

Responses of Serum Androgen and Insulin Resistance to Metformin and Pioglitazone in Obese, Insulin-Resistant Women with Polycystic Ovary Syndrome

C. Ortega-González, S. Luna, L. Hernández, G. Crespo, P. Aguayo, G. Arteaga-Troncoso, and A. Parra

Department of Endocrinology (C.O.-G., S.L., L.H., G.C., A.P.), Department of Sterility (P.A.), and Direction of Investigation (G.A.-T.), Instituto Nacional de Perinatología, 11000 México City, México

Severe insulin resistance is a key abnormality in obese women with polycystic ovary syndrome (PCOS). The purpose of this study was to evaluate whether pioglitazone decreases insulin resistance (IR) and hyperandrogenism to the same extent as metformin in obese women with PCOS who have not received any previous treatment. Fifty-two women with PCOS were randomly allocated to receive either pioglitazone (30 mg/d, $n = 25$) or metformin (850 mg three times daily, $n = 27$) and were assessed before and after 6 months. Body weight, body mass index, and waist to hip ratio increased significantly ($P \leq 0.05$) after pioglitazone treatment but not after metformin treatment. Fasting serum insulin concentration ($P < 0.001$ for both drugs) and the area under the insulin curve during a 2-h oral glucose tolerance test decreased after pioglitazone ($P <$

0.002) or metformin ($P < 0.05$) treatment. IR (homeostasis model of assessment-IR index) decreased and insulin sensitivity (elevation of the quantitative insulin sensitivity check index and the fasting glucose to insulin ratio) increased ($P \leq 0.008$) after treatment with either drug. Hirsutism ($P < 0.05$) and serum concentrations of free testosterone ($P < 0.02$) and androstenedione ($P < 0.01$) declined to a similar extent after treatment with the drugs. Treatment with pioglitazone or metformin was associated with the occurrence of pregnancy ($n = 5$ and $n = 3$, respectively). These results suggest that pioglitazone is as effective as metformin in improving insulin sensitivity and hyperandrogenism, despite an increase in body weight, body mass index, and the waist to hip ratio associated with pioglitazone. (*J Clin Endocrinol Metab* 90: 1360–1365, 2005)

POLYCYSTIC OVARY SYNDROME (PCOS) is the most common endocrine disorder in women during their reproductive years, with an estimated frequency between 4% and 7% (1). According to the recently revised criteria for PCOS (2), diagnosis of PCOS requires two of the following three features: oligo- and/or anovulation; clinical and/or biochemical signs of hyperandrogenism; and polycystic ovaries by ultrasound and the absence of other endocrine conditions, such as hypothyroidism, Cushing's syndrome, congenital virilizing adrenal hyperplasia, or hyperprolactinemia.

Since 1980, PCOS has been strongly associated with the presence of insulin resistance (IR) (3) and secondary hyperinsulinemia, mainly but not exclusively, in obese women. The prevalence of IR among these women varies according to the sensitivity and specificity of the assays used and the population of women studied (4).

Previous studies have demonstrated that secondary hyperinsulinemia is the key factor responsible for the hyperandrogenism characteristic of the syndrome (4–6), which is

attributed to an increased stimulation of the activity of the cytochrome P450c 17 α in the ovary (7, 8). Hyperinsulinemia also decreases the circulating concentrations of SHBG and contributes to greater concentrations of free androgens in the blood (8). Women with PCOS and IR have a greater risk for carbohydrate intolerance and type 2 diabetes mellitus (DM) (9, 10), dyslipidemia (11), arterial hypertension (12), coagulation disorders induced by endothelial dysfunction (13), and probably cardiovascular disease (14).

Because IR is a cardinal feature of PCOS, one therapeutic approach is to use drugs to improve insulin sensitivity and ovarian function (15). Metformin, a biguanide class drug used in obese patients with type 2 DM, has become the most widely used drug to treat women with IR and PCOS (6, 16–20). Other drugs include thiazolidinediones (TZD) like troglitazone, which was introduced in 1997 (21) but was later withdrawn because of its hepatotoxic side effects. Most studies using these drugs in women with PCOS did not report serious adverse reactions (22–24). A new TZD, pioglitazone, has been used in women with PCOS who did not respond previously to metformin (25) or in women naive to any medication to improve insulin sensitivity (26, 27).

The aim of this study was to compare the effectiveness of pioglitazone and metformin in ameliorating IR and hyperandrogenism in obese women with PCOS and IR who were naive to previous treatment with drugs intended to improve insulin sensitivity.

Subjects and Methods

The study protocol was approved by the Internal Review Board and the Human Ethical Committee of the Instituto Nacional de Perinatología

First Published Online December 14, 2004

Abbreviations: ALT, Alanine aminotransferase; AST, aspartate aminotransferase; AUC-glucose, area under the glucose curve; AUC-insulin, area under the insulin curve; BMI, body mass index; DM, diabetes mellitus; F-G, Ferriman-Gallwey; HDL, high-density lipoprotein; HOMA, homeostasis model of assessment; IR, insulin resistance; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome; PRL, prolactin; QUICKI, quantitative insulin sensitivity check index; T, testosterone; TC, total cholesterol; TG, total triglycerides; TZD, thiazolidinedione.

