Original Article

Serum copper, zinc and risk factors for cardiovascular disease in community-living Japanese elderly women

Ayaka Tsuboi NRD[1], Mayu Terazawa (Watanabe) NRD[1], Tsutomu Kazumi MD, PhD[1-4], Keisuke Fukuo MD, PhD[1-3]

[1]*Postgraduate School of Food Sciences and Nutrition, Mukogawa Women's University, Hyogo, Japan*
[2]*Department of Food Sciences and Nutrition, School of Human Environmental Sciences, Mukogawa Women's University, Hyogo, Japan*
[3]*Research Institute for Nutrition Sciences, Mukogawa Women's University, Hyogo, Japan*
[4]*Diabetes Center, Myodani Hospital, Hyogo, Japan*

Background: Associations of copper (Cu) and zinc (Zn) serum levels with risk factors for cardiovascular disease (CVD) have not been extensively studied in elderly Asian people. Methods: Relationships to CVD risk factors were examined in 202 freely-living elderly Japanese women. Results: By univariate analysis, log high-sensitivity C-reactive protein (hsCRP) and non-HDL cholesterol were associated with serum Cu concentrations. An independent predictor of Cu was log hsCRP. Serum Zn concentrations decreased with age. After adjustment for age, serum albumin, HDL cholesterol and red blood cell (RBC) were positively and serum insulin and log hsCRP were inversely associated with serum Zn. In stepwise multiple regression analysis (model 1), serum albumin and HDL cholesterol were associated with serum Zn. In analysis excluding albumin from model 1 (model 2), independent determinants were log hsCRP (inverse) and the total number of RBC. In analysis including serum creatinine in model 2, creatinine has emerged as a determinant in addition to log hsCRP and RBC number. In analysis including estimated glomerular filtration rate (eGFR) instead of creatinine and excluding age in model 2, eGFR has emerged as a determinant of serum Zn in addition to log hsCRP and RBC number. Conclusions: Systemic low-grade inflammation may contribute to elevated serum Cu and decreased serum Zn concentrations in the elderly, and may represent an important confounder of the relationship between the serum trace elements and mortality in this population.

Key Words: Cu, Zn, inflammation, women, elderly

INTRODUCTION

Although diabetes, hypertension, smoking and dyslipidemia are major risk factors for atherosclerotic cardiovascular disease (CVD), they cannot fully explain variation in the incidences of the diseases. In addition, these traditional risk factors are useful for predicting incident CVD in younger populations whereas their predictive values decrease with age.[1] Recent attention has focused on the discriminative ability of novel risk markers in elderly cohort.[2] Animal and human studies have shown the role of essential trace elements, copper (Cu) and zinc (Zn), in atherogenesis and carcinogenesis.[3-5]

Several studies reported that high serum Cu and low serum Zn have been associated with risk factors for and mortality from CVD.[6-11] However, majority of these studies were done in younger population of western countries. In contrast, these associations have not been extensively studied in community-living elderly population of Asian origin. Because women as compared to men as well as older as compared to younger persons had higher serum Cu and lower Zn,[6,12] we examined relationships between these 2 variables and traditional and non-traditional risk factors for CVD in 202 community-living Japanese elderly women.

PARTICIPANTS AND METHODS

We examined 202 free-living elderly Japanese women whose details have previously been reported elsewhere.[13] They were all Japanese, participated on foot and were residents in Nishinomiya, Hyogo, Japan. Nobody reported to have cancer, or clinically diagnosed acute or chronic inflammatory diseases. Of 202 elderly women, 54 (26.7%), 12 (5.9%), and 74 women (36.6%) reported to be receiving statins, antidiabetic and antihypertensive drugs, respectively. This research followed the tenets of the Declaration of Helsinki. The design of this study was approved by the Ethical Committees of Mukogawa Women's University and written informed consent was obtained from all participants.

Anthropometric indices and blood pressure were meas-

Corresponding Author: Dr Tsutomu Kazumi, Research Institute for Nutrition Sciences, Mukogawa Women's University, 6-46, Ikebiraki-cho, Nishinomiya, Hyogo, 663-8558, Japan.
Tel: +81-798-45-3566; Fax: +81-798-45-3566
Email: kazumi@mukogawa-u.ac.jp
Manuscript received 24 May 2013. Initial review completed 04 July 2013. Revision accepted 26 October 2013.
doi: 10.6133/apjcn.2014.23.2.04

ured between breakfast and lunch and thereafter, blood-samples were obtained from the cubital vein. Fat mass was measured using an impedance method (InBody 430, Biospace, Tokyo, Japan). Blood pressure was measured using an automated sphygmomanometer (BP-203RV II, Colin, Tokyo, Japan) after participants had rested at least 5 mins. Muscle strength was assessed by handgrip strength using a handheld dynamometer (T.K.K.5401, Takei Scientific Instruments, Tokyo, Japan). Two trials for the dominant hand were performed and the stronger result was used in analyses.

