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ORIGINAL ARTICLE

The effect of curcumin *(Curcuma longa L.)* on circulating levels of adiponectin in patients with metabolic syndrome

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Abstract In modern societies, metabolic syndrome (MetS) is a highly common disease, which is closely associated with the increased risk of cardiovascular disease (CVD). Metabolic syndrome is usually accompanied by low levels of adiponectin, which is a key regulator of insulin sensitivity and reduced inflammation of the tissue. Adiponectin also reduces systemic insulin resistance and predicts cardiovascular disease. Curcumin has several beneficial effects on risk factors of metabolic syndrome. This polyphenol can affect almost all components of metabolic syndrome including insulin resistance, hypertension and obesity. According to the low oral bioavailability of curcumin, several phospholipid-complex formulations have been developed to address this issue. The present study aims to evaluate the impact of unformulated curcumin and a phospholipid complex of curcumin on serum adiponectin in subjects with metabolic syndrome. Subjects (n = 120) with metabolic syndrome were randomly assigned to three groups which received capsules of phospholipidated curcumin (1 g/day), (n = 40), unformulated curcumin (n = 40) and placebo (n = 40) for a period of 6 weeks. The serum concentrations of adiponectin were measured at baseline and at the end of study using ELISA. The results showed a significant elevation of serum adiponectin concentrations in the curcumin group (mean change 28.9 ± 30.5) in comparison to both curcumin-phospholipid complex (mean change 4.1 ± 15.4) and placebo (mean change −3.5 ± 20.4) groups. Curcumin supplementation increased serum adiponectin concentrations, but this effect was not caused by phospholipid-curcumin complex.

Keywords Metabolic syndrome · Curcumin · Phospholipid complex of curcumin · Adiponectin

Introduction

Metabolic syndrome (MetS) is a serious public health condition around the world, which can increase the risk of diabetes type II (by five times) and cardiovascular disease (by two to three times). This disease is mainly caused by increased urbanization,

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unhealthy food habits, physical inactivity and lack of fitness (Kaur 2014). Improvement in the economic situation and prevalence of obesity in developing countries, especially in South Asia, are two underlying factors contributing to the expansion of metabolic syndrome (Misra and Bhardwaj 2014). The general pervasiveness of metabolic syndrome in Iranian grown-up population has been cited to be 34.7 to 41.6 % as per the diverse criteria with respect to age (Mahjoub et al. 2012).

Metabolic abnormalities and metabolic syndrome are a known cause of cardiovascular disease. In addition, insulin resistance is a key factor in pathogenesis of metabolic syndrome (Qin et al. 2010). Adiponectin is a protein hormone with 244 amino acids that moderates a number of metabolic processes including glucose regulation and oxidation of fatty acids (Whitehead et al. 2006). Adiponectin is an important adipokine produced by adipose tissues (white and brown), which is circulated in the bloodstream with high concentrations. Adiponectin is regarded as a key regulator of insulin sensitivity and reduced inflammation of the tissue. It also reduces systemic insulin resistance and overall predicts cardiovascular disease (Rodina and Severin 2012). Moreover, low levels of adiponectin have been found to be associated with increased risk of diseases such as diabetes, dyslipidemia, hypertension and cardiovascular and metabolic syndrome (Rodina and Severin 2012).