JCEM is published monthly by The Endocrine Society (<http://www.endo-society.org>), the foremost professional society serving the endocrine community.

(México City, México), and written informed consent was obtained from all volunteers. The study was conducted according to the Declaration of Helsinki (as amended in October 2000).

Study population

Women with PCOS ($n = 52$), aged 18–35 yr, whose chief complaints were hirsutism [Ferriman-Gallwey (F-G) score > 8] and/or sterility, were recruited from the outpatient Endocrinology and Sterility Clinics of the Instituto Nacional de Perinatología. The diagnosis of PCOS was based on at least two of the three following abnormalities: oligomenorrhea or amenorrhea, a serum androstenedione concentration more than 2.9 ng/ml (> 10.1 nm), or a serum free testosterone (T) concentration more than 2.5 pg/ml (> 8.6 pM) and polycystic ovaries by ultrasound (2). All women had a body mass index (BMI) ≥ 25 kg/m², acanthosis nigricans, fasting hyperinsulinemia greater than 16 μ U/ml (≥ 114.8 pM), and a fasting glucose to insulin ratio of less than 4.5 (28). The presence of the following disorders was excluded by specific laboratory tests: impaired glucose tolerance test or type 2 DM, hyperprolactinemia, thyroid disorders, late-onset congenital adrenal hyperplasia, and Cushing's syndrome. None of the women had been taking clomiphene citrate, oral contraceptives, antiandrogens, or drugs to control their appetite during the previous 6 months. We confirmed the absence of unsuspected pregnancy in all participants before including them in the study. Criteria for exclusion during the study included diagnosis of pregnancy, loss to follow-up, and increased concentration of serum transaminases.

Study design

Treatments. Patients were randomly allocated to one of the following two groups: group 1 ($n = 25$) received pioglitazone (Zactos; Eli Lilly de México, S.A. de C.V., México City, México) 30 mg/d in an oral single dose for 24 wk; and group 2 ($n = 27$) received metformin (Ficonax; PISA Farmacéutica de México, S.A. de C.V., México City, México) orally administered at a dose of 850 mg three times daily for 24 wk. Randomization was by random number tables. The patients' number treatment codes were retained until the end of the trial in a sealed envelope by a third party who did not participate in the study; patients' names were disclosed after completion of the study. Because the drugs had different daily dose schedules (*i.e.* once a day for pioglitazone and three times a day for metformin), the study had an open design. All women were on an unrestricted diet and were instructed not to modify their usual eating or physical exercise patterns during the study period. Subjects began taking the drugs 2 wk after written consent was obtained, and the results of the basal (metabolic and hormonal) studies were available. The women were given extensive contraceptive counseling and were carefully instructed to stop taking the drug immediately upon confirmation of pregnancy (quantitative serum β -human chorionic gonadotropin by RIA).

Assessment program. All patients underwent clinical, metabolic, and hormonal evaluations at baseline that included height, weight, BMI, waist to hip ratio, and hirsutism (F-G) score (29). In the baseline study, vaginal bleeding was induced by progesterone withdrawal, and the following studies were performed on d 3–5: After a 12-h overnight fast, a non-heparinized venous blood sample was obtained between 0800 and 0830 h to measure the circulating concentrations of prolactin (PRL), total T₃, free T₄, TSH, LH, FSH, estradiol, insulin, cortisol, dehydroepiandrosterone sulfate, androstenedione, 17 α -hydroxyprogesterone, free T, glucose, total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and liver function tests, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase. Immediately after the basal blood sample was obtained, a 2-h oral glucose tolerance test (OGTT) was performed with an oral glucose load of 75 g, and non-heparinized blood samples were obtained after 30, 60, 90, and 120 min to measure serum glucose and insulin concentrations. At the end of month 6 of treatment, the same clinical, metabolic, and hormonal evaluations were performed (except for the thyroid function tests and measurements of serum concentrations of PRL, dehydroepiandrosterone sulfate, 17 α -hydroxyprogesterone, and cortisol) on d 3–5 of a spontaneous menstrual cycle. In addition, at baseline and at the end of the study, serum pro-

gesterone concentration was determined on d 18–21 of the menstrual cycle as an index of ovulation.

Methods

The waist and hip circumferences were measured to the nearest centimeter with a soft tape measure according to the World Health Organization criteria. BMI was calculated using the following equation: weight (kg)/height (m²). Hirsutism was clinically evaluated using the F-G score obtained by the same observer (C.O.-G.); a score of greater than 8 was defined as hirsutism (29).

Assay methods

Hormone concentrations were determined in duplicate, and in each assay, the samples were distributed equally relative to each group to minimize the effect of intra- and interassay variability. Concentrations of FSH, LH, TSH, and PRL were analyzed using commercially available immunoradiometric kits (Diagnostic Products Corp., Los Angeles, CA); the intra- and interassay coefficients of variation were $\leq 6\%$ and $\leq 7.8\%$, respectively. The concentrations of the other hormones were measured using commercially available RIA kits (Diagnostic Products Corporation); the intra- and interassay coefficients of variation were $\leq 8\%$ and $\leq 9.2\%$, respectively.

