Randomized Placebo-Controlled Trial of Metformin for Adolescents With Polycystic Ovary Syndrome

Tracey Bridger, MD, FRCPC; Suzanne MacDonald, MD, FRCPC; Franziska Baltzer, MD, FRCPC; Celia Rodd, MD, FRCPC

Objective: To determine whether metformin or placebo could, in conjunction with healthy lifestyle counseling, decrease serum testosterone levels and related aberrations in adolescents with hyperandrogenism, hyperinsulinemia, and polycystic ovarian syndrome.

Design: Randomized, placebo-controlled, double-blind trial.

Setting: Pediatric university teaching hospital.

Participants: Twenty-two adolescents aged 13 to 18 years with hyperinsulinemia and polycystic ovarian syndrome.

Intervention: Participants were randomly assigned to take a 12-week course of either metformin or placebo.

Main Outcome Measures: Pretreatment and post-treatment oral glucose tolerance tests, fasting lipid profiles, and clinical measurements.

Results: There was a significant decline in mean serum testosterone concentration with metformin (−38.3 ng/dL) compared with placebo (−0.86 ng/dL) (95% confidence interval, −0.39 to −0.29 for the mean difference between groups). At completion, the relative risk of menses was 2.50 times higher in the metformin group compared with the placebo (95% confidence interval, 1.12 to 5.58). Measures of insulin sensitivity, including insulin area under the curve and HOMA (homeostasis model assessment), demonstrated improvement only with metformin, but these did not reach statistical significance. High-density lipoprotein cholesterol levels increased by 6.98 mg/dL with metformin vs a decrease of −2.33 mg/dL with placebo (95% confidence interval, 0.78 to 18.23 for the mean difference between groups). There were no significant changes in body mass index, hirsutism, triglyceride levels, or total and low-density lipoprotein cholesterol levels.

Conclusion: Metformin significantly lowered total testosterone concentrations, increased the likelihood of menses, and improved high-density lipoprotein cholesterol levels without affecting measures of insulin sensitivity or body weight.

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cebo-controlled studies of metformin in adolescents with PCOS.14,18

The primary objective of this study was to determine whether metformin or placebo, in conjunction with healthy lifestyle counseling, could reduce serum testosterone levels in adolescents with hyperandrogenism, hyperinsulinemia, and PCOS. Secondary objectives centered on the efficacy of metformin in restoring menses, attenuating insulin resistance, and/or improving lipid profiles in adolescents with this disorder.

**METHODS**

**STUDY PARTICIPANTS**

We enrolled 22 adolescents with PCOS and concomitant hyperinsulinemia from the Endocrinology and Adolescent Medicine clinics of the Montreal Children’s Hospital (Montreal, Quebec) between 1999 and 2002. Participants were at least 12 years old and had a history of menarche at least 2 years prior to enrollment. Diagnosis of PCOS was based on previously reported criteria. All subjects had chronic oligomenorrhea (≤6 menses in the preceding year) and clinical or biochemical evidence of hyperandrogenism. We excluded subjects with other causes of hyperandrogenism, such as hyperprolactinemia, androgen-secreting tumors, or late-onset congenital adrenal hyperplasia. Congenital adrenal hyperplasia was specifically ruled out by measuring 17 hydroxyprogesterone levels using an adenocorticotropin (ACTH) stimulation test.

Sample size was based on power calculations and the published effects of metformin treatment in adult women. We approached eligible candidates sequentially until this goal was achieved, and baseline demographic features did not differ between participants and nonparticipants (not shown). Exclusion criteria included diabetes mellitus, renal or hepatic disease, pregnancy, allergies to metformin, taking oral contraceptives in the 6 months prior to enrollment, or taking medications that could influence the effects of insulin or androgens.

The study was approved by the research ethics board of the Montreal Children’s Hospital. Each young woman gave informed consent and/or assent, and informed consent was obtained from their parents.

**STUDY PROTOCOL**

After a 12-hour overnight fast, the adolescents came to the study center and underwent a standard 75-g oral glucose tolerance test (OGTT). At baseline, serum was collected to measure total testosterone, progesterone level, and lipid profile. At 0-, 30-, 60-, 90-, and 120-minute intervals after the glucose load, glucose, triglyceride, and total cholesterol levels were immediately analyzed on the Vitros (Ortho-Clinical, Johnson and Johnson, New Brunswick, NJ). High-density lipoprotein cholesterol was analyzed on the Cobas Miro platform (Roche Diagnostics, Hoffmann La Roche Ltd, Basel, Switzerland). Progesterone was assayed by Centaur chemiluminescence platform (Chiron Corp, Emeryville, Calif). Insulin, dehydroepiandrosterone sulfate, and prolactin were analyzed by the chemiluminescent Immulite platform (Diagnostic Systems, Webster, Tex). Serum was analyzed by radio immunoassay kits for total testosterone (Pantax, Santa Monica, Calif), 17 beta estradiol, 17 hydroxyprogesterone (Diagnostic Systems, Amerinado) and luteinizing hormone and follicle-stimulating hormone (Diagnostic Products Corp, Los Angeles, Calif).