Metabolic syndrome is a set of disorders related to obesity. As such, it makes it difficult for patients to perform exercises or follow diets required to improve their condition. Despite the undisputed effect of statin therapy on the alleviation of LDL-c levels and cardiovascular morbidity, there is still a significant risk that requires therapeutic effects beyond statins (Fruchart et al. 2008). To this end, several factors have been considered as a supplement to statins including fibrates, nicotinic acid, omega-3 fatty acids and CETP inhibitors (Karalis 2008). Phytochemicals are important compounds with significant benefits for cardiovascular diseases and metabolic syndrome. Plant polyphenols have been widely studied for their biological activities (Asensi et al. 2011; Mudgal et al. 2010; Visioli 2011; Visioli and Davalos 2011). Since oxidative stress and inflammation are associated with obesity, insulin resistance and high blood pressure, it seems that polyphenols and medicinal compounds such as curcumin with anti-inflammatory (Panahi et al. 2015b, 2015c, 2014d, 2012b; Sahebkar 2014a) and anti-oxidant (Panahi et al. 2014c, 2012a; Sahebkar et al. 2013, 2015) properties can be useful for treatment of metabolic syndrome (Perez-Torres et al. 2013). Curcumin is a bioactive yellow-orange pigment of turmeric and extracted from the rhizomes of *Curcuma longa* Linn. (*Zingiberaceae*) (Ravichandran 2013). Therapeutic effects of curcumin and its analogues have been shown against a variety of pathological conditions such as cancer (Mirzaei et al. 2016; Momtazi and Sahebkar 2016; Momtazi et al. 2016), osteoarthritis (Panahi et al. 2014b; Sahebkar and Henrotin 2016), non-alcoholic fatty liver disease (Panahi et al. 2016d; Rahmani et al. 2016), anxiety and depression (Esmaily et al. 2015; Panahi et al. 2015a), pulmonary diseases (Panahi et al. 2015b; Panahi et al. 2016a) and ischemia/reperfusion injury (Sahebkar 2010). It has been shown that curcumin can influence almost all components of metabolic syndrome, including insulin resistance, low HDL-C, high blood pressure and obesity. This is due to the reaction of phytochemical materials with various molecular targets, such as transcription factors, receptors, enzymes, growth factors, hormones, cell adhesion molecules, lipoproteins and anti-oxidants, which are involved in the pathophysiology of metabolic syndrome (Panahi et al. 2014a; Sahebkar 2013, 2014b). As a result, studies on absorption, tissue distribution, metabolism and half-life of curcumin reveal that low absorption, rapid metabolism and rapid excretion of curcumin from the body are main reasons for low availability of curcumin. Adjuvant and nanoparticles, liposomes, micelles and phospholipid complex procedures are new procedures in the new formulation, which seen to have longer circulation, permeability and resistance against metabolic processes (Shoba et al. 1998).

The present study was undertaken to assess the impact of curcuminoid supplementation on serum levels of adiponectin in patients with metabolic syndrome.

Material and methods

Subjects and study design

This study was a double-blind clinical trial undertaken in the period between September 1 and December 30, 2015, in the Nutrition clinic of Ghaem Hospital in the city of Mashhad, Iran. The study protocol was approved by the Ethics Committee of the Mashhad University of Medical Sciences and all participants signed a written informed consent. The current trial has been registered in Iranian Registry of Clinical Trials (IRCT) whit a registration number IRCT2014052014521N3.

The study was conducted on subjects aged 18 to 65 years who had been diagnosed with metabolic syndrome based on the International Diabetes Federation (IDF) guidelines. The IDF (2006) is defined based on the abdominal obesity (an abdominal circumference of 94 cm for men and over 80 cm for women) as a mandatory component for the diagnosis of metabolic syndrome. Moreover, the IDF criterions require at least two of the following four features:

- High triglyceride (150 mg/dl or more)
- Low HDL-c (less than 40 mg/dl in men and less than 50 mg/dl in women)
- High blood pressure (130/85 mmHg or higher)
- High blood sugar (100 mg/dl or higher)

In this study, the inclusion criteria were as follows: consent to participate in research projects, men and women aged 18 to 65 years, lack of food supplements and lack of taking any drug within the last 3–6 months (participants should not have a history of treatment with lipid lowering drugs, diabetes, blood pressure and insulin within the previous 3–6 months). Those who were excluded were as follows: lack of consent to participate in research projects, infection or a history of systemic disease such as lupus and kidney disease, pregnancy or breast-feeding and taking cholesterol medication and other drugs within the last 3–6 months. The dose for curcumin was determined to be 1 g/day based on our previous study. Moreover, there were no considerable adverse effects after the intervention in this study (Mohammadi et al. 2013).

