Comparative Clinical Pathology
https://doi.org/10.1007/s00580-017-2624-y

ORIGINAL ARTICLE

Evaluation of the effects of curcumin in patients with metabolic syndrome

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Received: 17 February 2017 / Accepted: 13 December 2017

Abstract

Curcumin is a yellow pigment derived from rhizomes of turmeric (*Curcuma longa* L.) and can affect multiple components metabolic syndrome (MetS). In the current study, we aimed to evaluate the effects of curcumin on several CVD risk factors, including indices of depression and anxiety in individuals with MetS. This randomized clinical trial was undertaken in the Nutrition Clinic of the Ghaem Hospital. One hundred and twenty subjects (18–65 years old) were randomly assigned to one of three treatment groups: a group receiving phospholipidated curcumin (PC) capsules (1 g/day) for 6 weeks)$n = 40$), a group receiving unformulated curcumin (UC) capsules (1 g/day) for 6 weeks ($n = 40$), and a control group who received a placebo capsule ($n = 40$). Socio-demographic status of all participants was documented using a self-administered questionnaire. Blood samples were collected after a 12-h fasting. All biochemical factors and anthropometric indices were measured in all patients at baseline and after 6 weeks intervention. Complete blood count (CBC), serum levels of FBG, lipid profile, apolipoproteins, and hs-CRP were assessed. Physical activity level was measured using a standard questionnaire. At the beginning and end of study, Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) were completed by all volunteers. According to the self-reported adverse effects, one subject in the PC-treated group reported hypersensitivity. Also, there were reports of cold sore ($n = 1$) and nausea ($n = 1$) in the UC group. Statistical analyses were performed using SPSS software. A total of 109 subjects completed the study. There were no significant differences between the three study groups for any of the variables at baseline, nor after the 6 weeks intervention, including anthropometric indices, serum biochemical factors, systolic and diastolic blood pressures, and CBC. However, subjects with severe anxiety appeared to be significantly improved by treatment with the PC and UC compared with the placebo group ($p = 0.01$). Curcumin supplementation did not improve any of the cardiovascular risk factors associated with MetS.

Keywords *Curcuma longa* · Curcumin · Metabolic syndrome

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Published online: 04 January 2018

Introduction

Metabolic syndrome (MetS) is an important risk factor for cardiovascular disease (CVD) (Grundy et al. 2004). It is defined by a clustering of CVD risk factors that include central obesity, increased blood pressure, insulin resistance, hypertriglyceridemia, decreased plasma high-density lipoprotein cholesterol (HDL-C), and impaired glucose tolerance (Eckel et al. 2005). In addition, individuals with MetS have a significantly higher serum concentration of inflammatory cytokines and a higher prevalence of elevated serum hs-CRP that may be related to their abdominal obesity (Grundy et al. 2004, Eckel et al. 2005, Pan et al. 2012). A growing body of evidence shows that depression is related to MetS (Grundy et al. 2004, Huffman et al. 2009, Den Engelsen et al. 2012). The early screening and coordinated care of patients with depression and MetS (or its components) could alleviate the future risk of diabetes and vascular disease (Grundy et al. 2004).

Previous studies have shown a high prevalence of the MetS in Iran (Fakhrzadeh et al. 2006). The Tehran Lipid and Glucose Study (TLGS) has reported that the prevalence of the MetS is 10.1% among Iranian adolescents, and higher among overweight boys (41.1%) and girls (43%) (Esmaillzadeh et al. 2006), and in Mashhad, Mirhosseini et al. have shown that 6.5% of the total population and 45% of obese adolescent girls have MetS (Mirhosseini et al. 2009).

