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Dietary Zinc Intake and Plasma Zinc Concentrations in Children with Short Stature and Failure to Thrive

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Key Words
Nutrition · Growth · Trace elements · Zinc

Abstract
Background: The burden of zinc deficiency on children includes an increased incidence of diarrhea, failure to thrive (FTT) and short stature. The aim of this study was to assess whether children with FTT and/or short stature have lower dietary zinc intake and plasma zinc concentrations compared to controls. ***Methods:*** A case–control study conducted at the American University of Beirut Medical Center included 161 subjects from 1 to 10 years of age. ***Results:*** Cases had a statistically significant lower energy intake (960.9 vs. 1,135.2 kcal for controls, p = 0.010), lower level of fat (30.3 vs. 36.5 g/day, p = 0.0043) and iron intake (7.4 vs. 9.1 mg/day, p = 0.034). There was no difference in zinc, copper, carbohydrate and protein intake between the 2 groups. The plasma zinc concentration did not differ between the cases and controls (97.4 vs. 98.2 μg/dl, p = 0.882). More cases had mild-to-moderate zinc deficiency when compared to controls with 10.3 vs. 3.6%, p = 0.095. ***Conclusion:*** Our study did not show statistically significant difference in dietary zinc intake and plasma zinc concentrations between children with FTT and/or short stature compared to healthy controls. A prospective study is planned to assess the effect of zinc supplementation on growth parameters in FTT children.

Introduction

Zinc is an essential trace element to all forms of life. It plays a fundamental role in gene expression, cell development and replication [1]. Zinc interacts with important hormones involved in bone growth such as somatomedin-C, testosterone, thyroid hormones and insulin. It is intimately linked to bone metabolism and acts positively on growth and development [2]. Zinc deficiency per se may lead to anorexia and therefore may also contribute to growth delay indirectly by reducing the intake of other growth limiting factors, such as energy and protein [3].

Zinc is present in a wide variety of foods especially in red meat, oysters and shellfish. Its concentration in plants can be affected by the soil content of zinc, and its bioavailability is related to the phytate content of the food [4]. Phytate, mainly present in legumes, vegetables and cereals is a strong chelator of minerals including zinc. The

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phytate concentration in food is highly variable and influenced by environmental factors such as growing location, irrigation conditions, type of soil, fertilizer applications, plant variety and harvest and food processing methods [5].

Clinical manifestations of severe zinc deficiency in children are characterized by short stature, hypogonadism, impaired immune response, skin disorders, cognitive dysfunction and anorexia [6]. Severe zinc deficiency remains, however, a rare condition, while nowadays mild-to-moderate zinc deficiency is prevalent throughout the world. The burden of zinc deficiency on children mainly in developing countries includes an increased incidence of diarrheal illness, pneumonia, malaria as well as failure to thrive (FTT) and short stature [7, 8].

Many studies from developing countries have found an association between zinc deficiency and short stature. Zinc deficiency is thought to be common in the Middle East and has been described in Iran, Egypt and Iraq where FTT and/or short stature due to zinc deficiency are frequently observed due to a low intake of animal products and a diet rich in cereal proteins [9–12]. The estimated prevalence of inadequate zinc intake for the year 2005 in Lebanon was 14.3% and in the developing neighboring countries was 16.3% in Jordan, 15.2% in Syria, 21.7% in Turkey and 15.3% in the occupied Palestinian territory versus the developed neighboring countries: Israel, 5.5%; Greece, 7.2%; France, 3.9% and Italy, 5.8%. These estimates were calculated using the composite nutrient composition database, the International Zinc Nutrition Consultative Group (IZiNCG) physiological requirements, the Miller equation to estimate zinc absorption and an assumed 25% inter-individual variation in zinc intake [13].

While plasma zinc level has been investigated in the adult Lebanese population [14, 15], no study to date has evaluated the zinc status and dietary intake in Lebanese children and their association with growth delay. Lebanese children are expected to be at high risk of zinc deficiency since the Lebanese Mediterranean diet is rich in phytate and children usually do not consume food rich in zinc such as oyster, liver and pork.

We were not able to identify any studies that report the proportion of Lebanese children who follow the Lebanese Mediterranean diet as opposed to the westernized dietary pattern. In a study by Naja et al. [16] a sample of adolescent Lebanese with a mean age of 16.41 years were found to have 2 main dietary patterns, which together explained 22.6% of the total variance in dietary intake, with the largest variance being explained by the traditional Lebanese pattern (13.19%). The following food groups were the most commonly consumed in the traditional Lebanese pattern: vegetables, legumes, bread, rice, pasta and cereals, bulgur, fruits, fish and vegetable oils, most of which are high in phytate.

The primary aim of this study was to assess whether children with FTT and/or short stature have lower dietary zinc intake and plasma zinc concentration as compared to healthy controls.

