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Original article

The effects of curcumin supplementation added to diet on anthropometric and biochemical status in women with polycystic ovary syndrome: A randomized, placebo-controlled trial

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Abstract. Clinical manifestations of polycystic ovary syndrome (PCOS) include infrequent or absent menses, abdominal obesity, acanthosis nigricans and signs of androgen excess which include acne or seborrhea and insulin resistance. We hypothesized that curcumin added to diet would modulate anthropometric and biochemical status in women with PCOS. This study was performed with the participation of 30 individuals diagnosed with PCOS by physicians. Participants were randomly assigned to curcumin (at a dose of 93.34 mg) or placebo groups. After a period of eight weeks of curcumin supplementation added to diet, body weight, body fat mass and waist circumferences (WC) were found lower in the curcumin group than the placebo group ($p<0.05$). Body weight decreased by 5.8 ± 2.3 kg after intervention in curcumin group ($p<0.05$) and 3.2 ± 2.5 kg in placebo group ($p<0.05$). In addition, waist circumferences decreased by 7.2 ± 3.5 cm after intervention in curcumin group ($p<0.05$) and 4.1 ± 2.1 cm in placebo group ($p<0.05$). Between-group difference analysis showed that there were significant differences in fasting blood glucose levels, fasting insulin levels, homeostasis model assessment for insulin resistance (HOMA-IR) and C-reactive protein (CRP) levels in curcumin group ($p<0.05$). On the other hand, between-group difference analysis showed no significant differences in lipid parameters (total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglyceride levels) and hormone levels ($p>0.05$). These results indicated that curcumin supplementation added to diet in women with PCOS improved the anthropometric measurements and glysemic parameters; however, it did not restore the hormone and lipid profiles.

Keywords: Polycystic ovary syndrome (PCOS), curcumin, obesity, insulin resistance, hyperlipidemia

1. Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder that is defined by a combination of signs and symptoms of androgen excess (hirsutism and/or hyperandrogenaemia) and ovarian dysfunction [oligoovulation and/or polycystic ovarian morphology (PCOM)], provided that other specific diagnoses, such as hyperprolactinaemia and nonclassic congenital ad-renal hyperplasia, have been excluded (1). PCOS is a disease that affects 6–10% of females worldwide. In Turkey, the reported overall prevalence of PCOS (95% CI) according to diagnostic criteria of the *National Institutes of Health* (NIH), Rotterdam and the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society is 6% (5-8%, n = 18 trials), 10% (8-13%, n = 15 trials) and 10% (7-13%, n = 10 trials), respectively (2).

PCOS is associated with a range of reproductive (hyperandrogenism, oligo or anovulation, infertility); metabolic (gestational diabetes mellitus), impaired

glucose tolerance, type 2 diabetes, cardiovascular disease, cardiovascular risk factors; and psychological (depression, anxiety, poor self-esteem, disordered eating, psychosexual dysfunction) features (3). Clinical manifestations of PCOS include infrequent or absent menses, abdominal obesity, acanthosis nigricans and signs of androgen excess (hyperandrogenism) which include acne or seborrhea and insulin resistance. The etiology of PCOS is not clearly understood, but lipid imbalance, oxidative stress, insulin resistance and genetics are some of the contributing factors (4).

Obesity is one of the most studied subjects in PCOS patients. The incidence of obesity in PCOS is reported to be 40-60% (5). The majority of women with PCOS (50%-90%) are insulin resistant and insulin resistance underlies association of PCOS with dysmetabolic features. Compensatory hyperinsulinaemia is secondary to insulin resistance in PCOS and has multiple effects on peripheral tissues. Weight-gain and obesity worsen insulin resistance and features of the metabolic syndrome. The effects of weight-gain on insulin resistance and hyperinsulinaemia, and the dysmetabolic and steroidogenic implications of the impaired PI3-kinase and intact MAP kinase post-receptor insulin pathways, respectively, form a central component of PCOS pathogenesis and underlie the association of weight-gain and obesity with PCOS (6). The problem of ovulation increases with increasing obesity in PCOS patients, which in turn creates difficulties in achieving weight loss. Patients with PCOS generally have central obesity and their waist/hip ratios are found to be increased when compared to healthy controls (5). Increased adipose tissue is specifically associated with hyperandrogenemia, glucose intolerance, insulin resistance and dyslipidemia (7).

