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Chromium picolinate reduces insulin resistance in polycystic ovary syndrome: Randomized controlled trial

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Abstract

Aim: To investigate the effect of chromium picolinate (CrP) on insulin resistance (IR) in polycystic ovary syndrome (PCOS).

Methods: This double blinded randomized controlled trial was conducted in the Gynecology outpatient clinics at Ain Shams University Women's Hospital. Using closed and randomly mixed envelopes, 100 women were selected out of 400 PCOS patients. Eighty-five patients finished the study and were analyzed, 44 in group I and 41 in group II. They were randomly allocated to 6 months of either 1000 μg CrP (50 patients), or placebo capsules (50 patients). Patients were seen monthly to encourage similar diet control and physical exercise plans. The primary outcome was fasting glucose insulin ratio (FGIR), secondary outcomes included ovulation, regularity of the cycle, body mass index (BMI), fasting blood sugar (FBS), fasting serum insulin (FSI), and serum testosterone level.

Results: There were no significant differences between women of both groups regarding pretreatment levels of FBS, FSI, FGIR, and serum testosterone. Use of CrP for 6 months was associated with significant reduction of BMI ($P < 0.001$) and FSI ($P = 0.007$), and significant rise in FGIR ($P = 0.045$). CrP significantly increased the chances of ovulation ($P = 0.011$) and regular menstruation ($P = 0.002$) by almost twofold after the fifth month of treatment.

Conclusion: Chromium picolinate is useful in PCOS to reduce IR and stimulate ovulation.

Key words: chromium picolinate, infertility, insulin resistance, ovulation, polycystic ovary.

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder of reproductive-age women, affecting 11–18% of the population.[1] It is defined as the presence of any two of the following three criteria: oligo-ovulation or anovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovaries on ultrasound.[2] PCOS is diagnosed in most oligomenorrheic women (90%), most hirsute women (80%), and nearly one-third of amenorrheic women.[3]

Insulin resistance (IR) and the resultant hyperinsulinemia are key metabolic features in the pathogenesis of PCOS.[4] Both lean and obese women with PCOS have IR, although it is more pronounced in obese women.[5] Several studies have demonstrated a positive correlation between fasting insulin and androgen.[6] Furthermore, the severity of hyperinsulinemia correlates with the degree of clinical expression of the syndrome.[7]

Trivalent chromium (Cr^{3+}) is found naturally in foods and is associated with nutritional supplements in various forms, the most popular of which is chromium picolinate (CrP). It improves insulin sensitivity at the insulin receptor level,[8] which should theoretically help with the IR and the obesity seen in PCOS. Chromium supplements have become, for instance, the second most commonly taken nutritional supplement in the USA.[9] Chromium is probably the only nutritional mineral that

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has a several hundred-fold difference between the acceptable daily intake level and the calculated reference dose.[10] Several *in vivo* studies showed minimal or no toxicity with the use of trivalent (Cr^{3+}) forms, such as CrP.[11]

Chromium picolinate contains 12.4% elemental trivalent chromium (Cr^{3+}). The suggested minimum amount of elemental chromium to exhibit efficacy in glucose and lipid metabolism, is 200 μg elemental Cr^{3+} (corresponding to a total daily intake of 1600 μg).[12] Previous studies on the use of CrP in PCOS patients showed promising results, but were relatively weak due to low sample size,[13] low CrP dose,[14] or short duration of treatment.[13] Lydic *et al*. showed that a high CrP dose (1000 μg/day), for just 2 months, led to an improvement in IR in PCOS patients. The main criticism, however, was related to the very low sample size of only five obese subjects.[13] Lucidi *et al*. found an improvement in glucose tolerance following only 200 μg CrP daily when taken for a longer duration (4 months), but no improvement in the frequency of ovulation or hormonal parameters. They suggested higher doses and longer duration of treatment in future studies.[14] Potential explanations of the aforementioned results include inadequate study design due to small sample size, inadequate dosage, short duration of treatment, problems with bioavailability, or non-compliance and lack of efficacy of chromium supplementation.

The use of a high dose and a long duration of treatment were thus cornerstones of any future study on CrP, to ensure larger effect size and higher power of the results.

In view of standing controversies regarding the usefulness of CrP in reducing IR,[8] and the lack of sufficient well-designed studies to investigate its value in PCOS, this study examined the clinical effects of CrP on Egyptian women with PCOS, using a relatively higher dose and longer duration than those described in older studies.