Plasma glucose, serum insulin, lipids and lipoproteins were assayed as previously reported.[14,15] Because of non-fasted blood sampling; non-HDL cholesterol was calculated as the difference between total and HDL cholesterol. Serum albumin[16] and prealbumin[17] were measured as previously reported. Adiponectin, leptin and hsCRP were assayed by commercially available kits as previously reported.[14,15] Complete blood cell count was analyzed using an automated blood cell counter (Sysmex XE-2100，Sysmex, Kobe, Japan). Serum copper was measured using a commercially available kit (Quick-auto Neo Cu 7070, Shino-test Co, Tokyo, Japan). Serum zinc was measured using atomic absorption spectrophotometry (AA240FS/Agilent, Agilent Technologies Japan, Hachioji, Japan).

Serum creatinine was measured enzymatically using an Autoanalyzer (AU 5200, Olympus, Tokyo, Japan). The estimated glomerular filtration rate (eGFR) was determined using the equation recommended by the Japanese Society for Nephrology[18] and participants with eGFR<60 mL/min/1.73 m^2 was considered as having chronic kidney disease (CKD). Women with hemoglobin level <12 g/dL were considered as anemic.[19]

Data were presented as mean±SD unless otherwise stated. Due to deviation from normal distribution, hsCRP was logarithmic transformed for analysis. Differences between 2 groups were analyzed by t test and frequencies of conditions by Chi-square tests. Differences among 3 groups were analyzed using analysis of variance. When p values in analysis of variance were $p<0.05$, Bonferroni's multiple comparison procedure was performed. Bivariate correlations were evaluated by Pearson correlation analysis. Stepwise multiple regression analyses were performed to further identify the most significant variables contributing to the variation of Cu and Zn. A two-tailed $p<0.05$ was considered statistically significant. All calculations were performed with SPSS system 15.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

Table 1 shows anthropometric, biochemical and hematological characteristics of Japanese elderly women studied. Underweight (BMI<18.5 kg/m^2) and hypoalbuminemia (albumin<3.5 g/dL), both of which are considered a hallmark of malnutrition, were found in 18 (7.9%) and only 1 (0.4%) out of 202 women, respectively. No subjects had total cholesterol<130 mg/dL, another marker of malnutrition. Anemia and CKD were found in 11 (20.3%) and 33 (33.7%) women, respectively, in the current study and were similar in prevalence to Japanese women aged 70 and older in the general population (21.1 and 31.3%, respectively).[20,21]

Serum Cu was positively associated with log hsCRP, total and non-HDL cholesterol and platelet count (Table 1). Stepwise multiple regression analysis revealed an independent association of serum Cu with log hsCRP (standardized β= 0.395, R^2=0.152, $p<0.0001$).

Serum Zn was associated negatively with age and positively with handgrip strength and serum albumin (Table 1). In addition, serum Zn was associated positively with HDL cholesterol and eGFR and negatively with serum insulin and creatinine. Further, it showed positive associations with red blood cell count (RBC), hemoglobin (Hb) and hematocrit (HCT). After adjustment for age (Table 1), association of serum Zn with log hsCRP became significant. Associations remained significant with albumin, HDL cholesterol, insulin and RBC count.

Stepwise multiple regression analysis for serum Zn as a dependent variable were done which included age and all variables that showed significant associations with serum Zn after controlling for age as independent variables i.e. albumin, HDL cholesterol, insulin, log hsCRP and RBC (Table 2, model 1). Independent determinants of serum Zn were serum albumin and HDL cholesterol. Because strong association between serum Zn and albumin may result from the fact that most Zn is bound primarily to albumin in the circulation, multiple regression analysis was done in which independent variables were limited to variables of interests (model 2). Log hsCRP, RBC and serum creatinine emerged as independent determinants of serum Zn. These 3 variables explained 11.6% of serum Zn variability. In model 3, creatinine was replaced by eGFR, and age was excluded from independent variables because eGFR was calculated using age. EGFR has emerged as an independent determinant of serum Zn in addition to HDL cholesterol and RBC number.

Elderly women were divided into 3 groups according to tertiles of Zn (Table 3). Women in the lowest as compared to the highest third of serum Zn were older and had weaker handgrip strength. In addition, they had lower serum albumin and HDL cholesterol. Further, they had higher insulin, creatinine and hsCRP and lower eGFR. Finally, they had lower RBC, Hb, HCT and hence higher prevalence of anemia (30.0, 21.6 and 10.3% in the lowest, median and highest serum Zn tertiles, respectively, p=0.02) and of eGFR<45 mL/min/1.73 m^2 (11.7, 5.4 and 1.5%, respectively, p=0.05). After taking into accounting age, differences remained significant in handgrip strength, albumin, RBC and Hb (data not shown).

