Journal of Dietary Supplements

ISSN: 1939-0211 (Print) 1939-022X (Online) Journal homepage: http://www.tandfonline.com/loi/ijds20

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To cite this article: Farzaneh Mohammadi, Maryam Ghazi-Moradi, Majid Ghayour-Mobarhan, Habibollah Esmaeili, Mohsen Moohebati, Maryam Saberi-Karimian, Hamideh Safarian, Shima Tavallaie, Gordon A. Ferns & Amirhosein Sahebkar (2018): The Effects of Curcumin on Serum Heat Shock Protein 27 Antibody Titers in Patients with Metabolic Syndrome, Journal of Dietary Supplements, DOI: 10.1080/19390211.2018.1472710

To link to this article: https://doi.org/10.1080/19390211.2018.1472710

Published online: 29 Jun 2018.

JOURNAL OF DIETARY SUPPLEMENTS
https://doi.org/10.1080/19390211.2018.1472710

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ARTICLE

The Effects of Curcumin on Serum Heat Shock Protein 27 Antibody Titers in Patients with Metabolic Syndrome

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ABSTRACT

Metabolic syndrome (MetS) is associated with an increased risk of cardiovascular disease and diabetes mellitus. Inflammation and oxidant stress are features of MetS that can enhance the expression and release of heat shock proteins (Hsps), including the small heat shock protein, Hsp 27, and that may subsequently lead to the production of Hsp27 antibodies (anti-Hsp 27). Curcumin is an anti-inflammatory and antioxidant phytochemical that may ameliorate these features of MetS. We investigated the effects of unformulated curcumin and phospholipidated curcumin on antibody titers to heat shock protein 27 (anti-Hsp 27) in patients with MetS. A randomized double-blind, placebo-controlled clinical trial design was used in 120 patients with MetS (diagnosed according to the International Diabetes Federation [IDF] criteria). Participants were randomly allocated to 3 groups, with 40 individuals per group, that received either 1 g/d curcumin, phospholipidated curcumin, or a placebo for 6 weeks. The changes in serum concentrations of anti-Hsp 27 did not differ significantly between study groups ($p = .283$). There was no significant difference between baseline and end-of-trial concentrations of anti-Hsp 27 in groups supplemented with curcumin ($p = .177$), phospholipidated curcumin ($p = .798$), or placebo ($p = .663$). Curcumin supplementation (1 g/d) has no significant effects on anti-Hsp 27 titers in patients with MetS.

KEYWORDS

metabolic syndrome; heat shock protein 27; curcumin

Introduction

Metabolic syndrome (MetS) is a major public health problem globally and is defined by a cluster of clinical, biochemical, physiological, and metabolic factors that are associated with

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an increased risk of atherosclerotic cardiovascular disease, type 2 diabetes mellitus (T2DM), and all-cause mortality (Grundy et al., 2005; Wilson, D'Agostino, Parise, Sullivan & Meigs, 2005). It is also associated with chronic low-grade inflammation, insulin resistance, visceral adiposity, atherogenic dyslipidemia, endothelial dysfunction, increased blood pressure (BP), hypercoagulable state, and chronic stress (Grundy et al., 2005; Wilson et al., 2005). The prevalence of MetS is approximately 25% in the United States, 17.8%–34% in Europe, 12.8%–41% in the Asian Pacific region, and 30% in Iran (Azimi-Nezhad et al., 2008; Azizi et al., 2003; Grundy, 2008). MetS is associated with a five-fold risk of T2DM and a two-fold risk of cardiovascular disease (CVD) over the next 5 to 10 years (Alberti et al., 2009).

CVD is the main cause of global mortality. Established risk factors for CVD are age, male gender, and family history of CVD, hypertension, hypercholesterolemia, smoking, diabetes mellitus, low socioeconomic status, obesity, and developing risk factors such as markers of oxidative stress, inflammation, and autoimmunity (Ferns, 2008; Ross, 1993). Oxidative stress induces the expression and release of heat shock proteins (Hsps).

