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Oral Zinc Supplementation Positively Affects Linear Growth, But not Weight, in Children 6-24 Months of Age

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ABSTRACT

Background: Childhood zinc deficiency is a common problem in many developing countries where people rely mainly on plant based diets with low zinc contents. Zinc supplementation is one of strategies to combat zinc deficiency and its consequences in children. The aim of this community trial was to examine the effect of zinc supplementation on the linear growth of children 6-24 months of age and to examine the feasibility of its implementation in the context of primary health care (PHC).

Methods: Rural community health centers providing maternal and child care in two areas with moderate rates of malnutrition were randomly assigned to intervention and control groups, including 393 and 445 children 6-24 months of age, respectively. Children in both groups received routine iron and multivitamin or vitamin A and D supplements through PHC services. Mothers of children in the intervention group were asked to give a single dose of 5 ml/day zinc sulfate syrup (containing 5 mg elemental zinc) to their children for 3 months while children in the control group did not receive the supplement.

Results: Anthropometric measurements were performed at baseline and on a monthly basis in both groups. We found a 0.5 cm difference in the height increment in the intervention group as compared with the control ($P < 0.001$). Zinc supplementation had no effect on weight increment of children.

Conclusions: Oral zinc supplementation was found to be both practical and effective in increasing linear growth rate of children less than 2 years of age through PHC.

Keywords: Community trial, height, linear growth, zinc supplementation

INTRODUCTION

Zinc is intimately linked to growth and development. Zinc interacts with important hormones involved in bone growth and its concentration in bone matrix is very high compared with that in other tissues.[1] Childhood zinc deficiency remains a common problem in much of the developing world.[2] About 50 years ago, a clinical syndrome characterized by dwarfism, hypogonadism and anemia was first attributed to zinc deficiency in Iranian boys.[3] More recently, a national survey of micro-nutrient status in Iran revealed that based on serum zinc concentration, prevalence of zinc deficiency among children 15-23 months of age ranged from 6.3% to 70.2% with a mean of 19.4% across the country.[4] The same study also reported zinc deficiency among 31% of 6-year-old children, 28.0% of adolescents and 39% of pregnant women of gestational age 5 months and above.[4]

The Iranian national food consumption and dietary intake data suggests that many Iranian children might be at risk of zinc deficiency beyond early infancy.[5] The major sources of zinc are animal products, which are consumed in low or very low amounts by people in many parts of Iran. Moreover, phytic acid in plant sources forms an insoluble zinc chelate, which markedly reduces zinc bioavailability from food.[6] Consequences of zinc deficiency other than growth failure include poor appetite, skin lesions and delayed wound healing, immunosuppression and increased rates of infections.[7]

Fortification of staple foods with zinc has been suggested to improve the zinc status in adults.[8] However, zinc intake by means of food might not be sufficient to cover the increased need of growing children. Zinc-responsive stunting has been identified in many parts of the world and several studies have found that malnourished children gain weight more rapidly during the nutritional rehabilitation when they are supplemented with zinc.[9,10] On the other hand, studies from some developing countries have failed to identify a growth response to zinc supplementation,[11-14] so the importance of zinc supplementation as a means to improve linear growth in at risk children remains controversial. Because of the widespread occurrence of zinc deficiency in Iran and the important functional and growth consequences that have been reported in association with it and since there exists not much international experience and no local evidence on the feasibility and effectiveness of a zinc supplementation program, we carried out this pilot community trial to investigate the effect of supplemental zinc on linear growth of children 6-24 months of age in a disadvantaged setting and through primary health care (PHC) system.

METHODS

Setting

The study was carried out from August to November 2009 in rural areas of districts of Damavand and Varamin at the Northeast and South of Tehran, respectively. These areas were reported to have the highest rates of malnutrition among children under five.[15] Diet in this area contains little animal protein and low amounts of zinc with high bioavailability, which places the children at higher risk of zinc deficiency.[5]

Both rural and urban areas in Iran are under the coverage of health houses (HH). HH is the first point of contact in service delivery within the health system for preventive public health measures, medical assistance and routine check-ups, which covers an average population of 1200-1600 and is staffed by one or two trained community health workers named Behvarz. Behvarz is a young man or woman with high school education who is specifically trained to deliver maternal and child care, family planning and environmental/occupational health care. HHs are supervised by physicians who are based in the health centers and manage any emergency or complicated case of illness. In rural areas, every HH covers one main village and one or more satellite villages.

