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Abstract

Background. The associations among dietary zinc intakes and biomarkers of zinc status are unknown in apparently healthy children at high risk for zinc deficiency.

Objective. To assess associations among zinc-related parameters in a sample of Guatemalan school-aged children.

Methods. We assessed total dietary intakes and biomarkers of zinc status before and after receiving 6 months of zinc supplementation or placebo in 691 Guatemalan schoolchildren aged 6 to 11 years. Most of the children also received zinc-fortified milk from a government program that started shortly after the trial began. We assessed associations between zinc intakes and serum zinc, alkaline phosphatase (ALP), and albumin.

Results. At baseline, the prevalence of serum zinc < 65 μg/dL and dietary zinc intake below Estimated Average Requirements (EAR) (< 4 and < 7 mg/day for children < 9 and ≥ 9 years, respectively) were 21.6% and 39.4%, respectively. Pearson correlations between serum zinc concentration and dietary zinc intake, serum ALP, and serum albumin were $r = 0.07$, $0.15$, and $0.07$, respectively. At the 6-month follow-up, low serum zinc and low total (diet plus fortified milk) zinc intakes were observed in 1.2% and 0.0% of children in the zinc-supplemented group and 4.0% and 34.1% in the placebo group, respectively. Pearson correlations between serum zinc concentration and total zinc intake, serum ALP, and serum albumin were 0.10, 0.06, and −0.11 in the zinc-supplemented group and −0.04, 0.05, and 0.01 in the placebo group, respectively.

Conclusions. Zinc intake was inconsistently associated with markers of serum zinc concentration. Zinc fortification or supplementation attenuated the associations.

Key words: Albumin, dietary zinc intake, serum alkaline phosphatase, serum zinc, zinc deficiency

Introduction

Zinc deficiency is ranked 11th among global risk factors for mortality and 12th for burden of disease [1]. Approximately 20% of the world’s population is zinc deficient, based on food intake patterns and dietary zinc intakes [2]. Plasma (or serum) zinc concentration is considered to be a sensitive indicator of zinc status in individuals. A systematic review by Lowe et al., which included 32 potential biomarkers from 48 studies (randomized controlled trials, controlled clinical trials, and before-and-after studies), concluded that plasma, urinary, and hair zinc are reliable biomarkers of zinc status in healthy individuals [3].

In severe zinc deficiency, serum alkaline phosphatase (ALP) activity and albumin concentration decrease [4–6]. However, these markers of zinc status may not be sensitive to changes in dietary zinc intake in populations with marginal zinc deficiency. Even when dietary zinc intakes decrease, zinc balance remains stable, without significant changes in circulating plasma zinc [7–10]. When whole-body zinc content is reduced by approximately 30% after prolonged zinc restriction, zinc concentrations drop in plasma but remain constant in other tissues, such as skeletal muscle and skin, so that plasma serum zinc concentration is considered the most useful biomarker of zinc status [11]. Other zinc-related biomarkers may be altered...
in zinc deficiency but have been rarely investigated in controlled trials and repletion studies [3]. Lowe et al. reported that among 50 studies that measured plasma or serum zinc, only 6 studies measured plasma ALP and none assessed serum albumin [3].

We therefore assessed associations among zinc-related variables (dietary zinc intakes and serum zinc concentration, ALP activity, and albumin) in a sample of Guatemalan school-aged children presumed to be at risk for zinc deficiency, both before and after a 6-month zinc supplementation and fortification program.

Subjects and methods

Study design and population

We analyzed data from a randomized, controlled, double-blinded supplementation trial of 10 mg of zinc oxide daily versus placebo in children 6 to 11 years of age from five schools in a low-income community of Guatemala City, Guatemala [12]. The study was a collaborative effort between the Hubert Department of Global Health at the Rollins School of Public Health, Emory University, Atlanta, Georgia, USA, and the Institute of Nutrition of Central America and Panama (INCAP) in Guatemala City. The study protocol was reviewed and approved by the ethics committees of both institutions.

