

Endocrine and Metabolic Effects of Rosiglitazone in Non-obese Women with Polycystic Ovary Disease

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Abstract. We hypothesized that the administration of rosiglitazone, an insulin-sensitizing agent of the thiazolidinedione class, would improve the ovulatory dysfunction, hirsutism, hyperandrogenemia, and hyperinsulinemia of polycystic ovary syndrome (PCOS) patients. Forty women with PCOS and impaired glucose tolerance test (IGT) were randomly assigned to the 8-month treatment with rosiglitazone at either 2 mg/day or 4 mg/day. We compared changes in ovulatory function, hirsutism, hormonal levels (total and free testosterone, estradiol, estrone, androstenedione, LH and FSH), and measures of glycemic parameters (fasting and post-challenge levels of glucose and insulin, HOMA-IR, hemoglobin A1c), between the study groups. The patients' baseline characteristics were similar across all treatment arms. Fifteen of 20 women in the 2 mg group and 19 of 20 women in the 4 mg group achieved normal glucose tolerance; 14 of 20 women in the 2 mg group and 17 of 20 women in the 4 mg group achieved ovulatory menses at the end of the study period. The decreases of free testosterone levels were better in the 4 mg group than the 2 mg rosiglitazone group (-1.89 ± 0.35 pg/ml vs. -2.21 ± 0.39 pg/ml; $P < 0.01$). There were neither any serious adverse events nor any liver enzyme elevations in our study patients during the treatment period. This study demonstrated that rosiglitazone improves the ovulatory dysfunction, hirsutism, hyperandrogenemia, and insulin resistance of PCOS in a dose-related fashion, with minimal adverse effects. This drug may be a good choice for lifetime treatment of patients with PCOS, especially for the ones who failed to show satisfactory results in metformin therapy.

Key words: Polycystic ovary syndrome, Insulin resistance, Hyperandrogenemia, Rosiglitazone

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POLYCYSTIC ovary syndrome (PCOS) is a form of functional ovarian hyperandrogenism, which affects approximately 5–10% of women of reproductive age, and is characterized by menstrual abnormalities, hirsutism and infertility [1]. Insulin resistance and its concomitant hyperinsulinemia are now being accepted as characteristics of most of the women with PCOS [2]. The insulin resistance acts conjointly with alterations in beta-cell function to impart a high risk for the development of early-onset type II diabetes mellitus [3]. Approximately 40% of PCOS women display glucose intolerance (either impaired glucose tolerance or type

II diabetes) in their third decade [4]. There is evidence that hyperinsulinemia also contributes to the ovarian androgen overproduction in PCOS [5]. Hyperandrogenism-related anovulation and its outcome, progesterone deficiency, cause endometrial hyperplasia and increase the risk of carcinoma [4]. All risks must be considered while deciding a lifetime treatment in women with PCOS. Insulin-sensitizing agents such as metformin or thiazolidinediones are being evaluated for the treatment of PCOS [6–8]. Most of the studies were performed in infertility clinics and metformin was the commonly used agent with or without clomiphene citrate (CC) to induce ovulation [9–16]. However, the results in some of these studies were not satisfactory [13–16].

Another class of insulin sensitizing agents, thiazolidinedione, produces marked dose-related improvements in muscle insulin sensitivity [17]. There are six

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published clinical trials demonstrating successful outcomes of troglitazone treatment in PCOS [18–23]. Troglitazone was the first agent of the thiazolidinedione family; unfortunately it was withdrawn from the market because of its serious hepatic toxicity. Rosiglitazone is a novel agent of this family without any known serious adverse effects [24].

We hypothesized that the administration of rosiglitazone would demonstrate a dose-related improvement in glucose metabolism, ovulatory dysfunction and hirsutism of PCOS. To test our hypothesis we conducted an 8 month trial of PCOS patients using two (2 mg/day and 4 mg/day) different doses of rosiglitazone.

Materials and Methods

Study population

Two hundred sixty-four women with the diagnosis of PCOS were evaluated for this study. Among them 40 women who had fulfilled the inclusion and exclusion criteria were randomly assigned to the 8-month treatment with rosiglitazone at either 2 mg/day or 4 mg/day. BMI ≥ 27 kg/m² was an exclusion criterion for our study to rule out the effect of obesity on insulin sensitivity [25, 26].

