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Effects of supplementation with curcumin on serum adipokine concentrations: A randomized controlled trial

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ABSTRACT

Objective: Previous experimental studies have suggested curcumin as a safe phytochemical that can improve insulin resistance through effects on adiponectin and leptin. This study aimed to investigate the effect of curcumin on circulating adiponectin and leptin concentrations in patients with metabolic syndrome.

Methods: In this pilot, randomized, double-blind, placebo-controlled trial, subjects who met the criteria of metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Panel III criteria were randomly assigned to curcumin (n = 59; 1000 mg/d) or a placebo (n = 58) for 8 wk. Serum adiponectin and leptin concentrations were determined before and after intervention. The pooled effect size for the impact of curcumin supplementation on serum adiponectin and leptin levels was also estimated using random-effects metaanalysis.

Results: Eight-week supplementation with curcumin was associated with a significant increase in serum adiponectin levels ($P < 0.001$) and a reduction in serum leptin concentrations ($P < 0.001$). Serum leptin:adiponectin ratio was also improved by curcumin ($P < 0.001$). These beneficial effects of curcumin remained significant after adjustment for changes in serum lipids and glucose concentrations and baseline differences in body mass index and serum levels of glucose and glycated hemoglobin as potential confounders of treatment response. Metaanalysis suggested that curcumin supplementation can increase adiponectin levels by 76.78% (95% CI: 6.14–147.42; $P = 0.0330$), and reduce leptin by 26.49% (95% CI: −70.44 to 17.46), however this latter effect size did not reach statistical significance ($P = 0.238$).

Conclusions: Curcumin can improve serum levels of adiponectin and leptin in patients with metabolic syndrome. This trial was registered at the UMIN Clinical Trials Registry (http://www.umin.ac.jp/ctr/) under Trial No. UMIN000018339.

Introduction

Metabolic syndrome (MetS), also known as syndrome X, is a cluster of several cardiometabolic risk factors, including abdominal adiposity, hyperglycemia, hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C), and hypertension [1,2]. MetS prevalence ranges between 10% and 84% worldwide. According to Azimi-Nezhad et al., 55.0% of Iranian females and 30.1% of Iranian males have MetS [3]. Insulin resistance and

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visceral adiposity are the key factors underlying MetS pathophysiology. Visceral adipose tissue acts as an endocrine organ and releases different kinds of cytokines named adipokines. These adipokines mediate multiple processes such as insulin sensitivity, oxidative stress, and inflammation; hence their imbalance could contribute to the development of type 2 diabetes mellitus and atherosclerosis.

Adiponectin and leptin are the most studied adipokines, and their levels are known to be altered in patients with MetS. Adiponectin is a cardioprotective adipokine with antiinflammatory properties that improve lipid and glucose metabolism, increase insulin sensitivity [4], and prevent atherogenesis [5]. Several observational studies have reported an inverse association between circulating adiponectin concentrations and body weight, total cholesterol, triacylglycerols, blood pressure, and insulin resistance, and a positive association with HDL-C levels [6,7]. Leptin is another adipokine with a pivotal role in the regulation of energy balance in the body [8]. Plasma concentrations of leptin increase with adiposity and correlate with insulin resistance [9,10]. Elevated plasma levels of leptin have been suggested as an independent risk factor for coronary artery disease [10,11].

Curcumin is the orange-yellow pigment extracted from the famous spice turmeric. Curcumin is a unique phytochemical, owing to its numerous molecular targets and diversity of biological activities. The efficacy of curcumin supplementation has been shown against a wide range of diseases, including anxiety and depression [12,13], osteoarthritis [14,15], MetS [16], dyslipidemia [17–19], atherosclerosis [20,21], chronic complications due to sulfur-mustard intoxication [22–25], solid tumors [26], inflammation [27], oxidative stress [28], and non-alcoholic fatty liver disease [29].