Serum glucose concentration was measured using a glucose oxidase method (GOD-PAP; Diagnostica Merck, México City, México) using an automatic enzymatic autoanalyzer (Vitalab Scientific, Dieren, The Netherlands). The intra- and interassay coefficients of variation were $\leq 2.5\%$ and $\leq 3.9\%$, respectively. Using the serum glucose and insulin concentrations during fasting and the 2-h OGTT, we calculated the following parameters: homeostasis model of assessment (HOMA)-IR (30, 31) = fasting serum insulin (μ U/ml) \times fasting serum glucose (mmol/liter)/22.5; quantitative insulin sensitivity check index (QUICKI) (31, 32) = $1/[\log(I_0) + \log(G_0)]$, where I_0 = fasting serum insulin (μ U/ml) concentration and G_0 = fasting serum glucose (mg/dl) concentration; β -cell function index (20) = $20 \times$ [fasting serum insulin (μ U/ml) concentration/fasting serum glucose concentration (mmol/liter)] - 3.5; fasting glucose to insulin ratio (4, 28) = fasting serum glucose concentration (mg/dl)/fasting serum insulin concentration (μ U/ml); and area under the glucose curve (AUC-glucose) and area under the insulin curve (AUC-insulin) using a trapezoidal method (33).

Serum TC, TG, HDL and LDL cholesterol, ALT, AST, and alkaline phosphatase were measured using an automatized spectrophotometer (Hitachi-912; Roche Mexico, México City, México). The interassay coefficient of variation was $\leq 3.9\%$.

Role of the pharmaceutical companies providing the drugs under study

The pharmaceutical companies providing the drugs played no role in the study design, data collection, data analysis, data interpretation, or writing of the report. No funding of any kind was received to perform the study or by any of the participants in the study. None of the authors has any type of collaboration or working position in any of the drug companies.

Statistical analysis

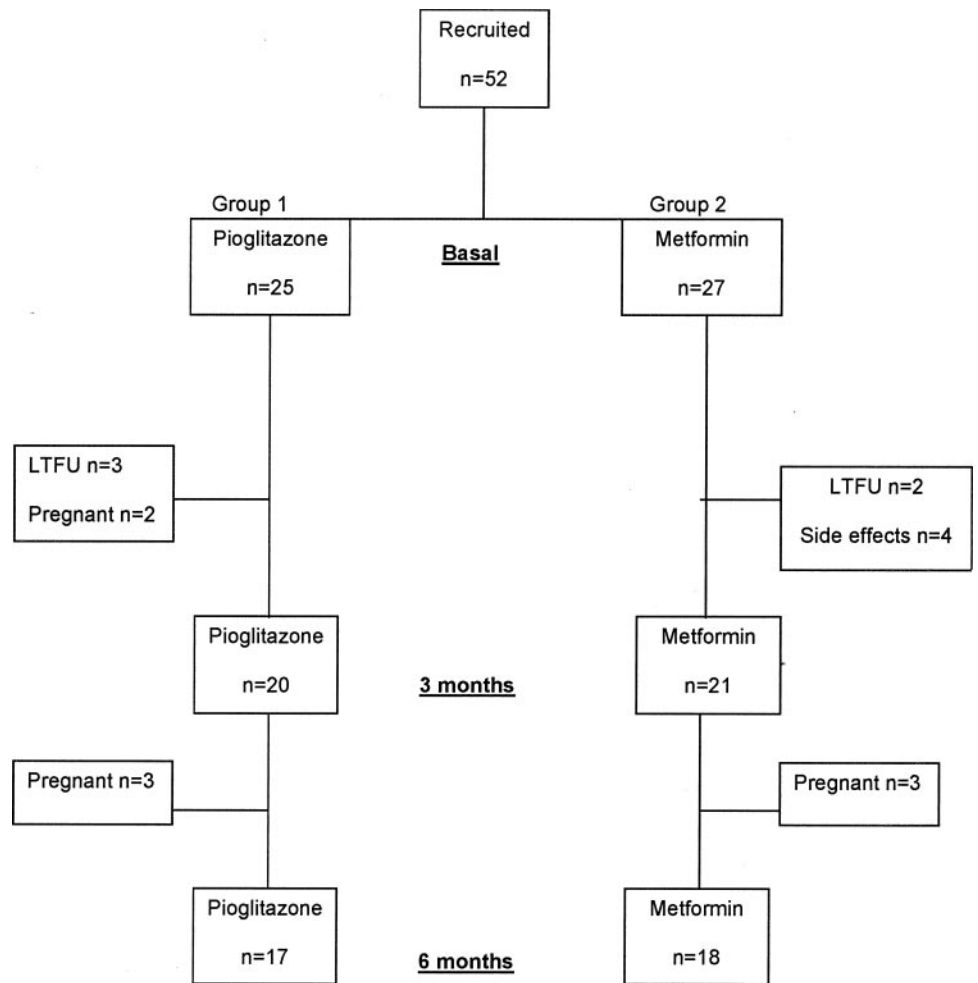
All data are presented as mean \pm SEM, unless stated otherwise. Descriptive statistics were used for continuous data at each visit. Changes in parameters over time were assessed using repeated measures ANOVA, and differences between groups were evaluated using a nonparametric test (Mann-Whitney). Within-group differences were analyzed by the paired Student's *t* test. $P < 0.05$ was considered significant. Data analysis was performed using the statistical software package SPSS for Windows (SPSS, Inc., Chicago, IL).