INCLUSION CRITERIA:

1. The diagnosis of PCOS.
2. BMI < 27 kg/m².
3. The diagnosis of impaired glucose tolerance test.
4. HOMA > 2.7
5. Acceptance of the study protocol.

EXCLUSIONARY CRITERIA:

1. Unresolved medical conditions,
2. Hysterectomy and/or oophorectomy,
3. Type 1 or type 2 diabetes mellitus,
4. Significant cardiovascular disease, active cancer within the past 5 years.
5. Participation in another investigational study within the past 30 days.
6. The use of medications known or suspected to affect reproductive or metabolic functions within 60 days of study entry.

The diagnosis of PCOS was based on NICHD criteria: (i) hyperandrogenism and/or hyperandrogenemia, (ii) oligo-anovulation, (iii) exclusion of other known disorders, such as Cushing's syndrome, hyperprolactinemia or nonclassic congenital adrenal hyperplasia

(CAH). Polycystic ovary appearance at ultrasonography was not considered a criterion for the diagnosis of the syndrome [27].

Oligomenorrhea was defined as bleeding episodes occurring less than six times per year. Anovulation was confirmed in all patients with serial weekly serum progesterone levels (< 2.5 ng/mL = < 8.0 nmol/L) starting on the 21st day of their menstrual cycle. Blood samples were obtained at 7 : 30–8 : 15 AM during the early follicular phase (1st–5th days) after spontaneous or in progesterone-induced menses. Medroxyprogesterone acetate (Farlutal, Deva, Istanbul; 10 mg/D for 10 days) was prescribed to induce progesterone withdrawal bleeding, when necessary. The serum samples were stored at -20°C until assayed.

Early follicular phase serum 17-OH progesterone levels were measured in the morning to avoid later elevations, with more than 1.5 ng/mL were considered as suspected levels for late-onset CAH; 1 hour 0.25 mg ACTH stimulation test for serum 17-OHP levels were performed at 8 : 00 AM on early follicular phase. An ACTH-stimulated 17-OHP levels > 10 ng/mL was considered as the criterion of late-onset 21-hydroxylase deficiency [28].

Thyroid dysfunction, hyperprolactinemia and hypercortisolism were all excluded using appropriate tests. Patients had not received any oral contraceptives or any medications that are known to alter hormone, lipid and insulin metabolism within 3 months before the study.

A 2-hour oral glucose tolerance test was performed. PCOS women with diabetes mellitus and normal glucose tolerance were excluded from the study. World Health Organization 1998 criteria were used for diagnosis of IGT [29]. HOMA-IR was used to evaluate insulin sensitivity and the value > 2.7 was accepted as insulin resistant [30].

Randomization of patients:

Patients entering the trial received a code provided by a computer program generating random numbers at the trial centre. Each code corresponded to one of the treatments.

Study protocol

The whole study protocol was approved by the institutional review board of Ege University and written informed consent was obtained from all subjects.

A basal hormonal (FSH, LH, prolactin (PRL), free

and total testosterone (FT-TT)], and metabolic profile [lipid profile (total cholesterol, triglyceride, HDL and LDL), renal and liver function tests, HbA1c] was obtained and a 75 g OGTT was performed for measuring glucose and insulin levels (visit-1) at the beginning of the study. Therapy with rosiglitazone 2 mg or 4 mg was then initiated in a randomized open labeled trial. Women then returned monthly. Progesterone (P) levels were determined in the serum samples from visits 1, 4 and 8; as well as in blood samples obtained on the 21st day of menses and repeated if basal body temperature showed a temperature rise later than day 21 to assess if ovulation had occurred. Hormonal profiles and glucose tolerance tests were reevaluated on the 4th and the 8th visits. Hirsutism scores were measured by a modification of the Ferriman-Gallwey method [31]; and were evaluated at the beginning and at the end of the study by the same dermatologist. Metabolic profile was performed at all eight visits. Pill bottles were returned at each visit, any remaining pills were counted, and pills for the next month were dispensed.

Patients were asked to follow a weight maintenance diet throughout the study to minimize the effect of weight changes on the disease state. Pregnancy was restricted during the study where all nonsterilized patients were asked to use a barrier method of contraception (condom or diaphragm). The compliance with contraception was reminded on every visit to every patient.

Methods for assay

The serum concentrations of FSH, LH, E2, progesterone, prolactin and cortisol were measured by chemiluminescent enzyme immunoassay (ASC 180 (+) Ciba Diagnostics, USA) with an average inter-assay coefficient variation (CV) of 6% and intra-assay CV of 6.7%. The serum concentrations of DHEA-S, 17-OH progesterone, free testosterone, free T4 and TSH were measured according to standard radioimmunoassays.