Whilst the use of statins and anti-hypertensive drugs may be useful in the treatment of MetS, there remains a need to address the residual CVD risk. Phytochemicals are compounds that have several metabolic and health benefits (Karalis 2008, Visioli and Davalos 2011). Curcumin [diferuloylmethane; (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione)] is a plant polyphenol with various positive biological activities. Curcumin is a yellow pigment derived from rhizomes of turmeric (*Curcuma longa* L.). There are two other analogues along with curcumin in turmeric: demethoxycurcumin and bisdemethoxycurcumin that are generally called curcuminoids (Epstein et al. 2010, Lao et al. 2006). There is a large body of biomedical literature on curcumin (Garcia-Toro et al. 2016). Curcumin has been shown to be well tolerated and safe in long-term studies (Dunbar et al. 2008) and is known to be safe up to dose of 10 g/day (Fakhrzadeh et al. 2006, Esmaillzadeh et al. 2006). Curcumin is a multifunctional phytopharmaceutical, having what appears to be beneficial effects on several conditions that include components of MetS and cardiovascular risk factors (Mirhosseini et al. 2009, Karalis 2008, Visioli and Davalos 2011, Epstein et al. 2010, Lao et al. 2006, Strimpakos and Sharma 2008, Jurenka 2009, Shureiqi and Baron 2011, Basile et al. 2009, Panahi et al. 2014a, 2015a, Sahebkar et al. 2013, Mohammadi et al. 2013). Furthermore, the clinical effects of supplementation with curcuminoids on pulmonary function and systemic inflammation were investigated by Sahebkar et al. who found that curcuminoids had a significant effect on several inflammatory mediators under study that included: IL-6, IL-8, TNFα, and hs-CRP (Sahebkar et al. 2013, Panahi et al. 2014b, 2015b).

In the current study, we aimed to evaluate the effects of curcumin on some serum biochemical factors and depression as well as anxiety in subjects with metabolic syndrome.

Materials and methods

Study population and design

This study was a double-blind placebo-controlled trial with a study population initially of 120 patients with MetS who were referred to the Nutrition Clinic of the Ghaem Hospital, Mashhad, Iran. An explanation of the goals and protocols of the study was given to each participant before the study. They received information both in form of verbal explanation and written sheets. The inclusion criteria consisted of an age of 18–65 years and a history of metabolic syndrome in accordance with the IDF (International Diabetic Federation) criteria. A history of known systemic diseases, pregnancy, lactation, and intake of the anti-dyslipidemic, anti-hypertensive, or anti-diabetic drugs as well as nutritional supplements during the course of study were exclusion criteria. Accordingly, 11 volunteers were excluded from the study as a result of reported adverse effects, reluctance to take part in the study, and personal problems. The sample size was determined to be 35 subjects per group (considering $\alpha = 0.05$ and $\beta = 0.02$) using the following formula and changes in serum triglycerides concentrations based on our previous study (Mohammadi et al. 2013):

$$n = \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2 \left(s_1^2 + s_2^2\right)}{\left(\overline{x}_1 - \overline{x}_2\right)^2}$$

This randomized clinical trial was undertaken in the Nutrition Clinic of the Ghaem Hospital, Mashhad, Iran. The flowchart of the study design is shown in Fig. 1. For the purpose of the study, patients were randomly assigned to one of three treatment groups: a group receiving absorption-enhanced curcumin capsules (1 g/day which is equal to 200 mg pure curcumin/day) for 6 weeks)$n = 40$), a group receiving unformulated curcumin capsules (1 g/day) for 6 weeks (n = 40), and the control group who received a placebo capsule containing lactose and starch with a ratio of 2:1 during the study period ($n = 40$).

The participants were asked to take one 500 mg/day capsule, which was contained in an unlabeled bottle, twice a day (total of two capsules per day) for a period of 6 weeks. During this time, all volunteers received nutritional advice about maintaining an iso-caloric diet. One hundred and nine subjects completed the study.