Curcumin is known as a natural dietary polyphenol which is extracted from Curcuma longa L. It has been shown that curcumin has a variety of pharmacological effects such as antioxidant, anti-cancer, anti-inflammatory, and anti-microbial activities (8). Curcumin intake has been suggested to improve weight and metabolic status through increasing basal metabolic rate, which may in turn cause increased en-ergy expenditure (9). A bioavailable form of curcumin has been reported to result in improved weight man-agement in overweight subjects (10). Among people with non-alcoholic fatty liver disease, a substantial decline in BMI and liver fat status was observed following the intake of 70 mg/day curcumin for 8 weeks (11). Two weeks of high dietary curcumin supplementation feeding in rats reduced epididymal adipose tissue and increased fatty acid β-oxidation, indicating the increase of energy expenditure after curcumin treatment (12). Curcumin also shows anti-inflammatory functions. Curcumin regulates local and systemic targets to suppress inflammation, to inhibit preadipocyte differentiation, and to activate potent cellular antioxidants. Obesity promotes a chronic low-grade inflammation, contributing to the development of metabolic dysfunction and the worsening of insulin resistance and symptoms of type 2 diabetes. Curcumin directly interacts with adipose tissue to suppress inflammation (13).

Curcumin, which has a very limited solubility in water (<0.005%), has a low bioavailability due to its hydrophobic structure (14). In a study on the pharmacokinetic properties of curcumin, it is reported that its oral absorption is low and its use with piperine in the structure of black pepper increases the absorption (15).

Currently, many therapies are in use to manage PCOS condition and to induce ovulation. But these therapies have been reported to cause severe side effects ranging from arthritis, joint or muscle pain to psychological disturbances. Therefore, the focus is currently being laid on medicines from natural sources which show minimal or no side effects (4). Reddy et al. (4) reported that curcumin showed many beneficial effects similar to Clomiphene citrate in treating PCOS condition and inducing ovulation. Curcumin restored the hormone and lipid profile, antioxidant and glycemic status as well as ovarian morphology in Letrozole induced PCOS animals. These effects may be ascribed to its multiple pharmacological activities like estrogenic, antihyperlipidemic, antioxidant and hypoglycemic effects which could be useful in managing PCOS condition and preventing ovarian cell dysfunc-tion, ovulation, and thereby improving fertility. This broad spectrum of biological effects of curcumin make it a promising drug for treating clinical and pathologi-cal abnormalities in PCOS cases.

In a joint report of the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) in 2000, the temporary accepted

daily curcumin intake of 0-1 mg/kg body weight was extended until 2001 (16). However, a few studies showed that the chronic use of curcumin can cause liver toxicity (17) and high doses of curcumin can induce gastrointestinal upset, inflamed skin, and chest tightness in a phase II trial in patients with advanced pancreatic cancer (18). Gupta (19) states that the United States Food and Drug Administration (FAD) has approved curcumin as GRAS (generally recognized as safe), and the polyphenol is now used as a supplement in several countries. Also, Sharifi-Rad et al. (20) state that "the FDA concluded that curcuminoids used as antioxidant and flavoring agents at maximum levels of >20 mg/serving in specific foods are safe, however, the agency has not made its own determination regarding the GRAS status of the subject use of curcuminoids".

The aim of this study is to investigate the effect of curcumin supplementation added to diet on anthropometric measurements and biochemical parameters in women with PCOS.

2. Material and Methods

2.1. Subjects

This study was performed with the participa-tion of 30 individuals who were newly diagnosed with PCOS through endocrine, metabolic and gynecologi-cal evaluation by the physicians at Private Jimer Hos-pital between 2017 and 2018. The diagnosis of PCOS was based on Rotterdam European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) criteria from 2003 (21). Women aged between 20-35 years, without regular physical activity and with a body mass index (BMI) between 25.0-35.0 kg/m2 and who volunteered to participate were included in the study. Patients suffering from Cushing's syndrome, thyroid dysfunctions, androgen secreting tumor, and enzyme deficiency (21-hydroxylase in particular), decreased ovary reserves, type 1 and 2 diabetes were excluded. Any pharmacological therapy, smoking and alcohol abuse were also among the exclusion criteria. All pa-tients provided written informed consent. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and the study was approved by the Human Research Ethics Committee at Acıbadem Mehmet Ali Aydınlar University.