Blood samples for hormonal tests were collected after a 16-hour period of fasting; after collection, the blood samples were immediately placed on ice and then centrifuged at 3,500G for 30 minutes at +4°C. The plasma was separated within 1 hour and then stored at -70°C.

Plasma glucose was measured by the glucose oxidase technique (Biobak Laboratory Supplies Trade, Ankara, Turkey) with an inter-assay CV of 1.7% and

intra-assay CV of 0.8%. Insulin levels were measured by micro-particle enzyme immunoassay (Abbott, Wiesbaden-Delkenheim, Germany) with intra-assay and intra-assay CVs 2.4%.

HOMA-IR was calculated according to the following formula:

$$\text{HOMA-IR} = \text{FIRI} \times \text{FPG}/22.5$$

[FIRI: fasting plasma insulin level (IU/ml) and FPG is fasting plasma glucose level (mmol/L)] [30]

Statistical analysis

The Statistical Package for the Social Sciences (SPSS version 10.0 for Windows) was used for statistical analyses. The efficacy analysis was performed on an intention-to-treat (ITT) basis. The ITT population was defined as any patient randomized to treatment with a baseline visit and at least one follow-up measurement (at 4 wk or later). Patients who withdrew or were withdrawn before completing the study were included in the ITT analysis using the last observation carried forward rule. The characteristic of distribution was tested with the Kolmogorov-Smirnov test. Results were expressed as mean \pm SD. Where there were normally distributed variables, ANOVA for repeated measures was used to compare the clinical, metabolic and hormonal parameter changes within all two groups during the treatment, either with or without logarithmic transformation. The Wilcoxon unpaired test was used for variables with persisting skewed distribution after log transformation.

For comparison between the two rosiglitazone groups before and at 3 and 8 months of treatment, Student's two-tailed t test was used for normally distributed variables, either with or without log transformation. The Mann-Whitney U test was used for variables with persisting skewed distribution after log transformation. Relations between insulin sensitivities and free testosterone levels of the two groups were assessed with simple linear regression analysis, and Pearson (r) correlation coefficients were presented. P values smaller than 0.05 was regarded as statistically significant.

Results

Patient flow

Two hundred sixty-four women with the diagnosis

of PCOS were evaluated for this study. Two hundred twenty-four patients did not enter randomization because of the following reasons: BMI>27 kg/m² (n = 74), normal glucose tolerance tests (n = 104), consent withdrawn (n = 14), FBG>126 mg/dl (n = 14), and protocol violation (n = 18). In the rosiglitazone 4 mg group, 1 patient discontinued the study because she moved out of the city (6th month), and 1 patient discontinued because she wanted to get pregnant (5th month). In 2 mg group 1 patient discontinued because she wanted to get pregnant (5th month), one patient discontinued for other, unknown, reasons (4th month). The difference between the two groups was not statistically significant (P>0.1).

Clinical features and baseline data-first visit

The mean age was 31.4 ± 0.9 and 29.4 ± 1.7 years and the mean body mass index was 24.2 ± 1.3 kg/m² and 23.9 ± 1.9 kg/m², in the rosiglitazone 4 mg group and the rosiglitazone 2 mg group, respectively, there were no significant difference between two groups for age and BMI (P>0.05). The clinical features, results of baseline glucose tolerance test, and mean HOMA-IR levels of both groups are summarized as “visit-1” in Table 1. All of the women with PCOS had impaired glucose tolerance according to WHO criteria by design. Fifteen women in the 4 mg group and 12 women in the 2 mg group had abnormal HbA1c levels at the beginning of the study. Baseline hormonal parameters were summarized as “visit-1” in Table 2. All women had

Table 1.

