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ORIGINAL ARTICLE

Copper and zinc blood levels among children with nonorganic failure to thrive

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Abstract—Background and Aims: Copper and zinc deficiency are commonly reported among children with organic failure to thrive. In contrast, reports on copper and zinc status in children with non-organic failure to thrive are scarce. The goal of this study was to evaluate copper and zinc blood levels and nutritional intake among children with non-organic failure to thrive.

Methods: A study group of 32 children with non-organic failure to thrive were investigated and compared with 32 healthy controls. Each child had copper and zinc blood level measurements. In addition, the study group underwent evaluation of thyroid function, immunoglobulins, endomesial antibodies and xylose test. A dietary questionnaire that included a diet history and a 24-h dietary recall was administered to parents by a dietician. Weight for height, height for age and mean daily intake of calories, protein, copper and zinc were calculated.

Results: There were no significant differences between the two groups in either socioeconomic status or caloric, copper or zinc intake. Protein intake was significantly lower in the study group ($P<0.0001$). Plasma copper levels were within the normal range in both groups (P=0.3). Zinc plasma levels were significantly higher in the study group as compared to controls (P=0.03); however, they remained within the normal range in both groups.

Conclusions: Children with non-organic failure to thrive can maintain plasma copper and zinc levels within normal range and similar to normal controls.

Key words: copper; zinc, non-organic failure to thrive

Introduction

Failure to thrive (FTT) usually refers to decreased growth that has crossed two major growth percentiles (i.e. from about the 75th percentile to below the 25th) in a short time (1, 2). The prevalence of FTT depends on the population sampled (2). Most cases of FTT are non-organic. Children with non-organic FTT (NOFTT) have multifactorial contributors, environmental neglect or poor children-parent interaction (3).

It has been shown that zinc supplementation has a positive effect in young children with low growth percentiles from low-income families (4). The decreased growth of children with NOFTT might thus be attributable, in part, to zinc deficiency. It is hypothesized that the deficiency may have started in infancy and that an inadequate provision of zinc is one factor contributing to NOFTT (5).

Most studies on the association between trace elements deficiency and FTT relate to zinc (4–12). Zinc is a constituent of more than 300 enzymes and its deficiency has been implicated in anemia, dermatitis, stunted growth, hepatosplenomegaly and impaired immune function (12, 13). A few studies have investigated the role of copper deficiency among children with FTT (14, 15).

Copper is essential for the production of red blood cells, hemoglobin formation, absorption of iron and for the activity of various enzymes. Its deficiency may cause refractory anemia, osteoporosis, neutropenia, depigmentation, delayed bone age, bone infarctions, pseudoparalysis and ataxia (14, 15). These studies usually report on the status of one trace element at a time. In our study, we hypothesized that a combination of copper and zinc deficiency might play a role in NOFTT. We aimed to concomitantly evaluate copper and zinc blood levels as well as nutritional intake in a group of children with NOFTT as compared with controls.

Methods

The study group comprised children referred to the ambulatory pediatric clinic at Assaf Harofeh Medical Center for the evaluation of FTT. FTT was defined as decreased growth that has crossed two major growth percentiles in a short time (1, 2). The evaluation included a complete blood count (CBC), electrolytes, liver enzymes, thyroid studies (TSH, free T4), glucose, cholesterol, triglycerides, immunoglobulins, endomesial antibodies, antigliadin antibodies, xylose test, copper and zinc, urinalysis, stool culture for bacteria and stool evaluation for parasites. Each child was examined by a pediatrician and the parents were interviewed by a dietician. Children who were small for gestational age, had FTT either due to prematurity or organic disease were excluded from the study.

The control group consisted of children with normal growth according to weight and height for age charts admitted to the pediatric surgery ambulatory day center for elective procedures. Children in the control group had blood withdrawn for complete blood count, copper and zinc. The parents in the control and study groups were interviewed by the same dietician. The study was approved by the local ethics committee, and written, informed consent was obtained from the parents of each child.

Anthropometry

Children in both NOFTT and control groups were weighed on a regularly calibrated scales and their heights were measured on an infantometer upon entering the study. All measurements were performed by the same investigator (IMK). The weight and the height measurements were marked on the National Center of Health Statistics (NCHS) weight for age and height for age charts.

Blood measurements

Blood samples from a peripheral vein were drawn in the morning after a 10-h fast into Hemogard vacutainer test tubes for trace metal analyses pre-coated with sodium heparin (Becton-Dickinson, UK). Following 10 min centrifugation, the plasma was collected in polystyrene test tubes and stored at −25°C until the analyses were performed.