Hsps are intracellular proteins, and their upregulation protects cells during stressful conditions (Pourghadamyari et al., 2011). Hsp27 is a member of the small Hsp family. Its functions include protein chaperone activity, regulation of cellular glutathione, apoptosis signaling, and modifying inflammatory response. It is expressed in many cell types, including cardiomyocytes and endothelial cells (Ghayour-Mobarhan, Rahsepar, Tavallaie, Rahsepar, & Ferns, 2009; Tucker, Ustyugov, Bryantsev, Konkel, & Shelden, 2009). According to several past studies, circulating levels of Hsp27 and its corresponding antibody (anti-Hsp27) increase in conditions such as coronary artery disease (Pourghadamyari et al., 2011), acute coronary syndrome (Ghayour-Mobarhan et al., 2008; Heidari-Bakavoli et al., 2012), and MetS (Sahebkar et al., 2011).

Curcumin (diferuloyl methane; $C_{21}H_{20}O_6$) is a hydrophobic polyphenol and yellow pigment that is extracted from dried rhizomes of the herb *Curcuma longa* L. (turmeric). Turmeric is a common spice in Indian, Middle Eastern, and Southeastern Asian cooking and has been used as an herbal remedy in traditional medicine (Anand et al., 2008; Lao et al., 2006). Recent investigations have reported that curcumin has several important biological activities that include anti-inflammatory, antioxidant, immunomodulatory, and neuro- and cardioprotective properties. Its use has been proposed for the treatment of different types of cancer, arthritis, cardiometabolic diseases, cystic fibrosis, and pulmonary disorders (Panahi et al., 2012; Panahi et al., 2014; Panahi, Badeli, Karami, & Sahebkar, 2015; Sahebkar, 2013; Sahebkar, Chew, & Watts, 2014). Although curcumin has several potentially beneficial effects, it has low bioavailability (Anand, Kunnumakkara, Newman, & Aggarwal, 2007) because of its hydrophobic nature. Some methods have been used to improve the bioavailability, including consuming liposomal curcumin, curcumin nanoparticles, curcumin phospholipid complex, and structural analogs of curcumin and using adjuvants such as piperine that inhibit glucuronidation of curcumin (Shoba et al., 1998). In this study, we use phospholipidated curcumin to increase the bioavailability of curcumin.

Therefore, with regard to the role of stress and inflammation in the development of CVD and MetS and release of Hsp 27 in these conditions and with regard to the antioxidant and anti-inflammatory role of curcumin, we evaluated the effect of two preparations of curcumin (unmodified and phospholipidated formulations) on serum anti-Hsp 27 levels.

Methods and materials

In this randomized double-blind clinical trial, patients were recruited and treated for six weeks between September and October 2014. The study was approved by the Ethics Committee of

Mashhad University of Medical Sciences (Mashhad, Iran) and was carried out at the Nutrition Clinic of Ghaem Hospital (Mashhad, Iran).

Study population

People who were 18–65 years old and had MetS according to International Diabetes Federation (IDF) criteria (IDF, 2010) were included in this study. Inclusion criteria were based on the IDF citeria: a waist circumference (WC) > 94 cm in men and > 80 cm in women plus any two of the following: (1) triglyceride (TG) ≥ 150 mg/dL or specific treatment for this condition, (2) HDL-C < 40 mg/dL in men and < 50 mg/dL in women or specific treatment for this condition, (3) systolic blood pressure (SBP) ≥ 130 or diastolic blood pressure (DBP) ≥ 85 mmHg or treatment of previously diagnosed hypertension, (4) fasting plasma glucose (FPG) ≥ 100 mg/dL or previously diagnosed T2DM. Altogether, 120 individuals were eligible for inclusion into this study. Exclusion criteria were a history of systemic disease such as lupus or rheumatoid arthritis, kidney disease, pregnancy, lactation, and using any supplements or drugs for decreasing BP, glucose, and lipids during the previous six months.

