Complementary Therapies in Medicine 47 (2019) 102201

Contents lists available at ScienceDirect

Complementary Therapies in Medicine

journal homepage: www.elsevier.com/locate/ctim

The effects of curcumin supplementation on glycemic status, lipid profile and hs-CRP levels in overweight/obese women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled clinical trial

Sara Sohaei[a], Reza Amani[a,*], Mohammad Javad Tarrahi[b], Hatav Ghasemi-Tehrani[c]

[a] Department of Clinical Nutrition, School of Nutrition and Food Science, Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[b] Department of Epidemiology and Biostatistics, School of Health, Isfahan University of Medical Sciences, Isfahan, Iran
[c] Gynecologist and fellowship of infertility assistant professor of OB & GYN of Isfahan University of Medical Sciences, Isfahan, Iran

ARTICLE INFO

Keywords:
Curcumin
PCOS
Hyperlipidemia
Insulin resistance
Infertility
hs-CRP

ABSTRACT

Objective: The aim of the current study was to assess the effects of curcumin supplementation on glycemic status, lipid profile and high sensitivity C-reactive protein (hs-CRP) serum levels in women with polycystic ovary syndrome (PCOS).
Design: This randomized double-blind placebo-controlled clinical trial was conducted on 60 women who were randomly assigned to the intervention or control groups using block randomization.
Setting: Infertility referral center.
Interventions: Curcumin (500 mg/d) or placebo twice daily for 6 weeks.
Main outcome measures: Serum evaluation of lipid profile (triglycerides (TG), low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol concentrations, LDL/HDL-C and TG/HDL-C ratios), glycemic index (fasting blood sugar (FBS), insulin concentrations, homeostasis model of assessment insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI)) and hs-CRP levels.
Results: Glycemic index, lipid profile and hs-CRP serum levels were measured at first and at the end of trial. Serum insulin ($p = 0.020$) and Quantitative Insulin Sensitivity Check Index (QUICKI) ($p = 0.003$) were improved significantly, while Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) ($p = 0.067$) improved marginally in curcumin treated group (within group analysis).
Conclusions: Curcumin supplementation might be beneficial for improving serum insulin and QUICKI, however, future investigations are suggested in order to draw a firm link between curcumin and glycemia control.

1. Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder that affects 5–10% of women during their reproductive years. [1] Prevalence of PCOS varies between 2.2%–26%, depending on different diagnostic criteria used. [2–4] In Iran, prevalence of PCOS has been reported as high as 15.2%, using the Rotterdam 2003 criteria. [5] To date, the etiology of PCOS is known as an obscure phenomenon, however, it is primarily considered as a multifactorial disturbance in origins with genetic context that is secondarily affected by environmental factors. [6,7]

PCOS is characterized by chronic anovulation, hyperandrogenism and metabolic derangements (insulin resistance, obesity, hyperinsulinemia, and acanthosis nigricans). [8] The prevalence of metabolic disturbances from the hyperinsulinemia and dyslipidemia viewpoint is about 70% and 50–75% in subjects with PCOS, respectively (51, 52). Insulin resistance (IR) is strongly associated with increased body fat, dyslipidemia and systemic inflammation. [9–12] In addition, biomarkers of oxidative stress and inflammation in PCOS patients may predict abnormal metabolic profile through the different ways including decreased insulin signaling. [13] Moreover, increased risk of type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD) and also cancer in hormone-related tissues may occur due to long term consequences of syndrome. [14] Previous studies have reported that hyperglycemia lowers antioxidant levels while elevates lipid peroxidation which in turn leads to abnormal metabolic profile. [13,15] In other word, PCOS is not only a reproductive endocrine disorder that ultimately leads to infertility or subfertility, [16] but it is also a sex-specific form of the metabolic disorder. [17]

* Corresponding author at: Nutrition Science, Department of Clinical Nutrition, School of Nutrition and Food Science, Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, 81746-73461, Iran.
E-mail address: r_amani@nutr.mui.ac.ir (R. Amani).

https://doi.org/10.1016/j.ctim.2019.102201
Received 23 June 2019; Received in revised form 24 September 2019; Accepted 25 September 2019
Available online 26 September 2019

(15)Studies have addressed severe side effects of therapies to manage PCOS including muscle or joint pain and arthritis. [18] Due to these concerns, it is salient to use natural remedies with minimal or no side effects. Curcumin (diferuloylmethane), a lipophilic yellow pigment of turmeric with polyphenol agent due to its biological and pharmacological properties including antioxidant and anti-inflammatory features has attracted considerable attention as the most bioactive molecule. [19] It also influences a wide spectrum of diseases, for instance, it has been reported to exert protective effects against cancer, memory decline, Parkinson's diseases, atherogenic dyslipidemia, inflammatory disorders, and osteoarthritis. [19,20] There is also evidence for its beneficial hypoglycemic and hypolipidemic effects in different pathological conditions in humans and various experimental models. [16,21,22]

Taking into consideration wide-ranging pharmacological and biological properties and the safety of curcumin while we lack controlled trials assessing the effects of curcumin among PCOS patients, the purpose of this study was to investigate the effects of curcumin supplementation on glycemic status, lipid profile and hs-CRP levels in women with PCOS.