Neither serum Zn nor serum Cu was associated with BMI, percentage fat mass, abdominal circumference, blood pressure, serum leptin and adiponectin.

In stepwise multiple regression analysis for hsCRP as a dependent variable and serum Zn and serum Cu as independent variables, serum Cu was a determinant of log hsCRP (standardized β=0.402) and explained 15.8% of the variability.

DISCUSSION

To the best of our knowledge, this is the first report to date to assess the relationship of serum Cu and Zn with a broad range of risk factors for CVD in elderly women of Asian origin. The present study has demonstrated that

serum Cu was independently associated with hsCRP, a marker of systemic low-grade inflammation, in the elderly. Determinants of serum Zn were HDL cholesterol and serum albumin. It is noted that these findings were observed in community-living elderly women in whom prevalence of anemia and CKD were similar to Japanese women aged 70 and older in the general population.

Increases in serum copper concentrations have been cited in response to inflammation and infections and in various chronic diseases such as arthritis and cancer.[22] The present study has shown in community-living elderly women that modest increase in serum Cu has been associated with systemic low-grade inflammation, i.e. higher hsCRP, as previously reported in elderly community-living Italian people[12,23,24] and in the hospitalized Japanese elderly.[25] It has been proposed that increased mortality in subjects with increased serum Cu is unlikely to result from dietary imbalance but rather from secondary compartmentalization in the body caused by inflammatory processes.[7]

It is well-known that Zn deficiency causes impairments in both adaptive and innate immune responses, and pro

Table 1. Anthropometric and biochemical characteristics of 202 free-living elderly women studied and correlation coefficients of serum copper and zinc

Variables	Mean±SD	Zinc		Copper
		Simple	Partial	Simple
Age (years)	76.3 ± 8.2	-0.256***	adjusted	-0.032
BMI (kg/m^2)	22.5 ± 3.1	-0.035	0.035	-0.012
Body fat percentage (%)	31.8 ± 7.1	-0.021	0.051	0.049
Abdominal circumference (cm)	86.5 ± 9.3	-0.036	0.088	-0.016
Hand grip strength (kg)	20.4 ± 5.3	0.280***	0.121	-0.062
Systolic blood pressure (mmHg)	143 ± 22	-0.054	-0.029	0.011
Diastolic blood pressure (mmHg)	84 ± 13	0.009	0.043	-0.027
Albumin (g/dL)	4.4 ± 0.3	0.411***	0.430***	-0.010
Plasma glucose (mg/dL)	100 ± 29	0.019	-0.111	0.010
Insulin (μU/mL)	8.3 ± 7.5	-0.178*	-0.217*	-0.046
Total cholesterol (mg/dL)	219 ± 31	0.166*	0.146	0.162*
HDL-cholesterol (mg/dL)	64 ± 14	0.186**	0.190*	-0.010
nonHDL-cholesterol (mg/dL)	155 ± 33	0.078	0.052	0.158*
TG (mg/dL)	142 ± 79	-0.056	-0.156	-0.074
Serum creatinine (mg/dL)	0.69 ± 0.15	-0.195**	-0.180	0.021
eGFR (mL/min/1.73m^2)	65 ± 13	0.215**	0.174	-0.051
Iron (μg/dL)	94 ± 28	0.133	0.085	-0.119
Copper (μg/dL)	109 ± 15	-0.020	-0.013	1.000***
Zinc (μg/dL)	78 ± 12	1.000***	1.000	-0.020
hsCRP (μg/dL)	85 ± 109	-0.173*	-0.239**	0.356***
log hsCRP	1.7 ± 0.4	-0.109	-0.191*	0.402***
TNF-α (pg/mL)	1.6 ± 1.0	-0.131	-0.155	0.081
Leptin (ng/mL)	7.7 ± 4.7	-0.055	0.020	-0.026
Adiponectin (μg/mL)	14.1 ± 7.8	0.010	0.150	0.085
PAI-1 (ng/mL)	26.5 ± 16.5	0.179*	-0.003	0.108
White blood cells (×10^3/μL)	6.1 ± 1.6	-0.078	-0.115	0.089
Red blood cells (×10^4/μL)	424 ± 38	0.272***	0.198*	0.105
Hemoglobin (g/dL)	12.9 ± 1.2	0.325***	0.169	0.041
Hematocrit (%)	40.9 ± 3.4	0.279***	0.121	0.083
Platelets (×10^4/μL)	22.9 ± 5.6	-0.056	0.012	0.164*

BMI: body mass index, eGFR: estimated glomerular filtration rate, hsCRP: high-sensitivity C-reactive protein, TNF-α: tumour necrosis factor-α, PAI-1: plasminogen activator inhibitor-1. Associations of zinc were adjusted for age. Blood was drawn between breakfast and lunch. *, $p<0.05$, **, $p<0.01$, ***, $p<0.001$.