Study design

Written informed consent was recorded for all participants. Demographic data, anthropometric and BP measurements, and laboratory tests were recorded before and after the intervention period. Patients were randomized according to the tables of the Fleiss book into three groups of 40 (Fleiss, 2011). One of the groups was assigned to receive 500 mg curcumin twice a day (1 g/d) for six weeks. The other groups were assigned to receive phospholipidated curcumin or placebo in the same amount as the first group. They received the dietary recommendation of the American Heart Association and 24-hour dietary recalls were recorded. Patients were followed up every two weeks to receive their capsules and record BP and anthropometric measures.

Blood sampling

Before and after the intervention period, 20 ml blood was taken after 12 hours of fasting. Then the blood samples were centrifuged, and isolated sera were stored at −20°C prior to performing the laboratory tests.

Curcumin capsule preparation

Participants were given unlabeled bottles containing capsules filled with 500 mg of unformulated or phospholipidated curcumin and were asked to take two capsules per day. Phospholipidated curcumin (Meriva, Indena S.p.A., Italy) contained a complex of curcumin and soy phosphatidylcholine in a 1:2 weight ratio and two parts of microcrystalline cellulose to improve flowability, with an overall content of curcumin in the final product of around 20% (Belcaro et al., 2010; Semalty, Semalty, Rawat, & Franceschi, 2010). The shape, weight, and color of the placebo capsules were the same as those containing the curcumin.

Blood pressure measurement

BP was measured in the right arm while it was supported at heart level. The patients were comfortable and in a sitting position at least five minutes before the measurement (Pickering et al., 2005).

Anthropometric measurements

Anthropometric parameters included height, weight, WC, and hip circumference (HC). Height was measured using a stadiometer with a fixed vertical backboard and an adjustable headpiece. The patients removed their shoes, and back of the head, shoulder blades, buttocks, and heels were in contact with the backboard. HC and WC were measured by a tape measure to the nearest 0.1 cm. WC was measured above the uppermost lateral border of the right ilium of the pelvis and below the chest. Maximum HC was measured for HC measurement (McDowell et al., 2008). Weight, body mass index (BMI), and percentage of total body fat were measured using a bioelectrical impedance analysis (BIA) device (TANITA BC-418, UK).

Dietary intake analysis

Dietary intakes were recorded by 24-hour recalls and analyzed by Nutritionist 4 software (First Databank Inc., Hearst Corp., San Bruno, CA, USA).

Serum anti-Hsp27 assay

An in-house enzyme-linked immunosorbent assay (ELISA) was used to measure serum anti-Hsp27 levels. Microtiter plates (Nunc Maxisorb, UK) were coated with 50 µL carbonate buffer (pH 9.6) and 100 ng recombinant human Hsp27 (Stressgen, Canada) in each well and incubated for 18–24 hours at 4°C under humidified conditions. Wells were washed three times with 250 µL phosphate-buffered saline (PBS) containing 0.05% Tween-20 (PBST). For blocking and reduction of nonspecific binding, 250 µL 2% goat serum dissolved in PBS was added. Then the plate was incubated for 30 minutes at 37°C and for 30 min at room temperature. Wells were washed three times with 250 µL PBS. Serum diluted 1:100 with 2% goat serum in PBS was added to the wells and incubated for 30 min at room temperature. Wells were washed four times with 250 µL PBST and two times with PBS. After that, 100 µL peroxidase-conjugated goat antihuman IgG (Sigma-Aldrich, USA) diluted 1:500 with 2% goat serum in PBS was added to wells and incubated for 30 min at room temperature. After washing six times as per the previous process, 100 µL of tetramethylbenzidine (TMB) substrate (200 µL of 6 mg/mL TMB in dimethyl sulfoxide [DMSO] was added to 10 mL of 50 mmol/L acetate buffer, pH 4.5, containing 6 µL H_2O_2) was added per well, and plates were incubated for 15 min in a dark place at room temperature. Finally, the enzymatic reaction was stopped by adding 50 µL 2 mol/L HCl per well. Color density in each well was read using an ELISA reader (awareness, USA) at a wavelength of 450 nm (Sahebkar et al., 2011). The within- and between-assay precisions were 3.5% and 5.2%, respectively (Ghayour-Mobarhan et al., 2008).