2. Materials and methods

2.1. Subjects

In this double-blind placebo-controlled clinical trial, the criteria for diagnosis of PCOS was according to the American Society for Reproductive Medicine Guidelines (Rotterdam criteria, 2003) which require at least 2 out of the 3 following criteria: 1) oligo- and/or anovulation 2) clinical or biochemical signs of hyperandrogenism; and 3) polycystic ovary morphology shown on ultrasound examination. [23] The inclusion criteria included women willing to participate between the age of 18–40 years with BMI ≥ 25 and $\leq 35\,kg/m^2$. Exclusion criteria included being pregnant or lactating, patients who had elevated levels of prolactin, thyroid disorders, digestive problems, T2DM, congenital adrenal hyperplasia or any types of overt infection. Any concomitant disease was monitored and controlled by the physician. The type and dosage of medications used during the last 3 months prior to intervention were also controlled. At the onset of the study, all participants were requested to maintain their usual diet and also level of physical activity throughout the 6 weeks of intervention. In addition, during the last 3 months they should have not been taking any other medications or treatments that could affect insulin sensitivity, inflammatory and oxidative stress status, and also taking any forms of oral contraceptives (OCPs) as well as nutritional and antioxidant supplements that might affect the outcomes.

2.2. Study design

From April to August 2018, patients who were attending to Shahid Beheshti Infertility referral center, Isfahan University of Medical Sciences, Isfahan, Iran were recruited for this study. Out of 157 women with PCOS diagnosed by a gynecologist based on the Rotterdam criteria, 60 met our inclusion criteria.

Patient allocation was conducted by a biostatistician, using blocked randomization method with randomly permuted blocks sizes 4. Upon patient randomization, sequentially numbered, sealed envelopes were opened. Concealment of allocation group was maintained until the main analyses were completed and all process including randomized allocation, enrolling participants, and assigning participants to interventions was done by a trained midwife at the clinic. Participants were then allocated into 2 groups that placed them in either curcumin (n = 30) or placebo group (n = 30). Curcumin was administered at a daily dose of 1 g (500 mg twice daily) for a period of 6 weeks. Curcumin supplement contained standardized turmeric extract 95% in form of pellets (475 mg curcuminoids covering 70–80% curcumin, 15–20% demethoxycurcumin and 2.5–6.5% bisdemethoxycurcumin) that was produced by Karen Pharmaceutical and Food Supplement Company (Yazd, Iran). To preserve the validity of the study, curcumin and its placebo were made as the same in appearance and package. An individual other than the researchers encoded the supplements according to randomization list number. Due to the insolubility of curcumin in the aquatic phases, patients were asked to take supplements with each principal meal for better dissolution. To increase adherence, we sent short message to their cell phones every week. All patients were matched in terms of their medications including metformin.

All patients provided informed written consent. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. In addition, the Consolidated Standards of Reporting Trials (CONSORT) statement guidelines were used to design current study. This investigation was registered under the IRCT code of IRCT20180503039511N1 in clinical trials registry of Iran (available at: https://www.irct.ir) and the study protocol was approved by the Medical Ethics Committee at the Isfahan University of Medical Sciences, Isfahan, Iran under the identification number of IR.MUI.REC.1396.2.092.

2.3. Anthropometry measurements

All measurements were performed by trained personnel who were blind to the identity of samples. Height of participants was measured by a non-stretchable wall meter without shoes on the firm ground to the nearest 0.1 cm. Weight was measured at the baseline and post- intervention using a digital scale (Omron BF-511) (OMRON, Japan). This digital scale was also used to measure percent of body fat (PBF) by the bioelectrical impedance analysis (BIA) method between 8 and 10 a.m., while participates were fasting and having no metal objects, dry and cleaned bare hands and feet as recommended. [24] For more accurate measurements, we used this unit in the same environment and circumstances. Body mass index (BMI) was calculated as body weight (kg) divided by square height (m^2).

2.4. Dietary and nutrient assessments

All participants recorded a 3-day food diary (1 weekend day and 2 weekdays) in the first week and the last week of intervention. The portions of consumed foods were converted to grams and the encoded foods were analyzed for nutrients and amount of antioxidants consumed using a customized Nutritionist IV software (First Databank, San Bruno, CA, USA). [25]

2.5. Physical activity assessment

Participants filled in a validated form of 7 items International Physical Activity Questionnaire (IPAQ) at the beginning and the end of the trial. Data from this questionnaire were converted to metabolic equivalent-hour/week. [26]

2.6. Biochemical assessment

Serum insulin concentrations were assessed by ELISA kit (Monobind, CA, USA). Standard kits (BioSystems Co, Barcelona, Spain) were used to quantify fasting blood sugar (FBS), serum triglycerides (TG), low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol concentrations and serum hs-CRP level. LDL/HDL-C and TG/HDL-C ratios were also calculated. The homeostasis model of assessment insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) were calculated according to the suggested formula. [27]

2.7. Analytical measurements

After 12 h overnight fasting, 10 mL blood samples were taken at

baseline and after 6 weeks of intervention. For serum separation, blood samples were promptly centrifuged at 360 rpm for 10 min. The serums were stored at -80° until further measurements.

2.8. Statistical analysis

Statistical Analysis was made using SPSS 16 software (SPSS Inc., Chicago, IL, USA). Data were reported as mean ± SD or frequency (%). All variables had normal distribution and Kolmogorov–Smirnov test was used to examine distribution of the variables. Independent sample *t*-test and paired sample *t*-test were used for quantitative data to determine the differences between groups and also within group comparison, respectively. MANOVA test was conducted to report the between-group mean in variables at the end of the intervention. The value of $p < 0.05$ was considered statistically significant.

Based on previous study, [28] the sample size was calculated considering type one error (α) of 0.05 and type 2 error (β) of 0.20 (power of 80%) and the expectations value of 32 as the difference in mean (d) of TG levels as the key variable. We reached to 29 patients and final sample size was determined as 30 patients in each group.

3. Results

In total, 60 were recruited for this RCT and allocated into two groups of 30 in the beginning. Finally, 51 subjects completed the study: 27 in curcumin group and 24 in placebo group; all dropped out due to personal reasons (Fig. 1). During the trial, 3 patients reported gastrointestinal side effects in the curcumin group, however, they were not withdrawn from the study.