Table 2. Stepwise multiple regression analysis for serum zinc as a dependent variable in freely-living elderly women

Independent variables	Model 1	*p* values	Model 2	*p* values	Model 3	*p* values
Age	ns		ns		not included	
Serum albumin	0.398	<0.001	not included		not included	
HDL cholesterol	0.151	0.02	ns		0.196	0.021
Red blood cell count	ns		0.205	0.018	0.221	0.011
log hsCRP	ns		-0.200	0.019	ns	
Serum insulin	ns		ns		ns	
eGFR	not included		not included		0.190	0.028
Serum creatinine	ns		-0.176	0.044	not included	
Cumulative R^2	0.183		0.116		0.121	

Data is standardized beta. ns: not significant. Abbreviations are the same as in Table 1.
In model 1, eGFR was not included because it was calculated using age and creatinine.
In model 2 and 3, variables of interest were included as independent variables.

Table 3. Anthropometric, biochemical and hematological characteristics of elderly women grouped according to tertiles of serum zinc concentrations

Variables	Serum zinc (μg/dL)		
	Low 44-71 n=60	Medium 72-81 n=74	High 82-127 n=68
Age (years)	79.1 ± 6.6[a]	75.9 ± 8.5[b]	74.3 ± 8.6[b]
BMI (kg/m^2)	22.5 ± 3.2	22.8 ± 3.0	22.4 ± 3.1
Body fat percentage (%)	31.2 ± 8.0	32.1 ± 7.1	31.8 ± 6.2
Abdominal circumference (cm)	86.5 ± 9.8	86.4 ± 9.7	86.8 ± 8.6
Handgrip strength (kg)	18.4 ± 4.5[a]	20.7 ± 5.8[b]	21.8 ± 4.9[b]
Systolic blood pressure (mmHg)	144 ± 26	143 ± 17	143 ± 23
Diastolic blood pressure (mmHg)	83 ± 14	85 ± 12	84 ± 13
Albumin (g/dL)	4.2 ± 0.3[a]	4.4 ± 0.2[b]	4.5 ± 0.2[c]
Plasma glucose (mg/dL)	102 ± 38	97 ± 21	101 ± 26
Insulin (μU/mL)	10.9 ± 9.5[a]	7.4 ± 6.2[b]	7.1 ± 6.7[b]
Total cholesterol (mg/dL)	209 ± 31[a]	220 ± 32[b]	225 ± 30[b]
HDL-cholesterol (mg/dL)	60 ± 13[a]	64 ± 15[ab]	66 ± 14[b]
non-HDL-cholesterol (mg/dL)	149 ± 31	156 ± 36	159 ± 31
TG (mg/dL)	136 ± 74	155 ± 89	132 ± 71
Serum creatinine (mg/dL)	0.72 ± 0.17[a]	0.71 ± 0.17[a]	0.65 ± 0.10[b]
eGFR (mL/min/1.73 m^2)	62 ± 13[a]	64 ± 13[a]	69 ± 11[b]
Iron (μg/dL)	92 ± 28	94 ± 28	96 ± 29
Copper (μg/dL)	108 ± 18	111 ± 14	108 ± 14
Zinc (μg/dL)	65 ± 5[a]	76 ± 3[b]	91 ± 9[c]
Copper/zinc ratio	1.67 ± 0.32[a]	1.47 ± 0.19[b]	1.20 ± 0.19[c]
hsCRP (μg/dL)	118 ± 148[a]	71 ± 86[b]	71 ± 86[b]
log hsCRP	1.8 ± 0.5	1.7 ± 0.4	1.7 ± 0.4
TNF-α (pg/mL)	1.8 ± 1.4	1.5 ± 0.9	1.5 ± 0.8
Leptin (ng/mL)	8.1 ± 4.3	7.6 ± 5.1	7.4 ± 4.6
Adiponectin (μg/mL)	14.0 ± 8.7	14.3 ± 7.3	14.0 ± 7.4
PAI-1 (ng/mL)	25.4 ± 12.0	27.0 ± 16.8	26.9 ± 19.4
White blood cells (×10^3/μL)	6.2 ± 1.7	6.1 ± 1.5	5.9 ± 1.5
Red blood cells (×10^4/μL)	409 ± 34[a]	426 ± 40[b]	435 ± 34[b]
Hemoglobin (g/dL)	12.5 ± 1.1[a]	13.0 ± 1.2[b]	13.2 ± 1.1[b]
Hematocrit (%)	39.8 ± 3.4[a]	41.0 ± 3.5[b]	41.8 ± 3.2[b]
Platelets (×10^4/μL)	22.9 ± 6.2	23.2 ± 5.8	22.6 ± 4.7

Data are means±SD. Abbreviations are the same as in Table 1.
Means not sharing common alphabetical letters are significantly different each other at $p<0.05$ or less.

motes systemic inflammation.[26] We confirmed in Japanese elderly women that a subtle decrease in serum Zn was associated with higher hsCRP in the present study. Indeed, Zn supplementation has been shown to increase antioxidant power and decreased hsCRP in elderly subjects.[27] However, association of serum Zn with hsCRP abolished after controlling for albumin, suggesting that the association may be weak if any.

