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Original Article

Effects of Saffron on Serum Zinc, Copper and Superoxide Dismutase in Patients with Metabolic Syndrome: A Randomized Double-Blind Clinical Trial

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Abstract

Background and Aim: The prevalence pervasiveness of metabolic syndrome (MetS) is increasing worldwide. We aimed to examine the effects of saffron supplements on serum levels of Cu, Zn and superoxide dismutase (SOD) in subjects with MetS.

Materials and Methods: This randomized, double-blind clinical trial comprised 70 subjects with MetS, aged 18-75 years, who referred to the Nutrition Clinic in Ghaem Hospital from April to June 2014. They were randomly divided into 2 groups: a saffron group taking a capsule of saffron 100 mg/kg/day (50 mg twice a day) (n=35); and a placebo group taking a capsule of placebo (twice a day) (n=35), for a period of 12 weeks. We used atomic absorption spectrophotometry in order determine serum zinc and copper levels in all subjects. Serum SOD activity determined using pyrogallol indirect spectrophotometric assay.

Results: Fifty-six subjects completed the study. There were no significant differences in baseline characteristics between the saffron and placebo groups ($p > 0.05$). The change in mean serum zinc levels at baseline and following 12 weeks of intervention were significantly different between the saffron and placebo groups ($p=0.041$). However, there were no significant changes in serum copper, ZN/Cu and SOD1 between the study groups before and after the intervention.

Conclusion: Saffron supplementation for a period of 12 weeks was associated with a significant increase in serum Zn level in individuals with MetS ($p<0.05$). However, there were no significant effects on copper, Cu/Zn ratio, and superoxide dismutase. Only a single dose of saffron was used for a short period of time in this study, and the sample size was limited. It would be useful to investigate the effects of other doses and longer durations in larger subject samples.

Keywords: Metabolic syndrome, Saffron, Copper, Zinc, Superoxide dismutase

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Introduction

Metabolic syndrome (MetS) is a clustering of cardiovascular risk associated with an increased risk of cardiovascular disease, diabetes type 2 and ultimately with cardiovascular mortality. According to the criteria determined by International Diabetes Federation (IDF), abdominal obesity, hypertriglyceridemia, reduced serum HDL-C, glucose intolerance, and hypertension are the defining components of this syndrome (1, 2). The overall prevalence of MetS in Iran is approximately 27% (3), with a global prevalence of about 20 to 25 %, and it appears to be increasing (4).

Disturbances in the equilibrium between pro-oxidants and anti-oxidants cause oxidative stress, which could be highly influential in the pathogenesis of cardiovascular disease, hypertension and diabetes (5, 6). Oxidative stress might be related to the increased production of reactive oxygen radical species (ROS). According to certain reports, the oxidative stress associated with MetS has been increased (7). Hence, the activity of antioxidants can reduce the risk of this situation. Copper (Cu) and zinc (Zn) are crucial trace elements that play roles as structural ions for several proteins, receptors, and hormones (8). Moreover, they are considered as cofactors and structurally significant ions in antioxidant enzymes such as superoxide dismutase (SOD) (9, 10). Zn is essential for the insulin signaling, synthesis, storage, and release (11). Furthermore, deficiency of Zn might be related with increased oxidative stress, central obesity, abnormal insulin metabolism, triglyceride and HDL-C levels, and blood pressure which have essential roles in the pathophysiology of diabetes and MetS (12, 13). A high level of Zn in the diet might have a protective role against MetS (14, 15). Cu can bind to thiol groups in proteins and thus generate the ROS. Moreover, it can result in ROS mediated damage in biological systems (16). It has been shown that the balance between Cu and Zn has an effect on antioxidant mechanisms and imbalance of Cu/Zn might be associated with the MetS (13, 17-19).

Studies have shown that some foods and herbs have effects on diseases and their associated complications (20-22). Saffron (Crocus sativus) is a perennial stem-less herb from the Iridaceae family. It has been used as a spice and dye in food from ancient times, particularly in Iran (20). A Mediterranean diet, that often contains saffron, has beneficial effects on disease treatment and prevention. Saffron supplements can modulate serum levels of oxidant-antioxidant balance in people with MetS, which could be indicative of an improvement of some aspects of oxidative stress or protection of antioxidants (21). The importance of saffron as an antioxidant is because of three of its secondary metabolites, i.e. crocin, picrocrocin and safranal which are respectively responsible for color, taste and odor (21). It has been reported that saffron has anti-oxidative (especially due to crocin and crocetin) (22), anti-inflammatory, anticancer and hypolipidemic effects (23). Studies that have been recently conducted have shown that saffron supplement can modulate the serum level of oxidant-antioxidant balance (PAB) in patients with MetS, and this suggests the improvement in the protection brought about by antioxidants (21).

Due to the significance of Cu and Zn in people with MetS and the anti-oxidative effects of saffron, we aimed to evaluate the effects of using saffron supplement on serum levels of Cu, Zn and SOD in individuals with MetS.

Materials and Methods

The study protocol was approved by Mashhad University of Medical Sciences (ID: 971230).