Statistical analysis

Data analysis was performed using Statistical Package for Social Sciences (SPSS) (version 16:0, SPSS Inc., Chicago, IL, USA) software. A value of $p < .05$ was considered significant. Data were reported as mean ± standard deviation (SD) for normally distributed data and as median and interquartile range for nonnormally distributed variables. Chi-square test and ANOVA were used to test the homogeneity between groups, and Kruskal-Wallis test was performed for nonnormally distributed quantitative variables. Wilcoxon and ANOVA tests were done to

Table 1. Baseline characteristics of participants within the different treatment groups.

Variables		Phospholipidated curcumin	Curcumin	Placebo	*p* value
Sex	Female % (*n*)	62.5 (25)	77.5 (31)	75.0 (30)	.280
	Male % (*n*)	37.5 (15)	22.5 (9)	25.0 (10)	
Age (years)		40.05 ± 10.48	37.52 ± 9.47	38.59 ± 10.28	.534
Weight (kg)		84.06 ± 14.67	80.61 ± 11.71	82.12 ± 12.68	.803
BMI (kg/m^2)		30.66 ± 5.06	30.67 ± 3.57	31.22 ± 4.67	.828
WC (cm)		103.00 ± 10.24	99.94 ± 9.37	102.49 ± 9.41	.341
Body fat %		34.51 ± 8.07	35.42 ± 6.12	35.21 ± 7.86	.848
FBG (mg/dl)		95.97 ± 19.97	98.72 ± 27.17	92.82 ± 16.62	.479
SBP (mmHg)		120.82 ± 10.24	119.74 ± 11.87	120.26 ± 11.50	.914
DBP (mmHg)		83.48 ± 9.17	81.26 ± 10.06	81.70 ± 10.76	.589
Current smoker % (*n*)		15.4 (6)	26.3 (10)	13.9 (5)	.318

Values are expressed as mean ± standard deviation (SD). Comparisons between groups were assessed by ANOVA and chi-square tests for quantitative and qualitative variables, respectively. BMI = body mass index; WC = waist circumference; FBG = fasting blood glucose; SBP = systolic blood pressure; DBP = diastolic blood pressure.

determine the impact of intervention and to compare the effectiveness of the three groups, respectively.

Results

Altogether, 109 patients entered into the study (Figure 1). Eleven participants were lost to follow-up, three persons in the curcumin group, four persons in the phospholipidated curcumin complex group, and four persons in the placebo group, due to difficulties in maintaining their diet, personal or family reasons, or side effects and unwillingness to continue with the study. There were no significant difference among the three groups in baseline characteristics ($p > .05$) (Table 1) or in changes of the serum level of anti-Hsp 27 ($p = .283$), (Figure 2). There were no significant differences in anti-Hsp 27 levels among groups supplemented with curcumin ($p = .177$), phospholipidated curcumin ($p = .798$), or placebo ($p = .663$) (Table 2). The changes of weight ($p = .143$), WC ($p = .979$), BMI ($p = .574$), and percentage of total body fat ($p = .276$) had also no significant difference. In addition, analysis of food intakes demonstrated no significant difference in the changes of macronutrients and micronutrients ($p > .05$) except saturated fatty acids ($p = .045$) (Table 3).

