MEDICAL SCIENCE MONITOR

REVIEW ARTICLES

Received: 2012.07.02
Accepted: 2012.09.18
Published: 2013.01.01

Zinc, copper, and blood pressure: Human population studies

1 William E. Carpenter
1 Derek Lam
2 Glenn M. Toney
3 Neal L. Weintraub
1 Zhenyu Qin

1 Division of Vascular Surgery, Department of Surgery, University of Texas Health Science Center at San Antonio, San Antonio, TX, U.S.A. / 2 Department of Physiology, University of Texas Health Science Center at San Antonio, San Antonio, TX, U.S.A. / 3 Division of Cardiovascular Disease, Department of Medicine, University of Cincinnati, Cincinnati, OH, U.S.A.

Author's address: Zhenyu Qin, e-mail: qinz@uthscsa.edu

Source of support: This work was supported by an AHA National Scientist Development Grant (0835268N, ZQ), and by NIH grant HL076684 (NW) and HL62948 (NW). The works of Derek Lam are supported by Voelcker Biomedical Research Academy

Summary

Copper and zinc are essential trace biometals that regulate cardiovascular homeostasis, and dysregulation of these metals has been linked to vascular diseases, including hypertension. In this article, we review recent human population studies concerning this topic, focusing on: 1) the relationship between blood pressure and levels of zinc and copper; 2) correlations between trace metals, the renin-angiotensin system, obesity, and hypertension; 3) the relationship between environmental metal pollution and the development of hypertension; and 4) methods commonly employed to assay zinc and copper in human specimens. Moreover, based on the findings of these studies, we suggest the following topics as the basis for future investigations: 1) the potential role of environmental metal pollution as a causal factor for hypertension; 2) metal profiles within specific pathogenic subsets of patients with hypertension; 3) standardizing the experimental design so that the results between different studies are more comparable; and 4) the requirement for animal experiments as complementary approaches to address mechanistic insight that cannot be studied in human populations.

key words: copper zinc hypertension

full-text PDF: ICID 883708 PMID 23291705

2708 2 — 41

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Background

An estimated 1 billion individuals worldwide have high blood pressure, which is associated with approximately 7.1 million deaths per year [1]. In the United States, at least 50 million individuals are using hypertension treatment [2-3]. Therefore, the prevention and management of hypertension are major public health challenges [2–6]. Although a number of important nutritional and metabolic factors for hypertension are identified, including inadequate intake of fruits, vegetables, and potassium; excess sodium (sodium chloride) intake; excess body weight; inadequate physical activity; and excess alcohol intake [7–9], it is important to recognize that many other factors also play a role in this heterogeneous disorder. One of these factors, in particular, is the influence of essential trace metals, such as copper and zinc, on blood pressure. The involvement of copper and zinc in blood pressure regulation is particularly hinted in the human studies via manipulation of dietary copper and zinc levels. For example, copper deficiency reduces hemoglobin synthesis and leads to anemia [10], and anemia is considered as a contributor to increase cardiac output and blood pressure. Deficiency in zinc intake has been proposed to play a role in blood pressure regulation by altering the taste of salt [10]. Indeed, higher dietary zinc intake results in a better taste acuity for salt in healthy young females [11]. Thus, people with zinc deficiency tend to increase salt intake, which can lead to an increase in blood pressure [10]. It has been posited that an imbalance in the homeostasis of zinc metabolism can lead to high blood pressure [12], while copper deficiency can enhance the vulnerability of the heart and blood vessels [13]. Although these dietary studies imply a relationship between inadequate intake of these metals and high blood pressure, it is important to ask a more direct question whether copper and zinc levels are altered in patients with hypertension. Thus, in this article, we will examine reported correlations between tissue copper and zinc levels and high blood pressure, focusing on recent human population studies. We specifically highlight the challenges in data interpretation and describe gaps in knowledge that should addressed in future investigations. Please note that, in this article, we do not attempt an analysis of the large body of observations now on record regarding the action of these metals in animal models; such a review of zinc metabolism in arterial hypertension has been provided by Tubek [12].

Relationship Between Blood Pressure and Levels of Zinc and Copper

Many studies in humans hint a correlation between zinc and copper levels and hypertension. For example, zinc and the zinc/copper ratio are decreased in hypertensives as compared with normotensives [14,15]. Chiplonkar et al. reported lower erythrocyte membrane zinc in hypertensive compared to normotensive lacto-vegetarians [16]. Suliburska et al. reported lower zinc in hair of obese hypertensives [17]. Olatunbosun found significantly increased serum copper levels in hypertensive patients [18]. In contrast, Taneja and colleagues reported increased serum zinc, and decreased levels of copper, in hypertensives, while urinary levels of both zinc and copper were increased in hypertensives [19]. Ghayour-Mobarhan et al. reported that serum copper is higher in hypertensives [20]. However, de la Sierra A et al. reported that there is no correlation between the degree of endothelial dysfunction and serum copper or zinc levels [21].

