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Original article

# Serum zinc and copper concentrations and socio-economic status in a large Persian cohort

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***Background:*** We have previously reported that serum zinc (Zn) and copper (Cu) are affected by a number of factors. In the current investigation we have investigated the association between serum Zn and Cu concentrations and socio-economic factors in an Iranian population.

***Materials and methods:*** A Persian sample population (n = 2233; n = 1106 (49.5%) males and n = 1127 (50.5%) females) was recruited by cluster-stratified sampling. Individuals were aged 15-65 years, and included urban and rural residents of the Great Khorasan province, Iran. Anthropometric measurements, serum Zn and Cu analysis and socio-economic status were determined using standard protocols.

***Results:*** The mean serum Cu and Zn concentrations for the whole group were 14.7±3.3 μmol /L (range 4.5-28.4 μmol /L), and 11.7±1.9 μmol/L (range 3.6-28.3 μmol/L) respectively, and the mean serum Zn:Cu ratio for the group was 0.83±0.2. The highest mean copper concentrations were found in the age range 50-59 years ($p < 0.01$). The total population of urban residents had higher serum zinc ($p <0.01$) and lower serum copper concentrations ($p <0.05$) than rural residents. Poorly educated male subjects had significantly higher serum concentrations of copper than males in the other subgroups ($p <0.001$). Serum Cu and Zn:Cu ratio were associated with height and body mass indices ($p <0.01$).

***Conclusion:*** Low serum zinc and copper appears to be common in Persian individuals. Urbanization and also educational attainment may contribute to changes in serum levels of Cu and Zn. This is probably related to lifestyle habits.

***Keywords:*** Serum copper and zinc, socio-economic status

Copper is essential in normal cell metabolism and is present in all cells and tissues [1]. Zinc is also an important trace element and is a constituent of the active center of approximately 300 enzymes [2]. High serum copper and a low serum zinc concentrations [3] have been reported to be associated with an increased risk of mortality in middle-aged men [3], including an increased cardiovascular morbidity and mortality [4-6]. Elderly hospitalized patients have been reported to have a high prevalence of low serum zinc [7].

Acquired copper deficiency has been known to be an uncommon cause of anaemia and neutropenia for several years, however recently a specific type of copper deficiency myelopathy has been identified which is treatable [8].

Malnutrition, alcoholism, inflammatory bowel disease and malabsorption are the known risk factors which make individuals susceptible to acquired zinc

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deficiency [9]. Severe zinc deficiency may be associated with several clinical abnormalities including: hypogeusia, hyposmia, growth retardation, dermatitis, alopecia, gonadal hypofunction, abnormal pregnancy, susceptibility to infections, delayed wound healing, impaired glucose tolerance, and increased carcinogenesis [2].

The relationship between socio-economic status and serum concentration of zinc and copper has been demonstrated in studies of a Chinese population [10] and a population sample from the United States [11]. However, a study of a Spanish population did not confirm a relationship between socio-economic factors and serum trace element concentrations [12]. From the first report on the prevalence of zinc deficiency among Iranians by Prasad in 1974 [13], there was little information available on the factors determining serum trace element levels. We therefore wished to investigate the association between serum trace element concentrations and socio economic factors in a large Persian cohort.

## Material and methods

### *Subjects*

A large Persian population sample (n = 2,233; comprising 1,106 (49.5%) males and 1,127 (50.5%) females) was recruited using a cluster-stratified sampling method. A power calculation was used to determine the number of subjects for each cluster. Individuals were aged 15–65 years, and included urban and rural residents of the Great Khorasan province, Iran. Great Khorasan is located in the northeast of Iran and has an estimated population of 6,200,000. Great Khorasan province has recently been divided into three regions: Razavi, and North and South Khorasan. Subjects were recruited by researchers who visited each subject in their home. Less than one percent of subjects invited to participate refused to do so. Subjects were invited to attend their nearest health center after an overnight fast.

A sequential cross-sectional sampling technique was used allowing a representative sample to be recruited from all urban and rural areas of the region. None of the subjects had a past medical history of any major disease (malignancy, cardiac heart disease, connective tissue disease and gastrointestinal disease including malabsorption). At the time of sampling, based on past medical history and physical examination, we only include the individuals who did not prove any signs and symptoms of overt infectious diseases.

Each patient gave informed written consent to participate in the study, which was approved by the Mashhad University of Medical Science Ethics Committee.