Study Design and Subjects

The present study was a part of a double-blind clinical trial which was conducted from April to June 2014 (24), (IRCT20110726007117N10). Figure 1 has summarized the flow chart of the study design.

Seventy subjects with MetS, aged 18-75 years, who were referred to the Nutrition Clinic in Ghaem Hospital were randomly assigned to 2 groups: a saffron group taking a capsule of saffron 100 mg/kg/day (50 mg twice a day) (n=35), and a placebo group taking a capsule of placebo (twice a day) (n=35), for a period of 12 weeks. A computer-generated code was used for randomization. MetS was defined according to the criteria proposed by the International Diabetic Federation (IDF; 2005).

Participants of 18-75 years of age with MetS were included into the study according to the IDF inclusion criteria. Exclusion criteria included suffering from systemic diseases (such as lupus, kidney disease, acquired immunodeficiency syndrome and rheumatoid arthritis), being pregnant and lactating, and taking drugs, including lipid-lowering, antihypertensive and antidiabetic drugs.

All subjects were provided with a nutritional advice about maintaining an iso-caloric diet. Compliance was assessed by counting capsules every three weeks. Refraining from taking capsules regularly (<90% compliance) by the subjects led to exclusion from the study.

Saffron and placebo capsules were prepared by the Novin Saffron Co. (Mashhad, Iran). Saffron capsules were formulated as a capsule containing 50 mg dried saffron. The placebo capsules were similar to saffron capsules with regards to size, color and shape. All volunteers, health professionals and statistician were blinded after assignment to intervention. The capsules containers were coded as A and B by a non-researcher person and remained confidential until data analysis.

Written informed consent was obtained for every participant. Demographic data, anthropometric indices and biochemical laboratory tests were documented at baseline and 12 weeks after the drug/placebo intake. The study protocol was confirmed by the Ethics Committee of Mashhad University of Medical Sciences (MUMS), Mashhad, Iran (ID: IR.MUMS.MEDICAL.REC.1398.739).

Sample Size Calculation

This study was a sub-study from our previous work (33), in which the sample size was calculated based on 27.6% changes in HDL-C concentration after taking crocin, considering the type one error of 0.050 (α=0.050) and power of 0.900 by Stata Statistical Software, Release 11.0 (College Station, TX, USA).

Blood Sampling

A fasted blood sample (after 12 hours fast) was collected from all the participants. Whole blood samples were centrifuged at 10000g for 15 min, then serum aliquots were frozen at -80°C after separating and kept until analysis.

Serum Zinc, Copper and SOD Measurements

An atomic absorption spectrophotometer (Varian AA 240 FS model- America) was used to measure serum zinc and copper levels in all the subjects (10, 11). Serum SOD activity was determined using pyrogallol indirect spectrophotometric assay (27).

Statistical Analysis

Statistical analysis was carried out by SPSS version 18 (SPSS Inc. Chicago, IL, USA). Data were reported as Mean±SD for quantitative data or number and percentage for qualitative data. Paired sample t-test was performed for analysis before and after the intervention. Student t-test and chi-square test were used to analyze the data at baseline and changes after the intervention. Data analysis was per-protocol basis and the p-value< 0.05 was considered to be statistically significant.

Results and Discussion

As indicated in Table 1, no significant differences

Table 1: The baseline characteristics of the study population.

		Saffron Group (N= 26)	Placebo group (N= 30)	P-value
Sex	**Women (n)**	21	19	0.121
	Men (n)	5	11	
Age (year)		42.19 (11.52)	43.60 (9.05)	0.25
Waist circumference (cm)		105.76 (9.01)	103.36 (12.09)	0.11
Diabetics % (n)		23% (5)	20% (4)	0.097
Hypertensive % (n)		23% (5)	23.3% (5)	0.87
Dyslipidemic % (n)		23% (5)	23.3% (5)	0.91

Quantitative data expressed as Mean(standard deviation or SD).

Table 2: The comparison between serum trace elements and SOD1 levels in the saffron and placebo groups.

		Saffron Group	P-value[1]	Placebo Group	P-value[1]	P-value[2]
Zinc (µg/dl)	Before	73.96(13.3)	0.077	64.71(10.21)	0.65	
	After	85.15(16.19)		69.88(22.12)		
	Change	6.19(19.85)		-1.76(14.72)		0.041
Copper (µg/dl)	Before	77.96(13.3)	0.054	83.46(14.92)	0.12	
	After	79.15(16.19)		85.7(13.29)		
	Change	-4.36(14.49)		4.4642(50.51)		0.39
Zn/Cu	Before	0.9(0.22)	0.15	0.87(0.36)	0.89	
	After	1.01(0.38)		0.88(0.16)		
	Change	0.103(0.33)		0.009(0.37)		0.34
SOD1 (Unit/ml)	Before	0.6(0.23)	0.11	0.53(0.26)	0.7	
	After	1.22(0.34)		0.58(0.56)		
	Change	0.61(1.74)		0.057(0.76)		0.13

Quantitative data expressed as Mean (standard deviation or SD).
[1] using a paired t-test
[2] using a t-test.

were observed in baseline features between the saffron and placebo groups (p> 0.05).

