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Effects of Curcumin on Serum Vitamin E Concentrations in Individuals with Metabolic Syndrome

Akram Mohammadi,[1] Hamid Reza Sadeghnia,[2] Maryam Saberi-Karimian,[3] Hamideh Safarian,[4] Gordon A. Ferns,[5] Majid Ghayour-Mobarhan[6]* and Amirhossein Sahebkar[7]*

[1]Department of Modern Sciences and Technologies, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[2]Department of Pharmacology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[3]Student Research Committee, Department of Modern Sciences and Technologies, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[4]Department of Biochemistry, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[5]Division of Medical Education, Brighton and Sussex Medical School, Falmer, Brighton, Sussex BN1 9PH, UK
[6]Biochemistry and Nutrition Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[7]Biotechnology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

Vitamin E is an important lipid-soluble antioxidant. The aim of the present study was to investigate the effect of curcumin on serum vitamin E levels in subjects with metabolic syndrome (MetS). A total of 120 subjects aged 18–65 years old with MetS were recruited in this study according to the International Diabetic Federation Criteria. Included subjects were randomized into three groups: subjects receiving lecithinized curcumin (1 g/day equivalent to 200-mg pure curcumin per day) for a period of 6 weeks (n = 40), patients receiving unformulated curcumin (1 g/day) for a period of 6 weeks (n = 40) and a control group receiving placebo for the same period (n = 40). Vitamin E was determined in all patients before and after the intervention using high-performance liquid chromatography method. Results showed that curcumin has no improving effect on serum levels of vitamin E ($p > 0.05$). There were significant differences between pre-trial and post-trial levels of vitamin E/low-density lipoprotein cholesterol ratio ($p < 0.05$), vitamin E/high-density lipoprotein cholesterol ratio ($p < 0.05$), vitamin E/total cholesterol ratio ($p < 0.01$) and vitamin E/triglyceride ratio ($p < 0.05$) between the three groups of the study. Results of the present study did not suggest any improving effect of curcumin supplementation on serum vitamin E concentrations in subjects with MetS. Copyright © 2017 John Wiley & Sons, Ltd.

Keywords: metabolic syndrome; vitamin E; curcuminoids; turmeric.

INTRODUCTION

Curcuma longa is a perennial plant that grows in Central America and tropical areas of Asia. Turmeric, extracted from dried rhizomes of the plant, is known in Asian medicines, and it is applied for the treatment of rheumatism, biliary disorders, diabetic wounds, anorexia, cough and hepatic disorders. It also is widely used as food seasoning (Miquel *et al.,* 2002). The main chemical components of turmeric are called curcuminoids, which include curcumin (diferuloylmethane), bisdemethoxycurcumin and demethoxycurcumin (Sahoo *et al.,* 2008). A number of studies have shown that curcumin exhibits important biological effects including antioxidant (Sahebkar *et al.,* 2013; Panahi *et al.,* 2016), antiinflammatory (Sahebkar, 2014a), immunomodulatory (Karimian *et al.,* 2016; Derosa *et al.,* 2016; Sahebkar *et al.,* 2016; Panahi *et al.,* 2012), antitumour (Mirzaei *et al.,* 2016; Momtazi *et al.,* 2016), lipid-modifying (Mohammadi *et al.*, 2013; Panahi *et al.,* 2014a; Sahebkar, 2014b), cardioprotective (Sahebkar, 2013), anti-arthritic (Panahi *et al.,* 2014b), analgesic (Sahebkar and Henrotin, 2016), anti-ischaemic (Sahebkar, 2010) and antidepressant (Esmaily *et al.,* 2015; Panahi *et al.,* 2014b) properties. Metabolic syndrome (MetS) is a clustering of metabolic disturbances that result from several cardiovascular risk factors including hyperglycaemia, diabetes, central obesity dyslipidemia, dyslipidemia and hypertension (Lakka *et al.,* 2002). MetS has various definitions by different health organizations (Lakka *et al.,* 2002). A high prevalence of MetS has been reported in developed countries (Grundy, 2008). Studies have shown that in the presence of the MetS, the risks of developing cardiovascular disease and mortality are increased at approximately two-fold (Isomaa *et al.,* 2001; Hu *et al.,* 2004). Insulin resistance and central obesity are two accompanying features of MetS and may be causative factors for its pathogenesis (Lakka *et al.,* 2002; Alberti *et al.,* 2006). Decreased weight and increased physical activity with drug treatment can be appropriated to treat the many diseases associated with MetS such as diabetes and cardiovascular disease (Eckel *et al.,* 2005).