### *Anthropometric measurement*

For all patients, anthropometric parameters including: weight, height, and waist circumference were measured using a standard protocol as previously described [14]. Calculated body mass index (BMI) was used to classify individuals into underweight (BMI<18 kg/m2), normal weight (18-24.9 kg/m2), overweight (25-29.9 kg/m2) and obese ($\geq$ 30 kg/m2) groups [15].

### *Serum zinc and copper analysis*

Serum copper and zinc concentrations were measured by flame atomic absorption spectrometry (Perkin Elener 3030 USA 1980) following a one in four dilution with distilled water as previously reported [16]. Typical between-batch precision coefficients of variations [CVs] for these assays were 3.6% and 2.3% respectively.

The reference ranges for the serum copper and zinc were as follows:

- Copper: Men: 10.99-21.98 (μmol/L); Women: 12.56-24.34 (μmol/L) [17].
- Zinc: 10.7-18.4 (μmol/L) for both men and women [17].

### *Socio-economic status*

Data related to socio-economic status was gathered using a questionnaire completed at the time of blood sample collection.

### *Statistical analysis*

The data were subjected to statistical evaluation, using MiniTab (release 13, Minitab Inc, 2000, USA), with descriptive statistics (mean, median, standard deviation [SD] and inter-quartile range) being determined for all variables. Data for groups and subgroups were compared using t-tests and chi-square tests were used for quantitative and qualitative variables using a Bonferonni correction for multiple comparisons. Analysis of covariance (ANCOVA) was used to assess differences after adjustment for important confounding factors including age, gender, smoking habit, blood pressure, fasting blood sugar, lipid profile and BMI.

## Results

### *General characteristics of the sample group*

The demographic data for the entire sample are shown in **Table 1**.

### *Biochemical data*

The mean serum Cu and Zn concentrations for the whole subject group were 14.7±3.3 μmol/L (range 4.5-28.4 μmol/L), and 11.7±1.9 μmol/L (range 3.6-28.3 μmol/L) respectively, and the mean serum Zn/Cu ratio for the group was 0.83±0.2. The percentage of individuals with serum Zn concentrations outside the reference range was 25.2% with 22.1% below and 3.1% above the reference range in the whole population sample. In regard to serum copper concentrations, 35.7% were outside the reference range with 32.1% below and 3.6% above the reference range (**Table 1**).

**Table1.** Characteristics of total population sample (n = 2233).

| Characteristics | n (%) |
|---|---|
| **Age** (Years; mean±SD) 43.0±12.4 | |
| <20 | 62 (2.8) |
| 20-29 | 334 (15.0) |
| 30-39 | 507 (22.7) |
| 40-49 | 588 (26.3) |
| 50-59 | 478 (21.4) |
| >60 | 264 (11.8) |
| **Residency location** | |
| Urban | 1315 (58.9) |
| Rural | 918 (41.1) |
| **Marital status** | |
| Married | 1950 (87.3) |
| Single | 202 (9.0) |
| Divorced | 81 (3.7) |
| **Education** | |
| Illiterate | 642 (28.7) |
| Under diploma | 1148 (51.4) |
| Diploma | 272 (12.2) |
| University | 171 (7.7) |
| **Weight (kg)** | 66.1 ± 13.4 |
| **BMI (kg/m$^2$)** | 25.3 ± 4.8 |
| **Waist (cm)** | 89.1 ± 13.9 |
| **Zn (μmol/L)** | 11.7 ± 1.9 |
| **Cu (μmol/L)** | 14.7 ± 3.3 |
| **Zn/Cu ratio** | 0.83 ± 0.20 |
| **Zinc** | |
| lower than the normal range | 493 (22.1) |
| above the normal range | 70 (3.1) |
| **Copper lower than the normal range** | 717 (32.1) |
| Males | 326 (29.5) |
| Females | 391 (34.7) |
| **Copper above the normal range** | 81 (3.6) |
| Males | 67 (6.0) |
| Females | 14 (1.2) |

Values expressed as Mean ± SD for normally distributed data and Median and Interquartile range for not normally distributed data; BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; FBS, Fasting blood sugar; TC, Total cholesterol; TG, Triglycerides; LDL-C, Low density lipoprotein cholesterol; HDL-C, High density lipoprotein cholesterol; Zn, Zinc; Cu, Copper; DM, Diabetes mellitus; IFG, Impaired Fasting glucose. Normal ranges of trace elements are considered as below: Zinc: [70-120 (μmol/L)] Copper: Males, [10.99-21.98 (μmol/L)], Females [12.56-24.34 (μmol/L)]

**Table 2** shows the mean values for serum copper concentrations was significantly higher in females compared to males in the group as a whole ($p < 0.001$), and the mean value of the Zn/Cu ratio was significantly higher in males compared to females ($p < 0.001$), which remained significant after adjusting for important confounding factors including age and BMI. The highest serum levels of copper were found in the subjects aged between 50-59 years ($p < 0.01$). No significant differences in serum zinc concentrations with age were found ($p > 0.05$).

