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Effect of the Insulin Sensitizer Pioglitazone on Insulin Resistance, Hyperandrogenism, and Ovulatory Dysfunction in Women with Polycystic Ovary Syndrome

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Polycystic ovary syndrome (PCOS) is characterized by hyperandrogenism, chronic anovulation, and insulin resistance; long-term consequences include diabetes mellitus type 2. The aim of this randomized, double-blind, controlled trial was to investigate whether the thiazolidinedione derivative pioglitazone diminishes insulin resistance and hyperandrogenism and enhances ovulation rates in women with PCOS. Forty premenopausal women with PCOS were randomly allocated to treatment with either pioglitazone (30 mg/d) or placebo for periods of 3 months. Administration of pioglitazone resulted in a remarkable decline in both fasting serum insulin levels ($P < 0.02$) and the area under the insulin response curve after an oral glucose load ($P < 0.02$). This represented an increase in insulin sensitivity and a decrease in insulin secretion ($P < 0.05$). Furthermore, pioglitazone increased serum SHBG ($P < 0.05$), resulting in a significant decrease in the free androgen index ($P < 0.05$ compared with placebo). Treatment with pioglitazone was also associated with higher ovulation rates ($P < 0.02$). Thus, pioglitazone significantly improved insulin sensitivity, hyperandrogenism, and ovulation rates in women with PCOS, thereby providing both metabolic and reproductive benefits. (*J Clin Endocrinol Metab* 89: 3835–3840, 2004)

POLYCYSTIC OVARY SYNDROME (PCOS) is one of the most common endocrine disorders in women, affecting approximately 6% of all women during their reproductive life (1–3). It is a heterogeneous condition characterized mainly by hyperandrogenism, chronic anovulation, and infertility. The long-term consequences are similar to those of the metabolic syndrome, including an elevated risk for myocardial infarction (4–6), diabetes mellitus (7, 8), endothelial dysfunction, hemostatic abnormalities, hypertension, and dyslipidemia (9).

Although the precise pathogenesis of PCOS remains uncertain, insulin resistance and consecutive hyperinsulinemia are found in approximately 80% of affected women (10). Although PCOS and obesity have a synergistic deleterious effect on glucose tolerance, insulin resistance is also found in nonobese PCOS patients (11), representing a significant marker of excess cardiovascular risk among these women (12).

Existing therapies for PCOS have focused on the suppression of androgen production or induction of ovulation. More recently, several studies have demonstrated that effective reduction of insulin resistance induces regular menstrual cycles and fertility. This has been mainly achieved by administration of diazoxide (13) and metformin (14–17).

Thiazolidinediones belong to a new class of antidiabetic drugs acting as insulin sensitizers (18). Various thiazolidinedione compounds have been developed; troglitazone (19, 20), rosiglitazone, and recently pioglitazone (21–23) have shown beneficial effects in PCOS. Meanwhile, due to significant hepatic toxicity, troglitazone, the only compound that has been tested in prospective controlled trials, has been withdrawn from the market (24, 25).

Pioglitazone is a new thiazolidinedione derivative that has been approved for the treatment of type 2 diabetes (26). Furthermore, it has both antiinflammatory and antiarteriosclerotic properties, which may be useful for reducing the mortality of cardiovascular disease (27). However, the effect of pioglitazone in PCOS has not been assessed previously in a prospective, randomized controlled trial.

Subjects and Methods

Subjects

Forty patients with established PCOS (criteria as described in Ref. 28) were randomly allocated to treatment with either pioglitazone (30 mg/d) or placebo (20 patients in each group).

PCOS was diagnosed by the presence of 1) long-standing ovulatory dysfunction (oligo- or amenorrhea), 2) hirsutism (Ferriman-Gallwey score, ≥7) and/or circulating serum total testosterone greater than 2.5 nmol/liter and SHBG concentrations less than 50 nmol/liter, and 3) exclusion of other endocrine disorders, such as thyroidal dysfunction, adrenal diseases, and hyperprolactinemia. Other exclusion criteria were desire for pregnancy or existing pregnancy, basal FSH concentration greater than 20 IU/liter, diabetes mellitus, past hysterectomy, intake of medication known or suspected to affect reproductive or metabolic function, history of liver disease and/or alcohol abuse, elevated liver enzymes, or severe uncontrolled illness. All subjects showed a polycystic appearance of the ovaries on transvaginal ultrasound examination. All potentially fertile patients were asked to use barrier methods of contraception during the entire study period.