Results

Clinical characteristics and compliance of the patients

Figure 1 shows the randomization of patients at the start of the study and data on subject retention to the end of the

FIG. 1. Randomization and the retention of patients from recruitment to completion of treatment after 6 months of treatment with either pioglitazone or metformin. LTFU, Lost to follow-up.



6 months of treatment with either pioglitazone or metformin. In the pioglitazone group, three women were lost to follow-up, and five became pregnant; in the metformin group, two women were lost to follow-up, four abandoned the study because of severe gastrointestinal side effects, and three became pregnant. The clinical, metabolic, and hormonal measures at the baseline evaluation did not differ significantly between women lost to follow-up or the women who became pregnant and the remaining 35 women who completed the study. The five women lost to follow-up left the study for socioeconomic reasons. The final numbers of patients were 17 in the pioglitazone group and 18 in the metformin group,

and the statistical analysis was performed on data from these 35 women only.

Table 1 presents the subjects' clinical characteristics at baseline and after 6 months of treatment. There were no significant differences in clinical baseline characteristics between groups 1 and 2, and their ages were comparable. All subjects were overweight (BMI ≥ 28 kg/m²), had waist to hip ratios of more than 0.80, and had considerable hirsutism with F-G scores ≥ 10 . After 6 months of treatment with pioglitazone, body weight increased by 4.7 kg and BMI increased (both $P < 0.05$); treatment with metformin caused nonsignificant decreases in body weight and BMI. The waist to hip

TABLE 1. Clinical characteristics of the patients

Parameter	Pioglitazone		Metformin	
	Baseline (n = 17)	6 Months (n = 17)	Baseline (n = 18)	6 Months (n = 18)
Age (yr)	28.8 \pm 0.9		29.0 \pm 0.8	
Weight (kg)	77.6 \pm 2.6	82.3 \pm 3.0 ^a	83.7 \pm 3.8	80.5 \pm 3.9
BMI (kg/m ²)	32.2 \pm 1.0	34.0 \pm 1.2 ^a	34.1 \pm 1.6	32.9 \pm 1.7
W/H ratio	0.90 \pm 0.01	0.95 \pm 0.02 ^b	0.89 \pm 0.01	0.89 \pm 0.01
Hirsutism, F-G score	14.9 \pm 1.0	10.4 \pm 0.6 ^a	16.0 \pm 0.8	11.1 \pm 0.8 ^c

Values are mean \pm SEM. W/H ratio, Waist to hip ratio.

^a $P < 0.05$ compared with baseline.

^b $P = 0.02$ compared with baseline.

^c $P < 0.001$ compared with baseline.

ratio increased significantly ($P = 0.02$) after pioglitazone treatment and remained unchanged after metformin treatment. The F-G score decreased from baseline values in both groups.

Metabolic parameters

Table 2 presents the subjects' metabolic parameters. None of the women had any degree of glucose intolerance at baseline because this was a criterion for exclusion from the study. At baseline, the metabolic parameters were comparable in both groups, which had clear hyperinsulinemia during both fasting and in response to the oral glucose challenge as indicated by the AUC-insulin. The baseline HOMA-IR index was elevated, whereas QUICKI and the fasting glucose to insulin ratio were similarly low in both groups.

The AUC-glucose decreased significantly after treatment with either drug ($P = 0.05$). Treatment with pioglitazone resulted in significant decreases in fasting serum insulin concentration ($P < 0.001$), the AUC-insulin during the 2-h OGTT ($P < 0.002$), and the HOMA-IR index ($P < 0.001$). Pioglitazone treatment increased the QUICKI ($P < 0.001$) and the fasting glucose to insulin ratio ($P < 0.001$). Treatment with metformin decreased fasting serum insulin concentration ($P < 0.001$), the AUC-insulin ($P < 0.05$), and the HOMA-IR index ($P < 0.001$). Metformin treatment increased significantly the QUICKI ($P < 0.008$) and the fasting glucose to insulin ratio ($P < 0.001$). After 6 months of treatment, the AUC-insulin was significantly lower in the pioglitazone group compared with the metformin group ($P < 0.05$).

Serum concentrations of TG, TC, HDL and LDL cholesterol, AST, and ALT were within the normal ranges at baseline in both groups and remained unchanged during the study, except for a slight decrease in serum TG concentration ($P = 0.05$) in the metformin group.

Hormonal parameters

Table 3 presents the hormonal parameters. The baseline hormone concentrations were similar in both groups. Pioglitazone and metformin had similar effects on androgen serum concentrations, causing significant decreases in the

concentrations of free T ($P < 0.02$ and $P < 0.05$, respectively) and androstenedione (both $P < 0.01$). Serum LH concentrations decreased slightly but significantly in both groups ($P < 0.05$). The concentrations of the other hormones remained unchanged throughout the study in both groups.