Methods

This was a case–control study conducted at the American University of Beirut Medical Center (AUBMC) between January 2010 and January 2012. AUBMC is a tertiary care center located in Beirut Lebanon and receiving referrals from all over the country. The study protocol was approved by the Institutional Review Board of the hospital (Protocol PED.NY.02). Written informed consent was obtained from the parents. In addition, assent was obtained from children above the age of 7 years.

Subjects

The subjects were children from 1 to 10 years of age presenting to the pediatric private clinics and outpatient department at AUBMC for evaluation of short stature and/or FTT.

FTT was defined as weight-for-age that falls below the 5th percentile on at least 3 occasions or weight deceleration that crosses 2 major percentile lines on a growth chart. The 5th, 10th, 25th, 50th, 75th, 90th and 95th percentiles were defined as the major percentiles [17]. Short stature was defined as height that is more than 2 SDs below the mean height-for-age and sex (or below the 2.5th percentile) [18].

The controls were children with normal growth (as documented by weight and height-for-age charts) within the same age group presenting for well-child visits to the pediatric private clinics and outpatient department at AUBMC.

Exclusion criteria included any recent febrile illness or antibiotic intake within 2 weeks prior to presentation or any multivitamin supplementation within 2 months of enrollment as febrile illness and/or infection might lower the plasma zinc concentrations and multivitamins might contain zinc.

Anthropometric Measurements

For children below the age of 2 years, weight was measured on a regularly calibrated infant scale (Detecto infant scale 450 series Weigh Beam; maximum of 20 kg, accuracy of 10 g) without clothes on except for a clean diaper. Length was measured in the supine position using a rigid pediatric length rod with a measuring range of 0–100 cm and an accuracy of 0.1 cm. Weight and length were plotted on the World Health Organization (WHO) Child Growth Standards (http://www.who.int/childgrowth/en) [19]. Children above the age of 2 years were weighed on a regularly calibrated scale barefoot with light clothes on. Height was measured in the standing position using a height rod with a measuring range of 85–200 cm and an accuracy of 0.1 cm (Detecto physician's scale Weigh Beam Eye-Level). Weight and height were plotted on the

Center for Disease Control and Prevention clinical growth charts (National Health Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion – 2000). A trained pediatric nurse carried all the measurements in duplicate.

Blood Samples

The blood collection procedures were in accordance with the guidelines of the IZiNCG [4]. Non-fasting morning venipuncture blood samples were collected from all children by a pediatric phlebotomist on the day of enrollment. The child was put in a seated position, the tourniquet applied for a standardized time of 1 min and a butterfly stainless steel needle (Greiner Bio-one 0.5–0.75 inch) was used to draw 2 ml of whole blood into a special trace elements tube (BD Vacutainer Trace Element K2EDTA 10.8 mg). Within 2 h of withdrawal, plasma was then separated (Eppendorf Centrifuge 5804 at 4,000 rpms for 5 min) and transferred to clean tubes and stored at –20°C until the analyses were performed in the reference laboratory CERBA (95066 Cergy Pontoise Cedex 9; France). Plasma zinc concentrations were determined by using atomic absorption spectrometry (Atomic Absorption Spectrometer AAnalyst 300 Perkin Elmer). The method included internal and external quality controls (SFBC trace element EQA). All measurements had intra- and inter-assay coefficient of variation <5 and 6.16%, respectively. Zinc deficiency was then calculated according to the cutoff values stated by the WHO and the National Health and Nutrition Examination Survey [20, 21]. Plasma zinc concentrations range was considered normal between 65 and 150 μg/dl. Severe zinc deficiency was considered at a concentration <50 μg/dl and mild-to-moderate between 51 and 64 μg/dl.

Dietary Assessment

The dietary zinc intake was assessed by a 3-day dietary recall administered by the dietitian to all subjects included in the study. The first recall was done on the day of enrollment; subsequently data regarding dietary recall of another weekday and one weekend day were collected by phone. The recalls were mainly done with the primary caretaker and with the child when able to communicate. During the first day recall, we used the guide for portion sizes by the Academy of Nutrition and Dietetics (online suppl. Appendix 1, see www.karger.com/doi/10.1159/000447648). The data were entered by a trained research assistant into the Nutritionist Pro software (AXXYA systems Stafford, Tex., USA). The program calculated the amount of zinc, iron, copper, fat, carbohydrate, protein and caloric intake, which were compared to the recommended daily allowance (RDA). The items of every composite dish were entered separately on the Nutritionist Pro software and compiled to obtain the full analysis. The carbohydrate, protein, fat, zinc, copper and iron intakes were compared to the RDA and expressed as percent of RDA based on the recommendations of the American Dietetic Association for each age group [22].