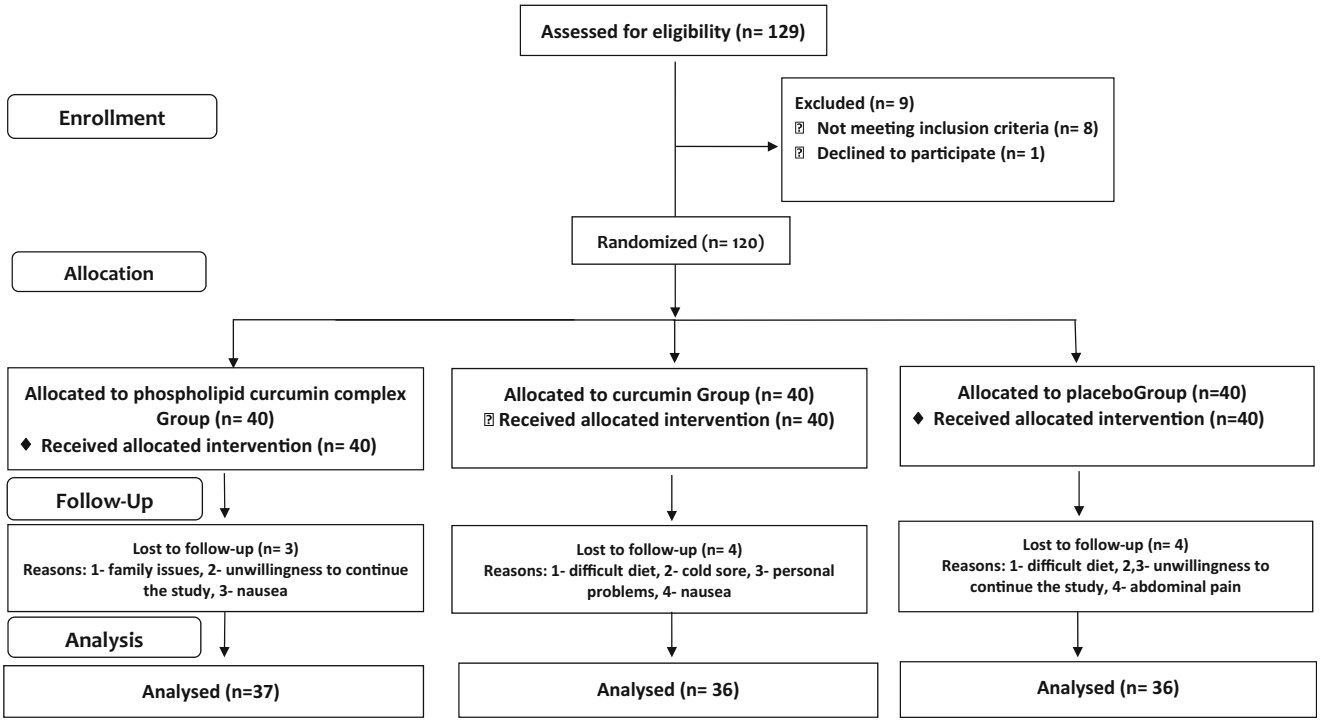

Fig. 1 The flow chart of the study design

Demographic and anthropometric measurements

All participants were asked to complete a self-administered questionnaire that required some information about socio-demographic status, medical history, employment status, alcohol consumption, smoking habit, and exercise. The questionnaire was reviewed by experienced and trained interviewers**.** Waist circumference was measured using standard protocols in all subjects. The height, weight, and body mass index (BMI) as well as percentage of total body fat were measured using a bioelectrical impedance analysis (BIA) device (TANITA BC-418).

Blood sampling

The blood sample of each subject was collected into plain plastic tubes in the morning, after a 12-h fast. The haemolysed samples were excluded from the analysis. After separating serum from blood samples by means of centrifugation at 10000 g for 15 min, aliquots of serum were preserved frozen at − 80 °C to be used in the analysis.

Measurements

The biochemical parameters were measured in all participants at baseline and after 6 weeks of intervention. Systolic and diastolic blood pressures were measured using a standard mercury sphygmomanometer on the left arm in the sitting position following a 15-min rest by a standard procedure. Complete blood count (CBC) was measured using the Sysmex autoanalyzer system KX-21 N in whole blood samples. Serum FBG and lipid profile were assessed using Pars Azmoon kits (Tehran, Iran). Serum apolipoproteins A, B, and Lp(a) as well as hs-CRP levels were measured using Biosystem kits (Barcelona, *Spain*).

Physical activity level

Physical activity level was assessed using a standard questionnaire (Vasconcellos and Anjos 2003), and subjects classified according to the human energy requirement as described below: (1) extremely inactive (PAL < 1.40), (2) sedentary (1.40–1.69), (3) moderately active (1.70–1.99), (4) vigorously active (2.00–2.40), or (5) extremely active (> 2.40) (James and Schofield 1990).

