Estradiol-to-Testosterone Ratio Is Associated with Response to Metformin Treatment in Women with Clomiphene Citrate-Resistant Polycystic Ovary Syndrome (PCOS)

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Background: To investigate intrinsic alterations in ovarian steroidogenesis in women with clomiphene citrate (CC)-resistant polycystic ovary syndrome (PCOS) who ovulated after metformin treatment.

Methods: Fifty-six women of reproductive age (18-40 years) diagnosed with CC-resistant PCOS received metformin for 12 weeks. If ovulation was successfully induced by CC after metformin treatment, the women were classified as responders. Circulating levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), testosterone (T), free testosterone (freeT), fasting insulin and sex hormone-binding globulin (SHBG) were determined at weeks 0, 4 and 12 of metformin treatment.

Results: Thirty-seven women with CC-resistant PCOS finished the treatment course. There were no significant differences in circulating levels of FSH, E2, T, freeT and fasting insulin at weeks 0, 4, and 12 between responders and non-responders. At week 4, responders showed significantly higher LH levels and higher LH/FSH ratios than non-responders ($p < 0.005$ and $p < 0.05$, respectively). After the 12-week treatment, responders demonstrated higher serum E2/T ratios and lower freeT levels than non-responders ($p < 0.05$ and $p < 0.05$, respectively).

Conclusions: The results suggest that in women with CC-resistant PCOS, elevated E2/T is associated with a better response to metformin.

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Key words: polycystic ovary syndrome, metformin, clomiphene citrate, estradiol, testosterone

Polycystic ovary syndrome (PCOS) is a common endocrine disorder and affects 5-10% of women of reproductive age.(1) Women with PCOS may present with menstrual irregularities (oligomenorrhea, or amenorrhea), chronic anovulation, infertility, obesity and hyperandrogenism. Insulin resistance with compensatory hyperinsulinemia is a prominent feature of PCOS. Hyperinsulinemia causes increased production of ovarian androgen and decreased synthesis of sex hormone-binding globulin (SHBG), which results in hyperandrogenism and leads to symptoms and signs of PCOS, including anovulation.(2) Clomiphene citrate (CC) has been used as the first-line drug for ovulation induction for women with PCOS. Successful ovulation has been reported in 70-85% of women, resulting in a pregnancy rate

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of 40-50%.[3] In CC-resistant PCOS, administering a higher dose of CC for a longer period or adjuvant use of dexamethasone has shown limited efficacy.[4,5]

Metformin has been used in treating PCOS. The proposed relationship between hyperinsulinaemia and anovulation led to the use of metformin.[6] The effect of metformin in successful restoration of menstrual regularity has been reported in the most previous publications, with ovulation rates ranging from 78 to 96%.[7-10] Vandermolen *et al* first reported the successful use of metformin in treating women with CC-resistant PCOS, showing that 75% of women ovulated.[11] Several studies also confirmed the beneficial effects of metformin on CC-resistant PCOS.[12-14] In those studies demonstrating an increased ovulation rate with treatment using meformin plus CC, ovulation rates were 75% (with a metformin dose of 1500 mg/day for 7 weeks),[11] 77.7% (1700 mg/day for 2 cycles),[12] 89.5% per cycle (500-1500 mg/day for 4 weeks)[13] and 47.4% (1700 daily for 6 months).[14] The effect of metformin in improving the ovulation rate was proposed to be a local action. After metformin treatment, estrogen levels were increased and testosterone levels were decreased in the treatment group but not in placebo group, suggesting that metformin was associated with intrinsic alterations in follicle steroidogenesis.[12] On the other hand, Kriplani *et al*. demonstrated that women with PCOS with initially higher follicle-stimulating hormone (FSH)-to-luteinizing hormone (LH) ratios and lower testosterone (T) levels had a good response, whereas those with higher testosterone levels had a poor response after 6 months of metformin treatment.[15] It is likely that the response of women with CC-resistant PCOS to metformin treatment is highly related to the initial status or alterations in ovarian steroidogenesis, i.e. a shift from an androgen to an estrogen dominant environment in the follicles. In this study, we present the changes in the hormone profiles in responders and non-responders during the course of metformin treatment.