Study protocol

The protocol of the study was approved by the regional ethics committee. After having given written and signed informed consent, pa-

Abbreviations: BMI, Body mass index; oGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome.

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tients were asked to adapt to a written list of recommendations concerning a healthy diet and physical activity for weight maintenance during a period of 4 wk while knowingly receiving a placebo (run-in phase). Thereafter, randomization was performed, and treatment with either 30 mg pioglitazone or placebo (identical tablets, taken once daily) was started. Both patients and physicians were blinded to treatment. Every second week each patient was examined by the treating physician; vital signs and body measurements were determined, and serum was taken for the measurement of progesterone concentrations. Compliance with the medication was determined by pill count.

Hormonal parameters

Blood samples were drawn after an overnight fast in cyclic women in the follicular phase (d 3–8) of the cycle, at the end of the run-in phase, and at the end of the treatment phase for measurement of serum testosterone, SHBG, dihydroepiandrosterone sulfate, FSH, LH, progesterone, low density lipoprotein, high density lipoprotein, cholesterol, triglycerides, and liver enzymes. An LHRH test with measurement of concentrations of LH and FSH after iv injection of 100 μg LHRH (Ferring, Wallisellen, Switzerland) was performed to assess pituitary function, and an oral glucose tolerance test (oGTT) was conducted to assess glucose tolerance, insulin sensitivity [using the model of Matsuda and De Fronzo (29)], and β-cell function using homeostasis model assessment indexes (30).

Serum samples were frozen at −70 C, and measurements were performed after completion of the study (laboratories Schönenbuch/Allschwil, Switzerland); serum progesterone (reference range, follicular phase, 0.6–4.7 nmol/liter), LH (reference range, follicular phase, 0.4–12.6 IU/liter; Second NIBSC 80/552), FSH [reference range, follicular phase, 3.5–12.5 IU/liter; Second International Reference Preparation (World Health Organization) 78/549], testosterone (reference range, 2.7–2.9 nmol/liter), dihydroepiandrosterone sulfate (reference range, 2.7–9.2 μmol/liter), and insulin [reference range, 21–118 pmol/liter; First International Reference Preparation (World Health Organization) 66/304] were measured by electrochemiluminescence immunoassays (Roche, Rotkreuz, Switzerland). Liver enzymes, glucose, and lipids were measured using enzymatic methods (Roche Hitachi). The free androgen index was calculated as: testosterone (nmol/liter) × 100/SHBG (nmol/liter) (31).

The occurrence of ovulation was assessed for each patient by serial measurement of serum progesterone together with self-reported menstruation. Ovulation was defined if progesterone levels exceeded 9 nmol/liter (32) with consecutive menstruation after 2 wk as an indicator of menstruation. The inaccuracy of the test systems (interassay coefficient of variation) was, on the average, less than 5%.

Statistical methods

The Gaussian distribution of all parameters was confirmed by Kolmogorov-Smirnov tests. The efficacy of treatment (placebo *vs.* pioglitazone; within-subject effects before *vs.* after treatment) was compared between the two study groups by ANOVA with repeated measurements; ovulation rates were compared by χ^2 tests. For evaluation of the results of the oGTT and LHRH tests, the areas under the curves of the measured parameters were calculated using the trapezoidal rule. Data are the mean ± SEM. Data analysis was performed using the statistical software package SPSS for Windows (SPSS, Inc., Chicago, IL).

Results

Clinical characteristics (Table 1) and compliance of the patients

Of the 40 patients included into the study, 35 (87.5%) finished the trial, and data were available for analyses. The number of patients not completing the study and the reasons for termination were similar among both groups (loss to follow-up and protocol violation). The ethnic background of the subjects was similar to that of other women attending our hospital; in 26 (65%) it was European, in 12 (30%) it was Turkish, and in 2 (5%) it was Asian, and the distribution was equal in both study groups.

