Effect of chromium supplementation on insulin resistance and ovarian and menstrual cyclicity in women with polycystic ovary syndrome

In women with polycystic ovary syndrome, chromium picolinate (200 µg/d) improves glucose tolerance compared with placebo but does not improve ovulatory frequency or hormonal parameters. This pilot study indicates that future studies in the polycystic ovary syndrome population should examine higher dosages or longer durations of treatment. (Fertil Steril 2005;84:1755–7. ©2005 by American Society for Reproductive Medicine.)

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder of reproductive-age women, affecting 5%–10% of this population (1). Women with PCOS face varying degrees of hirsuitism, obesity, irregular menses, and infertility. Over the long term, women with PCOS face increased risks for developing type 2 diabetes and dyslipidemia (2).

Insulin resistance and the resultant hyperinsulinemia are key metabolic features in the pathogenesis of PCOS (3, 4). Both lean and obese women with PCOS have insulin resistance, although it is more pronounced in obese women (5, 6). Insulin sensitizers have been shown to regulate menstrual cycles and improve rates of spontaneous ovulation (7–13).

Trivalent chromium is an essential element that plays a role in glucose and insulin homeostasis. Chromium deficiency as a cause of glucose intolerance was recognized first in 1977, when a trauma patient receiving total parenteral nutrition developed severe diabetes refractory to insulin. Symptoms completely resolved when chromium chloride was added to the total parenteral nutrition (14). Until recently, not much was known about the mechanism of chromium action other than that it appeared to improve the effects of insulin and worked at the level of the cell membrane (15). The interaction between chromium and insulin has been elucidated by the discovery of low–molecular weight chromium-binding substance, which binds chromium and the insulin receptor, activating the insulin receptor’s kinase activity (16, 17).

In patients with impaired glucose tolerance on a low-chromium diet, chromium supplementation significantly improved glucose and insulin values after an oral glucose challenge (18). In a randomized, double-blind, placebo-controlled study in type 2 diabetics, fasting and 2-hour insulin levels were improved after 2 and 4 months’ treatment with both the 200-µg/d and the 1,000-µg/d dose of chromium picolinate compared with placebo (19).

Because other insulin sensitizers have been shown to improve rates of spontaneous ovulation, we sought to determine whether chromium supplementation would change insulin sensitivity in women with PCOS and restore normal ovulation. Approval for this study was obtained from the institutional review board of the University of Texas Health Science Center at San Antonio.

Ten nonpregnant women, aged 18 to 39 years and who had established PCOS according to the 1990 National Institutes of Health criteria, were allocated via random number table to treatment with oral chromium picolinate (200 µg/d) or to placebo for 4 months. Both subjects and physicians were blinded to treatment.

Measurement of serum hormonal and metabolic parameters and a 2-hour oral glucose tolerance test after a 75-g glucose load were obtained before and after treatment. Subjects also underwent a frequently sampled IV glucose tolerance test before and after treatment, and insulin sensitivity was assessed by the minimal model approach (20).

Subjects were asked to keep a menstrual calendar and basal body temperature chart to document ovulation. On cycle day 26 of each cycle, a serum P level was drawn to confirm evidence of ovulation by basal body temperature.

Subjects were instructed not to use hormonal methods of contraception or intrauterine devices during the study. Women attempting pregnancy were advised to take a folate supplement during the study. Subjects were encouraged to not change their diet or exercise plan from their established routines for the duration of the study.
Changes in insulin sensitivity and ovulation rates were the main outcome measures. Glucose tolerance and metabolic and hormonal parameters were secondary outcomes. For parametric outcomes, the efficacy of treatment (chromium vs. placebo; within-subject effects before vs. after treatment) was compared by repeated measures analysis of variance. Ovulation rates were compared by Fisher’s exact test.

Six patients were randomized to treatment with chromium, and four patients, to treatment with placebo. There were no significant differences in baseline characteristics between the treatment groups, including age, body mass index, and number of menses per year. The ethnic background of the patients (50% Caucasian, 50% Mexican American) was similar to that seen in our practice, and the distribution was similar for treatment groups. No clinical adverse events occurred during this study.

Treatment with chromium was not associated with any significant differences in serum hormone levels, insulin sensitivity, fasting glucose, fasting insulin, triglycerides, or cholesterol (Table 1).

