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Chromium Supplementation and the Effects on Metabolic Status in Women with Polycystic Ovary Syndrome: A Randomized, Double-Blind, Placebo-Controlled Trial

Mehri Jamilian[a] Zatollah Asemi[b]

[a]Department of Gynecology and Obstetrics, School of Medicine, Arak University of Medical Sciences, Arak, I.R., [b]Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, I.R., Iran

Key Words
Chromium · Supplementation · Polycystic ovary syndrome · Insulin metabolism · Lipid concentrations

Abstract
Background: The aim of the present study was to evaluate the beneficial effects of chromium intake on markers of insulin metabolism and lipid profiles in women with polycystic ovary syndrome (PCOS). ***Methods:*** In a prospective, randomized, double-blind, placebo-controlled trial, 64 women with PCOS were randomized to receive 200 μg chromium picolinate supplements (n = 32) or placebo (n = 32) for 8 weeks. Fasting blood samples were obtained at baseline and 8 weeks after the intervention to quantify markers of insulin metabolism and lipid concentrations. ***Results:*** Chromium supplementation in women with PCOS resulted in significant decreases in serum insulin levels (–3.6 ± 7.4 vs. +3.6 ± 6.2 μIU/ml, p < 0.001), homeostasis model of assessment-insulin resistance (HOMA-IR; –0.8 ± 1.6 vs. +0.9 ± 1.5, p < 0.001), homeostatic model assessment-beta cell function (HOMA-B; –15.5 ± 32.3 vs. +13.6 ± 23.1, p < 0.001), and a significant increase in quantitative insulin sensitivity check index (QUICKI) score (+0.02 ± 0.03 vs. –0.008 ± 0.02, p = 0.001) compared with the placebo. In addition, a trend toward a significant effect of chromium supplementation on decreasing serum triglycerides (–12.4 ± 74.4 vs. +15.2 ± 32.4 mg/dl, p = 0.05), very low-density lipoprotein-cholesterol (–2.5 ± 14.9 vs. +3.0 ± 6.5 mg/dl, p = 0.05), and cholesterol concentrations (–8.6 ± 21.9 vs. +0.7 ± 22.4 mg/dl, p = 0.09) was seen. ***Conclusions:*** Eight weeks of chromium supplementation among PCOS women had favorable effects on markers of insulin metabolism.

Introduction

Polycystic ovary syndrome (PCOS) is an endocrine-metabolic disorder among women in their reproductive age [1]. It affects 6–25% of women depending on the definition [2]. Impaired insulin metabolism and dyslipidemia are key pathophysiologic features of PCOS, which is strongly associated with increased risk of cardiovascular disease and type 2 diabetes mellitus (T2DM) [3]. The prevalence of insulin resistance in patients with PCOS ranges from 44 to 70% [4]. This wide range may be due to several factors including the genetic background among the assessed patients [5] and differences in used methods for defining insulin resistance [6]. As a consequence, one of the most desirable goals of treatment for subjects with PCOS is increasing insulin sensitivity and improved lipid profiles in vivo.

Lifestyle modifications including weight loss (if overweight), a healthy diet such as DASH diet [7] and regular

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E-Mail karger@karger.com
www.karger.com/anm

Zatollah Asemi, PhD
Department of Nutrition
Kashan University of Medical Sciences
Kashan, PO Box 8715988141 (Iran)
E-Mail asemi_r@yahoo.com

exercise are first-line therapy for the management of PCOS [2]. Recently, micronutrient supplementation is proposed for improved metabolic profiles in PCOS women [8]. Chromium is an essential element that is involved in the metabolism of carbohydrates and lipid [9]. Data on mineral levels in patients with PCOS have not been adequately addressed. In a study by Chakraborty et al. [10], decreased chromium levels were reported in PCOS women with insulin resistance. A pilot study by Lucidi et al. [11] has also reported that 200 μg chromium supplementation daily among PCOS women for 3 months resulted in improved glucose tolerance but did not affect ovulation or hormonal profiles. In addition, 200 μg chromium picolinate supplements daily decreased fasting blood glucose and insulin levels in clomiphen citrate–resistant PCOS patients for 3 months compared with metformin [12].