Methods

The current study was a double blinded randomized controlled trial (RCT), conducted on 100 female PCOS patients (20–35 years old), at the gynecological outpatient clinics in Ain Shams University Women's Hospital, during the period from April 2013 to December 2014. The research protocol was studied and approved by the department's ethics committee on 13 February 2012.

On their first visit to the clinic, 100 PCOS patients were selected using 400 closed and randomly mixed envelopes containing 100 'selected' and 300 'non-selected' cards, left in the office of the head nurse at the door of the clinic. Selected patients were counseled and consented to participate in the study, then returned to the head nurse to receive a sealed black bag containing either CrP or placebo, sufficient for the entire study duration. Four hundred and thirty-eight patients were approached, 38 declined participation. All of the included women gave their informed consent prior to inclusion in the study.

Patients were randomly allocated to 6 months of either 1000 μg CrP (group I) in divided doses (5 tablets of 200 μg), or a similar regimen of placebo tablets (group II). Randomization was done using sequentially numbered, opaque, sealed envelopes (SNOSE) containing allocation cards. The latter were prepared according to computer-generated tables, and were kept with the outpatient clinics head nurse. The patients and managing clinicians were blinded to the allocation groups.

Exclusion criteria included receiving corticosteroids, ovulation induction, contraception, insulin-sensitizing agents, adrenergic agonists, psychotropic drugs, diuretics, beta-blockers, HMG CoA reductase inhibitors, or any other medications known to affect insulin sensitivity, carbohydrate or lipid metabolism, or vitamin and/or mineral supplements such as selenium, zinc and antioxidants, within the last 3 months prior to inclusion. Based on the initial clinical, biochemistry and ultrasound assessment done at the gynecology outpatient clinic, patients diagnosed with frank diabetes mellitus or impaired glucose tolerance (IGT), Cushing syndrome, thyroid disease, associated causes of infertility other than anovulation, adult-onset congenital adrenal hyperplasia, hepatitis, asthma, renal disease, androgen-secreting ovarian or adrenal tumors were also excluded.

The included women underwent complete clinical, biochemical, and ultrasound examination for detection of PCOS according to Rotterdam diagnostic criteria.[2] Anovulation was recorded as amenorrhea, oligomenorrhea, varying cycle length >3 days from the patient's average, absence of a growing dominant follicle on serial ultrasonographic folliculometry, and/or anovulatory infertility.

Diet control (restricting simple sugars and saturated fats, limiting the total caloric intake to a maximum of 35 kcal/kg/day) and physical exercise plans (light walking for 30 minutes twice weekly) were advised initially and during monthly ultrasounds. Blood samples were taken at the beginning of the study and at the end of the sixth month, primarily for assessment of the fasting glucose insulin ratio (FGIR). Secondary outcomes included regularity of the cycle, ovulation, body mass

index (BMI), cumulative pregnancy rate, fasting blood sugar (FBS), fasting serum insulin (FSI), and total testosterone.

The BMI and the degree of hirsutism, according to Ferriman–Gallwey (F-G) score,[15] were recorded at the beginning and the end of the 6-month study. Ovulation was checked monthly, starting day 12–14 of every cycle, using serial ultrasound folliculometry to check for a growing eventually ovulating dominant follicle and for the endometrial thickness.

Sample size calculation

Although this was originally meant to be a pilot study, the calculated sample size (44 in each arm) was lower than the number originally recruited to participate (100 patients), and almost the same as the actual number of patients who finished the study (85 patients). This encouraged us to publish this study. The sample size was calculated using G*Power© version 3.1.9.2 (Universität Kiel, Germany) using a two-tailed *t*-test and assessing the difference between two independent means. The calculation used the effect size obtained using the post-treatment difference in FGIR between the study and control groups. The effect size used was 0.61, with a power of 80% and an α of 0.05.

Statistical analysis

The results were collected, tabulated, then analyzed using Vassarstats© (www.vassarstats.net). Categorical data (proportions) are expressed as number and percentage. They were compared using the chi-squared test. Numeric data are presented as mean ± SD and range, and were compared using Mann–Whitney *U*-test. The probability of error was considered significant at $P < 0.05$.

Results

Eighty-five patients finished the study (Fig. 1), 44 in group I and 41 in group II (study and control groups, respectively). There were no significant differences between the two groups regarding age, initial BMI, family history of diabetes mellitus, rate of anovulatory cycles, or F-G score for hirsutism (Table 1). The two groups had a similar rate of hirsutism (31/44 vs 24/41, $P = 0.251$). Initial (pretreatment) FBS, FSI, FGIR, and serum testosterone were statistically significantly similar between the two groups (Table 1).