Statistical Analysis

Sample size calculation was performed using the OpenEpi software for unmatched case–control studies. With a power of 80, a 2-sided confidence level of 95, a case/control ratio of 1 to 1, an OR set at 3 and estimating the prevalence of zinc deficiency among the Lebanese population [19] to be 14.3%, we needed a total of 158 children to be included in the study.

Table 1. Demographic characteristics of cases and controls

	Cases (n = 78), n (%)	Control (n = 83), n (%)	p value
Gender			0.803
Male	41 (52.6)	42 (50.6)	
Female	37 (47.4)	41 (49.4)	
Age, years			0.712
1–4	32 (46.4)	37 (53.6)	
4–8	31 (47.7)	34 (52.3)	
>8	15 (55.6)	12 (44.4)	

Table 2. Comparison of the mean levels of nutrients intake and plasma zinc concentrations between cases and controls using Student t test

	Cases (n = 78), mean ± SD	Controls (n = 83), mean ± SD	p value
Plasma zinc concentration, μg/dl	97.4±37.3	98.2±28.0	0.882
Energy intake, kcal/day	960.9±317.9	1,135.2±500.0	**0.010**
Carbohydrates, g/day	144.3±96.7	160.9±91.2	0.264
Carbohydrates, % RDA	111±74.4	123.8±70.2	0.264
Protein, g/day	37.3±12.3	41.3±16.6	0.088
Protein, % RDA	213.4±88.8	242.6±108.8	0.065
Fat, g/day	30.2±12.4	36.5±13.8	**0.003**
Fat, % RDA	94.8±40.5	114.9±46.5	**0.004**
Zinc, mg/day	4.4±1.7	4.7±1.9	0.248
Zinc, % RDA	104.2±54.7	113.4±53.5	0.280
Iron, mg/day	7.4±3.4	9.1±6.2	**0.034**
Iron, % RDA	90.1±43.3	108.3±64.0	**0.038**
Cu, mg/day	0.6±0.4	0.7±0.3	0.447
Cu, % RDA	153.1±103.2	163.3±78.5	0.481

The Statistical Package for Social Sciences (SPSS) program version 23.0 for Windows was used for data analysis (IBM, Armonk, N.Y., USA). Demographic characteristics were described as percentages and numbers (table 1). Student t test was performed to compare and assess statistical mean levels of nutrients between cases and controls (table 2). Chi-square test and logistic regression analysis were used to assess difference among categorized plasma zinc concentrations between cases and controls (table 3). Statistical significance was considered below a type-1 error threshold (alpha level) of 0.05.

Results

A total of 161 subjects were included: 78 cases and 83 controls. Among the cases 57 children had FTT, 47 were stunted and 26 had both FTT and stunting.

Table 3. Comparison of the plasma zinc concentration categories between cases and controls using chi-square test

Plasma zinc concentration, μg/dl	Cases (n = 78), n (%)	Controls (n = 83), n (%)	p value	OR (95% CI)
Severe zinc deficiency (<50)	0 (0)	0 (0)		
Mild-to-moderate deficiency (51–64)	8 (10.3)	3 (3.6)	0.095	3.048 (0.778–11.935)
Sufficient ≥65	70 (89.7)	80 (96.4)		

The 2 groups were comparable in terms of gender (p value = 0.803) and age distribution (p value = 0.712; table 1).

The mean levels of nutrients intake between cases and controls along with the corresponding SD are described in table 2. The cases had a statistically significant lower energy intake (960.9 ± 317.9 vs. 1,135.2 ± 500.0 kcal for controls with a p value of 0.01) as well as lower level of fat intake (30.2 ± 12.4 vs. 36.5 ± 13.8 g with a p value of 0.003) and iron intake (7.4 ± 3.4 vs. 9.1 ± 6.2 mg with a p value of 0.034). There was no difference in zinc, copper, carbohydrate and protein intake between the 2 groups. It was noted that zinc intake in both groups was found to be slightly higher than the estimated average requirement (EAR) for age [4].

The main items contributing to iron intake in children were meat, poultry and to a lesser extent dried beans, green leafy vegetables (spinach) and egg yolk. The main items contributing to zinc intake were meat, poultry, milk and to a lesser extent dried beans, and the main items rich in phytate were whole wheat bread, crushed wheat (bulgur), breakfast cereals as well as vegetables and fruits.

Moreover, the plasma zinc concentration did not differ between the cases and controls (97.4 vs. 98.2 μg/dl, p value = 0.882). This value did not reach statistically significant difference even when sub-group analysis of only short stature children were compared to controls (98.3 vs. 98.2 μg/dl, p value = 0.987) and FTT children alone were compared to controls (99.7 vs. 98.2 μg/dl, p value = 0.794). There was no significant difference between both genders regarding the mean levels of zinc intake (p value = 0.919) and the plasma zinc concentrations (p value = 0.908).