Although there is evidence to suggest that chromium administration may improve markers of insulin metabolism and lipid profiles in PCOS individuals, the favorable effects of chromium intake in PCOS women on these markers compared with the control group, to our knowledge, have not yet been established. Therefore, we hypothesized that chromium intake might affect metabolic status of PCOS population. This study aimed at investigating the effect of chromium administration on markers of insulin metabolism and lipid profiles of PCOS women.

Methods and Materials

Participants

The current randomized double-blind, placebo-controlled, clinical trial was performed from February 2015 to April 2015 among women with PCOS (according to Rotterdam criteria) referred to Taleghani and Emam Reza Clinics, affiliated to Arak University of Medical Sciences, Arak, Iran. Women aged 18–40 years and diagnosed with PCOS based on the Rotterdam criteria were included in the study. Women with hyperprolactinemia, diabetes mellitus, thyroid disease, and adrenal hyperplasia who followed a special diet or consumed effective drugs on hormonal profile like oral contraceptives, ovulation induction agents, anti-obesity and antidepressants in the last 3 months before enrollment were excluded from the current study. Diagnosis of PCOS was done on the basis of the Rotterdam criteria [13]: those with two of the following criteria were considered having PCOS: oligo- and/or anovulation, hyperandrogenism, and polycystic ovaries. Clinical hyperandrogenism was assessed as the self-reported degree of hirsutism using the modified Ferriman Gallwey scoring method based on a chart displaying the degree of hair growth in nine regions. To fill the modified Ferriman Gallwey score, we applied form validated for the Iranian population [14]. Polycystic ovaries were diagnosed using ultrasonography in patients with menstrual dysfunction and/or hirsutism. In this study, the primary outcome variable was the homeostasis model of assessment-insulin resistance (HOMA-IR). For estimating the sample size, we used the standard formula suggested for parallel clinical trials by considering type 1 error (α) of 0.05 and type 2 error (β) of 0.20 (power = 80%). Based on a previous study [15], we used 9.3 as SD and 7.0 as the difference in mean (d) of HOMA-IR as key variable. Based on this, we needed 27 patients in each group. Considering 5 dropouts in each group, the final sample size was determined to be 32 patients per group. This study was done according to the guidelines laid down in the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Arak University of Medical Sciences, Arak, Iran, and the approval of the Ethics Committee was also obtained before beginning the trial. In addition, written informed consents were obtained from all patients. This trial was registered in the Iranian website (www.irct.ir) for registration of clinical trials (IRCT code: IRCT201502055623N34).

Study Design

At the beginning of the study and after stratification for pre-intervention (<25 and ≥25 kg/m^2) and age (<30 and ≥30 years), patients were randomly allocated into 2 groups. Group A received 200 μg/day chromium picolinate (chromium picolinate American 21st century medical industries USA) as tablet (n = 32) and group B received placebo (n = 32) each day. Chromium placebos (cellulose) were manufactured by Barij Essence Pharmaceutical Company (Kashan, Iran). Chromium supplements and placebos were packed in similar skins and the patients and researcher weren't aware of the content of the pack until the end of the analysis. Randomization was done using a random number table by one of the investigators who had no clinical involvement in the study. Randomization and allocation were concealed from the researcher and patients until the main analyses were completed. At the beginning of the study, all patients were requested to follow their usual diet and maintain their usual levels of physical activity throughout the study period; they were also advised not to take any lipid-lowering medications and other medications that might influence their reproductive physiology during the 8-week intervention. The use of chromium supplements and placebos throughout the trial was checked by asking patients to bring the medication containers. To increase the compliance, all subjects received short messages on their cell phones as reminders to take the supplements each day. For all participants, both dietary and physical activity records were provided at weeks 2, 4, and 6 of the intervention. The dietary records were based on estimated values in household measurements. In the current study, to obtain nutrient intakes of patients with PCOS based on these 3-day food diaries, we used Nutritionist IV software (First Databank, San Bruno, CA) modified for Iranian foods.

Assessment of Anthropometric Measures

Height and weight (Seca, Hamburg, Germany) were determined using standard protocols with subjects wearing a light gown and without shoes. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2).

Outcomes

As insulin resistance is the most important variable in patients with PCOS, we considered markers of insulin resistance as primary outcomes. Secondary outcomes were lipid concentrations.