Treatment with CrP for 6 months brought no significant changes in FBS in the control or study groups ($P = 0.594$ and 0.32, respectively). Conversely, women in group I had a significant reduction in FSI ($P = 0.007$) and BMI ($P < 0.001$), coupled with a significant rise in FGIR ($P = 0.047$). Their serum-free testosterone and mean F-G score were statistically unchanged after 6 months (Table 2). The difference in the percentage of women with an improved F-G score was not significant (n = 11, 35.48% vs n = 8 33.33% in groups I and II, respectively; $P = 0.862$).

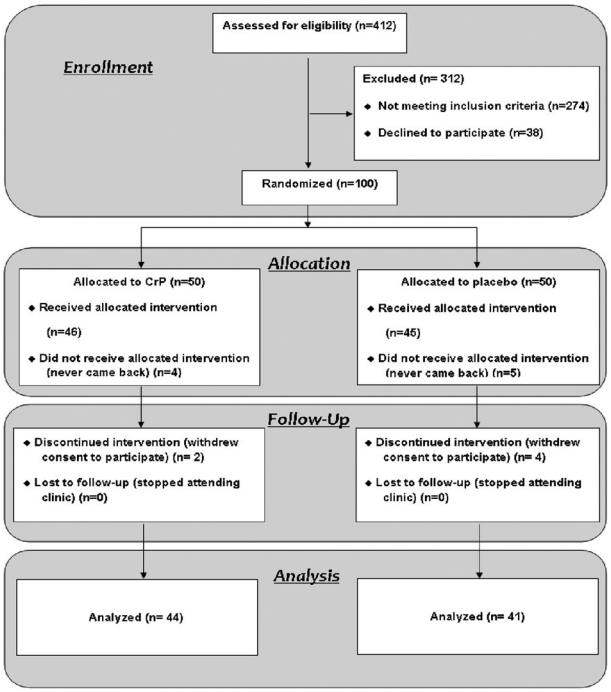

Figure 1 CONSORT flow diagram. CrP, chromium picolinate.

Ovulation and restoration of regular menstrual cycle were similarly uncommon between the two groups over the first 4 months of treatment, but ovulation was seen more often in the study group 5 months (n = 20, 45.5% vs n = 8, 19.5%; $P = 0.011$) and 6 months (n = 26, 59.1% vs n = 8, 19.5%; $P < 0.001$) after starting treatment (Fig. 2) CrP treatment significantly increased the rate of ovulation by almost twofold after 5 months (RR, 2.33; 95% CI: 1.16–4.69) and another threefold after 6 months (RR, 3.03; 95%CI: 1.55–5.91). Similarly, the rate of developing a regular menstrual cycle was significantly higher in group I after 5 months (n = 25, 56.8% vs n = 13, 31.7%; $P = 0.02$) and after 6 months of treatment (n = 33, 75% vs n = 19, 46.3%; $P = 0.007$). Use of CrP significantly increased the rate of developing regular menstruation by almost twofold after 5 months (RR, 1.79; 95%CI: 1.07–3.01) and almost 1.5-fold after 6 months (RR, 1.62; 95%CI: 1.12–2.34).

Table 1 Baseline patient characteristics

	CrP group (Group I) (n = 44) Mean ± SD range, or n (%)	Control group (Group II) (n = 41) Mean ± SD range, or n (%)	*P*-value
Age (years)	24.7 ± 3.7 17–31	24.6 ± 4 18–32	0.889†
Initial BMI (kg/m^2)	30 ± 3.3 26–39	29.7 ± 3.1 25–36	0.640†
Anovulatory cycle	35 (79.5)	34 (82.9)	0.689‡
FBS (mg/dL)	83.07 ± 8.88 68–101	81.34 ± 7.03 69–96	0.325†
FSI (IU/L)	15.95 ± 2.57 10–20	16.39 ± 3.38 9–23	0.503†
FGIR	5.36 ± 1.33 3.8–8.4	5.06 ± 1.26 3.1–9.5	0.277†
Testosterone (ng/dL)	65.86 ± 25.81 27–93	61.29 ± 26.44 23–94	0.422†
F-G score	23.03 ± 4.43 14–32	21.17 ± 4.98 12–30	0.072†

†Mann–Whitney *U*-test. ‡Chi-squared test. BMI, body mass index; CrP, chromium picolinate; F-G score, Ferriman–Gallwey score for hirsutism;[15] FBS, fasting blood sugar; FGIR, fasting glucose insulin ratio; FSI, fasting serum insulin.