	2 mg Rosiglitazone			4 mg Rosiglitazone		
	Beginning	3rd month	Final visit	Beginning	3rd month	Final visit
AGE	29.4 ± 1.7			31.4 ± 0.9		
BMI (kg/m ²)	23.9 ± 1.9 ^{bc}	24.5 ± 1.8 ^b	24.7 ± 2.9 ^{cd}	24.2 ± 1.3 ^{bc}	24.7 ± 2.1 ^b	25.1 ± 2.1 ^{cd}
FER-GAL	14.1 ± 3.8 ^c		12.9 ± 3.4 ^{cd}	14.2 ± 4.1 ^c		12.1 ± 3.5 ^{cd}
F. Glucose (mg/dl)	99 ± 1.8 ^c	93.6 ± 5.4	90 ± 5.1 ^c	97.2 ± 3.6 ^c	94.6 ± 5.7	88.2 ± 6.2 ^c
2nd h. Glucose (mg/dl)	167.7 ± 7.4 ^{bc}	129.3 ± 9.3 ^b	120.7 ± 3.6 ^{cd}	165.6 ± 7.2 ^{bc}	118.8 ± 10.3 ^b	115.9 ± 3.6 ^{cd}
F. Insulin (μU/ml)	21.05 ± 2.42 ^{bc}	18.4 ± 1.21 ^c	16.8 ± 1.2 ^{cd}	20.34 ± 2.2 ^{bc}	17.0 ± 1.9 ^b	15.7 ± 1.3 ^{cd}
2nd h Insulin (μU/ml)	181.9 ± 20.1 ^{bc}	170.2 ± 16.3 ^b	165.4 ± 15.1 ^{cd}	182.3 ± 12.4 ^{bc}	154.51 ± 16.2 ^b	152.2 ± 16.2 ^{cd}
HbA1c (%)	6.12 ± 0.09 ^{bc}	5.89 ± 0.05 ^b	5.68 ± 0.09 ^{cd}	6.11 ± 0.11 ^{bc}	5.74 ± 0.09 ^b	5.44 ± 0.12 ^{cd}
HOMA-IR	3.5 ± 0.3 ^{bc}	3.0 ± 0.4 ^b	2.55 ± 0.16 ^{cd}	3.4 ± 0.2 ^{bc}	2.8 ± 0.3 ^b	2.27 ± 0.12 ^{cd}
SGOT (U/L)	18.9 ± 2.7	22.3 ± 2.1	21.6 ± 2.4	21.4 ± 2.7	22.1 ± 2.3	22.4 ± 2.1
SGPT (U/L)	18.9 ± 2.7	18.5 ± 2.4	19.1 ± 1.9	18.6 ± 2.9	19.3 ± 1.5	19.6 ± 1.9
T. Chol (mg/dl)	179.6 ± 5.8	167.9 ± 4.9	160.4 ± 3.2	178.4 ± 6.1	170.4 ± 7.2	162.3 ± 3.9
HDL (mg/dl)	44.8 ± 2.7	50.4 ± 1.9	57.8 ± 2.7	45.9 ± 2.1	51.9 ± 2.8	61.3 ± 3.9
LDL (mg/dl)	118.9 ± 8.2	112.4 ± 7.1	109.3 ± 4.7	119.2 ± 7.9	112.8 ± 6.7	106.3 ± 3.9
T. G. (mg/dl)	116.3 ± 28.8	113.7 ± 17.5	112.3 ± 9.6	115.5 ± 22.7	112.9 ± 19.2	110.2 ± 18.3

Table 2.

	2 mg Rosiglitazone			4 mg Rosiglitazone		
	Beginning	3rd month	Final visit	Beginning	3rd month	Final visit
LH (IU/L)	9.82 ± 2.98 ^{bc}	7.72 ± 2.48 ^b	7.01 ± 1.64 ^{cd}	9.79 ± 3.17 ^{bc}	7.63 ± 2.15 ^b	6.53 ± 1.51 ^{cd}
FSH (IU/L)	4.51 ± 1.02	4.32 ± 1.14	4.31 ± 1.13	4.41 ± 1.13	4.47 ± 1.21	4.34 ± 1.12
PRL (μg/l)	12.6 ± 10.1	12.1 ± 9.5	12.7 ± 10.5	13.1 ± 10.4	13.4 ± 10.7	13.2 ± 11.7
E2 (ng/L)	75.5 ± 16.7 ^{bc}	80.4 ± 13.2 ^b	85.1 ± 10.1 ^{cd}	74.8 ± 17.9 ^{bc}	83.7 ± 17.6 ^b	87.7 ± 14.1 ^{cd}
F. Testo (pg/ml)	5.69 ± 1.1 ^{bc}	4.68 ± 1.2	3.8 ± 1.3 ^{cd}	5.73 ± 1.2 ^c	4.28 ± 1.4 ^b	3.61 ± 1.22 ^{cd}
PERIOD (Days)	95.33 ± 9.23 ^{bc}	64.21 ± 8.29 ^b	45.18 ± 8.22 ^{cd}	96.12 ± 12.9 ^{bc}	56.18 ± 17.5 ^b	36.15 ± 14.3 ^{cd}
OVULATION	0 ^{bc}	4 ^b	14 ^{cd}	0 ^{bc}	6 ^b	17 ^{cd}

