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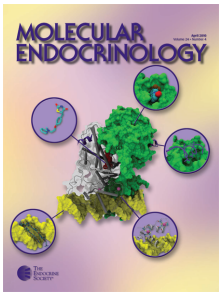


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# Metformin and Weight Loss in Obese Women with Polycystic Ovary Syndrome: Comparison of Doses

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**Context:** Metformin treatment of women with polycystic ovary syndrome (PCOS) is widespread, as determined by studies with diverse patient populations. No comparative examination of weight changes or metabolite responses to different doses has been reported.

**Objective:** The aim of this study was to determine whether different doses of metformin (1500 or 2550 mg/ d) would have different effects on body weight, circulating hormones, markers of inflammation, and lipid profiles.

**Design:** The study included prospective cohorts randomized to two doses of metformin.

**Setting:** The study was performed at a university teaching hospital with patients from gynecology/endocrinology clinics.

**Patients:** The patients studied were obese (body mass index, 30 to $<37$ kg/m$^2$; n = 42) and morbidly obese (body mass index, $\geq 37$ kg/m$^2$; n = 41) women with PCOS.

**Intervention:** Patients were randomized to two doses of metformin, and parameters were assessed after 4 and 8 months.

**Main Outcome Measures:** The main outcome measures were changes in body mass, circulating hormones, markers of inflammation, and lipid profiles.

**Results:** Intention to treat analyses showed significant weight loss in both dose groups. Only the obese subgroup showed a dose relationship (1.5 and 3.6 kg in 1500- and 2550-mg groups, respectively; $P = 0.04$). The morbidly obese group showed similar reductions (3.9 and 3.8 kg) in both groups. Suppression of androstenedione was significant with both metformin doses, but there was no clear dose relationship. Generally, beneficial changes in lipid profiles were not related to dose.

**Conclusion:** Weight loss is a feature of protracted metformin therapy in obese women with PCOS, with greater weight reduction potentially achievable with higher doses. Additional studies are required to determine whether other aspects of the disorder may benefit from the higher dose of metformin. **(*J Clin Endocrinol Metab* 90: 4593–4598, 2005)**

AFTER THE FIRST publications reporting the treatment of women with polycystic ovary syndrome (PCOS) with oral antihyperglycemic medications (1–4), there was an enthusiastic subsequent exploration of effects. Recent objective reviews (5, 6) determined that the effects of metformin on ovarian activity were beneficial, and that a number of other potential benefits were observable in appropriately controlled studies. These include improvements in lipid profiles and reductions in the circulating concentrations of androstenedione, if not always testosterone. However, in the Cochrane database review (6), despite a number of reports observing weight loss during treatment, the meta-analysis of current studies did not confirm that weight loss was a significant factor. This contrasts with the comprehensive data provided by the use of metformin in patients with glucose intolerance in the Diabetes Prevention Program (7), in whom significant and prolonged weight loss was recorded. Furthermore, there had been debate over whether some of the apparent improvement in ovarian function associated with metformin treatment, such as circulating androgen and lipid profiles, may be directly related to changes in body constitution (2).

One placebo-controlled trial of metformin in women with PCOS (8) observed that the biochemical effects and reductions in body mass were more consistent in the lean and obese (Ob) patients than in the morbidly obese (Mob) group [body mass index (BMI), $>37$ kg/m$^2$]. This paper suggested that such (Mob) cases are either refractory to the effects of metformin, or they may require increased doses. One recent study (9) also substantiated the view that obesity may reduce the benefit of metformin treatment. Many of the studies with metformin in women with PCOS have included large proportions of Ob and Mob women, and this may be a confounding feature in the conclusion of the Cochrane database review (6). Furthermore, the relationships between metformin and dose, and weight changes, endocrine changes, and cardiovascular risk factors such as lipid profiles (10) and C-reactive protein (CRP) (11) have only been sparsely examined.

The aim of this study was to examine the efficacy of metformin at two different doses (1500 and 2550 mg/d) in Ob and Mob women. The primary end point was weight loss, with the secondary intent to examine the effects of treatment or weight loss on cardiovascular risk factors, because these latter measures may be an important part of the case for

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Abbreviations: BMI, Body mass index; CRP, C-reactive protein; DHEAS, dehydroepiandrosterone sulfate; HDL, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; Mob, morbidly obese; Ob, obese; PCOS, polycystic ovary syndrome.