2.2. Study design

This randomized, single-blinded, placebo-controlled clinical trial was performed on 30 women who were newly diagnosed with PCOS, aged 20-35 years old. The sample size was determined by Power Analysis. Participants were randomly assigned to curcumin (n=15) or placebo (n=15) groups (Figure 1). A highly bioavailable formulation of curcumin was used in the study and it was administered at a daily dose of 93.34 mg (2 capsules), as advised by the manufacturer, for a period of 8 weeks. Each capsule contained 46.67 mg gel optimised curcumin which is the equivalent of 950 gr dry extract Curcuma longa L. Bioavailability improvement was based on the increase of curcumin solubility in duodenal conditions; higher solubility was achieved by the pre-formulation of potential micro-emulsions, obtained in the digestive system (stomach, intestine) after disintegration of the capsule (22). The diet energy calculation in accordance with the weight loss diet plan was designed by using Harris-Bene-dict formulation: by decreasing 500 kcal off the total energy to be taken daily in order to attain 0.5-1 kg weight loss per week. A weight loss diet was organ-ized for the participants in both groups in light of the recommended dietary treatment factors for PCOS patients, provided that 50% of the dietary energy came from carbohydrates (complex carbohydrates), 20% from proteins, and 30% from fat. In order to check the dietary compliance of all groups, 3-day food consump-tion records were taken.

2.3. Anthropometric measurements

Height, weight, waist and hip circumferenc-es were measured from 08:00 am to 10:00 am after a 12-h fast. Height was measured by using a stadi-ometer accurate to ±0.5 cm, and weight was obtained by using a calibrated scale accurate to ±0.1 kg (Seca, Inc.) with participants wearing light clothing and no shoes. The BMI was calculated using the standard equation (kilograms per meters squared). The waist

