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Association Between Hypertension in Healthy Participants and Zinc and Copper Status: a Population-Based Study

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Abstract

The prevalence of hypertension (HTN) is increasing globally. It has been shown that there is an association between micronutrient deficiency and HTN. In the current study, we aimed to assess the association between HTN with serum copper and zinc concentrations in a large representative Iranian population. The participants were enrolled into the Mashhad stroke and heart atherosclerotic disorders study (MASHAD study), a cohort study that was initiated in 2010. Anthropometric indices were assessed using standard procedures. Systolic (SBP) and diastolic (DBP) blood pressures were measured using a standard mercury sphygmomanometer. Fasting blood glucose (FBG), lipid profile, uric acid and blood urea nitrogen (BUN), and hs-CRP were measured using routine methods. HTN defined as persons who had SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg and/or medication use. Flame atomic absorption (Varian AA240FS) was used to measure serum Zn and Cu concentrations. SPSS software was used for all statistical analyses. A total of 9588 participants were recruited into the MASHAD study project. Participants were divided into two groups; 5695 healthy (non-hypertensive) (mean age 45.85 ± 7.5 years) and 3893 hypertensive participants (mean age 51.18 ± 7.67 years). Systolic ($p < 0.001$) and diastolic blood pressure ($p < 0.001$) were significantly different for different serum copper quartiles. The participants with serum copper levels < 80 μg/dl had 1.33 times greater risk of an increased blood pressure than other participants. Participants with serum copper levels > 130 μg/dl had a 1.94-fold higher risk of raised blood pressure. Serum zinc was not associated with systolic blood pressure, but individuals in the first quartile level of serum zinc had a diastolic blood pressure that was significantly higher than other quartiles ($p = 0.035$). Serum copper is associated with blood pressure status in adults in a U-shaped relationship, with a range of serum copper between 80 and 130 μg/dl being associated with normal blood pressure.

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Introduction

Hypertension (HTN) is one of the most important risk factors for cardiovascular disease (CVD) [32]. It is known as "silent killer" because it typically lacks any associated symptoms [14].

The prevalence of HTN is increasing globally [18, 27] and in Iran [6]. Ghanbarian et al., from the Tehran Lipid and Glucose Study (TLGS), reported that the prevalence of myocardial infarction based on ECG results in participants with hypertension (aged ≥ 30 years), was twofold higher than in participants with normal blood pressure [11]. In 2006, it was reported from the TLGS that 36% of Iranian adults aged 20–69 years old suffer from the increased blood pressure [10]. Esteghamati et al. have showed that the prevalence of HTN was almost 25% and the prevalence of pre-HTN was around 46% in Iranian adults [9]. It has been reported that the prevalence of HTN in Korea was 33.3% in men and 29.8% in women aged over 30 years old in 2012, an increase of 25% since 2007 [27].

It is well known that there is an association between hypertension with dyslipidemia, gender, and diabetes [3]. The risk factors for hypertension include unmodifiable risk factors such as genetics, race, and aging, and modifiable factors such as living habit or diet [22]. It has also been shown that there are associations between early under nutrition with hypertension, diabetes, and cardiovascular disease; therefore, it may be that child under nutrition may also cause a high adult health care costs [17].

Among several modifiable risk factors, dietary trace elements appear to have a key role to prevent the cardiovascular diseases through their anti-oxidative function [15, 25]. Zinc and copper are two of the most abundant trace elements in the human body that possess antioxidant and pro-oxidant properties [26]. It has been reported that there is an association between a low serum level of zinc and copper with coronary artery disease. It seems that these trace elements probably exert their effects through effects on vascular function or an inflammatory response [21, 31].

Copper is known as an essential trace element for several antioxidant enzymes including the superoxide dismutase, catalase, and cytochrome oxidase. Zinc is an essential micronutrient for the cell division and differentiation, and participates in metabolism of carbohydrates and proteins and synthesis of nucleic acids [2].

It has been shown that there is an association between micronutrient deficiency and increased blood pressure [19]. Micronutrient deficiency is a serious health problem in several countries. In the current study, we aimed to assess the associations between HTN with serum levels of copper and zinc in a large Iranian population.

Materials and Methods

Participants

The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences (MUMS) and written informed consent was obtained from all participants prior to participation in the study. The Mashhad stroke and heart atherosclerotic disorders study (MASHAD study) is a cohort study which started in 2010. A total of 9588 participants were recruited into the study as previously described [13].

