ZINC AND COPPER STATUS IN CHILDREN WITH HIGH FAMILY RISK OF PREMATURE CARDIOVASCULAR DISEASE

Roya Kelishadi, MD; Hassan Alikhassy, MS;
Masoud Amiri, MS

Background: Zinc and copper are beneficial to health, growth and development, and also for the prevention of cardiovascular disease (CVD) with regards to improved dietary habits as a preliminary step in CVD prevention. This study was conducted among 2-18-year-old children with high family risk of premature CVD in comparison to controls.

Subjects and Methods: One hundred randomly selected children whose parents had premature myocardial infarction were included in the study. The controls were 100 individuals randomly selected from the case group's neighbors and matched for age, sex and socioeconomic status. A four-day food record questionnaire was used to assess zinc and copper intakes, and their serum levels were determined using Flame-Atomic Absorption Spectrophotometry. The data were analyzed by SPSS/Windows V6 software, using the Student's *t* and Mantel-Hanzel tests. Significance of differences was considered at $P<0.05$.

Results: The daily zinc intake was significantly lower in the case than control group (6.89±2.97 vs. 8.30±2.45 mg, $P=0.047$). The mean serum zinc level was not significantly different between both groups (82.12±14.1 vs. 92.26±23.7 µg/dL, $P>0.05$). Zinc deficiency was more prevalent among the case in boys than their controls (58% vs.18%, $P=0.04$). This difference was not significant in girls (44% vs. 40%). The daily intake and serum level of copper were not significantly different between the case and control groups. No case of copper deficiency was found. The mean systolic blood pressure was not significantly different between the zinc-deficient and zinc-sufficient subjects. Although the mean diastolic blood pressure of the former was higher than the latter, there was no statistically significant difference. About 23.7% of all studied sample had mild-to-moderate degrees of failure to thrive, with significantly lower daily intake and serum zinc level than other subjects (5.41±1.06 mg, 82.09±12.74 µg/dL vs. 6.89±2.14 mg, 99.25±27.15 µg/dL, respectively, $P<0.05$).

Conclusion: It is recommended that emphasis be placed on the consumption of food rich in zinc by children, especially those with high family risk of premature CVD.
Ann Saudi Med 2002;22(5-6):291-294.

Key words: Zinc, copper, premature cardiovascular disease, blood pressure.

Interest in the importance of trace elements to human health has increased considerably during last decades. Zinc and copper are known to be essential trace elements to the human body.[1-4] Zinc deficiency in human beings was first reported in 1960 from Iran, Egypt and Turkey,[5-6] and has always been a nutritional problem in the Middle East. This may be due to the prevalence of diets typically low in zinc and high in fiber and phytates impairing zinc absorption.[6-7]

More than 100 enzymes require zinc as a co-factor for different metabolic pathways, especially important for growth and development, but there is also considerable evidence showing a possible involvement of zinc and copper in the pathogenesis of cardiovascular disease (CVD). Different hypotheses have been proposed for this effect. Briefly, it can be said that low zinc concentration is believed to be able to cause atherosclerosis in cases where minimal traumas inside the vessels do not have sufficient zinc for their repair.

Copper is known to be essential for the enzyme activity which forms the cross-linkages of normal elastin in vessels. A deficient copper intake may lead to abnormal vessel wall formation and thus to pathological changes, which may lead to CVD.[8-12] Also, it has been shown that the copper/zinc ratio has an inverse correlation with blood pressure.[13]

The idea that atherosclerosis begins in childhood goes back to the 1950s when Holman and his colleagues focused attention on juvenile atherosclerosis.[14] Although early prevention from atherosclerosis is recommended for all children, it is more vital for children with high family risk of premature CVD (such as myocardial infarction, stroke,

From the Departments of Pediatrics, Nutrition and Epidemiology, Isfahan Cardiovascular Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.