Subjects (n = 120) were randomly assigned to three groups of people with each group receiving 1 g/day dose of drug for a period of 6 weeks in the following groups:

- Curcumin-phospholipid complex group (curcumin-phospholipid complex capsules equivalent to 200 mg pure curcumin/day)
- Curcumin group (curcumin capsules contained pure curcumin)
- Placebo group (placebo capsules involved lactose and starch with a ratio of 2:1).

Metabolic syndrome is related to obesity. It has been shown that low adiponectin levels are associated with increased risk of diabetes, hyperlipidemia, augmented blood pressure, and cardiovascular and metabolic syndrome (Rodina and Severin 2012). Therefore, in this study, anthropometric indices, blood pressure and FBG were measured. Systolic and diastolic blood pressures were used to measure blood pressure (BP) by an Omron digital pressure and proper cuff around the arm of each volunteer. Weight, body mass index (BMI) and percentage of total body fat were determined by a bioelectrical impedance analysis (BIA) device (TANITA BC-418). Serum level of FBG was assessed using Pars Azmoon kits (Tehran, Iran). Further, data on demographic features, smoking habit and medical history were gathered by a questionnaire. All participants in the study received the same diet for 6 weeks.

Measurement of adiponectin

The fasting blood samples (12 h fasting) were taken before and after the intervention. Then the blood samples were centrifuged and isolated sera stored at −20 °C prior to detect the biochemical variables. The serum level of adiponectin was measured by human adiponectin ELISA kits (Boster Biological Technology Co., Wuhan, China, Lot number 3001144608).

Statistical analysis

Statistical analyses were performed by the Statistical Package for Social Sciences (SPSS) program. Quantitative data were expressed as the mean ± SD. The ANOVA and Chi-square tests were used to compare quantitative and qualitative variables between the groups.

Results

Figure 1 shows the flowchart of the study design. Table 1 shows the clinical and biochemical features in subjects before

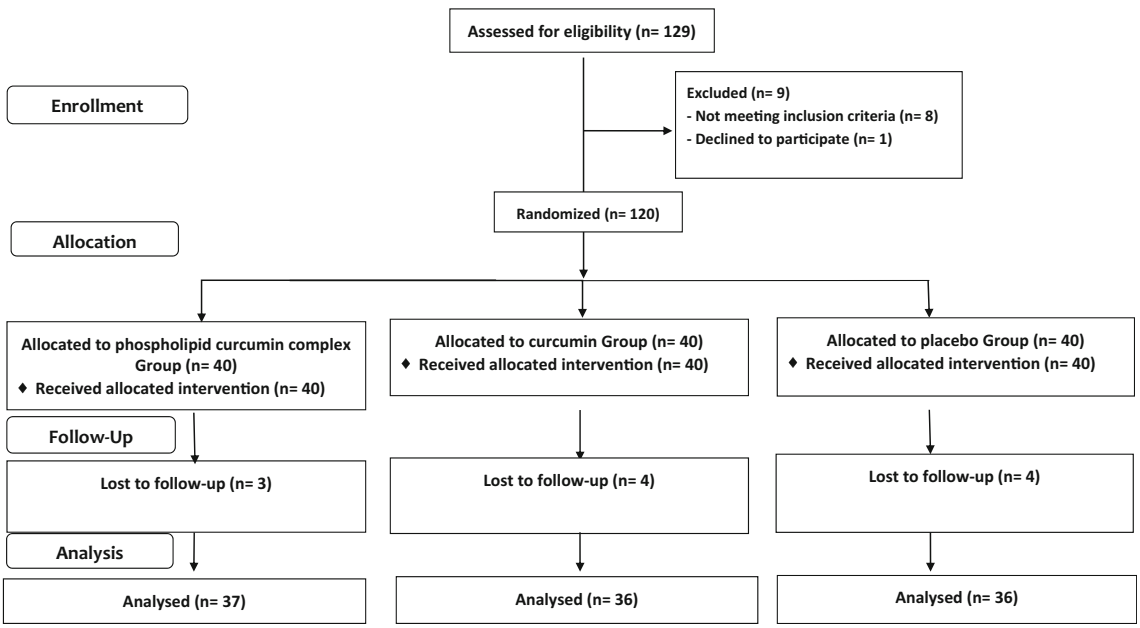

Fig. 1 The flow chart of the study

Table 1 Clinical and biochemical features in subjects before the intervention

Variables	Curcumin-phospholipid complex	Curcumin	Placebo	*P* value
Age (year)	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
FAT%	34.51 ± 8.07	35.42 ± 6.12	35.21 ± 7.86	0.848
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
Current smoking % (*n*)	15.4 (6)	26.3 (10)	13.9 (5)	0.318