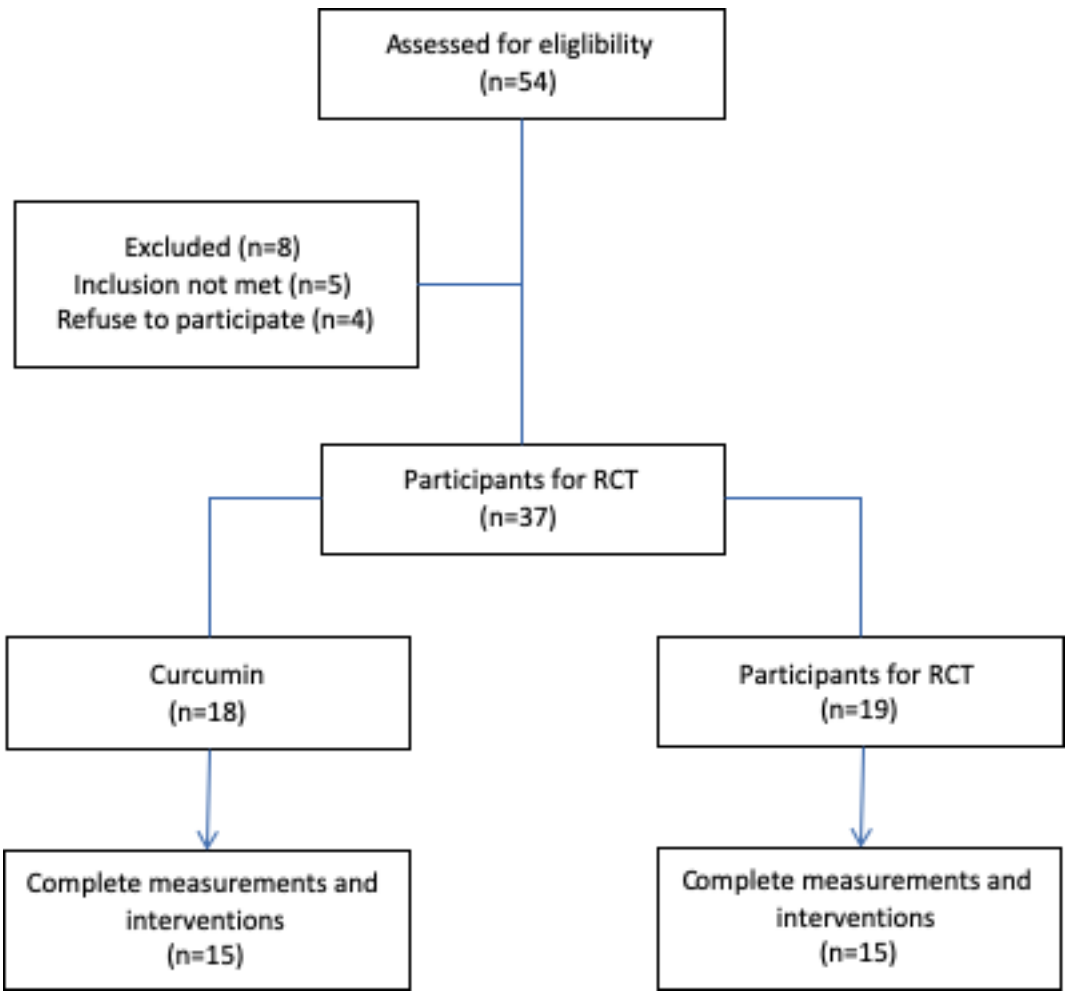

Figure 1. Flow chart of participants

circumference was measured with participants in the standing position, midway between the lower margin of the last rib and the iliac crest, at mid-exhalation. The hip circumference was measured at the widest point of the hip/buttocks area with the measuring tape parallel to the floor. The waist-to-hip ratio was calculated by dividing waist circumference by hip circumference. Anthropometric measurements were taken twice by the researchers, and the mean values were used in all analyses. The percentage of body fat was estimated by electrical bioimpedance by using a Tanita BC - 418 MA body fat analyzer. Adiposity was stratified as global adiposity (excessive adipose tissue, independent of site) and abdominal adiposity. BMI and percentage of body fat were used as global adiposity parameters. The waist circumference and waist-to-hip ratio were used to evaluate abdominal adiposity.

2.4. Biochemical analysis

Blood samples were collected after a 12-h fasting period. Biochemical evaluation included glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triacylglycerols, hemoglobin A1c (HbA1C), follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone (total T), dehydroepiandrosterone-sulfate (DHEAS) and Sex Hormone Binding Globulin (SHBG). Fasting plasma glucose, insulin, total cholesterol, HDL-cholesterol,

LDL-cholesterol, triglycerides (TG) and HbA1C were measured using original kits and an Abbott-Aeroset autoanalyser (Architect C-8000, Chicago, Illinois, USA). Insulin resistance was estimated from fasting serum measurements using the homeostasis model assessment-insulin resistance (HOMA-IR) [insulin (μU/mL) X glucose (mg/dL) ÷ 425]. Hormonal tests were performed by using Chemiluminescent Microparticle Immunoassay (Architect Abbott Lab, IL, USA).

2.5. Statistical analysis

Statistical analysis of the data collected during the study was performed in SPSS v.21 package program (SPSS 2013). Numerical variables were expressed as mean, standard deviation (SD), median, lower and upper values; and categorical variables were expressed as number (n) and percentage (%). Shapiro-Wilk test was used to test whether continuous variables were compatible with normal distribution. Descriptive statistics for continuous variables conforming to normal distribution are expressed as mean ± standard deviation, and as median (minimum-maximum) for continuous variables not conforming to normal distribution. For categorical variables, descriptive variables are given as frequency and percentage. Fisher's Exact test and Fisher-Freeman-Halton test were used to compare categorical variables between groups. Kruskal-Wallis test, one way analysis of variance, Wilcoxon Sign test, paired sample t-test, Mann-Whitney U test and independent sample t-test were used to compare continuous variables between groups. In comparison of categorical variables between groups, $p < 0.05$ was considered statistically significant.

3. Results

The mean age, weight, body mass index, body fat and waist circumferences of participants in the intervention groups were not significantly different ($p>0.05$). The mean age was 27.6 ± 3.6 years in curcumin group and 28.3 ± 5.9 years in placebo group ($p>0.05$); and the baseline BMI of participants was 29.8 ± 6.3 kg/m2 in curcumin group and 30.9 ± 4.6 kg/m2 in placebo group ($p>0.05$). After eight weeks, body weight decreased by 5.8 ± 2.3 kg in curcumin group ($p<0.05$) and 3.2 ± 2.5 kg in placebo group ($p<0.05$). Body fat mass descreased by 3.4 ± 1.5 in curcumin group ($p<0.05$) and 2.4 ± 0.9 in placebo group ($p<0.05$). In addition, waist circumferences decreased by 7.2 ± 3.5 cm in curcumin group ($p<0.05$) and 4.1 ± 2.1 cm in placebo group ($p<0.05$). Between-group difference analysis showed that there were significant differences in body weight, fat mass and waist circumferences in curcumin group than placebo group ($p<0.05$).

Table 2 indicates the biochemical parameters of the participants. Fasting blood glucose level decreased by 6.8 ± 3.8 mg/dL after intervention in curcumin group ($p<0.05$) and 1.2 ± 3.5 mg/dL in placebo group ($p>0.05$). Fasting plasma insulin, HOMA-IR, total cholesterol, TG, and CRP all decreased to the same extent only in curcumin group ($p<0.05$). Between-group difference analysis showed that there were significant differences in fasting blood glucose level, fasting insuline level, HOMA-IR and CRP level in curcumin group ($p<0.05$). However, between-group difference analysis showed no significant differences in lipid pa-rameters (total cholesterol, LDL-cholesterol, HDL-cholesterol and triglyceride levels) ($p>0.05$). Within-group difference of biochemical parameters specified that the serum fasting glucose, insulin, CRP, total cho-lesterol, triglyceride and HOMA-IR were improved significantly in curcumin group ($p<0.05$). However, within-group analysis of all biochemical parameters did not reach statistically significant difference in the placebo group ($p>0.05$).

