021) respectively. In addition, Metformin had no significant effect on BMI in case group.

Conclusion: Treatment with metformin during 3 months causes not only the increase in ovulation and pregnancy rates but also the decrease in insulin resistance and lipid profile changes.

Key words: metformin, PCO syndrome, lipid profile, hyperinsulinemia

Polycystic ovary syndrome is one of the most common metabolism and endocrine disorders among women with the prevalence of about %5- %10 worldwide (1). One study investigated its prevalence among girl students in Yazd, Iran and reported the prevalence of %16 (2). This disorder affects women in reproductive age. The signs of PCOS include hyperandrogenism and anovulation. Since the cause of this syndrome has not been diagnosed yet, therefore its treatment will be depending on signs and patients characteristics such as: hirsutism, obesity, menstrual disorder and infertility (3).

The long – term damages such as heart complication, diabetes and endometrial cancer should be considered important in this syndrome. Therefore, many researches lead to investigate the lipid
PCO patients are resistance to insulin and it is not related to obesity (1), while different studies have shown that insulin has a main role in pathogenesis of this syndrome and has direct effect on ovarian steroidogenesis and consequently, it stimulates the synthesis of androgens in theca cells and reduces steroid hormone binding globulin (SHGC) in liver and increases the level of androgen (4).

Some randomized clinical trials indicated that treatment with metformin in PCOS decreased the insulin resistance and corrected lipid metabolism (5, 6, 7). The other studies reported that using this drug in PCO patients reduced serum androgens level and consequently menstrual periods became regular (6, 8,9).

Banaszewska et al (2006) have concluded that metformin therapy in hyperinsulinemic women was associated with a significant decrease of insulin level, total cholesterol, LDL and TG that this drug may be considered as a prophylactic therapy lowering cardiovascular risk factors in hyperinsulinemic women with PCOS (10)

Our aim is to investigate the effect of metformin on lipid profile changes, insulin resistance and BMI, ovulation and pregnancy rates in PCO patients.

MATERIALS AND METHODS

A randomized controlled trial was conducted to compare the effect of metformin on lipid profile changes, insulin resistance, BMI, ovulation and pregnancy rates in PCO patients before and after treatment between August 2005 and September 2006. Ethical committee of Yazd Shahid Sadughi University of Medical Science approved this study.

In total, 200 women (The range of age was 20-35 years) who have referred to our clinic because of menstrual disorder, hirsutism and infertility were diagnosed with PCOS. PCOS was diagnosed according to its definition in 2003 Noterdam meeting namely by the existence of at least two of the following criteria: oligomenorrhea (the length of period days is more than 35 days) or hypomenorrhea, Clinical signs of hirsutism, hyperandrogenism, and sonographic evidence of PCO (such as ovarian volume>10cm3 and small (6-8mm) follicles more than 12 arranged in the periphery of the ovary).

The exclusion criteria were included other endocrinological abnormalities such as hyperprolactinaemia, and thyroid dysfunction, Cushing syndrome, congenital adrenal hyperplasia.

BMI was measured and recorded in all patients before and after treatment. The sample of fasting peripheral blood was taken in order to measure cholesterol, HDL, LDL, triglyceride, FBS and fasting insulin. Then patients were randomly (Randomization was performed using computer-generated sequences that were sealed in number opaque envelopes) divided into two groups. Metformin was prescribed for case group (n=100) and placebo for control group (n=100).

Both women and the doctor were blinded to the content of tablet which had identical appearance and were packaged by the clinic pharmacist. The dose of metformin was started from one tablet 500 mg /day and increased to three tablets daily during a week with respect to the patient’s tolerance. Placebo was prescribed for control group in the same method. After three months, the sample of blood peripheral was taken again in order to check the mentioned parameters. Then the data was compared with these amounts before treatment. All patients were asked to report all the side effects such as nausea, vomiting and diarrhea during the treatment.

Ovulation rates were determined by progesterone levels of more than 10ng/ml in the luteal phase (timed 21 days after the first spontaneous menstruation) for both groups. Pregnancy outcomes included serum B-HCG of more than 50IU/L, and fetal heart activity on abdominal ultrasound scan, after 8 weeks of gestation.

SSPS version 13 was used to do the appropriate statistical tests including Student's T Test (two-tailed), Fisher exact test. The results are expressed as means and standard deviation. Differences were considered to be statistically significant if p-value was <0.05.

RESULTS

In this study, 200 PCO patients were recruited during 1 year. 100 patients were in the metformin group and 100 in the placebo group. The mean age of patients was 27.2±6.8 and 28.6±7.4 years in case
and control group respectively (P-value=0.42). Duration of infertility was 5.6±1.9 and 6.2±1.8 years in case and control groups respectively (P-value=0.28). Before treatment, the patients with oligomenorrhea were 82% and 75% in case and control groups respectively (P-value=0.31). While it was 23% and 70% in case and control groups after treatment (P-value=0.003). Hirsutism was 86% and 82% in case and control groups (P-value=0.51), while it was 50% and 70% in case and control groups after treatment (P-value=0.07).