Although a close association between serum Zn and albumin found in the present study appeared to be due to the fact that Zn is primarily bound to albumin (70%) in the circulation,[28] a low concentration of serum albumin, commonly used as a nutritional marker, has been shown to be associated with a higher risk of myocardial infarction in men and women and all-cause mortality in women in the Framingham Offspring Study.[29] In addition, a decrease over time in serum albumin, even within the normal range, has been shown to be associated with a higher risk for incident CVD.[30] These findings suggest that serum albumin seems to be not only a nutritional marker but a CVD risk factor.

Low serum Zn levels have been reported in patients with nephrotic syndrome.[31] A linear correlation between proteinuria and urinary zinc excretion suggests that low zinc in nephrotic syndrome may be related in part to increased urinary zinc losses.[31] However, there was only one participant with serum albumin <3.5 g/dL, a diagnostic criteria for nephrotic syndrome in the present study although urine tests were not undergone.

Low serum Zn has been reported in patients with end-stage renal failure.[32-34] Low Zn might occur because of anorexia, alterations in gastrointestinal absorption, inflammation, hypoalbuminemia and the dialysis procedure per se.[34] In the present study, there was no participant with end-stage renal failure (eGFR <30 mL/min/1.73 m^2). In addition, the association of serum Zn with eGFR was independent of serum albumin and hsCRP. We have no explanation for the association. However, we have confirmed independent association of Zn with cystatin C-based eGFR, a superior marker of renal function than creatinine-based eGFR, in a separate group of elderly Japanese women (paper in preparation).

Zn is clearly involved in several aspects of normal haematopoiesis by virtue of its role in many enzyme systems involved with DNA synthesis,[35,36] and are key structural components of a large number of proteins. As previously reported in Japanese middle-aged women and endurance female runners,[37,38] association between marginal

Zn deficiency and anemia has been confirmed in elderly Japanese women in the present study.

Serum Zn concentrations readily decrease after a meal,[39] This decrease represents a redistribution of Zn from the small, vulnerable pool to the tissue.[40] In the present study, blood was taken in the fed state in the morning in elderly women and the serum Zn averaged 77.3 μg/dL. This is consistent with the observation by Kubori et al,[41] who measured serum Zn in blood samples taken in the morning and found that mean concentrations ranged from 75.6 to 78.3 μg/dL in a total of 1017 the Japanese elderly recruited from 6 areas in Nagano, Japan.

Although animal and human studies suggest that zinc has the potential to affect lipoprotein metabolism, significant effects of Zn supplementation were not observed for serum lipids and lipoproteins in a meta-analysis of 33 randomized controlled trials.[42] We found a positive association between serum Zn and HDL cholesterol in community-dwelling elderly women, as previously reported in 189 employees in UK.[6] However, serum Zn correlated with LDL cholesterol in 778 US adults.[43] As far as we know, there was no data on the relationship between serum trace elements and lipids and lipoproteins in healthy Japanese population.

Several limitations must be acknowledged. We did not have information on food intake, which is one of major determinants of Cu and Zn serum levels.[6,11] The cross-sectional design did not allow causal relationship. The recruitment procedure may also have some potential impact on the results. As the participation was voluntary, women who pay more attention to health may be more likely to participate. Participants were recruited from one area in Japan. Those on medication for cardiovascular diseases were excluded. Therefore, the generalization of the results is limited. Biochemical parameters were measured only once. We did not measure erythrocyte zinc concentrations which do not change significantly in response to meal or inflammation.[44] We did not have detailed information on drugs and supplements, which may contain Zn and/or Cu. Finally, Cu has both prooxidant and antioxidant effects, as reviewed by Ferns et al.[45] Copper ions can catalyse the oxidative modification of LDL whereas they also form an intrinsic constituent of superoxide dismutase and caeruloplasmin, enzymes that may be involved in preventing oxidative injury. Also, Cu is an essential component of lysyl oxidase, an enzyme involved in the biosynthesis of collagen, which is a major constituent of the extracellular matrix of arterial wall.

