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Zinc, Copper, and Growth Status in Children and Adolescents

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ABSTRACT. The associations between serum zinc and copper concentrations and anthropometric variables in 3415 3-, 6-, 9-, 12-, 15-, and 18-y-old Finnish girls and boys were investigated to identify groups with low serum zinc or copper concentrations and retarded growth, possibly suggesting deficiencies. Serum zinc levels and height, wt, body mass index, and skinfold thickness were not strongly related. Serum copper levels were negatively correlated with height and positively with wt, body mass index, and skinfold thickness. These relationships were clearest in both sexes between the ages of 9 and 15 y. Height, wt, body mass index, and skinfold thickness in subjects with very low or high serum values were in agreement with the correlations between these anthropometric variables and serum levels. Groups with clear deficiencies of zinc or copper could not be identified. We conclude that copper levels especially are correlated with stature between the ages of 3 and 18 y. In addition, the results suggest that deficiency states affecting growth are not very likely in healthy Finnish children and adolescents. (*Pediatr Res* 25:323–326, 1989)

Abbreviations

S-Zn, serum zinc concentration
S-Cu, serum copper concentration
BMI, body mass index
ST, sum of triceps and subscapularis skinfold thicknesses

Almost 30 years ago, Zn deficiency was discovered in Iran and Egypt. Retarded growth and delayed sexual development in adolescent males responded to Zn supplementation (1, 2). Since then, clinical Zn deficiency has been estimated to be quite prevalent in the developing countries (3), and cases of possible Zn deficiency as a cause of retarded growth have been reported from Europe and from the United States of America (4, 5).

Deficiency of Cu has been considered a rarity. However, reports of increased Cu requirements in association with fructose consumption (6), and observations from the United States of America that the intake of Cu is often below the recommended intake (6, 7), suggest that subclinical Cu deficiency may be rather common. Cu deficiency has usually been associated with anemia, but hypercholesterolemia and disturbances in cardiac conductivity seem to appear before anemia in experimental deficiency in humans (8). In rats and mice, the main findings in Cu deficiency are hematologic changes, reduced body wt, and changes in the structure of heart muscle (9).

In spite of the associations between growth or stature and Zn and Cu mentioned above, data on whole populations are still inadequate. In this study, we measured S-Zn and S-Cu and height, wt, BMI, and the amount of subcutaneous fat in 3415 3-, 6-, 9-, 12-, 15-, and 18-y-old girls and boys. The purpose was to identify subgroups with possibly marginal Zn or Cu status, and also to analyze relationships between stature and S-Zn and S-Cu.

SUBJECTS AND METHODS

S-Zn, S-Cu and anthropometric variables used in this study were determined as part of the Multicentre Study of Atherosclerosis Precursors in Finnish children and adolescents in 1980 (10–12). The study was carried out in five university cities and in 12 rural communities in their vicinity in different parts of Finland. Equal numbers of girls and boys aged 3, 6, 9, 12, 15 and 18 y were recruited, and their medical and socioeconomic characteristics were representative of the whole country (10). Of the subjects, 19.5% had a history of some long-term disease, usually an allergic disease (11%).

After girls using contraceptive pills were excluded, the total number of girls and boys in this analysis was 3415 (Table 1).

S-Zn and S-Cu were determined from morning fasting blood samples collected in acid-washed test tubes; after clot separation, serum was stored at −18°C. The duplicate determinations were performed using the flame technique of atomic absorption spectrophotometry (12). Height, wt, BMI, and ST were used as anthropometric variables. BMI was calculated as wt/height^2 (kg/m^2). ST was measured by Harpenden calipers. The techniques used in these measurements have been explained in detail previously (11). The number of missing values was under 1.1% for all these variables in all age groups, except for ST in 3-y-old girls and 6-y-old boys (5.3 and 4.7%, respectively).

The subjects were divided into subgroups for analyses. The subjects whose S-Zn or S-Cu fell between the 2.5th and 97.5th percentiles formed medium-Zn and medium-Cu groups; the remaining subjects belonged to low or high groups. Each group included at least seven subjects.

