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Zinc Supplementation for Four Months Does Not Affect Growth in Young North Indian Children[1–4]

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Abstract

Our objective in this trial was to assess the impact of daily zinc supplementation on growth in young children. A double-blind, randomized, placebo-controlled trial was conducted in New Delhi, India. We enrolled 2482 children aged 6–30 mo who were supplemented daily with placebo or zinc (10 mg elemental zinc to infants and 20 mg to older children) for 4 mo. At enrolment, all children also received a single dose of vitamin A (104.7 μmol for infants and 209.4 μmol for older children). Weight and length were measured at enrolment and 4 mo later. Weekly visits were conducted by field workers to ascertain morbidity in the previous 7 d. Change in length, weight, length-for-age Z-scores (LAZ), and weight-for-length Z-scores (WLZ) after 4 mo of supplementation were assessed in the zinc and placebo groups. After 4 mo of supplementation, the weight and length gains in the 2 groups did not differ and there was no impact on LAZ, weight-for-age, and WLZ in the 2 groups. There was no substantial effect in any of the subgroups defined for age, income, gender, zinc levels in the crude analysis nor after adjusting for age, gender, income, breast-feeding status, and baseline anthropometric status. Despite successful zinc supplementation reflected in increased plasma zinc concentration and a substantially reduced incidence of diarrhea and pneumonia in zinc-supplemented children, the intervention did not have a beneficial effect on growth. J. Nutr. 140: 630–634, 2010.

Introduction

Zinc is a nutrient essential for maintaining structure and functions of several enzymes, including those that are involved in the production of growth hormones and in transcribing and translating deoxyribonucleic acid and therefore cell division (1). Poor zinc nutrition increases the burden of infections and, presumably, zinc supplementation to zinc-deficient individuals reduces the burden of common infections, which is important for growth (2–7). Zinc supplementation may also induce changes in growth by 1 or more of the following: an increase in lean tissue accretion, an improvement in appetite and thus energy intake, or improvement in the use of dietary energy and protein (8).

Zinc deficiency is common in developing countries due to low consumption of animal source foods and limited bioavailability of zinc from phytate-rich diets that are commonly consumed. The deficiency is compounded by losses during recurrent infections (9).

It is therefore not surprising that 75% of the 33 clinical trials summarized in a metaanalysis demonstrated that routine zinc supplementation enhanced linear growth in children (10). The effect was demonstrated in both those who were stunted at baseline as well as in those who were not, but the efficacy among those stunted was almost twice as in the nonstunted. The authors concluded that zinc supplementation produced highly significant, positive responses in length and weight increments (10). Results from large clinical trials published after this pooled analysis have shown conflicting results; the largest of these was undertaken in Burkina Faso (11) and a multicenter trial in Asia in infants 4–6 mo of age (12). In the trial in Burkina Faso, 72% of the 709 children enrolled had low (<13 μmol/L) serum zinc. Although zinc supplementation significantly increased the plasma zinc concentration and reduced diarrhea incidence, there was no measurable effect on linear or ponderal growth (11). In the multicenter Asian trial, there was no overall effect of zinc supplementation. However, a post hoc subgroup analysis suggested a small, significant effect on linear growth in anemic

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[3] This trial was registered at www.clinicaltrials.gov as NCT00272116.
[4] Supplemental Figure 1 is available with the online posting of this paper at jn.nutrition.org.
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children (12). Furthermore, in a recent metaanalysis, Ramakrishnan et al. (13) found a small positive effect of zinc supplementation on change in weight-for-height Z-scores but no improvement in length or weight in children receiving zinc interventions. We previously demonstrated that daily zinc for 4 mo substantially reduced the incidence of diarrhea and pneumonia in North Indian children 6–30 mo of age (6,7). In the same children, we analyzed the anthropometric data to examine the impact on linear and ponderal growth. The overall and subgroup effects of zinc on length-for-age and weight-for-length increments are presented in this article.

Participants and Methods

Study setting. The trial was implemented in the urban slum of Dakshinpuri in New Delhi, which comprises of a population of ~75,000 residing in 15,000 dwellings. The details of the study setting have previously been published (6,7).

Clearances were obtained from the ethics committee of the All India Institute of Medical Sciences.

Randomization and blinding. The randomization scheme (in blocks of 8) was generated off-site by a statistician at Statens Serum Institute, Copenhagen, Denmark, who was not otherwise involved with this study, using SAS software (version 8.1; SAS Institute). Eligible children were individually allocated to zinc or placebo groups. Zinc and placebo syrups were similar in appearance, taste, and packaging and were prepared, packaged, and labeled with a unique identification number according to the randomization scheme by "GK Pharma Aps, Koge, Denmark "in unbreakable bottles. The supplies for each child (6 bottles, 1 for each month and 2 extra in case of loss) were packed in a labeled plastic bag before the commencement of the study.

