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REPRODUCTIVE MEDICINE

Metformin 2,500 mg/day in the treatment of obese women with polycystic ovary syndrome and its effect on weight, hormones, and lipid profile

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Abstract
Purpose The objective of this study was to assess the efficacy and safety of metformin at the dosage of 2,500 mg/day in the treatment of obese women with PCOS and also to evaluate its effect on weight, hormones, and lipid profile.
Method This study was a 4-month open-label clinical trial. Sixty-nine PCOS patients aged 20–35 were recruited in the study. Testosterone, free testosterone, sex hormone-binding globulin (SHBG), fasting insulin, dehydroepiandrostenedione-sulphate (DHEAS), FBS, LDH, HDL, TG, total cholesterol, body mass index (BMI), and waist-to-hip ratio were measured before treatment and after 4 months of treatment.
Results Significant reductions in serum insulin, BMI, waist/hip ratio, and LDL were observed. In addition, a significant increase in SHBG was obtained. Over the 4 months of the trial, 12 patients faced nausea, six patients had bloating, five patients had diarrhea and two had headache; none of these symptoms were severe except for two cases that dropped out due to severe vomiting.
Conclusion The results of this study show that 2,500 mg daily dose of metformin in obese patients with PCOS is effective in the reduction of BMI, waist hip/ratio, LDL, serum insulin and increases SHBG. In general this dose was relatively safe and well tolerated.

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Introduction

PCOS (polycystic ovary syndrome) is the most common cause of female infertility and affects 5–10% of women of reproductive age [1]. It is characterized by chronic anovulation with oligo-/amenorrhea, infertility, typical sonographic appearance of the ovaries, and clinical or biochemical hyperandrogenism [1, 2]. The majority of women with PCOS are insulin-resistant (IR) and IR has a central role in the pathogenesis of this syndrome [3, 4]. A significant percentage of the patients become obese or overweight, with a body mass index (BMI) greater than 27 [5]. It was reported that 65–70% of women with PCOS are IR and many of these women are obese, a condition that aggravated their IR [6]. Insulin stimulates LH-dependent ovarian androgen production and secretion. It also acts directly on the liver to inhibit sex hormone-binding globulin (SHBG) [3, 7, 8]; hyperinsulinemia itself leads to follicular atresia and arrest [9]. Metformin is an oral biguanide and was first used to treat type 2 diabetes mellitus. It acts primarily in the liver by inhibiting gluconeogenesis and also by increasing peripheral insulin sensitivity [3, 8]. On the other hand, it is reported that obesity may reduce the beneficial effects of metformin as the response to metformin in PCOS patients is related to BMI and the dosage of metformin. It seems that the dose of metformin might be critical for response to treatment in obese patients [10]. Maciel et al. in their study concluded that non-obese patients with PCOS benefit more than obese patients from 1,500 mg/day of metformin. It is however, believed that obese patients may respond to metformin with a greater

dose [7]. Harbone et al., compared the doses of 1,500 and 2,500 mg\day in obese patients (BMI > 30) and in morbid obese patients (BMI > 40) and they reported a greater weight reduction with higher doses of metformin [10]. Bruno et al. [11] assessed the efficacy of two different doses of metformin (2,500 and 1,500 mg) on BMI and waist circumference in overweight PCOS patients and showed a significant reduction with higher doses. Therefore, beneficial effects of metformin on weight, lipid profile, and hormones may be obtained with a higher dose in the obese PCOS patients [10]. The objective of this study was to assess the efficacy and safety of metformin at dosage of 2,500 mg/day in the treatment of obese women with PCOS and its effect on weight, hormones, and lipid profiles.