Values are expressed as mean ± SD

BMI body mass index, *WC* waist circumference, *FBG* fasting blood glucose, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

the intervention. Some demographic, clinical and anthropometric features in subjects before and after interventions are shown in Tables 2–4

The mean adiponectin concentrations for all three groups of participants are shown in Table 4. The results showed a significant elevation of serum adiponectin concentrations in the curcumin group (mean change 28.9 ± 30.5) in comparison to both curcumin-phospholipid complex (mean change 4.1 ± 15.4) and placebo (mean change −3.5 ± 20.4) groups.

Discussion

The results showed that curcumin supplementation has increased serum adiponectin concentrations in subjects with metabolic syndrome, but this effect was not observed by phospholipid complex of phytochemical. There is an accumulating body of evidence that show adiponectin in circulation is directly associated with insulin sensitivity. Moreover, low levels of adiponectin have been found to be associated with increased risk of diseases such as diabetes, dyslipidemia, hypertension and cardiovascular and metabolic syndrome (Rodina and Severin 2012). It seems that polyphenols and medicinal compounds such as curcumin with anti-inflammatory and anti-oxidant properties can be useful for treatment of metabolic syndrome (Perez-Torres et al. 2013).

The subcutaneous adipose tissues and peripheral abdominal surgery in seven patients were collected and cultured at different concentrations of curcumin (10 and 100 μg/ml) by Qu et al. (2008). The results showed that culturing at a concentration of 100 μg/ml increased adiponectin secretion and lessened IL-6 secretion in cultured human adipose tissues (Qu et al. 2008). The effect of curcumin on the expression of adiponectin in mice model has also been documented. In this study, 64 mice were divided into three groups, i.e. the control group, the group receiving 50 mg of curcumin and the group receiving 250 mg of curcumin for 11 weeks. In the group receiving 250 mg of curcumin, a significant increase in adiponectin levels was observed compared to the control group (Bai et al. 2013). In another study on ob/obC57BL/6J mice, Weisberg et al. found that the intake of 30 % dietary curcumin for 10 weeks increased the adiponectin level (Weisberg et al. 2008). These findings are to some extent expected owing to the known immunomodulatory actions of curcumin in different models (Derosa et al. 2016; Panahi et al. 2016a; Sahebkar et al. 2016).

In addition, there is evidence from previous clinical trials suggesting the adiponectin-increasing effects of curcumin in subjects with pre-diabetes taking curcumin (1500 mg/day) for 9 months, subjects with type 2 diabetes taking curcumin (1500 mg/day) for 6 months and subjects with metabolic syndrome taking a combination of curcumin (1000 mg/day) and piperine (10 mg/day) for 8 weeks (Panahi et al. 2016b).

Table 2 Clinical and biochemical features in subjects after intervention

Variables	Curcumin-phospholipid complex	Curcumin	Placebo	*P* value
Weight (kg)	84.06 ± 14.67	79.76 ± 11.52	81.32 ± 11.26	0.388
BMI (kg/m^2)	31.03 ± 5.11	30.36 ± 3.80	31.30 ± 4.87	0.718
WC (cm)	100.82 ± 11.57	97.01 ± 11.14	99.42 ± 11.86	0.455
FBG (mg/dl)	103.49 ± 15.27	102.00 ± 14.90	100.94 ± 16.74	0.793
FAT%	35.19 ± 8.48	36.08 ± 6.72	34.57 ± 9.05	0.773

Values expressed as mean ± SD

BMI body mass index, *WC* waist circumference, *FBG* fasting blood glucose

Table 3 Changes in anthropometric indices 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
FAT%	−0.03 ± 2.09	0.33 ± 1.88	0.71 ± 1.44	0.276