Interestingly, curcumin could modify almost all features of MetS [30]. There is evidence indicating that curcumin lowers plasma levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), triacylglycerol, and glucose, and increases those of HDL-C [19,31–35]. Insulin-sensitizing [36–39], antiobesity [40–42], and antihypertensive [43] effects of curcumin are other properties of this natural product reported in experimental studies. Experimental studies have also identified adiponectin and leptin as targets of curcumin [44,45]. However, clinical evidence on the impact of curcumin supplementation on circulating levels of these two adipokines has been scarce. Hence, this study aimed to evaluate changes in serum levels of adiponectin and leptin as well as the ratio of these two adipokines after curcumin supplementation in patients with MetS. A secondary aim was to pool the results of clinical trials to estimate the effect size for the impact of curcumin on circulating adiponectin and leptin concentrations.

Materials and methods

Subjects

This study is a post-hoc analysis performed on the samples obtained from our previous investigation [17]. Participants were recruited from the Cardiology and Endocrinology Clinics of the Baqiyatallah Hospital (Tehran, Iran). Inclusion criteria were males and females who were not originally receiving lipid-lowering therapy, and for whom a diagnosis of MetS was made according to the criteria defined by the National Cholesterol Education Program Adult Treatment Panel III guidelines, which require ≥3 of the following conditions: waist circumference ≥102 cm (male) or ≥88 cm (female), blood pressure ≥130/85 mmHg, triacylglycerols ≥1.7 mmol/L, HDL-C <1.03 mmol/L (males) or <1.29 mmol/L (females), and fasting blood glucose ≥6.1 mmol/L [46].

Exclusion criteria were pregnancy or breast-feeding, lack of compliance with the study medication (defined as not using the medication for >1 wk), participation in a concomitant trial, hypersensitivity to the study medication, presence of malignancies, and inability to give informed consent. The study protocol was given approval by the Institutional Ethics Committee and written informed consent was obtained from participants.

Study design

This study was designed as a randomized, double-blind, placebo-controlled trial with a parallel-group design. Subjects who met the inclusion criteria were randomly assigned to either curcumin (Curcumin C3 Complex, Sami Labs Ltd., Bangalore, India; n = 59) or a matched placebo (n = 58) for a period of 8 wk. Curcumin was administered at a daily dose of 1 g (500 mg twice daily) based on the use of the same dose in our previous trial in obese individuals [19]. To improve the bioavailability of curcumin, 5 mg piperine (BioPerine, Sami Labs Ltd., Bangalore, India) was added to each 500-mg curcumin capsule [47]. The C3 Complex (Sami Labs Ltd.) preparation that was used in the present study contained three major curcuminoids (i.e., curcumin, demethoxycurcumin, and bisdemethoxycurcumin) in a patented ratio. Placebo capsules contained the same amount of lactose plus 5 mg piperine. This trial was registered at the UMIN Clinical Trials Registry (http://www.umin.ac.jp/ctr/) under Trial No. UMIN000018339.

Blood sampling

Overnight fasting blood samples were collected at baseline and at study end. The samples were allowed to clot for about 30 min and then centrifuged at 750 *g* for 10 min to obtain serum. Sera were aliquoted and frozen at −80°C until measurement.

Measurements

Serum concentrations of leptin and adiponectin were determined using the enzyme linked immunoassay technique with commercial kits (eBioscience, San Diego, CA, USA). Weight, height, and systolic and diastolic blood pressures were measured according to standard procedures [48]. BMI was calculated as weight in kilograms divided by height in meters squared.

Statistical analyses

Statistical analyses were performed using the SPSS 11.5 software (IBM, Armonk, NY, USA). Data were expressed as mean ± standard deviation (SD) or number (%). Within-group comparisons were performed using paired samples *t* test (for normally distributed data) or the Wilcoxon signed-rank test (for nonnormally distributed data). Between-group comparisons were performed using independent sample *t* test (for normally distributed data) or the Mann-Whitney U test (for nonnormally distributed data). Categorical variables were compared using the χ^2 test.