Measurements

Anthropometric measurements were made using standard procedures. Serum levels of fasting blood glucose (FBG), lipid profile, uric acid, blood urea nitrogen (BUN), and Hs-CRP were measured using routine methods as described previously [13].

Measurement of Blood Pressure

HTN was defined in accordance with the International Diabetic Federation (IDF) criteria for a SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg and/or if antihypertensive medication was used.

We measured SBP and DBP using a sphygmomanometer twice in exactly the same manner. It was measured on the left arm when the individuals remained seated at rest for 15 min. We took the third measurement and averaged of the two closest readings, if the first two readings differ by more than 15 mmHg in diastolic or more than 25 mmHg in systolic blood pressure [7]. HTN defined as participants with systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or a history of antihypertensive drug treatment.

Measurement of Serum Zinc and Copper Concentrations

Serum samples were diluted with nitric acid at a ratio of 1:10. Flame atomic absorption (Varian AA240FS) was used to measure serum Zn and Cu concentrations. Zn and Cu standard curves were constructed using a Zn and Cu standard (Merck and Co. Pharmaceutical Company). The accuracy of methods was 93 ± 4.8% for Zn and 95 ± 3.75 for Cu, estimated by measuring a certified reference material (Merck KGaA 64271 Darmstadt, Germany) containing a known amount (1000 ± 2 mg/L) of Zn and Cu. The intra-assay and inter-assay coefficient of variation (CV) were 1.5 ± 0.2% and 2.6 ± 0.4% for Zn and 1.3 ± 0.12% and 2.11 ± 0.32% for Cu. The limit of detection was less than 0.1 mg/L.

Statistical Analysis

SPSS version 18(SPSS Inc. Chicago, IL, USA) was used for all statistical analyses. The normality of the data was assessed using the Kolmogorov-Smirnov test. Normally distributed data are expressed as mean ± standard deviation (SD) and non-Normally distributed data as median ± IQR. The differences in the mean values of clinical and baseline demographics characteristics between two groups were evaluated using analysis of covariance (ANCOVA) with age and gender as model covariates. For categorical parameters, a chi-square or Fisher exact tests were used. Pearson and Spearman's correlation were undertaken for investigating the relationship between serum zinc and copper, and systolic, diastolic blood pressure, and quartiles of zinc and copper with systolic, diastolic blood pressure. Logistic regression analysis was used to evaluate the association of quartiles for serum Zn, Cu, and Zn/Cu ratio with the presence of HTN in individuals with a normal BMI. All analyses were two-sided and p value less than or equal to 0.05 was considered as significant. For figures, GraphPad Prism 6 was used.

Results

A total of 9588 participants were recruited into the MASHAD study. Baseline characteristics of the participants are shown in Table 1. The population sample was divided into two groups: 5695 healthy (aged 45.85 ± 7.5 years old) and 3893 hypertensive participants (aged 51.18 ± 7.67 years old). There was no significant difference in the gender distribution between two groups ($p = 0.48$).

Table 1 Anthropometric and biochemical characteristics of the study population with and without hypertension ($n = 9588$)

		HTN negative	HTN positive	p value
Age (y)		45.85 ± 7.5	51.18 ± 7.67	< 0.001
Sex	Male (3839)	2279 (40%)	1560 (40.1%)	0.48
	Female (5749)	3416 (60%)	2333 (59.9%)	
Weight (kg)		69.95 ± 12.6	74.52 ± 12.81	< 0.001
BMI (kg/m^2)		27.11 ± 4.62	29.08 ± 4.67	< 0.001
Waist circumference (cm)		92.93 ± 11.79	98.59 ± 11.6	< 0.001
Smoking	No	3887 (68.3%)	2694 (69.2%)	< 0.001
	Former	498 (8.7%)	439 (11.3%)	
	Current	1307 (23%)	760 (19.5%)	
PAL		1.61 ± 0.28	1.56 ± 0.28	< 0.001
Zinc (μg/dl)		84.71 ± 18.96	85.02 ± 19.13	0.4
Copper (μg/dl)		103.29 ± 36.31	107.68 ± 40.98	< 0.001
Zinc-copper ratio		1.009 ± 0.77	1.017 ± 0.85	0.7

Data are presented as mean (SD) or interquartile range. Differences in variables among hypertension status participants determined using ANCOVA analyses with age and gender included as model covariates. *PAL*, physical activity level

Hypertensive participants had a higher mean age, BMI, waist circumference, serum levels of FBS, uric acid, BUN, cholesterol, triglyceride, LDL-C, and serum hs-CRP compared with the healthy individuals ($p < 0.001$ for all variables). Moreover, the serum Cu was significantly higher in participants with HTN (107.68 ± 40.98 μg/dl) compared to the healthy individuals (103.29 ± 36.31 μg/dl; $p < 0.001$) (Table 1). Figure 1 shows a comparison of serum Zn, Cu, and Zn/Cu in participants with and without HTN.