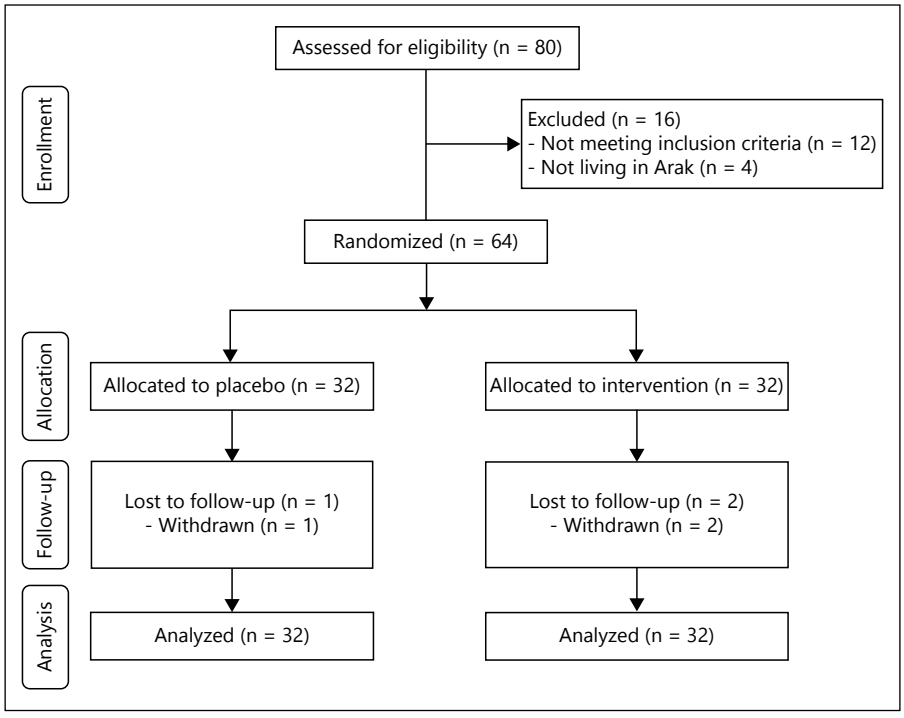

Fig. 1. Summary of patient flow diagram.

Biochemical Assessment

Fasting blood samples (10 ml) were collected at baseline study and end-of-trial at the Arak reference laboratory in the early morning after an overnight fast. Blood samples were immediately centrifuged (Hettich D-78532, Tuttlingen, Germany) at 3,500 rpm for 10 min to separate serum. Then, the samples were stored at –80°C before analysis at the AUMS reference laboratory. Commercial kits were used to determine fasting plasma glucose (FPG), serum triglycerides, very low-density lipoprotein (VLDL)-, total-, low-density lipoprotein (LDL)- and high-density lipoprotein (HDL)-cholesterol concentrations (Pars Azmun, Tehran, Iran). All inter- and intra-assay CVs for FPG and lipid profiles measurements were less than 5%. Serum insulin concentrations were determined using the ELISA kit (Monobind, California, USA) with the intra- and inter-assay CVs 2.8 and 4.9%, respectively. HOMA-IR, homeostatic model assessment-beta cell function (HOMA-B) and the quantitative insulin sensitivity check index (QUICKI) were calculated based on suggested formulas [16].

Statistical Methods

Normal distribution of variables was assessed by visual inspection of histograms. The analysis was conducted according to the intention-to-treat principle. Missing data from dropped out participants were imputed using the method of 'Last Observation Carried Forward'. Independent samples Student's t test was used to detect differences in general characteristics and dietary intakes between the 2 groups. Paired-samples t test was used to detect within-group differences. To determine the effects of chromium supplementation on markers of insulin metabolism and lipid concentrations, 1-way repeated-measures ANOVA was used to evaluate the between-group changes in variables during the study. In this analysis, the treatment was regarded as between-subject factor and time with 2 time-points (baseline and end-of-trial) was considered the within-subject factor. To assess if the magnitude of the change depended on the baseline values, we adjusted all analyses for the baseline values, age and baseline BMI to avoid the potential bias that might have resulted. These analyses were done using analysis of covariance (ANCOVA). $p < 0.05$ was considered statistically significant. All statistical analyses were done using the Statistical Package for Social Science version 17 (SPSS Inc., Chicago, Ill., USA).