Table 3 indicates the hormone levels of the participants. FSH level decreased by 0.1 ± 2.6 mIU/mL after intervention in curcumin group ($p>0.05$) and 1.3 ± 5.1 mIU/mL in placebo group ($p>0.05$). Also, LH level decreased by 1.2 ± 8.3 mIU/mL after intervention in curcumin group ($p>0.05$) and 1.3 ± 5.2 mIU/mL in placebo group ($p>0.05$). Neither between-group analysis nor within-group analysis showed any significant differences in hormon levels among groups ($p>0.05$).

Table 1. Anthropometric characteristics of participants with PCOS at the baseline and after 8 weeks of curcumin supplementation to diet

Variable	Measurement period	Curcumin + Diet Group	Diet Group + Placebo Group	p-value
Age (year)		27.6 ± 3.6	28.3 ± 5.9	0.714 [b]
Height (cm)		165.2 ± 6.4	167.8 ± 5.3	0.233 [b]
Weight (kg)	Before intervention	80.4 ± 19.0	85.5 ± 12.3	0.187 [b]
	After intervention	74.7 ± 18.4	82.3 ± 11.9	0.098 [b]
	Mean difference	5.8 ± 2.3	3.2 ± 2.5	0.037 [b]
	p-value	0.001 [a]	0.001 [a]	
BMI (kg/m^2)	Before intervention	29.8 ± 6.3	30.9 ± 4.6	0.187 [b]
	After intervention	28.1 ± 6.7	29.2 ± 4.3	0.267 [b]
	Mean difference	2.5 ± 0.9	1.7 ± 0.9	0.081 [b]
	p-value	0.001 [a]	0.001 [a]	
Body fat (kg)	Before intervention	34.5 ± 15.2	37.2 ± 10.4	0.202 [b]
	After intervention	28.7 ± 14.5	35.1 ± 10.9	0.011 [b]
	Mean difference	3.4 ± 1.5	2.4 ± 0.9	0.048 [b]
	p-value	0.000 [a]	0.000 [a]	
Waist circumferences (cm)	Before intervention	92.7 ± 15.1	94.0 ± 10.6	0.345 [b]
	After intervention	85.5 ± 13.2	89.9 ± 10.6	0.367 [b]
	Mean difference	7.2 ± 3.5	4.1 ± 2.1	0.029 [b]
	p-value	0.000 [a]	0.000 [a]	

BMI: Body mass index

p-value[a] is reported based on the analysis of paired sample t-test (between baseline and after 8 weeks)

P-value[b] is reported based on the analysis of independent sample t-test (between curcumin + diet and placebo + diet)

Table 2. Serum biochemical levels of participants with PCOS at the baseline and after 8 weeks of curcumin supplementation to diet

Variable	Measurement period	Curcumin + Diet Group	Placebo + Diet Group	p-value
FBG (mg/dL)	Before intervention	94.1 ± 6.1	90.6 ± 5.1	0.067 [b]
	After intervention	87.3 ± 8.2	89.4 ± 6.8	0.713 [b]
	Mean difference	6.8 ± 3.6	1.2 ± 3.5	0.000 [b]
	p-value	0.001 a	0.191 [a]	
Insulin (µU/mL)	Before intervention	12.2 ± 8.9	8.0 ± 5.9	0.250 [b]
	After intervention	7.9 ± 9.3	8.1 ± 4.8	0.285 [b]
	Mean difference	4.2 ± 3.7	-0.1 ± 2.5	0.001 [b]
	p-value	0.001 [a]	0.531 [a]	