Particularly in rural areas, the system for service delivery within the PHC is active. All children 6-24 months of age receive iron (2 mg/kg body weight elemental iron in the form of ferrous sulfate) and vitamin A and D (or multivitamin) supplements from 15th day of life free of charge. Growth monitoring in terms of weight and height measurements in accordance with Well-Baby Integrated Program is in place and Behvarzes are actively involved in the early treatment of acute respiratory infections and control of diarrheal diseases.

Our study population consisted of children 6-24 months of age who lived in the households covered by HHs in the rural areas of Damavand and Varamin districts.

Sampling and recruitment

A multistage randomized sampling deign was used, with HHs as the unit of randomization and children 6-24 months of age as the unit of analysis. According to the health records and family logbooks, there were 815 and 2073 children under 2 years of age covered by rural HHs in Damavand and Varamin districts, respectively. At the first stage, seventeen HHs with a total of 837 children under coverage from both districts were randomly selected for the study. HHs were then randomly allocated to intervention (n = 8) and control (n = 9) arms within both districts. This type of randomization ensured the similarity of participants in both arms in terms of climate, socio-economic status, and access to health services. The study protocol was approved by the office of the World Health Organization in Tehran and by the Nutrition Department of the Iranian Ministry of Health and Medical Education.

With a 95% confidence interval (CI) ($z = 1.96$) to observe a difference of 0.6 cm in height increment within the intervention group compared to control group, with a type two error β=0.10 and assuming the same population standard deviation of $s = 2.6$ cm for intervention and control groups,[16] a sample of 400 children per group was needed.

Intervention

Behvarzes could not be blinded to the intervention because of the required training. Behvarzes running the HHs in the intervention group received 1-day training on the study rational and procedures. Mothers in the intervention villages were then invited to attend the HHs and asked by Behvarzes to participate in the study. To minimize potential bias, mothers were informed about the aim of this study, but not about the intervention or control groups. Verbal informed consent was obtained from the parents of eligible children during their visit to the HH.

Behvarzes were instructed to provide each infant in the intervention group with three 60-ml screw threaded vials containing sweet-tasting syrup of 5 mg zinc (22 mg zinc sulfate, $7H_2O$ and 1 mg sodium saccharin) per 5 mL for a 1-month period. Mothers were asked to collect the supplements on a monthly basis from the HH and to give a single dose of 5 mL/day of the syrup to their child, preferably after a meal. Behvarzes replaced the vials at each visit and monitored the intake by parent recall and recorded the compliance with supplementation as well as symptoms of illness. Mothers were also interviewed on the perceived side-effects of zinc supplement including abdominal pain, decreased appetite, vomiting, diarrhea, constipation and increased crying or fussiness.

Data collection

Anthropometric measurements were performed at baseline and followed-up on a monthly basis during the study period by Behvarzes in both intervention and control groups. Weight was measured to the nearest 0.02 kg with the use of a digital scale (Seca, Hamburg, Germany). Recumbent length was measured to the nearest 0.1 cm with the use of a locally produced wooden measurement board.

Statistical analysis

Data was analyzed using the SPSS for Windows statistical package (version 12; SPSS Inc., Chicago) and organized as means ± standard deviation for all children in one group. Mean values were compared within and between groups. General linear model and repeated measures' analysis of variance (ANOVA) were performed to examine the effect of zinc supplementation on height increment and the difference between intervention and control groups. Values of $P < 0.05$ were considered significant.

RESULTS

Of the 838 recruited children, 593 completed the study and had complete anthropometric data [Figure 1].

Side-effects (nausea and vomiting) were reported in 18 children (6.3%) in the supplemented group. This, however, did not affect the compliance since mothers were advised to change the timing of administration, which solved the problem.