Address reprint requests and correspondence to Dr. Kelishadi: Head of Pediatrics Department, Isfahan Cardiovascular Research Center, Isfahan University of Medical Sciences, PO Box 81465-1148, Isfahan, Iran.

Accepted for publication 20 June 2002. Received 02 December 2001.

TABLE 1. *Distribution of subjects according to sex and zinc status.*

Serum zinc level (μg/dL)	Boys Case	Control	Total	P*	Girls Case	Control	Total	P*
<80	29	9	38	0.04	22	20	42	0.35
80-120	20	36	56	0.07	28	26	54	0.26
>120	1	5	6	0.06	0	4	4	0.31
Total	50	50	100		50	50	100	

*Significance of differences considered at $P<0.05$ (Mantel-Hanzel test).

TABLE 2. *Comparison of mean serum zinc and copper levels for both groups.*

Elements (μg/dL)	Case (n=100) Mean±SD	Median	Control (n=100) Mean±SD	Median	P*
Zinc	82.12±14.1	70	92.26±23.7	87	0.09
Copper	123.78±29.37	118	121.12±17.81	122	0.89

*Significance of differences considered at $P<0.05$ (*t*-test).

TABLE 3. *Comparison of daily intake of zinc and copper for both groups.*

Elements (mg)	Case (n=100) Mean±SD	Median	Control (n=100) Mean±SD	Median	P*
Zinc	6.89±2.97	6.13	8.30±2.45	7.16	0.047
Copper	1.85±3.3	1.11	1.30±1.16	0.94	0.330

*Significance of differences considered at $P<0.05$ (t-test)

sudden death, peripheral vascular disease occurring in women below 65 and in men below 55 years of age). This study was carried out in Isfahan, in view of the increase in the prevalence of major CVD risk factors in children and adolescents in the community in recent years,[15] especially with regards to the history of zinc deficiency in the country. The main objective of the study was to compare serum levels and daily intakes of zinc and copper in the children of parents suffering from premature myocardial infarction (MI) with other children (matched for age, sex and socioeconomic status), and to find those foods and food habits that are different in the former group. Significant differences would then point to the need for action to be taken with regards to changing dietary habits as a preliminary step in the prevention of premature CVD.

Subjects and Methods

This was a descriptive analytical study conducted by the Pediatrics Department of Isfahan Cardiovascular Research Center in 2000. Using simple random sampling, 100 children and adolescents of parents with premature myocardial infarction (MI) who were hospitalized in the Coronary Care Units of hospitals affiliated with the Isfahan University of Medical Sciences were selected (CI=95%) and invited (by written invitation) to the Pediatric Preventive Cardiology Clinic of the Center. The control group included 100 children (aged 2-18 years) of neighbors of the case group subjects matched for age, sex and socioeconomic status. Eighty percent and 60% of the case and control groups, respectively, cooperated to be included in the survey. Body weight (with minimum clothing), height (barefoot, standing against the wall), and blood pressure (under WHO standards using a mercury manometer with a suitable cuff) were measured and recorded. Also, fasting venous blood samples were taken (8:30-10:00 AM) and transferred to acid-washed test tubes, the sera separated, kept at –18ºC, and sent to the laboratory of the School of Pharmacy of Isfahan University of Medical Sciences. The serum zinc and copper levels have been determined using Flame Atomic Absorption Spectrophotometry.

To determine the food and nutrient intakes, a four-day food record questionnaire was designed at our center. Using the questionnaire, an illustrated software (also developed by our center) and the Iranian Food Composition Tables, the daily zinc and copper intakes (mean of the 4 days) were calculated. The software contained pictures of different local foods and the usual amounts consumed, so that the interviewee—the mother in the household—could easily state how much of each food had been consumed. The data were analyzed by SPSS/Windows Version 6 using the Student's *t* and Mantel-Hanzel tests. The significance of differences was considered at $P<0.05$.