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extended use of oral antihyperglycemic medications in women with PCOS.

## Subjects and Methods

### *Study population*

Women with PCOS (n = 83), whose primary complaint was obesity, were recruited from the Reproductive Endocrinology/Assisted Conception Clinic at the Royal Infirmary (Glasgow, UK) and surrounding hospitals. The diagnosis of PCOS included at least two of the three features: oligomenorrhea (fewer than eight cycles per year)/amenorrhea (fewer than two cycles per year), polycystic ovaries determined by ultrasonography using the criteria of Adams *et al.* (12), or an elevated free androgen index. Exclusion criteria included contraindications to metformin or its use within the previous 4 months or oral contraceptive use within the previous 2 months. None of the women had thyroid dysfunction, hyperprolactinemia, diabetes mellitus, or late-onset or congenital adrenal hyperplasia. Women taking medication known to affect weight loss, gonadal or adrenal function, or carbohydrate or lipid metabolism were also excluded. Women were advised to use barrier contraception and were excluded if interest was expressed in immediate pregnancy.

Written informed consent was obtained from each woman, and the study was conducted at the Royal Infirmary after receiving approval from the ethics committee of the North Glasgow Hospitals University National Health Service Trust.

### *Study design*

The study was prospective, with dose-block randomization in two groups of patients with PCOS, defined as Ob (BMI, $\geq$30 and $<$37 kg/m$^2$) and Mob (BMI, $\geq$37 kg/m$^2$). The patient number treatment codes were held by a third party and were allocated after obtaining individual written consent. Metformin (Glucophage, Merck & Co., West Drayton, UK) doses were 500 and 850 mg, three times daily. Patients were not blinded to treatment dose. Study assessments were performed before treatment (T0) and after 4 months (T4) and 8 months (T8) of treatment and included anthropometric measurements (weight, BMI, and waist/hip ratio), ovarian structure, circulating hormones, and fasting glucose.

All patients were given the same advice concerning the benefits of lifestyle modification through diet and exercise. No additional advice or framework to assist weight reduction was given.

Although the study design would have been improved by inclusion of a placebo group, it was considered that the 8-month course of treatment was too excessive in the circumstances of these patients.

### *Assessment program*

At T0, T4 (after 4 months), and T8 (after 8 months), all patients underwent clinical and hormonal assessments. These included anthropometric measurements of height, weight (BMI), and waist/hip ratio as well as measurements of blood pressure, menstrual cyclicity, and hirsutism using the modified Ferriman-Gallwey score (13). Ultrasound assessments [all performed by the same observer (L.H.)] were also performed at 0-, 4-, and 8-month intervals to assess ovarian morphology and follicular growth (ovarian volume, numbers of follicles with diameter $<$10 mm, and diameter of the largest follicle).

Circulating blood samples taken at each assessment point were analyzed for fasting insulin, glucose, LH, FSH, estradiol, testosterone, SHBG, free androgen index, dehydroepiandrosterone sulfate (DHEAS), androstenedione, 17$\alpha$-hydroxyprogesterone, high sensitivity CRP, total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), leptin, IGF-I, and IGF-binding protein-3. Liver function, basic blood biochemistry, and thyroid function tests were also performed.

Although there was no specific diet or exercise regimen advice given as part of this trial, patients were asked to complete an exercise and dietary questionnaire at each time interval (T0, T4, and T8). A side-effect profile was also performed at 1 and 2 months.

### *Techniques*

BMI was calculated using the equation: weight (kilograms)/height$^2$ (meters). Waist and hip circumferences were measured to the nearest centimeter with a soft tape according to World Health Organization criteria. Waist circumference was obtained as the minimum value between the iliac crest and the lateral costal margin, whereas hip circumference was determined as the maximum value over the gluteal region. Ultrasound was performed by the transvaginal method using a vaginal probe (Sonoline Sienna Ultrasound Imaging System, Transducer 6.5EV13+; 6.5 MHz; Siemens, Erlangen, Germany). In each ovary, ovarian volume, greatest number of follicles in any one ovarian plane, and the diameter of the largest follicle were calculated.