Plasma copper and zinc levels were determined using atomic absorption spectrophotometer (SpectrAA 800, Varian, Australia). The method included internal and external quality controls and background correction. All the reagents, including water, were of atomic absorption purity grade. For copper measurement the absorbance of sample (A_s) and standard (A_{st}) was read at 582 nm against reagent blank, and was calculated by the equation: $(A_s/A_{st}) \times 100 = \mu g$ Cu/dl of sample. For zinc measurement, A_s and A_{st} was read at 560 nm against reagent blank, and was calculated by the equation: $(A_s/A_{st}) \times 200 = \mu g$ Zn/dl of sample. The coefficients of variation of copper and zinc plasma levels were calculated as percentage of standard deviation divided by mean (16). The coefficient of variation is yet another method used as an absolute measure of dispersion. The intra-assay coefficient of variation is $(SD/\bar{X}) \times 100\%$. The intra-assay coefficients of variation were 19.2% (within the study group) and 20.5% (within the control group) for copper, and 26.1 and 25.6% for zinc, respectively. The interassay coefficients of variation is $(\Delta SD/\Delta\bar{X}) \times 100\%$ where $\Delta SD = \Sigma(SD_1 = SD_2)$ and $\Delta\bar{X} = \sum(\bar{X}_1 - \bar{X}_2)$. The interassay coefficients of variation were 6.6% for copper and 1.03% for zinc.

Dietary assessment

Dietary assessment was performed by dietary history and 24-h recall (17). These methods, albeit having some limitations, are widely used for the evaluation of energy, nutrients and trace element intake (8, 17–22). Dietary history included questions regarding the overall eating pattern of each child, both at mealtimes and between meals. The information obtained included detailed description of foods, frequency of consumption and usual portion sizes (17). In the 24-h dietary recall method, parents or caretakers were asked to recall the exact food intake during the previous 24-h period or preceding day. Detailed description of all food and beverages consumed, including vitamin and mineral supplement was obtained (17).

Mean daily intakes of calories, protein, copper and zinc were calculated by the dietician based on The Food Composition Table by the Israeli Ministry of Health (23). The caloric, protein and zinc intakes were compared to the recommended daily allowances (RDA) and were expressed as a percent of RDA. Copper intake was compared to estimated safe and adequate daily dietary intake (ESADDI) (24) and was expressed as a percent of ESADDI.

Statistical analysis

A two-sample *t*-test was used for the comparison of age, sex, ethnic origin, socioeconomic parameters, calories, protein, zinc and copper intake as well as zinc and copper blood levels between the two groups. Chi-square test was used to evaluate differences in gender between the groups.

Results

The NOFTT and control groups included 32 children each, aged 14 ± 5.5 (8–30) and 22 ± 9.5 (8–45) months, respectively. Children in the control group were significantly older ($P < 0.0001$). No significant differences were found in the ethnic origin or the socio-economic variables between the NOFTT and control groups.

Intake of calories, protein, zinc, copper, plasma copper and zinc levels are presented in Table 1. Protein

Table 1 Measurements of growth, calories, protein, zinc and copper intake, and plasma zinc and copper concentrations in the NOFTT and the control groups (presented as mean ± SD)

Parameter	NOFTT ($N = 32$)	Control ($N = 32$)	P value
Gender: M/F	11/21	10/22	0.8
Age (months)	14.0 ± 5.5	22.6 ± 9.5	< 0.0001
Weight for height (percentile)	7 ± 3	60 ± 25	< 0.0001
Height for age (percentile)	20 ± 23	60 ± 25	< 0.0001
Caloric intake (kcal/kg body weight)	103 ± 28	98 ± 19	0.3
Caloric intake (% from RDA)	88.1 ± 23.7	94.8 ± 17.8	0.2
Protein intake (g/kg body weight)	3.3+1.2	5.5 + 1.3	< 0.0001
Protein intake (% from RDA)	158.3 ± 65.3	239.3 ± 78.1	< 0.0001
Zinc intake (% from RDA)	42.5 ± 26.4	39.4 ± 20.9	0.6
Copper intake (% from ESADDI)	80.4 ± 39.2	85.6 ± 61	0.7
Plasma zinc concentration (μg/dl)	93 ± 24.3	82 ± 21	0.03
Plasma copper concentration (μg/dl)	142 ± 27.4	134 ± 27.3	0.3

intake was significantly lower in the study group as compared to controls ($P < 0.0001$). Copper and zinc intakes were found to be lower than the recommended intake (based on the RDA and ESADDI, respectively) in both NOFTT and control groups. The average intake of zinc was about 40% of the RDA, and the average intake of copper was 83% of the ESADDI (Table 1). Nevertheless, plasma zinc levels were within the normal range in both groups (NOFTT and control). However, plasma zinc levels in the NOFTT group were significantly higher compared to those of the control group [93.0 ± 24.3 (51–141) and 82.0 ± 21.0 (41–119) μg/dl, respectively, $P = 0.03$]. No significant differences were observed in plasma copper levels between the two groups ($P = 0.3$) (Table 1).