Enrollment and intervention delivery. Enrollment commenced on February 15, 1998. Children aged 6–30 mo were identified through a door-to-door survey. All families intending to move out of the study area, requiring hospitalization on the day of enrollment, having received vitamin A within the previous 2 mo, or who refused to participate were excluded. Infants (6–11 mo) received 10 mg of elemental zinc as zinc gluconate daily; older (≥12–35 mo) children received 20 mg/d. All children received a massive dose of vitamin A (104.7 μmol to infants and 209.4 μmol to older children) at enrollment. The vitamin A capsules were provided by Sight and Life, Basel, Switzerland. The supplement (zinc or placebo syrup) was administered daily at home for 4 mo by a field attendant.

Trial size. Trial size was calculated using assumptions from a previous study in an adjacent slum. Assuming a mean change (± SD) of 0.7 ± 0.5 kg in weight and 3.5 ± 1.7 cm in length over a 4-mo period for detecting a 10% improvement in these variables at 90% power, 1073 and 496 children were required per group. The primary objective of the study was to detect reduction in diarrhea and pneumonia incidence, for which we required a higher sample size than that required for growth.

Measurement of outcomes. Throughout the 4-mo follow-up period, field workers visited households every 7th day to obtain information on morbidity for the previous 7 d. Information on history of fever, number of stools, and presence of cough was obtained at each visit. Growth was assessed through weight and length measurements at enrolment and at the end of the study using a Seca salter scale and locally manufactured infantometer that read to the nearest 0.1 kg and 0.1 cm, respectively. Nonfasting venous blood was drawn in zinc-free heparinized polypropylene tubes (Monovette) at enrolment and in a 30% subsample at the end of the study to assess plasma zinc, ferritin, and C-reactive protein (CRP).[13] About one-half of the plasma zinc specimens were analyzed using standard a flame furnace atomic absorption spectrophotometer technique (GBC Avanta) and the other one-half by inductively coupled plasma atomic emission spectrometry [Ash, IRIS/AP (14); Thermo Jasell (15)]. The plasma ferritin concentration was analyzed by a turbidimetric immunoassay and CRP was analyzed by immunoassay in a Roche/Hitachi Modular analyzer, Roche Diagnostics (16).

Standardization and quality control. Standardization exercises were conducted to achieve agreement within and between study field workers for weight and length measurements. Subsequent to practice sessions to measure weight and length, field workers participated in exercises where 10 sets of 10 children were measured twice. Standardization exercises for weight ended when all field workers obtained identical readings in both their measurements and were in perfect agreement with the group mean, i.e. the arithmetic mean of all the observations of the field workers for a set of 10 children. A difference of ± 0.5 cm between the reading of the field workers and group mean was considered acceptable for length.

Weighing scales were calibrated daily against known standard weights and infantometers with standard steel rods.

Data management and statistical analyses. The data entry forms were designed with FoxPro for Windows (Microsoft) with range and consistency checks incorporated. Double data entry followed by validation was completed within 48 h of form filling in the field. Statistical analysis was performed with Stata software version 10 (Stata Corp). Z-scores were calculated using the WHO child growth standards (17,18). Summary measures for continuous variables are reported as means or medians as appropriate and categorical variables are reported as proportions. Any differences in means between the zinc and placebo groups were assessed using Student's *t* test and proportions assessed with chi-square test. Crude overall estimates for changes in length, weight, length-for-age Z-score (LAZ), weight-for-age Z-score (WAZ), and WLZ were estimated. In addition to the overall effect, the effect in various subgroups adjusted for baseline age, breast-feeding status, anthropometric status, gender, and income was estimated. The interaction between zinc supplementation status and the subgrouping variables were also assessed in linear regression models. A *P*-value of < 0.05 was considered significant.

Results

A total of 2482 children were randomized (**Supplemental Fig. 1**). Eighty-eight percent (n = 1093) of those randomized to the zinc group and 91% (n = 1133) of those in the placebo group were available at the last scheduled follow-up visit and included in the analysis. Weight and length measurements were taken for all children available on the last follow-up visit. Measurements could not be obtained in 51 children who refused participation after enrollment, 184 who left the study area before completion of follow-up, and 3 who died (Supplemental Fig. 1).