Variable	Measurement period	Curcumin + Diet Group	Placebo + Diet Group	p-value
HOMA-IR	Before intervention	2.7 ± 1.9	1.8 ± 1.4	0.233 [b]
	After intervention	1.6 ± 1.9	1.7 ± 1.1	0.250 [b]
	Mean difference	1.1 ± 0.8	0.1 ± 0.5	0.000 [b]
	p-value	0.001 [a]	0.531 [a]	
Total Cholesterol (mg/dL)	Before intervention	200.9 ± 27.2	215.2 ± 29.9	0.367 [b]
	After intervention	187.5 ± 26.9	202.0 ± 20.9	0.106 [b]
	Mean difference	13.4 ± 22.3	13.1 ± 42.1	0.870 [b]
	p-value	0.017 [a]	0.306 [a]	
Triglyceride (mg/dL)	Before intervention	111.8 ± 54.3	132.5 ± 56.3	0.285 [b]
	After intervention	99.8 ± 44.5	135.8 ± 63.5	0.061 [b]
	Mean difference	12.1 ± 27.2	-3.3 ± 42.1	0.233 [b]
	p-value	0.034 [a]	0.247 [a]	
LDL (mg/dL)	Before intervention	124.7 ± 22.3	132.8 ± 22.5	0.486 [b]
	After intervention	116.1 ± 25.8	122.7 ± 26.0	0.436 [b]
	Mean difference	8.5 ± 17.2	10.1 ± 24.5	0.806 [b]
	p-value	0.093 [a]	0.393 [a]	
HDL (mg/dL)	Before intervention	53.9 ± 18.2	55.8 ± 17.6	0.653 [b]
	After intervention	51.4 ± 15.4	52.1 ± 18.5	0.838 [b]
	Mean difference	2.5 ± 6.1	3.7 ± 15.5	0.486 [b]
	p-value	0.172 [a]	0.333 [a]	
CRP (mg/dL)	Before intervention	± 0.9	0.3 ± 0.4	0.011 [b]
	After intervention	0.4 ± 0.5	0.6 ± 0.6	0.461 [b]
	Mean difference	0.7 ± 0.9	-0.3 ± 0.8	0.003 [b]
	p-value	0.019 [a]	0.099 [a]	

FBG: Fasting Blood Glucose; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; CRP: C-reactive protein.

p-value[a] is reported based on the analysis of paired sample t-test (between baseline and after 8 weeks)

P-value[b] is reported based on the analysis of independent sample t-test (between curcumin + diet and placebo + diet)

4. Discussion

To our knowledge, this is the first study to examine the effects of anthropometric and biochemical parameters of curcumin supplementation added to diet in women with PCOS. Our study showed that 8 weeks administration of oral curcumin supplementation added to diet in PCOS women revealed a significant effect on parameters of glycemic status, body weight, waist circumferences and body fat mass.

Type 2 diabetes is a common condition also characterized by insulin resistance and compensatory

Table 3. Serum hormone levels of participants with PCOS at the baseline and after 8 weeks of curcumin supplementation to diet

Variable	Measurement period	Curcumin + Diet Group	Placebo + Diet Group	p-value
FSH (mIU/mL)	Before intervention	4.9 ± 2.2	5.7 ± 2.1	0.202 [b]
	After intervention	4.8 ± 1.8	4.4 ± 3.6	0.436 [b]
	Mean difference	0.1 ± 2.6	1.3 ± 5.1	0.067 [b]
	p-value	0.460 [a]	0.191 [a]	
LH (mIU/mL)	Before intervention	12.2 ± 8.2	14.2 ± 7.8	0.436 [b]
	After intervention	11.1 ± 4.9	13.8 ± 7.6	0.267 [b]
	Mean difference	1.2 ± 8.3	1.3 ± 5.2	0.624 [b]
	p-value	0.532 [a]	0.117 [a]	
SHBG (nmol/L)	Before intervention	55.5 ± 47.6	82.4 ± 69.9	0.116 [b]
	After intervention	55.3 ± 47.1	81.1 ± 69.8	0.148 [b]
	Mean difference	0.1 ± 0.9	1.4 ± 4.7	0.174 [b]
	p-value	0.691 [a]	0.150 [a]	
Testosterone (ng/L)	Before intervention	1.8 ± 0.7	1.8± 1.2	0.624 [b]
	After intervention	2.0 ± 0.9	1.7± 1.3	0.174 [b]
	Mean difference	0.3 ± 0.8	0.2 ± 1.4	0.345 [b]
	p-value	0.255 [a]	0.459 [a]	
DHEAS (µg/dL)	Before intervention	260.2 ± 91.6	232.1 ± 84.1	0.161 [b]
	After intervention	245.5 ± 100.7	219.1 ± 80.1	0.683 [b]
	Mean difference	14.7 ± 85.6	12.9 ± 29.3	0.174 [b]
	p-value	0.280 [a]	0.136 [a]	

FSH: follicle-stimulating hormone, LH: luteinizing hormone, DHEAS: dehydroepiandrosterone-sulfate and SHBG: Sex Hormone Binding Globulin

p-value[a] is reported based on the analysis of paired sample t-test (between baseline and after 8 weeks)