METHODS

Subjects and protocol for metformin administration

From March 2002 to February 2005, women of reproductive age (18-40 years) presenting with oligomenorrhea or amenorrhea, symptoms or signs of hyperandrogenism (elevated serum testosterone and/or free testosterone, hirsutism, acne) and specific ultrasound findings of more than 10 small cysts (2-10 mm) in each ovary were included as PCOS patients. The diagnosis of PCOS was based on the United States National Institute of Health criteria.[16] The exclusion criteria included hyperprolactinemia, Cushing's syndrome, thyroid dysfunction, overt diabetes, hepatic or renal impairment, alcohol use, smoking, hormone use in the last 3 months, use of medications for psychological disorders or which could possibly influence carbohydrate metabolism, and extreme obesity (body mass index, or BMI, weight[kg]/height^2[m^2]) ≥ 35). All patients studied were first treated with CC at a daily dose of 150 mg from days 5 to 9 of the menstrual cycle for three cycles after appropriate induction of withdrawal bleeding. In patients with CC-resistant PCOS, who presented no ovulation after three cycles of CC treatment, metformin 1500 mg daily (divided into three doses) was administered for 12 weeks. Circulating levels of FSH, LH, estradiol (E2), T, free testosterone (free T), fasting insulin and SHBG were determined at week 0 (before treatment), week 4 and week 12 of metformin treatment. The collection of blood was performed on day 3 of spontaneous menstruation or withdrawal bleeding induced by progestin. All patients gave written informed consent to participate in the study, and the experimental design and involvement of human subjects in this study were approved by the ethical committee of Chang Gung Memorial Hospital.

Ovulation was evaluated each cycle during metformin treatment. After metformin administration for 12 weeks, CC 100 or 150 mg was added from days 5 to 9 of the menstrual cycle for up to 3 cycles to induce ovulation if no spontaneous ovulation was recorded. If ovulation could be successfully induced by CC after the metformin treatment, the women were classified as responders. The effectiveness of metformin treatment was evaluated by the presence of at least one episode of ovulation during or after treatment. Ovulation was confirmed by a biphasic pattern of basal body temperature with regular menstruation, ultrasound evidence of a dominant follicle defined as a follicle size greater than 16 mm, and positive results on a urinary LH test or spontaneous pregnancy.

Radioimmunoassays (RIA)

Serum levels of FSH were determined using a commercially available RIA kit (Dia Sorin, Saluggia, Italy). The detection limit of the FSH assay was 0.5 mIU. The intra-assay coefficients of variation were 3.65% at 5.06 mIU, 3.64% at 17.5 mIU and 2.10% at 47.0 mIU (n = 10). The interassay coefficients of variation were 6.73% at 4.69 mIU, 4.99% at 16.9 mIU and 3.67% at 45.7 mIU (n = 8).

Serum levels of LH were determined using a commercially available RIA kit (Dia Sorin). The detection limit of the LH assay was 0.5 mIU. The intra-assay coefficients of variation were 4.03% at 1.22 mIU, 3.18% at 16.1 mIU and 4.28% at 40.9 mIU (n = 10). The interassay coefficients of variation were 5.25% at 1.16 mIU, 6.21% at 15.1 mIU and 5.17% at 37.7 mIU (n = 8).

Serum levels of E2 were determined using a commercially available RIA kit (Diagnostic Systems Laboratories [DSL], Webster, Texas, U.S.A.). The detection limit of the E2 assay was 5 pg/ml. The intra-assay coefficients of variation were 4.51% at 42.7 pg/ml, 3.57% at 87.2 pg/ml and 4.85% at 291 pg/ml (n = 10). The interassay coefficients of variation were 7.97% at 37.9 pg/ml, 6.59% at 83.4 pg/ml and 8.22% at 277 pg/ml (n = 8).

Serum levels of T were determined using a commercially available RIA kit (DSL). The detection limit of the T assay was 0.1 ng/ml. The intra-assay coefficients of variation were 6.23% at 0.88 ng/ml, 5.89% at 4.45 ng/ml and 4.99% at 7.39 ng/ml (n = 10). The interassay coefficients of variation were 8.45% at 1.02 ng/ml, 7.38% at 4.75 ng/ml and 6.52% at 7.71 ng/ml (n = 8).

Serum levels of freeT were determined using a commercially available radioimmunoassay kit (DSL). The detection limit of freeT assay was 0.1 pg/ml. The intra-assay coefficients of variation were 7.42% at 2.80 pg/ml, 7.22% at 9.48 pg/ml and 8.53% at 17.3 pg/ml (n = 10). The interassay coefficients of variation were 9.29% at 2.30 pg/ml, 8.91% at 12.1 pg/ml and 9.12% at 21.4 pg/ml (n = 8).