Bivariate correlations between changes in serum levels of leptin, adiponectin, and leptin:adiponectin ratio were performed using Pearson's (for normally distributed data) and Spearman's (for nonnormally distributed data) correlation coefficients. Univariate analysis of covariance using a general linear model was used to adjust for the effect of potential confounders on the association between curcumin supplementation and changes in serum levels of adiponectin, leptin, and leptin:adiponectin ratio.

Quantitative data synthesis

Pooled analysis was performed using the Comprehensive Meta-Analysis V2 software (Biostat, Englewood, NJ, USA) [49]. Circulating adiponectin and leptin concentrations were collated in ng/mL. SDs at one time-point were calculated with the formula SD = SEM × $\sqrt{n}$ (SEM: standard error of the mean, *n*: number of participants). SDs of the mean difference were calculated using the formula square root [$(SD_{pretreatment})^2 + (SD_{posttreatment})^2 - (2\ R \times SD_{pretreatment} \times SD_{posttreatment})$], assuming a correlation coefficient (R) = 0.5. Net changes in measurements (change scores) were calculated as follows: (measure at end of follow-up in the treatment group − measure at baseline in the treatment group) − (measure at end of follow-up in the control group − measure at baseline in the control group). A random-effects model and the generic inverse variance method were used owing to the heterogeneity of studies in terms of design (parallel or crossover), dosage and formulation of curcumin, and interstudy variations in the inclusion criteria (underlying disease, age, sex, and anthropometric indices).

Results

One hundred seventeen subjects met the inclusion criteria and were assigned to either curcumin (n = 59) or placebo (n = 58). One hundred subjects completed the trial. Nine subjects in the curcumin group and eight subjects in the placebo group

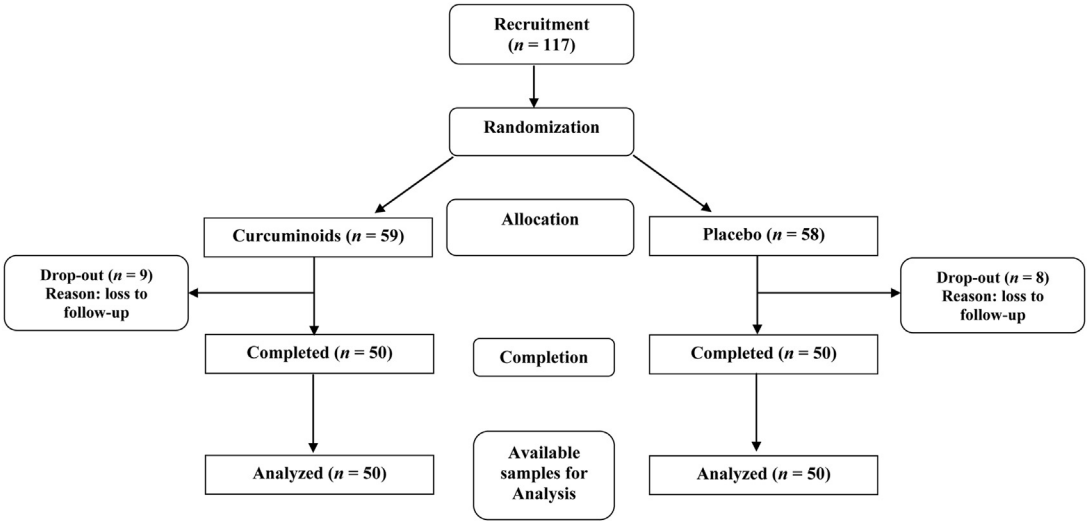

Fig. 1. Flow chart of the trial.

did not complete the study due to loss to follow-up (Fig. 1). The number of drop-outs was not different between the study groups.