It is critical to understand what underlies the discrepancies regarding trends of copper and zinc levels in these studies. First, we should notice that the study design is different between each study. Table 1 compares the differences in design of studies reviewed in this article. As we can see, the differences between each study include (but are not limited to) age, gender ratio, medication status, smoking and alcohol history, and hypertension evaluation procedures. Second, these discrepant results also suggest that the involvement of copper and zinc in hypertension appears far more complicated than is currently understood. Thus, using a global population approach to understand the relationship between trace zinc, copper and hypertension may not be optimal. In this article, we posit that instead of studying the whole hypertensive population, it is more important to investigate the specific pathogenic subsets of patients with hypertension, as indicated in the following sections.

Renin-Angiotensin System, Metal, and Blood Pressure

One important contributor for the pathogenesis of essential hypertension is the renin-angiotensin system (RAS) [22]. Generally, a decrease in circulating blood volume leads to lowered blood pressure. These circumstances trigger the kidneys to release renin. Mediated by angiotensin converting enzyme (ACE), renin transforms angiotensinogen into angiotensin II. Angiotensin II acts on multiple target organs throughout the body including the brain, promoting the generation of reactive oxygen species [23], vasoconstriction, the adrenal release of aldosterone, and the activation of sympathetic nerve discharge, ultimately increasing circulating volume and blood pressure [24]. Therefore, the levels of renin, ACE, and aldosterone in blood serve as an index of RAS activation. However, whether RAS activation is correlated with trace metal levels in the circulation, cardiovascular tissues and/or anatomic regions of brain is unknown. Tubek [25] studied the correlation between zinc metabolism and the RAS in patients with essential hypertension. This study included 38 patients, 24 men and 14 women,

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between 16–59 years of age. In women, plasma renin and ACE were negatively correlated to total zinc efflux from lymphocytes; ACE and serum aldosterone were negatively correlated to oubain-dependent zinc efflux from lymphocytes, and all three RAS parameters were positively correlated to lymphocyte zinc levels. In men, the only correlation observed was a

Table 1. A comparison in experimental design between recent human population studies related to copper, zinc and hypertension.

Year	Subject number	Inclusion criteria	Exclusion criteria	Detailed procedure to diagnosis hypertension	References
2009	Total 2233 (1106 males and 1127 female); hypertensives 731 (348 males and 383 females)	Age 15–65; urban and rural residents; 312 and 88 subjects on treatment with anti-hypertension and anti-diabetic medication, respectively; an overnight fast before biochemical measures	No past medical history of any major disease, no evidence of infectious disease	N/A	M. Ghayour-Mobarhan, et al.
2010	Hypertensives 78 (56 males, 22 females)	Age 27–59, never treated and newly diagnosed, 13% smoker	No hypercholesterolemia, diabetes mellitus, impaired renal function, coronary or cerebrovascular disease; exclude heavy drunker, chronic inflammatory disease, persistent atrial fibrillation or flutter, women with oral contraceptives or estrogen replacement therapy	When seated arterial blood pressure (after 10 min of rest) measured by sphygmomanometer thrice at 1-week intervals was consistently >140/90 mm Hg. Secondary forms of hypertension were excluded by routine diagnostic procedures	de la Sierra A, et al.
2011	Normotensives 40 (18 males, 22 females); obese hypertensives 40 (13 males, 27 females)	Age 25–65; normal renal and liver function; an overnight fast before biochemical measures	No history of coronary artery disease, stroke, congestive heart failure or malignacy. Secondary obesity, diabetes, other chronic disease, current use of dietary supplements; clinically evident inflammatory process	Resting seated blood pressure was measured three times and an average value was calculated according to The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines	Sulibursk, et al.
2009	Normotensives 114; hypertensives 90	Age normotensives 35–70, hypertensives 40–85. Part of subjects on treatment with anti-hypertension and anti-diabetic medication	The complete tooth without discoloration and deformity. No history of caries or any type of tooth filing	Blood pressure above 140/80 mmHg	Nagaraj, et al.
2007	Hypertensives 250 (all males); normotensives 250 (all males)	Mean age 49	Secondary hypertension	The blood pressures were measured regularly for 2 weeks before the samples of blood and urine were taken. The criteria for hypertension defined by the World Health Organization are systolic and diastolic blood pressures (SP and DP) greater than 140 and/or 90 mmHg, respectively. It was recorded in the seated position by the usual mercury sphygmomanometer	Taneja, et al.