The baseline characteristics including age and anthropometry were similar in the zinc and placebo groups. Sixty-nine percent of the children were breast-fed and a few more than one-half were male. Eighty-five percent of infants, i.e. 66% of the 12- to 23-mo-old and 41% of the 24- to 30-mo-old children, were breast-fed. Fewer than one-half of the children had low zinc concentrations (<9.2 μmol/L; **Table 1**). Plasma CRP concentrations at baseline and the study end did not differ between the groups.

Weight gain after 4 mo of supplementation was 0.675 kg in both groups. There was a 3.55-cm increase in the mean length during the follow-up period among the control group children; the mean increase in the zinc-supplemented children was 0.12 cm less (95% CI, −0.02 to 0.26), but the difference was not significant (P = 0.08) (**Table 2**). The mean changes in LAZ, WLZ, and WAZ did not differ between the zinc-supplemented (−0.14, −0.02, and −0.04, respectively) and placebo groups (−0.12, −0.07, and −0.06, respectively) ($P \geq 0.13$).

[13] Abbreviations used: CRP, C-reactive protein; LAZ, length-for-age Z-score; PCV, packed cell volume; WAZ, weight-for-age Z-score; WLZ, weight-for-length Z-score.

TABLE 1 Baseline characteristics of children aged 6 to 30 mo randomized in the zinc and placebo groups[1]

Characteristics	Zinc	Placebo
n	1240	1241
Boys, *n (%)*	682 (55.0)	617 (49.7)
Age, *mo*	15.00 ± 7.50	15.60 ± 7.50
Age, *n (%)*		
6–11 mo	525 (42.3)	480 (38.7)
12–23 mo	504 (40.6)	510 (41.1)
24–30 mo	211 (17.0)	251 (20.2)
Length, *cm*	72.40 ± 7.20	73.00 ± 7.10
Weight, *kg*	8.10 ± 1.60	8.0 ± 1.60
Family income, *rupees/y*	36000 (24000, 54000)	36000 (24000, 54000)
Z-scores		
HAZ	−1.79 ± 1.17	−1.85 ± 1.17
< −2 Z, *n (%)*	523 (42)	483 (39)
WAZ	−1.83 ± 1.08	−1.84 ± 1.11
< −2 Z, *n (%)*	517 (41.7)	512 (41.3)
Weight-for-height Z-score	−1.17 ± 1.0	−1.14 ± 1.05
< −2 Z, *n (%)*	237 (19.1)	230 (18.6)
Breast-fed, *n (%)*	857 (69.1)	865 (69.7)
Plasma zinc, *μmol/L*	9.49 ± 2.18	9.49 ± 1.71
<9.2 μmol/L[2,3,4]	553 ± 45.8	513 ± 42.0
Plasma CRP, *mg/L*	0 (0,2)[3]	0 (0,2)[3]
>10 mg/L, *n (%)*	43 (5.7)	44 (6.1)
Plasma ferritin, *μg/L*	7 (5,14)[5]	7 (5,14)[5]
<20 μg/L, *n (%)*	629 (84.3)	598 (83.6)
PCV,[6] %	32.92 ± 3.25	33.07 ± 3.11
<33%	501 (40.5)	504 (40.8)

[1] Values are mean ± SD, *n* (%), or median (IQR).
[2] Available for 1222 children in zinc group and 1126 children in placebo group.
[3] Available for 754 children in zinc group and 725 children in placebo group.
[4] To convert μg/dL to μmol/L, multiply by 0.1530.
[5] Available for 746 children in zinc group and 715 children in placebo group.
[6] Available for 1238 children in the zinc group and 1236 children in the placebo group.

TABLE 2 Unadjusted changes in anthropometric variables after 4 mo of daily administration of zinc or placebo syrup to north Indian children 6–30 mo of age