Pregnancy occurrence and outcomes

Although we did not precisely evaluate ovulation rates, the occurrence of eight pregnancies during month 6 of administration of the drugs (five pregnancies on pioglitazone and three on metformin) suggests that these drugs induced rapid normalization of menstrual cycles and ovulation in a subset of these women. This is supported by significant increases in serum progesterone concentrations from 1.6 ± 0.4 ng/ml (5.0 ± 1.2 nM) to 4.5 ± 0.7 ng/ml (14.3 ± 2.2 nM) in the pioglitazone group ($P < 0.04$) and from 1.4 ± 0.7 ng/ml (4.4 ± 2.2 nM) to 4.1 ± 0.3 ng/ml (13.0 ± 1.0 nM) in the metformin group ($P < 0.05$). In our laboratory, a serum progesterone concentration greater than 3.5 ng/ml (11.1 nM) is indicative of ovulation. Of the eight women who became pregnant, four had a first-trimester abortion (three women on pioglitazone and one on metformin), and three developed gestational DM (two women on pioglitazone and one on metformin), which was treated with dietary management and insulin administration (twice a day), and subsequently had an uneventful at-term delivery (>38 wk of gestation). Only one woman (on metformin) had a full-term normal pregnancy. All four newborns (two from mothers on each drug) had a normal weight for gestational age and were clinically healthy and without perinatal complications.

Discussion

Our study showed that 6 months of administration of pioglitazone to obese women with PCOS and severe IR was as effective as metformin in decreasing fasting blood serum insulin concentration and the AUC-insulin during a 2-h OGTT without significantly changing fasting blood glucose concentration or the AUC-glucose. Pioglitazone and metformin caused similar significant decreases in hirsutism and

TABLE 2. Metabolic parameters

Parameter	Pioglitazone		Metformin	
	Baseline (n = 17)	6 Months (n = 17)	Baseline (n = 18)	6 Months (n = 18)
Fasting glucose (mg/dl)	92.5 ± 2.6	88.6 ± 1.8	93.4 ± 2.9	88.7 ± 2.1
AUC-glucose (mg/dl·min)	16,383 ± 742	14,871 ± 734 ^a	17,337 ± 716	14,213 ± 684 ^a
Fasting insulin (μU/ml)	31.1 ± 1.1	11.1 ± 1.4 ^{b,c}	31.1 ± 1.5	11.0 ± 1.4 ^b
AUC-insulin (μU/ml·min)	14,884 ± 1,800	10,930 ± 1,241 ^{b,c}	16,027 ± 2,078	13,415 ± 1,830 ^a
HOMA-IR	7.03 ± 0.28	2.42 ± 0.31 ^b	7.21 ± 0.52	2.43 ± 0.3 ^b
QUICKI	0.29 ± 0.001	0.34 ± 0.004 ^b	0.29 ± 0.001	0.34 ± 0.003 ^b
Fasting G/I ratio	3.02 ± 0.13	9.38 ± 1.12 ^b	3.19 ± 0.13	9.33 ± 1.32 ^b
Serum TG (mg/dl)	158.6 ± 14.8	143.7 ± 14.4	151.4 ± 11.0	124.6 ± 8.96 ^b
TC (mg/dl)	189.4 ± 7.7	174.3 ± 7.6	183.1 ± 6.3	181.3 ± 7.3
HDL cholesterol (mg/dl)	41.1 ± 2.1	46.9 ± 3.0	38.7 ± 2.5	42.6 ± 1.9
LDL cholesterol (mg/dl)	120.5 ± 6.2	116.1 ± 5.8	111.3 ± 5.6	124.3 ± 6.3
AST (IU/liter)	20.35 ± 1.34	18.00 ± 1.57	21.78 ± 1.90	23.10 ± 1.68
ALT (IU/liter)	22.65 ± 1.31	19.90 ± 1.22	26.06 ± 2.50	24.33 ± 1.98

Values are means ± SEM. Conversion factors: glucose, 0.05551; insulin, 7.175; TG, 0.01129; TC, 0.02586; HDL cholesterol, 0.02586; LDL cholesterol, 0.02586; AST, 1.0; ALT, 1.0. G/I, Glucose to insulin.

^a $P = 0.05$ compared with baseline values of the corresponding group.

^b $P < 0.008$ compared with baseline values of the corresponding group.

^c $P < 0.05$ compared with the metformin group at 6 months.

TABLE 3. Hormonal parameters

Parameter	Pioglitazone		Metformin	
	Baseline (n = 17)	6 Months (n = 17)	Baseline (n = 18)	6 Months (n = 18)
DHEAS ($\mu\text{g}/\text{dl}$)	248.7 \pm 33.6	221.3 \pm 33.8	190.9 \pm 18.6	184.7 \pm 18.4
Free T (pg/ml)	3.07 \pm 0.39	2.12 \pm 0.35 ^a	2.67 \pm 0.32	1.81 \pm 0.29 ^a
Androstenedione (ng/ml)	3.81 \pm 0.32	2.50 \pm 0.26 ^a	3.62 \pm 0.17	2.07 \pm 0.14 ^a
LH (ng/ml)	4.53 \pm 0.46	3.08 \pm 0.29 ^a	5.19 \pm 0.59	3.41 \pm 0.47 ^a
FSH (mIU/ml)	4.13 \pm 0.40	4.68 \pm 0.73	3.34 \pm 0.35	3.25 \pm 0.26
Estradiol (pg/ml)	51.29 \pm 6.84	37.52 \pm 4.20	44.12 \pm 8.81	36.37 \pm 4.66

Values are means \pm SEM. Conversion factors: DHEAS, 0.002714; free T, 3.467; androstenedione, 3.492; LH, 1.0; FSH, 1.0; estradiol, 3.671. DHEAS, Dehydroepiandrosterone sulfate.