Insulin sensitivity was estimated by calculating the insulin area under the curve (AUC), a measure that has been validated in women with PCOS against the hyperglycemic-euglycemic clamp. We also calculated the homeostasis model assessment (HOMA=[fasting insulin result × fasting glucose result]/22.5) and quantitative insulin sensitivity check index (QUICKI=1/[logarithm of fasting insulin result + logarithm of fasting glucose result]), both previously validated using the hyperglycemic-euglycemic clamp.

**DATA ANALYSIS**

Statistical analysis was performed with R, version 2.1.1. For continuous variables, the difference between posttreatment and baseline values were calculated for each subject and the groups compared for equality of variance by F test. When variances were equal, the mean difference in each group and 95% confidence interval (CI) for the difference between the 2 means were tested for equality by a standard Welch t test procedure. The Satterthwaite method was invoked for unequal variances (null hypothesis, H0: mean difference, 0). Categorical data (eg, return of menses) were compared by Fisher exact test and expressed as a relative risk with associated 95% confidence interval (HR, relative risk, 1). In both cases, failure of the 95% confidence interval to cross the H0 value reflects P<.05.

Of 22 subjects recruited (n=11 in each group), only 1 subject did not complete the study. One adolescent in the placebo arm was able to provide information about her compliance and clinical well-being at the end of the study period but was unable to present for the OGTT and physical examination.

**PREINTERVENTION CHARACTERISTICS**

The clinical characteristics of the 2 groups of adolescent girls at baseline are depicted in Table 1. They ranged

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**RESULTS**

Blood samples were centrifuged immediately, and serum for hormones and high-density lipoprotein (HDL) cholesterol was stored at −20°C until assayed. Glucose, triglyceride, and total cholesterol levels were immediately analyzed on the Vitros (Ortho-Clinical, Johnson and Johnson, New Brunswick, NJ). High-density lipoprotein cholesterol was analyzed on the Cobas Miro platform (Roche Diagnostics, Hoffmann La Roche Ltd, Basel, Switzerland). Progesterone was assayed by Centaur chemiluminescence platform (Chiron Corp, Emeryville, Calif). Insulin, dehydroepiandrosterone sulfate, and prolactin were analyzed by the chemiluminescent Immulite platform (Diagnostic Systems, Webster, Tex). Serum was analyzed by radio immunoassay kits for total testosterone (Pantax, Santa Monica, Calif), 17 beta estradiol, 17 hydroxyprogesterone (Diagnostic Systems, Amerinado) and luteinizing hormone and follicle-stimulating hormone (Diagnostic Products Corp, Los Angeles, Calif).

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**PREINTERVENTION CHARACTERISTICS**