Curcumin and placebo groups were comparable at baseline with respect to age, sex, smoking frequency, systolic blood pressure, and diastolic blood pressure. However, BMI ($P = 0.002$) and serum levels of glucose ($P < 0.001$) and glycated hemoglobin (HbA1c) ($P = 0.035$) concentrations were higher in the curcumin group (Table 1). There was also no significant difference between the curcumin group and placebo group in terms of baseline serum adiponectin ($P = 0.795$) and leptin ($P = 0.292$) concentrations and leptin:adiponectin ratio ($P = 0.526$). Within-group analysis revealed a significant increase in serum adiponectin concentrations and reduction in leptin:adiponectin ratio in both curcumin ($P < 0.001$) and placebo ($P < 0.001$) groups. Serum leptin concentrations were reduced in the curcumin group ($P < 0.001$) but did not change significantly in the placebo group ($P = 0.078$) (Table 2).

Between-group comparison of the change values revealed a significant elevation of serum adiponectin ($P < 0.001$) and a significant reduction of serum leptin concentrations ($P < 0.001$) in the curcumin compared with the placebo group. Likewise, the serum leptin:adiponectin ratio was significantly reduced in the curcumin versus placebo group ($P < 0.001$) (Table 2).

To check the effect of changes in serum lipids and glucose as potential confounders in the observed changes in adipokines, univariate analysis of covariance was performed. Assignment to treatment group (yes or no) and changes in serum levels of LDL-C, HDL-C, total cholesterol, triacylglycerols, Lp(a), and glucose were separately entered into the model as independent variables. Another adjustment was also performed for baseline differences in BMI and serum concentrations of glucose and HbA1c. According to the results, the impact of curcumin supplementation on dependent variables including changes in serum concentrations of adiponectin ($P < 0.001$), leptin ($P = 0.044$), and leptin:adiponectin ratio ($P = 0.001$) remained statistically significant after adjustment for potential confounders. The impact of curcumin supplementation on the aforementioned efficacy measures also remained significant after adjustment for baseline differences in BMI, serum glucose, and HbA1c concentrations ($P < 0.001$).

As described in our previous report [17], curcumin was well tolerated during the study. There were two reports of diarrhea, two reports of constipation, one report of headache, and two reports of skin rash in the curcumin group. Headache (n = 2) and constipation (n = 1) were reported adverse events in the placebo group. None of the drop-outs in this trial were due to the aforementioned adverse events.

Bivariate correlations

Changes in serum adiponectin concentrations were correlated with changes in HDL-C ($P = 0.002$), whereas changes in serum leptin levels and serum leptin:adiponectin ratio were not found to be associated with any of the assessed parameters. In the placebo group, changes in serum adiponectin ($P = 0.010$) and leptin:adiponectin ratio ($P = 0.004$) were significantly correlated with triacylglycerol changes. There was no significant correlation between changes in serum adiponectin and leptin concentrations in either of the studied groups (Table 3).

Table 1
Baseline characteristics of study groups

Parameter	Curcumin	Placebo
Age (y)	44.80 ± 8.67	43.46 ± 9.70
Female	23 (46%)	27 (54%)
Smoking	12 (24%)	8 (16%)
BMI (kg/m^2)	25.46 ± 2.46	22.80 ± 5.37
SBP (mmHg)	135.56 ± 13.16	135.70 ± 14.74
DBP (mmHg)	88.34 ± 7.81	88.72 ± 8.18
Hs-CRP (g/L)	6.52 ± 2.16	7.10 ± 1.80
Adiponectin (ng/mL)	12.67 ± 2.13	12.78 ± 2.19
Leptin (ng/mL)	22.02 ± 2.93	22.64 ± 2.97
Leptin:adiponectin	1.77 ± 0.32	1.82 ± 0.37
LDL-C (mg/dL)	190.46 ± 20.05	157.10 ± 17.29
HDL-C (mg/dL)	31.50 ± 4.67	35.48 ± 6.54
Total cholesterol (mg/dL)	220.29 ± 37.72	184.08 ± 17.37
Triacylglycerols (mg/dL)	199.60 ± 23.44	185.64 ± 38.49
Lp(a) (mg/dL)	82.00 ± 7.35	84.48 ± 8.47
Glucose (mg/dL)	155.46 ± 40.89	136.98 ± 52.40
HbA1c (%)	6.69 ± 1.44	6.07 ± 1.33

BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); SBP, systolic blood pressure

Table 2
Changes in serum adipokines concentrations during the trial

Parameter	Curcumin			*P* value*	Placebo			*P* value*	*P* value†
	Before	After	Change		Before	After	Change		
Adiponectin (ng/mL)	12.67 ± 2.13	21.28 ± 4.40	8.61 ± 4.31	<0.001	12.78 ± 2.19	15.97 ± 2.69	3.19 ± 3.36	<0.001	<0.001
Leptin (ng/mL)	22.02 ± 2.93	17.50 ± 2.42	−4.52 ± 3.72	<0.001	22.64 ± 2.97	21.56 ± 3.82	−1.08 ± 4.25	0.078	<0.001
Leptin:adiponectin	1.77 ± 0.32	0.86 ± 0.20	−0.92 ± 0.37	<0.001	1.82 ± 0.37	1.39 ± 0.33	−0.43 ± 0.48	<0.001	<0.001

* Comparison of before versus after values in each group.
† Comparison of changes between the study groups.

Quantitative data synthesis

Metaanalysis of data from three RCTs (including the present study) using a random-effects model showed that curcumin supplementation can increase plasma adiponectin (weighted mean difference: 76.78%, 95% CI: 6.14–147.42; $P = 0.0330$). With respect to plasma leptin concentrations, a reduction by 26.49% was calculated (95% CI: −70.44 to17.46), yet this effect size did not reach statistical significance ($P = 0.238$) (Fig. 2).

Discussion

The findings of this randomized, controlled trial suggested a significant increase in serum levels of adiponectin and reduction in serum levels of leptin after 8 wk of supplementation with curcumin in patients with MetS. To the best of the authors' knowledge, this is among very few studies dealing with the effect of curcumin on adipokines and the first to explore this issue in patients with MetS. In a trial among subjects with prediabetes, supplementation with curcumin (1500 mg/d) for 9 mo was reported to increase plasma adiponectin concentrations by 23.5% [50]. In another study in patients with type 2 diabetes, 6-mo supplementation with curcumin (1500 mg/d) reduced plasma leptin levels by 65% and increased adiponectin by 152% [51]. In contrast with these results, in another trial in patients with major depressive disorder, 8-wk supplementation with curcumin (1000 mg/d) was found to increase plasma leptin levels by 23%, though this increase did not reach statistical significance [52].

Insulin resistance is defined as impairment of insulin action on glucose, lipid, and protein metabolism. It is closely associated with adipose tissue. Excessive visceral and subcutaneous adipose tissue causes adipocyte dysfunction, which can lead to inflammation through activation of JNK and NFκB. Inflammation causes impaired adipokine secretion, reflected as decreased adiponectin and increased leptin levels [53,54]. Adiponectin and leptin mediate insulin sensitivity through AMPK (5′AMP-activated protein kinase) pathway. AMPK is a master switch that controls energy status in the cell, and its activation leads to enhanced β to oxidation and reduced fatty acid esterification to triacylglycerols [55]. Moreover, several studies have suggested that leptin:adiponectin ratio could serve as a useful index of insulin resistance and atherogenic risk in both diabetic and non-diabetic populations [56–58]. There are also reports showing the association between leptin:adiponectin ratio and low-grade inflammation, carotid intima media thickness, arterial stiffness, first cardiovascular event, and number of MetS components [59,60].