Clinical evaluation and ratings of depression and anxiety

A self-rating scale of depression, the Beck Depression Inventory (BDI), was used in all subjects. Studies suggest that gaining a cut-off score of 10 points in the BDI is a good indicator of depressive symptoms in adults (Vasconcellos and Anjos 2003). The Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) (James and Schofield 1990, Sekita et al. 2013) were completed by the participants at the beginning and at the end of study. The BDI and BAI consist of 21 multiple-choice items, with each item having four options ranked according to severity. A score of 0 to 3 is assigned to each item and the aggregate score is calculated to determine

Table 1 Clinical and biochemical features in subjects at baseline

Variables		Curcumin-phospholipid complex	Curcumin	Placebo	*p* value
Age (years)		40.05 ± 10.48	37.52 ± 9.47	38.59 ± 10.28	0.534
Weight (kg)		84.06 ± 14.67	80.61 ± 11.71	82.12 ± 12.68	0.803
BMI (kg/m^2)		30.66 ± 5.06	30.67 ± 3.57	31.22 ± 4.67	0.828
WC (cm)		103.00 ± 10.24	99.94 ± 9.37	102.49 ± 9.41	0.341
FBG (mg/dl)		95.97 ± 19.97	98.72 ± 27.17	92.82 ± 16.62	0.479
Hs-CRP (mg/l)		3.54 (2.17 to 5.85)	3.75 (2.16 to 5.79)	3.29 (1.97 to 6.49)	0.976
FAT%		34.51 ± 8.07	35.42 ± 6.12	35.21 ± 7.86	0.848
Current Smoking % (*n*)		15.4 (6)	26.3 (10)	13.9 (5)	0.318
DM % (*n*)		10 (4)	10 (4)	2.5 (1)	0.692
Hypertension % (*n*)		27.5 (11)	32.5 (13)	25 (10)	0.750
SBP (mmHg)		120.82 ± 10.24	119.74 ± 11.87	120.26 ± 11.50	0.914
DBP (mmHg)		83.48 ± 9.17	81.26 ± 10.06	81.70 ± 10.76	0.589
MetS-IDF % (*n*)		47.5 (19)	47.5 (19)	45.0 (18)	0.967
CBC					
WBC ($10^3/\mu$)		6.26 ± 1.43	6.37 ± 1.37	6.40 ± 1.33	0.900
RBC ($10^3/\mu$)		4.80 (4.48 to 5.36)	4.65 (4.39 to 5.21)	4.64 (4.47 to 5.15)	0.548
Hemoglobin (g/dl)		12.30 (11.20 to 13.80)	12.30 (11.60 to 13.20)	12.30 (11.50 to 13.30)	0.893
Hematocrit (%)		43.50 (41.00 to 46.40)	44.00 (40.70 to 47.60)	43.30 (40.80 to 44.50)	0.698
MCV (fL)		91.10 (88.70 to 94.30)	93.20 (90.40 to 96.40)	91.00 (87.00 to 96.20)	0.314
MCH (Pg)		25.57 ± 2.78	26.20 ± 3.29	26.03 ± 3.05	0.668
MCHC ($10^3/\mu$)		28.23 ± 1.90	27.88 ± 3.53	28.77 ± 2.46	0.388
RDW (%)		12.90 (12.40 to 13.80)	12.80 (12.40 to 13.40)	13.20 (12.60 to 13.90)	0.465
Platelets ($10^3/\mu$)		227.86 ± 47.30	236.26 ± 71.57	232.08 ± 43.47	0.819
Neutrophils ($10^3/\mu$)		51.07 ± 10.17	53.22 ± 8.85	56.84 ± 8.80	0.037 (post hoc: A&C, $p = 0.011$)
Lymphocytes ($10^3/\mu$)		39.82 ± 7.04	38.92 ± 8.25	37.03 ± 8.02	0.317
Neutrophil/lymphocyte ratio		1.36 ± 0.52	1.48 ± 0.55	1.66 ± 0.63	0.098
HDL-C (mg/dl)		52.23 ± 12.91	53.33 ± 10.55	51.91 ± 10.62	0.844
LDL-c (mg/dl)		152.99 ± 38.84	165.90 ± 38.76	153.78 ± 40.40	0.262
TC (mg/dl)		241.28 ± 51.96	254.12 ± 43.64	242.12 ± 46.83	0.405
TG (mg/dl)		153.50 (102.50 to 217.00)	150.00 (108.25 to 234.25)	158.0 (128.5 to 216.25)	0.935
ApoA (mg/dl)		1.3330 ± 15.96	131.86 ± 13.73	128.72 ± 16.13	0.400
ApoB (mg/dl)		143.15 ± 34.44	157.39 ± 37.41	143.95 ± 30.42	0.133
Lp(a) (mg/dl)		18.67 ± 18.83	29.77 ± 30.68	15.02 ± 15.81	0.014
Physical activity level	Extremely inactive	27 (77.1)	28 (82.4)	33 (84.6)	0.894
	Sedentary	6 (17.1)	4 (11.8)	5 (12.8)	
	Moderately active	–	–	–	
	Vigorously active	–	–	–	
	Extremely active	2 (5.7)	2 (5.9)	1 (2.6)	