Materials and methods

This study was a 4-month open-label clinical trial performed in the infertility ward of Dr. Shariati Teaching Hospital (Tehran, Iran) during January 2008–January 2009. Sixty-nine PCOS patients aged 20–35 with PCOS and defined as obese (BMI, ≥30 and <37) were recruited in the study. The study was approved by the Ethics Committee of Tehran University of Medical Science (Grant No. 5740); all the patients were provided with the written informed consent before entering the study. According to the Rotterdam meeting in 2003, patients who have two out of the three following criteria, are defined as having PCOS: (1) chronic anovulation or oligoovulation, (2) presence of clinical or biochemical signs of hyperandrogenism, and (3) polycystic ovary [12]. The patients' hirsutism profiles were scored according to Ferriman and Gallwey score, a hirsutism scoring scale of androgen-sensitive hair in nine body areas rated on a scale of 0 to 4. Based on this scale, hirsutism is defined as a score higher than 8 [13]. Transvaginal sonography (Honda, Japan, 7 MHz) was performed in the follicular phase. The criteria to define PCO were: presence of 12 or more follicules in each ovary measuring 2–9 mm and/or ovarian volume >10 ml [12]. The patients had no history of taking antidiabetic or antilipidemic agents. All patients had normal renal and liver function. The exclusion criteria were the presence of any diagnosed endocrinopathy including late-onset 21-hydroxylase deficiency, Cushing syndrome, diabetes mellitus, thyroid disorders, and hyperprolactinemia. BMI (weight (kg)/height (m^2) and waist-to-hip ratio were calculated at the first visit and at the end of the study. The patients received 2,500 mg/day of metformin for 4 months (the initial dose was 500 mg per day and gradually increased to 2,500 mg/day during 6 weeks). Basal serum concentrations of LH, FSH, TSH, prolactin, and 17OH-Progesterone were assessed on menstrual cycle days 2–6 in every patient. After 12 h fasting, testosterone, free testosterone, sex hormone-binding globulin (SHBG), fasting insulin, dehydroepiandrostenedione-sulphate (DHEAS), FBS, LDH, HDL, LDL, total cholesterol, and TG were measured before treatment and after 4 months of treatment on menstrual cycle days 2–6 in every patient. Testosterone was measured by immunochemiluminescence system (APUIA Centour Bayer Coporation Tarytown, New York, USA) with an average inter-assay coefficient of variation (CV) of 9% and intra-assay CV of 8%. DHEAS and SHBG were measured by immunochemiluminescence (immunlite 1000, DPC, Los Angeles, California, USA) with intra-assay and inter-assay CVs of 5.1 and 6.4%, respectively. Oxidase method was used for serum glucose determination. Cholesterol, TG, LDL, and HDL levels were measured by enzymatic Kinetic Kit (DAX-48, Bayer Diagnostica, Germany). Free testosterone and insulin levels were measured by radioimmunoassay (Diagnostic System Lab. Inc Texas, USA). Patients were advised not to change their usual diet, and physical activity throughout the study.

Statistical analysis

The variables were analyzed using *t* tests between baseline and endpoint of the trial. All tests were two-tailed, with level of significance set at 0.05. Data were analyzed by using commercially available statistical packages (SPSS 13.00. Chicago, IL, USA).

Results

The baseline data and characteristics of patients are presented in Table 1. Table 2 shows the clinical and laboratory data before and after 4 months of treatment with metformin 2,500 mg/day. As the results showed significant reductions in serum insulin, BMI, waist/hip ratio and LDL were observed. In addition, increasing of SHBG levels was also obtained. Over the 4-month trial, 12 patients faced nausea, six patients had bloating, five patients had diarrhea, and two had headache but none of them were severe except for two cases that dropped out due to severe vomiting.

Discussion

There are several lines of evidence that suggest metformin can be effective in the treatment of clinical features associated with PCOS [2]. The primary clinical action of metformin is reducing the hypergluconeogenesis. Metformin also increases sensitivity to insulin. It has been reported that metformin dosage might be a critical factor

Table 1 Baseline and characteristics of the patients

Number of patients with Acne	9
Number of patients with Hirsutism	42
Number of patients with Alopecia	2
Age (year)	26.70 ± 4.19
TSH (mIU/ml)	1.96 ± 1.36
FSH (mIU/ml)	5.01 ± 2.14
LH (mIU/ml)	6.95 ± 1.95
17OH-progesterone (ng/ml)	1.15 ± 0.25
Prolactin (ng/ml)	17.65 ± 4.35

for a good response and a vital point for the treatment success particularly in obese women with PCOS [10]. Nevertheless, there are concerns regarding the side effects and tolerability with the higher doses of metformin.