As shown in Table 2, the mean systolic ($p < 0.001$) and diastolic blood pressure ($p < 0.001$) were significantly different based on the copper quartiles. In Table 3, we show that correlation between quartiles for serum zinc and copper with systolic diastolic blood pressure. As presented in Table 3, there was a weak negative correlation between diastolic blood pressure and zinc quartiles ($r = -0.024$, $p = 0.021$). Also, there were significant correlations between systolic ($r = 0.098$, $p < 0.001$) and diastolic ($r = 0.085$, $p < 0.001$) blood pressure and quartiles for serum copper. This finding is confirmed by Fig. 2. Figure 2 shows the correlation between serum levels of zinc and copper with systolic and diastolic blood pressures. The results showed that there was a correlation between the serum levels of copper with both SBP ($p < 0.001$) and DBP ($p < 0.001$).

As summarized in Table 4, the results of the current study showed that the participants with serum copper levels < 80 μg/dl had 1.33-fold higher risk of an increased blood pressure than normotensive individuals. This possibility was 1.94-fold for participants with serum copper levels > 130 μg/dl.

Discussion

There was a significantly higher mean age, BMI, serum levels of FBG, cholesterol, triglyceride, LDL-C, and hs-CRP in hypertensive participants compared to the normal individuals. These results are consistent with the previous findings. It is well documented that there is an association between hypertension with dyslipidemia, diabetes [3], and aging [22].

The most important result of the current study was the participants with serum copper levels < 80 μg/dl had 1.33-fold greater risk to have HTN than normotensive individuals. This risk was 1.99-fold for participants with serum copper levels > 130 μg/dl. Moreover, there was a correlation between the serum levels of copper with both SBP and DBP. Generally, if the serum levels of copper be outside the range of 80 to 130 μg/dl, the risk of HTN development will be increased among Iranian adults. This result is in line with the previous studies reported that there was an association between the copper deficiency with coronary artery disease [19, 21, 31].

Moreover, the results showed that DBP increased significantly with serum zinc ($p = 0.035$). Vivoli et al. have reported a positive relationship between DBP and serum zinc ($r =$

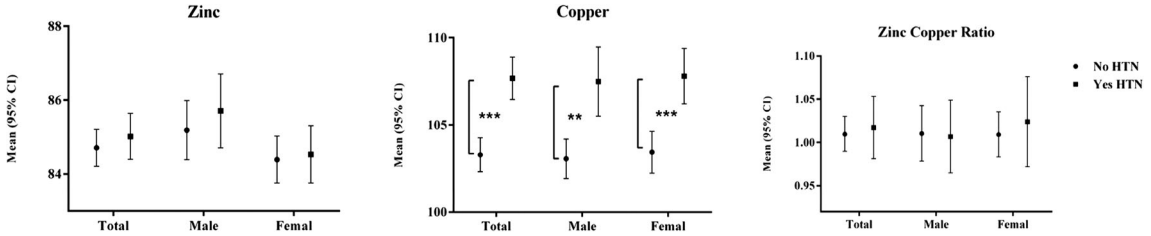

Fig. 1 Comparison of serum levels of zinc, copper, and zinc zopper ratio (Zn/Cu) in participants with and without HTN (hypertension). Data presented as mean ± 2SE; ***$p < 0.001$, **$p < 0.01$

0.370; $p = 0.041$) in normotensives participants ($n = 31$), [30]. It has been reported that Ang-II infusion increases blood pressure progressively in rat model of HTN, along with a hypomagnesuria and hyperaldosteronism. It has been suggested that an additive effect of Ang-II and an augmented Na load can effect on Zn and Cu balances [28]. A previous animal study showed that increased reactive oxygen species has a key role in the development of HTN [33]. It has been suggested that copper can promote HTN development through oxidative stress and inflammation [23], and its deficiency can induce impaired arterial relaxation in the endothelium [12].