	Zinc[1]	Placebo[1]	Difference in mean change (95% CI)
n	1093	1133	
Weight, *kg*	0.67 ± 0.47	0.68 ± 0.49	0.00 (−0.04−0.04)
Length, *cm*	3.43 ± 1.58	3.55 ± 1.74	−0.12 (0.26−0.02)
Z-scores, overall			
LAZ	−0.14 ± 0.44	−0.12 ± 0.43	−0.02 (−0.05−0.02)
WAZ	−0.04 ± 0.51	−0.06 ± 0.49	0.02 (−0.02−0.06)
WLZ	−0.02 ± 0.64	−0.07 ± 0.67	0.05 (−0.007−0.10)
Z-scores			
6–11 mo	*n* = 473	*n* = 418	
LAZ	−0.25 ± 0.44	0.28 ± 0.49	0.02 (−0.04–0.08)
WAZ	−0.49 ± 0.58	0.48 ± 0.58	−0.01 (−0.09–0.06)
WLZ	−0.49 ± 0.67	−0.46 ± 0.75	−0.03 (−0.13–0.59)
12–23 mo	*n* = 467	*n* = 445	
LAZ	0.10 ± 0.52	0.06 ± 0.45	0.04 (−0.03–0.09)
WAZ	−0.03 ± 0.37	−0.01 ± 0.33	−0.02 (−0.07–0.02)
WLZ	−0.04 ± 0.63	−0.01 ± 0.50	−0.03 (−0.10–0.05)
24–30 mo	*n* = 192	*n* = 229	
LAZ	−0.09 ± 0.62	−0.12 ± 0.46	0.03 (−0.08–0.13)
WAZ	0.08 ± 0.31	0.05 ± 0.37	0.03 (−0.04–0.09)
WLZ	0.06 ± 0.51	0.05 ± 0.53	0.00 (−0.09–0.11)

[1] Values are mean ± SD.

There was no substantial effect in any of the subgroups in the crude analyses or after adjusting for age, gender, breast-feeding status, income, and baseline anthropometric status on the effect of zinc supplementation on WAZ and LAZ in different subgroups (**Fig. 1**). In the subgroup consisting of those with < −2 WLZ and the subgroup of those with low plasma zinc, there was a small, negative, and significant effect of zinc on LAZ change. For the outcome WLZ, the *P* for interaction between baseline plasma zinc concentration and treatment was 0.04. For WAZ and packed cell volume (PCV), the *P*-values for interaction were 0.09 and 0.07, respectively. For the outcome LAZ, the *P*-value for interaction between baseline WLZ and treatment was 0.01.

Discussion

Daily zinc supplementation for 4 mo substantially and significantly increased plasma zinc concentration and reduced the incidence of diarrheal and respiratory tract infections in children enrolled in the trial (6,7), but there was no effect on linear or ponderal growth. These data therefore do not support the metaanalysis that included 33 studies demonstrating a significant effect (0.35; 95% CI, 0.189–0.511; $P < 0.0001$) of zinc on linear growth (10). Our findings are, however, consistent with the study in Burkina Faso, which included 709 children and is, after the study reported here, the largest one examining the effect of zinc on linear growth in children > 6 mo of age (11). The variability (SD) of the monthly growth increments was higher in the study in Burkina Faso than in the studies included in the metaanalysis, which may be due to suboptimal standardization of the field staff and/or greater variations in the actual weights and lengths of study children. Increased variability reduces the precision of measures and accordingly increases the risk of failing to identify an existing effect (type II error). However, it will not bias the growth effect measures toward no effect. Our study had lower variability (SD) in LAZ than the study in Burkina Faso, which, combined with our large sample size, contributed to our effect measures' very high precision, the upper 95% confidence limits of any impact of zinc on mean linear and ponderal growth being a mere 0.2 mm and 40 g, respectively.

Our findings are supported by the recent metaanalysis evaluating the effect of micronutrient interventions on the growth of children <5 y of age (13). Zinc interventions showed only a positive, albeit small, effect (effect size 0.06; 95% CI, 0.006–0.11) on change in WLZ and no significant effect on length or weight gain. The authors speculated that this was due to the improved nutritional status of children in the more recent studies (12). A possible criticism of the earlier metaanalyses is that the literature includes a preponderance of papers that show significant results and studies with negative results may not have been included. Thus, the metaanalyses may have overestimated the effect of zinc on growth.

A hypothetical explanation for our finding would be that zinc was not delivered effectively. However, the supplementation resulted in substantially increased plasma zinc concentrations and morbidity reduction (6,7), making this an unlikely explanation. Although information on the dietary intake of micronutrients in our study population is not available, considering the dietary patterns of the population, the diets consumed are moderately or severely limited in absorbable zinc. The lack of growth response may be attributed to other micronutrient

