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The Effect of Curcumin on Serum Copper and Zinc and Zn/Cu Ratio in Individuals with Metabolic Syndrome: A Double-Blind Clinical Trial

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ABSTRACT
Metabolic syndrome is a complex disorder with high socioeconomic costs and a high global prevalence. The serum concentrations of some trace elements are higher in people with metabolic syndrome compared to normal individuals. Curcumin is derived from turmeric and has antioxidant and anti-inflammatory properties. Curcumin may therefore have a potential role in the management of cardiovascular risk. The aim of this study was to investigate the effects of curcumin on serum copper (Cu), zinc (Zn), and Zn/Cu ratio levels in patients with metabolic syndrome. A double-blind clinical trial was designed in which 120 individuals with metabolic syndrome were randomly assigned to one of three groups: curcumin 1gr/day, phospholipidated curcumin 1gr/day, or a placebo, each taken for 6 weeks. Serum copper and zinc were measured before and after intervention. At baseline, in addition to obtaining the anthropometric characteristics of participants, a fasting blood sample was taken from each participant, and the concentrations of serum Cu and Zn were measured by atomic absorption (Varian AA 240 FS model). Serum Zn concentrations rose significantly in the phospholipidated curcumin and curcumin groups, being significantly higher ($p < .001$) in the phospholipidated curcumin group than in the curcumin group ($p < .05$). Serum Zn concentration fell in the control group ($p < .05$). Changes in serum Zn level from baseline to the levels after six weeks' intervention were significantly different between the groups, but changes in serum Cu from between baseline until after intervention were not significantly different. The serum Zn/Cu level in phospholipidated curcumin and curcumin groups after intervention was higher than for the control group, but it was more significant in the group taking phospholipidated curcumin ($p < .001$). Curcumin and phospholipidated curcumin complex, given at a dose of 1 g per day for six weeks, were associated with an increase in serum zinc and consequently zinc-to-copper ratio.

KEYWORDS
curcumin; metabolic syndrome; copper; zinc

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Introduction

Metabolic syndrome (MetS) is defined by the presence of abdominal obesity, elevated glucose and triglycerides, increased blood pressure, and low high-density lipoprotein cholesterol (HDL-C) levels. The prevalence of MetS has increased globally primarily because of excessive intake of energy-dense foods and decreaased physical activity. Asians have an ethnic predisposition to MetS, and it is of special concern for Middle Eastern populations, which are forecasted to experience the greatest universal burden of diabetes by 2020 (Amirkalali et al., 2015). As a country in this region, Iran has one of the highest prevalence rates of MetS worldwide (Amirkalali et al., 2015). According to the latest studies, 33% of the Iranian adult population has MetS (Noshad et al., 2016). In the future, MetS may surpass smoking as the chief risk factor for heart disease. Metabolic disorder increases the risk of cardiovascular diseases, non-alcoholic fatty liver disease (NAFLD), type 2 diabetes (T2D), cancer, dementia, infertility, and other diseases (Guo et al., 2016; Rashidy-Pour et al., 2009).

Research has shown the link between the level of zinc and the levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C) (Ranasinghe et al., 2015). Other studies have shown that the level of zinc varies under different conditions such as obesity and type 2 diabetes in human and animal models (Abdoljalal et al., 2015). A study in Korea has confirmed the relationship between serum zinc and MetS (Seo, Song, Han, Lee, & Kim, 2014).

Zn/Cu ratio, apart from showing the individual levels of each trace element, seems to exert a significant effect on metabolism, indicating the pivotal role of these trace elements in the pathogenesis of metabolic diseases. (Hamasaki, Kawashima, & Yanai, 2016)

The results of a study have shown the relationship between serum levels of copper and total cholesterol, LDL-C, and triglycerides. Epidemiological studies reveal a positive relationship between low levels of zinc and copper and increased risk of cardiovascular disease (Obeid et al., 2008).

Some studies have indicated that both Zn deficiency and excess Cu are related to high risk of cardiovascular disease (CVD) and diabetes. Epidemiological and biological investigations have demonstrated that an imbalance between serum Zn and Cu levels is a causative factor for different diseases, especially diabetes and CVD (Hamasaki et al., 2016).

Curcumin is a natural yellow pigment, also called turmeric yellow, extracted from *Curcuma longa* L. rhizomes. It has biological and pharmacological properties, including, immunomodulatory, antitumor, anti-inflammatory, antioxidant, cardioprotective, lipid modifying, antiarthritic, analgesic, anti-ischemic, and antidepressant properties (Gupta et al., 2013; Mohammadi et al., 2017).

