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COMPARISON OF FINASTERIDE, METFORMIN, AND FINASTERIDE PLUS METFORMIN IN PCOS

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Abstract

The effects of finasteride on insulin resistance and of metformin on hyperandrogenism in patients with polycystic ovary syndrome (PCOS) are not clear. This study therefore compared the effects of finasteride, metformin, and finasteride plus metformin treatments on hormone levels, insulin resistance, and hirsutism score in women with PCOS. Fifty-two patients with PCOS were randomly assigned to receive finasteride 5 mg/day, metformin 1700 mg/day or finasteride plus metformin for 12 months. Body mass index (BMI), Ferriman Gallway score (FGS), serum concentrations of estradiol, sex hormone-binding globulin, free testosterone, dehydroepiandrosterone sulfate (DHEAS), androstenedione, and homeostasis model assessment of insulin resistance (HOMA-IR) index and areas under the curve (AUC) for insulin and glucose were evaluated before and after 12 months of treatment. Reductions in FGS, free testosterone, DHEAS, androstenedione, HOMA-IR, AUC-insulin, and AUC-glucose were significant within each group, whereas BMI and estradiol were not. Comparisons of changes in parameters in the 3 groups did not clearly show the superiority of any treatment modality. The treatment with finasteride alone significantly reduced both androgen levels and parameters of insulin resistance. In addition, metformin alone was effective, and not inferior to finasteride, in the treatment of hyperandrogenism.

Key words: PCOS, finasteride, metformin.

INTRODUCTION

Hirsutism affects 5-15% of women of reproductive age, with approximately 80% of these women having polycystic ovary syndrome (PCOS) (1, 2). Features associated with PCOS include physical attributes of hyperandrogenism, such as hirsutism, acne, deepening of the voice, and male pattern baldness; as well as various disorders, such as ovulatory dysfunction, infertility, endometrial hyperplasia, endometrial cancer, mood disorders, obstructive sleep apnea, obesity, insulin resistance, hypertension, hyperlipidemia, and cardiovascular diseases (1-3). The frequency and degree of expression of these features varies among patients.

Although the etiopathogenesis of PCOS remains unclear, excess luteinizing hormone (LH) secretion, overproduction of androgenic hormones by adrenal glands and ovary theca cells, insulin resistance, and genetic predisposition were suggested to be contributing etiologic factors (2-5). Insulin resistance and associated compensatory hyperinsulinemia have been shown to aggravate hyperandrogenemia in patients with PCOS (4, 6, 7). Moreover, 30-60% of PCOS patients are obese, a factor that contributes to the development of insulin resistance (8, 9). However, insulin resistance is present also in non-obese patients with PCOS, although it is not as frequent or severe as in obese patients (10, 11). Thus, insulin sensitizing drugs like metformin and pioglitazone have been widely used in the treatment of PCOS (12, 13).

Insulin sensitizers and antiandrogens may have complementary effects in the treatment of PCOS. Metformin ameliorates hyperinsulinemia and hirsutism, and restores regular menses and spontaneous ovulation (14-16). Another drug, finasteride, is a competitive inhibitor of 5-alpha-reductase, which converts testosterone into its more potent androgenic metabolite, dihydrotestosterone (DHT). Finasteride is a well tolerated antiandrogen with very few adverse effects and has been successfully used in the PCOS treatment (1, 17, 18).

The effects of finasteride on the insulin resistance in patients with PCOS have not been determined, and the effects of metformin hyperandrogenism remain unclear. This study therefore evaluated and compared the effects of finasteride, metformin, and finasteride plus metformin treatments on hormone levels, insulin resistance, body mass index (BMI), and hirsutism score in women with PCOS.

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SUBJECTS AND METHODS

Patients

This study enrolled 70 patients admitted to the outpatient Endocrinology clinic of Erciyes University Medical School and either newly or previously diagnosed with PCOS. Of these patients, 13 did not attend follow-up visits, 2 stopped metformin therapy due to epigastric pain and diarrhea, and 3 became pregnant during the study. Thus, 52 patients completed the study. The study protocol was approved by the local ethics committee, and all participants provided written informed consent.