There were no significant differences in baselines features between the treatment groups. Seventy-one percent of patients in the pioglitazone group were overweight [body mass index (BMI), >25 kg/m^2], and their BMI ranged from 17.7–43.4 kg/m^2, compared with 61% overweight subjects in the placebo group (BMI range, 21.6–42.7 kg/m^2). With the exception of two subjects in each group, all subjects had a waist/hip ratio above 0.80. Except for one patient in each group, all women suffered from hirsutism. Waist/hip ratio, hirsutism, and BMI remained unchanged during the course of the study in both groups.

Metabolic parameters (Table 2)

Before the trial, three patients in each treatment group (pioglitazone/placebo) had impaired glucose tolerance compared with two and one patient after treatment, respectively. Treatment with pioglitazone resulted in a significant decrease in both fasting serum insulin levels and the area under the curve of serum insulin after the oGTT ($P < 0.02$ compared with placebo; Fig. 1). Consistent with these findings there was a significant increase in insulin sensitivity and a decrease in insulin secretion ($P < 0.05$; $P < 0.02$ compared with placebo, respectively).

Hormonal parameters (Table 3)

The baseline hormonal parameters were similar in the treatment groups. Treatment with pioglitazone was associated with a significant increase in SHBG, resulting in a significant decrease in the free androgen index ($P < 0.05$ compared with placebo; Fig. 2).

LHRH-stimulated levels of LH and FSH at 30 and 60 min as well as the area under the curve for LH were significantly lower after ($P < 0.01$, $P < 0.05$, and $P < 0.01$ respectively) than before treatment with pioglitazone.

For both metabolic and hormonal parameters, statistical

TABLE 1. Clinical characteristics of the patients

Parameter	Pioglitazone		Placebo	
	Before treatment	After 3 months	Before treatment	After 3 months
No.	17	17	18	18
Age (yr)	30.2 ± 1.4		30.6 ± 1.1	
BMI (kg/m^2)	29.4 ± 1.7	30.1 ± 1.7	27.5 ± 1.2	27.7 ± 1.2
Waist/hip ratio	0.9 ± 0.1	0.8 ± 0.0	0.9 ± 0.0	0.8 ± 0.0
Hirsutism (Ferriman-Gallwey score)	15.5 ± 1.2	15.6 ± 1.3	15.6 ± 2.0	15.9 ± 1.9

Values are the mean ± SEM. None of the differences between or within groups were statistically significant.

TABLE 2. Metabolic parameters

Parameter	Pioglitazone		Placebo	
	Before treatment	After 3 months	Before treatment	After 3 months
Fasting plasma glucose (mmol/liter)	4.8 ± 0.1	4.8 ± 0.1	4.8 ± 0.1	5.0 ± 0.1
Glucose AUC (mmol/liter·min)	789.9 ± 53.3	694.2 ± 42.9[a]	804.3 ± 52.6	788.8 ± 40.6
Fasting serum insulin (pmol/liter)	68.3 ± 9.7	53.2 ± 5.3[b]	47.8 ± 4.6	62.0 ± 8.4[a]
Insulin AUC (pmol/liter·min)	51,615.3 ± 6,910.5	33,506 ± 3,732[a,b]	37,731 ± 4,380	40,050 ± 4,680
HOMA index (mIU/liter/mg/dl)	16.1 ± 2.1	12.6 ± 1.1[a,b]	11.6 ± 1.1	14.1 ± 1.7
Insulin sensitivity index ($mmol^{-1}/pmol^{-1}$/liter)	16.3 ± 3.5	19.6 ± 2.7[c]	16.9 ± 2.0	15.2 ± 1.8
Serum triglycerides (mmol/liter)	1.2 ± 0.1	1.08 ± 0.1	1.2 ± 0.1	1.3 ± 0.1
Serum cholesterol (mmol/liter)	4.8 ± 0.2	4.6 ± 0.1	4.8 ± 0.2	4.7 ± 0.2

Values are the mean ± SEM. AUC, Area under the curve; HOMA, homeostasis model assessment.
[a] $P < 0.05$ *vs.* baseline (by ANOVA).
[b] $P < 0.02$, pioglitazone *vs.* placebo (by ANOVA).
[c] $P < 0.05$, pioglitazone *vs.* placebo (by ANOVA).