a = statistically significant difference between 2 mg and 4 mg groups in the beginning; b = significant change between 1st and 3rd month values (p<0.01) ; c = significant change between 1st and 8th month values (p<0.01) ; d = statistically significant difference between 2 mg and 4 mg groups at the end of the study.

elevated free testosterone, estradiol (E_2) and LH levels and there were no significant difference for these parameters between the two groups at the beginning of the study ($P>0.05$).

Third month's visit

In the third month of the study, there was a tendency towards weight gain in both rosiglitazone groups' women in a dose dependent manner and the differences from baseline BMI were significant ($p<0.01$ and $P<0.05$ for the 4 mg group and the 2 mg group, respectively). Eight women in the 4 mg group and 7 women in the 2 mg group had normal glucose tolerance in the third month of the study. The second hour glucose levels were significantly different between study groups ($P<0.01$). Free testosterone levels decreased in both treatment groups, but the highest reduction was seen in the rosiglitazone 4 mg group. The interval between menstrual periods shortened significantly in both study groups' women. Six women in the 4 mg group and 4 women in the 2 mg group were ovulatory in the third month of the treatment (Table 2). None of our patients reported any significant side effect, and their liver enzymes were within normal values in the third month of our study.

Final visit

The biochemical and anthropometric data of the last visit were summarized in Table 1. In the last visit of the study, the mean BMI's of both rosiglitazone groups were higher than the baseline values and the increase was not dose dependent. Hirsutism scores of women in rosiglitazone treatment group improved significantly. Nineteen women in the 4 mg group and 15 women in the 2 mg group had normal glucose tolerance at the end of the study. The second hour glucose levels were significantly different between study groups. The data of hormonal parameters of the same visit are summarized in Table 2. Free testosterone levels decreased in both treatment groups but the highest reduction was seen in the rosiglitazone 4 mg group ($P<0.01$). The HDL levels tended to increase and triglyceride levels tended to decrease in both rosiglitazone groups ($p>0.05$) (Table 2). The interval between menstrual periods shortened significantly in both groups and seventeen women in the 4 mg group and 14 women in the 2 mg group were ovulatory and eumenorrheic at the end of the treatment

period. All women who achieved regular and ovulatory menses also had normal glucose tolerance tests at the end of the study. Two women in the 4 mg group and 1 woman in the 2 mg group achieved normal glucose tolerance tests but were still anovulatory at the end of our study. None of our patients reported any serious side effects and their liver enzymes were within normal values.

There were significant negative correlations between the changes in free testosterone levels and in insulin sensitivity in both treatment groups. ($r = -7.4$; $P<0.01$ for 4 mg and $r = -6.9$; $P<0.01$ for 2 mg).

Discussion

The present investigation of non-obese women with PCOS and IGT demonstrates that 8-months of rosiglitazone therapy was associated with 1) improvement in insulin resistance, 2) improvement of glucose intolerance, 3) lowering of total and free testosterone 4) improvement in endogenous ovulatory function (Table 1).

Although the exact pathogenesis of PCOS is still unknown, insulin resistance and hyperinsulinemia appear to play a key pathogenetic role in ovarian androgen overproduction [32, 33]. This also brings an increased risk for IGT and type II diabetes to women with PCOS [34]. The prevalence of IGT is 31–35%, and that of type II diabetes is 7.5–10% among these women [35–39]. Existing therapies for PCOS have focused on suppressing androgen production or inducing ovulation [40, 41]. More recently, and consistent with the premise that insulin resistance is an important etiological cause of PCOS, several studies have demonstrated a beneficial effect of insulin-lowering agents in this disorder [8, 42]. The most extensively studied insulin-sensitizing drug in the treatment of PCOS is metformin [8–10, 44]. Its major action is suppression of hepatic glucose output [42] but it also improves insulin's action without affecting its secretion [43]. Troglitazone, another insulin-sensitizing agent from the thiazolidinedione family seemed favorable for treatment of PCOS but was withdrawn from the market because of its hepatic toxicity [8].