As expected, in this study, the patients who received metformin 2,500 mg/day had significant reduction in serum insulin, BMI, waist/hip ratio and LDL, while SHBG level was increased. There are conflicting data regarding the effects of metformin on BMI and waist/hip ratio. Some investigators have shown no effect of metformin on BMI and waist/hip ratio [14]. It is likely that the response to metformin is dose-dependent. The results of our study are in line with the study of Harbrone et al. [10] which suggested that a greater weight reduction in women with PCOS will be achieved with higher doses of metformin. Indeed they concluded that the effects of metformin on BMI and waist/hip ratio are dose-dependent and greater weight loss was observed with higher dose of metformin [10].

Bruno et al., concluded that higher dose of metformin is more effective. They compared metformin 1,500 mg/day with metformin 2,500 mg/day for reduction of BMI and waist circumference [11].

In general weight reduction has a critical role in the management of PCOS. Ciccone et al. [15] in their study showed early atherosclerosis changes in overweight and obese PCOS patients and concluded that this was due to their body weight. It has been reported that 5 to 10% weight loss reduces central fat up to 30% and as a result improves the insulin sensitivity as well [16]. There is no doubt that insulin resistance has an important role in the pathogenesis of PCOS [4]. The majority of PCOS patients are obese and most of them are insulin-resistant. Insulin resistance is associated with the pathogenesis of cardiovascular disease and diabetes. Evidence suggests that progesterone increases insulin resistance. Therefore, oral contraceptives should be used with caution in women with PCOS, in particular in obese women [17]. However, it was shown that there were no adverse effects of short-term cyclic medroxyprogesterone plus metformin treatment on metabolic parameters or insulin resistance in patients with PCOS over a 3-month treatment trial [18]. Teede et al. [19] in their study suggested that although OCP increases insulin resistance, it improves some circulating markers of endothelial function in overweight PCOS patients.

Exenatide is an antidiabetic agent, which often results in weight loss and further decreases insulin resistance. The combination therapy of metformin plus exenatide has additive effect on weight loss and better improvement of hormonal and metabolic features of PCOS than single therapy [20]. In the present study as we titrated up the dose of metformin to 2,500 mg/day over 6 weeks, metformin was generally well tolerated except in two patients who dropped out due to vomiting. However, to compare and detect the side effects of different doses of metformin, we need a randomized clinical trial with two arms and large sample size. Nevertheless, this preliminary open label trial reemphasizes the safety of higher dose of metformin on patients with PCOS and also gives us evidence of their compliance of the drug in the aforementioned dosage.

In conclusion, the results of this study show that 2,500 mg daily dose of metformin in obese patients with

Table 2 Clinical and laboratory data before and after 4 months of treatment with metformin 2,500 mg/day

	Baseline	After 4 months	*P*
Insulin serum (μIU/mL)	17.93 ± 9.48	12.35 ± 7.98	0.0004
FBS (mg/dL)	99.84 ± 21.21	94.50 ± 17.32	0.10
BMI ($kg/m^{2)}$	34.04 ± 3.86	31.58 ± 4.46	0.04
Waist/hip ratio	0.93 ± 0.06	0.91 ± 0.06	0.04
Cholesterol (mg/dL)	197.46 ± 34.75	186.90 ± 35.39	0.09
LDL (mg/dL)	122.13 ± 34.18	100.33 ± 32.70	0.0002
HDL (mg/dL)	45.46 ± 10.53	48.61 ± 10.32	0.08
Triglyceride (mg/dL)	141.72 ± 60.64	139.08 ± 56.13	0.80
Free testosterone (pg/mL)	2.39 ± 1.37	2.18 ± 1.30	0.37
Total Testosterone (ng/mL)	0.54 ± 0.32	0.51 ± 0.22	0.12
Sex hormone binding globulin (nmol/L)	33.89 ± 45.71	47.33 ± 29.50	0.04
DHEAS (μg/dL)	178.68 ± 107.12	164.51 ± 92.74	0.41

PCOS is effective in the reduction of BMI, waist hip/ratio, LDL, serum insulin and increases SHBG. In general this dose was relatively safe and well tolerated.

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Conflict of interest statement None.

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