Values expressed as mean ± SD for normally distributed data, and median and interquartile range for non-normally distributed data. Between groups, comparisons were assessed by parametric statistical analysis for normal distributed data and nonparametric test for non-normally distributed data

BMI body mass index, *WC* waist circumference, *FBG* fasting blood glucose, *Hs-CRP* high sensitive C-reactive protein, *DM* diabetes mellitus, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *CBC* complete blood count, *WBC* white blood cell, *RBC* red blood cell, *MCV* mean corpuscular volume, *MCH* mean corpuscular hemoglobin, *MCHC* mean corpuscular hemoglobin concentration, *RDW* red cell distribution width, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TC* total cholesterol, *TG* triglyceride, *ApoA* apolipoprotein A, *ApoB* apolipoprotein B, *Lpa* lipoprotein a

the severity of depression and anxiety (Beck et al. 1961, 1988).

Ethical considerations

Written informed consent form was completed by all participants. The Ethics Committee at the Mashhad University of Medical Sciences accepted the study protocol and has been registered in the Iranian Registry of Clinical Trials (IRCT) with a registration number IRCT2014052014521N3.

Statistical analysis

The statistical analyses were performed using SPSS software. The Kolmogorov-Smirnov test was used to assess the normal distribution of variables. The expression of quantitative data took the form of mean ± SD (for variables with normal distribution)

Table 2 Changes in clinical and biochemical features at baseline and after 6 weeks intervention

Difference	Curcumin-phospholipid complex	Curcumin	Placebo	*p* value
Weight (kg)	− 0.21 ± 1.19	− 1.13 ± 2.09	− 0.58 ± 1.94	0.143
BMI (kg/m^2)	− 0.19 ± 0.68	− 0.30 ± 0.76	− 0.10 ± 0.77	0.574
WC (cm)	− 3.53 ± 6.39	− 3.31 ± 4.68	− 3.58 ± 4.23	0.979
FBG (mg/dl)	8.42 ± 13.42	4.96 ± 23.05	7.02 ± 10.57	0.685
Hs-CRP (mg/l)	0.21 (− 1.66 to 1.52)	− 0.32 (− 1.29 to 1.26)	− 0.39 (− 1.35 to 0.67)	0.775
FAT%	− 0.03 ± 2.09	0.33 ± 1.88	0.71 ± 1.44	0.276
SBP (mmHg)	− 4.19 ± 9.61	− 4.22 ± 9.27	− 6.60 ± 12.90	0.654
DBP (mmHg)	− 3.22 ± 8.20	− 3.62 ± 10.37	− 4.92 ± 10.14	0.807
CBC				
WBC (10^3/μ)	− 0.04 ± 1.13	0.03 ± 1.08	− 0.01 ± 1.23	0.956
RBC (10^3/μ)	− 0.11 (− 0.29 to 0.03)	− 0.05 (− 0.22 to 0.11)	− 0.07 (− 0.22 to 0.01)	0.688
Hemoglobin (g/dl)	1.20 (0.40 to 1.50)	1.15 (0.17 to 1.62)	0.90 (− 0.30 to 1.40)	0.624
Hematocrit (%)	− 1.30 (− 2.10 to 0.00)	− 0.75 (− 2.27 to 1.15)	− 0.60 (− 1.70 to 0.60)	0.431
MCV (fL)	− 0.70 (− 1.60 to 0.30)	− 0.05 (− 1.50 to 2.90)	− 0.20 (− 1.60 to 3.00)	0.342
MCH (Pg)	3.2 (2.30 to 3.70)	3.35 (1.67 to 3.92)	3.10 (− 0.50 to 3.50)	0.232
MCHC (10^3/μ)	3.60 (1.80 to 4.10)	3.60 (1.40 to 4.42)	2.30 (0.00 to 4.10)	0.299
RDW (%)	− 0.10 (− 0.50 to 0.20)	− 0.20 (− 0.70 to 0.10)	− 0.20 (− 0.50 to 0.10)	0.862
Platelets (10^3/μ)	3.94 ± 40.08	− 10.60 ± 50.73	5.51 ± 22.91	0.185
Neutrophils (10^3/μ)	2.13 ± 10.05	0.46 ± 9.25	2.60 ± 8.99	0.628
Lymphocytes (10^3/μ)	− 4.09 ± 6.62	− 2.54 ± 6.47	− 6.59 ± 10.01	0.107
Neutrophil/lymphocyte ratio	0.17 (− 0.07 to 0.57)	0.10 (− 0.18 to 0.34)	0.44 (− 0.22 to 0.89)	0.234
HDL-C (mg/dl)	− 0.92 ± 5.53	0.18 ± 8.58	− 2.47 ± 8.10	0.339
LDL-c (mg/dl)	− 7.62 ± 21.46	− 1.19 ± 29.05	− 13.81 ± 26.33	0.151
TC (mg/dl)	− 9.25 ± 2.79	− 4.20 ± 2.95	− 22.08 ± 3.32	0.046 (post hoc: B&C, $p = 0.016$)
TG (mg/dl)	3.00 (− 39.00 to 23.00)	− 8.00 (− 40.00 to 2.00)	− 23.00 (− 59.00 to 4.00)	0.129
ApoA (mg/dl)	− 0.25 ± 10.04	0.78 ± 11.31	− 3.94 ± 12.71	0.198
ApoB (mg/dl)	− 4.38 ± 23.61	− 11.62 ± 21.18	− 14.69 ± 18.52	0.113
Lp(a) (mg/dl)	0.75 ± 3.93	− 1.78 ± 6.22	− 0.75 ± 4.36	0.103