In our study, the mean body mass indexes of the study groups elevated slightly during the treatment period (3.5% and 3.3% for the 4 mg and 2 mg rosiglitazone groups, respectively), but we can still demonstrate significant dose dependent improvements in in-

ulin sensitivity. HOMA-IR reduced 33.5% in the 4 mg and 27% in the 2 mg rosiglitazone groups (Fig. 1). Fasting and post-challenge glucose levels decreased significantly in both treatment groups but the reductions were much more pronounced with 4 mg. These were accompanied by decreases in circulating insulin levels, both basal and after a 75 gm. glucose load (Table 1). Rosiglitazone normalized glucose tolerances of 19 women in the 4 mg dose (95%) and 15 women in 2 mg dose groups respectively (75%). It is well documented that as little as a 7% decrease in body weight can improve reproductive and glucose metabolism abnormalities in PCOS [46, 47]. Our findings indicate that rosiglitazone is effective in improving insulin sensitivity in women with PCOS, and that this effect is independent of weight loss. In our study we demonstrated a 36.5% and 31.9% reduction in free testosterone levels after 4 mg and 2 mg rosiglitazone treatment, respectively (Fig. 2). These results demonstrated that rosiglitazone is effective in reduction of elevated androgens. Although the treatment period was not long enough to investigate hirsutism, we observed slight dose dependent reductions of Ferriman and Gallwey scores with rosiglitazone treatment. We demonstrated significant dose dependent elevations in estradiol and

declines in estrone concentrations, representing follicular maturation (Table 2). In the 6th month of the study 17 women in the 4 mg group (85%) and 14 women in the 2 mg group (75%) achieved regular ovulatory menses.

There are only a few studies about thiazolidinedione usage in PCOS [18–23, 50]. All of them, except a recent study from Zheng *et al.* [50], were made with troglitazone, the former agent of this group. Dunaif *et al.* used troglitazone in 21 women with PCOS for 3 months (200 mg/day in 10 women and 400 mg/day in another 11 women) and demonstrated dose dependent beneficial effects on insulin sensitivity and hyperandrogenism [18]. Only 2 women in the 400 mg/day group became ovulatory in their study. The reason for their low ovulation rate may be the short duration of the study. Ehrmann *et al.* used 400 mg troglitazone for 12 weeks in the treatment of 13 obese women with PCOS and IGT [19]. They have demonstrated significant improvements in insulin sensitivity and reductions in mean HbA1c levels (6.1 ± 0.1 vs. 5.7 ± 0.1 ; $P < 0.05$). We demonstrated similar but more significant reductions in HbA1c levels. The difference between the two study results may be because of the longer duration of our treatment period, as our 3rd month HbA1c levels

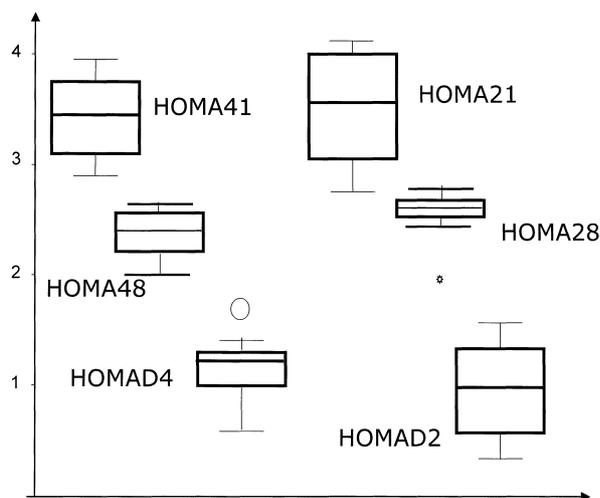


Fig. 1. HOMA-IR results.