Results

The mean age of the subjects was 11.8±8.7 years. With regards to the serum zinc level of the case and control groups combined, the mean value was not significantly different from the reference value (86.8±19.6 vs. 100.0±20.0 μg/dL, $P>0.05$). The difference between the mean daily zinc intake was not different between girls and boys (7.37±3.04 vs. 8.45±5.16 mg, $P=0.74$). As shown in Table 1, zinc deficiency was more prevalent among the case boys than their controls ($P=0.04$), but the difference was not significant between the case and control girls ($P=0.35$). No case of copper deficiency was found.

The mean serum copper level in both groups combined was highest in the 6-9 years (130.60±26.83 μg/dL) and lowest in the 14-18 years age group (107±16.97 μg/dL). With regards to zinc, the highest value was in the 6-9 years (83.47±23.84 μg/dL) and the lowest in the 10-13 years age groups (87.76±23.14 μg/dL). There was no fixed trend in serum zinc and copper values with increasing age. As shown in Table 2, there was no significant difference between the mean serum levels of zinc and copper in the case and control groups.

The daily intake of zinc (Table 3) was significantly lower in the case than in the control group ($P=0.047$). The intake of the two groups combined was 7.8±1.4 mg, the difference between the boys and girls being non-significant (8.5±5.1 vs. 7.4±3.0 mg, P=0.96).

As regards daily copper intake, there was no significant difference between the case and control groups (Table 3). Also, it was found that the difference was not significant between boys and girls (1.7±2.9 vs.1.3±1.2mg, P>0.05).

The mean systolic blood pressure was not significantly different between the zinc-deficient and zinc-sufficient subjects (103.06±17.98 vs. 103.59±15.04 mm Hg, P>0.05). Although the mean diastolic blood pressure of the former was higher than the latter, there was no statistically significant difference (72.22±14.87 vs. 66.87±8.3 mm Hg, P>0.05).

Using weight for height and weight/ideal weight ratios, 23.7% of studied sample had mild-to-moderate failure to thrive (FTT) and its prevalence was not different in case and control groups. The mean daily zinc intake in samples with FTT was significantly lower than those with normal growth (5.41±1.06 vs. 6.89±2.14 mg, P=0.04). Also, the mean serum zinc level in samples with FTT was significantly lower than those with normal growth (82.09±12.74 vs. 99.25±27.15 µg/dL, P=0.045). There was no significant difference in daily intake and serum copper levels between children with normal or retarded growth (1.4±0.5 mg, 120±20.19 µg/dL vs. 1.14±0.7 mg, 119.5± 20.5 µg/dL, respectively, P>0.05).

Discussion

In recent years, much research has been conducted on the status of trace elements, particularly zinc and copper, and the role they play in the early prevention of atherosclerosis. Many individuals afflicted with premature CVD are exposed to the major risk factors of atherosclerosis such as hyperlipidemia, hypertension, obesity and diabetes. However, in some cases, premature CVD may occur in a person without these risk factors. Therefore, other factors involved in the initiation and progression of atherosclerosis should be prevented from childhood, especially in children with high family risk for premature CVD. A deficiency of zinc and copper, which are involved in protection of the health of the endothelium and tissue repair can, in addition to interfering with growth and development, have a role in the initiation and progression of atherosclerosis.[1-4,8-12]

An extensive study on zinc and copper in Finland showed the serum zinc level of 3-18 year-old subjects to be 95.2±17.2 µg/dL.[16] In the present study, the serum level was 86.8±19.6 µg/dL, which was lower, although not significantly different from the reference value (100.0±20.0 µg/dL). Also, while the serum zinc and copper levels in girls were lower than in boys in the Finnish study, no sex difference was seen in our study. On the other hand, the serum copper level was higher in our study (122.2±23.6 µg/dL) than both the reference value and that of the Finnish children (115.6±35.9 µg/dL). Another finding of the Finnish study was that the serum levels of zinc and copper increased with age. In our study, there was no fixed trend, but in all age groups, the copper level was higher than the reference value.