The mean age of participants in intervention groups was not significantly different. Comparison of the baseline features of participants indicated no significant differences between curcumin and placebo groups (Table. 1). Moreover, 3-day dietary records including mean energy, macro and micro nutrient intake, indicated no significant changes between the two groups (Table. 2). Between-group analysis showed no significant differences in lipid parameters and glycemic indices. Within-group difference of glycemic indices specified that the serum insulin and QUICKI were improved significantly in curcumin treated group ($p < 0.05$). Also, HOMA-IR improved marginally in

Table 1
Baseline characteristics of the participants.

Variable	Curcumin group (n = 27)	placebo group (n = 24)	P-value
Age (yr.)	29.40 ± 5.33	29.58 ± 5	0.904
Height (cm)	161.70 ± 5.29	160.45 ± 6.92	0.471
Weight (kg)			
Baseline	77.58 ± 11.57	80.28 ± 11.39	0.405
End	77.63 ± 11.74	80.38 ± 11.54	0.404
BMI (kg/m^2)			
Baseline	29.67 ± 3.72	31.32 ± 4.6	0.166
End	29.63 ± 3.848	31.18 ± 4.68	0.201
Body fat (%)			
Baseline	% 43.40 ± 3.74	% 45.26 ± 3.69	0.129
End	% 43.20 ± 3.71	% 45 ± 4.70	0.135
Visceral fat (Kg)			
Baseline	7.14 ± 2.49	7.62 ± 2.68	0.514
End	6.77 ± 1.42	7.50 ± 2.22	0.169
Physical activity (MET-h/week)			
Baseline	26.61 ± 1.11	26.50 ± 1.26	0.750
End	26.62 ± 1.04	26.52 ± 1.26	0.765

Note: Values are presented as mean ± standard deviation (SD) and percentage (%).
P-value is reported based on independent samples t-tests; BMI: Body Mass Index.

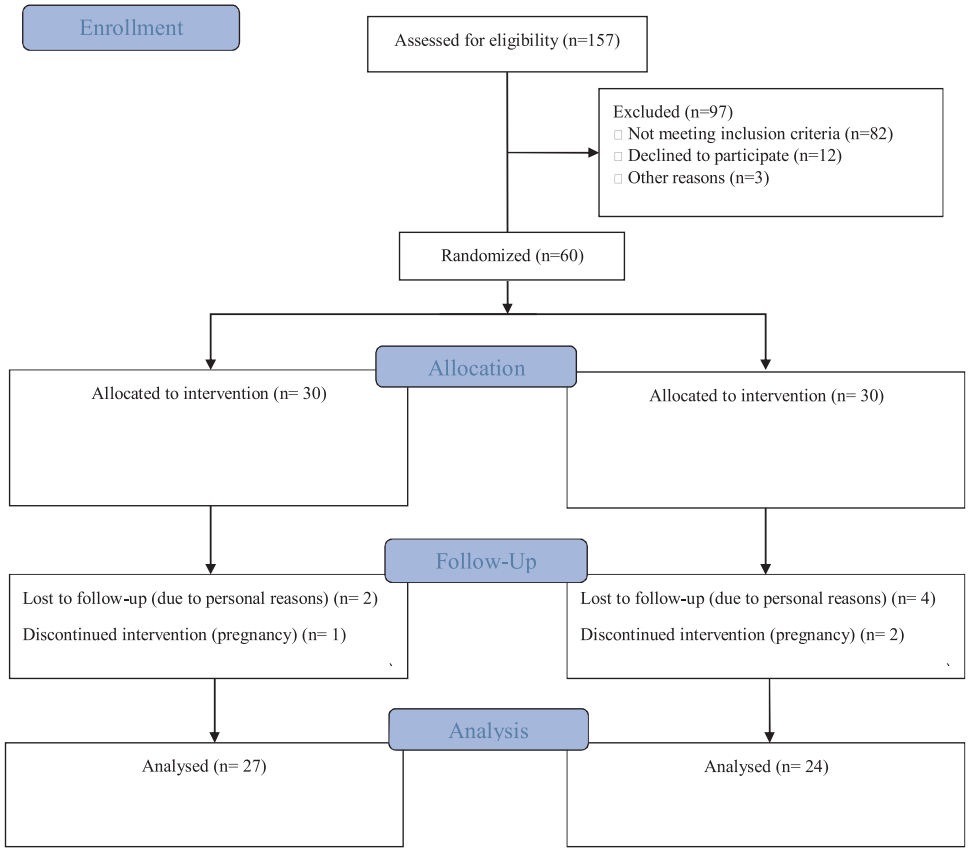

Fig. 1. Summary of patient Flowchart.

Table 2
Dietary energy and nutrients intakes of PCOS patients at the baseline and after 6 weeks of curcumin supplementation.