Children in grades 1 to 4 were recruited from five public schools in San José la Comunidad, a low-income area of Guatemala City. The exclusion criteria included any known severe illness affecting zinc status (e.g., sickle cell disease, cystic fibrosis, renal or liver disease, severe burns, or acrodermatitis enteropathica) [13] and other severe or chronic illness (e.g., cancer, diabetes, or seizures). Parental informed consent and child assent were obtained before data collection. Children were allocated to one of two groups: zinc or placebo. Investigators in each classroom received a list of names of participants with their assigned color: two colors for the zinc group and two for the placebo group. The colors were assigned by a computer that generated a list on the basis of a 1:1:1:1 allocation ratio without blocking constraints. Each child received one tablet each school day for 6 months. The tablets were either chewable zinc (10 mg of zinc oxide) or a placebo (10 mg of glucose) with the same appearance and taste. Each child consumed the tablet in front of the fieldworker.

Unbeknownst to our research group when we were launching the study, the Ministry of Education started a zinc-fortification program in the schools; children received 200 mL of fortified milk containing 1.6 mg of zinc oxide, except for 47 children attending one of the schools who received INCAPARINA, a cereal-based drink containing 2.1 mg of zinc oxide. The school fortification program was available 5 days per week. Consumption of the fortified milk or INCAPARINA was not measured.

Data collection procedures

Baseline data were collected from February to April 2006, and follow-up data were collected from August to October 2006. Investigators visited and interviewed the child’s mother or caregiver in the child’s home to obtain information on demographic variables and dietary intakes. Blood samples were collected at the study clinic.

Dietary assessments

Dietary intakes were reported by the mother or caregiver using a semiquantitative food frequency questionnaire (FFQ). Daily intakes of energy, zinc, and other nutrients in the diet were estimated using the Institute of Nutrition of Central America and Panama (INCAP) food composition tables [14]. Total zinc intakes were calculated as the sum of all intakes from the diet, fortified milk (assuming one serving per day for 5 days per week), and supplements. Total zinc intakes were adjusted for total energy intake using the residual method [15]. This controls for variation in intake attributable to variability in total energy intake or systematic bias in reporting of serving frequencies. In a separate validation study with 50 children not involved in the school-based trial, we compared results from the FFQ with three nonconsecutive 24-hour dietary recalls, all administered to the child’s mother. The correlation coefficient between residualized zinc intakes from the FFQ and the means of the 24-hour recalls was 0.41, indicating moderate cross-method reliability [15].

Biochemical measurements

A registered nurse drew venous blood samples between 9 a.m. and 12 noon, using standard procedures, into trace element-free vials (Becton Dickinson). The blood was centrifuged at 2,500 × g for 10 minutes at room temperature, aliquoted, and refrigerated at the study clinic. After transport to INCAP, it was frozen in trace element-free cryogenic vials (Blue cap tubes, Becton Dickinson) at −70°C, and then shipped on dry ice before being stored again at −70°C until analysis at the National Institute of Public Health laboratories, Cuernavaca, Mexico.

Serum zinc concentration was assessed with atomic absorption chromatography, using a graphite furnace (Analyzer 300, Perkin Elmer). Serum ALP activity was measured by the hydrolysis of p-nitro phenyl phosphate at 37°C (CE Human). Serum albumin was analyzed by a colorimetric method (Human Gesellschaft für
Biochemica und Diagnostica, Wiesbaden, Germany) and a Prestige 24i spectrophotometer (Tokyo Boeki Medical System). The accuracy of the determination was assessed by using certified material from the US National Institute of Standards and Technology and the UK National Institute of Biological Standard and Control. Precision was assessed through duplicate measurements on 20% of the sample. The between-assay coefficients of variation for serum zinc, ALP, and albumin were 4.8%, 3.4%, and 4.8%, respectively.