Values expressed as mean ± SD for normally distributed data, and median and interquartile range for non-normally distributed data. Between groups, comparisons were assessed by parametric statistical analysis for normal distributed data and nonparametric test for non-normally distributed data

BMI body mass index, *WC* waist circumference, *FBG* fasting blood glucose, *Hs-CRP* high sensitive C-reactive protein, *DM* diabetes mellitus, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *CBC* complete blood count, *WBC* white blood cell, *RBC* red blood cell, *MCV* mean corpuscular volume, *MCH* mean corpuscular hemoglobin, *MCHC* mean corpuscular hemoglobin concentration, *RDW* red cell distribution width, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TC* total cholesterol, *TG* triglyceride, *ApoA* apolipoprotein A, *ApoB* apolipoprotein B, *Lpa* lipoprotein a

or median and interquartile range (for variables without normal distribution). Moreover, for the comparison of clinical features and baseline demographics in the two groups, the ANOVA, Kruskal–Wallis, and Mann–Whitney tests were applied. As well as, data analysis was intention-to-treat basis. A p value of less than 0.05 was assumed to be statistically significant.

Results

A total of 109 subjects completed the study; 3, 4, and 4 subjects were lost to follow up in the curcumin group, the phospholipidated curcumin group, and placebo group, respectively. The reasons for not completing the study were difficulties in maintaining the diet, personal or family reasons, or side effects and unwillingness to continue the study.

There were no significant differences in any of the baseline variables including age, anthropometric indices, serum biochemical factors, systolic and diastolic blood pressures, CBC, and physical activity levels between the three study groups (Table 1). The changes in all variables at baseline and after 6 weeks of intervention were not significant between the three study groups (Table 2).

