Original Articles

Biochemical and body weight changes with metformin in polycystic ovary syndrome

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Summary

Objective: To evaluate the long-term effects of metformin on biochemical variables and body weight in polycystic ovary syndrome (PCOS).

Method: Fifteen obese PCOS patients that attended the university clinic were included to this prospective study. These patients used 1,500 mg of metformin daily for 12 months.

Result: We found a statistically different decrease in mean body mass index (t:4,369), (p:0.0002) at the end of the 12 months. In contrast to that there were no statistical differences in fasting serum insulin and testosterone levels. Metformin improved menstruel patterns (60% of cases) in obese PCOS patients.

Conclusion: Hyperinsulinemia and androgen excess in obese non-diabetic women with PCOS are not improved by the administration of metformin. Metformin treatment may have improved menstruel patterns by a mechanism independent of and unrelated to insulin sensitivity or circulating insulin concentrations.

Key words: Metformin; Polycystic ovary syndrome; Body mass index.

Introduction

Polycystic ovary syndrome (PCOS) is characterized by oligomenorrhea and clinical and biochemical hyperandrogenism. Many women with PCOS have anovulatory infertility, insulin resistance or hyperinsulinemia, and morbid obesity. Hyperinsulinemia plays a pathogenic role in PCOS and appears to contribute to both chronic anovulation and hyperandrogenism [1, 2]. Of note, obese women with PCOS are particularly resistant to ovulation. The first study in which metformin was administered, with the hypothesis that androgen reduction will follow from insulin reduction, was performed by Velazquez [3]. The subjects in this study lost weight, which was most likely a contributing factor in the reduction of insulin secretion on repeat oral glucose tolerance testing.

The effect of metformin on insulin secretion could not be clearly seperated from that of weight loss. Several other studies have examined the effects of metformin in women with PCOS [4-7]. Moghetti et al reported that metformin treatment reduced hyperinsulinemia and hyperandrogenemia, independently of changes in body weight [2]. These studies have varied widely in design. Biguanid metformin (dimetyl guanyl guanydine) is normally used in insulin-independent diabetes mellitus. It reduces plasma insulin levels by reducing hepatic gluconeogenesis and stimulating peripheral glucose uptake [8]. Metformin can also reduce serum LH and serum androgen levels while facilitating normal menses [3, 5, 7].

In this study we aimed to observe the effects of long-term use of metformin. The biochemical and body weight changes were examined after 12 months of metformin treatment in non-diabetic obese PCOS patients.

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Materials and Methods

The study population consisted of 15 obese non-diabetic PCOS patients. The control group consisted of 15 age and weight-matched normal menstruating, fertile women with benign, non-endocrinologic, gynecologic problems attending the Medical Faculty of Istanbul Outpatient Clinic. All patients gave signed informed consent. The diagnosis of PCOS was made on the basis of chronic oligomenorrhea, clinical and biochemical hyperandrogenism (hirsutism, severe acne, high levels of total testosterone, androstenedione and DHEAS). Participants were also required to have normal renal function (serum creatinine concentration < 1.4 mg/dl) and normal results on liver function tests. These two criteria were required to prevent risk of lactic acidosis due to metformin in the setting of impaired renal or liver function. Endocrinologic diseases such as hypothyroidism, hyperprolactinemia and congenital adrenal hyperplasia were excluded with normal thyroid stimulating hormone, normal prolactin and normal 17-hydroxyprogesterone levels. Blood samples were obtained after an overnight fast in the follicular phase of the menstruel cycle between November 1999 and January 2001. All samples were assayed simultaneously for the same patient. Total testosterone was measured by using coat-a count total testosterone solid phase recombinant immunoassay kit. Luteinizing hormone and FSH were measured by an immunoenzymatic assay. DHEAS and 17 hydroxyprogesterone were measured by recombinant immunoassay. Commercial kits were used for these analyses (Diagnostic system Laboratories, Inc., Webster, TX). The intraassay and interassay coefficients of variation were < 10%. Insulin levels were measured by using a radioimmunoassay kit from Linco Research Inc. (St. Charles, MO). The intraassay and interassay coefficients of variation were 3.9% and 2.6%, respectively. Diabetes mellitus was excluded with a standard 100 mg oral glucose tolerance test.

Polycystic ovaries were identified by the presence of >10 subcapsular follicles 2-8 mm in diameter on transvaginal pelvic

ultrasonography. Oligomenorrhea was defined as less than six menses per year. Subjects participating in dietary or exercise programs for weight reduction were excluded. There were no pregnancies or pregnancy desire in the study group. Body mass index (BMI) was evaluated with the formula kg/m^2. Patients with an index of more than 27 were included to the study population.

All patients in the study group treated with metformin (Glucophage, 500 mg tablets, Group Lipha, Lyon, France) 1,500 mg daily. Metformin was given continuously in a dose of 500 mg three times daily after main meals for 12 months. In this way all patients served as their own controls.

Statistical anlysis was performed with the Student's t test; p values less than 0.05 were considered statistically significant.