The distributions of variables were checked for normality by scatter plots. The distribution of ST was skewed, and logarithmic transformation was performed for the analyses. Because distributions of wt and BMI in some age groups were slightly skewed, analyses using these variables were also done after logarithmic transformation, but the results were essentially unchanged. The associations between anthropometric variables and S-Zn and S-Cu were determined by computing direct correlations and by multiple regressions of serum levels on anthropometric variables:

$$\text{S-Zn (or S-Cu)} = a + b \times \text{height} + c \times \text{ST}.$$

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Wt was highly correlated with height and ST and was excluded due to problems with multicollinearity. The nonparametric Kruskal-Wallis test was used to compare low, medium, and high groups, and if the differences were found significant, multiple comparisons based on Kruskal-Wallis rank sums were performed as described by Hollander and Wolfe (13). Hypothesis testing was based on 2-sided tests, when available, and probabilities less than 0.05 were considered significant.

The BMDP statistical software package was used for computations (14).

RESULTS

Minimum, mean, and maximum S-Zn and S-Cu, and the 2.5% and 97.5% values are presented in Table 1. S-Zn levels in boys were higher than in girls at the ages of 12, 15 and 18 y ($p < 0.05$, $p < 0.001$, and $p < 0.001$, respectively). S-Cu decreased in both sexes with increasing age up to 15 y ($p < 0.001$, ANOVA).

S-Zn was below 10.7 μmol/liter (70 μg/dL) (the criterion used in NHANES II study [15]) in 20 girls (2, 2, 3, 1, 3, 9, respectively for the age groups studied) and in 12 boys (4, 3, 1, 2, —, 2, respectively, for the age groups).

S-Zn was weakly correlated with wt ($r = 0.14$), BMI ($r = 0.13$), and ST (r = 0.14–0.18) in 9- and 12-y-old girls, and inversely with height ($r = -0.12$) and wt ($r = -0.12$) in 18-y-old girls (Table 2). In boys, no correlation between S-Zn and anthropometric variables was found.

S-Cu was correlated with BMI (r = 0.15–0.31) and ST (r = 0.13–0.32) in 9- to 18-y-old boys and girls; correlations with wt (r = 0.12–0.22) were significant in 9- to 15-y-old girls and in 9- and 18-y-old boys (Table 2). A weak inverse correlation between S-Cu and height was found in one age group in both girls ($r = -0.14$) and boys ($r = -0.21$).

In 12- and 15-y-old girls, differences between low-Zn and high-Zn groups were found in wt, BMI, or ST (Fig. 1); in boys, the differences were not significant. Wt, BMI, and ST in low-, medium-, and high-Cu groups in girls (Fig. 2) were in agreement with the correlations represented in Table 2. In boys, only ST values differed between the groups (Fig. 3). Height did not differ between low-, medium-, and high-Zn or between corresponding Cu groups.

Multiple regressions of S-Zn and S-Cu on the anthropometric variables were determined to eliminate the possible bias in direct correlations due to relationships between height, wt, and ST. Weight was related to height and ST ($r > 0.6$ in many age groups), and could be excluded from the regressions without essential loss of explanatory power of the regression (r^2). When the effects of other anthropometric variables were controlled, height and S-Cu tended to be inversely related (Table 3). The relationships between S-Zn and anthropometric variables (Table 2) were not essentially changed, due to adjustments for other anthropometric variables. Plotting S-Zn or S-Cu against each of the anthropometric variables did not reveal any subgroups with exceptional growth related to low or high S-Zn or S-Cu.

DISCUSSION

Agreement about indices of serum Zn and Cu deficiency, especially in subclinical conditions, has not been achieved. Plasma or serum Zn concentrations have recently been suggested to reflect Zn status (16–18). In Cu deficiencies, plasma or serum Cu concentrations have been reduced and Cu supplementation has resulted in increases in Cu concentrations (8, 19, 20). Blood samples are easily obtained, and the determination of serum or plasma levels of Zn and Cu is a relatively simple procedure. Serum or plasma levels of Zn and Cu are thus widely used as indicators of Zn and Cu deficiencies in population studies; at the individual level, each subject's condition must be taken into account in the interpretation of low values (17). Because high plasma Cu and low plasma Zn have been reported in users of oral contraceptives (21), the girls using oral contraceptives were excluded from our study.