Hormone concentrations were assayed in patient-specific batches to eliminate the effect of interassay drift. Testosterone and androstenedione were assessed using the semiautomated Immulite technology (Diagnostic Products Corp., Los Angeles, CA), and SHBG, DHEAS, IGF-I, and IGF-binding protein-3 were assessed by the Immulite 2000 analyzer (Diagnostic Products Corp.). 17$\alpha$-Hydroxyprogesterone was assayed using an in-house RIA (intraassay coefficient of variation, $<$12%).

Plasma glucose was measured using the glucose oxidase method (Bayer Advia 1650 Chemistry System, Bayer, Pittsburgh, PA), and insulin was measured using a competitive RIA (Coat-A-Count I, Diagnostic Products Corp.). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated from the fasting concentrations of insulin and glucose using the following formula: HOMA-IR = fasting serum insulin (microunits per milliliter) $\times$ fasting plasma glucose (millimoles per liter)/22.5.

Plasma total cholesterol, triglyceride, HDL-C, and LDL-C measurements were performed by a modification of the standard Lipid Research Clinics protocol (14). Serum leptin concentrations were measured by a validated in-house RIA (15). The intra- and interassay coefficients of variation were less than 7% and less than 10%, respectively, over the sample concentration range. The detection limit of the assay was 0.5 ng/ml.

### *Statistics*

Where distributions were normal, group statistical evaluations were compared using unpaired *t* tests, with Welch correction for unequal variances where necessary, and when distributions were non-Gaussian, the Mann-Whitney *U* test was applied. Changes in variables during treatment within groups were evaluated, on an intention to treat basis, using repeated measures ANOVA on values before treatment (T0) and after 4 and 8 months of treatment. Absent values were substituted with the most recent value per patient. Linear correlation examinations were effected (in patients with completed data only) to examine relationships between changes in weight and insulin metabolism and other parameters. Statistical analyses were performed using PRISM software GraphPad, San Diego, CA).

## Results

### *Patients*

The randomization of the 83 patients entering the study into the four treatment groupings produced an equal distribution of 21 patients in the Ob1500, Ob2550, and Mob2550, with 20 cases in the Mob1500 group. Within each BMI category, there was no difference between the dose subgroups for any parameter examined, whereas the differences between the Ob and Mob subgroups before treatment were in line with expected values. Specifically, the Mob group showed higher values for fasting insulin ($P = 0.025$), CRP ($P = 0.01$), leptin ($P < 0.001$), triglycerides ($P < 0.001$), and LDL-C ($P = 0.021$) and lower values for glucose/insulin ratio ($P = 0.003$), IGF-I ($P = 0.002$), and HDL-C ($P < 0.001$). The increase in the HOMA-IR evaluation in the Mob group was not statistically significant ($P = 0.063$).

Sixty-eight patients (82%) completed the course to the final 8 month assessment point. There was no difference in the proportions of patients completing the study in each group (Ob500, 18 of 21; Ob850, 17 of 21; Mob500, 18 of 20; Mob850,

15 of 21). The main reason for discontinuation was excessive gastrointestinal irritation.

*Weight reduction and metformin treatment*

Analyses of the changes in body mass in all patients receiving the 8-month metformin treatment (n = 83; intention to treat analysis) revealed that there was a highly significant reduction (3.8%) from a mean BMI of 37.2 kg/m$^2$, with 95% confidence limits of 35.9–38.5 at the start (T0) to a mean BMI of 36.1 (95% confidence limits, 34.7, 37.4) at T8 (by repeated measures ANOVA, $P < 0.0001$).

*Dose of metformin.* Table 1 examines the weight changes in the groups treated with different doses of metformin, and it reveals that both treatment doses were associated with significant weight reductions over the 8-month assessment period. At 8 months, the 1500-mg group showed a mean reduction of 2.5 kg (mean BMI, 36.8–37.9 kg/m$^2$), whereas the 2550-mg group lost a mean of 3.7 kg (mean BMI, 34.5–36.3 kg/m$^2$). The absolute weight lost did not differ between the dose groups ($P = 0.35$). The high dose of metformin showed a more consistent effect on weight loss, as evidenced by the degree of significance (by ANOVA, repeated measures), but there was no other statistical support for this concept.