In conclusion, the present studies have demonstrated that both serum Cu and Zn were associated with traditional and novel CVD risk factors, specifically hsCRP, in freely- and community-living elderly Japanese women. Higher hsCRP has been shown to be associated with higher CVD mortality in Japanese whose median CRP levels are low by western standards.[46] Therefore, systemic low-grade inflammation may contribute to elevated serum Cu and decreased serum Zn levels in the elderly, and may represent an important confounder of the relationship between the serum trace elements and mortality in this population.

ACKNOWLEDGEMENTS

We are indebted to all the participants for their dedicated and conscientious collaboration. This study was supported by KAKENHI (21300260) of a Grant-in-Aid for Scientific Research (B) from Japan Society for the Promotion of Science.

AUTHOR DISCLOSURES

There were no conflicts of interest.

REFERENCES

1. Kannel WB. Coronary heart disease risk factors in the elderly. Am J Geriatr Cardiol. 2002;11:101-7. doi: 10.1111/j.1076-7460.2002.00995.x.
2. Ruijter W, Westendorp RG, Assendelft WJ, den Elzen WP, de Craen AJ, le Cessie S et al. Use of Framingham risk score and new biomarkers to predict cardiovascular mortality in older people: population based observational cohort study. BMJ. 2009;8;338:a3083. doi: 10.1136/bmj.a3 083.
3. Valko M, Izakovic M, Mazur M, Rhodes CJ, Telser J. Role of oxygen radicals in DNA damage and cancer incidence. Mol Cell Biochem. 2004;266:37-56. doi: 10.1023/B:MCBI.0000049134.69131.89.
4. Chisolm GM, Steinberg D. The oxidative modification hypothesis of atherogenesis: an overview. Free Radic Biol Med. 2000;28:1815-26. doi: 10.1016/S0891-5849(00)00344-0.
5. Craig WY, Poulin SE, Palomaki GE, Neveux LM, Ritchie RF, Ledue TB. Oxidation-related analytes and lipid and lipoprotein concentrations in healthy subjects. Arterioscler Thromb Vasc Biol. 1995;15:733-9. doi: 10.1161/01.ATV.15.6.733.
6. Ghayour-Mobarhan M, Taylor A, New SA, Lamb DJ, Ferns GA. Determinants of serum copper, zinc and selenium in healthy subjects. Ann Clin Biochem. 2005;42:364-75. doi: 10.1258/0004563054889990.
7. Reunanen A, Knekt P, Marniemi J, Mäki J, Maatela J, Aromaa A. Serum calcium, magnesium, copper and zinc and risk of cardiovascular death. Eur J Clin Nutr. 1996;50:431-7.
8. Marniemi J, Järvisalo J, Toikka T, Räihä I, Ahotupa M, Sourander L. Blood vitamins, mineral elements and inflammation markers as risk factors of vascular and non-vascular disease mortality in an elderly population. Int J Epidemiol. 1998;27:799-807. doi: 10.1093/ije/27.5.799.
9. Leone N, Courbon D, Ducimetiere P, Zureik M. Zinc, copper, and magnesium and risks for all-cause, cancer, and cardiovascular mortality. Epidemiology. 2006;17:308-14. doi: 10.1097/01.ede.0000209454.41466.b7.
10. Ford ES. Serum copper concentration and coronary heart disease among US adults. Am J Epidemiol. 2000;151:1182-8. doi: 10.1093/oxfordjournals.aje.a010168.
11. Bo S, Durazzo M, Gambino R, Berutti C, Milanesio N, Caropreso A et al. Associations of dietary and serum copper with inflammation, oxidative stress, and metabolic variables in adults. J Nutr. 2008;138:305-10.
12. Malavolta M, Giacconi R, Piacenza F, Santarelli L, Cipriano C, Costarelli L et al. Plasma copper/zinc ratio: an inflammatory/nutritional biomarker as predictor of all-cause mortality in elderly population. Biogerontology. 2010;11:309-19. doi: 10.1007/s10522-009-9251-1.
13. Hagisato S, Tanino N, Yamamoto H, Fukada R, Kawabata M, Fukuo K. Effect of BMI on the relationship between the Mini-Nutritional Assessment (MNA) and serum prealbumin concentrations in community-dwelling elderly. J Metabo Clin Nutr. 2011;14:317-24. (in Japanese).
14. Tanaka M, Yoshida T, Bin W, Fukuo K, Kazumi T. FTO, Abdominal adiposity, fasting hyperglycemia associated with elevated HbA1c in Japanese middle-aged women. J