Metabolic syndrome is often characterized by oxidative stress and, as we know, cooper and zinc are antioxidants. Therefore, in this study, the effects of curcumin and phospholipidated curcumin, as substances with antioxidant properties, were evaluated on these elements in patients with metabolic syndrome.

Curcumin affects copper and zinc by reducing oxidative stress. Information is lacking on the effect of curcumin on trace elements copper and zinc and Zn/Cu ratio in patients with MetS. The aim of this study was to investigate the effects of curcumin on serum Cu, Zn, Zn/Cu ratio levels in patients with MetS.

Methods and materials

This study was a randomized double-blind clinical trial; patients were recruited and treated for six weeks between September and October 2014. The study protocol was approved by the local ethics committee of clinical trials of Mashhad University of Medical Sciences and was carried out at the Nutrition Clinic of Ghaem Hospital, Mashhad, Iran.

Study population

Inclusion criteria

One hundred twenty individuals were eligible if they were 18–65 and had MetS according to International Diabetes Federation (IDF) criteria (IDF 2010). IDF criteria are waist circumference (WC) > 94 cm in males and > 80 cm in females plus any two of the following: (1) triglyceride (TG) ≥ 150 mg/dL or specific treatment for this lipid abnormality, (2) HDL-C < 40 mg/dL in males and < 50 mg/dL in females or specific treatment for this lipid abnormality, (3) systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 85 mmHg or treatment of previously diagnosed hypertension, (4) fasting plasma glucose (FPG) ≥ 100 mg/dL or previously diagnosed type 2 diabetes.

Exclusion criteria

Exclusion criteria were (1) a history of systemic disease such as lupus or rheumatoid arthritis, kidney disease, pregnancy, lactation; (2) using any supplements or drugs for decreasing blood pressure, glucose, or lipid during the previous six months.

Study design

All participants provided written informed consent. A complete history (anthropometric and BP measurements) and a physical examination were done at baseline and after intervention. Following the Fleiss book (Fleiss, 2011), the patients were divided into three groups of 40 each. Assignment to curcumin, phospholipidated curcumin, and placebo was done. Following previous studies (Saberi-Karimian et al., 2018; Ganjali and Sahebkar, 2014), patients were given 500 mg curcumin, phospholipidated curcumin, or placebo twice a day (1 g/d) for six weeks (Figure 1). Patients were followed up every two weeks 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. Laboratory tests, including a complete blood count and blood chemistry, were performed at baseline and at the end of the treatment. Then all serum samples were aliquoted and stored at −20°C. Serum was separated from blood samples by centrifugation at 10,000 g for 15 min.

Measurements of copper and zinc

The serum levels of zinc and copper were measured by atomic absorption spectrophotometer (Varian AA 240 FS model, USA).

Curcumin capsule preparation

Each capsule contained 500 mg unformulated curcumin or phospholipidated curcumin (Meriva; Indena S.p.A., Italy) (Cuomo et al., 2011) and wasadministration twice a day. Phospholipidated curcumin contained a complex of curcumin and soy phosphatidylcholine in a 1:2 weight rxxxvatio and two parts of microcrystalline cellulose to improve flowability, with an