Vitamin E is a group of lipid soluble compounds including tocopherols and tocotrienols that exist in some

* Correspondence to: Dr. Majid Ghayour-Mobarhan, Biochemistry and Nutrition Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. Dr. Amirhossein Sahebkar, Department of Biotechnology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
E-mail: ghayourm@mums.ac.ir (Majid Ghayour-Mobarhan); sahebkara@mums.ac.ir (Amirhossein Sahebkar)

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dairy products like seeds, corn, oils, margarine, and whole wheat flour, soy, nuts, some meats and vegetables (Mardones *et al.,* 2002; Kitagawa and Mino, 1989). Vitamin E has antioxidant property and is a lipid-lowering compound that can significantly decrease the levels of total serum cholesterol and lipid peroxides in experimental animal models (Mardones *et al.,* 2002). Vitamin E has a defensive role against oxidative stress and scavenges free radicals in members and, therefore, inhibits the production of lipid peroxides (Verma *et al.*, 2001; Sen Gupta *et al.,* 2004).

The immunomodulatory, antioxidant and antiinflammatory effects of curcumin are well documented (Sahebkar *et al.,* 2013). In this study, we investigated the effect of curcumin therapy in simple and modified formulations on serum vitamin E (VitE) level in patients with MetS.

MATERIALS AND METHODS

Subjects. One hundred and twenty-nine patients with MetS (aged 18–65 years old) were chosen sequentially from clinic and randomly recruited from those referring to the Nutrition Clinic of the Ghaem Hospital, Mashhad, Iran. The objectives and protocol of the study were explained to each participant prior to the study. Members were provided with information about the study both by verbal explanation and written information sheets. Inclusion criteria were an age range of 18–65 years and having a MetS according to International Diabetic Federation criteria. Exclusion criteria included known systemic diseases; lactation; pregnancy; and consumption of the antihypertensive, antidyslipidemic or antidiabetic drugs; and nutritional supplements. Written information consent form was obtained from all participants. The study protocol was accepted by the Ethics Committee at the Mashhad University of Medical Sciences. The current trial has been registered in Iranian Registry of Clinical Trials whit a registration number IRCT2014052014521N3.

Study design. This was a 6-week randomized clinical trial. The study was conducted in the Nutrition Clinic of the Ghaem Hospital, Mashhad, Iran. Figure 1 shows the flowchart of the study design. Patients were randomly divided into three treatment groups: a group receiving capsules of absorption-enhanced curcumin (1 g/day equivalent to 200-mg pure curcumin/day) for a period of 6 weeks)n = 40), a group receiving capsules of unformulated curcumin (1 g/day) for a period of 6 weeks (n = 40) and a control group receiving a placebo capsule for the same period (n = 40). Placebo capsules contained lactose and starch with a ratio of 2:1.

All participants were instructed to take one capsule 500 mg/day with blinded labels twice a day (total of two capsules per day) for 6 weeks. All volunteers were given isocaloric diet advice during the study. Serum VitE concentrations were determined in all patients at baseline and at the end of the sixth week by high-performance liquid chromatography (HPLC) (Papas *et al.,* 2003).

Demographic and anthropometric measurements. All subjects completed a questionnaire to collect information on their socio-demographic status, occupation, smoking behaviour, medical history and medication. All subjects were measured for height, weight and waist circumference (in centimetres). Body mass index (BMI) was calculated by the following formula: BMI = weight (kg)/height (m^2).

Blood sampling. We collected blood samples into plain plastic tubes in the morning after a 12-h fasting from