Before the treatment, the BMI was 28.8±3.18 and 29.49±4.75 Kg/m² in case and control groups respectively (P-value=0.15). After treatment; it was 28.45±2.8 and 29.29±4.8 in case and control groups (P-value=0.18).

The degree of the sensitivity to insulin was 4.67±0.9 in case group and 5.03±1.3 in control group. After treatment, the sensitivity to insulin increased significantly to 6.07±1.4 in case and 5.05±1.3 in control group (P-value=0.0001); while it was not significant in control group (P-value=0.77) (Table 1).

As it is shown in table 1, although the amount of cholesterol reduced from 203.04±47.2 to 188.04±58.5 in case group, this reduction was not significant statistically (p=0.069); while no change was seen in control group (199.4±42.5). After treatment, cholesterol level reduced from 203.04±47.2 to 188.04±58.5 in case group (p=0.0001), while it was not significant in control group (P-value=0.77).

In addition, triglyceride level reduced from 208.96±58.4 to 191.54±55.9 in case group (p=0.004), while it did not reduce in control group (196.56±54.3 vs. 205.26±53.4) (p=0.063). Similarly, HDL level increased from 26.65±9.9 to 33.19±9.9 after metformin treatment (P-value=0.0001), while this change was not seen in control group. Finally, LDL level was not changed in both groups.

Ovulation rate was significantly higher in case group than in control group (86% vs. 20%) (P-value=0.003). Also, clinical pregnancy rate was significantly more in case group than in control group (40% vs. 11%) (P=0.021). Four pregnancies in case group and three in group B ended with miscarriage at 8 weeks of gestational age (P-value=0.092). In addition, Metformin had no significant effect on BMI in case group.

Side effects in metformin treatment were 30% nausea, 10% diarrhea and 15% vomiting. These side effects were not severe and they were disappeared with continuing treatment.

DISCUSSION

Hyperinsulinemia and hyperandrogenism increase the risk of diabetes in PCO patients (1). In addition, hyperinsulinemia causes hypertension and increases the risk of ischemic heart disease (IHD) in these patients (11). The other risk factor of IHD is insulin resistance which is accompanied with increasing of triglyceride and reduction of HDL level (11).

Women with anovulation, hyperandrogenism and hyperinsulinemia are more exposed to the risk of diabetes mellitus independent from insulin (1).
Different studies have shown that continuous anovulation made the patients three times more susceptible to endometrial cancer (12).

On the other hand, the risk of breast cancer increases in patients with chronic anovulation three or four times (1). Metformin increases the sensitivity to insulin that decreases the chance of diabetes (13-15). This drug is available in the market for treatment of diabetes more than 10 years. In fact, it is the most prescribed medicine for the treatment of hyperglycemia. The primary effect of metformin is a significant reduction in gluconeogenesis. Not only decreases glucose production but also increases target tissue sensitivity to insulin. Metformin has useful effects in reduction of the cardiovascular risk factors and it is the early available medication against hyperglycemia which decreases macrovascular complications in diabetic patients (16). It was shown that treatment with 1500 mg of metformin for 8 weeks decreases the level of serum insulin (8, 17).

Our results showed that sensitivity to insulin (FBS/insulin ratio) has increased in the case group compared to the control group. Although, the rise of androgen and consequently the lipid changes in PCO patients cause to protect against osteoporosis but its bad effect on heart disease is very important (16). Atherosclerosis is more common among women who have anovulation and PCOD. Cheang and et al (2004) showed that metformin not only recommended for PCO patients because of its effect on induction ovulation, but also for its useful influence on lipid metabolism (18). Our results showed that treatment with metformin caused a significant increase in HDL and a decrease in triglyceride level. However, although cholesterol and LDL serum levels decreased after treatment with metformin, it was no significant difference between before and after treatment in case group. Therefore, treatment with metformin may cause the prevention of long term risk of cardiovascular and diabetes through correcting all or some of risk factors and lipid profile changes (19).

Tang and co-workers (2006) have indicated that there were no significant changes in insulin sensitivity or lipid profiles after treatment with metformin. Also, in this study, metformin did not improve weight loss or menstrual frequency in patients with PCOS (20).

The effect of metformin has been controversial; with some suggestion that the ovulatory response is the result of the weight loss that often accompanies its use. In a study designed to control the effect of body weight, the administration of metformin was without effect on insulin resistance in extremely overweight women with polycystic ovaries (21). In another-well designed study, metformin again had no effect on insulin resistance when body weights remained unchanged, and baseline weights and hyperinsulinemia were only modestly increased (22). In contrast to some of the studies that metformin has a good effect on the reduction of weight and BMI (23, 24), our investigation showed that there was no significant difference in weight and BMI after treatment with metformin.

Santana et al (2004) have shown that treatment with metformin increased HDL level while serum total cholesterol and LDL levels reduced. Also, there were no changes in BMI after metformin treatment (25).

Aruna’s study (2004) indicated that significant improvement menstrual cyclicity, ovulation and pregnancy rates were noted after treatment with metformin (26). Our results were the same as this study.

However, Treatment with metformin will decrease insulin resistance and lipid profile changes and increase ovulation and pregnancy rates.

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