A study in Japan showed an inverse relationship between the serum copper level and age of the children and a normal level for copper.[17] In the Finnish subjects, there was a similar relationship with regards to copper, whose serum level was higher than that of the Japanese children. In our study, the serum copper level increased with age up to the age of 13 years, and had a decreasing trend between 14 to 18 years. The serum copper level was higher than that reported for Finland and Japan and than the reference value. There was no case of copper deficiency in our study.

Another study in Finland showed the average daily zinc intake to be higher in boys than in girls,[18] but there was no statistically significant sex difference in our study. On the whole, the daily zinc intake in our study population was less than 60% of the recommended daily allowance. Similarly, while the average copper intake of the Finnish children was 1.47 mg/day, and being lower in girls, it was 1.56±2.4 mg/day in our study, and there was no sex difference.

In a study in Norway, serum copper concentration was shown to be higher in females than in males,[19] but the difference was not significant in our study.

The differences in serum zinc and copper levels and their daily intakes between the Iranian and Western populations can be explained by differences in food habits and type of foods consumed. For example, Iranian foods contain large amounts of fiber and phytates that interfere with zinc absorption. In addition to adequate copper intake from foods, many families still use copper containers.

To the best of our knowledge, there has been no previous study in children with high family risk for CVD. The findings of our study show that zinc intake of children with high family risk of premature CVD was significantly lower than that of other children and adolescents matched for age, sex and socio-economic status. Further studies are needed to find reasons for this difference. It is important to recommend increase in the consumption of zinc food sources, such as wheat germs, nuts (walnuts, etc.), meat and dairy products.

Another finding in our study was that despite the non-existence of a statistically significant difference between the high-risk family boys and girls as regards daily zinc intake, the boys' serum zinc level was significantly lower than the girls, but there was no such difference in the controls. Considering that the males are at a higher risk of CVD, it is possible that in addition to the known causes (e.g., hormonal differences), there exist differences in the metabolism of elements involved in the etiology or prevention of atherosclerosis between males and females, as well as between high-risk family members and those not at risk. Many studies have shown a deficiency of zinc in subjects with atherosclerotic lesions.[20-22]

In some studies it has been observed that the serum copper level and zinc-to-copper ratio have an inverse relationship with blood pressure in adolescents. The effect of these trace elements on the blood pressure of adult subjects with atherosclerotic lesions has also been proven.[13] In our study, there was no difference between zinc-sufficient and zinc-deficient individuals with regards to systolic blood pressure; similarly no statistically significant difference was observed as regards to diastolic blood pressure, although the diastolic blood pressure was higher in zinc-deficient subjects. It is likely that an effect of these two trace elements on blood pressure will be seen in older individuals.

Zinc has beneficial effects on children's growth and health. Regarding the high prevalence of failure to thrive (FTT) condition in our community and the results of this study on the low zinc intake in children, special attention should be paid to the zinc status in growing children and adolescents, especially those with high family risk for CVD. Physicians, particularly pediatricians, should make recommendations to families to consume more zinc-rich foods, with special emphasis on families at risk of premature CVD. This is an important step in promoting growth as well as preventing the initiation and progression of atherosclerosis. Certainly, more extensive research on the role of zinc and copper in the initiation of cardiovascular diseases is essential.

Acknowledgements

We thank Mr. M.Rafiei for preparing the illustrated nutrition software, and Dr. N. Sarraf-Zadegan, Dr. S. Asgary and Dr. Gh. Naderi for their helpful suggestions. We also thank members of the Laboratory of the Pharmacy Faculty of Isfahan University of Medical Sciences, and also members of the Computer Unit of Isfahan Cardiovascular Research Center for their assistance.