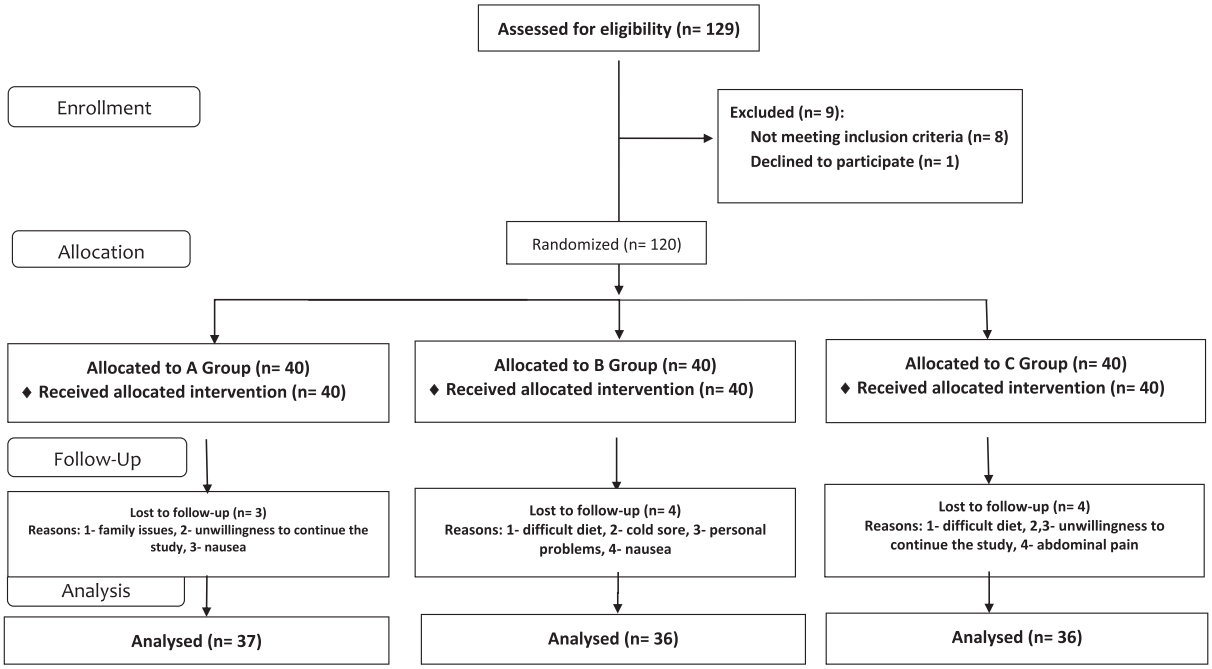

Figure 1. The flowchart of the study design. A, curcumin–phospholipid complex group; B, curcumin group; C, placebo group.

each subject. We excluded haemolysed samples from analysis. After separation, aliquots of serum were frozen at −80°C until analysis. Separation of serum from blood samples was conducted by centrifugation at 10 000 *g* for 15 min.

Serum vitamin E assay. Serum levels of VitE (α-tocopherol) were measured by HPLC using a modification of the method of Papas *et al.* (2003). Briefly, 750 μL ethanol was added to 250-μL serum and centrifuged at 5000–7000 rpm for 10 min. After that, 1 mL *n*-hexane was added to supernatant, vortex-mixed and centrifuged again. Then, the supernatant was evaporated under nitrogen gas, and the residue was reconstituted in 250 μL methanol. Twenty-five microlitres of the solution was then injected to the HPLC column. Methanol was used as the mobile phase, and detection was carried out at 295 nm using UV detector (Waters 486, Milford, MA, USA). The samples were eluted isocratically at a flow rate of 1 mL/min.

Statistical analysis. All statistical analyses were performed using the Statistical Package for Social Sciences version 16 software. Normal distribution of variables was assessed using the Kolmogorov–Smirnov test. Quantitative data were expressed as the mean ± SD (for normally distributed variables) or as the median and interquartile range in the case of serum VitE (for none normally distributed data). The analysis of variance, Kruskal–Wallis and Mann–Whitney tests were used to compare the clinical characteristics and baseline demographics between the groups. A *p*-value of less than 0.05 was considered as statistically significant.

Table 1. Sex distribution of the study groups

Group	Female % (*n*)	Male % (*n*)	*p*-value
Curcumin–phospholipid complex (*n* = 40)	62.5 (25)	37.5 (15)	0.280
Curcumin (*n* = 40)	77.5 (31)	22.5 (9)	
Placebo (*n* = 40)	75.0 (30)	25.0 (10)	

RESULTS

Study population

A total of 129 subjects aged 18–65 years with MetS were initially enrolled in this study (Fig. 1). Nine volunteers had exclusion criteria including taking pharmacotherapy, surgery, pregnancy or unwillingness to participate in the study. One hundred and twenty subjects were randomly allocated into the three groups. During the study, 11 volunteers dropped out because of reported adverse effects, personal problems or unwillingness to continue the study.

Adverse effects

As shown in Fig. 1, one subject from the curcumin–phospholipid complex-treated group reported hypersensitivity (sneezing and cold sore). In the curcumin-treated group, a few subjects reported minor symptoms including cold sore (one subject) and nausea (one subject).

Table 2. Clinical and biochemical features in subjects at baseline

Variables	Curcumin–phospholipid complex group	Curcumin group	Placebo group	*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
Vitamin E (μmol/L)	2.41(1.78 to 7.21)	2.90(1.43 to 6.50)	2.43(1.77 to 5.25)	0.873

BMI, body mass index; WC, waist circumference.
Values expressed as mean ± SD for normally distributed data, and median and interquartile range for non-normally distributed data. Between-group comparisons were assessed by parametric statistical analysis for normal distributed data and nonparametric test for non-normally distributed data.