Table 2 Change in parameters after CrP treatment

		Initial assessment mean ± SD, range	After 6 months mean ± SD, range	*P*-value†
FBS (mg/dL)	Group I	83.07 ± 8.88 68–101	81.29 ± 7.53 67–98	0.320
	Group II	81.34 ± 7.03 69–96	80.68 ± 7.08 68–94	0.594
FSI (IU/L)	Group I	15.95 ± 2.57 10–20	14.57 ± 2.99 9–19	0.007
	Group II	16.39 ± 3.38 9–23	16.32 ± 3.12 9–21	0.888
FGIR	Group I	5.36 ± 1.33 3.8–8.4	5.9 ± 1.42 3.5–9.2	0.047
	Group II	5.06 ± 1.26 3.1–9.5	5.29 ± 1.47 3.4–9.5	0.237
Testosterone (ng/dL)	Group I	65.86 ± 25.82 27–93	68.16 ± 22.23 25–94	0.151
	Group II	61.29 ± 26.44 23–94	65.27 ± 22.21 26–93	0.054
F-G score	Group I	23.03 ± 4.43 14–32	21.77 ± 4.14 13–32	0.093
	Group II	21.17 ± 4.98 12–30	20.33 ± 5.15 12–33	0.206
BMI (kg/m^2)	Group I	30.04 ± 3.34 26–39	27.21 ± 3.37 22–37	<0.001
	Group II	29.71 ± 3.31 25–36	29.22 ± 3.12 25–38	0.158

†Mann–Whitney *U*-test. BMI, body mass index; CrP, chromium picolinate; F-G score, Ferriman–Gallwey score for hirsutism;[15] FBS, fasting blood sugar; FGIR, fasting glucose insulin ratio; FSI, fasting serum insulin; SD, standard deviation.

Infertility, due to chronic anovulation, was reported by 38 patients (86.4%) in group I and 36 patients (87.8%) in group II. There were slightly higher cumulative pregnancy rates (Fig. 3) among the infertile women of group I, after 4, 5 and 6 months of treatment (RR, 1.42, 2.52, 2.52, respectively). These higher rates, however, did not reach statistical significance (P = 0.526, 0.112, 0.112, respectively).

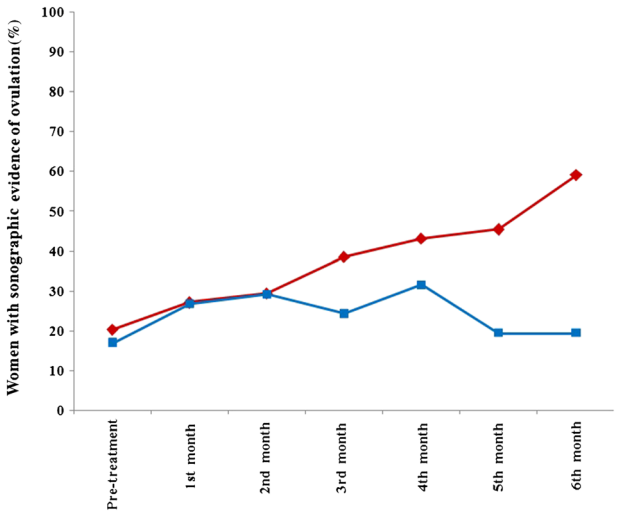

Figure 2 Percentage of women with sonographic evidence of ovulation over the study duration. (♦) Chromium picolinate group (I); (■) control group (II).

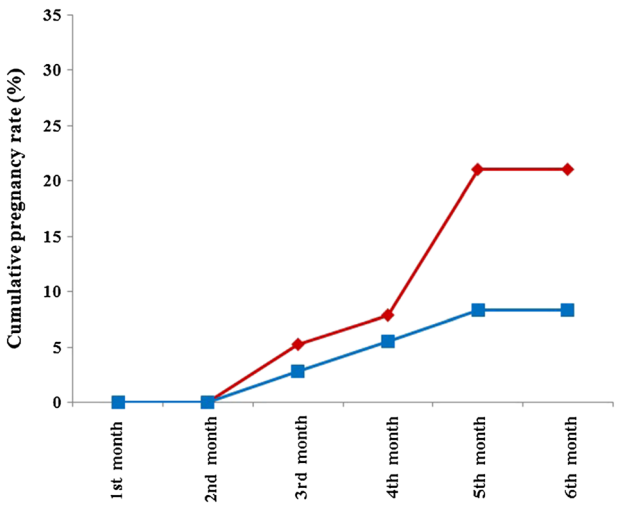

Figure 3 Non-significant improvement in cumulative pregnancy rates of the (♦) Chromium picolinate group (I); (■) control group (II).