Study design

Age, marital status, menstrual cycle regularity, medical history, and physical examination findings including BMI (kg/m^2), acne, and hirsutism score were recorded at enrollment. PCOS was diagnosed in women who met at least 2 of the following 3 criteria: oligomenorrhea or amenorrhea; clinical or biochemical evidence of hyperandrogenism; and the presence of polycystic ovaries on ultrasonography (19). To exclude causes of hirsutism other than PCOS, all patients underwent abdominopelvic ultrasonography to assess the presence of adrenal and ovarian tumors. Cortisol level after 1 mg dexamethasone suppression test, 17-OH progesterone and 11-deoxycortisol responses to 250 mg adrenocorticotropic hormone (ACTH) stimulation test, thyroid function test, and levels of insulin-like growth factor-I (IGF-I) and prolactin were initially evaluated to rule out Cushing's syndrome, congenital adrenal hyperplasia, thyroid dysfunction, acromegaly, and hyperprolactinemia, respectively. Patients with chronic systemic diseases, continuous drug use, and those who were treated for PCOS during the previous year were excluded. All patients enrolled into the study were hirsute and had polycystic ovaries on ultrasonography. Patients were evaluated by the modified Ferriman-Gallwey scoring (FGS) system, and those with scores ≥8 were defined as hirsute (20). Hirsutism scores were evaluated before and after 12 months of treatment by a single physician (F. Bayram) blinded to treatment modalities. Patients were advised to avoid mechanical modifiers, such as shaving, depilation, electrolysis, laser epilation, and creams that slow hair growth, as well as not to change their usual eating habits and physical activities, throughout the treatment period. The 52 patients were randomly assigned to 3 treatment groups. Group-1 (n: 16) received finasteride (Proscar, Merck Sharp Dohme, UK) 5 mg/day, group-2 (n: 19) was treated with metformin (Glukofen, Sandoz, Turkey) 850 mg twice daily (1700 mg/day), and group-3 (n: 17) received both with the same doses. Patients were informed of the potential side effects of the drugs prior to starting treatment. During the first week of treatment, metformin was administered at a dose of 425 mg twice daily to avoid gastrointestinal side effects, and thereafter at a dose of 850 mg twice daily. All sexually active patients were advised to use barrier contraception throughout the study. The safety controls, which comprised complaints of patients, their physical examinations, complete blood count and biochemistry tests including plasma glucose, liver and renal functions, and electrolytes, were performed before treatment and at 3-month intervals during the study.

Laboratory analyses

Hormone concentrations were assayed before and after 12 months of treatment in the Nuclear Medicine Laboratory of Erciyes University Medical School. Blood samples were collected during the early follicular phase (day 3 to 7) of the menstrual cycle in the morning. Hormones assayed before treatment, their methods, and commercial kits were as following: beta-human chorionic gonadotropin (beta-hCG, chemiluminescens, Immulate-2000), free T4 (immunoassay, Advia centaur XP), thyroid stimulating hormone (TSH, immunoassay, Advia centaur XP), cortisol (RIA, DSL-2100), follicle stimulating hormone (FSH, chemiluminescens, ACS: 180), LH (chemiluminescens, ACS:180), estradiol (E2, chemiluminescens, ACS:180), 11-Deoxycortisol (RIA, ICN Pharmaceuticals), dehydroepiandrosterone sulfate (DHEAS, RIA, Immunotech), 17-hydroxyprogesterone (17-OHP, RIA, DSL-3500), androstenedione (A, RIA, DSL-3800), free testosterone (T, RIA, Biosource), and sex hormone-binding globulin (SHBG, IRMA, Zentch). E2, SHBG, free T, DHEAS, and A concentrations in the early follicular phase were measured again at the end of the treatments. Oral glucose tolerance test (OGTT) and serial serum glucose and insulin concentrations were measured before and 12 months after the treatments to assess the insulin resistance. Patients were instructed to fast for 8–12 hours prior to OGTT; blood samples were obtained in the morning before the patient drank the solution containing 75 g of glucose, as well as after 30, 60, 90, and 120 minutes. Glucose concentrations were measured spectrophotometrically (Konelab-60), and insulin concentrations were measured using an immunochemiluminometric assay (Biosource). Homeostasis model assessment of insulin resistance

(HOMA-IR) index was calculated using the formula: [fasting glucose concentration (mg/dL) × fasting insulin concentration (uIU/mL)] ÷ 405. Areas under the curve (AUC) of glucose and insulin concentrations during OGTT were calculated using the trapezoid rule.