Results

In this study, 64 women met the inclusion criteria based on Rotterdam criteria and were enrolled in the study. The groups were well matched for age and BMI at baseline. Among patients in the chromium group, 2 subjects [withdrawn due to personal reasons (n = 2)] and in the placebo group, 1 women [withdrawn due to personal reasons (n = 1)] did not complete the intervention (fig. 1). However, as the analysis was done based on intention-to-treat principle, all 64 patients with PCOS were included in the final analysis. On average, the rate of compliance in our study was so high that more than 90% of tablets were taken throughout the study by those in both groups. No side effects were reported following the administration of chromium supplements in PCOS women throughout the study.

Table 1. General characteristics of study participants

	Placebo group (n = 32)	Chromium group (n = 32)	p[a]
Age, years	24.4±4.4	24.9±5.0	0.67
Height, cm	161.9±6.4	161.4±6.5	0.74
Weight at study baseline, kg	66.6±11.1	67.4±13.7	0.80
Weight at end-of-trial, kg	66.6±11.2	67.4±13.4	0.79
Weight change, kg	–0.06±1.0	–0.04±0.8	0.94
BMI at study baseline	25.4±4.0	25.8±5.1	0.71
BMI at end-of-trial	25.4±4.1	25.8±5.0	0.69
BMI change	–0.02±0.4	–0.01±0.3	0.84

Data are means ± SDs.
[a] Obtained from the independent t test.

Table 2. Dietary intakes of study participants throughout the study

	Placebo group (n = 32)	Chromium group (n = 32)	p[a]
Energy, kcal/day	2,300±244	2,351±244	0.40
Carbohydrates, g/day	313.8±50.8	332.4±55.7	0.17
Protein, g/day	83.6±12.9	84.4±17.2	0.84
Fat, g/day	82.3±11.0	79.8±16.5	0.48
Saturated fatty acid, g/day	24.9±5.2	24.3±5.1	0.66
Poly unsaturated fatty acid, g/day	25.4±5.4	26.1±7.9	0.67
Mono unsaturated fatty acid, g/day	22.4±6.1	21.9±6.3	0.76
Cholesterol, mg/day	220.3±107.9	185.1±103.5	0.19
Total dietary fiber, g/day	18.6±5.0	18.7±5.1	0.91
Chromium, μg/day	24.2±2.4	23.8±2.3	0.49
Magnesium, mg/day	267.1±71.4	282.6±63.5	0.37
Zinc, mg/day	10.3±2.4	10.0±2.8	0.66

Data are means ± SDs.
[a] Obtained from the independent t test.

The mean age and height of study subjects were not statistically different between chromium and placebo groups. The baseline weight and BMI as well as their means before and after trial were not significantly different comparing the 2 groups (table 1).

Based on the 3-day dietary records obtained throughout the intervention, any statistically significant change was not seen between the 2 groups in terms of dietary intakes of energy, carbohydrates, proteins, fats, saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids, cholesterol, total dietary fiber, chromium, magnesium and zinc (table 2).

At the end of the 8 weeks, chromium supplementation in women with PCOS resulted in significant decreases in serum insulin levels (–3.6 ± 7.4 vs. +3.6 ± 6.2 μIU/ml, $p < 0.001$), HOMA-IR (–0.8 ± 1.6 vs. +0.9 ± 1.5, $p < 0.001$), HOMA-B (–15.5 ± 32.3 vs. +13.6 ± 23.1, $p < 0.001$) and a significant increase in QUICKI score (+0.02 ± 0.03 vs. –0.008 ± 0.02, $p = 0.001$) compared with the placebo (table 3). In addition, a trend toward a significant effect of chromium supplementation on decreasing serum triglycerides (–12.4 ± 74.4 vs. +15.2 ± 32.4 mg/dl, $p = 0.05$), VLDL-cholesterol (–2.5 ± 14.9 vs. +3.0 ± 6.5 mg/dl, $p = 0.05$), and cholesterol concentrations (–8.6 ± 21.9 vs. +0.7 ± 22.4 mg/dl, $p = 0.09$) was seen. Within-group differences revealed a significant reduction in serum insulin levels ($p = 0.01$), HOMA-IR ($p = 0.01$), HOMA-B ($p = 0.01$), and cholesterol concentrations ($p = 0.03$) in the chromium group. Moreover, within-group differences demonstrated a significant increase in serum insulin levels ($p = 0.002$), HOMA-IR ($p = 0.002$), HOMA-B ($p = 0.002$), serum triglycerides ($p = 0.01$) and VLDL-cholesterol concentrations ($p = 0.01$) in the placebo group.