Variable	Measurement period	Curcumin group (n = 27)	Placebo group (n = 24)	P-value
Energy (kcal/day)	Baseline	1838.14 ± 236.76	1828.6 ± 214.43	0.875
	After intervention	1813.94 ± 225.85	1790.22 ± 178.33	0.682
	Mean difference	−24.19 ± 118.64	−37.83 ± 104.89	
Carbohydrate (g/day)	Baseline	229.32 ± 51.70	221.79 ± 34.73	0.565
	After intervention	228.95 ± 35.20	230.54 ± 43.75	0.388
	Mean difference	8.75 ± 34.96	−8.75 ± 34.96	
Protein (g/day)	Baseline	75.96 ± 15.23	79.87 ± 23.30	0.478
	After intervention	76.83 ± 21.62	78.76 ± 26.53	0.776
	Mean difference	0.86 ± 22.30	−1.10 ± 34	
Total fat (g/day)	Baseline	72.54 ± 18.10	75.68 ± 20.59	0.565
	After intervention	71.18 ± 18.24	67.03 ± 15.50	0.388
	Mean difference	−1.35 ± 17.79	−8.65 ± 19.06	
Cholesterol (mg/dl)	Baseline	214.90 ± 240.20	207.71 ± 146.76	0.899
	After intervention	189.17 ± 152.35	228.89 ± 254.20	0.496
	Mean difference	−25.72 ± 293.37	21.18 ± 314.33	
MUFA (g/day)	Baseline	18.18 ± 5.64	19.36 ± 7.58	0.530
	After intervention	16.55 ± 5.05	16.76 ± 5.25	0.888
	Mean difference	−1.63 ± 4.61	−2.60 ± 6.25	
PUFA (g/day)	Baseline	24.69 ± 7.87	27.50 ± 10.33	0.278
	After intervention	26.53 ± 9.39	22.90 ± 6.85	0.126
	Mean difference	1.83 ± 11.11	−4.60 ± 11.01	
SFA (g/day)	Baseline	16.99 ± 6.37	15.94 ± 6.26	0.558
	After intervention	14.58 ± 7.99	14.79 ± 5.50	0.913
	Mean difference	−2.41 ± 6.76	−1.15 ± 7.09	
Fiber (g/day)	Baseline	27.92 ± 11.14	31.08 ± 10.08	0.295
	After intervention	26.44 ± 10.18	25.23 ± 10.70	0.680
	Mean difference	−1.47 ± 13.92	−5.85 ± 15.98	

MUFA: mono unsaturated fatty acid; PUFA: poly unsaturated fatty acid; SFA: saturated fatty acid.
Note: The results are described as mean ± standard deviation (SD). P-value is reported based on the analysis of independent sample *t*-test.

curcumin treated group (p = 0.067). However, within-group analysis of lipid parameters did not reach statistical significant difference in the curcumin treated group. Other lipid parameters and the ratios were also non-significant in the curcumin group at the end of the trial. Serum hs-CRP level was not affected by curcumin supplementation (Table. 3).

No significant changes in FBS, serum insulin, HOMA-IR, and QUICKI were seen. However, the intragroup comparison showed that except FBS, other glycemia variables improved in the intervention group.

4. Discussion

To the best of our knowledge, this study is the first RCT that has assessed the effects of curcumin intake on glycemic status, lipid profile and hs-CRP levels in PCOS women. Our study showed that 6 weeks administration of oral curcumin in PCOS women did not support any significant effect on parameters of glycemic status except insulin level and also QUICKI which improved significantly in the curcumin group based on within-groups analyses. Na et al. have reported reduction in HOMA-IR, HbA1c and FBS levels following 300 mg/day curcuminoids supplementation for 3 months in overweight diabetic subjects. [29] In another study by Kocher et al., [30] 6 weeks supplementation with 294 mg highly bioavailable curcuminoids did not change glucose homeostasis. Our finding is supported by some human reports. [31–33] As for the experimental animal findings, Mohammadi et al. [34] showed significant decrement of insulin level, as well as HOMA-IR in curcumin-treated PCOS groups. Taking curcumin supplements by PCOS women did not change lipid profiles. Actually, hyperlipidemia plays a key role in a number of diseases such as obesity, diabetes, inflammation, and atherosclerosis which is more pronounced in women with PCOS. [35,36] Decreased HDL-c, increased triglycerides and LDL-c concentrations are the most common lipid disturbance in PCOS subjects. [37,38] In agreement with our findings, Baum et al. [39] in a 6 months human study showed that consumption of 1 g/d or 4 g/d of curcumin in elderly individuals did not significantly alter serum lipids. They also found a positive association between cholesterol concentrations and absorbed curcumin. Similarly, a systematic review and meta-analysis, [19] reported no effects of curcumin supplementation on any lipid profile components among heterogeneous populations. Moreover, the lack of effectiveness of supplementation with curcumin is also in line with previous reports. [30,33,39,40] However, some studies reported optimistic claims regarding the beneficial impact of curcumin supplementation on lipid profile. [40,41] A cross-over trial following 30 days curcuminoid supplementation (1 g/day) in obese subjects has reported significant reduction in serum TG levels, but no changes in other lipid parts. [28] Numerous animal studies have been conducted with favorable results on hypolipidemic effects of curcumin. [38,42,43] Nevertheless, in a study by Manjunatha and Srinivasan, no significant changes of cholesterol, TG and HDL-c was reported in hypercholesterolemic rats. [44] Overall, in a systematic review and meta-analysis on metabolic syndrome and related disorders patients by Tabrizi et al., [45] it was indicated that consumption of curcumin did a significant reduction in FBS, HbA1c, HOMA-IR, TG and total cholesterol levels but no effects on HDL-c and LDL-c levels in addition to significant increase of insulin levels. Also, curcumin intake at a dosage of ≤500 mg/day was associated with significant decline in FBS levels, HbA1c and TG. Furthermore, it was mentioned that the majority of the RCTs duration was ≤ 8 weeks.

CRP is regarded as a low-grade inflammation marker and also the mediator of the disease [46,47] has been associated to IR. [48] Chronic low-grade inflammation is considered as a hallmark of PCOS. [49] Our findings demonstrated that daily administration of curcumin does not positively affect serum hs-CRP level. Current evidence represents the inconclusive effect of curcumin on inflammation. [50] Our results also were in line with the previous studies. [28,30] PCOS rats treated with curcumin (100 and 300 mg/kg body weight) showed reduction in CRP levels after 14 days. [34] Surprisingly, Gonza´lez et al. suggesting that hyperandrogenism may possess anti-inflammatory effect in obese PCOS women. [51] There are some proposed explanations. Due to the different lipid metabolism pathways in animals (e.g. mouse and rat), their studies cannot be easily generalized to humans. [19] Concentrations, conditions and different cell types, as well as absorption and distribution of curcumin in the tissues are clearly important for its biological activities. [35,52] Accordingly, our results might be due to individual's variability in

Table 3
Serum levels of glycemic, lipid profile and hs-CRP in PCOS women at the baseline and after 6 weeks of curcumin supplementation.