Statistical analyses

SPSS 15.0 (IBM Inc, USA) was used for all statistical analyses. Data were expressed as the mean ± standard deviation (SD). Data were tested for normal distribution before comparison analyses. Mean values among treatment groups were compared by one-way ANOVA test with Scheffe's procedure for post-hoc analysis. Within group parameters before and after treatment were compared by paired t-tests. Mean percentage changes in parameters from before to after treatment in the three groups were compared by ANOVA test. A probability (p) <0.05 was considered statistically significant.

RESULTS

The demographic and clinical characteristics of patients in the three groups are shown in Table 1. None of the 52 patients was amenorrheic, whereas 28 (53.8%) were oligomenorrheic. Patient ages in the three groups were similar (p >0.05). No side effects or changes in the biochemical and hematochemical parameters assessed at every 3 months were observed with finasteride and/or metformin.

Baseline and post treatment mean BMI, FGS, and hormone values in the three groups are presented in Table 2. Mean baseline FSH and LH concentrations were similar in the three groups. Mean baseline FSH values (normal: 2.5-12.5 mIU/mL) were 6.5 ± 2.8, 6.2 ± 2.6, and 6.3 ± 21.3 mIU/mL, and LH values (normal: 1.9-12.5 mIU/mL) were 8.4 ± 6.1, 7.8 ± 4.7, and 8.3 ± 8.9 in group-1, 2, and 3, respectively. Comparisons of mean BMI, DHEAS, and A values, but not FGS, E2, SHBG, and free T values, between the three groups before treatment showed no significant differences (p >0.05 each). Within each group, the percentage changes (% of baseline) in FGS, free T, DHEAS and A were significant, whereas the changes in BMI and E2 were not. The percent increase in SHBG level was higher in the group-3 than in the other two groups, whereas the percent reduction in DHEAS level was the greatest in the group-1.

Table 3 shows parameters of insulin resistance in the three groups at baseline and after 12 months of

Table 1. Demographic and clinical features of the three treatment groups

	Group-1 (finasteride) (no: 16)	Group-2 (metformin) (no: 19)	Group-3 (combination) (no: 17)	All Patients (n: 52)
Mean age (years)	25.8±4.1	26.4±7.2	25.0±6.1	25.8±4.3
Number of married/single patients	3/13	9/10	4/13	16/36
Presence of oligomenorrhea	9 (56.3%)	10 (52.6%)	8 (47.1%)	28 (53.8%)
Presence of acne	10 (62.5%)	9 (47.4%)	6 (35.3%)	27 (51.9%)

Table 2. Baseline and 12 month endocrine profiles and comparisons within and between the patient groups

	Normal Values	Months	Group-1 (finasteride)	Group-2 (metformin)	Group-3 (combination)
BMI (kg/m^2)	18.5-25	0.	27.4 ± 4.3	27.1 ± 4.3	27.6 ± 4.2
		12.	26.7 ± 2.2	26.9 ± 4.2	26.6 ± 4.4
FGS	0-7	0.	17.3 ± 5.1	16.0 ± 4.9[a]	19.2 ± 5.0[a]
		12.	11.7 ± 5.2*	11.1 ± 5.0*	12.1 ± 5.5*
E2 (pg/mL)	11-69	0.	82.6 ± 63.2[b]	50.8 ± 29.4[b]	65.8 ±34.4[b]
		12.	90.2 ± 35.0[b]	56.9 ± 39.5[b]	80.9 ± 59.5[b]
SHBG (nmol/mL)	12-155	0.	33.1 ± 20.1	27.4 ± 13.6[c]	33.0 ± 21.3
		12.	40.9 ± 20.0	29.4 ± 13.7[c]	41.9 ± 20.2*
Free T (pg/mL)	0.3-3.2	0.	2.4 ± 0.6[d]	2.8 ± 1.4	3.1 ± 1.8[d]
		12.	2.1 ± 0.5*	2.4 ± 1.1*	2.0 ± 1.2*
DHEAS (ng/mL)	1950-5070	0.	3458 ± 1535	3846 ± 2060	3325 ± 2234
		12.	2421 ± 1098*	3090 ± 1199*[c]	2619 ± 1081*
A (ng/mL)	0.1-3.0	0.	3.8 ± 1.4	3.7 ± 1.3	4.0 ± 2.5
		12.	2.6 ± 0.6*	2.3 ± 0.7*	2.5 ± 0.6*