^a $P < 0.05$ compared with baseline value in the same group.

serum concentrations of free T and androstenedione. Five women on pioglitazone (29%) and three on metformin (17%) became pregnant during the study. The lipid profile was within normal limits at the start of the study and remained unchanged after the study, and the drugs did not alter liver enzyme concentrations.

Two points deserve comment. First, because we selected only markedly obese PCOS women with acanthosis nigricans and the most advance degree of IR, our results may not apply strictly to all women with PCOS. Second, the reported values of free T were obtained using a competitive RIA test, which is less reliable than those obtained by calculating the free androgen index.

Our results agree with previous reports using other TZDs (22, 24) or metformin (6, 17, 19) and with recent studies in obese women with PCOS and IR taking either pioglitazone (25–27) or metformin (15, 17, 34). However, in our head-to-head trial with metformin, pioglitazone seemed to be more effective in improving insulin sensitivity because both fasting serum insulin concentration and the AUC-insulin were significantly lower after pioglitazone than after metformin treatment. The same observation has been reported recently in patients with type 2 DM (35). This is particularly interesting because, in our study, a submaximal dose of pioglitazone was given (maximum dose recommended for treatment of DM is 45 mg/d), whereas metformin was given in the maximal dose (2.5 g/d).

Recent data suggest that the amelioration of clinical and hormonal hyperandrogenism induced by specific treatment in women with PCOS could be jeopardized by an increase in body weight and BMI (36). However, we found that both drugs caused similar improvements in clinical and hormonal hyperandrogenism and that pioglitazone was more effective in reducing IR and improving the indices of insulin sensitivity. These changes occurred despite a significant increase in body weight, BMI, and waist to hip ratio associated with the use of pioglitazone but not with metformin. Similar findings have been reported in obese male and female patients with type 2 DM and IR treated with other TZDs (35–37). These paradoxical results can be explained by the beneficial shift from abdominal to sc fat and the simultaneous improvement in insulin sensitivity induced by TZD (37–39).

Pioglitazone may improve hyperandrogenism through a similar mechanism as troglitazone. The putative ligand-mediated activation of PPAR γ 2 by troglitazone impairs androgen and stimulates progesterone biosynthesis in primary cultures of porcine theca cells (40) by blocking the expression of the cyto-

chrome P450–17 α hydroxylase/C17–20 lyase gene and cytochrome P450 protein phosphorylation, which decreases the LH–insulin-driven theca cell androgen production (41).

Obese women with PCOS may demonstrate higher intra- and interindividual variation in the IR calculated using the HOMA method than obese control women without PCOS (42). It has been proposed that, at any level of IR, a decline by more than 31% is needed in a subsequent sample to ascribe any change to a therapeutic intervention (42). We found decreases of 66% and 67% in the HOMA-IR index after 6 months of treatment with pioglitazone and metformin, respectively, and decreases of 59% and 40% in fasting serum insulin concentration after treatment with pioglitazone and metformin, respectively. These changes suggest that the amelioration of the IR status in these obese women with PCOS can be attributed to the effects of pioglitazone or metformin.

Pregnancy events and complications (*e.g.* abortions and gestational DM) seemed to occur more frequently in the pioglitazone than in the metformin group, although the sample size is too small to draw any final conclusions. We believe that it is necessary to comment on the safety of TZD and metformin in women who may become pregnant, such as those in our study. Pioglitazone and rosiglitazone are classified as pregnancy category C drugs because of animal evidence showing growth retardation in mid to late gestation. Thus, women with PCOS being treated with either drug should be given extensive contraceptive counseling at the onset and carefully instructed to stop taking the drug immediately if pregnancy be confirmed (43, 44). This contrasts markedly with metformin, which is classified as a pregnancy category B drug and which appears to be safe during pregnancy for mother and fetus and even seems to reduce the risk of first-trimester abortion (45, 46).

In summary, our head-to-head study demonstrated that administration of pioglitazone for 6 months was as effective as metformin in improving severe IR and hyperandrogenism in obese women with PCOS. Pioglitazone, but not metformin, caused a simultaneous increase in body weight, BMI, and the waist to hip ratio. Pioglitazone was not hepatotoxic and did not cause substantial side effects. Further studies are needed to measure the effects of pioglitazone on fat tissue metabolism, the distribution of visceral and sc fat, and IR in obese women with PCOS. Pioglitazone's potential therapeutic value of promoting a beneficial shift from abdominal to sc fat tissue may outweigh the increase in body weight and BMI and perhaps total body fat level.

Acknowledgments

We express our gratitude to all volunteers who participated in the study. We are also indebted to Eli Lilly de México, S.A. de C.V., and to PISA Farmacéutica de México, S.A. de C.V., for the unconditional supply of pioglitazone and metformin, respectively.