Definitions of variables

Continuous variables were categorized using study-specific cutoffs or conventional definitions [16–18]. Low total zinc intake was defined as total zinc intake less than the Estimated Average Requirement (EAR) for zinc (4 and 7 mg/day for children 4 to 8 and 9 to 13 years of age, respectively), based on the International Zinc Nutrition Collaborative Group (IZiNCG) recommendation for high-phytate, unreﬁned cereal–based diets [16]. Low serum zinc was deﬁned as serum zinc concentration < 65 μg/dL (9.9 mmol/L) [16–18]. Serum ALP and albumin distributions were dichotomized at their respective medians. Age was dichotomized as < 9 years and ≥ 9 years, based on conventional age groups defined by IZiNCG [16].

Statistical analyses

We analyzed data from children with complete measurements for the four key variables (total zinc intake, serum zinc, ALP, and albumin) at each time point. The resulting sample sizes (691 children at baseline and 659 children at follow-up) provided 80% power to detect correlations ≥ 0.11 at p < .05.

Normality of the distributions was assessed by the Kolmogorov–Smirnov test. Summary statistics were described as means and standard deviations for continuous variables and frequencies for binary variables. Associations between continuous variables were assessed by Pearson’s correlation coefﬁcients, and associations between binary variables were assessed by chi-square statistics and Cohen’s kappa; agreement was categorized as none (kappa < 0), slight (kappa 0 to 0.20), fair (kappa 0.21 to 0.40), moderate (kappa 0.41 to 0.60), substantial (kappa 0.61 to 0.80), or almost perfect (kappa 0.81 to 1.00) [19]. We adjusted for age (< 9 vs ≥ 9 years) and gender by using linear and logistic regression models for continuous and binary outcomes, respectively. Serum C-reactive protein concentration was not included in the analysis because it was not associated with serum zinc, ALP, or albumin concentrations in children in our study or in published studies [20–23]. Correlation coefﬁcients were adjusted for measurement errors using deattenuation factors derived from the slopes of the linear associations between total zinc intakes from the FFQ and the three 24-hour recalls, as described by Willett [15, 24]. All statistical tests were two-sided, with signiﬁcance deﬁned as p < .05. All analyses were conducted with SAS version 9.2.

Results

Characteristics of the study population

The 691 children (346 in the zinc group and 345 in the placebo group) for whom complete data on zinc-related variables at baseline were available had a mean (± SD) age of 9.0 ± 1.2 years, with boys and girls equally represented (table 1). Stunting was present in 14.8%, low total zinc intakes in 39.4%, and low serum zinc (< 65 μg/dL) in 21.6% of the children. None of the children had ALP activity < 54 U/L or albumin < 3.9 mg/dL.

There were no differences between the supplemented and placebo groups in age, gender, height-for-age z-score, or any of the measures of zinc status. At 6-month follow-up, complete data were available for 659 children (333 and 326 in the zinc and placebo groups, respectively). In the zinc and placebo groups, serum zinc and total zinc intakes (which include intake from the fortified milk and the supplement) increased over baseline. The prevalence of low serum zinc declined to 2.6% overall, with small differences between groups. Provision of the supplement resulted in all children in the zinc group having a total zinc intake greater than the EAR; among the placebo group, 31.6% remained below the EAR. Serum ALP rose in both groups from baseline (p < .05), while serum albumin decreased (p < .05).

Associations among continuous variables

At baseline, correlations among the four continuous variables were of low order (table 2). The highest correlation coefficient observed was that between serum ALP and serum albumin (0.20). In general, the correlations were similar in magnitude (but the statistical signiﬁcance was less due to the reduced sample size) for the children randomized to zinc or to placebo. Exceptions were the correlation between serum zinc and serum ALP (0.22 in the zinc group and 0.08 in the placebo group) and serum ALP and serum albumin (0.29 in the zinc group and 0.09 in the placebo group).