Baseline levels of FPG and HOMA-B were significantly different between the 2 groups. Therefore, we controlled the analyses for the baseline levels, age, and baseline BMI. However, after this adjustment no significant changes in our findings occurred, except for finding a significant effect of chromium supplements on serum triglycerides ($p = 0.008$), VLDL-cholesterol ($p = 0.008$) and cholesterol concentrations ($p = 0.03$; table 4).

Discussion

Our study evaluated the effects of chromium administration on glucose homeostasis parameters and lipid concentrations among PCOS women. The major finding was that taking chromium supplements improved markers of insulin metabolism in PCOS patients. To the best of our knowledge, this study is the first of its kind that reports the effect of chromium intake on insulin metabolism parameters and lipid concentrations in women with PCOS compared with the placebo.

Patients with PCOS are sensitive to impaired insulin metabolism, hirsutism, and increased lipid concentrations [17]. Findings from the current study demonstrated that chromium administration for 8 weeks among women with PCOS resulted in significant decreases in serum insulin levels, HOMA-IR, HOMA-B, and a significant rise in QUICKI score compared with the placebo, but did not affect FPG levels. Some studies have reported the

Table 3. The effect of chromium administration on markers of insulin metabolism and lipid profiles

	Placebo group (n = 32)			Chromium group (n = 32)			p[a]
	baseline	end-of-trial	change	baseline	end-of-trial	change	
FPG, mg/dl	94.4±6.7	94.5±9.3	0.6±6.1	84.8±7.9	86.4±8.5	1.6±6.5	0.31
Insulin, μIU/ml	10.9±3.2	14.5±6.1*	3.6±6.2	13.3±8.4	9.7±7.5*	−3.6±7.4	<0.001
HOMA-IR	2.5±0.7	3.4±1.5*	0.9±1.5	2.8±1.8	2.0±1.6*	−0.8±1.6	<0.001
HOMA-B	38.5±13.2	52.1±22.8*	13.6±23.1	53.1±36.0	37.6±31.1*	−15.5±32.3	<0.001
QUICKI	0.33±0.01	0.32±0.02	−0.008±0.02	0.34±0.03	0.36±0.04	0.02±0.03	0.001
Triglycerides, mg/dl	108.4±55.7	123.6±64.8*	15.2±32.4	106.3±77.7	93.9±42.5	−12.4±74.4	0.05
VLDL-cholesterol, mg/dl	21.7±11.1	24.7±13.0*	3.0±6.5	21.3±15.5	18.8±8.5	−2.5±14.9	0.05
Total cholesterol, mg/dl	160.5±36.1	161.2±31.8	0.7±22.4	154.9±24.4	146.3±27.4*	−8.6±21.9	0.09
LDL-cholesterol, mg/dl	53.3±10.2	57.5±22.0	4.2±18.7	54.6±8.6	52.9±9.1	−1.7±8.1	0.10
HDL-cholesterol, mg/dl	85.5±27.2	78.9±28.0	−6.6±28.6	79.0±20.1	74.6±21.1	−4.4±18.5	0.72

All values are means ± SDs.
[a] Obtained from the repeated measures ANOVA test (time × group interaction).
* Significant difference from baseline.

Table 4. Adjusted changes in metabolic variables in PCOS patients

	Placebo group (n = 32)	Chromium group (n = 32)	p[a]
Fasting plasma glucose, mg/dl	0.6±1.2	1.1±1.2	0.77
Insulin, μIU/ml	3.1±1.1	−3.0±1.1	<0.001
HOMA-IR	0.8±0.2	−0.7±0.2	<0.001
HOMA-B	10.0±4.3	−11.9±4.3	0.001
QUICKI	−0.01±0.006	0.02±0.006	<0.001
Triglycerides, mg/dl	16.6±7.8	−13.8±7.8	0.008
VLDL-cholesterol, mg/dl	3.3±1.6	−2.8±1.5	0.008
Total cholesterol, mg/dl	1.6±3.7	−9.7±3.6	0.03
LDL-cholesterol, mg/dl	4.2±2.5	−1.7±2.5	0.10
HDL-cholesterol, mg/dl	−5.2±3.8	−5.8±3.8	0.91