Serum levels of insulin were determined using a commercially available RIA kit (Linco, St. Charles, MO, U.S.A.). The detection limit of the insulin assay was 2 ng/ml. The intra-assay coefficients of variation were 5.69% at 9.59 ng/ml, 4.16% at 50.6 ng/ml and 7.01% at 136 ng/ml (n = 10). The interassay coefficients of variation were 7.01% at 9.45 ng/ml, 6.31% at 56.6 ng/ml and 8.16% at 164 ng/ml (n = 8).

Serum levels of SHBG were determined using a commercially available RIA kit (DSL). The detection limit of the SHBG assay was 5 nmol/L. The intra-assay coefficients of variation were 4.7% at 2.95 nmol/L, 2.4% at 100 nmol/L and 3.8% at 125 nmol/L (n = 10). The interassay coefficients of variation were 3.7% at 28.4 nmol/L, 2.7% at 97.5 nmol/L and 3.4% at 114 nmol/L (n = 8).

Statistical analysis

Age, BMI, and endocrine parameters between responders and non-responders were analyzed by Student's *t* test. Hormone levels at weeks 0, 4 and 12 of treatment were analyzed by repeated measures and multiple comparisons of analysis of variance (ANOVA), using the least significant difference (LSD) test as the post-hoc test. The correlation between hormones was analyzed by linear regression. In all cases, a p value < 0.05 was considered statistically significant.

RESULTS

Fifty-six women with CC-resistant PCOS were enrolled in treatment. However, 19 of them dropped out of the treatment program due to intolerance to the adverse effects of metformin. Seventeen of the 37 patients with CC-resistant PCOS who completed the 12-week metformin treatment demonstrated spontaneous ovulation. Among the 20 who had no evidence of spontaneous ovulation, 7 demonstrated ovulation after induction by CC and 13 still did not ovulate even after CC treatment Collectively, the 24 patients who had spontaneous ovulation (n = 17) and ovulation induced by CC (n = 7) were referred to as responders and the other 13 patients were referred to as non-responders. The age and BMI of the responders and non-responders were similar (Table 1).

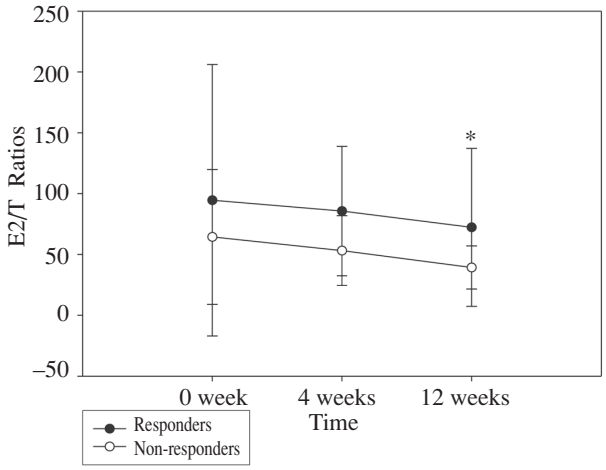
At week 4 of metformin treatment, responders showed significantly higher LH and LH/FSH levels than non-responders ($p < 0.05$ and $p < 0.005$, respectively) (Table 1). In addition, responders demonstrated higher serum E2/T ratios than non-responders after 12 weeks of metformin treatment (Table 1 and Fig. 1). After the 12-week treatment with metformin, the serum SHBG was significantly decreased in responders but not in non-responders ($p < 0.05$). This decrease reached statistical significance at week 12

Table 1. Clinical Data and Hormone Profiles of Responders and Non-responders before and after Metformin Treatments