*: p <0.05 compared with before treatment in the same group; a: p <0.05 when group-2 compared to group-3; b: p <0.05 in comparisons between groups; c: p <0.05 when group-2 compared to other groups; d: p <0.05 between the groups 1 and 3.
(BMI: Body Mass Index, FGS: Modified Ferriman-Gallwey scoring, E2: Estradiol, SHBG: Sex hormone-binding globulin, T: Testosterone, DHEAS: Dehydroepiandrosterone sulfate, A: Androstenedione).

Table 3. Insulin resistance parameters at baseline and after 12 months of treatment, and comparisons within and between patient groups

	Months	Group-1 (finasteride)	Group-2 (metformin)	Group-3 (combination)
HOMA-IR	0.	2.6 ± 0.6	3.5 ± 3.5[a]	2.3 ± 1.7
	12.	1.2 ± 0.7[*b]	1.4 ± 1.3[*]	1.6 ± 1.2[*b]
AUC-Glucose	0.	13098 ± 2895[b]	15018 ± 5023	15939 ± 5195[b]
	12.	12124 ± 1568[*]	11961 ± 3542[*]	13606 ± 3522[*c]
AUC-Insulin	0.	5356 ± 4101	7203 ± 5044[a]	5087 ± 2145
	12.	1689 ± 1652[*d]	4109 ± 3213[*]	3039 ± 1928[*]

*: p <0.05 compared with before treatment in the same group; a: p <0.05 when the group-2 compared to the other two groups; b: p <0.05 when the group-3 compared to the group-1; c: p <0.05 when the group-3 compared to the other two groups; d: p <0.05 when the group-1 compared to the other two groups. (HOMA-IR: Homeostasis model assessment of insulin resistance index, AUC: Area under curve).

treatment. HOMA-IR, AUC-insulin, and AUC-glucose were not comparable in the three groups before and after 12 months of treatment (p: <0.05 each). Within each group, the percent decreases in HOMA-IR, AUC-insulin, and AUC-glucose were statistically significant. The percent reduction in HOMA-IR was smaller in the group-3 than in the other 2 groups, whereas the percent decrease in AUC-insulin was greater in the group-1 than in the other 2 groups. Percent reductions in AUC-glucose were similar in the three groups. In addition, none of the patients showed glucose intolerance, either before or after treatment.

DISCUSSION

The main therapy of PCOS, pharmacological treatment, involves oral contraceptive pills, spironolactone, cyproterone acetate, GnRH analogues, clomiphene, metformin, pioglitazone, finasteride, and flutamide, which can be used alone or in combination. In clinical practice, the choice of treatment is based on the features of PCOS such as menstrual irregularity, infertility, obesity, insulin resistance or hirsutism in individual patients. (21, 22). Although monotherapy regimens are effective in most patients, combinations of two drugs with different mechanisms of action may be superior. However, previous studies have yielded conflicting results regarding the advantages of drug combinations (23-26).

Metformin in patients with PCOS acts by reducing insulin resistance in the liver, decreasing androgen secretion by adrenal glands and ovaries, and increasing the production of SHBG in the liver, thus reducing free T concentrations (7, 12, 15). Although metformin primarily improves insulin resistance, all of these mechanisms interact. For example, ovulatory women with PCOS were less insulin resistant than anovulatory women with PCOS (27). Barber *et al.* observed that women with oligomenorrheic but normoandrogenemic PCOS were not insulin resistant, whereas women with oligomenorrhea and hyperandrogenemia were insulin resistant (28). These studies suggest that there is a strong association among menstrual irregularity, hyperandrogenemia, and insulin resistance in PCOS. Although metformin has been reported to have limited clinical effectiveness and is inferior to anti-androgen drugs in treating hirsutism, androgenic alopecia, and acne in patients with PCOS (21, 29), studies have clearly shown that metformin has significant beneficial effects on those features of PCOS (12, 30, 31).