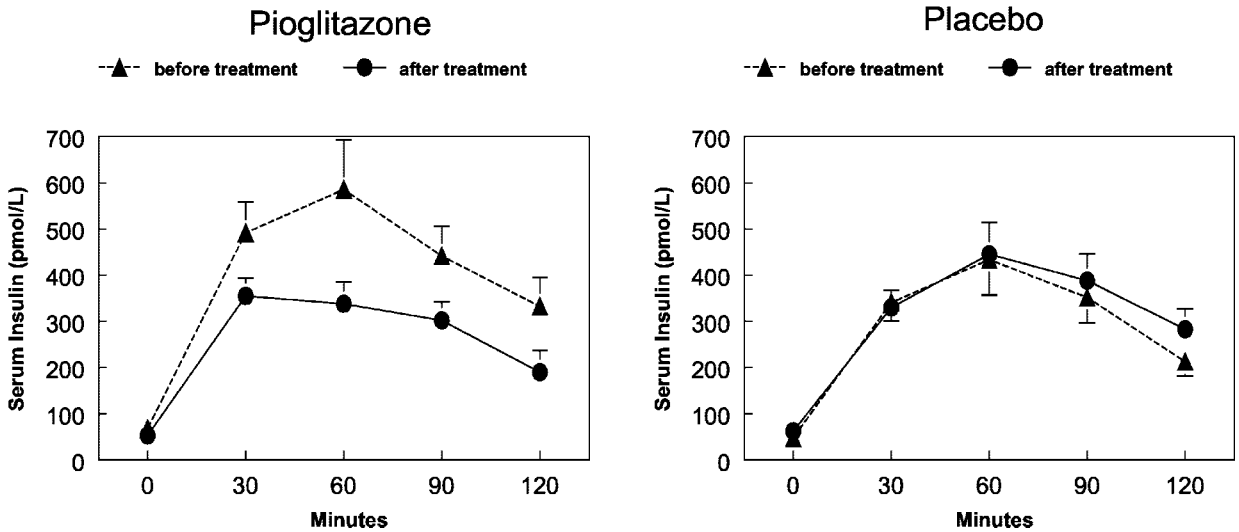

FIG. 1. Serum insulin concentrations during oGTT before (*dashed line*) and after (*solid line*) treatment. Both fasting levels and the area under the curve of serum insulin decreased significantly from before to after pioglitazone ($P = 0.01$), whereas there were no changes after placebo treatment. Data are the mean ± SEM.

significance remained unchanged after including BMI as a covariate.

Ovulation rates

Some 41.2% of the patients treated with pioglitazone had laboratory and clinical signs of normal regular cycles (*i.e.* three ovulations during the study period) compared with 5.6% of those treated with placebo ($P < 0.02$).

Side effects and liver enzymes (Table 4)

Pioglitazone was well tolerated. Besides mild peripheral edema (18% *vs.* 0%; pioglitazone *vs.* placebo, respectively), mastopathy (11.7% *vs.* 5%), muscle cramping (29% *vs.* 10%), sleeping disorders (23% *vs.* 5%), headache (23% *vs.* 5%), and stomach pain (23% *vs.* 5%), no adverse events were observed during treatment. No elevation of liver enzymes was found. Instead, treatment with pioglitazone resulted in significant decreases in γ-glutamyl transferase ($P < 0.02$) and alkaline phosphatase ($P < 0.02$) after 3 months.

Discussion

Administration of pioglitazone for a period of 3 months resulted in a remarkable decline in fasting serum insulin levels, insulin resistance, and insulin secretion in women with PCOS. Associated with these changes, serum levels of SHBG increased, resulting in a decrease in the free androgen index. Furthermore, ovulation rates increased during treatment with pioglitazone.

The decline of both total testosterone and lipid parameters did not reach statistical significance, which may be a reflection of the short duration of the trial and the known high interindividual variability of testosterone and SHBG levels in PCOS (33). Because PCOS patients have been reported to be overresponsive to LHRH (34), we measured LH and FSH levels after LHRH stimulation. The values declined significantly after treatment with pioglitazone, which has been also reported previously (23). We have no explanation for the similar decrease in the placebo group.