*Influence of the degree of obesity.* Table 1 also shows that the Ob group treated with 1500 mg underwent no effective weight loss, whereas all other subgroups demonstrated significant weight reductions. Correspondingly, the Ob group showed a metformin dose effect with respect to weight loss, because the absolute weight lost was significantly different between the dose groups (0 = 0.04). However, this was not mirrored in the Mob group, which showed similar weight losses in both dose groups.

Figure 1 shows that, with the exception of the Ob group treated with 1500 mg metformin, there was a general decline in weight of approximately 4% over the 8 months of treatment.

*Effects of metformin treatment and/or weight change*

*Menstrual frequency.* There was effectively a doubling of the frequency of menses during metformin treatment in those patients with oligomenorrhea in both dosage groups. In the 1500-mg group, the mean frequency increased from 3.8 to 6.7 menses/yr ($P < 0.0001$, by paired *t* test), and in the 2550-mg group, the increase was from a mean of 3.8 to 6.8 menses/yr ($P < 0.0001$).

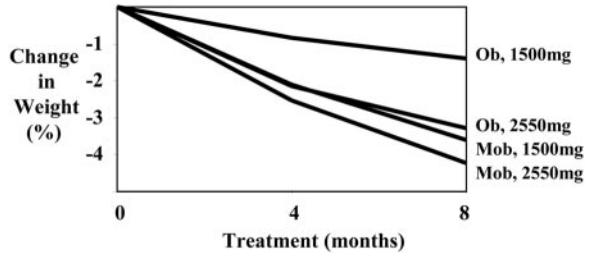


FIG. 1. Decline in weight (percentage) of the metformin treatment groups over 8 months according to obesity category and daily metformin dose.

There was no apparent difference between either the dose or obesity subgroups in the menstrual response to treatment. The proportion of patients with oligomenorrhea who achieved normal menstrual rhythm (≥10 menstrual cycles/yr) during treatment was 36% in the 1500-mg group and 48% in the 2550-mg group ($P = 0.41$). There was also no difference between the Ob and Mob groups in the proportion attaining normal menstrual rhythm.

*Blood analytes and metformin dose*

*Insulin metabolism.* Markers of insulin resistance (fasting insulin, glucose/insulin ratio, and $\log_{HOMA\text{-}IR}$) revealed modest improvements associated with treatment in the high dose group only (Table 2). Although there were significant changes in the glucose/insulin ratio and HOMA-IR in the 2550-mg dose group that were not observed in the 1500-mg dose group, absolute values at 8 months did not differ significantly between the two dose groups (by unpaired *t* tests: fasting insulin, $P = 0.29$; glucose/insulin ratio, $P = 0.47$; HOMA-IR, $P = 0.15$).

*Reproductive metabolites.* Table 2 also shows that circulating androstenedione underwent a marked reduction in patients treated with 2550 mg metformin (mean reduction, 2.5 ng/ml), whereas the decline appeared less in the group treated with 1500 mg (1.8 ng/ml). However, neither the concentration declines ($P = 0.29$) nor the absolute values at 8 months ($P = 0.81$) differed significantly between the two dose groups. Neither circulating testosterone nor SHBG showed changes, and correspondingly, the free androgen index was

**TABLE 1.** Mean weights of all patients (all cases) and Ob and Mob subgroups treated with metformin at doses of 1500 or 2550 mg/d