	Non-responders (n = 13)	Responders (n = 24)
Age (year)	26.7 ± 4.9	26.6 ± 5.1
BMI (kg/m^2)	28.0 ± 2.1	27.8 ± 1.1
Week 0 (before metformin treatment)		
E2 (pg/ml)	66.3 ± 9.8	72.1 ± 13.5
FSH (mIU/ml)	5.0 ± 0.6	5.3 ± 0.4
LH (mIU/ml)	9.5 ± 1.4	10.3 ± 5.1
Testosterone (ng/ml)	1.2 ± 0.1	0.9 ± 0.1
Free testosterone (pg/ml)	3.0 ± 0.2	2.7 ± 0.2
Fasting insulin (μIU/ml)	28.2 ± 8.2	18.8 ± 2.1
SHBG (pg/ml)	47.5 ± 8.1	57.8 ± 9.4§
LH/FSH	1.6 ± 0.1	2.0 ± 0.2
E2/T	64.4 ± 17.5	94.6 ± 26.3
E2/freeT	24.4 ± 5.3	26.5 ± 3.7
Week 4 of metformin treatment		
E2	54.6 ± 7.2	72.4 ± 9.8
FSH	5.8 ± 0.6	4.9 ± 0.3
LH	7.4 ± 0.7*	12.0 ± 1.7*
Testosterone	1.1 ± 0.1	0.9 ± 0.1
Free testosterone	2.7 ± 1.0	2.5 ± 1.0
Fasting insulin	20.4 ± 2.2	17.8 ± 1.9
SHBG (pg/ml)	36.5 ± 7.8	42.9 ± 5.3
LH/FSH	1.3 ± 0.1†	2.5 ± 0.3†
E2/T	54.3 ± 8.6	83.7 ± 16.1
E2/freeT	21.3 ± 2.8	32.4 ± 34.9
Week 12 of metformin treatment		
E2	40.8 ± 5.6	59.6 ± 11.2
FSH	6.5 ± 0.7	5.8 ± 0.4
LH	8.0 ± 1.4	9.8 ± 1.1
Testosterone	1.1 ± 0.1	0.9 ± 0.1
Free testosterone	2.9 ± 0.2	2.4 ± 0.2
Fasting insulin	23.7 ± 3.6	18.5 ± 2.1
SHBG	33.4 ± 6.1	35.2 ± 4.2§
LH/FSH	1.2 ± 0.1	1.8 ± 0.2
E2/T	39.8 ± 5.1‡	70.5 ± 14.1‡
E2/freeT	15.4 ± 2.0	30.4 ± 7.6

Values are mean ± S.E.

Abbreviations: E2: estradiol; FSH: follicle-stimulating hormone; LH: luteinizing hormone; SHBG: sex hormone-binding globulin; *: $p < 0.05$, Student's *t*-test; †: $p < 0.005$, Student's *t*-test; ‡: $p < 0.05$, Student's *t*-test; §: $p < 0.05$, repeated measures ANOVA.



*: $p < 0.05$, Student's *t*-test.

Fig. 1 E2/T Ratios in responders and non-responders at weeks 0, 4, and 12 of metformin treatment.

compared with that at week 0 ($p < 0.05$, multiple comparisons of ANOVA) (Table 1). The SHBG were significantly decreased after the 12-week metformin treatment ($p < 0.001$) in all patients in this study. The difference was statistically significant between weeks 0 and 12 ($p < 0.05$, multiple comparisons of ANOVA) (Table 2).

Table 2. Hormone Profiles of All Study Patients before and after Metformin Treatment (n = 37)

	Week 0 (before metformin treatment)	Week 4 of metformin treatment	Week 12 of metformin treatment
E2 (pg/ml)	70.8 ± 9.4	66.5 ± 7.1	53.2 ± 7.5
FSH (mIU/ml)	5.6 ± 0.4	5.2 ± 0.3	6.1 ± 0.4
LH (mIU/ml)	10.1 ± 0.8	10.5 ± 1.3	9.3 ± 0.9
Testosterone (ng/ml)	1.1 ± 0.2	1.0 ± 0.5	1.0 ± 0.6
Free testosterone (pg/ml)	2.9 ± 0.2	2.6 ± 0.2	2.6 ± 0.2
Fasting insulin (μIU/ml)	22.1 ± 3.2	18.7 ± 1.5	20.1 ± 1.9
SHBG (pg/ml)*	54.2 ± 6.8	40.7 ± 4.4	34.6 ± 3.4
LH/FSH	1.9 ± 1.5	2.2 ± 0.3	1.6 ± 0.2
E2/T	83.8 ± 18.0	74.6 ± 11.2	60.3 ± 9.5
E2/freeT	26.2 ± 3.1	28.7 ± 3.5	25.2 ± 5.1

Values are mean ± S.E.

Abbreviations: E2: estradiol; FSH: follicle-stimulating hormone; LH: luteinizing hormone; SHBG: sex hormone-binding globulin; *: $p < 0.001$, repeated measures ANOVA.