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Table 1 continued. A comparison in experimental design between recent human population studies related to copper, zinc and hypertension.

Year	Subject number	Inclusion criteria	Exclusion criteria	Detailed procedure to diagnosis hypertension	References
2004	Hypertensives 109 (male 83, female 26), normotensive 115 (male 85, female 30); match age-gender-socio-economic status	Age 30-58, lacto-vegetarian, rural and urban communities. Around 70% of the subjects had a sedentary level of physical activity	Smokers and alcohol consumtion	diastolic blood pressure of 90 mmHg or higher or systolic blood pressure of 140 mmHg or higher	Chiplonkar, et al.

positive correlation between aldosterone and serum zinc. With regard to blood pressure, women showed a negative correlation to lymphocyte zinc, serum zinc, oubain-dependent zinc efflux from lymphocytes, and total zinc efflux from lymphocytes. Men had a negative correlation to lymphocyte zinc as well. These results indicate that there are notable gender differences in the relationship between zinc metabolism and the RAS. Also, this study shows a connection between these specific parameters and blood pressure in patients with primary hypertension. The author posited that women with mild hypertension, but not men, exhibit an association between zinc regulation and RAS activation. Determination of the underlying mechanisms for these gender differences and the reasons for the observed correlations will require more focused investigations.

Obesity, Trace Metals, and Blood Pressure

Leptin is predominantly produced by adipocytes, and serum leptin concentration is correlated with obesity [26]. Olusi et al. investigated associations among serum leptin, zinc, copper, and zinc/copper ratio in healthy individuals (n=570; 223 males *vs.* 347 females; aged 15 yr and older) in the normal Arab population [27]. Interestingly, this study showed that serum leptin was positively associated with serum copper, but negatively associated with the zinc/copper ratio, while there was no significant association between serum leptin and zinc [27]. Because leptin can also induce sodium retention and systemic vasoconstriction leading to an elevation in blood pressure [28], it is considered to be a contributing factor in essential hypertension. Canatan et al. [14] investigated plasma levels of leptin, zinc and copper in primary essential hypertensives (n=35; 18 female *vs.* 17 male) and healthy normotensives (n=50; 28 female *vs.* 22 male). The authors reported a negative correlation between leptin and zinc as well as leptin and the zinc/copper ratio; in obese patients with primary hypertension, leptin levels were increased, zinc and zinc/copper ratio were decreased. However, copper alone did not show significant correlation with leptin in this study [14]. Because obesity contributes to increased blood pressure in most patients with essential hypertension, which appears to be mediated in part by increased levels of leptin [29], the population study by Canaton et al. suggests an interesting link between copper, zinc, and leptin in obesity. The role of trace metals in regulating leptin function and metabolism, and the mechanistic basis for the observed correlations, are deserving of further investigation.

Environmental Metal Pollution and Blood Pressure

Environmental factors, such as diet, physical activity, and water and air pollution, affect the development of cardiovascular disease [30]. Iron and copper are two common elements of particulate matter contributing to air pollution. Air pollution is a mixture of gases, liquids, and particulate matter, and there is increasing concern regarding its potential deleterious effects on human health. After being released into the atmosphere (troposphere), pollutants are carried back in rainwater to further generalize environmental pollution. Tubek et al. calculated the yearly average number of hospitalizations caused by certain diseases in the region of Opole Voivodship, Poland [31]. Using rainwater as a monitor for environmental pollution, they investigated the correlation between chemical elements in rainwater and the hospitalization frequency of certain diseases. This study hinted a mild correlation between zinc and cadmium levels and hospitalizations for hypertension. The authors also posited that absorption of zinc through the lungs is a contributing factor, because ACE is highly localized to lung and requires zinc for its activity [31].

Chandigarh is a city with high occurrence of hypertension in India. Interestingly, in this city, zinc concentrations are higher in vegetables (reddish, turnip, and carrot) irrigated with

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underground water (120 mg/kg diet) compared with vegetables irrigated with surface water (40 mg/kg diet), while the copper concentrations are not different. Taneja et al. [19] measured dietary intake of zinc and copper in the hypertensive (n=250) and normotensive (n=250) men in this city. This study revealed a positive correlation between serum zinc and blood pressure, and a negative correlation between copper and blood pressure. There was also a positive correlation between urinary zinc and copper and blood pressure. Thus, increased intake of zinc seems to correlate with the increased prevalence of hypertension in Chandigarh, hinting that a dietary-derived disturbance of metal homeostasis might be an important factor contributing to primary hypertension. Moreover, it is notable that soft water areas have a 10-15% higher rate in cardiovascular disease mortality than the areas with medium hardness in water [32].