Table 1. *Minimum, 2.5%, mean, 97.5%, and maximum S-Zn and S-Cu; and number of subjects by sex in each age group*

		S-Zn (μmol/liter)					S-Cu (μmol/liter)				
Age (y)	n	Min	2.5%	Mean	97.5%	Max	Min	2.5%	Mean	97.5%	Max
Girls (n = 1707)											
3	255	8.6	11.2	14.6	18.3	23.9	10.0	14.5	21.3	31.2	40.0
6	287	10.5	11.3	14.6	18.0	18.6	8.7	13.7	19.8	27.3	30.6
9	316	9.1	11.0	14.5	18.0	20.7	12.5	13.7	19.1	25.9	29.8
12	327	10.6	11.9	14.5	17.8	20.4	9.6	11.5	16.6	23.3	28.7
15	296	10.2	11.1	14.2	17.5	21.0	7.6	11.5	15.7	21.3	28.3
18	226	9.0	11.0	14.1	17.2	20.6	8.5	10.9	15.8	21.5	26.1
Boys (n = 1708)											
3	270	9.5	11.0	14.3	18.1	19.6	10.6	14.5	21.1	30.5	36.1
6	273	7.7	11.5	14.6	18.2	21.9	10.9	14.7	20.1	28.4	32.2
9	315	9.4	11.7	14.7	18.2	19.3	10.0	14.1	19.1	26.2	29.0
12	316	9.4	11.7	14.8	18.0	20.4	9.3	11.3	17.8	25.4	30.9
15	282	10.8	11.9	14.8	18.4	20.7	9.0	10.7	15.0	21.0	24.8
18	252	10.1	11.4	15.0	18.8	21.0	8.6	10.5	15.1	22.2	24.8

Table 2. *Significances of direct correlations between S-Zn and S-Cu, and anthropometric variables (height, wt, BMI, and ST)*

	Girls								Boys							
Age	Height		Wt		BMI		ST		Height		Wt		BMI		ST	
(y)	Zn	Cu	Zn	Cu	Zn	Cu	Zn	Cu	Zn	Cu	Zn	Cu	Zn	Cu	Zn	Cu
3	NS	NS	NS	NS	NS	NS	NS	+	NS	NS	NS	NS	NS	NS	NS	NS
6	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
9	NS	NS	+	+++	+	+++	++	+++	NS	NS	NS	++	NS	+++	NS	+++
12	NS	NS	+	++	+	+++	+	+++	NS	−−−	NS	NS	NS	++	NS	+++
15	NS	NS	NS	+	NS	++	NS	++	NS	NS	NS	NS	NS	+	NS	+++
18	−	−	−	NS	NS	+	NS	+	NS	NS	NS	+	NS	+++	NS	+++

Abbreviations: + : correlation coefficient positive; − : correlation coefficient negative; +, − : $0.01 < p < 0.05$; ++, −− : $0.001 < p < 0.01$; +++, −−− : $p < 0.001$.