DISCUSSION

The response of ovulation to metformin might be related to various factors. Moghetti *et al*. showed that higher plasma insulin, lower serum androstenedione and less severe menstrual abnormalities are baseline predictors of clinical response to metformin.[9]

It is evident that decreased aromatase activity may be a possible mechanism underlying the arrested follicular growth in PCOS.[17-21] This was suggested by the a study that showed that follicles in women with PCOS contain low levels of estradiol, aromatase mRNA and aromatase activity.[17] PCOS follicular fluid contains one or more endogenous inhibitors of aromatase activity. 5α-androstane-3, 17-dione, a 5α-reduced androgen, is a competitive inhibitor of aromatase activity, it is markedly elevated in PCOS follicular fluid.[20] In addition, 5α-reductase activity is substantially higher in PCOS follicles than in control follicles, leading to increased production of 5α-androstane-3, 17-dione in women with PCOS.[21] Collectively, the decreased estradiol production and increased androgen production in women with PCOS may be a result of elevated 5α-reductase activity and decreased aromatase activity.

In the present study, a trend of decreased E2/T ratios was observed in both responders and non-responders after metformin treatment (Table 1), with a higher E2/T ratio in responders than that in non-responders (p = 0.4, 0.09 and 0.04 at weeks 0, 4 and 12, respectively), suggesting that there might be a greater intrinsic inhibiting activity on aromatase in non-responders. It is evident that the inhibitory effect of androgen on the aromatase in the antral follicles can be reversed by estrogen.[22] Notably, there was a trend of higher estradiol in association with lower testosterone in responders at each time interval after metformin treatment compared to those in non-responders (Table 1). Collectively, these results indicate that metformin treatment might activate aromatase activity, but fail to inhibit the production of testosterone in PCOS follicles. Furthermore, the present results showing a trend of higher LH and E2/T ratios in association with lower testosterone in responders than non-responders at each time interval after metformin treatment (Table 1) also suggests that elevated E2/T might reflect slightly higher aromatase activity and acts as a good indicator for response to metformin treatment.

A trend of higher E2/freeT ratios and elevated LH was found in responders than non-responders. The results from the present study suggest that the regulation between LH and ovarian steroids might be functional in ovulatory PCOS women. The present results were similar to previous observations by Kriplani and Agarwal that initial mean testosterone levels were lower in responders than non-responders.[15] In addition, there was no significant reduction in the circulating levels of free and total testosterone after the 12-week metformin treatment in this study (Table 2). This is not in agreement with previous studies describing a significant reduction in testosterone and fasting insulin levels after metformin treatment.[6,7,15,23,24] The discrepancy is likely related to the selection criteria, treatment duration and racial factors, and also suggests that the action of metformin might be also on the peripheral tissues and that it may work in a far more subtle and complicated way.[15, 25]

In summary, we conclude that in women with CC-resistant PCOS, an elevated E2/T is associated with a better response to metformin.

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雌激素／睪固酮比和克羅米芬抗藥性之多囊性卵巢以克醣治療之後其反應的關係

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背 景： 瞭解對克羅米芬 (clomiphene) 抗藥性之多囊性卵巢之女性，在以克醣 (metformin) 治療之後其反應及卵巢荷爾變化之關係。

方 法： 分析 56 位診斷爲克羅米芬抗藥性之多囊性卵巢之女性 (18-40 歲)，以克醣治療 12 週，評估治療之後是否恢復排卵功能，並在 0, 4, 12 週時抽血分析濾泡刺激素 (FSH)，黃體刺激素 (LH)，雌激素 (E2)，睪固酮 (T)，游離態睪固酮 (freeT)，空腹之胰島素 (fasting insulin) 及性荷爾蒙結合球蛋白 (SHBG)。

結 果： 共 37 位病人完成療程。反應組及不反應組在 0, 4, 12 週時之 FSH, E2, T, freeT 及 fasting insulin 並無顯著差異。在治療 4 週時，反應組之 LH 及 LH/FSH 明顯高於不反應組 ($p < 0.005$；$p < 0.05$)。治療 12 週後，相較於不反應組，反應組明顯有較高的E2/T 比及較低的游離態睪固酮 ($p < 0.05$；$p < 0.05$)。

結 論： 克羅米芬抗藥性之多囊性卵巢之女性，如果有較高的 E2/T 比，在以克醣治療之後有較佳的反應。

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