Methods Commonly Employed to Assay Zinc and Copper in Human Specimens

Several methods have been applied to assay trace metals in human studies. First, the metal concentration can be measured in plasma [14], serum [19], urine [19], and hair or fingernail specimens [33]. These methods are commonly employed because the samples are easily collected. Tooth has also been used in one study [34]. The turnout rate of trace metals in the blood and urine is rapid; whereas the hair, fingernail and tooth accumulate these elements over a long period. Tang et al. reported metal contents in human serum, hair, and fingernails between aged patients with hypertension and coronary heart disease (diseased group) versus aged healthy controls (healthy group) [33]. The zinc content and Zn/Cu ratio in serum of the diseased group were significantly higher than that of the healthy group. Conversely, the zinc content in the hair and fingernails, and Zn/Cu ratio in the hair, of the diseased group were significantly lower than that of the healthy group. Thus, the source of biological material for copper and zinc content analysis must be taken into account when comparing results from different clinical studies.

However, the limitations of these measurements are that they only provide information about trace metals at the tissue levels. Thus, several complementary methodologies have been devised to measure metal concentrations and efflux in blood cells, such as lymphocytes [25] and erythrocytes [35]. For example, in order to measure zinc efflux from lymphocytes, the cells are first incubated with zinc chloride to increase cellular zinc content. Then, the cells are treated with medium free of zinc chloride to determine time-dependent zinc release, which is used to calculate the efflux rate coefficient (ERC). Alternatively, metal content within the erythrocyte membranes can be measured [16,36], which is considered as a more sensitive measurement of zinc [16].

Another way to study metal metabolism in humans is to record their dietary intake of metal, because dietary patterns play an important role in the pathogenesis of many diseases [37], including hypertension. By conducting a food frequency questionnaire documenting specific quantities of food items consumed throughout the year, an estimate of the average daily intake of nutrients and metals can be determined [16]. Dietary metal intake varies from one population to the next due to the wide variations of diet around the world. Thus, it is not uncommon for certain communities to be exposed to different levels of metals due to different life styles and environmental conditions. For example, the traditional Indian diet, known as the lacto-vegetarian diet, consists of high levels of fiber and minerals and reduced fat content. Recently, Chiplonkar et al. [16] determined whether there was an association between dietary metal intake and hypertension in Indian lacto-vegetarians. The authors compared normotensives (n=115; 30 female *vs.* 85 male) with hypertensives (n=109; 26 female *vs.* 83 male). This study showed that copper intake was significantly lower in hypertensive compared with normotensive subjects. In addition, erythrocyte membrane zinc was negatively associated with systolic blood pressure.

Table 2 summarizes the representative methods and reference values for each metabolic parameter discussed above. It should be noted that atomic absorption spectrometry (AAS) is widely applied in human populations, presumably due to its lower cost. However, AAS only can detect one element in a single analysis of biological samples. There are several new techniques with multielemental capability, such as inductively coupled plasma mass spectrometry and synchrotron radiation X-ray fluorescence spectrometry, as recently reviewed [38,39]. Finally, the activity and expression of copper containing enzymes might also provide supplemental information about copper status in humans (see review by Danzeisen et al. [40]).

Suggestions and Future Directions

Many human population studies suggest a relationship between copper, zinc and hypertension, although currently we cannot distinguish between causality and association. It is also not surprising that some results are apparently contradictory. In addition to the differences in experimental design between different population studies, the contradictory results also suggest that the relationship between copper, zinc and hypertension is highly complex; depending on the levels, duration of exposure, geographic location, and other preconditions, either promotion of or protection against hypertension

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Table 2. Common metal metabolic parameters used for human studies.