During the study period only clinically minor adverse events occurred, which did not lead to discontinuation of the study in any of the patients. There was no significant difference in the number and severity of these adverse events between groups. Muscle cramping, peripheral edema, and mastopathy, side effects that have been described in the investigator's brochure, occurred in more than one patient and more often during treatment with pioglitazone than with

TABLE 3. Hormonal parameters

Parameter	Pioglitazone		Placebo	
	Before treatment	After 3 months	Before treatment	After 3 months
DHEAS (μmol/liter)	5.4 ± 0.6	5.8 ± 0.7	6.3 ± 0.6	6.8 ± 0.5
Testosterone (nmol/liter)	2.4 ± 0.3	2.1 ± 0.2	2.8 ± 0.2	2.5 ± 0.2[a]
SHBG (nmol/liter)	36.8 ± 4.3	40.8 ± 3.3[b]	40.9 ± 3.5	35.8 ± 4.0[a]
Free androgen index (U)	9.3 ± 2.2	6.4 ± 1.2[b]	8.5 ± 1.6	9.8 ± 2.0
LH/FSH	2.0 ± 0.3	1.4 ± 0.2	2.2 ± 0.3	1.8 ± 0.3
LH, 0 min (IU/liter)	10.6 ± 1.6	7.9 ± 1.8[a]	13.3 ± 1.8	10.7 ± 2.4
LH, 20 min	44.4 ± 7.2	25.6 ± 6.1[a]	48.6 ± 7.6	34.0 ± 8.8
LH, 30 min	53.6 ± 9.2	25.2 ± 5.0[a]	61.5 ± 10.3	41.1 ± 14.3
LH, 60 min	57.6 ± 11.3	21.0 ± 3.5[a]	57.3 ± 10.4	34.5 ± 7.8
FSH, 0 min (IU/liter)	5.8 ± 0.5	5.3 ± 0.6	6.2 ± 0.3	6.0 ± 0.6
FSH, 20 min	9.0 ± 1.4	8.5 ± 2.0	8.4 ± 0.5	6.8 ± 0.7
FSH, 30 min	10.6 ± 1.6	6.7 ± 0.7[a]	9.9 ± 0.7	7.5 ± 0.9[a]
FSH, 60 min	12.2 ± 2.0	7.4 ± 1.0[a]	10.9 ± 0.9	8.1 ± 1.0[a]
AUC LH (IU/liter·min)	2708 ± 467	1282 ± 246[a]	2951 ± 488	1957 ± 543
AUC FSH (IU/liter·min)	588.3 ± 86.9	426.9 ± 53.1	548.7 ± 36.8	434.3 ± 44.4[a]

Values are the mean ± SEM. DHEAS, Dehydroepiandrosterone sulfate.
[a] $P < 0.05$ *vs.* baseline (by ANOVA).
[b] $P < 0.05$, pioglitazone *vs.* placebo (by ANOVA).

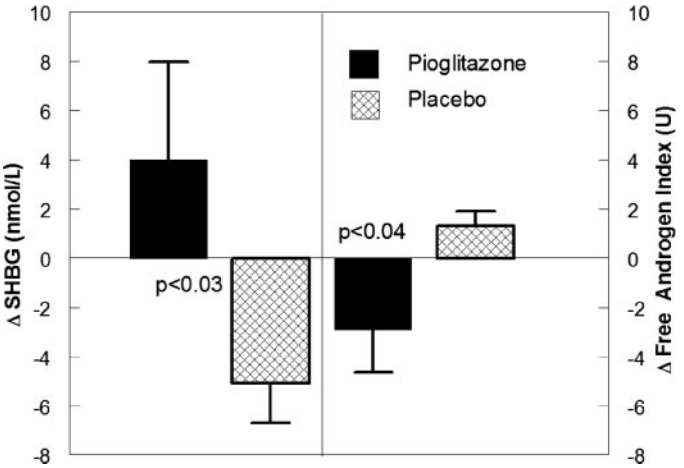

FIG. 2. Changes in serum SHBG (*left panel*) and the free androgen index (*right panel*) from baseline after treatment. The changes were statistically different between groups ($P < 0.03$ and $P < 0.04$, respectively). Data are the mean ± SEM.