At the 6-month follow-up, the correlations were generally attenuated relative to baseline. The strongest correlation was again between serum ALP and serum albumin (r = 0.14). There were no major differences between the zinc and placebo groups in the magnitude of these correlations.
TABLE 1. Selected characteristics at baseline and measures of zinc status at baseline and follow-up among children 6 to 11 years of age who participated in a 6-month zinc supplementation trial in Guatemala, 2006

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline</th>
<th>Zinc</th>
<th>Placebo</th>
<th>6-mo follow-up</th>
<th>Zinc</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Zinc</td>
<td>Placebo</td>
<td>Total</td>
<td>Zinc</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>(n = 691)</td>
<td>(n = 346)</td>
<td>(n = 345)</td>
<td>(n = 659)</td>
<td>(n = 333)</td>
<td>(n = 326)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>9.0 ± 1.2</td>
<td>9.0 ± 1.2</td>
<td>8.9 ± 1.2</td>
<td>9.5 ± 1.2</td>
<td>9.5 ± 1.2</td>
<td>9.4 ± 1.2</td>
</tr>
<tr>
<td>Age &lt; 9 yr</td>
<td>51.7%</td>
<td>50.6%</td>
<td>52.8%</td>
<td>51.3%</td>
<td>49.9%</td>
<td>52.8%</td>
</tr>
<tr>
<td>Male sex</td>
<td>50.7%</td>
<td>51.2%</td>
<td>50.1%</td>
<td>49.8%</td>
<td>50.8%</td>
<td>48.8%</td>
</tr>
<tr>
<td>HAZ</td>
<td>–1.2 ± 0.9</td>
<td>–1.2 ± 0.9</td>
<td>–1.2 ± 0.9</td>
<td>–1.2 ± 0.9</td>
<td>–1.2 ± 0.9</td>
<td>–1.1 ± 0.9</td>
</tr>
<tr>
<td>HAZ &lt; –2</td>
<td>14.8%</td>
<td>14.2%</td>
<td>15.4%</td>
<td>15.3%</td>
<td>15.3%</td>
<td>15.3%</td>
</tr>
<tr>
<td>Serum zinc (µg/dL)</td>
<td>75.3 ± 12.9</td>
<td>75.0 ± 13.0</td>
<td>75.7 ± 12.7</td>
<td>108.9 ± 31.2</td>
<td>111.0 ± 30.9</td>
<td>106.8 ± 31.4</td>
</tr>
<tr>
<td>Zinc &lt; 65µg/dL</td>
<td>21.6%</td>
<td>23.4%</td>
<td>19.7%</td>
<td>2.6%</td>
<td>1.2%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Total zinc intake (mg/day)</td>
<td>6.2 ± 1.5</td>
<td>6.2 ± 1.5</td>
<td>6.1 ± 1.5</td>
<td>12.2 ± 2.8</td>
<td>17.3 ± 2.6</td>
<td>7.0 ± 2.8</td>
</tr>
<tr>
<td>Total zinc intake &lt; EAR</td>
<td>39.4%</td>
<td>40.2%</td>
<td>38.6%</td>
<td>15.6%</td>
<td>0.0%</td>
<td>31.6%</td>
</tr>
<tr>
<td>Serum ALP (IU/L)</td>
<td>552.9 ± 119.7</td>
<td>546.4 ± 122.6</td>
<td>559.5 ± 116.5</td>
<td>660.2 ± 150.4</td>
<td>663.5 ± 151.3</td>
<td>656.7 ± 149.6</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>6.0 ± 0.5</td>
<td>6.0 ± 0.5</td>
<td>6.0 ± 0.5</td>
<td>5.8 ± 0.3</td>
<td>5.8 ± 0.3</td>
<td>5.8 ± 0.4</td>
</tr>
</tbody>
</table>

ALP, alkaline phosphatase; EAR, estimated average requirement appropriate to age and cereal-based diet; HAZ, height-for-age z-score

a. Values are means ± SD or percentages, as appropriate.
b. Total zinc intake includes intake from the study supplement and the school-provided fortified milk and was adjusted for total calorie intake by the residual method following Willett [15].
c. EAR for zinc is 4 and 7 mg/day for children 4 to 8 and 9 to 13 years of age, respectively.