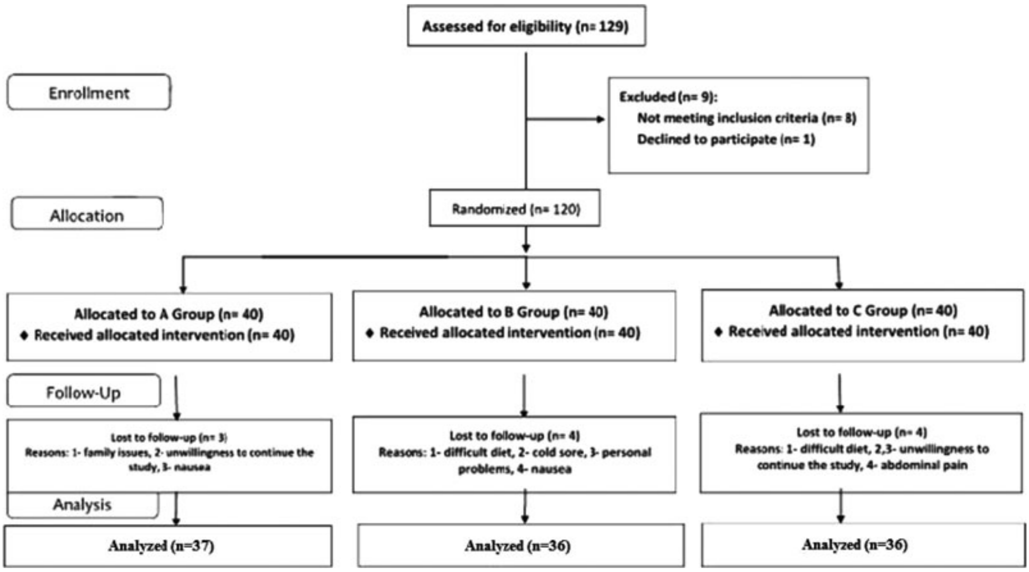

Figure 1. Summary of the study design, randomization, and clinical outcomes of the six weeks of treatment. A = phospholipidated curcumin group; B = curcumin group; C = placebo group.

overall content of curcumin in the final product of around 20% (Belcaro et al., 2010; Semalty et al., 2010). The shape, weight, and color of placebo capsules were the same as the curcumin capsules.

Statistical analysis

All data analyses were performed using the Statistical Package for Social Sciences (SPSS version 16). The normality of distribution was evaluated by the Kolmogorov-Smirnov test. Data are presented as the mean ± standard deviation value or median and interquartile range (IQR). For the analysis of each group before and after the intervention, paired-samples *t* test was used. To examine changes in three groups, one-way ANOVA was employed. Then, using Tukey test, significant changes in the three groups were studied. A *p* value less than .05 was considered statistically significant.

Result

A total of 129 patients with MetS entered the study at the Nutrition Clinic of Ghaem Hospital, Mashhad, Iran, between September and October 2014. All groups had the same diet. One patient dropped out (for personal reasons) and 8 patients were excluded; 120 patients were randomly divided into three groups for trial intervention (two intervention groups [phospholipidated curcumin and curcumin] and a control [placebo] group).

To calculate drug compliance, the date of first and last use of each capsule was recorded for each participant. During the midterm and final visit, volunteers were asked to bring the remaining capsules for counting. The compliance was calculated according to the following formula for each study group:

$$\text{Number of remaining pills} - \text{number of distributed pills/number of pills to be consumed} \times 100.$$

Table 1. Baseline Demographic and clinical characteristics.

Variable	Phospholipidated curcumin (n: 36)	Curcumin (n:37)	Placebo (n:36)	p-value
Sex				
Men(n)	15	9	10	0.28
Women(n)	25	31	30	
Age (years)	40 ± 10.4	37.5 ± 9.4	38.5 ± 10.2	0.46
Systolic blood pressure (mmHg)	120.82 ± 10.24	119.74 ± 11.87	120.26 ± 11.50	0.91
Diastolic blood pressure(mmHg)	83.48 ± 9.17	81.26 ± 10.06	81.70 ± 10.76	0.58
HDL-C(mg/dl)	52.23 ± 12.91	53.33 ± 10.55	51.91 ± 10.62	0.84
LDL-C(mg/dl)	152.99 ± 38.84	165.90 ± 38.76	153.78 ± 40.40	0.26
Total cholesterol(mg/dl)	241.28 ± 51.96	254.12 ± 43.64	242.12 ± 46.83	0.40
Triglyceride (mg/dl)	153.50 (102.50-217.00)	150.00 (108.25-234.25)	158.0 (128.5-216.25)	0.93
Fasting blood glucose (mg/dl)	95.97 ± 19.91	98.72 ± 27.17	92.82 ± 16.62	0.47
Albumin (g/dl)	4.89 ± 0.39	4.91 ± 0.46	5.22 ± 0.44	0.001
Total protein (g/dl)	7.59 ± 0.42	7.65 ± 0.67	7.91 ± 1.29	0.097
Direct Bilirubin(mg/dl)	0.32 ± 0.14	0.31 ± 0.13	0.38 ± 0.17	0.114
Lactate Dehydrogenase(U/L)	139.05 ± 42.14	125.69 ± 32.06	130.81 ± 34.09	0.22
Alkaline phosphatase(U/L)	131.5 ± 35.52	122.38 ± 35.62	146.93 ± 31.94	0.005
Aspartate transaminase (U/L)	12.69 ± 7.87	10.19 ± 5.8	11.14 ± 8.02	0.22
Alanine transaminase(U/L)	12.19 ± 10.31	8.24 ± 7.13	12.43 ± 10.79	0.075
Waist circumference (cm)	103 ± 10.24	99.94 ± 9.34	102.49 ± 9.21	0.34
Weight (kg)	84 ± 14.67	80.6 ± 11.7	82.1 ± 12.68	0.80
BMI (Kg/m^2)	30.66 ± 5.06	30.67 ± 3.57	31.22 ± 4.67	0.82
FAT%	34.51 ± 8.07	35.42 ± 6.12	35.21 ± 7.86	0.84

The result of the Chi-square test showed that compliance in the group receiving the phospholipidated curcumin, curcumin and placebo were 93.55 ± 7.17%, 95.74 ± 5.78% and 95.02 ± 7.48%, respectively, and no significant difference was observed ($P = 0.411$).