The clinical characteristics of the 2 groups of adolescent girls at baseline are depicted in Table 1. They ranged
Table 1. Clinical Characteristics and Serum Hormone Concentrations in Adolescents With PCOS at Baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Metformin Group</th>
<th>Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>16.07 ± 0.97</td>
<td>16.08 ± 1.39</td>
</tr>
<tr>
<td>Body mass index, mean ± SD*</td>
<td>33.6 ± 5.6</td>
<td>30.81 ± 3.0</td>
</tr>
<tr>
<td>Ferriman and Gallwey score, mean ± SD</td>
<td>5.3 ± 5.0</td>
<td>7.2 ± 7.6</td>
</tr>
<tr>
<td>Total testosterone, mean ± SD, ng/dL (mmol/L)</td>
<td>174.3 ± 54.0 (6.03 ± 1.88)</td>
<td>167.3 ± 46.0 (5.80 ± 1.58)</td>
</tr>
<tr>
<td>Insulin AUC, mean ± SD, µU/mL - min (pmol/L - min)</td>
<td>15,246 ± 10,997 (109,374 ± 72,433)</td>
<td>15,460 ± 12,377 (110,905 ± 88,788)</td>
</tr>
<tr>
<td>Fasting glucose, mean ± SD, mg/dL (mmol/L)</td>
<td>77.9 ± 7.2 (4.33 ± 0.4)</td>
<td>80.6 ± 8.3 (4.48 ± 0.46)</td>
</tr>
<tr>
<td>HOMA, mean ± SD</td>
<td>5.75 ± 10.08</td>
<td>2.79 ± 1.45</td>
</tr>
<tr>
<td>QUICKI, mean ± SD</td>
<td>0.34 ± 0.07</td>
<td>0.36 ± 0.05</td>
</tr>
<tr>
<td>Total cholesterol, mean ± SD, mg/dL (mmol/L)</td>
<td>164.9 ± 27.5 (4.25 ± 0.71)</td>
<td>171.1 ± 48.9 (4.41 ± 1.26)</td>
</tr>
<tr>
<td>LDL cholesterol, mean ± SD, mg/dL (mmol/L)</td>
<td>88.5 ± 19.8 (2.28 ± 0.51)</td>
<td>93.5 ± 41.9 (2.41 ± 1.08)</td>
</tr>
<tr>
<td>HDL cholesterol, mean ± SD, mg/dL (mmol/L)</td>
<td>45.8 ± 18.6 (1.18 ± 0.48)</td>
<td>42.3 ± 10.9 (1.09 ± 0.28)</td>
</tr>
<tr>
<td>Triglycerides, mean ± SD, mg/dL (mmol/L)</td>
<td>133.9 ± 55.1 (1.53 ± 0.63)</td>
<td>168 ± 77.9 (1.92 ± 0.89)</td>
</tr>
<tr>
<td>Ethnicity, No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Black, non-Hispanic</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Menses in 6 months before enrollment, No.</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Girls with menses during 6 months before enrollment, No.</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under the curve; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; LDL, low-density lipoprotein; PCOS, polycystic ovarian syndrome; QUICKI, quantitative insulin sensitivity check index.

*Body mass index is calculated as weight in kilograms divided by the square of height in meters.

in age from 13 to 18 years with an average age of 16.0 years at the start of the study period. All were overweight or obese with body mass index (BMI), calculated as weight in kilograms divided by the square of height in meters, ranging from 26.0 to 44.7. By definition, all were hyperandrogenemic with significantly elevated levels of total testosterone. Subjects in both groups came from similar ethnic backgrounds. All participants had had fewer than 6 menses in the year preceding the study with no significant difference in the 2 proportions at baseline.

**POSTINTERVENTION CHARACTERISTICS**

At completion, the weights and BMI had not significantly changed. Total testosterone levels dropped significantly in the cohort treated with metformin (mean difference, −38.3 ng/dL) compared with placebo (mean difference, −0.86 ng/dL) (95% CI, −∞ to −0.29 for the difference between group means). In neither group was there a change in the Ferriman and Gallwey scores or acanthosis nigricans (Table 2). Ten of 11 adolescents in the metformin group experienced menses, compared with only 4 of 11 adolescents in the placebo group. The relative risk of menses was statistically significant at 2.50 (95% CI, 1.12 to 5.58).

**GLUCOSE AND INSULIN PROFILES**

Fasting blood glucose levels were all normal at baseline and remained this way at the end of the study regardless of the treatment prescribed. None of the study recruits were diabetic based on the American Diabetes Association interpretation of the OGTT, a requirement for participation. The baseline OGTTs revealed that 1 adolescent in the metformin arm had impaired glucose tolerance. At the end of the study, her results demonstrated persistent impaired glucose tolerance. None of the girls in the placebo arm had any glucose intolerance at baseline, but 1 developed this at the end of the 12-week interval.

The areas under the insulin response curve were elevated and were not significantly different in the 2 arms at baseline. With metformin, there was a suggestive trend toward lower insulin AUC with treatment, but this was not statistically significant (with metformin, insulin AUC declined by −3662 µU/mL-minute, compared with +2093 µU/mL-minute for placebo; 95% CI, −17 531 to 6024 for the mean difference between groups). Homeostasis model assessment calculations also showed a trend toward improved insulin sensitivity with metformin treatment, but again these were not statistically significant (HOMA: metformin therapy [mean difference, −1.06] compared with placebo [mean difference, 0.86] [95% CI, −9.26 to 5.42 for the difference between group means]; QUICKI: metformin therapy [mean difference, 0.00] compared with placebo [mean difference, −0.01] [95% CI, −0.03 to 0.05 for the difference between group means]).