References

1. King JC, Keen CL. Zinc. In: Shils. M, Olson M, Shike M, Ross A, editors. Modern Nutrition in Health and Disease 9th edition. Philadelphia: Lippincott Williams & Wilkins, 1999;223-39.
2. Sauberlich HE. Zinc. In: Sauberlich Howerde E. Assessment of nutritional status. 2nd edition. Florida: CRC Press, 1999;383-96.
3. Pennington JAT, Schoen SA. Contribution of food groups to estimated intakes of nutritional elements: results from the FDA Total Diet Studies. Int J Vit Nutr Res 1996;66:342.
4. Todd WR, Elwehjem CA, Hart EB. Zinc and growth. Am J Physiol 1984;107:146-56.
5. Prasad AS, Scharlet AR, Miale A, Farid Z, Sandstead H. Zinc and iron deficiencies in male subjects with dwarfism and schistomiasis or severe anemia. Am J Clin Nutr 1963;12:437.
6. Prasad AS, Halsted JA, Nadimi M. Spectrum of human zinc deficiency Am J Med 1961;31:532-46.
7. Prasad AS. Clinical manifestations of zinc deficiency. Ann Rev Nutr 1985:341.
8. Ripa S, Ripa R. Zinc and atherosclerosis. Minerva Med 1994;5:647-54.
9. Vlad M, Berdas E, Tomas R, Sava D, Frakas E, Usa G. Effect of copper sulfate in experimental atherosclerosis. Biol Trace Elem Res 1993;38:47-54.
10. Klevay LM. Elements of ischaemic heart disease. Perspect Biol Med 1977;20:186-92.
11. Pories WJ, Henzel JH, Hennesen JA, Underwood EJ. Trace elements in human and animal nutrition. 4th edition. New York: Academic Press, 1977:219.
12. Klevay LM. Coronary heart disease: the zinc/copper hypothesis. Am J Clin Nutr 1975;28:764-74.
13. Medeiros DM, Pellum LK, Brown BJ. The association of selected hair minerals and anthropometric factors with blood pressure in a normotensive adult population. Nutr Res 1983;3:51-60.
11. Holman RM, Gill HC, Strong JP, Geer JC. The natural history of atherosclerosis: the early aortic lesions as seen in New Orleans in the middle of the 20th century. Am J Pathol 1958;34:209-35.
12. Kelishadi R, Hashemipour M, Sarraf-Zadegan N, Amiri M. Trend of atherosclerosis risk factors in children of Isfahan. Asian Cardiovasc Thoracic Ann 2001;9:36-40.
16. Vuori E, Salmela S, Akerblom HK, Viikari J, Uhari M, Suonien P, et al. Atherosclerosis precursors in Finnish children and adolescents. Serum and hair copper and zinc concentrations. Acta Pediatr Scand 1985(Suppl);318:205-12.
17. Hatano S, Nishi Y, Usui T. Copper levels in plasma and erythrocytes in healthy Japanese children and adults. Am J Clin Nutr 1982; 35: 120-6.
18. Rasanen L, Ahola M, Kara R, Uhari M. Atherosclerosis precursors in Finnish children and adolescents. VIII. Food consumption and nutrient intake. Acta Pediatr Scand 1985(Suppl);318:135-53.
19. Helgeland K, Haider T, Jonsen J. Copper and zinc in human serum in Norway. Relationship to geography, sex and age. Scand J Clin Lab Invest 1982;42:35-9.
20. Piorunska Stolzmann M, Iskra M, Pateiski J, Mayewaski W. Serum glycerol ester hydrolase activity is related to zinc and copper concentration in atherosclerosis obliterans and aneurysm. J Trace Elem Med Biol 1998;12:39-43.
21. Fang X, Werntraub NL, Rios CD, Chappell DA, Zwacka RM, Engelhardt JF, et al. Overexpression of human superoxide dismutase inhibits oxidation of low density lipoprotein by endothelial cells. Circ Res 1998;82:1289-97.
22. Hilton T, Lvama J, Nikkari T, Yia Herttuaia S. Induction of 15 lipoxygenase mRNA and protein in early atherosclerotic lesion. Circulation 1995;92:3297-303.