Bergomi et al. have shown that there was no significant difference in serum levels of zinc, copper, and their dependent enzyme systems between participants with high and normal blood pressure. However, there was an association between increased serum levels of copper with HTN [4]. Vivoli et al. have also reported that there was no significant difference in serum and urine levels of zinc, copper, activity of zinc (AP and LDH), or copper (Cu–Zn SOD, LOX, and MAO)-dependent enzymes between participants with HTN compared with healthy ones. They suggested that an imbalance of zinc and copper status may be involved in human HTN [30].

These controversial results may be because of different sample size or race used. The results of current study showed that increased or decreased level of copper can effect on blood pressure status in adults, so that a narrow range of serum copper between 80 and 130 μg/dl is observed in normotensive participants. It is necessary to consider that there are several other factors affecting on the relationship between copper with blood pressure including inflammation-sensitive plasma proteins (ISPs), which also should be taken into consideration in future studies to determine their effects on increased blood pressure levels. Engström et al. have evaluated the association of ISPs with HTN in a cohort by 2262 healthy men (aged 35 to 50 years), initially without taking any treatment. Their results showed that plasma levels of ISPs including fibrinogen, α1-

Table 2 Mean of systolic and diastolic blood pressure according to zinc and copper quartile

	Systolic blood pressure(mmHg)	Diastolic blood pressure(mmHg)
Zinc		
Quartile 1(< 70)	121.83 ± 18.55	79.42 ± 12.27
Quartile 2, 3 (70–95)	121.96 ± 18.41	78.83 ± 11.49
Quartile 4 (> 95)	121.35 ± 20.65	78.86 ± 10.86
p value	0.54	0.035
Copper		
Quartile 1 (< 80)	120.22 ± 18.64	78.39 ± 11.64
Quartile 2, 3 (80–130)	121.97 ± 18.68	79.2 ± 11.46
Quartile 4(> 130)	125.01 ± 19.13	80.8 ± 12.26
p value	< 0.001	< 0.001

Table 3 Correlation between zinc and copper quartiles and systolic blood pressure and diastolic blood pressure

		Systolic blood pressure	Diastolic blood pressure
Zinc quartiles	*r* (correlation coefficient*)	− 0.012	− 0.024
	p value	0.264	0.021
Copper quartile	*r* (correlation coefficient)	0.098	0.085
	p value	< 0.001	< 0.001