- HOMA41: HOMA-IR of the 4 mg group at visit 1
- HOMA48: HOMA-IR of the 4 mg group at visit 8
- HOMAD4: HOMA-IR change between 1st and 8th visit in 4 mg group
- HOMA21: HOMA-IR of the 2 mg group at visit 1
- HOMA28: HOMA-IR of the 2 mg group at visit 8
- HOMAD2: HOMA-IR change between 1st and 8th visit in 2 mg group

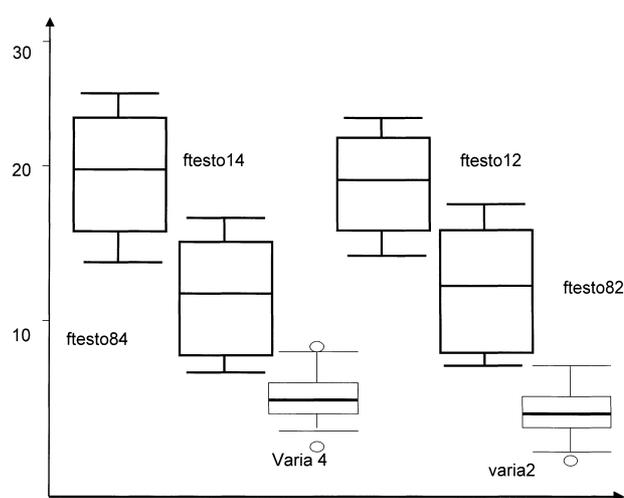


Fig. 2. Free testosterone results.

- FTESTO14: free testosterone levels of the 4 mg group at visit 1
- FTESTO84: free testosterone levels of the 4 mg group at visit 8
- VARIATION4: free testosterone level changes between 1st and 8th visit in 4 mg group
- FTESTO12: free testosterone levels of the 2 mg group at visit 1
- FTESTO82: free testosterone levels of the 2 mg group at visit 8
- VARIATION2: free testosterone level changes between 1st and 8th visit in 2 mg group

were more close to their results. Ehrmann *et al.* demonstrated an average 12% reduction in fasting and 15% reduction in post-challenge glucose levels. We demonstrated a 9.2% and 9% reduction in fasting glucose levels with 4 mg and 2 mg doses, respectively. The reductions in the post-challenge glucose levels of our study population were more evident than Ehrmann *et al.*'s results. Although weight gain is a common side effect of the thiazolidinedione group, these two studies did not demonstrate any BMI changes with troglitazone treatment [18, 19]. There were slight but significant increases in the mean BMI's of our groups with rosiglitazone treatment. This weight gain may be the reason for the different changes in the pattern of OGTT results that we have observed with rosiglitazone therapy. The reductions that they have demonstrated in free and total testosterone levels were similar to our study results. Hasegawa *et al.* used 400 mg troglitazone in 13 women for 12 weeks [20]. They have demonstrated significant reductions in insulin and androgen levels in their study. Eleven of 26 cycles of their patients were ovulatory with troglitazone treatment (42.3%). This ovulation rate is similar to our 3rd month results and significantly lower than the 8th month's results. This finding gives a clue about benefits of lifetime treatment with insulin sensitizing drugs. Azziz *et al.* investigated

the effects of troglitazone on ovulatory dysfunction, hirsutism, hyperandrogenemia and hyperinsulinemia in 410 women with PCOS [22]. Patients were randomly assigned to 44 weeks of treatment with placebo, troglitazone 150 to 300 mg/day or troglitazone 600 mg/day. Analysis of data from 305 patients showed a 57% ovulation rate in the troglitazone 600 mg/day groups, compared to 12% in the placebo group. Serum free testosterone decreased and sex hormone binding globulin (SHBG) increased in a dose related fashion with troglitazone treatment, and there were no significant adverse effects. We obtained higher ovulation percentages than these authors. The possible explanation for this contradiction is the difference between the mean body mass indexes of the study populations. Azziz *et al.* performed their study in obese PCOS women, but we performed our study in non-obese PCOS women (BMI <27 kg/m²).

Although studies have demonstrated beneficial effects of the thiazolidinediones on metabolic and ovulatory dysfunctions, it is unclear whether this is secondary to increased insulin sensitivity or the direct effects on steroidogenesis. Troglitazone inhibits 3-β hydroxy-