Received October 7, 2004. Accepted December 6, 2004.

Address all correspondence and requests for reprints to: C. Ortega-González, M.D., Instituto Nacional de Perinatología, Department of Endocrinology, Montes Urales 800, Lomas Virreyes, 11000 México City, México. E-mail: ortegacarlos@hotmail.com.

References

- Lobo RA 2003 What are the key features of importance in polycystic ovary syndrome? *Fertil Steril* 80:259–261
- The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2004 Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod* 19:41–47
- Burghen GA, Givens JR, Kitabchi AE 1980 Correlation of hyperandrogenism with hyperinsulinemia in polycystic ovarian disease. *J Clin Endocrinol Metab* 50:113–116
- Dunaif A 1997 Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. *Endocr Rev* 18:774–800
- Richardson MR 2003 Current perspectives in polycystic ovary syndrome. *Am Fam Physician* 68:697–704
- Baillargeon JP, Iuorno MJ, Nestler JE 2002 Comparison of metformin and thiazolidinediones in the management of polycystic ovary syndrome. *Curr Opin Endocrinol Diabetes* 9:303–311
- Nestler JE, Jakubowicz DJ, de Vargas AF, Brik C, Quintero N, Medina F 1998 Insulin stimulates testosterone biosynthesis by human thecal cells from women with polycystic ovary syndrome by activating its own receptor and using inositolglycan mediators as the signal transduction system. *J Clin Endocrinol Metab* 83:2001–2005
- Azziz R 2003 Androgen excess is the key element in polycystic ovary syndrome. *Fertil Steril* 80:252–254
- Solomon CG, Hu FB, Dunaif A, Rich-Edwards J, Willett WC, Hunter DJ, Colditz GA, Speizer FE, Manson JE 2001 Long or highly irregular menstrual cycles as a marker for risk of type 2 diabetes mellitus. *JAMA* 286:2421–2426
- Legro RS 2002 Diabetes prevalence and risk factors in polycystic ovary syndrome. *Curr Opin Endocrinol Diabetes* 9:451–458
- Legro RS, Kunselman AR, Dunaif A 2001 Prevalence and predictors of dyslipidemia in women with polycystic ovary syndrome. *Am J Med* 111:607–613
- Bjorntorp P 1996 The android woman—a risky condition. *J Intern Med* 239:105–110
- Paradisi G, Steinberg HO, Hempfling A, Cronin J, Hook G, Shepard MK, Baron AD 2001 Polycystic ovary syndrome is associated with endothelial dysfunction. *Circulation* 103:1410–1415
- Legro RS 2003 Polycystic ovary syndrome and cardiovascular disease: a premature association? *Endocr Rev* 24:302–312
- Lord JM, Flight IH, Norman RJ 2003 Insulin-sensitizing drugs (metformin, troglitazone, rosiglitazone, pioglitazone, d-chiro-inositol) for polycystic ovary syndrome. *Cochrane Database Syst Rev* 3:CD003053
- Ibañez L, Valls C, Ferrer A, Ong K, Dunger DB, De Zegher F 2002 Additive effects of insulin-sensitizing and anti-androgen treatment in young, nonobese women with hyperinsulinism, hyperandrogenism, dyslipidemia, and anovulation. *J Clin Endocrinol Metab* 87:2870–2874
- Harborne L, Fleming R, Lyall H, Norman J, Sattar N 2003 Descriptive review of the evidence for the use of metformin in polycystic ovary syndrome. *Lancet* 361:1894–1901
- Haas DA, Carr BR, Attia GR 2003 Effects of metformin on body mass index, menstrual cyclicity, and ovulation induction in women with polycystic ovary syndrome. *Fertil Steril* 79:469–481
- Velazquez EM, Mendoza S, Hamer T, Sosa F, Glueck CJ 1994 Metformin therapy in polycystic ovary syndrome reduces hyperinsulinemia, insulin resistance, hyperandrogenemia, and systolic blood pressure, while facilitating normal menses and pregnancy. *Metabolism* 43:647–654
- Lord JM, Flight IH, Norman RJ 2003 Metformin in polycystic ovary syndrome: systematic review and meta-analysis. *BMJ* 327:951–953
- Ehrmann DA, Schneider DJ, Sobel BE, Cavaghan MK, Imperial J, Rosenfield RL, Polonsky KS 1997 Troglitazone improves defects in insulin action, insulin secretion, ovarian steroidogenesis, and fibrinolysis in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 82:2108–2116
- Dunaif A, Scott D, Finegood D, Quintana B, Whitcomb R 1996 The insulin-sensitizing agent troglitazone improves metabolic and reproductive abnormalities in the polycystic ovary syndrome. *J Clin Endocrinol Metab* 81:3299–3306
- Ehrmann DA, Cavaghan MK, Imperial J, Sturis J, Rosenfield RL, Polonsky KS 1997 Effect of metformin on insulin secretion, insulin action, and ovarian steroidogenesis in woman with polycystic ovary syndrome. *J Clin Endocrinol Metab* 82:524–530