TABLE 2. Pearson correlations among zinc-related variables at baseline and follow-up among children 6 to 11 years of age who participated in a 6-month zinc supplementation trial in Guatemala, 2006

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>6-mo follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Totalb</td>
<td>Zinc</td>
</tr>
<tr>
<td></td>
<td>(n = 691)</td>
<td>(n = 346)</td>
</tr>
<tr>
<td>Serum zinc—Total zinc</td>
<td>.08</td>
<td>.06</td>
</tr>
<tr>
<td>r</td>
<td>&lt;.05</td>
<td>.3</td>
</tr>
<tr>
<td>Serum zinc—serum ALP</td>
<td>.15</td>
<td>.22</td>
</tr>
<tr>
<td>r</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Serum zinc—serum albumin</td>
<td>.07</td>
<td>.09</td>
</tr>
<tr>
<td>r</td>
<td>.08</td>
<td>.11</td>
</tr>
<tr>
<td>Total zinc—serum ALP</td>
<td>-.06</td>
<td>-.05</td>
</tr>
<tr>
<td>r</td>
<td>.13</td>
<td>.4</td>
</tr>
<tr>
<td>Total zinc—serum albumin</td>
<td>-.05</td>
<td>0.00</td>
</tr>
<tr>
<td>r</td>
<td>.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Serum ALP—serum albumin</td>
<td>.20</td>
<td>.29</td>
</tr>
<tr>
<td>r</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

ALP, alkaline phosphatase

a. Pearson correlations are adjusted for age (<9, ≥9 years) and gender, as partial correlation coefficients using multiple linear regression models.
b. Also adjusted for intervention group.
Associations and agreement among binary variables

At baseline, low serum zinc was associated with low serum ALP and albumin levels (both \( p < .05 \)), and low serum ALP was associated with low albumin level, \((p < .05)\) in the whole sample (table 3). The results for the two treatment groups were generally consistent; notable exceptions were for the association of low total zinc with low serum ALP in the placebo group only. At the 6-month follow-up, only low serum ALP was associated with low serum albumin \((p < .05)\), although we note that power was low for these analyses, as the prevalence rates of low total intake of zinc and low serum zinc were very low. Kappa coefficients suggested minimal to slight levels of agreement, with the highest value at baseline being 0.12 and at follow-up 0.17 (table 4).

### Discussion

This study showed that the strength of associations among variables related to zinc status was low in a sample of Guatemalan schoolchildren at high risk for zinc deficiency (21.6% with zinc intake less than EAR and 39.4% with low serum zinc) [25]. At baseline,
serum zinc concentration was positively associated with total zinc intakes and serum ALP activity. Zinc status improved at follow-up, as evidenced by higher total zinc intake, serum zinc, and serum ALP. At follow-up, serum zinc concentration was associated only with serum ALP activity, and all correlation coefficients were smaller than at baseline. Zinc intake was weakly correlated with the other zinc-related variables at both time points. The correlations were similar in the zinc and placebo groups, although the power of the study to detect significance was reduced. Our results indicate that serum zinc is a reliable biomarker of body zinc status in children [3, 26].

Total zinc was only weakly associated with the biomarkers. Previous studies using the 24-hour recall method did not show a significant association between total zinc intakes and serum zinc concentrations among Guatemalan schoolchildren aged 7.0 ± 0.5 years or among Iranian adolescents aged 13.2 ± 1.0 years [27, 28]. Use of 24-hour recalls may not have adequately controlled for between-day variability of zinc intake, as zinc is concentrated in a limited set of foods. Using the FFQ method, a study among adults in western India observed a positive association between total zinc intakes and plasma zinc [29]. The variation in these results may reflect the instruments used to measure total zinc intake. The FFQ method is typically better than the 24-hour recall for estimation of long-term total intake [30], but even so it may not be precise enough to estimate zinc intakes due to limitations of the method and of the accompanying food composition tables [15].