**Table 2.** Relationship between socioeconomic factors and serum zinc, copper and Zn/Cu ratio.

| | Zn (μmol/liter) | | | Cu (μmol/liter) | | | Zn/Cu Ratio | | |
|---|---|---|---|---|---|---|---|---|---|
| | Male | Female | Total | Male | Female | Total | Male | Female | Total |
| Gender | | | | | | | | | |
| Male (n=1106; 49.5%) | | 11.8±1.8 | | | 13.9±2.9*** | | | 0.89±0.27*** | |
| Female (n=1127; 50.5%) | | 11.7±1.9 | | | 15.6±3.39 | | | 0.79±0.33 | |
| Age decade | | | | | | | | | |
| <20 | 12.0±1.5 | 12.1±3.2 | 12.1±2.5 | 13.5±2.9*** | 15.2±3.4 | 14.4±3.2** | 0.92±0.18** | 0.81±0.19 | 0.86±0.19* |
| 20-29 | 11.8±1.9 | 11.5±1.6 | 11.7±1.7 | 13.3±2.7 | 15.0±3.9 | 14.2±3.5 | 0.92±0.20 | 0.84±0.46 | 0.88±0.36 |
| 30-39 | 11.8±1.6 | 11.7±1.5 | 11.7±1.5 | 13.8±3.1 | 15.4±3.4 | 14.6±3.3 | 0.91±0.38 | 0.79±0.19 | 0.85±0.31 |
| 40-49 | 11.8±1.8 | 11.6±2.0 | 11.7±1.9 | 13.7±2.6 | 15.7±3.2 | 14.7±3.1 | 0.89±0.23 | 0.77±0.20 | 0.83±0.23 |
| 50-59 | 11.5±1.7 | 11.6±1.8 | 11.6±1.8 | 14.5±2.9 | 15.7±3.2 | 15.1±3.1•• | 0.82±0.20 | 0.79±0.47 | 0.81±0.36 |
| >60 | 12.0±2.2 | 11.7±2.0 | 11.8±2.1 | 14.1±2.8 | 15.7±2.9 | 14.9±2.9 | 0.88±0.25 | 0.76±0.17 | 0.82±0.22 |
| Total | 11.8±1.8 | 11.6±1.8 | 11.7±1.8 | 13.9±2.9 | 15.5±3.3 | 14.7±3.2 | 0.88±0.27 | 0.79±0.32 | 0.84±0.30 |
| Marital Status | | | | | | | | | |
| Married | 11.8±1.8 | 11.6±1.8 | 11.7±1.8 | 14.8±3.0 | 14.8±3.3 | 14.8±3.3** | 0.80±0.30 | 0.81±0.37 | 0.84±0.31 |
| Single | 11.6±2.0 | 11.8±1.9 | 11.7±2.2 | 14.6±2.6 | 14.7±3.4 | 14.2±3.4 | 0.83±0.21 | 0.85±0.22 | 0.87±0.21 |
| Divorced | 11.6±1.3 | 11.5±1.4 | 11.7±1.4 | 14.9±2.9 | 14.9±2.0 | 15.1±2.6•• | 0.85±0.19 | 0.83±0.13 | 0.80±0.18 |
| Residency Location | | | | | | | | | |
| Urban | 11.9±1.9 | 11.9±2.0** | 11.9±1.9*** | 13.6±2.9*** | 15.6±3.5 | 14.6±3.3* | 0.91±0.29** | 0.80±0.29 | 0.85±0.30** |
| Rural | 11.7±1.8 | 11.4±1.6 | 11.6±1.7 | 14.3±2.9 | 15.46±3.2 | 14.9±3.1 | 0.85±0.22 | 0.78±0.36 | 0.81±0.30 |
| Education | | | | | | | | | |
| Illiterate | 11.7±2.2 | 11.5±1.8 | 11.5±1.9** | 14.7±2.9*** ••• | 15.60±3.0 | 15.3±3.0*** | 0.82±0.22*** | 0.77±0.37 | 0.79±0.33*** |
| Sub diploma | 11.8±1.8 | 11.8±2.0 | 11.8±1.9 | 13.8±2.87 | 15.59±3.5 | 14.6±3.3 | 0.89±0.29 | 0.80±0.31 | 0.85±0.30 |
| Diploma | 11.9±1.8 | 11.8±1.8 | 11.9±1.8 | 13.4±2.9 | 15.3±3.5 | 14.2±3.3 | 0.92±0.22 | 0.80±0.21 | 0.87±0.22 |
| University | 11.7±1.7 | 11.9±1.7 | 11.8±1.67 | 13.3±2.6 | 15.2±3.9 | 14.0±3.2 | 0.90±0.22 | 0.83±0.23 | 0.88±0.22 |
| Total | 11.8±1.8 | 11.7±1.9 | 11.7±1.9** | 13.9±2.9 | 15.5±3.9 | 14.7±3.2 | 0.88±0.27 | 0.79±0.32 | 0.84±0.30 |
| Anthropometric indices (Body mass index) | | | | | | | | | |
| Normal | | 11.71±1.77 | | | 14.49±3.19 | | | 0.85±0.32 | |
| Overweight | | 11.83±2.04 | | | 14.80±3.29ЖЖ | | | 0.84±0.30ψ | |
| Obese | | 11.66±1.80 | | | 15.41±3.30 ψψψ | | | 0.79±0.20ψψ | |