| | n | Dose (mg/d) | T0 (kg) | T4 (kg) | T8 (kg) | P (ANOVA) | Weight lost (kg) |
|---|---|---|---|---|---|---|---|
| All cases (95% CL) | 42 | 1500 | 104.3 (98.2–110.5) | 102.7 (96.6–108.8) | 101.9 (95.6–108.1) | 0.0024 | 2.5[a] |
| | 41 | 2550 | 96.4 (92.1–100.7) | 94.2 (89.8–98.6) | 92.7 (88.2–97.3) | <0.0001 | 3.7[a] |
| Ob group (95% CL) | 21 | 1500 | 92.0 (86.2–97.8) | 91.3 (85.4–97.3) | 90.9 (84.3–97.6) | 0.236 | 1.5[b] |
| | 21 | 2550 | 85.2 (82.1–88.2) | 83.0 (79.6–86.4) | 81.6 (77.8–85.4) | <0.0001 | 3.6[b] |
| Mob group (95% CL) | 20 | 1500 | 117.3 (109.4–125.1) | 114.7 (106.5–122.8) | 113.4 (104.8–121.9) | 0.010 | 3.9[c] |
| | 21 | 2550 | 107.1 (103.0–111.1) | 104.8 (100.4–109.2) | 103.3 (98.7–108.0) | 0.007 | 3.8[c] |

Changes were evaluated using ANOVA; *P* values are shown. CL, Confidence limits. Unpaired *t* test (Welsh correction for unequal variances) significance is indicated in [abc].

[a] $P = 0.35$.

[b] $P = 0.04$.

[c] $P = 0.94$.

**TABLE 2.** Mean concentrations of analytes at start of treatment [with SD] and the average changes (8 months to T0) during treatment with metformin in the two dose groups of patients (Ob and Mob patients combined) treated with 1500 or 2550 mg/d

| | 1500 mg/d | | | 2550 mg/d | | | Dose effect (p) |
|---|---|---|---|---|---|---|---|
| | T0 | 8m–T0 | P | T0 | 8m–T0 | P | |
| Fasting insulin (mU/liter) | 17.1 [9.9] | 1.0 | 0.746 | 16.4 [9.3] | −1.9 | 0.043 | 0.23 |
| Glucose (mM/liter) | 5.07 [0.46] | −0.09 | 0.468 | 4.93 [0.48] | −0.13 | 0.181 | 0.73 |
| Glucose/insulin ratio | 0.38 [0.21] | 0.01 | 0.640 | 0.37 [0.14] | 0.06 | 0.026 | 0.16 |
| HOMA-IR | 3.96 [2.8] | 0.24 | 0.711 | 3.73 [1.9] | 0.47 | 0.050 | 0.29 |
| IGF-I (ng/ml) | 187 [98] | 1.0 | 0.856 | 197.0 [79] | −13.9 | 0.373 | 0.42 |
| Androstenedione (ng/ml) | 11.2 [4.0] | −1.7 | 0.009 | 11.4 [4.9] | −2.5 | 0.0001 | 0.36 |
| Testosterone (nmol/liter) | 5.2 [2.1] | 0.2 | 0.59 | 5.4 [3.2] | −0.3 | 0.067 | 0.25 |
| SHBG | 29.9 [18.5] | −1.9 | 0.201 | 28.5 [9.1] | −1.2 | 0.049 | 0.85 |
| Free androgen index | 10.3 [6.1] | 1.3 | 0.19 | 11.2 [7.8] | −0.5 | 0.640 | 0.09 |
| LH (IU/liter) | 11.07 [5.8] | −1.64 | 0.605 | 10.3 [6.0] | −0.8 | 0.305 | 0.75 |
| DHEAS (μg/liter) | 5.86 [2.6] | 0.67 | 0.023 | 6.81 [2.7] | 0.47 | 0.133 | 0.67 |
| Triglycerides (mmol/liter) | 1.59 [0.9] | −0.05 | 0.75 | 1.86 [1.0] | −0.14 | 0.41 | 0.57 |
| Total cholesterol (mmol/liter) | 5.13 [0.92] | −0.29 | 0.0007 | 4.99 [0.83] | −0.27 | 0.004 | 0.76 |
| HDL-C (mmol/liter) | 1.10 [0.29] | 0.05 | 0.070 | 0.97 [0.26] | 0.0 | 0.73 | 0.83 |
| LDL-C (mmol/liter) | 3.30 [0.75] | −0.32 | 0.0001 | 3.12 [0.85] | −0.23 | 0.004 | 0.36 |
| Leptin (ng/ml) | 69.1 [21.8] | −11.8 | 0.0001 | 66.3 [28.7] | −15.3 | 0.0001 | 0.43 |
| CRP | 6.89 [5.6] | −1.49 | 0.098 | 6.54 [7.4] | −0.8 | 0.503 | 0.65 |