Discussion

The children in the NOFTT group were significantly younger than the children in the control group. Plasma zinc and copper levels have been reported to reach their adult range at the age of 3 months (25, 26), and 1 month (27), respectively. Since all the patients in our study were older than 8 months, it is unlikely that the difference in age between the groups affected the results.

No significant difference in caloric intake was found between the two groups of children ($P = 0.2$). However, 16 (50%) children in the NOFTT group had caloric intake of ≤80% of the recommended daily caloric intake, while only 2 (6%) children in the control group had caloric intake of ≤80% of the recommended daily caloric intake ($P = 0.0001$). This finding is in correlation with the definition of NOFTT where caloric intake is usually low.

Protein intake was significantly higher in the control group ($P < 0.0001$). This is probably due to the fact that children in the control group were older and, consequently, their diet included more protein-rich products such as meat and eggs.

We have found no gender-related differences in plasma copper or zinc levels within any group of the present study. This would confirm previously published reports in which plasma copper and zinc were shown not to be affected by sex (8, 14, 15). On the other hand, a number of studies have demonstrated that when supplemental zinc is administered, boys show substantial improvement in growth indices while girls are irresponsive to the zinc supplement (28–30). A reasonable explanation for the different response of boys vs girls to zinc supplement is not yet available. Some authors have suggested that boys have elevated zinc requirements compared with girls, while others have stated that the distinct effect of zinc is mediated by changes induced in growth hormone and testosterone concentrations (7, 28).

Among the NOFTT group, girls had significantly lower zinc intake as compared to boys ($P = 0.03$). However, no significant differences in plasma zinc levels were observed between the genders. Similarly, no significant differences were observed between genders in copper intake and plasma copper level. In the control group, no differences were observed between boys and girls in zinc and copper intake, nor in zinc and copper plasma levels.

Although zinc and copper intakes in our study were found to be lower than the recommended intakes (based on the RDA and ESADDI, respectively), in both NOFTT and control groups, plasma zinc and copper concentrations were within the normal range. This would imply that low copper and zinc intakes were not reflected by zinc and copper plasma levels. Although the intakes of zinc and copper were low, they were still adequate to maintain the normal balance of zinc and copper in plasma. It is possible, that absorption of zinc and its bioavailability increase in conditions of low intake, similarly to the phenomenon observed for iron bioavailability (31). It should be noted that most studies on trace elements deficiencies have been conducted in developing countries, while ours was performed in a developed country. Perhaps, subtle differences in other nutrients have some effect on copper and zinc metabolism.

Plasma zinc level was significantly higher in the NOFTT group compared to the control subjects

($P = 0.03$). However, zinc plasma levels were within the normal range in both populations. The control group included healthy children admitted to the pediatric surgery ambulatory day center for elective procedures such as inguinal hernia repair. They had normal body temperature and no signs and symptoms of infection. Zinc intake was higher in the NOFTT group as compared to the control, but not significantly so (Table 1), and therefore cannot explain the difference in plasma level.

Most zinc and copper are stored in the erythrocytes and tissues, which thus better reflect the total zinc and copper body status. However, measurements of zinc and copper in hair have not proven to be very useful, since they can vary as a result of the action of external agents, including environmental contamination with these elements (11, 15, 32–36). Assessment of trace elements in erythrocytes or in saliva is also of a limited value (11). Only the response to the supplementation may confirm a marginal zinc or copper deficiency (4, 8, 11, 15, 27). Despite these limitations, measurement of zinc and copper in plasma is a simple and less expensive method currently used for the routine clinical assessment (8, 11, 15, 27).

Marginal zinc and copper deficiencies are difficult to detect by testing only their concentrations in the plasma. It seems that practically, the substantial improvement in linear growth following zinc or copper supplements to children with FTT may supply the evidence that marginal zinc or copper deficiency do exist.

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