The baseline demographic and clinical characteristics of the study groups are presented in Table 1. Because the present research is part of a larger study, the results of curcumin intervention were published in the previous article. Therefore, here only the results of clinical and biochemical features in participants at baseline are presented (Saberi-Karimian et al., 2018).

The serum Zn, Cu, and Zn/Cu levels of the phospholipidated curcumin, curcumin, and control groups of MetS patients are shown in Table 2. Serum Cu concentration in three groups was increases after intervention, but it was significantly higher ($p < .05$) in the phospholipidated curcumin group than in curcumin and control groups after intervention.

Serum Zn concentration was increased significantly in the phospholipidated curcumin and curcumin groups after intervention, and it was significantly higher ($p < .001$) in the phospholipidated curcumin group than in the curcumin group ($p < .05$). Serum Zn concentration significantly ($p < .05$) was decreased in the control group. Changes in serum Zn level at baseline and after six weeks of intervention were significantly different between groups, but changes in serum Cu level from baseline until after intervention were not different.

Zn/Cu level in phospholipidated curcumin and curcumin groups after intervention was higher than in the control group, but it was more significant in the phospholipidated curcumin group ($p < .001$). Zn/Cu level in the control group was significantly ($p < .05$) decreased.

Logistic regression analysis was performed to determine the odds ratio (OR) of the association between Zn, Cu, and Zn/Cu before and after intervention with phospholipidated curcumin, curcumin, and control groups (Table 3). Results obtained from univariate analysis for intervention demonstrated that changes in Zn are associated with phospholipidated curcumin and changes in and Zn/Cu are associated with curcumin.

Table 2. Comparison between mean copper and mean zinc levels (ug/dl) in all groups of the study.

		Phospholipidated curcumin ($n = 36$)	p value	Curcumin ($n = 37$)	p value	Placebo ($n = 36$)	p value	Total p value
Cu concentration (μg/dl)	Before	116.19 ± 26.18	.011	98.69 ± 33.36	.41	108.54 ± 31.79	.36	.45
	After	129.08 ± 19.34		103.72 ± 36.97		110.64 ± 29.83		
	Changes	− 22.29 ± 36.86		5.02 ± 36.2[a]		1.88 ± 30.02[a]		.001
Zn concentration (μg/dl)	Before	51.48 ± 14.18	< .001	80.43 ± 22.53	.046	83.93 ± 16.03	.023	< .001
	After	76.26 ± 13.56		90.38 ± 26.53		75.30 ± 18.34		
	Changes	− 12.46 ± 29.9		9.95 ± 28.84[a]		− 7.21 ± 18.21[b]		
Zn/Cu concentration (μg/dl)	Before	0.50 (0.4–0.6)	.010	0.81 (0.59–1.24)	.82	0.78 (0.64–0.89)	.028	< .001
	After	0.5 (0.39–0.7)		0.95 (0.63–1.24)		0.71 (0.63–0.81)		
	Changes	− 0.3 (−0.16–0.21)[a]		0.42 (0.16–0.75)[b]		−0.013 (−0.23–0.1)[a b]		

[a]Curcumin and placebo versus phospholipidated curcumin.
[b]Curcumin versus placebo.

Table 3. Changes in serum trace elements before and after intervention.

		Reference group and phospholipidated curcumin	Reference group and curcumin
Cu concentration (μg/dl)	Before	1.04 (0.921–1.196)	0.9 (0.779–1.039)
	After	0.938 (0.831–1.059)	1.152 (0.976–1.365)
	Changes	0.995 (0.965–1.027)	1.002 (0.965–1.041)
Zn concentration (μg/dl)	Before	0.907 (0.749–1.098)	1.105 (0.939–1.301)
	After	1.104 (0.895–1.361)	0.913 (0.724–1.153)
	Changes	1.081 (1.022–1.144)**	1.029 (0.972–0.972)
Zn/Cu concentration (μg/dl)	Before	0.341 (0–18)	− 6.3 (−1.18–34.29)
	After	0 (0–11)	0 (−1.1–3.49)
	Changes	3.59 (0.273–47.22)	18.78 (1.83–191.93)*

Reference group is placebo. $^{***}p < .001$. $^{**}p < .01$. $^{*}p < .05$.