Table 3 Comparison of changes in the assessed efficacy measures between the study groups

Group	Anxiety			Depression		
	Before the intervention	After the intervention	Changes	Before the intervention	After the intervention	Changes
Curcumin-phospholipid complex	29.94 ± 8.82	25.58 ± 4.97	− 4.11 ± 7.97	33.00 ± 13.63	28.75 ± 8.51	− 3.05 ± 9.06
Curcumin	29.77 ± 7.69	25.30 ± 4.48	− 3.44 ± 5.14	29.46 ± 10.28	24.22 ± 4.08	− 4.05 ± 8.29
Placebo	31.47 ± 8.13	27.64 ± 4.71	− 3.60 ± 7.47	30.64 ± 10.03	27.78 ± 7.43	− 2.93 ± 6.66
p value	0.391	0.032 (Post hock test: $P_{A\&B} = 0.82$, $P_{B\&C} = 0.021$, $P_{A\&C} = 0.028$)	0.988	0.239	0.026 (Post hock test: $P_{A\&B} = 0.01$, $P_{B\&C} = 0.038$, $P_{A\&C} = 0.735$)	0.679

Kruskal–Wallis and Mann–Whitney tests were used

Analysis of the effects of curcumin on indices of depression and anxiety is shown in Tables 3 and 4. Changes in these scores at baseline and after 6 weeks of intervention were not significantly different between the study groups ($p > 0.05$) (Table 3). The results showed that there was a significantly lower severity of anxiety in the curcumin-treated groups compared with placebo (Table 4). Although severe anxiety is alleviated by phospholipidated and unformulated curcumin by 26 and 24%, respectively, but as shown in Table 5, the results of the current study show that curcumin supplementation does not significantly improve anxiety and depression in subjects with MetS ($p > 0.05$).

Adverse effects One of the participants in the phospholipidated curcumin group reported hypersensitivity (manifested as sneezing and cold sore). Also, a number of subjects in the curcumin-treated group reported minor symptoms such as cold sore ($n = 1$) and nausea ($n = 1$).

Discussion

There were no significant differences in serum lipid profile, apolipoproteins, hs-CRP, and anthropometric indices after taking curcumin over the 6 weeks intervention period between the study groups. In the current study, it may have been expected that curcumin-phospholipid complex would have a greater effect than simple curcumin because of its potentially greater bioavailability. It is reported that just like curcumin, the phospholipidated curcumin is characterized by no safety concerns and no side effects were observed when it was administered at 1.2 g/day to over 100 volunteers for 18 months (Belcaro et al. 2010, Marczylo et al. 2007). It has been shown that the phospholipidated curcumin can increase the oral absorption of curcuminoids by nearly 30-fold (Anand et al. 2007). But it seems that this particular curcumin complex did not significantly affect the different components of the MetS in the current study.

Table 4 Comparison of the effects of curcumin on depression and anxiety levels between the study groups

Variables		Scores classification	Curcumin-phospholipid complex	Curcumin	Placebo	*p* value
Anxiety	Before the intervention	Minimum (0 to 7)	–	–	–	0.221
		Mild (8 to 15)	–	–	–	
		Moderate (16–25)	16 (41.0)	17 (42.5)	9 (25.0)	
		Severe (26 to 63)	23 (59.0)	23 (57.5)	27 (75.0)	
	After the intervention	Minimum (0 to 7)	–	–	–	0.01 (Post hock test: $P_{A\&B} = 0.599$, $P_{A\&C} = 0.009$, $P_{B\&C} = 0.009$)
		Mild (8 to 15)	–	–	–	
		Moderate (16–25)	24 (66.7)	24 (66.7)	13 (36.1)	
		Severe (26 to 63)	12 (33.3)	12 (33.3)	23 (63.9)	
Depression	Before the intervention	Minimum (0 to 9)	–	–	–	0.645
		Mild (10 to 18)	–	1 (2.6)	–	
		Slight (19 to 29)	22 (59.5)	26 (66.7)	22 (64.7)	
		Sevier (30 to 63)	15 (40.5)	12 (30.8)	12 (35.3)	
	After the intervention	Minimum (0 to 9)	–	–	–	0.089
		Mild (10 to 18)	–	–	–	
		Slight (19 to 29)	23 (63.9)	31 (86.1)	26 (70.3)	
		Sevier (30 to 63)	13 (36.1)	5 (13.9)	11 (29.7)	

Chi-square test was used

Table 5 Improvements of anxiety and depression in subjects with MetS by supplementation with curcumin

		Groups			*p* value
Disorder	Subjects	Curcumin-phospholipid complex	Curcumin	Placebo	
Anxiety	Not improved, *n*	25	26	27	0.548
	Improved, *n*	10	10	6	
Depression	Not improved, *n*	28	29	28	0.959
	Improved, *n*	6	6	5	