Metformin has been used alone (14, 30) or in dual combinations with other drugs to treat PCOS 2, (24, 25). The combination of metformin and flutamide in overweight-obese women with PCOS showed the specific effects of each compound, with the metformin reducing hyperinsulinemia and normalizing menstrual pattern and the flutamide reducing hyperandrogenism, without an additive effect (32). In contrast, patients treated with metformin and spironolactone showed greater improvements in menstrual irregularity, hirsutism score, AUC-glucose, AUC-insulin, and serum free T levels than patients treated with either alone (25). Our study showed that treatment with metformin alone decreased mean BMI, albeit nonsignificantly, while significantly reducing hirsutism score, androgenic hormone levels, and parameters of insulin resistance, suggesting that the beneficial effects of metformin in PCOS may be independent of its effects on BMI. However, Pasquali *et al.* reported that the improvements in serum androgen and insulin levels associated with metformin were enhanced when the metformin was combined with a hypocaloric diet, resulting in greater reductions in BMI (33). Importantly, our results confirm that metformin alone is effective, and not inferior to finasteride, in the treatment of hyperandrogenism, because it significantly reduced the hirsutism score and levels of androgens, such as free T, DHEAS, and A.

Treatment with finasteride has been shown to be effective in reducing hirsutism and hyperandrogenemia

resulting from PCOS (17, 34-36), but may be more effective when combined with other drugs used to treat PCOS. For example, changes in hirsutism scores were significantly greater in patients treated with spironolactone and finasteride than in patients treated with spironolactone alone (23). Furthermore, addition of finasteride to Diane-35 resulted in greater reductions in FGS, but not in androgenic hormones other than DHT and 3α-androstanediol glucuronide (37). In contrast, the addition of finasteride to Diane-35 therapy yielded additional reductions in serum DHT and 3α-androstanediol glucuronide concentrations, reflecting reductions in 5-alpha-reductase activity (38).

Although finasteride is an anti-androgenic agent, it may also be effective in improving insulin resistance in patients with PCOS, due to the association between hyperandrogenemia and insulin resistance, the two major pathophysiological derangements in PCOS (25). Thus, treatment with finasteride alone would significantly decrease both androgen levels and parameters of insulin resistance in our study. Although one limitation of our study was that pretreatment FGS, E2, SHBG, free T, and insulin resistance parameters were not similar among the three groups, all three treatment modalities effectively improved FGS, free T and A values, and insulin resistance. The improvements in the insulin resistance appear to be independent of its effects on BMI, since no significant decreases in the BMI values were found. To our knowledge, this study is the first to show that finasteride improves insulin resistance in PCOS. Other anti-androgenic agents, such as flutamide and spironolactone, have also been reported to improve parameters of insulin resistance in PCOS (25, 32), although contrary results have also been reported (39, 40).

Furthermore, no previous study investigated the effects of finasteride plus metformin in women with PCOS. While the two together induced greater improvements in hirsutism score and free T and A concentrations than did either agent alone, the differences were not statistically significant. Although the increase in SHBG value was significantly higher in the combination group than in either of the monotherapy groups, the decline in free T, the expected result of an increase in SHBG, was not. In contrast, combination treatment was not superior to monotherapy in improving HOMA-IR, AUC-insulin, and AUC-glucose. Thus, inter-group comparisons in percent changes did not clearly show that any of the regimens was superior. However, among the limitations of our study were the small numbers of patients in the treatment groups, and lack of evaluation of improvements in oligomenorrhea and acne.

In conclusion, management of PCOS should address the components of the disease in individual patients and prioritize the features needing treatment. The present study showed that finasteride, metformin, and their combination are effective and safe in patients with PCOS due to the beneficial effects of these agents on both hyperandrogenism and insulin resistance. The finasteride improved insulin resistance, but the addition of the metformin did not have an additive effect. Similarly, the metformin improved hyperandrogenism, but the addition of the finasteride did not show a significant additive effect. Thus, these results indicate that hirsutism and insulin resistance are the interacting causes that play key roles in the pathogenesis of PCOS.

Conflict of interest

The authors declare that they have no conflict of interest concerning this article.

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