Table 2 exhibits the comparison between trace elements and SOD1 levels in the saffron and placebo groups. The mean serum zinc levels in the saffron group before and after the intervention were 73.96(13.3) (µg/dl) and 85.15 (16.19) (µg/dl), respectively. In the saffron group, the mean serum copper and Zn/Cu before the intervention were 77.96(13.3) and 0.9(0.22) (µg/dl), and after the intervention were 79.15(16.19) and 1.01(0.38) (µg/dl), respectively. The mean serum SOD1 in the saffron group was 0.6(0.23) (Unit/ml) at baseline and 1.22(0.34) (Unit/ml) after the intervention. There were no significant differences between the serum zinc (p: 0.077), copper (p: 0.054), Zn/Cu (p: 0.15) and SOD1 (p: 0.11) levels before and after the intervention. The changes in serum zinc levels at baseline and after 12 weeks of intervention were significant between the saffron and placebo groups (p: 0.041). However, there were no significant differences in serum copper (p: 0.39), Zn/Cu (p: 0.34) and SOD1 (p: 0.11) changes between the two study groups before and after the intervention.

We have evaluated the effect of saffron supplements on the serum levels of Zn, Cu, Zn/Cu and SOD1 in individuals with MetS in comparison with the placebo group. Our findings showed that the use of saffron supplement 100 mg/kg/day for 12 weeks increased serum Zn levels in comparison with the group using the placebo (p=0.041); whereas, there was no significant change in the serum Cu, Zn/Cu ratio and SOD1 levels between the two study groups. According to the information we have, this study is the first investigation conducted on the effect of saffron on the serum levels of copper, zinc, and SOD1 in patients with metabolic syndrome.

Recent investigations have shown that saffron and its constituent active components, affect metabolic syndrome characteristics, such as diabetes, obesity and increased blood pressure. Various studies have described the therapeutic impacts of saffron on the risk factors of metabolic syndrome such as diabetes, hypertension and obesity (28).

Kermani *et al*. demonstrated that consuming crocin at a dose of 100 mg/days for 6 weeks changes laboratory parameters in individuals with MetS. Lipid profile including Chol (P<0.001) and TG (P=0.003) levels was significantly decreased after the intervention but the reductions were not significant in comparison with the placebo group (4). In a similar study conducted by Modaghegh *et al*. on 30 healthy people in the three groups of placebo, 200, and 400 mg saffron tablets for 7 days no changes were observed in the lipid profile after saffron consumption (29). In these studies, prolongation of the duration of treatment or increasing the dose of crocin might change the effects on these factors.

Moreover, it has been shown that there is a relationship between an imbalance of redox pathways to all components of MetS (21, 24). Serum Zn/Cu ratio has a potentially significant role in the pathogenesis of MetS, diabetes and CVD (25). Copper (Cu) and zinc (Zn) are the elements which are important as structural ions in receptors, hormones and proteins. They are also considered as cofactor for various enzymatic reactions, particularly for superoxide dismutase (SOD) (26).

Zn and Cu are both involved in the mechanism of redox control, and hence deficiency may cause an augmentation in oxidative injury (30, 32). Shemshian *et al*. showed that saffron supplements (100 mg/kg/day (50 mg twice a day) for 12 weeks) in patients with metabolic syndrome could significantly affect serum PAB values in patients with metabolic syndrome (21). Nikbakht-jam *et al*. conducted a study on serum PAB levels in patients with metabolic syndrome. Sixty persons were divided into two groups (case and control) using crocin tablets (30 mg/d) for 8 weeks. The results demonstrated that daily use of crocin causes a decrease in serum PAB concentrations, whereas there no significant changes were observed in fasting blood glucose or lipid profile (33).

Moreover, it was concluded in an animal study that saffron could reduce lipid peroxidation and increase superoxide dismutase enzyme activity in all tissues in comparison with the control group ($p<0.05$) (34). In our stud, there were no significant changes in serum SOD levels between the case and control groups. The contrast in results is due to differences in the nature of the study.

Rahaiee *et al*. concluded that there are different reasons for the antioxidant activity of saffron (35), but our results showed that the antioxidant properties of saffron might be due in part to its role in increasing serum Zn level. The limitations of the present research include the small number of participants and a short follow-p period. We hope that they will be considered in future studies.

According to the results of our study and the significance of maintaining oxidative and antioxidant balances in metabolic syndrome patients and given the antioxidant properties of saffron (36), it could be suggested as a therapeutic agent against metabolic syndrome.

Study Limitations

Only a single dose of saffron was used for a short period of time in this study, and the sample size was limited. It could be useful to investigate the effects of other doses and longer durations in larger subject samples.

Conclusion

The results of the present study indicated that saffron supplementation for a period of 12 weeks could increase serum Zn level in patients with MetS. However, there were no effects on copper, Cu/Zn ratio, and superoxide dismutase.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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