*Spearman correlation has been done

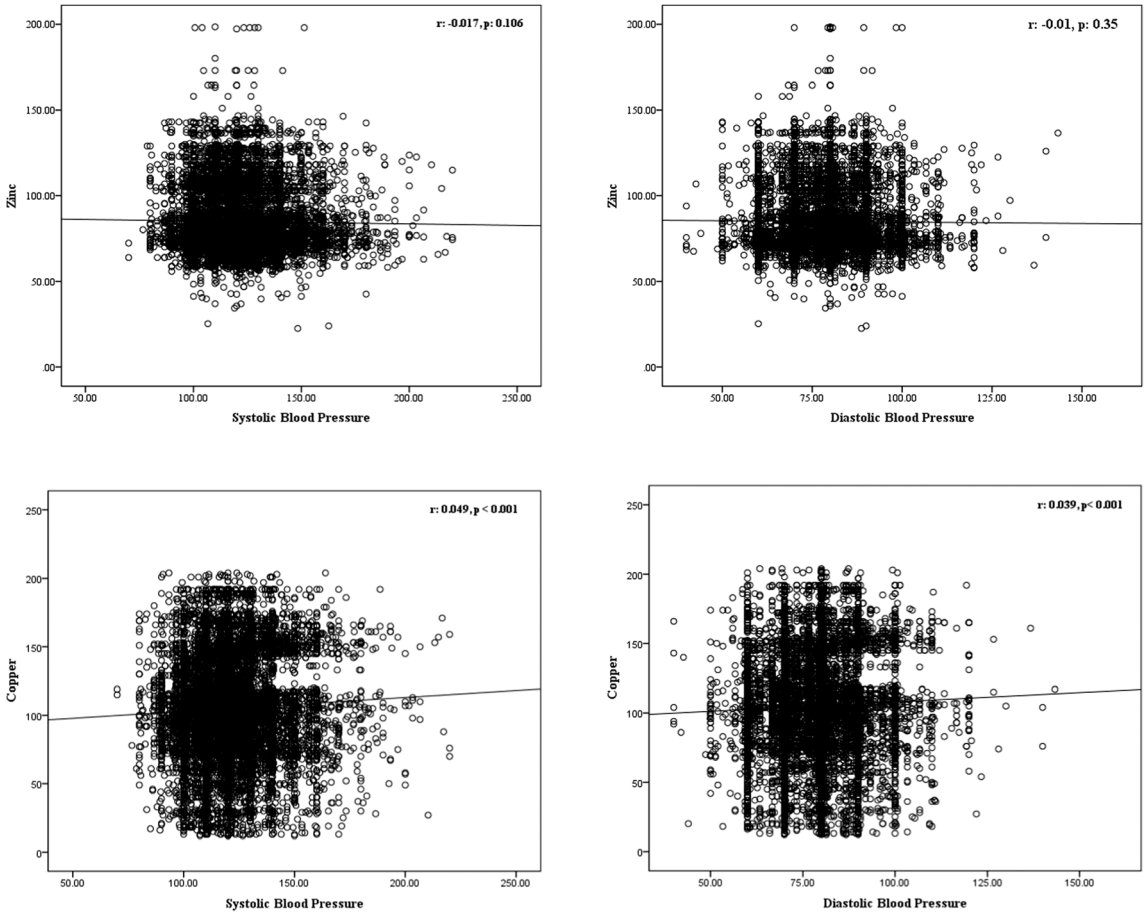

Fig. 2 Correlation between serum levels of Zinc and copper with systolic and diastolic blood pressures

antitrypsin, orosomucoid, haptoglobin, and ceruloplasmin are associated with an increased blood pressure in future. Ceruloplasmin, a multi-copper enzyme, carries about 95% of circulating Cu. It has been shown that it is associated with an increased risk of myocardial infarction and stroke, but it is unclear whether its relation to vascular diseases can be ascribed to an oxidative effect on LDL-C or its effect as an inflammation marker [5, 20, 29]. Altamura et al. have assessed the effects of Cu and ceruloplasmin on the pathophysiology of acute stroke among small samples of 35 acute stroke patients and 44 controls. They showed that total serum Cu levels are increased in patients with compared to controls, whereas systemic "free" Cu did not differ between two study groups. They have suggested that Cu can cause redox toxic reactions in brain lesion [1]. Homocysteine mediates LDL oxidation in the presence of Cu ions changes in redox thiol status, and alteration in mitochondrial gene expression. Previous studies showed that copper ions are required to provoke the Hcy-induced cellular injury [8, 24]. Halvorsen et al. reported that decreased homocysteine levels enhance lipid peroxidation in the presence of Cu ions, whereas its increased levels can protect lipids against oxidative change [16].

Our study has some strengths. Firstly, this is the first study assessed the association between the serum copper and zinc with HTN in Iran. Another strength of the current study was using a large sample size of Iranian adults.

Table 4 Odds ratio and 95% confidence intervals of copper quartiles according to hypertension

	OR	*p* value
Unadjusted		
Quartile 2, 3	Reference	
Quartile 1	1.33 (1.201–1.473)	< 0.001
Quartile 4	1.939 (1.753–2.144)	< 0.001
Model 1		
Quartile 2, 3	Reference	
Quartile 1	1.306 (1.172)	< 0.001
Quartile 4	1.99 (1.789–2.214)	< 0.001
Model 2		
Quartile 2, 3	Reference	
Quartile 1	1.304 (1.169–1.458)	< 0.001
Quartile 4	1.989 (1.787–2.214)	< 0.001

Model 1 adjusted by age; Model 2 adjusted by age, smoking, and physical activity level

Study Limitations

This was a cross-sectional study with a limited methodology and cannot explain the mechanism by which copper is related to blood pressure. Moreover, we did not evaluate the mineral intakes of participants and also activity of Cu/Zn-related enzymatic systems. Future studies with more related biomarkers with blood pressure are necessary.

Conclusion

The results of the current study showed that there is a weak association in the blood pressure with serum copper in Iranian adults. Moreover, the serum levels of copper above 130 μg/dl can increase the susceptibility of HTN by 1.99-fold. Although more studies are needed to confirm this observation.

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Compliance with Ethical Standards

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

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