Values expressed as Mean SD. Data for groups and subgroups were compared using t-tests and chi-square tests were used for quantitative and qualitative variables using a Bonferonni correction for multiple comparisons. For comparison of more than two subgroups post-hoc test was conducted. In order to delete the effects of confounding factors ANCOVA test was used • $p < 0.05$ between married and single groups in females; ••$p < 0.01$ between divorced subgroup of total population. ••$p < 0.05$ between $\psi = p < 0.05$, $\psi\psi = p < 0.001$ between normal and obese, Ж = $p < 0.05$, ЖЖ = $p < 0.001$ between overweight and obese group. •• $p < 0.05$ copper level of total subjects in 50-59 years old subgroup and the other age subgroup between total individuals of each subgroup with each other. ••• $p < 0.001$ between illiterate men copper concentrations and the other educational level subgroups. ANOVA test: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ Zn, Zinc; Cu, Copper. N, number.

***Relationship between socio-economic factors and serum trace elements***

There was no significant difference in either serum zinc or copper concentrations between married and single individuals, however widows and widowers had higher serum copper than single and married subjects ($p < 0.05$), which remained significant after adjustment for confounding factors including age and BMI. Urban residents had higher serum zinc ($p < 0.01$) and lower serum copper concentrations ($p < 0.05$) than rural residents. Male rural residents had significantly higher serum copper concentrations, and female urban residents had significantly higher zinc concentrations ($p < 0.001$). Illiterate male subjects had significantly higher serum concentrations of copper than the males in the other subgroups ($p < 0.001$). Serum trace element concentrations varied according to educational attainment with significantly higher serum copper concentrations and lower Zn/Cu ratio in the illiterate subgroup ($p < 0.001$).

Overweight subjects had significantly higher copper and lower Zn/Cu ratio than normal weight subjects ($p < 0.01$). Also, obese subjects had significantly higher serum copper and lower Zn/Cu ratio than overweight subjects ($p < 0.01$) as can be seen in **Table 3**.

***Relationship between anthropometric indices and serum trace elements***

**Table 3** shows Serum copper and Zn/Cu ratio demonstrated positive correlation with anthropometric indices including height, waist and body mass index ($p < 0.01$). However, there was not an association between serum zinc and anthropometric indices ($p > 0.05$).

## Discussion

***Reference values of serum concentrations of copper and zinc***

We have obtained a similar concentration range for serum zinc and copper in our population sample as previously reported for other populations [mean serum concentrations of copper (14.7±3.3 μmol/L), and zinc (11.7±1.9 μmol/L)] [17]. The mean serum zinc concentrations for both genders were also similar to those reported for a Greek population [18] but lower than reported for a Kuwaiti population [19], whereas values for serum copper were lower than for both these latter populations [19]. The Zn/Cu ratio in the males in our study was similar to that reported for the Kuwaitian males, a healthy Caucasian population from the UK [20] and Iranian subjects [14], but this ratio was higher in the females in our population sample than Kuwaitian subjects [19].