P-value[b] is reported based on the analysis of independent sample t-test (between curcumin + diet and placebo + diet)

hyper-insulinaemia. Long-term studies have discovered a higher incidence of type 2 diabetes in women with a past history of PCOS compared to control populations. If insulin resistance and hyper-insulinaemia have an important role in determining ovarian morphology, it can be hypothesized that polycystic ovaries and their clinical expression will be more frequent in women with type 2 diabetes (23). The effects of curcumin in a wide spectrum including anti-inflammatory, antioxidant, anticarcinogenic, antimutagenic, anticoagulant, antidiabetic, antibacterial, antiviral and nerve sparing have been reported (24). Curcumin has been reported to have antidiabetic effect in type 2 diabetes patients and in many diabetic animal models. In a study, adding curcumin to the diets of obese rats was found to improve the symptoms of diabetes and insulin resistance; and also relieve low-grade chronic inflammation, increase anti-inflammatory adiponectin production and reduce hepatic NF-kB activity. Therefore, the effects of curcumin supplementation on

lowering inflammation and improving glycemic status have been reported when blood glucose levels are evaluated in obese rats (4). In another study performed with curcumin supplementation with a high-fat diet for 28 weeks, blood glucose levels improved, inhibition of hepatic gluconeogenesis and increased insulin sensitivity were observed (25).

One of the human studies reported reduction in HOMA-IR, HbA1c and FBG levels following 300 mg/day curcuminoids supplementation for 3 months in overweight diabetic subjects (24). In contrast, Sohaei et al. (26) showed that 6 weeks administration of oral curcumin in women with PCOS did not support any significant effect on parameters of glycemic status except insulin level and also quantitative insulin sensitivity check index (QUICKI) which improved significantly in the curcumin group based on within-groups analyses. Similarly, another study reported that 6 weeks supplementation with 294 mg highly bioavailable curcuminoids did not change glucose homeostasis (27). In a randomized double-blind placebo-controlled trial of curcumin in the prevention of type 2 diabetes, 240 volunteers with prediabetes criteria were evaluated by giving them curcumin supplementation. The results showed that HOMA and C-peptide values were lower in the curcumin supplemented group than the placebo group, and it was reported that it could be useful to take precautions for the prediabetic population (28).

On the other hand, PCOS patients suffer from impaired insulin secretion which carries an associated risk of progression to type 2 diabetes that has an earlier onset compared to normal population. Insulin resistance is commonly found in various pathophysiological states, including type 2 diabetes and obesity. Park et al. (29) reported that women with PCOS have significant insulin resistance which is independent of adiposity. Curcumin administration in rats decreased glucose and glycated hemoglobin (HbA1c) levels by improving β-cell function and insulin secretion (30, 31), improving glucose homeostasis (32), suppressing gluconeogenic enzymes (33), and by recruiting glucose transporters to the cell surface (34). Jamilian et al. (35) found that curcumin, compared with the placebo, significantly reduced fasting glucose, serum insulin, insulin resistance, and significantly increased insulin sensitivity in women with PCOS. Nevertheless, in clinical practice, studies based on turmeric and curcumin supplementation delivered controversial results. For example, in type 2 diabetes subjects, curcumin supplementation of 300 mg/day has been shown to be effective to reduce fasting plasma glucose (24). However, this effect was not observed in other clinical trials conducted with type 2 diabetes subjects (36) and in individuals with diabetic nephropathy treated with 1.5 g of curcuminoids per day (37). This is just one example of how many factors like ethnicity, dose, type of curcuminoids employed, and the bioavailability of curcumin are crucial to obtain reliable and reproducible results through a good study design (38). In a recent study, Sohaei et al. (26) reported that curcumin supplementation might be beneficial for improving serum insulin and QUICKI in women with PCOS. Significant changes in FBG serum insulin and HOMA-IR were observed by curcumin supplementation added to diet.

Based upon previous studies, curcumin supplementation could influence anthropometric measures, especially weight reduction (39, 10). A study in women with PCOS showed that curcumin significantly decreased weight and BMI (35). In overweight and obese subjects with type 2 diabetes, the oral intake of curcumin (300 mg/daily) decreases fasting blood glucose, HbA1c, HOMA-IR index, levels of triglycerides, and an increase in lipoprotein lipase (LPL) activity after 3 months of treatment is observed (24). In another study, 6 months of curcumin supplementation (1.5 g/daily) decreased serum triglycerides, uric acid, visceral fat, total body fat, and IR (assessed by HOMA-IR) in type 2 diabetes subjects. These effects were associated with a decrease in adiponectin levels and high concentrations of leptin in serum (36). In a recent meta-analysis, curcumin supplementation revealed a significant reduction in BMI, weight and WC levels (40). Similary, a significant reduction was found in BMI, weight, fat mass and WC levels in curcumin groups. However, some studies did not observe such useful effects of curcumin intake on BMI and body weight. For instance, anthropometric parameters such as BMI, weight, waist and hip circumference, and total body fat were not affected after the intake of curcumin at a dosage of 1 g/day in obese people (41).