Furthermore, even precise estimates of total zinc intake may provide little help in the assessment of individual zinc status due to the ability of the body to adapt to very low or very high zinc intakes, unless total zinc intake has been reduced for a long time [31]. A healthy adult with an average weight of 50 kg having zinc intakes ranging from 107 to 231 µmol/day, equivalent to 14 to 30 mg/kg, will show unchanged serum zinc concentration even when zinc intake is as little as 22 µmol/day (2.8 mg/kg) or as much as 306 µmol/day (40 mg/kg) [7]. Therefore, total zinc intake may have a limited role in the assessment of marginal zinc deficiency in individuals.

Serum zinc concentration was associated with serum ALP activity at both time points. The association between serum zinc concentration and other biomarkers may be stronger in persons with marginal zinc deficiency than in those with zinc-replete status. When serum zinc concentration drops, other zinc biomarkers will subsequently decrease. When individuals are given high amounts of zinc, their serum zinc concentration increases, but the production of other zinc biomarkers in specific tissues is either saturated or weakened. Previous studies reported significant correlations between serum or plasma ALP activity and zinc concentration in Guatemalan schoolchildren aged 7.0 ± 0.5 years ($r = 0.16$, $p < .05$) [27]. Other studies that have measured serum ALP and serum zinc concentrations did not address their within-individual association [32, 33].

Serum zinc concentration was not associated with serum albumin at either time point. Several studies have demonstrated a positive correlation between serum zinc and serum protein concentrations in patients with severe zinc deficiency [4, 5, 34]. In presumably healthy populations, serum albumin was reported to be positively associated with serum zinc in Guatemalan schoolchildren ($r = 0.3$, $p < .001$) and inversely associated in adults participating in the US National Health and Nutrition Examination Survey (NHANES) 2005–2006 ($r = -0.15$, $p < .001$) [27, 35]. The differences between our results and those of previous studies may reflect differences in baseline characteristics. Baseline albumin concentrations were higher in our study (mean, 5.99 g/dL) than in the previous studies in Guatemala (mean, 4.46 and 4.61 g/dL in males and females, respectively) and the United States (mean, 4.20 g/dL) [27, 35]. This suggests that serum zinc concentration is closely associated with serum albumin in individuals with low albumin concentrations but not in those with higher albumin concentrations.

The strength of association between pairwise variables was lower at follow-up than at baseline. This may be due to differences in body zinc status before and after the interventions. Body zinc status was improved even in the placebo group, most likely due to the supplementation with fortified school milk in both groups. Therefore, more deficient body zinc status may be associated with lower total zinc intake, serum zinc, ALP, and albumin and may induce stronger relationships among such variables. The binary measures of low status were at very low prevalence at follow-up, reducing the power to detect associations.

Our study has some limitations. We conducted a secondary analysis of data collected from a sample of participants in a randomized, controlled trial. The results may not be generalizable to school-aged children living in other areas or to younger or more stunted children. The estimation of children's dietary zinc intake by FFQs was based on information provided by the mother or caregiver, which increases measurement error. Although many previous studies suggest high phytate:zinc ratios in diets of Guatemalan children and women [36, 37], phytate information is not available in the Guatemalan food composition database. This may affect the classification of children's diets as based on unrefined cereals with high phytate. Finally, serum ALP levels in children have wide variation and depend on age [38]. Therefore, the results of this study should be cautiously interpreted in younger children or adolescents.

In conclusion, the four measures of zinc status that...
we examined were associated at baseline, but the correlations were of low order, and generally weakened further following consumption of fortified milk, with or without supplemental zinc. Serum zinc levels increased following supplementation, suggesting that serum zinc is a reliable measure of zinc status at the sample or population level. Dietary zinc is poorly measured and is likely to have a marginal role in screening for marginal zinc deficiency in individuals.

Acknowledgments

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VQB analyzed the data and wrote the manuscript; JM analyzed the data; RCF-A contributed to the study design; MR-Z led the field activities; SV assayed the samples; RM contributed to the study design; AMD designed the randomized trial and contributed to the study design; ADS contributed to the study design. All authors critically reviewed the manuscript and approved the final version.

The authors confirm that the manuscript is an original work and has not been submitted for publication elsewhere. There are no potential financial or other conflicts of interest.

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