Atheroscler Thromb. 2012;19:633-42. doi: 10.5551/jat.11940.
15. Wu B, Fukuo K, Suzuki K, Yoshino G, Kazumi T. Relationships of systemic oxidative stress to body fat distribution, adipokines and inflammatory markers in healthy middle-aged women. Endocr J. 2009;56:773-82. doi: 10.1507/endocrj.K08E-332.
16. Doumas BT, Watson WA, Biggs HG. Albumin standards and the measurement of serum albumin with bromcresol green. Clin Chim Acta. 1971;31:87-96. doi: 10.1016/0009-8981(71)90365-2.
17. Shima H, Okano H, Tadokoro S. Evaluation of the assays of serum transferrin, retinol binding protein, and prealbumin by Behring Nephelometer Analyzer (BNA). Igaku to Yakugaku. 1994;32:145-53. (in Japanese).
18. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2009;53:982-92. doi: 10.1053/j.ajkd.2008.12.034.
19. World Health Organization. Nutritional anaemias. Report of a WHO scientific group. Genevad: World Health Organization;1968.
20. The National health and Nutrition Survey in Japan 2010. [cited 2013/5/24]; Available from: http://www.e-stat.go.jp/SG1/estat/ GL08020 101.do?_toGL08020101_&tstatCode=000001041744&requestSender=dsearch.
21. Epidemiology of chronic kidney disease. In: Japanese Society of Nephrology, editors, clinical practice guideline for diagnosis and treatment of chronic kidney disease 2012. Tokyo: Igakushya, 2012.
22. Beshgetoor D, Hambidge M. Clinical conditions altering copper metabolism in humans. Am J Clin Nutr. 1998;67:S 1017-21.
23. Mocchegiani E, Malavolta M, Lattanzio F, Piacenza F, Basso A, Abbatecola AM et al. Cu to Zn ratio, physical function, disability, and mortality risk in older elderly (ilSIRENTE study). Age (Dordr). 2012;34:539-52. doi: 10.1007/s11357-011-9252-2.
24. Mezzetti A, Pierdomenico SD, Costantini F, Romano F, De Cesare D, Cuccurullo F et al. Copper/zinc ratio and systemic oxidant load: effect of aging and aging-related degenerative diseases. Free Radic Biol Med. 1998;25:676-81. doi: 10.1016/S0891-5849(98)00109-9.
25. Saito N. Copper metabolism and aging. Biomed Res Trace Elements. 2009;20:3-18. (in Japanese).
26. Wong CP, Ho E. Zinc and its role in age-related inflammation and immune dysfunction. Mol Nutr Food Res. 2012;56:77-87. doi: 10.1002/mnfr.201100511.
27. Bao B, Prasad AS, Beck FW, Fitzgerald JT, Snell D, Bao GW et al. Zinc decreases C-reactive protein, lipid peroxidation, and inflammatory cytokines in elderly subjects: a potential implication of zinc as an atheroprotective agent. Am J Clin Nutr. 2010;91:1634-41. doi: 10.3945/ajcn.2009.28836.
28. Gibson RS, Hess SY, Hotz C, Brown KH. Indicators of zinc status at the population level: a review of the evidence. Br J Nutr. 2008;99:S14-23.doi: 10.1017/S00071145080 06818.
29. Djoussé L, Rothman KJ, Cupples LA, Levy D, Ellison RC. Serum albumin and risk of myocardial infarction and all-cause mortality in the Framingham Offspring Study. Circulation. 2002;106:2919-24. doi: 10.1161/01.CIR.0000042673.07632.76.
30. Schalk BW, Visser M, Bremmer MA, Penninx BW, Bouter LM, Deeg DJ. Change of serum albumin and risk of cardiovascular disease and all-cause mortality: Longitudinal Aging Study Amsterdam. Am J Epidemiol. 2006;164:969-77. doi: 10.1093/aje/kwj312.
31. Stec J, Podracká L, Pavkovceková O, Kollár J. Zinc and copper metabolism in nephrotic syndrome. Nephron. 1990; 56:186-7. doi:10.1159/000186130.
32. Tonelli M, Wiebe N, Hemmelgarn B, Klarenbach S, Field C, Manns B. Trace elements in hemodialysis patients: a systematic review and meta-analysis. BMC Med. 2009;7:25. doi: 10.1186/1741-7015-7-25.
33. Mahajan SK. Zinc in kidney disease. J Am Coll Nutr. 1989; 8:296-304. doi: 10.1080/07315724.1989.10720305.
34. Lobo JC, Aranha LN, Moraes C, Brito LC, Mafra D. Linking zinc and leptin in chronic kidney disease: future directions. Biol Trace Elem Res. 2012;146:1-5.doi: 10.1007/s12011-011-9211-x.
35. Prasad AS, Oberleas D, Miller ER, Luecke RW. Biochemical effects of zinc deficiency: Changes in activities of zinc-dependent enzymes and ribonucleic acid and deoxyribonucleic acid content of tissues. J Lab Clin Met. 1971;77:144-9.
36. Prasad AS, Oberleas D. Changes in activities of zinc-dependent enzymes in zinc-deficient tissues of rats. J Appl Physiol. 1971;31:842-6.
37. Nishiyama S, Inomoto T, Nakamura T, Higashi A, Matsuda I. Zinc status relates to hematological deficits in women endurance runners. J Am Coll Nutr. 1996;15:359-63. doi: 10.1080/07315724.1996.10718610.
38. Nishiyama S, Irisa K, Matsubasa T, Higashi A, Matsuda I. Zinc status relates to hematological deficits in middle-aged women. J Am Coll Nutr. 1998;17:291-5. doi: 10.1080/07315724.1998.10718762.
39. King JC, Hambidge KM, Westcott JL, Kern DL, Marshall G. Daily variation in plasma zinc concentrations in women fed meals at six-hour intervals. J Nutr. 1994;124:508-16.
40. King JC. Zinc: an essential but elusive nutrient. Am J Clin Nutr. 2011;94:679S-84S. doi: 10.3945/ajcn.110.005744.
41. Kubori S, Kurasawa R, Okada S. Differences in the serum zinc level of rural and urban residents in a city in the central part of Japan, examined at annual community-wide health examination. Biomed Res Trace Elements. 2006;17:335-8.
42. Foster M, Petocz P, Samman S. Effects of zinc on plasma lipoprotein cholesterol concentrations in humans: a meta-analysis of randomised controlled trials. Atherosclerosis. 2010;210:344-52. doi:10.1016/j.atherosclerosis.2009.11.038.
43. Hiller R, Seigel D, Sperduto RD, Blair N, Burton TC, Farber MD et al. Serum zinc and serum lipid profiles in 778 adults. Ann Epidemiol. 1995;5:490-6. doi: 10.1016/1047-2797(95)00066-6.
44. Wallock LM, King JC, Hambidge KM, English-Westcott JE, Pritts J. Meal-induced changes in plasma, erythrocyte, and urinary zinc concentrations in adult women. Am J Clin Nutr. 1993;58:695-701.
45. Ferns GA, Lamb DJ, Taylor A. The possible role of copper ions in atherogenesis: the Blue Janus. Atherosclerosis. 1997; 133:139-52. doi: 10.1016/S0021-9150(97)00130-5.
46. Iso H, Cui R, Date C, Kikuchi S, Tamakoshi A; JACC Study Group; C-reactive protein levels and risk of mortality from cardiovascular disease in Japanese: the JACC Study. Atherosclerosis. 2009;207:291-7. doi: 10.1016/j.atherosclerosis.2009.04.020.