Mean ages (14.5 ± 5.4 months in the intervention group and 14.6 ± 5.4 months in the control group) and key anthropometric measurements, namely height (77.4 ± 6.2 vs. 77.5 ± 6.2) and weight (10.2 ± 1.6 vs. 10.0 ± 1.5) in the two groups were not significantly different at baseline. Age distribution of children were similar in the intervention and control groups both at baseline and at the end of the study indicating that drop outs were similar with regard to age [Table 1].

At the end of the study, the mean height of children in the intervention group was 81.5 ± 6.2 cm compared with 81.0 ± 6.0 cm in children in the control group and the difference was not statistically significant [Table 2]. Furthermore, no difference was observed with regard to measurement of weight. However, examination of height velocity i.e., rate of change in height, over the 3-month period revealed a

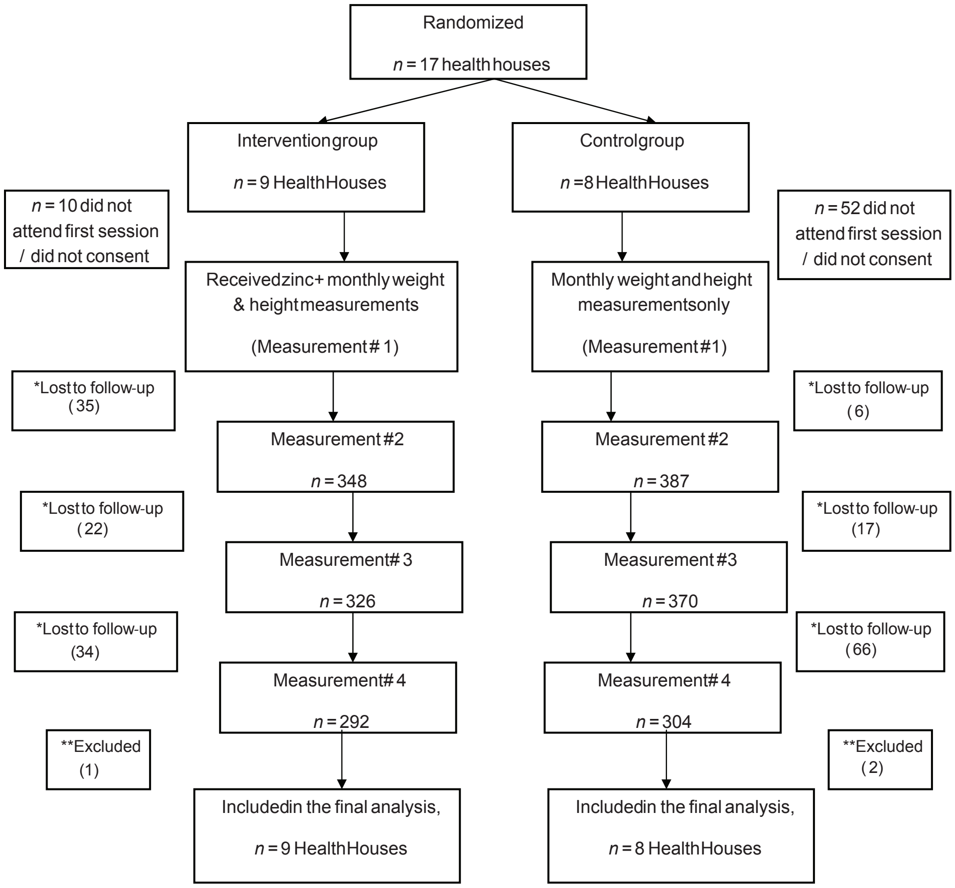

Figure 1: Flow diagram of the process of clusters and individuals through the phases of trial. *Lost to follow up (moved, travel, did not attend at least one of monthly visits) **Excluded (incomplete data)

Table 1: Age and sex distribution of participating children before and after the intervention

Sex	Group	Age group *n* (%)			
		6 to<12 m	12 to<18 m	18 to 24 m	Total
Boys	Control				
	Before	75 (38.7)	57 (29.4)	62 (32.0)	194
	After	63 (42.6)	41 (27.7)	44 (29.7)	148
	Intervention				
	Before	64 (31.1)	77 (37.4)	65 (31.6)	206
	After	54 (34.0)	55 (34.6)	50 (31.4)	159
Girls	Control				
	Before	70 (35.2)	71 (35.7)	58 (29.1)	199
	After	51 (33.1)	56 (36.4)	47 (30.5)	154
	Intervention				
	Before	76 (42.9)	44 (24.9)	57 (32.2)	177
	After	59 (44.7)	27 (20.5)	46 (34.8)	132

mean difference of 3.5 ± 2.0 cm and 4.0 ± 1.6 cm in height increment in control and intervention groups, respectively, which was statically significant (2 tailed $P < 0.001$) [Table 3]. Furthermore, comparison of height increment between groups by the general linear model and repeated measurements ANOVA method revealed that height velocity was significantly greater in the intervention group compared with the control group.