In a study evaluating CRP as an indicator of inflammation, rats fed with a high-fat diet to observe the association of curcumin with cardiovascular diseases were administered 20 mg/kg of curcumin daily for 3 months. According to the results of the study, it has been reported that curcumin supplementation provides a decrease in CRP levels in rats fed with a fatty diet (42). In our study, a significant difference was found in CRP levels in curcumin group. Hyper-lipidemia plays a key role in a number of diseases such as diabetes, inflammation, obesity and atherosclerosis which is more pronounced in women with PCOS. In a study by Moohebati et al. (43), it was reported that four-week supplementation of 1000 mg/day of curcuminoids was not associated with any signifi-cant alteration in LDL-cholesterol concentrations in dyslipidemic obese people. In a similar study, it was found that there was no change in LDL concentrations as a result of curcumin supplementation, but a significant hypotriglyceridemic effect was shown (44). In our study, the initial LDL-cholesterol, triglyceride and total cholesterol levels of most of the patients were close to normal values. However, total cholesterol and triglyceride levels decreased significantly in the group receiving curcumin supplementation, and there was no significant decrease in lipid levels in the placebo group. Similar to our findings, Jamilian et al. (35) found that taking curcumin was associated with a significant reduction in total cholesterol, LDL-cholesterol and to-tal-/HDL-cholesterol ratio, and a significant increase in HDL-cholesterol levels compared with the placebo. Also, in a study on Letrozole induced PCOS in female Wistar rats, curcumin displayed its antihyperlipidemic action by considerably decreasing serum total cholesterol, triglyceride, LDL- cholesterol while increasing HDL-cholesterol levels (4). On the other hand, meta-analysis and a systemic review of randomized controlled studies on the effects of curcumin supple-mentation on blood lipid profile reported that curcum-in supplementation had no effect on total cholesterol, HDL, LDL and TG levels. It has been reported that this result may be due to heterogeneous populations and short-term studies, and longer-term studies are needed (44).

High circulating insulin levels resulting from in-sulin resistance stimulate ovarian androgen production both via direct actions on the ovary and by stimulating the release of luteinizing hormone (LH). Hyperinsulinemia may also enhance the bioavailability of androgens by reducing sex hormone binding globulin (SHBG) and thus increasing the level of free androgens. Also, visceral obesity is a major cause for age-related insulin resistance and a risk factor for metabolic syndrome. Hyperandrogenemia is also one of the features of PCOS in women contributing to reduced fertility, and insulin-sensitizing agents or anti-androgens improve ovarian performance (45). Curcumin is effective on the reproductive system with both protective and anti-androgenic effects. In one of the studies, curcumin (100 mg/kg body weight) has been reported to show decreased protective testoster-one levels such as using metrodozol (46). In addition, damage caused by excessive chromium and cadmium intake and falling testosterone levels were found to be maintained by the application of curcumin (47).

In a study examining the effect of curcumin on serum estrogen, progesterone, LH and FSH values in diabetic rats due to antioxidant and hypoglycemic properties (using 100 and 200 mg/kg curcumin for 25 days), estrogen, progesterone, LH and FSH levels were found increased in both curcumin supplemented groups. Curcumin has been reported to be effective in achieving hormonal healing in diabetic patients (48). In the current study, hormone levels were not improved significantly in the curcumin group. Inano et al. (49) found that when curcumin was added to rats' diet, LH levels were observed to increase, yet prolactin and FSH levels were observed to show no change. In a similar study, it was reported that no change in LH and FSH values was observed in rats with 1% curcum-in added to their diets (50).

Some of the limitations of this study were the small sample size and the duration of the supplementation. The major limitation is that the eight weeks intervention period might not be sufficient to assess all the potential effects of curcumin.

In conclusion, we found that curcumin supplementation added to diet in women with PCOS improved anthropometric measurements and glysemic parameters. Curcumin has not restored the hormone and lipid profile in women with PCOS. Longer use of curcumin may be required in order to observe

changes in hormone and lipid profiles. Our results support that curcumin supplementation may be useful in weight control and glucose metabolism in women with PCOS. Additional studies with larger numbers of patients, longer period of treatment, and different genetic backgrounds are required to determine a definitive improvement in the clinical conditions.

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