Original Article

Serum copper, zinc and risk factors for cardiovascular disease in community-living Japanese elderly women

Ayaka Tsuboi NRD[1], Mayu Terazawa (Watanabe) NRD[1], Tsutomu Kazumi MD, PhD[1-4], Keisuke Fukuo MD, PhD[1-3]

[1]*Postgraduate School of Food Sciences and Nutrition, Mukogawa Women's University, Hyogo, Japan*
[2]*Department of Food Sciences and Nutrition, School of Human Environmental Sciences, Mukogawa Women's University, Hyogo, Japan*
[3]*Research Institute for Nutrition Sciences, Mukogawa Women's University, Hyogo, Japan*
[4]*Diabetes Center, Myodani Hospital, Hyogo, Japan*

社区居住的日本老年女性血清铜和锌与心血管疾病危险因素的关系

背景：铜和锌的血清水平与心血管疾病危险因素之间的关系尚未在亚洲老年人中进行广泛研究。方法：在 202 名自由居住的日本老年女性中检测了血清铜和锌与心血管疾病危险因素的关系。结果：单因素分析显示：高敏 C 反应蛋白(hsCRP)的对数和非高密度脂蛋白胆固醇均与血清铜浓度有关。铜的独立预测因子是 hsCRP 的对数。随着年龄的增长，血清锌的浓度下降。校正年龄之后，血清白蛋白，高密度脂蛋白胆固醇和红细胞与血清锌成正相关，而血清胰岛素和 hsCRP 的对数与血清锌成负相关。在多元逐步回归分析(模型 1)中，血清白蛋白和高密度脂蛋白胆固醇均与血清锌有关。在将清蛋白从模型 1 中剔除的分析中(模型 2)，血清锌的独立决定因素是 hsCRP 的对数(负相关)和总红细胞数。在包括血清肌氨酸酐的分析中(模型 2)，血清肌氨酸酐是除 hsCRP 的对数和总红细胞数之外的又一个决定因素。在用估计的肾小球滤过率代替肌氨酸酐并排除年龄的分析中(模型 2)，估计的肾小球滤过率是除 hsCRP 的对数和总红细胞数之外的又一个决定因素。结论：老年人全身性低度炎症可能有助于升高血清铜的浓度，降低血清锌的浓度，并可能代表这个人群中血清微量元素和死亡率之间关系的一个重要的混杂因素。

关键词：铜、锌、炎症、女性、老年人