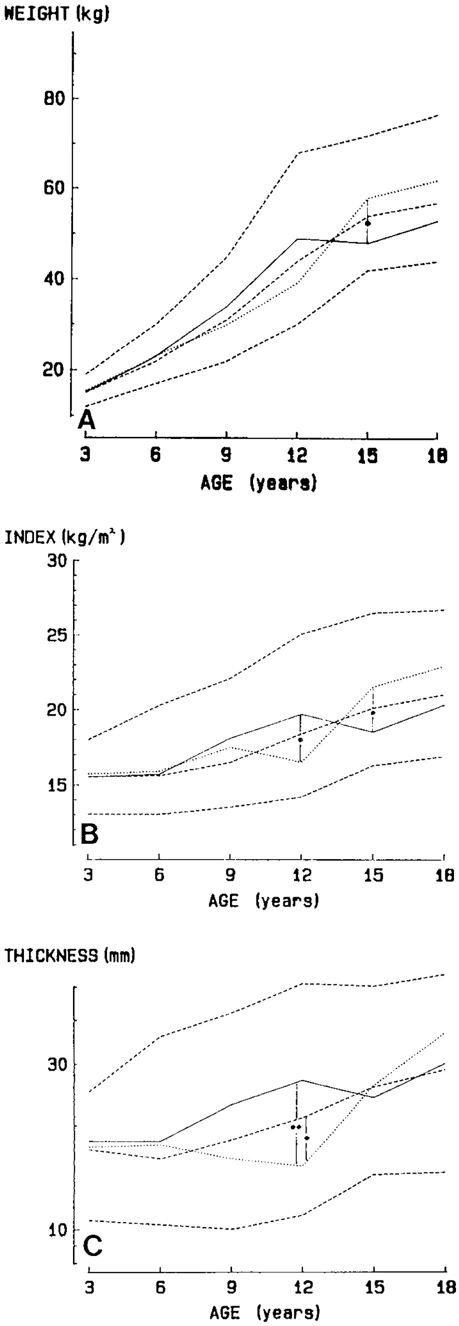

Fig. 1. Mean values of wt (*A*), BMI (*B*), and ST (*C*) in low-, medium-, and high-Zn groups, and the significance levels of the differences between groups in girls. --:2.5 and 97.5% levels of the anthropometric variables; · · ·,--,—: mean values of the anthropometric variables in low, medium and high groups of serum levels; •,••,•••: significance levels ($0.01 < p < 0.05$, $0.001 < p < 0.01$, $p < 0.001$, respectively) of the differences in anthropometric variables between low, medium, and high groups.

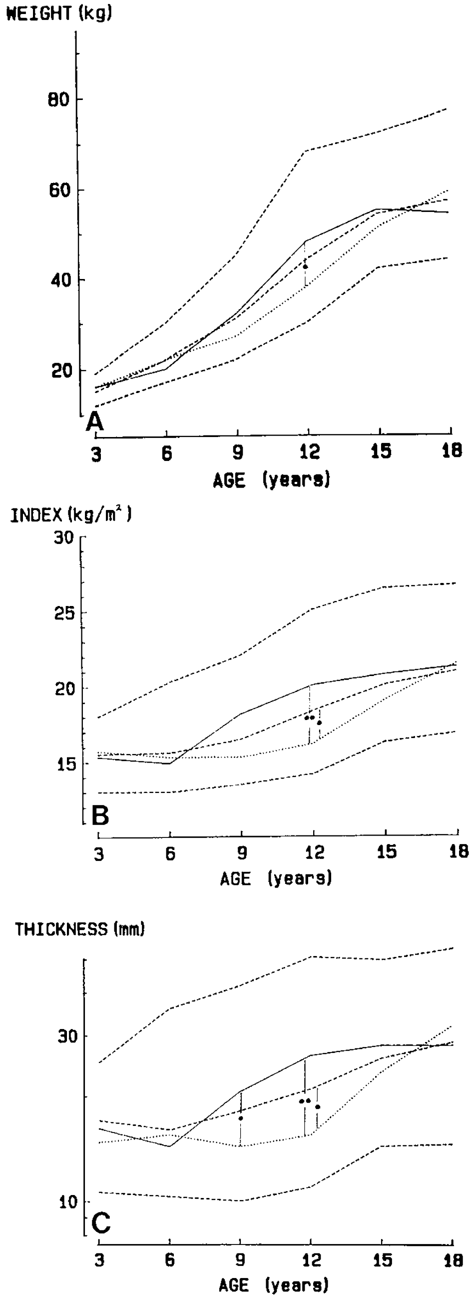

Fig. 2. Mean values of wt (*A*), BMI (*B*), and ST (*C*) in low-, medium-, and high-Cu groups, and the significance levels of the differences between groups in girls. Symbols as in Figure 1.

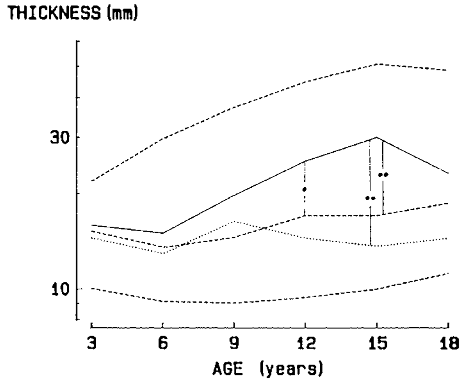

Fig. 3. Mean values of ST in low-, medium-, and high-Cu groups, and the significance levels of the differences between groups in boys. Symbols as in figure 1.