Values are shown for pretreatment (T0) and the difference after 8 months. The statistical evaluation within groups represents repeated measures ANOVA assessment for values at T0 and 4 and 8 months. The dose effect is a comparison of the changes between the dose groups.

unaffected by either treatment dose. The increase in DHEAS recorded in the 1500-mg group was not replicated in the 2550-mg group, and there was no difference between the groups in the final concentration of DHEAS at T8 ($P = 0.37$).

The highly significant decline in leptin concentrations in both groups also showed no significant difference between the treatment groups.

The circulating concentrations of LH showed no indication of a change in either treatment group. This was despite the changes in ovarian activity evidenced by menstrual frequency noted above. Analysis of the LH values in those cases undergoing the change from oligomenorrhea (fewer than nine menses per year) to normal menstrual rhythm (more than nine menses per year) revealed that these individuals ($n = 21$) showed modest reduction in circulating LH ($P = 0.042$, by paired *t* test) with absolute values at T0 (12.2 IU/liter) decreasing from 11.4 IU/liter at 4 months to 7.6 IU/liter at 8 months. This latter value would be considered to represent the high-normal range.

*Lipid profiles and inflammatory markers.* Table 2 also shows the changes in lipid and inflammatory marker profiles observed during treatment with the two doses of metformin. Significant reductions in total cholesterol and LDL-C were observed in both dosage groups, with no apparent dose effect. There was no effect of either treatment dose on circulating triglycerides or HDL. The highly significant reductions in leptin in both groups were not reflected by changes in circulating CRP, which showed no change in either dose group.

### *Roles of changes in weight and insulin metabolism*

Changes in variables were examined with respect to weight change and the glucose/insulin ratio over the 8-month treatment period regardless of obesity category and dose of metformin. It is not surprising that the weight lost (kilograms) correlated strongly with the change in the glucose/insulin ratio ($r^2 = 0.16$; $P = 0.0008$). However, Table 3 shows that the changes in androstenedione were significantly correlated only to changes in the glucose/insulin ratio, whereas changes in circulating leptin correlated strongly ($r^2 = 0.37$) with the changes in weight and less strongly with the glucose/insulin ratio. The changes in lipids appeared unrelated to either marker.

### *Influence of the obesity subgroup on changes in metabolites*

The degree of obesity (Ob group compared with Mob group) appeared to have little influence on the absolute changes in the metabolites assessed. The Ob group treated with 2550 mg metformin showed a mean decline in the circulating androstenedione concentration of 3.7 ng/ml, compared with only 1.6 ng/ml in the Ob group treated with 1500 mg metformin. These differences were not significantly different ($P = 0.07$), and data for the Mob group (decline of 2.1 ng/ml for the 1500-mg group and 1.8 ng/ml for the 2550-mg group) revealed smaller nonsignificant differences.

Most other metabolites showed no difference between the obesity categories, with the possible exception of IGF-I. The Ob group showed a mean decrease in circulating IGF-I of 25 ng/ml, whereas the Mob group showed a mean increase of 12.7 ng/ml. This difference was statistically significant ($P = 0.02$).

**TABLE 3.** Correlation evaluations (Spearman's test where distributions were non-Gaussian) of the changes in parameters related to changes in weight and glucose/insulin ratio in all patients completing treatment

| | Change in weight | | Change in glucose/insulin ratio | |
|---|---|---|---|---|
| | $r^2$ | *P* | $r^2$ | *P* |
| Androstenedione | 0.05 | 0.07 | 0.07 | 0.028 |
| Total cholesterol | 0.03 | 0.151 | 0.00 | 0.659 |
| LDL-C | 0.00 | 0.54 | 0.04 | 0.13 |
| Leptin | 0.37 | <0.0001 | 0.15 | 0.001 |

## Discussion

To our knowledge, this is the first systematic, randomized study of the effects of different doses of metformin in obese women with PCOS. The data reveal that women with PCOS respond to metformin in a manner related to dose and possibly also body mass, but to only a limited degree. The dose effect was revealed by the observation that changes in markers of insulin sensitivity were significant only in the higher dose group. It was also shown that the degree of weight reduction in the Ob group was dose related, whereas no such relationship was determined in the Mob group. Profiles suggesting dose effects on circulating androstenedione concentrations were not statistically significant. None of the other metabolites showed sensitivity to the metformin dose.