Values expressed as mean ± SD

BMI body mass index, *WC* waist circumference, *FBG* fasting blood glucose

According to the results of the present study, unformulated curcumin supplementation increased serum adiponectin concentrations in subjects with metabolic syndrome but this effect was not significant in the phospholipidated curcumin group. A plausible explanation for not detecting a significant elevation (in spite of an increasing trend) in serum adiponectin with phospholipidated curcumin could be the short duration of supplementation compared with the above-mentioned trials in which duration of supplementation ranged between 8 weeks and 9 months. Moreover, administered dose of phospholipidated curcumin in this study was 1000 mg/day which is equivalent to 200 mg/day of pure curcumin; hence, it is open to question if higher doses could bring about greater changes in serum adiponectin levels. This hypothesis could be justified by the increasing trend in serum adiponectin levels that was observed in the phospholipidated curcumin group. Another hypothesis for the lack of efficacy of phospholipidated curcumin in this study could be the potential inhibitory effects of phosphatidylcholine (a component of phospholipidated curcumin preparation) on adipose tissue. Injection of phosphatidylcholine to the adipose tissue for a period of 7 days has been reported to reduce adipose tissue. Also, by increasing lipolysis and decreasing the expression of adipose tissue hormones such as adiponectin, phosphatidylcholine can lessen fat tissue (Won et al. 2013).

In comparison with unformulated curcumin, phospholipid complex of curcumin has several improved properties in terms of membrane permeability, absorption, bioavailability and resistance to hydrolytic degradation. It has been shown that curcumin-phospholipid complex could significantly increase curcumin's bioavailability. The peak plasma concentration of curcumin after the administration of phosphatidylcholine-curcumin complex was five times greater than plasma curcumin after the injection of unformulated curcumin (Anand et al. 2007). It has been reported that increased dose of curcumin has no additive effect on inflammatory cytokines, and lower doses are more effective (Hasan et al. 2014). In the current study, comparison of concentration of serum adiponectin before and after treatment showed significant differences in curcumin group, although the comparison of serum adiponectin before and after treatment in curcumin-phospholipid complex and placebo groups was not significantly different. According to the above studies, because of increased gastrointestinal absorption of curcumin, the curcumin-phospholipid complex group dose has increased, and possibly, the lower dose in the curcumin group would be more effective in enhancing adiponectin.

Increased fat mass is directly associated with oxidative stress. ROS production was found to increase lean mass and decrease the expression of anti-oxidant enzymes. In fat cells, culturing environment, an increase in the fatty acids, raises oxidative stress through NADPH oxidase activation and lessens adiponectin production (Furukawa et al. 2004). As such, the anti-oxidant effect in the curcumin group, due to its lower dose, could be more effective than curcumin-phospholipid group.

Study limitations

This study had a number of limitations such as short duration of follow-up and administration of a single dose of curcumin.

Table 4 Changes in adiponectin levels at baseline and after intervention

Adiponectin (μg/ml)	Curcumin-phospholipid complex	Curcumin	Placebo	*P* value
Before intervention	33.9 ± 18	28.3 ± 17.2	52.2 ± 24.9	0.001
After intervention	38.1 ± 20.4	57.3 ± 36.6	48.6 ± 25.8	0.05
Changes in adiponectin levels at baseline and after intervention	4.1 ± 15.4	28.9 ± 30.9	3.5 ± 20.4	0.001

Values expressed as mean ± SD

Conclusion

There was a significant increase in the serum adiponectin level in the unformulated curcumin group compared to the curcumin-phospholipid and placebo groups. In this study, no side effect associated with this curcumin dose (1 g/day) was observed. Our study showed the usefulness of curcumin in a 1 g/day dosage in patients with metabolic syndrome. However, further studies are required to evaluate the findings.

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Compliance with ethical standards The current trial has been registered in Iranian Registry of Clinical Trials (IRCT) whit a registration number IRCT2014052014521N3.

Conflict of interest The authors declare that they have no conflict of interest.

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Ethical approval This research 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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