placebo. We do not have an explanation for the occurrence of sleep disorders, headache, and stomach pain in the pioglitazone group. A significant decrease in liver enzymes (γ-glutamyl transferase; $P < 0.02$) and alkaline phosphatase ($P < 0.02$) could be observed, whereas mean levels of aspartate aminotransferase and alanine aminotransferase also decreased without reaching statistical significance *vs.* placebo. This phenomenon has been described recently (35) and could be the result of enhanced hepatic insulin sensitivity.

The present data support the hypothesis that insulin resistance and hyperinsulinemia may play a pathogenic role in PCOS and that administration of glitazones ameliorates the associated symptoms.

All available thiazolidinedione derivatives have been shown to improve insulin sensitivity and dyslipidemia (18). The antiinflammatory and antiatherosclerotic effects of these compounds (27) are due to activation of nuclear peroxisome proliferator-activated receptors, which regulate the expression of numerous genes affecting glycemic homeostasis, lipid metabolism, vascular tone, inflammation, and arteriosclerosis (36). Thiazolidinediones may have androgen-lowering effects due to inhibition of P450c17 and 3β-hydroxysteroid dehydrogenase, two key enzymes in human androgen synthesis (37).

TABLE 4. Side effects

	No. of patients	
	Pioglitazone	Placebo
Upper respiratory tract infection	1	1
Headache	4	1
Muscle cramping	5	2
Tiredness	1	1
Peripheral edema	3	0
Sleeping disorders	4	1
Mastopathy	2	1
Stomach pain	4	1
Lower abdomen pain	4	4
Minor depression	1	0

Our results are in agreement with observations from previous studies with troglitazone (19), rosiglitazone (22), and pioglitazone (23, 38). However, troglitazone has been withdrawn from the market due to hepatic toxicity (25, 39–40), rosiglitazone has been tested only in obese, clomiphene-resistant women, and a preliminary effect of pioglitazone has been reported recently in a small uncontrolled study (23) as well as in an observational study in women not optimally responsive to metformin (38). Current evidence supports the conclusion that pioglitazone does not share the hepatotoxic profile of troglitazone (41).

The value of the antidiabetic agent metformin (21), which enhances insulin sensitivity in both liver and peripheral tissue (*e.g.* muscle) (32), has also been assessed in women with PCOS. A randomized placebo controlled study in 23 women demonstrated that menstrual cyclicity improved significantly with daily administration of 500 mg metformin; however, only some of these women were tested for actual incidence of ovulation (42). Furthermore, metformin was not

universally effective in reducing free testosterone or fasting serum insulin levels, and most studies were performed predominantly in obese women. Recent data indicate that a positive effect of treatment on androgen production and clinical androgenic symptoms could be negatively influenced by an increased BMI (43), and metformin has proven its ability, in combination with oral contraceptives (44), to improve insulin sensitivity and hyperandrogenism in nonobese patients.

In a recently published head-to-head trial with metformin (35), pioglitazone was significantly more effective in improving indicators of insulin sensitivity in patients with type 2 diabetes, emphasizing its potential in reducing the mortality of cardiovascular disease (27). Buchanan *et al.* (45) showed that administration of an insulin-sensitizing drug reduced the incidence of diabetes mellitus by more than 50% in high risk Hispanic women, and the protection from diabetes in these women persisted even after the medication was stopped. Therefore, there is still a need for further research with drugs, effective in both lowering circulating insulin levels and antagonizing hyperandrogenism in women suffering from PCOS.

In summary, the present prospective, placebo-controlled study demonstrates for the first time that pioglitazone improves insulin resistance, ovulatory dysfunction, and hyperandrogenism in women with PCOS. It provides a starting point to explore the relative efficacy of thiazolidinediones not only in head to head trials with metformin regarding improvement of fertility, but also concerning their potential role in preventing the long-term complications of PCOS, such as type 2 diabetes mellitus.

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