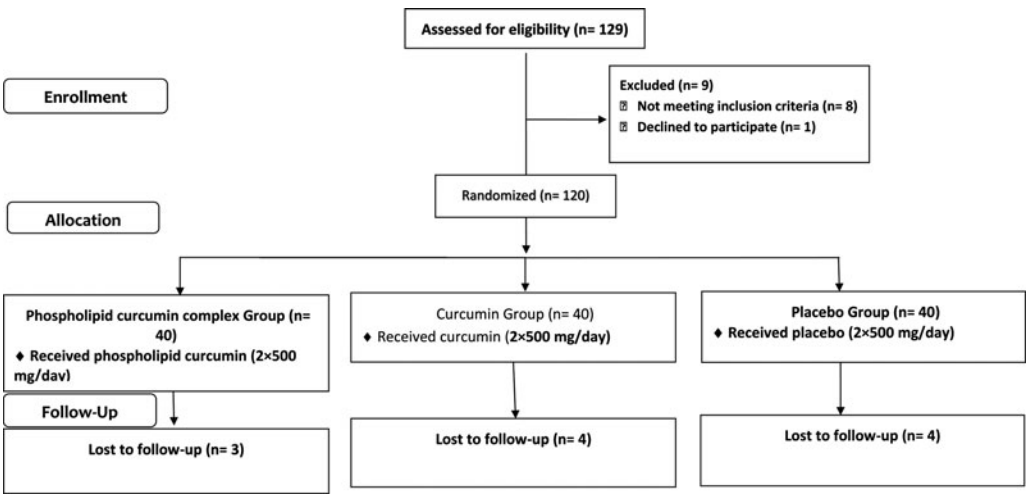

Figure 1. Flow chart of the study design.

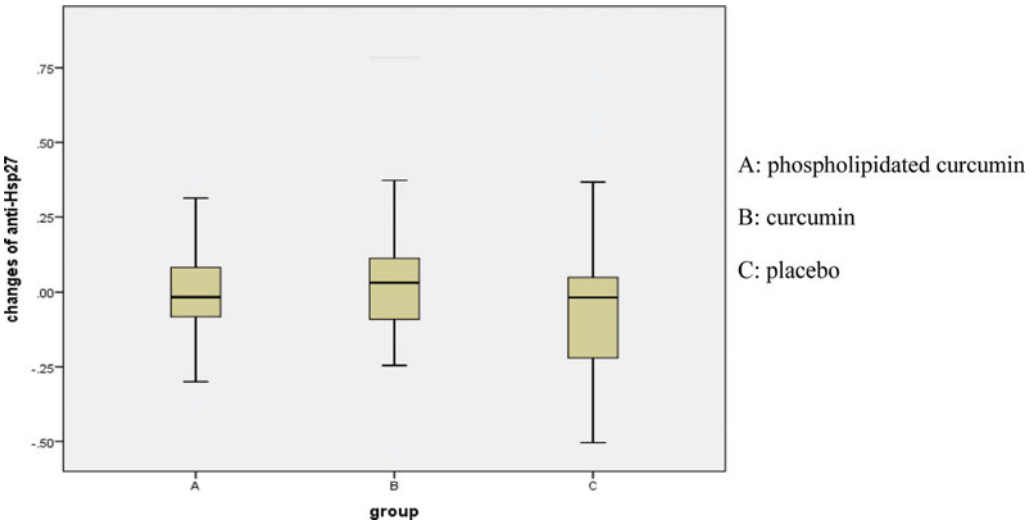

Figure 2. Changes in the serum anti-HSP27 titers at baseline and after six weeks intervention.

Discussion

The changes in serum anti-Hsp 27 was not significantly different between the 3 treatment groups.

Curcumin is the polyphenolic pigment contained in turmeric. It modulates the activity of inflammatory enzymes, cytokines, adhesion molecules, and heat shock proteins by affecting transcription factors such as nuclear factor κB (Goel, Kunnumakkara, & Aggarwal, 2008). It also improves the immune system and protects against neurological damage by increasing glutathione (GSH), superoxide dismutase, and catalase (Al-Omar, Nagi, Abdulgadir, Al Joni, & Al-Majed, 2006). Studies have shown that curcumin increases the mitogen- and antigen-induced proliferation potential of T cells (Varalakshmi et al., 2008). Curcumin functions as a free-radical scavenger and inhibits the generation of metal ion–induced radical oxygen species (Baum & Ng, 2004; Daniel, Limson, Dairam, Watkins, & Daya, 2004). It has shown remarkable anti-inflammatory and antioxidant effects in previous studies (Ak et al., 2008; Panahi et al., 2012; Panahi et al., 2014; Sahebkar et al., 2014).