Table 3. Clinical and biochemical features in subjects after intervention

Variables	Curcumin–phospholipid complex group	Curcumin group	Placebo group	*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)	100.8 ± 11.57	97.01 ± 11.14	99.42 ± 11.86	0.455
Vitamin E (μmol/L)	2.36 (1.78 to 5.00)	2.36 (1.49 to 4.28)	3.87 (2.20 to 6.28)	0.90

BMI, body mass index; WC, waist circumference.
Values expressed as mean ± SD for normally distributed data, and median and interquartile range for non-normally distributed data. Between-group comparisons were assessed by parametric statistical analysis for normal distributed data and nonparametric test for non-normally distributed data.

Baseline characteristics of case and control groups

Tables 1 and 2 show the sex distribution and baseline characteristics of 120 subjects. There were no significant differences between three groups in regard to gender distribution, age, weight, BMI, waist circumference and serum VitE levels before the intervention ($p > 0.05$, Tables 1 and 2). Table 3 shows the clinical

Table 4. Changes in parameters at baseline and after 6 weeks

Changes in parameters at baseline and after 6-week intervention	Curcumin–phospholipid complex group	Curcumin group	Placebo group	*p*-value	*Post hoc* (Mann–Whitney)		
					$p_{A\&B}$	$p_{A\&C}$	$p_{B\&C}$
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	—	—	—
Vitamin E (μmol/L)	−0.12 (−2.36 to 0.37)	0.00 (−2.19 to 0.12)	0.29 (0.00 to 2.43)	0.004	0.834	0.004	0.005

BMI, body mass index; WC, waist circumference; A, curcumin–phospholipid complex group; B, curcumin group; C, placebo group.
Values expressed as mean ± SD for normally distributed data, and median and interquartile range for non-normally distributed data. Between-group comparisons were assessed by parametric statistical analysis for normal distributed data and nonparametric test for non-normally distributed data.

Table 5. The effect of curcumin and curcumin–phospholipid complex on serum VitE in subjects with central obesity

	Variables (μmol/mmol)	Group	Mean ± SD	*p*-value	*Post hoc* (Mann–Whitney)		
					$p_{A\&B}$	$p_{A\&C}$	$p_{B\&C}$
Before intervention	VitE/LDL	A	0.69 (0.40 to 1.68)	0.812	—	—	—
		B	0.72 (0.33 to 1.33)				
		C	0.94 (0.35 to 1.20)				
	VitE/TC	A	0.42 (0.27 to 1.15)	0.808	—	—	—
		B	0.46 (0.23 to 0.90)				
		C	0.51 (0.24 to 0.82)				
	VitE/TG	A	2.01 (1.02 to 3.66)	0.526	—	—	—
		B	1.74 (1.01 to 4.04)				
		C	1.65 (0.91 to 2.49)				
	VitE/HDL	A	2.25 (1.27 to 5.03)	0.898	—	—	—
		B	2.23 (1.02 to 5.47)				
		C	2.23 (1.25 to 4.21)				
After intervention	VitE/LDL	A	0.69 (0.38 to 1.51)	0.026	0.433	0.117	0.006
		B	0.61 (0.44 to 1.10)				
		C	1.05 (0.65 to 1.91)				
	VitE/TC	A	0.41 (0.24 to 0.99)	0.053	—	—	—
		B	0.41 (0.29 to 0.61)				
		C	0.65 (0.38 to 0.98)				
	VitE/TG	A	1.78 (0.66 to 3.68)	0.087	—	—	—
		B	1.71 (0.86 to 2.65)				
		C	2.56 (1.35 to 3.58)				
	VitE/HDL	A	2.10 (1.14 to 3.68)	0.076	—	—	—
		B	1.83 (1.15 to 2.58)				
		C	2.93 (1.75 to 4.51)				
Changes in parameters at baseline and after 6-week intervention	VitE/LDL	A	0.02 (−0.40 to 0.38)	0.028	0.589	0.055	0.009
		B	0.00 (−0.49 to 0.32)				
		C	0.48 (−0.8 to 0.72)				
	VitE/TC	A	−0.01 (−0.43 to 0.18)	0.006	0.796	0.009	0.004
		B	0.00 (−0.42 to 0.14)				
		C	0.27 (0.00 to 0.43)				
	VitE/TG	A	−0.03 (−0.66 to 0.72)	0.023	0.792	0.013	0.028
		B	0.05 (−0.99 to 0.73)				
		C	0.80 (0.03 to 1.92)				
	VitE/HDL	A	−0.04 (−1.54 to 0.71)	0.010	0.540	0.028	0.004
		B	−0.22 (−3.05 to 0.44)				
		C	0.51 (0.06 to 1.72)				