Plasma glucose levels at 1 and 2 hours during the oral glucose tolerance test were not significantly different when comparing baseline with the case after treatment. However, because at both 1 and 2 hours the plasma glucose decreased with chromium but increased with placebo (i.e., the effect was in opposite directions), there was a significant difference for these parameters when comparing treatment effect (chromium vs. placebo; within-subject effects before vs. after treatment).

Two patients (one in each treatment group) ovulated twice, and one patient from the placebo group ovulated once during the 4 months of the study. The remaining patients had no evidence of ovulation by basal body temperature chart or serum P. Therefore, of 24 possible ovulatory cycles in the chromium group (four cycles for six patients), 8% (2/24) were ovulatory; and of 16 possible ovulatory cycles in the placebo group (four cycles for four patients), 19% (3 of 16) were ovulatory. This difference was not statistically significant ($P=.63$).

After 4 months’ treatment with chromium picolinate (200 µg/d orally), there were no significant differences in the primary outcome measures, namely ovulation rates and insulin sensitivity, in the PCOS patients studied. There was, however, a significant improvement in glucose tolerance at 1 and 2 hours. This improvement in plasma glucose is consistent with prior studies (18, 19, 21). Although the plasma glucose after treatment did not change significantly from baseline, there were significant differences when comparing chromium with placebo. We believe that these differences in plasma glucose are caused by worsening of insulin resistance in the placebo group.

Failure to show a significant effect of chromium picolinate on ovulation rate or insulin sensitivity in PCOS patients may be because of the short duration of the study (4 months), small treatment dose (200 µg/d), or small

### TABLE 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Chromium</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Total testosterone (ng/dL)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>55.3 ± 5.2</td>
<td>58.3 ± 7.0</td>
</tr>
<tr>
<td>Free testosterone (pg/mL)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.2 ± 0.5</td>
<td>2.9 ± 0.4</td>
</tr>
<tr>
<td>DHEAS (µg/dL)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>211.2 ± 28.5</td>
<td>220.3 ± 53.1</td>
</tr>
<tr>
<td>FSH (mIU/mL)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.1 ± 0.3</td>
<td>4.9 ± 0.9</td>
</tr>
<tr>
<td>LH (mIU/mL)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6.4 ± 1.8</td>
<td>9.8 ± 4.0</td>
</tr>
<tr>
<td>Insulin sensitivity (mU/L&lt;sup&gt;-1&lt;/sup&gt;, min&lt;sup&gt;-1&lt;/sup&gt;]&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.68 ± 0.14</td>
<td>1.12 ± 0.20</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>96.2 ± 3.5</td>
<td>88.5 ± 3.2</td>
</tr>
<tr>
<td>Fasting insulin (mU/L)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>54.5 ± 18.5</td>
<td>37.7 ± 12.7</td>
</tr>
<tr>
<td>OGTT 1 h glucose (mg/dL)&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>177.0 ± 16.3</td>
<td>132.8 ± 9.2</td>
</tr>
<tr>
<td>OGTT 2 h glucose (mg/dL)&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>134.8 ± 13.6</td>
<td>112.5 ± 9.3</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>145.8 ± 20.3</td>
<td>86.8 ± 24.6</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>186.2 ± 17.1</td>
<td>154.5 ± 14.9</td>
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</tbody>
</table>

Note: Values are mean ± SEM.

<sup>a</sup> No comparison is statistically significant.
<sup>b</sup> No significant difference, baseline vs. after treatment.
<sup>c</sup> $P<.05$, chromium vs. placebo (by repeated-measures analysis of variance).

sample size. Prior studies have shown an effect after ≤4 months (18, 19); however, the effect was greatest with 1,000 µg/d dosing. Assuming a 16% ovulation rate in the placebo group (22) and an 80% ovulation rate in the chromium group, on the basis of studies with metformin (8, 9) and with α = 0.05, we would need 10 patients in each group to achieve a power of 0.80. Smaller differences, as implied by this pilot study, would require larger sample sizes. This pilot study indicates that future studies in the PCOS population should examine higher dosages or longer durations of treatment. Future studies in the PCOS population may corroborate the positive effect that we saw on improved glucose tolerance. Additional findings may be discovered with a larger sample size, longer duration of treatment, or higher doses. Also, chromium picolinate may play a role as a supplement to treatment with other insulin sensitizers, which was not examined in the current study.

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REFERENCES