All values are means ± SEs.
[a] Obtained from the repeated measure ANOVA test adjusted for baseline values, age, and baseline BMI.

benefits of supplementation with chromium for glucose homeostasis parameters. Supporting our study, in a study by Martin et al. [18] it was observed that 1,000 μg of chromium picolinate supplementation for 6 months resulted in significant improvements in insulin sensitivity and glycemic control compared with the placebo group. In addition, a 12-week supplementation with 200 μg of chromium picolinate significantly improved glycemic control and insulin levels in patients with T2DM [19]. Similar findings have been reported among subjects with T2DM following the supplementation with 200 to 1,000 μg of chromium picolinate for 4 months [20] and among subjects consuming controlled low-chromium diets with 200 μg chromium intake [21]. However, some researchers did not observe such beneficial effects of chromium supplementation on markers of insulin metabolism. For example, chromium therapy (500 μg twice a day) among nonobese, normoglycemic subjects for 16 weeks did not improve insulin sensitivity [22]. Moreover, supplementation with 800 μg of chromium picolinate did not affect insulin sensitivity among subjects with impaired glucose tolerance after 3 months [23]. Insulin resistance is one of the important factors associated with the typical clinical signs and hormonal disorders in patients with PCOS, and this trait has cause-consequence relationship with increased risk of cardiovascular disease [24], gestational diabetes and T2DM [25] as well as dyslipidemia [26]. Furthermore, few studies have reported that there may be an inverse relationship between chromium levels and the risk of myocardial infarction in the general population [27, 28]. Chromium intake increases the amount of a chromium-containing oligopeptide present in the insulin-sensitive cells that bind to the insulin receptor, significantly increasing the activity of insulin-stimulated tyrosine kinase and glucose transporter 4 [29], which in turn, would result in improved markers of insulin metabolism.

The results of this study revealed that chromium intake in PCOS women resulted in a trend toward a significant effect on decreasing serum triglycerides, VLDL-cholesterol, and cholesterol concentrations compared with the placebo, but did not influence LDL- and HDL-cholesterol levels. However, some studies have reported

the benefits of chromium administration on lipid profiles among subjects without PCOS. In a study by Sharma et al. [30] it was seen that supplementation with 9 g of beer yeast containing 42 μg of chromium among subjects newly diagnosed with diabetes for 3 months led to significant improvements in the levels of total-, LDL-cholesterol and triglycerides. Furthermore, a significant decrease in total cholesterol and a trend toward lowered triglycerides levels were observed following the administration of 200 μg chromium supplements for 3 weeks among patients with T2DM [31]. However, Guimarães et al. [32] did not show benefits of chromium intake on lipid profiles, regardless of the dose taken (50 or 200 μg of chromium as chromium nicotinate). In addition, the serum lipid concentrations were not significantly influenced by 100 μg chromium supplementation among patients with T2DM treated with insulin [33]. The inhibition of circulating levels of inflammatory factors including tumor necrosis factor alpha and interleukin 6 (IL-6) may be reasons for the decreasing effects of chromium intake on lipid profiles levels [34]. Moreover, increased insulin sensitivity due to chromium intake may improve lipid profiles. Different study designs and different dosages of chromium used along with characteristics of study patients might provide some reasons for the discrepancy in the findings.

In the interpretation of our findings, some limitations must be considered. First, due to budget limitations, we did not assess the effect of chromium administration on chromium levels. Second, the follow-up period of this trial was relatively of a short duration; some nonsignificant changes in lipid concentrations may have become statistically significant with longer follow-up. In addition, the effect of chromium intake on the post-prandial glycaemia and dyslipidemia would be of interest, may be as a topic for a future study.

Taken together, 8 weeks of 200 μg/day chromium supplementation among PCOS women had favorable effects on markers of insulin metabolism; however, it did not affect FPG and lipid profiles.

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Authors' Contributions

Z.A. contributed in conception, design, statistical analysis, and drafting of the manuscript. M.J. contributed toward data collection and manuscript drafting. Z.A. supervised the study. Both authors approved the final version for submission.

Disclosure Statement

None of the authors had any personal or financial conflict of interest.

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Clinical Trial Registration Number

www.irct.ir: IRCT201502055623N34.

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