A, curcumin–phospholipid complex group; B, curcumin group; C, placebo group; VitE; vitamin E; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein.
Values expressed as median and interquartile range for non-normally distributed data. Between group comparisons were assessed by non-parametric test for non-normally distributed data.

and biochemical features in subjects after the intervention. There were no significant differences in serum VitE levels after the intervention.

Comparison of vitamin E concentration in three groups of the study

There was a significant difference in serum VitE in the placebo group between the pre-trial and post-trial of the study compared with the curcumin–phospholipid complex and curcumin groups ($p < 0.01$), (Table 4). There was a significantly higher VitE/low-density lipoprotein cholesterol ratio in the placebo group after the intervention than in group B ($p < 0.05$) (Table 5).

There were significant differences between pre-trial and post-trial in the VitE/low-density lipoprotein cholesterol ratio ($p < 0.05$), VitE/total cholesterol ratio ($p < 0.01$), VitE/triglyceride ratio ($p < 0.05$) and VitE/high-density lipoprotein cholesterol ratio ($p < 0.05$) between the three groups of the study (Table 5).

DISCUSSION

To our knowledge, there has been no previous study of the effects of curcumin and curcumin–phospholipid complex on serum VitE in human subjects. The results of the present study indicate that curcumin supplementation did not have any improving significant effect on serum VitE levels after 6-week treatment in individuals with MetS.

The results showed that in the curcumin–phospholipid complex and curcumin groups, VitE was decreased after 6 weeks. However, in the placebo group, VitE was increased after 6 weeks. It has been well documented that polyphenolic compounds have not only antioxidant but also pro-oxidant activities in certain conditions. Oxidized phenolics are regenerated by interactions with other antioxidants such as glutathione and ascorbate (Meister, 1994). Hadi *et al.* have reported that curcumin can act as a pro-oxidant and promote reactive oxygen species generation mostly in the form of hydroxyl radicals at higher doses or in the presence of transition metal ions (Hadi *et al.,* 2000).

We have previously reported the effects of curcumin on the pro-oxidant–antioxidant balance in obese individuals (Sahebkar *et al.,* 2013). We have also demonstrated the antioxidant effects of curcuminoids in patients suffering from knee osteoarthritis. In this latter study, the subjects were given curcuminoid capsules (1500 mg/day in three divided doses) for a period of 6 weeks. There was a significant elevation in serum superoxide dismutase activities, a borderline significant elevation in reduced glutathione levels and a significant reduction in malondialdehyde concentrations in the curcuminoids compared with the placebo group (Panahi *et al.* 2015a).

Kamal-Eldin *et al.* (2000) investigated the effects of dietary phenolic compounds on tocopherol, cholesterol and fatty acids in rats. Their results are consistent with our finding. They found that curcumin did not affect plasma tocopherol levels. The effects of the phenolic compounds butylated hydroxytoluene, sesamin, curcumin and ferulic acid on plasma, liver and lung concentrations of α-tocopherol and γ-tocopherol; on plasma and liver cholesterol; and on the fatty acid composition of liver lipids were studied in male Sprague Dawley rats. Administration of curcumin raised the concentration of α-tocopherol in the lung but did not affect the plasma values of any of the tocopherols.

DiSilvestro *et al.* (2012) showed that plasma catalase activities were increased by curcumin treatment in healthy middle-aged people. Biswas *et al.* reported that curcumin can increase the level of catalase, superoxide dismutase and glutathione peroxidase activities (Biswas *et al.,* 2010). Therefore, our results suggest that curcumin can improve the enzymatic antioxidants but does not affect serum VitE antioxidant concentration.

CONCLUSION

The results of the present study did not suggest any significant effect of curcumin, in either unformulated or lecithinized form, on serum levels of VitE. It appears that the putative antioxidant effects of curcumin are mainly driven by the modulatory effects of this phytochemical on enzymatic antioxidant elements rather than VitE. However, still further dose-ranging studies with longer durations of follow-up are required to confirm the present results.

COMPLIANCE WITH ETHICAL STANDARDS

Ethical approval

This research was 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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Conflict of Interest

The authors confirm no conflict of interest.

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