S-Zn was correlated with wt, BMI, and ST in 9- and 12-y-old girls, and was inversely related to wt and height in 18-y-old girls. The relationships were, however, weak, and possibly due to chance without biologic basis. S-Zn and stature were not correlated in boys. S-Cu, by contrast, was correlated to weight, BMI, and ST both in girls and boys. The inverse relationship between S-Cu and height became apparent only after the effect of other anthropometric variables was taken into account by using multiple regression analysis.

In addition to general associations between stature and serum levels, we were interested in very low and high values of both anthropometric variables and serum Zn and Cu; therefore, the

Table 3. *Significances of partial correlations between S-Cu and height and ST in regression of S-Cu (S-Cu = a + b × height + c × ST)*

Age (y)	Girls		Boys	
	Height	ST	Height	ST
3	NS	++	NS	NS
6	NS	NS	−	NS
9	−−	+++	NS	+++
12	−−	+++	−−−	+++
15	−−	+++	−	+++
18	−−−	+	NS	+++

Abbreviations: + : correlation coefficient positive; − : correlation coefficient negative; +, − : $0.01 < p < 0.05$; ++, −− : $0.001 < p < 0.01$; +++, −−− : $p < 0.001$.

sizes of the low and high groups were chosen to be small. Because the sample parameters and distributions of these groups were based on seven or eight observations, nonparametric methods were used for statistical analyses (22). The medium group consisted of about 95% of the cases, and this inequality in sizes might have influenced test statistics. However, the confidence intervals of the means of the groups were in agreement with the results obtained using the Kruskal-Wallis test statistic.

Only a few studies on the relationship between anthropometric variables and S-Zn and S-Cu in normal, healthy children and adolescents have been reported. Neither in Canadian preschool children (23) nor in adolescent girls in the United States of America (24), was there a relationship between S-Zn and either height or wt. In Swedish adolescents, no relationship between S-Zn and height, wt, or skinfold thickness was found (25). By contrast, studies from Yugoslavia (4) and the United States of America (26) found positive relationships between height and plasma Zn. Our results are similar to those from Canada (23), the United States of America (24), and Sweden (25), as the observed relationships between S-Zn and stature in this study were weak, and the significances partly due to the large number of participants. In agreement with our results, an inverse correlation between S-Cu and height (24), and a positive correlation between plasma Cu and wt (26) were also found in American adolescent girls.

The lack of association between S-Zn and growth in our study might be due to the low number of children and adolescents with marginal Zn status. We found S-Zn concentrations below 10.7 μmol/liter (70 μg/dL), used as a lower limit of the normal range (15), only in 20 girls and 12 boys.

The correlations between S-Cu and height, wt, BMI, and ST were weak before the age of 9 y. Estrogens are reported to raise S-Cu levels by increasing ceruloplasmin concentrations (27, 28), and in obesity increased conversion of androgens to estrogens takes place (29). By contrast, estrogens accelerate the ossification of growth plates without corresponding growth acceleration (30).

Groups with deficiencies of Zn or Cu on the basis of serum levels and short stature could not be identified. However, neither could mild deficiencies be excluded, and one group that might be susceptible to Zn deficiency is 18-y-old girls. Of the 18-y-old girls in this study, 4% had low S-Zn (<10.7 μmol/liter), and in the dietary survey of 1768 girls and boys participating in this study, the mean intake of Zn and also of Cu in 18-y-old girls remained almost at the 3-y-old level (8 mg *versus* 10 mg, 1.1 mg *versus* 1.3 mg, respectively). In boys the intakes doubled between 3 and 18 y of age (9 mg *versus* 18 mg, 1.1 mg *versus* 2.1 mg) (31).

In spite of the associations between serum levels and growth variables, no conclusions about stature on the basis of single S-Zn or S-Cu determinations can be drawn. At the moment, it is not known whether individual S-Zn or S-Cu fluctuates during growth or if everybody has an individual, quite stable level. The results of this cross-sectional study, however, suggest that neither Zn nor Cu is a distinct growth-limiting factor in healthy Finnish children or adolescents.

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