We have previously shown a potential association between serum trace element and development of cardiovascular diseases in Iranian population [6, 16]. According to our study findings the current status of zinc serum level does not seem critical compared with western and middle eastern regions [18, 19]. We have demonstrated an inverse association between the serum zinc/copper ratio and calculated 10 years' coronary risk in Iranian population [16]. It could be concluded that in respect to trace element status, Iranian females have a more favorable profile for copper and zinc with respect to cardiovascular risk compared to the Kuwaiti population.

***Demographic factors and serum copper and zinc***

Serum copper was strongly associated with age. The highest mean copper concentrations were found in the sub-population with an age between 50-59 years. According to our previous studies, a high concentration of serum copper is associated with an increased risk of cardiovascular disease [6, 16]. It is of interest that the highest serum copper concentrations were found in the groups of Iranian population most susceptible to cardiovascular disease [21]. An increase in serum copper with age is in agreement with previous reports [22]. According to our findings after 60 years of age, the levels of copper fell and this may be due to differences in diet, copper absorption or the effects of an inflammatory response with the aging [23]. No

**Table 3.** Pearson correlation between zinc, copper and Zn to Cu ratio with some anthropometric indices.

| | Zinc (μmol/liter) | Copper (μmol/liter) | Zn/Cu |
|---|---|---|---|
| Height (m) | 0.1*** | 0.2*** | 0.01 |
| Weight (kg) | 0.01 | -0.02 | 0.02 |
| Waist (cm) | 0.07* | 0.09*** | 0.01 |
| Body mass index (kg/m$^2$) | -0.06** | 0.1*** | 0.02 |

*p value < 0.05, **p value < 0.01,***p value < 0.001.

differences in serum zinc concentrations with age were detected which is in agreement with some previous reports [24]. However Sfar et al reported the increased prevalence of zinc deficiency with age in Tunisian subjects [25].

According to the findings of this investigation the mean serum Cu concentration in females was higher than in males; however serum Zn concentration did not vary significantly with the gender. Our findings are consistent with those of D az Romero et al in a Spanish population [12].

There were significant differences in serum zinc and copper levels with place of residence. This may be related to differences in dietary intake and lifestyles associated with rural versus urban dwelling.

Significantly higher serum copper concentrations were found among poorly educated, illiterate subjects, however this difference did not remain significant after multivariate analysis. Diaz Romero et al concluded that there was no significant relationship between socio-economic status and educational level with respect to the serum Cu and Zn concentrations in a Spanish population, which is not consistent with our results [12]. Zhang et al in an investigation of Chinese population reported that an inverse relationship of serum Zn and Zn/Cu was demonstrated with social-economic status, however this association was not significant [10]. Zhang et al could not demonstrate a relationship between educational attainment with serum Zn and Cu concentrations and Zn/Cu [10]. Cole et al in a study of low-income African American and Hispanic children in Atlanta proved that the main sources of zinc in the diets were meat products and cereals and finally demonstrated that the prevalence of zinc deficiency was high in the studied population [11]. There was no dietary information collected in the survey, which is the limitation of this study. However, we have previously shown that weak associations between dietary trace elements intake and their serum concentrations were observed for zinc and copper concentrations [20].

### *Relationship between serum copper and zinc concentrations*

The positive association between serum zinc and copper that we found in this current study is in contrast with a report by Abiaka and colleagues for an Arabian population [19], and Arvanitidou et al have reported a significant negative correlation between zinc and copper levels in a young Greek population aged between 3-14 years [26]. The differences may be explained by differences in dietary intake and age.

## Conclusion

A low zinc and copper status appears to be a common feature in our Persian population sample from northwestern Iran. It is not possible from our data set to determine to what extent serum copper and zinc are affected by dietary intake, and indeed whether the population had an adequate intake. In the sixth decade of life, which is one of the most vulnerable periods for morbidity and mortality of cardiovascular disease, the serum Cu concentrations were found to reach a peak. However it is unclear whether this is an aetiological determinant of morbidity or a reflection of underlying inflammatory disease. It is suggested to have an interventional study for Persian population in regard to zinc and copper to see the beneficial effect of these trace elements for global decision in Iran.

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