The observations confirm that a significant weight reduction is to be expected with protracted metformin treatment, but they do not support the concept that the degree of obesity is influential. This contrasts with the subgroup analysis previously reported suggesting that Mob patients may be refractory to the treatment benefits (9). Notwithstanding this, ovarian function appeared to show general improvement in all subgroups. It is interesting to record that although measures of insulin resistance changed only in the high dose group, some markers of cardiovascular risk showed apparent improvements with both metformin doses and both BMI groups.

The recent Cochrane Library review and its summary (6) concluded that metformin treatment of women with PCOS was effective in increasing ovulation rates and suppressing androstenedione in women with PCOS, but it could not confirm effects on weight reduction. Many of the studies quoted in the review included relatively small numbers and were of generally short duration, and most of the primary end points were related to ovarian function and fertility. All these characteristics may reduce the validity of the conclusions with respect to the nonfertility end points. This conclusion also contrasts with the findings of the diabetes prevention study (7), with large numbers of individuals (not PCOS patients) in whom weight loss was consistent and long lasting. The study reported here was designed to address weight loss during metformin treatment among PCOS patients given standard weight-reducing advice, and it shows convincing evidence supporting a pharmacological effect. Moreover, although we did not include a placebo group, the continued weight reduction beyond 4 months in all groups is notable and differs from the pattern seen with lifestyle changes, which might have occurred as a study effect.

The effects of metformin on lipid profiles and markers or risk factors for vascular disease were generally beneficial, but complex. Total cholesterol showed a general decrease, mainly through a decrease in LDL-C, and there was a trend toward increased HDL-C. None of these changes in lipid profiles correlated with changes in weight or the glucose/insulin ratio. The absence of an effect on circulating CRP levels also contrasts with previous studies using relatively low metformin doses, but in less obese patients (11). It should be restated that most of these patients remained severely obese.

Additional examination of the relative importance of weight loss or change in insulin sensitivity revealed little clear information, except that weight change correlated strongly with circulating leptin, whereas androstenedione appeared to be influenced more by the change in insulin sensitivity.

The changes in lipid profiles showed no dose differential in either BMI category. It is perhaps not surprising that there was no consistent change in total triglycerides, because a large series of women with PCOS, treated with three doses of troglitazone similarly showed no change in circulating triglycerides (10), and furthermore, only nonsignificant trends for a reduction of LDL-C and an increase in HDL-C were recorded. The review (6) of studies using metformin for variable durations revealed consistent changes only in LDL-C. This was in accord with the observations presented above, along with beneficial changes in total cholesterol.

It is acknowledged that the absence of a placebo group of patients limits the validity of observations of weight changes, but a previous study in our unit with placebo in similar patients given identical advice showed a modest, but significant, weight increase over 16 wk (8).

Although relative insulin resistance and its compensatory hyperinsulinemia or insulin hypersecretion are thought to underpin the etiology of PCOS, the origins of the ovarian disorder (excessive primordial, primary, and small antral follicular development) may be established at birth (16). Correspondingly, a cure at this level is unlikely until a means of influencing the rate of initial follicle recruitment and survival to the antral stage can be elucidated. However, the effects of increasing body mass and hyperinsulinism appear to have a profound impact on ovarian function and fertility in women with PCOS, and metformin appears to be defining a role for itself in this specific area. This study appears to suggest that the doses used hitherto in Ob and Mob women with PCOS may be suboptimal, because more consistent effects appear to be obtained with the higher doses.

It is likely that most of the immediate symptoms of PCOS will continue to be treated using a symptom-specific approach, but the role of oral antihyperglycemic medications in the treatment of these disorders remains to be determined. With the exception of fertility issues, the principle symptoms for considering treatment generally require protracted treatment, often in conjunction with other medications.