**LIPID PROFILE**

On average, the baseline levels of total, low-density lipoprotein and HDL cholesterol were normal for all participants (Table 1). At the end of the trial, metformin had significantly improved HDL cholesterol concentrations compared with placebo. The increase with treatment was +6.98 mg/dL vs −2.33 mg/dL for placebo (95% CI, 0.78 to 18.23 for the mean difference between groups). Other cholesterol parameters were not significantly different (Table 2). Triglycerides were elevated in both baseline cohorts and fell with metformin treatment, but this did not reach statistical significance. No decline was noted with placebo. All young women were in the follicular phase of their menstrual cycle at baseline; 1 participant...
in the placebo group was excluded from the comparisons because she was in the luteal phase at completion of the study.

**COMPLIANCE**

Pill counts were performed at the end of the trial. Two adolescents in the placebo arm admitted to not taking all the required tablets. One of them stated that they caused gastrointestinal adverse effects and discontinued the pills after taking about 45% of them. The second participant did not return for the second OGTT and stated that she only took about 50% of the pills. In the metformin treatment arm, 5 of 11 admitted to poor compliance (defined as <70% of pills taken), citing gastrointestinal disturbances. Based on pill counts, 8% to 60% of the metformin tablets were not consumed. Of note, in the metformin group, all of the noncompliant subjects and 6 of 7 compliant subjects had least 1 menses during the study period; therefore, metformin treatment was associated with restoration of menses in 10 of 11 treated subjects.

**COMMENT**

To our knowledge, this is the first study to evaluate the effect of metformin and lifestyle counseling on insulin levels, testosterone levels, and menstrual patterns in adolescent girls with hyperinsulinemia and PCOS in a randomized, double-blind, placebo-controlled study. We found that metformin resulted in a clinically significant impact on menses, significantly reduced serum testosterone levels, and significantly increased HDL cholesterol levels.

All of our study subjects were overweight or obese at baseline and did not achieve a significant reduction in BMI with lifestyle intervention and metformin or placebo. In the 2 published pediatric, unrandomized, and uncontrolled studies using metformin for PCOS, a moderate reduction in weight was noted. Both studies by Glueck et al\(^2\) and Arslanian et al\(^3\) were small in sample size, and in the latter, the BMI was significantly lowered because of a significant increase in height. Two small, randomized, double-blind, placebo-controlled trials by Kay et al\(^2\) and Freemark and Bursey\(^3\) evaluated metformin in obese adolescents (not with PCOS) and showed that those treated with metformin had a significantly greater weight loss compared with the placebo groups, although the differences were modest. Of note, the subjects in the Kay et al\(^2\) and Freemark and Bursey\(^3\) studies were also prescribed weight-reduction diets. The adult literature is equally inconclusive with regard to weight reduction, which suggests that metformin may not contribute to weight loss directly.

Metformin did, however, result in a significant reduction in total testosterone levels compared with placebo. Our study design could not determine whether reduced androgen levels were a consequence of the downward trend in insulin levels or some other biologic effects of metformin. Given the duration of the study, it comes as little surprise that this did not necessarily translate into a change in degree of hirsutism. Two earlier studies in overweight adolescents with PCOS demonstrated conflicting results; Arslanian et al\(^3\) described significant reductions in both free and total testosterone levels with metformin, and Glueck et al\(^2\) noted a nonsignificant downward trend in testosterone levels. In both studies, moderate weight loss was noted and only in the former study were insulin levels measured, which were decreased with metformin. The small (n=10) study by Ibanez et al\(^2\) in nonobese adolescent girls with PCOS observed a decrease in both androgen levels and hirsutism with metformin, associated with a concomitant decrease in insulin concentrations and without any weight loss.

We found a significant rise in HDL cholesterol levels in the metformin group compared with the placebo group by the end of the study period. We did not find significant changes in other lipid parameters. The mean triglyceride concentrations were elevated in both study groups at the start of the study, with a nonsignificant re-

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**Table 2. Change From Baseline in Clinical Characteristics and Blood Tests After Administration of Metformin or Placebo for 12 Weeks**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean Difference Between Groups</th>
<th>95% Confidence Interval for the Mean Difference Between Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Metformin Group</td>
<td>Placebo Group</td>
</tr>
<tr>
<td>Body mass index</td>
<td>-0.16</td>
<td>-0.19</td>
</tr>
<tr>
<td>Ferriman and Gallwey score</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total testosterone, ng/dL</td>
<td>-38.3</td>
<td>-0.86</td>
</tr>
<tr>
<td>Insulin AUC, µU/mL - min</td>
<td>-3662</td>
<td>2093</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>0.31</td>
<td>0.36</td>
</tr>
<tr>
<td>HOMA</td>
<td>-1.06</td>
<td>0.86</td>
</tr>
<tr>
<td>QUICKI</td>
<td>0.00</td>
<td>-0.01</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>-0.78</td>
<td>-8.15</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>-3.10</td>
<td>-7.76</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>6.98</td>
<td>-2.33</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>-13.13</td>
<td>7.00</td>
</tr>
<tr>
<td>Girls with restored menses, No.</td>
<td>10/11</td>
<td>4/11</td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under the curve; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; LDL, low-density lipoprotein; NA, not applicable; QUICKI, quantitative insulin sensitivity check index.