Variable	Measurement period	Curcumin group (n = 27)	Placebo group (n = 24)	P-value
FBS (mg/dL)	Baseline	102.22 ± 9.75	99.87 ± 10.99	0.423[a]
	After intervention	104.85 ± 7.68	104.37 ± 8.94	0.374 [c]
	Mean difference	2.62 ± 9.48	4.50 ± 10.80	
	P-value[b]	0.162	0.053	
Insulin (μU/mL)	Baseline	15.42 ± 8.09	14.17 ± 5.03	0.518[a]
	After intervention	12.35 ± 6.79	13.29 ± 6.17	0.798[c]
	Mean difference	−3.06 ± 6.44	−0.88 ± 5.93	
	P-value[b]	0.020	0.474	
HOMA-IR	Baseline	3.95 ± 2.30	3.52 ± 1.40	0.428[a]
	After intervention	3.26 ± 2.26	3.45 ± 1.66	0.990[c]
	Mean difference	−0.69 ± 1.87	−0.07 ± 1.65	
	P-value[b]	0.067	0.840	
QUICKI	Baseline	0.32 ± 0.02	0.32 ± 0.01	0.646[a]
	After intervention	0.33 ± 0.03	0.32 ± 0.25	0.572 [c]
	Mean difference	0.01 ± 0.01	0.00 ± 0.01	
	P-value[b]	0.003	0.340	
Total Cholesterol (mg/dL)	Baseline	185.85 ± 35.96	175.79 ± 39.49	0.346[a]
	After intervention	182.51 ± 38.35	177.87 ± 32.68	0.913[c]
	Mean difference	−3.33 ± 18.58	2.08 ± 33.67	
	P-value[b]	0.360	0.765	
Triglyceride (mg/dL)	Baseline	157.25 ± 75.41	170.08 ± 84.81	0.570[a]
	After intervention	166.07 ± 110.53	148.45 ± 95.48	0.196[c]
	Mean difference	8.81 ± 70.73	−21.62 ± 53.96	
	P-value[b]	0.523	0.062	
LDL (mg/dL)	Baseline	92.96 ± 24.89	92.12 ± 29.41	0.913[a]
	After intervention	96.16 ± 29.31	90.32 ± 22.58	0.968[c]
	Mean difference	3.20 ± 21.82	−1.79 ± 23.34	
	P-value[b]	0.453	0.710	
HDL (mg/dL)	Baseline	49.00 ± 6.65	51.64 ± 11.58	0.317[a]
	After intervention	50.83 ± 8.14	52.67 ± 11.25	0.430 [c]
	Mean difference	1.82 ± 6.30	1.03 ± 7.99	
	P-value[b]	0.144	0.533	
LDL/HDL	Baseline	1.92 ± 0.53	1.80 ± 0.47	0.426[a]
	After intervention	1.89 ± 0.47	1.75 ± 0.46	0.751[c]
	Mean difference	−0.03 ± 0.38	−0.05 ± 0.38	
	P-value[b]	0.682	0.483	
TG/HDL	Baseline	3.36 ± 1.94	3.55 ± 2.11	0.738[a]
	After intervention	3.48 ± 2.75	3.01 ± 2.15	0.171 [c]
	Mean difference	0.11 ± 1.68	−0.54 ± 1.40	
	P-value[b]	0.731	0.070	
hs-CRP (mg/dL)				
	Baseline	4.82 ± 4.53	3.94 ± 2.50	0.405[a]
	After intervention	4.62 ± 4	3.83 ± 3.38	0.495[c]
	Mean difference	−0.19 ± 3.01	−0.12 ± 2.33	
	P-value[b]	0.742	0.795	

FBS: Fasting Blood Glucose; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; QUICKI: Quantitative Insulin Sensitivity Check Index; LDL: Low. Density Lipoprotein; HDL: High Density Lipoprotein; Hs-CRP: High sensitivity C-reactive protein.
Note: The results are described as Mean ± SD deviation (SD). P-value[a] is reported based on the analysis of independent sample *t*-test. P-value[b] is reported based on the analysis of paired sample *t*-test. P-value[c] is reported based on the multivariate analysis of variance (MANOVA).

absorption of curcumin. Another possible explanation for our results might also be due to duration of study, type and dosage of curcumin. It merits noting that some curcuma extract effects could be due to other active compounds (e.g. turmerones), therefore, it cannot entirely be attributable to curcumin. [53] The type of curcumin supplementation that affects its bioavailability and metabolism, is regarded as a key issue in such interventions. To minimize this problem, we asked patients to take supplements with meals. Studies have declared that fasting state or taking supplements as capsules may enhance absorption but not metabolism of curcumin, as compared to the consumption of curcumin with food (35).