Chi-square test was used

We have shown in a previous trial that curcumin supplementation 1 g/day for 30 days can decrease triglyceride concentration in obese subjects, while curcumin had no significant effect on serum levels of total cholesterol, HDL-c, LDL-c, hs-CRP as well as on BMI or body fat (Mohammadi et al. 2013). However, in this latter trial, the curcumin capsules also contained piperine. It has been shown in the literature that the concentration of free plasma curcumin are ≤25 nanomolar after an oral dosage of 3.6–12 g/day curcumin received for 1 week or more (Semalty et al. 2010, Villegas et al. 2008). It appears to be caused by the instability of curcumin at intestinal pH (Anand et al. 2007). Kaur et al. have reported that oral administration of combinatorial extract of curcumin with piperine and quercetin over 28 days can reduce plasma levels of glucose, TG, LDL-c, and total cholesterol in diabetic rats (Kaur and C 2012). Di Pierro et al. confirmed that curcumin is well tolerated. In their study, overweight people with metabolic syndrome received curcumin complexed with phosphatidylserine and piperine or pure phosphatidylserine for 30 days. Curcumin supplements were associated with a decreased weight, body fat, waist and hip circumferences as well as BMI (Di Pierro et al. 2015). It has been demonstrated that the piperine reduces the conjugation of curcumin and its rapid urinary elimination (Bishnoi et al. 2011), and the phytosome technology increases bioavailability of curcumin in rat and in human (Marczylo et al. 2007, Cuomo et al. 2011). Yang et al. have shown that taking curcumin extract 1890 mg/day over 12 weeks have lipid-lowering effects in the subjects with metabolic syndrome, while it did not improve weight and glucose homeostasis in these patients (Yang et al. 2014). In current study, it seems that simple curcumin dose was less effective in the MetS patients, while the modified curcumin dose was higher than has been shown to have beneficial effects in these patients. However, it is consistent with previous studies that suggested curcumin has a hormetic response (Scapagnini et al. 2006); "a biphasic dose–response with a low-dose stimulation or beneficial effect and a high dose inhibitory or toxic effect" (Mattson 2008). More studies are needed to determine the mechanism of curcumin's hormetic effects on cardiovascular risk factors.

The present study is among the first clinical trials assessing the effect of curcumin supplementation on depression and anxiety in patients with MetS. The results showed that anxiety is significantly alleviated by curcumin-phospholipid complex and simple curcumin by 26 and 24%, respectively. It has been reported that curcumin affects several pathways related to depression, and is an effective treatment for depressive behavior (Panahi et al. 2015c, Lopresti et al. 2014). The results of a study on depressed individuals revealed that the efficacy of curcumin corresponded to that of a standard antidepressant medication. Nevertheless, curcumin not only lacks many of the side effects commonly found in drug therapies, but also is beneficial to human health in other ways (Sanmukhani et al. 2014). These findings are in accord with some data from animal studies that have shown that curcumin raised the levels of the neurotransmitters dopamine and serotonin (Kulkarni et al. 2008, Xu et al. 2005). Additionally, the antidepressant effect of curcumin was confirmed in different animal models of depression (Kulkarni et al. 2008, Yu et al. 2002). In spite of a promising effect of curcumin on the anxiety symptoms, the results showed that supplementation with curcuminoides 1 g/day over 6 weeks did not significantly improve anxiety and depression in subjects with MetS. Perhaps another long-term trials can alleviate these symptoms in MetS subjects.

Limitations

We did not examine the effects of different doses of phospholipidated and unformulated curcumin. Besides, we did not evaluate the impact of absorption-enhancing adjuvants on the efficacy of phospholipidated and unformulated curcumin in this study.

Conclusion

We could not demonstrate that curcumin supplementation at a dose of 1 g/day over 6 weeks improves features of the metabolic syndrome.

Acknowledgements We express our appreciation to the all patients who participated in this study. This research is financially supported by the Mashhad University of Medical Sciences. The authors are also thankful to

Indena S.p.A for providing curcumin supplements. The results presented in this work are part of Mrs Maryam Saberi Karimian's thesis in MUMS.

Funding This research is financially supported by the Mashhad University of Medical Sciences.

Compliance with ethical standards

Ethical approval This research is approved by the Mashhad University of Medical Sciences Ethics Committee.

Informed consent Informed consent was obtained from all individual participants included in the study.

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