Supplementation with curcumin (1 g/d for 30 days) has been shown to deceased pro-oxidant and anti-oxidant balance (PAB), but did not significantly change the concentration of anti-Hsp 27 or anti-oxLDL in obese patients (Sahebkar et al., 2013). No significant change was observed in the anthropometric measures such as weight, BMI, WC, and total body fat (Mohammadi et al., 2013). We used phospholipidated curcumin that is known to be more bioavailable compared to unformulated curcumin, but we could not find any significant

Table 2. Effects of intervention on anti-Hsp 27 level.

Treatment	Before the intervention (OD450)	After the intervention (OD450)	Differences (OD450)	*p* value (pre- vs. posttreatment)
Phospholipidated curcumin ($n = 40$)	0.18 (0.10–0.29)	0.20 (0.14–0.34)	−0.01 (−0.08–0.08)	.798
Curcumin ($n = 40$)	0.17 (0.07–0.24)	0.17 (0.08–0.29)	0.03 (−0.09–0.11)	.177
Placebo ($n = 40$)	0.23 (0.08–0.43)	0.17 (0.09–0.42)	−0.01 (−.22–0.06)	.663
p value	.144	.606	.283	

Values are expressed as the median (interquartile range). Wilcoxon and ANOVA tests were done to determine the impact of intervention and to compare the effectiveness of the three groups, respectively.

Table 3. Changes in macronutrients and micronutrients within the different treatment groups.

Parameter	Phospholipidated curcumin	Curcumin	Placebo	*p* value
		Macronutrients		
Calorie (Kcal)	− 290.21 ± 740.31	− 15.56 ± 841.15	− 293.08 ± 657.67	.288
Protein (g)	− 11.28 ± 37.78	2.79 ± 44.19	− 5.29 ± 26.10	.361
Carbohydrate (g)	− 30.91 ± 104.66	− 26.00 ± 107.20	− 36.87 ± 100.43	.926
Fat (g)	− 10.03 ± 38.43	7.80 ± 41.90	− 13.56 ± 28.90	.073
Cholesterol (mg)	− 42.41 ± 191.14	17.10 ± 170.09	− 42.11 ± 203.77	.402
Saturated fatty acid (g)	− 4.17 ± 11.90	2.80 ± 12.23	− 3.28 ± 9.24	.045
Dietary fiber (g)	− 2.21 ± 7.15	1.85 ± 9.41	2.76 ± 16.39	.241
		Micronutrients		
Zinc (mg)	− 1.08 ± 4.87	1.23 ± 6.68	0.08 ± 4.29	.276
Copper (mg)	0.07 ± 1.07	− 0.05 ± 0.88	0.15 ± 1.30	.934
Selenium (mg)	− 0.01 ± 0.03	− 0.01 ± 0.05	− 0.00 ± 0.02	.256
Vitamin A (RE)	− 315.35 ± 2729.74	− 756.51 ± 2881.97	− 1197.35 ± 2591.95	.855
Vitamin E (mg)	− 4.97 ± 8.46	2.26 ± 26.14	− 6.90 ± 10.51	.080
Vitamin C (mg)	− 20.59 ± 94.96	− 14.44 ± 77.79	− 3.48 ± 89.28	.761

Values are expressed as mean ± standard deviation (SD). Comparisons between groups were assessed by ANOVA and Kruskal-Wallis tests for normally and nonnormally distributed variables, respectively.

changes in serum anti-Hsp 27 and anthropometric measures in patients with MetS following supplementation. Due to limitations of this study such as short duration of follow-up, small population size, and lack of examining the effects of different dosages of curcumin on anti-Hsp27 antibody titers, future studies are recommended to verify the results.

Conclusion

Curcumin and phospholipidated curcumin complex supplementation (1 g/d for six weeks) had no effect on serum levels of anti-Hsp27 in patients with MetS. However, it remains to be checked whether curcumin supplementation has any impact on Hsp27 antigen.

Declaration of interest

The authors declare no conflicts of interest. The authors alone are responsible for the content and writing of the article.

Acknowledgment

The authors appreciate the cooperative staff of the Nutrition Clinic of the Ghaem Hospital and the participants of the study. The authors are also thankful to Indena S.p.A for their assistance in providing study supplements.

Funding

This work was supported by Mashhad University of Medical Science (MUMS), Iran.

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