- Azziz R, Ehrmann D, Legro RS, Whitcomb RW, Hanley R, Fereshetian AG, O'Keefe M, Ghazzi MN, PCOS/Troglitazone Study Group 2001 Troglitazone improves ovulation and hirsutism in the polycystic ovary syndrome: a multicenter, double blind, placebo-controlled trial. *J Clin Endocrinol Metab* 86:1626–1632
- Glueck CJ, Moreira A, Goldenber N, Sieve L, Wang P 2003 Pioglitazone and metformin in obese women with polycystic ovary syndrome not optimally responsive to metformin. *Hum Reprod* 18:1618–1625
- Romualdi D, Guido M, Ciampelli M, Giuliani M, Leoni F, Perri C, Lanzone A 2003 Selective effects of pioglitazone on insulin and androgen abnormalities in normo- and hyperinsulinaemic obese patients with polycystic ovary syndrome. *Hum Reprod* 18:1210–1218
- Brettenthaler N, De Geyter C, Huber PR, Keller U 2004 Effect of the insulin sensitizer pioglitazone on insulin resistance, hyperandrogenism and ovulatory dysfunction in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 89:3835–3840
- Parra A, Ramírez A, Espinosa de los Monteros A 1994 Fasting glucose/insulin ratio. An index to differentiate normo- from hyperinsulinemic women with polycystic ovary syndrome. *Rev Invest Clin* 46:363–368
- Ferriman D, Gallwey JD 1961 Clinical assessment of body hair growth in women. *J Clin Endocrinol Metab* 21:1440–1448
- Albareda M, Rodríguez-Espinosa J, Murugo M, de Leyva A, Corcoy R 2000 Assessment of insulin sensitivity and β -cell function from measurements in the fasting state and during and oral glucose tolerance test. *Diabetologia* 43:1507–1511
- Radziuk J 2000 Insulin sensitivity and its measurement: structural commonalities among the methods. *J Clin Endocrinol Metab* 85:4426–4433
- Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, Quon MJ 2000 Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. *J Clin Endocrinol Metab* 85:2402–2410
- Tai MM 1994 A mathematical model for the determination of total area under glucose tolerance and other metabolic curves. *Diabetes Care* 17:152–154
- Harborne L, Fleming R, Lyall H, Sattar N, Norman J 2003 Metformin or antiandrogen in the treatment of hirsutism in polycystic ovary syndrome *J Clin Endocrinol Metab* 88:4116–4123
- Pavo J, Jermendy G, Varkonyi TT, Kerenyi Z, Gyimesi A, Shoustov S, Shestakova M, Herz M, Johns D, Schluchter BJ, Festa A, Tan MH 2003 Effect of pioglitazone compared with metformin on glycemic control and indicators of insulin sensitivity in recently diagnosed patients with type 2 diabetes *J Clin Endocrinol Metab* 88:1637–1645
- Cibula D, Hill M, Fanta M, Sindelka G, Zivny J 2001 Does obesity diminish the positive effect of oral contraceptive treatment on hyperandrogenism in women with polycystic ovarian syndrome? *Hum Reprod* 16:940–944
- Kelly IE, Han TS, Walsh K, Lean MEJ 1999 Effects of a thiazolidinedione compound on body fat distribution of patients with type 2 diabetes. *Diabetes Care* 22:288–293
- Akazawa S, Sun F, Ito M, Kawasaki E, Eguchi K 2000 Efficacy of troglitazone on body fat distribution in type 2 diabetes. *Diabetes Care* 23:1067–1071
- Fonseca V 2003 Effect of thiazolidinediones on body weight in patients with diabetes mellitus. *Am J Med* 115(Suppl 8A):42S–48S
- Schoppee PD, Garmey JC, Veldhuis JD 2002 Putative activation of the peroxisome proliferator activated receptor γ impairs androgen and enhances progesterone biosynthesis in primary cultures of porcine theca cells. *Biol Reprod* 66:190–198
- Veldhuis JD, Zhang G, Garmey JC 2002 Troglitazone, an insulin sensitizing thiazolidinedione, represses combined stimulation by LH and insulin of *de novo* androgen biosynthesis by theca cells *in vitro*. *J Clin Endocrinol Metab* 87:1129–1133
- Jayagopal V, Kilpatrick ES, Holding S, Jennings PE, Atkin SL 2002 The biological variation of insulin resistance in polycystic ovarian syndrome. *J Clin Endocrinol Metab* 87:1560–1562
- Cataldo N, Abbasi F, McLaughlin T, Lamendola C, Reaven G 2001 Improvement in insulin sensitivity followed by ovulation and pregnancy in a woman with polycystic ovary syndrome who was treated with rosiglitazone. *Fertil Steril* 76:1057–1059
- Ghazeeri G, Kutteh WH, Bryer-Ash M, Haas D, Ke RW 2003 Effect of rosiglitazone on spontaneous and clomiphene citrate-induced ovulation in women with polycystic ovary syndrome. *Fertil Steril* 79:562–566
- Glueck C, Wang P, Goldenberg N, Sieve-Smith L 2002 Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin. *Hum Reprod* 17:2858–2864
- Jakubowicz DJ, Iuorno MJ, Jakubowicz S, Roberts KA, Nestler JE 2002 Effects of metformin on early pregnancy loss in the polycystic ovary syndrome. *J Clin Endocrinol Metab* 87:524–529