Discussion

The current study showed that CrP treatment was associated with a significant rise in FGIR, significant reduction in FSI and BMI, and a non-significant effect on serum testosterone. Ovulation and regular menstruation became significantly more common after 4 months of CrP treatment, while the rise in pregnancy rate did not reach significance.

Previous studies using low dose, small sample size, or short duration of CrP intake provided weak evidence for its value in PCOS.[13,14] A more recent RCT included a larger sample size, of 92 PCOS patients, over a borderline duration of 3 months, still using a dose of CrP 200 μg daily. It showed significant effect on IR and FGIR, but no effect on ovulation or hyperandrogenism.[16] Recently an Egyptian team published their successful control of anovulation and hyperandrogenism in a group of adolescent PCOS patients. They used a reasonably high dose (1000 μg daily) for a duration of 6 months, but they recruited a relatively small sample size (n = 35) in an observational, uncontrolled trial.[17]

In contrast, Masharani *et al*. concluded that CrP therapy does not improve insulin sensitivity in normal non-diabetic subjects,[18] most probably due to the absence of any IR in the study population. It also remains possible that patients with glucose intolerance may respond differently, due to effects of chromium on insulin secretion or glucose toxicity. Gunton *et al*. found no effect on insulin sensitivity among a mixed male and female population with IGT. They used smaller CrP doses and a shorter duration than the current study (3 months at 800 μg/day).[19]

Another argument in favor of longer duration and higher doses when investigating CrP, is the fact that the current study, as opposed to previous ones,[14,16] found significant changes in the rate of spontaneous ovulation and regular menses, beginning only after 4 months of treatment. The same reason may explain the inability to prove benefit from CrP on hirsutism and/or androgen level, which may need relatively longer durations of treatment to produce significant changes.[13,14,16] We share the view of Onakpoya *et al*. that future trials should be of at least 16 weeks in duration.[20]

Furthermore, the current study encouraged physical exercise and diet control, and produced significant weight loss, which may further explain why it produced better results than older studies.[13,14,16] Some degree of IR is seen in all PCOS patients, with or without obesity.[14] It is already known that the ovulation rate and hormone profile improve following weight loss, and vice versa.[21,22] All patients were seen monthly in the gynecologic ultrasound department for scans. The diet and exercise plans were re-emphasized at every visit, and patients generally had similar levels of compliance, although this was not objectively recorded. We still rely on the fact that this study was designed as a double-blinded RCT with the view to minimize similar confounding issues.

So far, there are still contradictory results from the available meta-analyses on the value of CrP in reducing IR in diabetic, obese or IGT patients.[8,18,19,23–27] For instance, a meta-analysis concluded that chromium effects were non-relevant after stratifying the studies according to methodological quality, sponsor involvement, and a Western versus non-Western study location![24] The latter is not a valid justification for excluding a study from a meta-analysis, given that gene, lifestyle and population variation all have an impact on the prevalence of PCOS and IR in any population.[28,29]

While previous meta-analyses failed to show a beneficial effect of chromium supplementation,[25,26] a more recent meta-analysis suggested favorable effects of chromium on blood sugar level in diabetic patients.[8] It may be worth noting that some of the aforementioned analyses used poorly absorbed forms of chromium (chromium chloride, chromium yeast) or niacin-bound chromium (niacin is known to cause IR).[27]

Finally, this is so far the largest RCT with the most adequate CrP dose. Its limitations are still mainly related to the number of patients, given that this was originally meant to be a preliminary pilot study. We still must admit that a longer study duration and/or larger sample size may have been better for evaluating the role of CrP in PCOS. We showed that CrP improved IR, fasting insulin level, and bodyweight; and induced ovulation and regular menstrual cycles in PCOS patients. We admit that controversy still surrounds the use of CrP at least in regard to the IR associated with PCOS. But in any event, given the relative safety and low cost of chromium supplements, the benefit-to-risk ratio available so far still favors their use, while further investigations are carried out as to their true value.

Disclosure

The authors explicitly declare that there are no conflicts of interest in connection with this article. This study was self-funded by the authors.

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Supporting Information

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Table S1 CONSORT Format Table