Optimal doses of metformin in these circumstances have not been elucidated, but the indication from this study is that more obvious benefit, subsequent to changes in hormones, lipids, and weight, may be obtained with doses higher than those previously explored, particularly in patients with excessive body mass. However, specific evidence underwriting this statement is not strong, and additional explorations will be required.

We conclude that weight loss is a feature of protracted metformin therapy in women with PCOS, with greater weight reduction potentially achievable with higher doses of metformin. Future studies should examine whether higher metformin doses yield greater clinical benefit, although this examination indicates that large numbers of patients will be required to show convincing differences in many parameters.

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## References

1. **Velazquez EM, Mendoza S, Hamer T, Sosa F, Glueck CJ** 1994 Metformin therapy in polycystic ovary syndrome reduces hyperinsulinaemia, insulin resistance, hyperandrogenaemia, and systolic blood pressure, while facilitating normal menses and pregnancy. Metabolism 43:647–654
2. **Crave JC, Fimbel S, Lejeune H, Cugnardey N, Dechaud H, Pugeat M** 1995 Effects of diet and metformin administration on sex hormone-binding globulin, androgens and insulin in hirsute and obese women. J Clin Endocrinol Metab 80:2057–2062
3. **Ehrmann DA, Cavaghan MK, Imperial J, Sturis J, Rosenfield RL, Polonsky KS** 1997 Effects of Metformin on Insulin secretion, insulin action, and ovarian steroidogenesis in women with polycystic ovary syndrome. J Clin Endocrinol Metab 82:524–530
4. **Nestler JE, Jakubowicz DJ** 1997 Lean women with polycystic ovary syndrome respond to insulin reduction with decreases in ovarian P450c17$\alpha$ activity and serum androgens. J Clin Endocrinol Metab 82:4075–4079
5. **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
6. **Lord JM, Flight IH, Norman RJ** 2003 Metformin in polycystic ovary syndrome: systematic review and meta-analysis. BMJ 327:951–953
7. **Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM** 2002 Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin N Engl J Med 346:393–403
8. **Fleming R, Hopkinson ZE, Wallace AM, Greer IA, Sattar N** 2002 Ovarian function and metabolic factors in women with oligomenorrhea treated with metformin in a randomized double blind placebo-controlled trial. J Clin Endocrinol Metab 87:569–574
9. **Maciel GA, Soares Junior JM, Alves da Motta EL, Abi Haidar M, de Lima GR, Baracat EC** 2004 Nonobese women with polycystic ovary syndrome respond better than obese women to treatment with metformin. Fertil Steril 81:355–360
10. **Legro RS, Azziz R, Ehrmann D, Fereshetian AG, O'Keefe M, Ghazzi MN** 2003 Minimal response of circulating lipids in women with polycystic ovary syndrome to improvement in insulin sensitivity with troglitazone. J Clin Endocrinol Metab 88:5137–5144
11. **Morin-Papunen L, Rautio K, Ruokonen A, Hedberg P, Puukka M, Tapanainen JS** 2003 Metformin reduces serum C-reactive protein levels in women with polycystic ovary syndrome. J Clin Endocrinol Metab 88:4649–4654
12. **Adams JM, Polson JW, Franks S** 1986 Prevalence of polycystic ovaries in women with anovulation and idiopathic hirsutism. Br Med J 293:355–359
13. **Ferriman D, Gallwey JD** 1961 Clinical assessment of body hair growth in women. J Clin Endocrinol Metab 21:1440–1448
14. **Lipid Research Clinics Program** 1975 Lipid and lipoprotein analysis. Manual of laboratory operations. Vol 1. Bethesda, MD: DHEW Publications (NIH); 75
15. **McConway MG, Johnson D, Kelly A, Griffin D, Smith J, Wallace AM** 2000 Differences in circulating concentrations of total, free and bound leptin relate to gender and body composition in adults humans. Ann Clin Biochem 37: 717–723
16. **Webber LJ, Stubbs S, Stark J, Trew GH, Margara R, Hardy K, Franks S** 2003 Formation and early development of follicles in the polycystic ovary. Lancet 362:1017–1021