Curcumin acts as a free radical scavenger and contributes to lipid homeostasis in plasma, cells or tissues with a decreased risk for atherosclerosis and inflammation. [35] Several mechanisms are accounted for the effects of curcumin on glucose homeostasis parameters comprising activation of peroxisome proliferator-activated receptor gamma (PPAR-γ) in adipocytes. PPAR-γ has a key role in controlling the genes involved in metabolic homeostasis, lipid, glucose metabolism, adipogenesis and inflammatory response. [54] Besides, increasing glucokinase activity through affecting hepatic glucose regulating enzymes [55] and reduction of circulating free fatty acids (FFAs), [56] could be regarded as other mechanisms which exert by curcumin. Curcumin also affects the expression of antioxidant genes. [35] It has been postulated that curcumin induces adiponectin, and hence could boost anti-inflammatory and insulin sensitizing responses. [10] In a study by Nabiuni et al., [57] they showed improved initiation of ovulation and PCOS through the curcumin as a promising agent. The main anti-adiposity mechanism of curcumin, is related to its anti-inflammatory effects on pro-inflammatory mediators. [58] Actually, previous findings have shown that high blood levels of CRP and TG are ascribed to increased levels of glucose and insulin levels. [59] Furthermore, there is an interrelation between oxidative stress and IR, which promotes dyslipidemia and CVD disorders. [60] It is well established that oxidative stress condition through the activation of stress sensitive signaling pathways, originating from hyperglycemia and in PCOS women occurs due to the reduction of antioxidant levels. [61] Oxidative stress also causes elevated levels of free fatty acids. [60] Besides, oxidative stress can affect membrane integrity, gene expression and organelle function. [62] Oxidative

stress-induced injuries can be considered as an originating or exacerbating agent for some diseases including type 2 diabetes. [63,64] Based upon previous studies, curcumin supplementation could influence anthropometric measures especially weight. [65,66] Moreover, prevalence of obesity was associated with low quality of diet and sedentary lifestyles, [67] both related to low grade chronic inflammation and metabolic abnormalities in such patients. [68] There were no differences in terms of dietary energy and nutrients intakes between the two groups. There were also no significant differences between the groups regarding the anthropometric indices.

Strengths points:

We conducted our trial on a homogenous population which literatures have pointed out that dyslipidemia is more pronounced in such population (34, 66). Moreover, controlling the dietary intake, physical activity and anthropometric parameters, as well as the percentage of body fat were of positive points of our work.

Limitations

Our trial had a relatively small sample size that may make it difficult to detect small changes due to curcumin treatment. Our research was limited to selected metabolic parameters and we were not able to measure other biomarkers namely, endogenous antioxidants such as superoxide dismutase (SOD), catalase and glutathione levels. Investigating the effects of curcumin on reproductive hormones including androgen levels and also sex hormone-binding globulin (SHBG) would be of value. Also, the quantification of serum or plasma curcumin levels is suggested. Future trials with larger scale using different doses and duration to support the findings are warranted.

As conclusion, curcumin supplementation might be beneficial for improving serum insulin and QUICKI, however, future investigations are suggested in order to draw a firm link between curcumin and glycemia control.

Funding

The study was financially supported by a grant of Vice-Chancellor for Research, Isfahan University of Medical Sciences, Isfahan, Iran under the registration code of 296092.

Declaration of Competing Interest

All authors declared that they have no personal or financial conflicts of interest.

Acknowledgement

The study was a part of Sara Sohaei's MSc thesis that was financially supported by a grant from Vice-Chancellor for Research, Isfahan University of Medical Sciences, Isfahan, Iran under the code of 296092.