Results

The study group covered 15 PCOS patients. Mean characteristics of the control group and study group are summarized in Table 1. Age was similar in both groups. BMI, total testosterone, DHEAS, LH, FSH and insulin levels were significantly different in the study group. Table 2 shows the pretreatment and post-treatment values of BMI and biochemical variables. At the end of the 12 months BMI was reduced significantly (t. 4,369) (p: 0.0002) although the patients were maintaining their usual eating habits. Testosterone (t: 1,788), (p: 0.085) and insulin levels (t: 0.514), (p: 0.611) were reduced but this reduction was not found to be statistically significant. Nine women (60%) with oligomenorrhea experienced more regular cycles (less than 35 days) during metformin treatment especially after the third month of treatment. Metformin was well tolerated by all patients.

Table 1. — *Characteristics of the study group (polycystic ovary syndrome patients) and control group.*

	Controls	Study group	p value
Age	27.31±1.46	26.42±1.13	NS
Body mass index (kg/m^2)	22.95±0.80	28.71±1.37	0.0001
Luteinizing hormone (mIU/ml)	8.11±0.73	9.44±0.89	0.0001
Follicle stimulating hormone (mIU/ml)	5.89±0.28	5.67±0.22	0.02
Total testosterone (ng/ml)	0.41±0.07	0.68±0.05	0.0001
DHEAS (ng/ml)	1371±122	1764±191	0.0001
17-hydroxyprogesterone (ng/ml)	0.44±0.07	0.49±0.09	NS
Fasting insulin (µU/ml)	15.2±8.22	22.4±11.1	NS

Values are means ± SD.

Table 2. — *Changes after 12 months of metformin use in PCOS patients. (Values are means ± SD).*

	Pretreatment	Posttreatment	p value
Body mass index (kg/m^2)	28.71±1.37	26.41±1.51	0.0002
Luteinizing hormone (mIU/ml)	9.44±0.89	8.31±0.87	0.001
Follicle stimulating hormone (mIU/ml)	5.67±0.22	4.91±0.66	0.0002
Total testosterone (ng/ml)	0.68±0.05	0.62±0.12	NS
DHEAS (ng/ml)	1764±191	1689±134	NS
17-hydroxyprogesterone (ng/ml)	0.77±0.09	0.79±0.08	NS
Fasting insulin (µU/ml)	22.4±11.1	20.2±12.3	NS

Discussion

Polycystic ovary syndrome (PCOS) is a complex clinical entity that probably includes several different pathologies. Hyperandrogenism is the pre-eminent biochemical abnormality in women with PCOS. However, the cause of this hyperandrogenism and its relation to the central clinical component of PCOS, chronic anovulation, are only partly understood. Prevelic *et al.* pointed out that hyperinsulinemia was observed in 30% of slim women and in 75% of obese women with PCOS [9]. Despite certain conceptual problems about PCOS, hyperinsulinemia and insulin resistance, it seems evident that insulin and obesity are strongly correlated and that both influence each other regardless of whether women are normal or have PCOS [10]. In some studies, it has been reported that both obese and non-obese women with PCOS were more insulin-resistant and hyperinsulinemic than age and weight-matched normal women [1]. However, other studies have failed to find hyperinsulinemia in slim women with PCOS [10, 11].

It remains difficult to explain why metformin successfully lowers insulin and androgen levels in some studies but not in others [12-14]. Several hypotheses have been proposed, including variations in body weight, dosing, entry criteria and genetic background. The original Velazquez study reported a small but significant decrease in body weight in the obese women studied, and reductions in weight have been clearly demonstrated to improve the clinical features of PCOS [5]. Whether all of the therapeutic effects of metformin in women with PCOS are mediated directly by insulin-lowering effects remains to be determined. Ehrmann et al. reported that metformin has no effect on insulin, androgen levels, and BMI [14]. In the study of Kolodziejczyk *et al.*, 12 weeks of metformin use resulted in a significant decrease in fasting insulin and total testosterone and mean BMI [7]. In this study, we found a significant decrease in BMI and improvement in menstruel patterns of PCOS patients. This may depend on the long-term use of metformin or heterogenity of the original disease. In contrast, we did not find significant changes in androgen levels and fasting insulin levels after 12 months of treatment. Although serum DHEAS levels have been significantly reduced with metformin therapy in some studies [10], another study which evaluated androgen responses to adrenocorticotropic hormone before and after metformin administration failed to demonstrate any change in adrenal androgen secretion [14]. In our study, we found a slight decrease in serum DHEAS and testosterone levels, but this was not a significant decrease.

Some studies have focused on the ability of metformin to improve menstruel regularity, and have reported that 30% to 68.8% of treated women experienced regular cycles [5, 6]. In our study group, 60% of women experienced regular cycles, which may be related to the 12 months of metformin treatment.

Although the prospect of drug therapy to correct the underlying pathophysiology of PCOS directly is extremely attractive, metformin cannot be adopted as first-line

therapy for women with PCOS. However it can be used as an adjuvant therapy in obese PCOS patients and long-term studies should be performed to evaluate the endocrine effects of metformin in women with PCOS. This is the only study which reports a 12-month period of metformin use in obese PCOS patients. A limitation of our study is that we did not directly assess insulin sensitivity but measured one of the surrogate markers of insulin sensitivity such as fasting serum insulin levels. Hyperinsulinemia and androgen excess in obese nondiabetic women with PCOS were not improved by the administration of metformin. Finally, metformin treatment may have improved menstruel patterns by a mechanism independent of and unrelated to insulin sensitivity or circulating insulin concentrations.

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