*Body mass index is calculated as weight in kilograms divided by the square of height in meters.
duction in triglyceride levels observed in the metformin-treated group alone. Again, the impact of metformin in adolescents has been inconsistent. Glueck et al observed a significant reduction in total cholesterol levels in a nonrandomized study while Arslanian et al saw no significant change in cholesterol or triglyceride levels. In the randomized double-blind placebo-controlled trial by Kay et al of obese adolescents (not with PCOS), a significant improvement in the lipid profile was seen with metformin treatment (decreased total cholesterol and triglyceride levels). In all 3 of these studies, metformin treatment was associated with weight loss. In 2 of these studies, insulin levels were assessed and found to be reduced with metformin.

Most importantly, menses was 2.5 times more likely to occur in the metformin group compared with the placebo group. Metformin has been deemed to be beneficial in the restoration of menses in other studies, from 40% to 100% (40%, Glueck et al; 91%, Arslanian et al; and 100%, Ibanez et al). Indeed, Ibanez et al confirmed that menses returned, and the majority of these cycles were ovulatory.

We noted an improvement in measures of insulin sensitivity, including the insulin AUC and HOMA, in the adolescents treated with metformin, but not in the control group. However, this trend failed to achieve statistical significance, possibly reflecting sample size and inherent variability of the measure. Because some clinical benefits were noted, we postulate that this reduction may have had biologic effects. Earlier studies by Arslanian et al and Ibanez et al in adolescents with PCOS have demonstrated a significant decline in insulin levels assessed by both fasting insulin-glucose ratios and formal pharmacokinetic AUC. However, most studies in female and male adolescents have also demonstrated a decrease in BMI or body weight with metformin treatment, which could conceivably alter insulin sensitivity.

Poor compliance in nearly half (5/11) of the adolescents randomized to metformin and/or our small sample size may have limited the ability to detect statistically significant differences in insulin concentrations despite the clinical impact on menses and testosterone levels. Comparing our results with the other trials carried out in adolescents suggests that important biologic effects can occur without weight loss and without statistically significant improvements in measures of insulin sensitivity. This raises the question as to whether metformin has additional biologic actions besides that of an insulin sensitizer or whether the impact of metformin is noted with very small decreases in insulin concentrations.

The use of insulin-sensitizing agents, especially metformin, has generally been accepted in adult women with PCOS although not all studies have demonstrated consistent benefits. In adolescents with PCOS, there have been fewer studies of metformin, and controversy remains with regards to its benefits and mechanisms of action. It is difficult to directly compare our study with those previously published because of the inherent differences in study design, although most appear to demonstrate that metformin treatment leads to clinical improvement. The goal of this therapy in the adolescent is more likely to focus on the reduction of hirsutism and acne with return of menses as a less important outcome. Fertility and long-term cardiovascular health appear more remote concerns for these young adults.

Our randomized placebo-controlled study, albeit small in sample size, demonstrated a significant decrease in testosterone levels and an increase in the frequency of menses in adolescents with oligomenorrhea or amenorrhea. Measures of insulin sensitivity improved, although not significantly. Poor compliance with metformin and/or sample size were major limitations as was the short duration of the study.

Despite other adolescent preoccupations, the increased frequency of menses observed with a combination of metformin and lifestyle therapy may benefit uterine health. In addition, the significant increase in HDL cholesterol levels may benefit overall health in the future, as might the trend toward improvement in insulin AUC, although most trend follow-up studies will be needed to explore these questions.

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REFERENCES


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Announcement

Submissions. The Editors welcome contributions to Picture of the Month. Submissions should describe common problems presenting uncommonly, rather than total zebras. Cases should be of interest to practicing pediatricians, highlighting problems that they are likely to at least occasionally encounter in the office or hospital setting. High-quality clinical images (in either 35-mm slide or electronic format) along with parent or patient permission to use these images must accompany the submission. The entire discussion should comprise no more than 750 words. Articles and photographs accepted for publication will bear the contributor’s name. There is no charge for reproduction and printing of color illustrations. For details regarding electronic submission, please see: http://archpedi.ama-assn.org.