References

1. Homburg R. Polycystic ovary syndrome. *Best Pract Res Clin Obstet Gynaecol.* 2008;22(2):261–274.
2. March WA, Moore VM, Willson KJ, Phillips DI, Norman RJ, Davies MJ. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. *Hum Reprod.* 2009;25(2):544–551.
3. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. *J Clin Endocrinol Metab.* 2004;89(6):2745–2749.
4. Knochenhauer E, Key T, Kahsar-Miller M, Waggoner W, Boots L, Azziz R. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: A prospective study. *J Clin Endocrinol Metab.* 1998;83(9):3078–3082.
5. Mehrabian F, Khani B, Kelishadi R, Ghanbari E. The prevalence of polycystic ovary syndrome in Iranian women based on different diagnostic criteria. *Endokrynol Pol.* 2011;62(3):238–242.
6. De Leo V, Musacchio M, Cappelli V, Massaro M, Morgante G, Petraglia F. Genetic, hormonal and metabolic aspects of PCOS: An update. *Reprod Biol Endocrinol.* 2016;14(1):38.
7. Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. *Lancet.* 2007;370(9588):685–697.
8. Trikudanathan S. Polycystic ovarian syndrome. *Med Clin North Am.* 2015;99(1):221–235.
9. Raji A, Seely EW, Arky RA, Simonson DC. Body fat distribution and insulin resistance in healthy Asian Indians and Caucasians. *J Clin Endocrinol Metab.* 2001;86(11):5366–5371.
10. Hajri T, Tao H, Wattacheril J, Marks-Shulman P, Abumrad NN. Regulation of adiponectin production by insulin: Interactions with tumor necrosis factor-alpha and interleukin-6. *Am J Physiol-Heart Circul Physiol.* 2010.
11. Skrypnik D, Bogdanski P, Skrypnik K, et al. Influence of endurance and endurance–Strength training on mineral status in women with abdominal obesity: A randomized trial. *Medicine.* 2019;98(12):e14909.
12. Skrypnik K, Bogdański P, Sobieska M, Suliburska J. The effect of multistrain probiotic supplementation in two doses on iron metabolism in obese postmenopausal women: A randomized trial. *Food Funct.* 2019;10(8):5228–5238.
13. Rains JL, Jain SK. Oxidative stress, insulin signaling, and diabetes. *Free Radic Biol Med.* 2011;50(5):567–575.
14. Barry JA, Azizia MM, Hardiman PJ. Risk of endometrial, ovarian and breast cancer in women with polycystic ovary syndrome: A systematic review and meta-analysis. *Hum Reprod Update.* 2014;20(5):748–758.
15. Yeon Lee J, Baw C-K, Gupta S, Aziz N, Agarwal A. Role of oxidative stress in polycystic ovary syndrome. *Curr Womens Health Rev.* 2010;6(2):96–107.
16. Reddy PS, Begum N, Mutha S, Bakshi V. Beneficial effect of Curcumin in Letrozole induced polycystic ovary syndrome. *Asian Pacific J Reprod.* 2016;5(2):116–122.
17. Ehrmann DA. Polycystic ovary syndrome. *N Engl J Med.* 2005;352(12):1223–1236.
18. Badawy A, Elnashar A. Treatment options for polycystic ovary syndrome. *Int J Womens Health.* 2011;3:25.
19. Sahebkar A. A systematic review and meta-analysis of randomized controlled trials investigating the effects of curcumin on blood lipid levels. *Clin Nutr.* 2014;33(3):406–414.
20. Ghosh S, Banerjee S, Sil PC. The beneficial role of curcumin on inflammation, diabetes and neurodegenerative disease: A recent update. *Food Chem Toxicol.* 2015;83:111–124.
21. Rahmani S, Asgary S, Askari G, et al. Treatment of non-alcoholic fatty liver disease with curcumin: A randomized placebo-controlled trial. *Phytother Res.* 2016;30(9):1540–1548.
22. Chuengsamarn S, Rattanamongkolgul S, Luechapudiporn R, Phisalaphong C, Jirawatnotai S. Curcumin extract for prevention of type 2 diabetes. *Diabetes Care.* 2012;35(11):2121–2127.
23. ESHRE TR. Group A-SPCW. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril.* 2004;81(1):19–25.
24. Eke CB, Chukwu BF, Ikefuna AN, Ezenwosu OU, Emodi IJ. Bioelectric Impedance Analysis of Body Composition of Children and Adolescents with Sickle Cell Anemia in Enugu, Nigeria. *Pediatr Hematol Oncol.* 2015;32(4):258–268.
25. Razavi M, Jamilian M, Kashan ZF, et al. Selenium supplementation and the effects on reproductive outcomes, biomarkers of inflammation, and oxidative stress in women with polycystic ovary syndrome. *Horm Metab Res.* 2016;48(03):185–190.
26. Vasheghani-Farahani A, Tahmasbi M, Asheri H, Ashraf H, Nedjat S, Kordi R. The Persian, last 7-day, long form of the International Physical Activity Questionnaire: Translation and validation study. *Asian J Sports Med.* 2011;2(2):106.
27. Cutfield WS, Jefferies CA, Jackson WE, Robinson EM, Hofman PL. Evaluation of HOMA and QUICKI as measures of insulin sensitivity in prepubertal children. *Pediatr Diabetes.* 2003;4(3):119–125.
28. Mohammadi A, Sahebkar A, Iranshahi M, et al. Effects of supplementation with curcuminoids on dyslipidemia in obese patients: A randomized crossover trial. *Phytother Res.* 2013;27(3):374–379.
29. Na LX, Li Y, Pan HZ, et al. Curcuminoids exert glucose-lowering effect in type 2 diabetes by decreasing serum free fatty acids: A double-blind, placebo-controlled trial. *Mol Nutr Food Res.* 2013;57(9):1569–1577.
30. Kocher A, Bohnert L, Schiborr C, Frank J. Highly bioavailable micellar curcuminoids accumulate in blood, are safe and do not reduce blood lipids and inflammation markers in moderately hyperlipidemic individuals. *Mol Nutr Food Res.* 2016;60(7):1555–1563.
31. Yang YS, Su YF, Yang HW, Lee YH, Chou JI, Ueng KC. Lipid-lowering effects of curcumin in patients with metabolic syndrome: a randomized, double-blind, placebo-controlled trial. *Phytother Res.* 2014;28(12):1770–1777.
32. Franco-Robles E, Campos-Cervantes A, Murillo-Ortiz BO, et al. Effects of curcumin on brain-derived neurotrophic factor levels and oxidative damage in obesity and diabetes. *Appl Physiol Nutr Metab.* 2013;39(2):211–218.
33. Usharani P, Mateen A, Naidu M, Raju Y, Chandra N. Effect of NCB-02, atorvastatin and placebo on endothelial function, oxidative stress and inflammatory markers in patients with type 2 diabetes mellitus. *Drugs R D.* 2008;9(4):243–250.
34. Mohammadi S, Bardei LK, Hojati V, Ghorbani A, Nabiuni M. Anti-inflammatory effects of curcumin on insulin resistance index, levels of interleukin-6, C-reactive protein, and liver histology in polycystic ovary syndrome-induced rats. *Cell J (Yakhteh).* 2017;19(3):425.
35. Zingg JM, Hasan ST, Meydani M. Molecular mechanisms of hypolipidemic effects of curcumin. *Biofactors.* 2013;39(1):101–121.
36. Diamanti-Kandarakis E, Papavassiliou AG, Kandarakis SA, Chrousos GP. Pathophysiology and types of dyslipidemia in PCOS. *Trends Endocrinol Metab.* 2007;18(7):280–285.
37. Stepien M, Kujawska-Luczak M, Szulinska M, et al. Beneficial dose-independent