Further analysis of the plasma zinc concentrations showed that more cases (10.3%) had mild-to-moderate zinc deficiency when compared to controls (3.6%) with a p value of 0.095 and OR = 3.048, 95% CI 0.778–11.935. It should be noted that we did not have any case of severe zinc deficiency (table 3).

Discussion

Zinc insufficiency has been recognized as an important public health issue especially in developing countries. An estimated 17.3% (95% CI 15.9–18.8) of the global population is at risk of zinc deficiency [23] and as reported by Wessells and Brown [13], country-specific prevalence of inadequate zinc intake correlates with the prevalence of stunting in 138 low- and middle-income countries.

In this study, we found no difference in dietary zinc intake between FTT/stunted children and controls. Both had an intake slightly higher than the EAR for age. On the other hand, our cases had lower levels of energy, fat and iron intake, which could explain to some extent their FTT and or short stature. Berkovitch et al. [24] evaluated the blood levels of zinc and copper in children ranging from 8 to 45 months of age with non-organic FTT and compared them to healthy controls; they did not find a significant difference between the 2 groups with regards to zinc intake and the plasma zinc level was actually found to be higher in the study group. Our results are in disagreement with studies from both Thailand and India [25, 26]. In the study by Gibson et al. [25], stunted male Thai school-aged children had lower mean intakes of energy, protein, calcium, phosphorus and zinc, and a lower mean serum zinc level (9.19 vs. 9.70 μmol/l) than non-stunted males; no other biochemical differences were noted. In a study done in India, Indian girls aged 2–18 years with short stature (height for age z-scores HAZ <–2) had significantly lower intakes of calcium, zinc, iron, β-carotene, riboflavin, niacin, folate and ascorbic acid. The mean serum zinc level of thin girls (body mass index z scores BMIZ <–2) was significantly lower than those of both normal and overweight girls after adjusting for socioeconomic status [26].

Our study did not show a statistically significant difference in plasma zinc concentrations between Lebanese children with impaired growth and controls, with however higher percentage of low plasma zinc concentrations reached among cases. We have found no gender related differences in plasma zinc levels between the 2 groups whereas several other studies have reported that males are more prone to develop zinc deficiency than females [25], this being partially explained by a higher growth rate and greater muscle mass in males [4].

Although plasma zinc concentration is still the most widely used biochemical indicator of a population's zinc status, it is not considered to be very reliable in mild or moderate zinc deficiency since homeostatic mechanisms can maintain normal plasma zinc except when zinc depletion is severe and prolonged [27]. This is the reason zinc supplementation trials have become the best source of information about zinc nutriture especially in high-risk groups such as children [28, 29]. Brown et al. [28] conducted a meta-analysis of 37 randomized controlled intervention trials to assess the effect of zinc supplementation on the physical growth and serum zinc concentrations of prepubertal children. They concluded that zinc supplementation results in a highly statistically significant increase in the linear growth and weight gain of prepubertal children, but does not affect the weight-for-height index. Zinc supplementation also produced a large, highly statistically significant increase in children's serum zinc concentrations.

On the other hand, in a recent meta-analysis, Stammers et al. [30] did not find statistically significant improvement of several indices of childhood growth (weight gain, height for age, weight for age, length for age, weight for height (WHZ) or WHZ scores) following zinc supplementation in children aged 1–8 years of age. They conclude that since many of these children were already stunted and may have been suffering from multiple micronutrient deficiencies; zinc supplementation alone might not be sufficient to have an effect on growth. Moreover, in a study by Ramakrishnan et al. [31] evaluating the effect of micronutrient interventions on the growth of children <5 years, they found that interventions including zinc only had a small positive effect on change in WHZ but no significant effect on height or weight gain. Multiple micronutrient interventions improved linear growth.

Although our study is the first to investigate dietary zinc intake and plasma zinc concentration in relation to growth in the pediatric population in Lebanon, it is important to note certain limitations. This study might lack representation of children from different socioeconomic background since it was conducted in only one referral center in Lebanon introducing a referral bias. Furthermore, additional sociodemographic data should have been collected and accounted for in the analysis. Also, as mentioned previously in the discussion, plasma zinc is not considered to be very reliable in mild or moderate zinc deficiency since homeostatic mechanisms can maintain normal plasma zinc except when zinc depletion is severe and prolonged. However, the different available modalities to assess zinc status including hair zinc concentration, enzymes, circulating proteins, molecular techniques or kinetic pools either lack established cutoffs for most age groups, need large volumes of blood and/or are very costly [4].

In conclusion, our study failed to show statistically significant difference in dietary zinc intake and plasma zinc concentration between children with FTT and/or short stature compared to healthy controls; a follow-up prospective study encompassing different areas of the country is planned in the near future to assess the effect of supplementations with zinc alone versus zinc associated with other micronutrients on growth parameters in stunted and FTT children.

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Disclosure Statement

The authors report no conflict of interest.

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