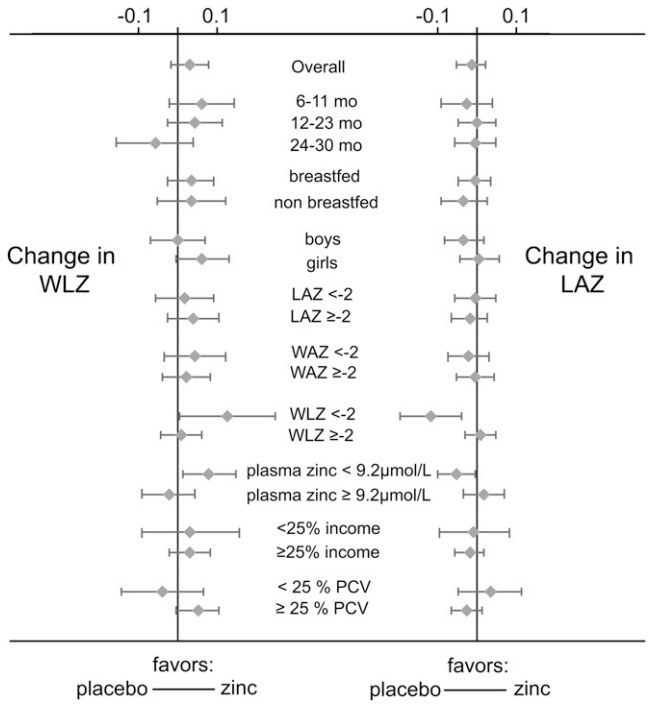

FIGURE 1 Effect of 4-mo daily zinc supplementation in various subgroups of Indian children on WAZ and LAZ. Adjusted for age, breast-feeding status, sex, income, and anthropometric status at baseline. For the outcome WLZ, the *P* for interaction between baseline plasma zinc concentration and treatment was 0.04. For WAZ and PCV, the *P*-values for interaction were 0.09 and 0.07, respectively. For the outcome LAZ, the *P*-value for interaction between baseline WLZ and treatment was 0.01. All other *P*-values for the interactions described in this figure were ≥0.1.

deficiencies that coexist in this population, limiting the response to zinc (19). However, in the SEAMTIZI trial on iron and zinc supplementation, zinc was beneficial for linear growth in anemic infants, but had a negative effect in nonanemic infants (12). We did not measure hemoglobin, but PCV, which can be used as a proxy for hemoglobin concentration, did not modify the effect of zinc on length gain. Furthermore, we had baseline ferritin concentrations from 1461 children that also did not modify the effect of zinc on the outcomes analyzed. Because nearly 20% of our study children were wasted, it would seem that energy and macronutrients may also have been a limiting factor. Thus, even if zinc had an effect, the energy requirements may not have been met for zinc to have an effect on growth. It would have strengthened the conclusion of the study if we had dietary intake or energy intake data for the children. Furthermore, we gave all enrolled children a dose of vitamin A. If there was an overall effect of vitamin A on growth, this could have masked a potential effect of zinc. The lack of growth observed may be due to the short duration of supplementation; however, 11 of 33 studies included in the metaanalysis had similar or shorter periods of supplementation (10). Nevertheless, a potential effect of zinc on growth would have been easier to detect if supplementation was for a longer period of time and among the very young, who have a greater growth potential than older children. However, there was no increased effect on linear growth even when restricting the analysis to the infants, but there was a trend toward better effect on ponderal growth in this age group, although the effect was small and did not reach statistical significance.

Low prevalence of zinc deficiency in the study population is not a likely explanation of poor impact, as 45% of the study children had plasma zinc concentrations that were <9.2 μmol/L at baseline (6).

Zinc supplementation reduces the burden of diarrhea and pneumonia (20), which was also shown in this trial (6,7). It is also likely that zinc reduces the burden of other and possibly even subclinical infections, such as small bowel bacterial overgrowth, a reduction that is expected to enhance growth. Thus, the effect of zinc on growth in other clinical trials could in part have been mediated by a reduction in infections among the zinc recipients. It is therefore surprising that we observed a substantial effect of zinc on morbidity but not on growth. This could to some extent be explained by our intense follow-up. Each household was visited every day and we can therefore assume that children in the study were treated relatively early in the disease compared with children who were not part of this trial. The threshold to visit study physicians was also low, because the study staff represented a reputed medical institution and the consultation and treatment were provided for free. Moreover, we followed integrated management of childhood illnesses guidelines for treating sick children (21); these have relatively low thresholds for treating childhood infections with antibiotics. Thus, our close monitoring and provision of outpatient services are likely to have reduced the overall disease burden and the effect of infection on growth. This reduction is seen in the zinc as well as in the placebo recipients and could have reduced somewhat the observed effect of zinc on growth.

Despite several possible explanations, it is still not clear why growth responses to zinc supplementation are inconsistent. The magnitude of effect depends on many factors, including the degree of zinc deficiency, deficiency of other nutrients, malabsorption chronic infections, and the quality of the diet. Growth is a complex process and zinc deficiency may be one of the limiting factors, although this is seemingly not the main limitation in this population.

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