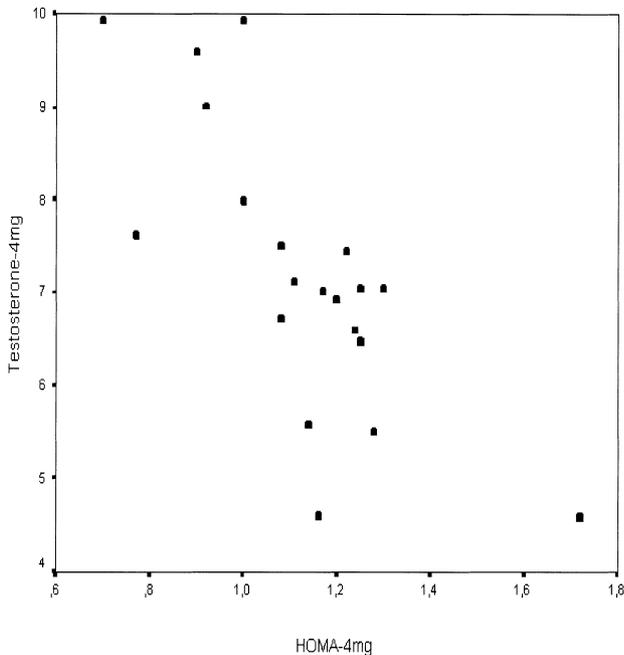


Fig. 3. Correlation between free testosterone and HOMA changes in 4 mg group.

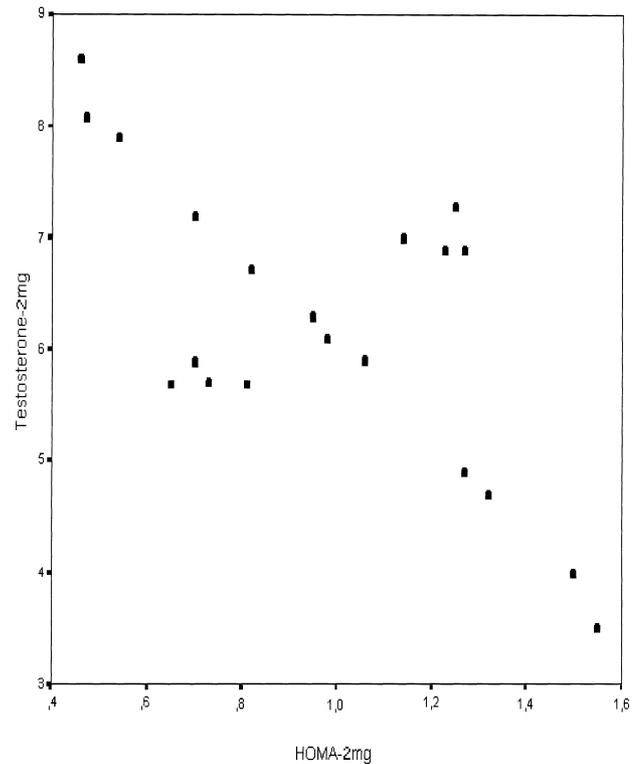


Fig. 4. Correlation between free testosterone and HOMA changes in 2 mg group.

steroid dehydrogenase type-2 and 17,20-lyase, the two enzymes that are necessary for androgen synthesis [51–53]. Rosiglitazone shows weaker inhibitory effect than troglitazone on both these enzymes [51]. For this reason the decrease in androgen levels and increase in ovulation rates are more likely to be related with the improvements in insulin sensitivity. New evidence for this theory is the significant negative correlations between the improvements of insulin sensitivity and changes in free testosterone levels in our study ($r = -7.4$ $p < 0.01$ for 4 mg and $r = -0.69$ $P < 0.01$ for 2 mg) (Fig. 3 and Fig. 4).

Recently Zheng *et al.* investigated rosiglitazone in women with PCOS. As the article is in Chinese, we can only compare our results with their results in the abstract of their study [50]. They have used 4 mg rosiglitazone in 30 patients with PCOS for 12 weeks. Their changes in sex hormones were similar with our 3rd month results with 4 mg dose. But they have demonstrated better improvements in HOMA-IR and ovulatory rates than our 3rd month results with 4 mg

rosiglitazone. We cannot give any explanation to this, as we do not know all the details of their study population. However, our final ovulation rates with both 4 mg and 2 mg rosiglitazone are better than they have demonstrated in their study, which again suggests the advantages of longer even lifetime treatment.

In conclusion, rosiglitazone therapy resulted in marked improvements in insulin sensitivity *per se*, independent of weight loss, in PCOS women. This was accompanied by a significant decrease in the best biochemical marker of hyperandrogenism, free testosterone levels, and restoration of ovarian functions. Many of the rosiglitazone actions were more evident with the 4-mg dose, suggesting that this dose should be used in PCOS. Rosiglitazone may be a good alternative for women with PCOS, mainly for the ones who failed to show satisfactory results with metformin therapy. Further studies are needed for comparing the efficacy of metformin versus rosiglitazone in women with PCOS especially for primary prevention of type II diabetes.

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