Discussion

Copper and zinc are essential rare elements that play an important role in biological processes. Zn, in serum and cellular concentration, is known to be altered in conditions such as obesity and type 2 diabetes (Klevay, 2010). The results of different studies indicate the relationship of copper and zinc with MetS (Diaz Romero et al., 2002; Ghayour-Mobarhan et al., 2008). Curcumin is able to apply antioxidant effects due to its ability to scavenge reactive oxygen and nitrogen free radicals or by modulating cellular defenses, which themselves exert antioxidant effects (Li et al., 2015). Curcumin antioxidant and anti-inflammatory properties, which increase the elimination of free radicals, can prevent the progression of inflammatory responses (Panahi, Ahmadi, Teymouri, Johnston, & Sahebkar, 2018).

There is a paucity of studies on the effect of curcumin and phospholipidated curcumin complex on the levels of trace elements in patients with MetS.

In the study by Afsaneh et al. (2014) on 30 obese patients, the results showed that consuming one gram of curcumin per day together with black pepper (with a dose of 10 g/day) for four weeks was associated with a significant increase in zinc-to-copper ratio. However, it did not affect the amounts of copper, zinc, and SOD enzyme (Afsaneh Mohajer, Parizadeh, & Sahebkar, 2014). On the other hand, a meta-analysis by Amirhossein Sahebkar, Ursoniu, and Banach (2015) revealed the significant effect of curcumin on increasing the serum activity of SOD enzymes and catalase and GSH concentrations and decreasing lipid peroxidation (Sahebkar et al., 2015).

Serum Zn/Cu ratio could be a better marker for human metabolism compared to Zn or Cu status alone, and it seems to have an important effect on metabolism, indicating that these trace elements may play a key role in the pathogenesis of metabolic diseases such as diabetes and CVD. Some studies have indicated that both Zn deficiency and excess of Cu are related to high risk of cardiovascular disease and diabetes (Hamasaki et al., 2016). In this study, differences in the amount of zinc and zinc-to-copper ratio before and after intervention were statistically significant. The variations of zinc and zinc-to-copper ratio were significant between phospholipidated curcumin and curcumin groups compared with the placebo group, respectively. In fact, phospholipidated curcumin significantly increased the amount of zinc amount in serum, while curcumin increased the ratio of zinc to copper. In the placebo group, we observe significant decreases.

There is growing evidence about the important role of oxidative free radicals in pathogenesis of coronary artery disease (CAD). Trace elements (e.g., zinc and copper) are also involved in the pathogenesis of CAD. Further studies on zinc and copper in patients with CAD are required because trace elements can act as a predictor of coronary artery disease, and adjusting the levels of these elements may prevent the occurrence of this disease (Lutfi et al., 2015)

In the study by Kazemi-Bajestani et al. (2007) on angiography patients, the copper-to-zinc ratio in patients with coronary artery disease was lower than in healthy individuals in the control group, as dyslipidemia caused by a reduction in the copper would lead to cardiovascular disorders. Therefore, a decreased zinc level seems to correlate with elevated risk for coronary artery disease (Bagheri, Akbari, Tabiban, Habibi, & Mokhberi, 2015). Serum Zn concentration was increased significantly in the phospholipidated curcumin and curcumin groups after intervention, and it was significantly higher ($p < .001$) in the phospholipidated curcumin group than in the curcumin group ($p < .05$). The effect of phospholipidated curcumin on zinc was higher than the effect of curcumin because phospholipidated curcumin has better bioavailability than curcumin (Gupta et al., 2013).

In this study, the effects of curcumin and phospholipidated curcumin on zinc-to-copper ratio and serum zinc were more significant than the effect of placebo.

This study had several limitations: (1) absence of a healthy control group and a diet-only group, (2) short treatment period, (3) failure to use different complexes and doses of curcumin. Despite these limitations, we concluded that curcumin and phospholipidated curcumin complex, by increasing serum zinc and consequently zinc-to-copper ratio, can exert a positive impact on the MetS. However, still further studies with longer periods of follow-up are required to confirm the present outcomes

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Declaration of interest

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

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Other information

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