Parameter	Methodology	Values	References
Zinc efflux from lymphocytes	Separate the lymphocytes from the peripheral blood and incubate with zinc chloride ($ZnCl_2$). Then, the cells are incubated in $ZnCl_2$-free medium to determine the efflux rate coefficient of zinc	Varies	S. Tubek, 2006
Zinc concentration in lymphocytes.	AAS	Hypertensive patients: Men: 0.22±0.13 µg/mg Women: 0.26±0.16 µg/mg	S. Tubek, 2006
Zinc and copper concentration in plasma	AAS (flame emission)	Normotensive subjects: Zinc: 75.34±13.33 µg/dL Copper: 117.51±36.73 µg/dL Hypertensive patients: Zinc: 89.62±23.79 µg/dL Copper: 81.50±15.48 µg/dL	Canatan, et al., 2003
Zinc and copper concentration in serum	Digest serum in 3: 1 nitric acid and perchloric acid. Dissolve the formed ash in 10 mM nitric and perchloric acid, filter and analyze the zinc and copper levels by AAS using hollow cathode lamps	Normotensive subjects: Zinc: 0.177±0.01 mg/dL Copper: 0.063±0.01 mg/dL Hypertensive patients: Zinc: 0.46±0.01 mg/dL Copper: 0.035±0.01 mg/dL	S. Taneja and R. Mandal, 2007
Zinc and copper concentration in urine	Same as described for zinc and copper measurement in serum	Normotensive subjects: Zinc: 0.180±0.01 mg/dL Copper: 2.70±0.10 mg/dL Hypertensive patients: Zinc: 0.369±0.01 mg/dL Copper: 2.70±0.10 mg/dL	S. Taneja and R. Mandal, 2007
Zinc concentration in erythrocyte membranes	Use concentrated nitric acid to ash the erythrocyte membranes, and then dissolve the ash in nitric acid (30 ml/l). Determine the zinc concentration using AAS (flame emission)	Normotensive subjects: Men: 0.51±0.1 µmol/g protein Women: 0.53±0.1 µmol/g protein Hypertensive patients: Men: 0.47±0.08 µmol/g protein Women: 0.50±0.1 µmol/g protein	M Ruz, et al., 1992 S. Chiplonkar, 2004
Daily dietary metal intake	Conduct a food frequency questionnaire documenting specific quantities of food items consumed throughout the year. A software program is then used to estimate trace metal intake	Normotensive subjects: Men: Zinc: 7.7±0.2 mg Copper: 2.3±0.16 mg Women: Zinc: 5.3±0.16 mg Copper: 1.62±0.14 mg Hypertensive patients: Men: Zinc: 7.3±0.3 mg Copper: 1.84±0.12 mg Women: Zinc: 5.2±0.3 mg Copper: 1.44±0.11 mg	S. Chiplonkar, 2004

AAS – Atomic Absorption Spectrometry.

is possible. Therefore, more studies are required to definitively establish their roles. Our following suggestions may be helpful.

1. **Involvement of environmental metal pollution in the prevalence of hypertension.** Chandigarh is a major city with high prevalence of hypertension; the study by Taneja et al. [19] hints that excess absorption and retention of zinc are common in the population of this city suffering from essential hypertension. And this is associated with higher zinc level in vegetables irrigated with underground water [19]. This finding raises an important question as to whether or not a

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long-term environmental metal pollution is a contributing factor for high blood pressure. Note that there is an increased prevalence of hypertension in rural and urban areas of developing countries, such as Sub-Saharan Africa [41]. It might be prudent to investigate the potential relationship between environmental metal pollution and hypertension in such areas.

2. **Determine metal profiles within specific pathogenic subsets of patients with hypertension.** Hypertension is a multifactorial disease that involves complex interactions between genetic and environmental factors. The study by Tubek [25] suggests that it may be of interest to compare metal metabolism between high-renin hypertensive versus low-renin hypertensive patients. The study by Canatan et al. [14] also raises an interesting future direction to study the role and/or mechanism of trace metals in obesity related hypertension.
3. **Standardization of the experimental design so that the results between different studies are more comparable.** The divergent results observed in human population studies that attempt to correlate metal concentrations with hypertension likely reflect a combination of factors. Amongst these factors, differences in experimental design probably play a role (Table 1). Therefore, to compare the results obtained by different groups, it is necessary to use similar experimental designs. Such standardized experimental designs should include a well accepted and well controlled approach to determine blood pressure and to define hypertension. Moreover, known factors that can influence copper and zinc levels in serum and other samples should be carefully excluded.
4. **The need for animal studies.** As an important complementary approach, animal studies should be conducted to address to mechanistic questions that cannot be studied in human populations. Such experiments enable investigators to study normotensive and hypertensive animals of similar genetic backgrounds and body weight in which dietary intake of trace metals can be precisely controlled, thereby leading to more reproducible results and mechanistic insights.

Abbreviations

AAS – atomic absorption spectrometry; **ACE** – angiotensin converting enzyme; **RAS** – renin-angiotensin system.

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