influence of Camellia sinensis supplementation on lipid profile, glycemia, and insulin resistance in an NaCl-induced hypertensive rat model. *J Physiol Pharmacol.* 2018;69:1–8.
38. Shin SK, Ha TY, McGregor RA, Choi MS. Long-term curcumin administration protects against atherosclerosis via hepatic regulation of lipoprotein cholesterol metabolism. *Mol Nutr Food Res.* 2011;55(12):1829–1840.
39. Baum L, Cheung SK, Mok VC, et al. Curcumin effects on blood lipid profile in a 6-month human study. *Pharmacol Res.* 2007;56(6):509–514.
40. Alwi I, Santoso T, Suyono S, et al. The effect of curcumin on lipid level in patients with acute coronary syndrome. *Acta Med Indones.* 2008;40(4):201–210.
41. Ramırez-Boscá A, Soler A, Carrion MA, et al. An hydroalcoholic extract of Curcuma longa lowers the apo B/apo A ratio: Implications for atherogenesis prevention. *Mech Ageing Dev.* 2000;119(1):41–47.
42. Jang E-M, Choi M-S, Jung UJ, et al. Beneficial effects of curcumin on hyperlipidemia and insulin resistance in high-fat–fed hamsters. *Metabolism.* 2008;57(11):1576–1583.
43. Pari L, Murugan P. Antihyperlipidemic effect of curcumin and tetrahydrocurcumin in experimental type 2 diabetic rats. *Ren Fail.* 2007;29(7):881–889.
44. Manjunatha H, Srinivasan K. Hypolipidemic and antioxidant effects of dietary curcumin and capsaicin in induced hypercholesterolemic rats. *Lipids.* 2007;42(12):1133.
45. Tabrizi R, Vakili S, Lankarani KB, et al. The effects of curcumin on glycemic control and lipid profiles among patients with metabolic syndrome and related disorders: A systematic review and meta-analysis of randomized controlled trials. *Curr Pharm Des.* 2018;24(27):3184–3199.
46. Verma S, Buchanan MR, Anderson TJ. Endothelial function testing as a biomarker of vascular disease. *Circulation.* 2003;108(17):2054–2059.
47. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med.* 2000;342(12):836–843.
48. Festa A, D'Agostino Jr R, Howard G, Mykkanen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome: The Insulin Resistance Atherosclerosis Study (IRAS). *Circulation.* 2000;102(1):42–47.
49. Repaci A, Gambineri A, Pasquali R. The role of low-grade inflammation in the polycystic ovary syndrome. *Mol Cell Endocrinol.* 2011;335(1):30–41.
50. Tabrizi R, Vakili S, Akbari M, et al. The effects of curcumin-containing supplements on biomarkers of inflammation and oxidative stress: A systematic review and meta-analysis of randomized controlled trials. *Phytother Res.* 2019;33(2):253–262.
51. González F, Sia CL, Stanczyk FZ, Blair HE, Krupa ME. Hyperandrogenism exerts an anti-inflammatory effect in obese women with polycystic ovary syndrome. *Endocrine.* 2012;42(3):726–735.
52. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: Problems and promises. *Mol Pharm.* 2007;4(6):807–818.
53. Shytle RD, Bickford PC, Rezai-zadeh K, et al. Optimized turmeric extracts have potent anti-amyloidogenic effects. *Curr Alzheimer Res.* 2009;6(6):564–571.
54. Bays H, Mandarino L, DeFronzo RA. Role of the adipocyte, free fatty acids, and ectopic fat in pathogenesis of type 2 diabetes mellitus: Peroxisomal proliferator-activated receptor agonists provide a rational therapeutic approach. *J Clin Endocrinol Metab.* 2004;89(2):463–478.
55. Seo KI, Choi MS, Jung UJ, et al. Effect of curcumin supplementation on blood glucose, plasma insulin, and glucose homeostasis related enzyme activities in diabetic db/db mice. *Mol Nutr Food Res.* 2008;52(9):995–1004.
56. Shimabukuro M, Zhou Y-T, Levi M, Unger RH. Fatty acid-induced β cell apoptosis: A link between obesity and diabetes. *Proc Natl Acad Sci.* 1998;95(5):2498–2502.
57. Nabiuni M, Mohammadi S, Kayedpoor P, Karimzadeh L. The effect of curcumin on the estradiol valerate-induced polycystic ovary in rats. *KAUMS Journal (FEYZ).* 2015;18(6):515–523.
58. Ziccardi P, Nappo F, Giugliano G, et al. Reduction of inflammatory cytokine concentrations and improvement of endothelial functions in obese women after weight loss over one year. *Circulation.* 2002;105(7):804–809.
59. Park HJ, Lee HJ, Choi MS, et al. JNK pathway is involved in the inhibition of inflammatory target gene expression and NF-kappaB activation by melittin. *J Inflamm.* 2008;5(1):7.
60. Macut D, Bjekić-Macut J, Savić-Radojević A. *Dyslipidemia and oxidative stress in PCOS. Polycystic Ovary Syndrome.* Vol 40. Karger Publishers; 2013:51–63.
61. Fenkci V, Fenkci S, Yilmazer M, Serteser M. Decreased total antioxidant status and increased oxidative stress in women with polycystic ovary syndrome may contribute to the risk of cardiovascular disease. *Fertil Steril.* 2003;80(1):123–127.
62. Brookheart RT, Michel CI, Schaffer JE. As a matter of fat. *Cell Metab.* 2009;10(1):9–12.
63. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. *Int J Biochem Cell Biol.* 2007;39(1):44–84.
64. Li L, Li J. Link between oxidative stress and insulin resistance. *Chin Med Sci J = Chung-kuo i hsueh k'o hsueh tsa chih.* 2007;22(4):254–259.
65. Hariri M, Haghighatdoost F. Effect of curcumin on anthropometric measures: A systematic review on randomized clinical trials. *J Am Coll Nutr.* 2018;37(3):215–222.
66. Di Pierro F, Bressan A, Ranaldi D, Rapacioli G, Giacomelli L, Bertuccioli A. Potential role of bioavailable curcumin in weight loss and omental adipose tissue decrease: Preliminary data of a randomized, controlled trial in overweight people with metabolic syndrome. Preliminary study. *Eur Rev Med Pharmacol Sci.* 2015;19(21):4195–4202.
67. Han JC, Lawlor DA, Kimm SY. Childhood obesity. *Lancet.* 2010;375(9727):1737–1748.
68. Jin T, Song Z, Weng J, Fantus IG. Curcumin and other dietary polyphenols: Potential mechanisms of metabolic actions and therapy for diabetes and obesity. *Am J Physiol-Endocrinol Metab.* 2017;314(3):E201–E205.