Some previous studies have revealed that curcumin could decrease insulin resistance by increasing fatty acid oxidation. Na et al. indicated that curcumin improves insulin resistance in skeletal muscles through activation of AMPK and fatty acid β-oxidation [60]. These findings were approved in a later trial in patients with type 2 diabetes [61]. Similarly, in an experimental study on C57BL/6J mice, it was indicated that curcumin can improve insulin resistance through inhibiting the expression of lipogenic genes and inflammation in the adipose tissue [41]. In another experimental study, Weisberg et al. reported that curcumin ameliorates inflammation due to visceral adiposity, and this effect is accompanied by adiponectin elevation and mitigation of insulin sensitivity [42]. There is also in vitro evidence indicating that curcumin blocks leptin-signaling and prevents hyperlipidemia-induced oxidative stress, hepatic stellate cell activation, and liver fibrogenesis [63]. The favorable impact of curcumin supplementation on adiponectin and leptin in this

Table 3
Bivariate correlations between changes in serum adiponectin, leptin, and leptin:adiponectin ratio with serum lipids and glucose

Parameter	Adiponectin		Leptin		Leptin:adiponectin	
	r	*P*	*r*	*P*	*r*	*P*
Curcumin group						
TC	0.231	0.114	−0.104	0.481	−0.186	0.205
LDL-C	0.298	0.036	−0.008	0.958	−0.220	0.124
HDL-C	0.430	0.002	−0.108	0.455	−0.250	0.080
TG	0.123	0.396	0.082	0.573	0.054	0.707
Lp(a)	0.051	0.727	−0.095	0.510	0.006	0.969
Glucose	−0.245	0.086	0.061	0.674	0.184	0.201
Placebo group						
TC	0.144	0.318	0.109	0.450	−0.052	0.722
LDL-C	0.022	0.881	0.007	0.962	−0.009	0.951
HDL-C	0.095	0.510	−0.044	0.760	−0.069	0.636
TG	−0.363	0.010	0.165	0.252	0.397	0.004
Lp(a)	0.108	0.456	−0.010	0.943	−0.074	0.609
Glucose	0.206	0.151	0.073	0.614	−0.084	0.561

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); TC, total cholesterol; TG, triacylglycerols
Bivariate correlations were assessed using Pearson's (for normally distributed data) and Spearman's (for non-normally distributed data) correlation coefficients

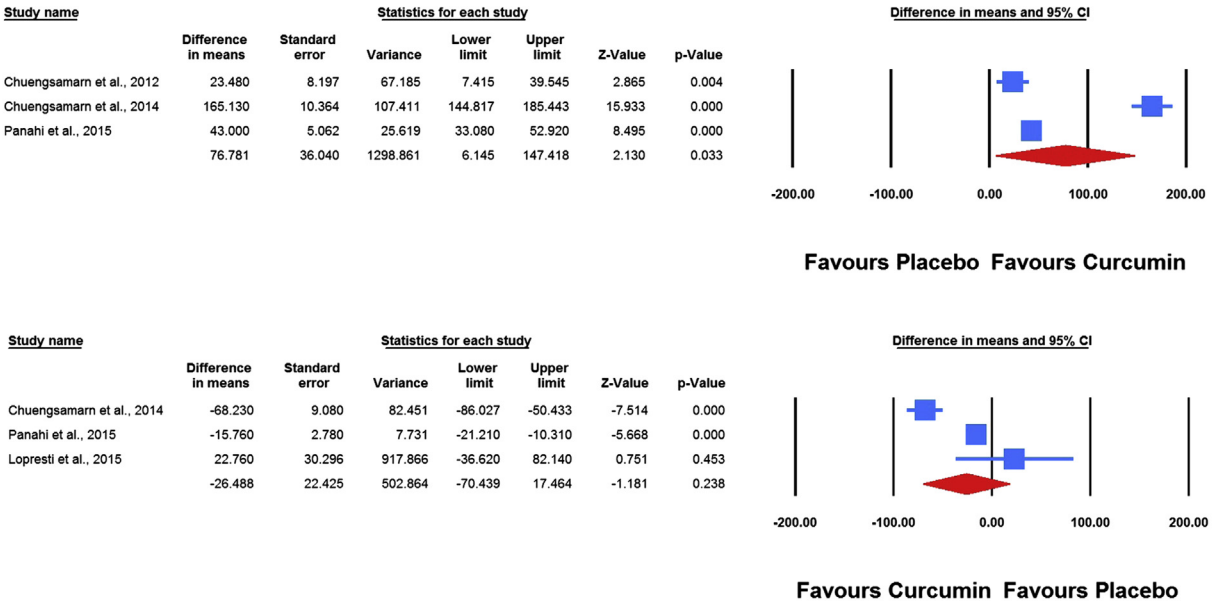

Fig. 2. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of curcumin on circulating adiponectin (upper plot) and leptin (lower plot) concentrations. The pooled effect size is shown as red diamond. There was significant pooled effect of curcumin on adiponectin concentrations, whereas for leptin meta-analysis (in which the red diamond crosses the vertical line that corresponds to the value of zero), the pooled effect did not reach statistical significance.

study is consistent with the reduction in serum glucose of the same individuals reported previously [16]. In our previous report, however, no significant effect could be detected in HbA1c, which might be due to the short duration of follow-up.

Aside from insulin resistance, dyslipidemia is another prevalent feature of MetS, commonly presented as low HDL-C concentrations and elevated levels of triacylglycerols. This phenotype is referred to as atherogenic dyslipidemia and is a promoter of insulin resistance. The beneficial effects of curcumin on lipid indices has been reported in our previous report from the same trial, indicating reductions in LDL-C, triacylglycerols, and Lp(a), and elevations in HDL-C [17]. This lipid-modifying effect of curcumin has also been reported in some other trials [19,51,62].

As reported previously [16,17], curcumin supplementation was safe in this trial. Curcumin has been approved by the US Food and Drug Administration as a supplement "generally recognized as safe," and its tolerability has been confirmed in several clinical studies. Therefore, owing to its safety and beneficial effects on several features of MetS, curcumin may be suggested as a routine supplement for patients with MetS.

Hitherto, several lines of evidence have suggested adiponectin as a key player in limiting the pathogenesis of obesity-related diseases including MetS, non-alcoholic fatty liver disease, and cardiovascular disease. The protective effects of adiponectin in reducing the risk of cardiometabolic diseases could be attributed to improvement of lipid and glucose metabolism as well as antioxidant, antiinflammatory, antithrombotic, antihypertensive, and antiatherosclerotic actions of this adipokine [64]. These beneficial effects are mediated by the capacity of these adipokines to interact with important mediators, signaling molecules, or pathways involved in cardiometabolic disturbances [65]. Interestingly, curcumin has been shown to have the same multitarget capacity of action, and its capacity to interact with several key regulators such as transcription factors (e.g., NFκB and activator protein 1), enzymes (cyclooxygenases, lipoxygenase, and AMPK), proinflammatory cytokines, acute phase proteins, antioxidants, growth factors, hormones, secondary messengers, and nitric oxide, along with direct effects on adipokines production, could justify the beneficial cardiometabolic effects of this phytochemical [65].

The present study was limited in a number of ways. First, this was a short-term trial, and it is unknown if longer durations of supplementation could cause further improvements in circulating adiponectin and leptin concentrations. Second, this study tested the effects of a single dose of curcumin, hence any dose-response association for the metabolic effects of curcumin remains unclear. Finally, although circulating leptin, adiponectin, and their ratio could serve as indirect biomarkers of insulin resistance, insulin resistance was not measured in this study.

Conclusion

In conclusion, the present trial provided the first evidence on the improvement of circulating adiponectin, leptin, and leptin:adiponectin ratio in patients with MetS. Future studies are encouraged to ascertain the impact of supplementation duration and curcumin dose on the observed beneficial effects and the value of improving adipokine status with curcumin in obese individuals and its plausible association with changes in body weight and fat content. Finally, evaluation of the impact of curcumin on known measures of insulin resistance, including hyperinsulinemic euglycemic clamp, homeostatic model assessment of insulin resistance, and quantitative insulin sensitivity check index is greatly recommended.

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