DISCUSSION

The main objective of this study was to investigate the effect of zinc supplementation on growth of children 6-24 months of age and to assess the feasibility of its implementation within PHC system in Iran.

The positive effect of zinc on children's linear growth in the current study is consistent with results from several other studies.[2,17-20] A meta-analysis of zinc supplementation and growth by Brown *et al.* using information from 33 data sets (including a total of 2637 study participants) demonstrated an average effect size of 0.350 cm (95% CI: 0.189, 0.511) of zinc supplementation on height increment of infants with an initial age of ≥6 months, which

Table 2: Details of follow-up of height and weight during the course of the study

Anthropometric Measurements	Groups	Mean	Standard deviation	*P* value* (2-tailed)
Weight (kg)				
At baseline	Control[a]	10.0	1.5	0.132
	Intervention[b]	10.2	1.6	
After 1 month	Control	10.4	1.5	0.146
	Intervention	10.6	1.7	
After 2 months	Control	10.7	1.5	0.062
	Intervention	10.9	1.7	
After 3 months	Control	11.0	1.6	0.128
	Intervention	11.2	1.7	
Height (cm)				
At baseline	Control	77.4	6.2	0.902
	Intervention	77.5	6.2	
After 1 month	Control	78.7	6.2	0.784
	Intervention	78.9	6.2	
After 2 months	Control	79.7	6.1	0.313
	Intervention	80.3	6.2	
After 3 months	Control	81.0	6.1	0.289
	Intervention	81.5	6.2	

*Student's *t* test. [a]*n*=302, [b]*n*=291

Table 3: Monthly and total height increments during the course of the study

Height increment	Groups	Mean (cm)	Standard deviation	*P* value* (2-tailed)
After 1 month	Control[a]	1.27±0.92	0.92	0.312
	Intervention[b]	1.34±0.91	0.91	
After 2 months	Control	1.02±0.79	0.79	<0.001
	Intervention	1.39±0.88	0.88	
After 3 months	Control	1.17±0.82	0.82	0.690
	Intervention	1.19±0.72	0.72	
From baseline	Control	3.46±1.53	1.53	<0.01
	Intervention	3.94±1.40	1.40	

*Student's *t* test. [a]*n*=302, [b]*n*=291

was significantly greater than zero ($P < 0.0001$).[19] Furthermore, a more recent meta-analysis of the effect of zinc supplementation on linear growth in children under 5 years of age in developing countries has shown a net gain of 0.36 (±0.18) cm in the zinc supplemented group compared with control, with a mean supplementation duration of 7.03 months and the dose range of 1-20 mg/day [weighed mean difference 0.19 (95% CI: 0.08, 0.30).[21]

Our findings however, are not consistent with results from other developing countries, which demonstrated no effect of zinc supplementation on linear growth of children.[11-13,22] Müller *et al.* and Taneja *et al.* found no effect of zinc supplementation on length/weight and z scores for height-for-age of children in rural Burkina Faso and an urban Indian slum, respectively.[12,13] However, their results have to be interpreted with caution since neither study was primarily designed to investigate the effect of zinc on linear growth of children. Moreover, the pattern of observed growth velocity in these trials could be negatively affected by the presence of infectious and parasitic diseases.

Past research also indicates that a number of micronutrients in addition to zinc are implicated in linear growth and supplementation with zinc plus other micronutrients can have a greater effect in increasing the growth velocity of children.[14] It has been shown that mild to moderate zinc deficiency in otherwise normal infants and children can contribute to low growth percentiles, which is correctable by the provision of supplemental zinc.[18] Given that children in the current study did receive iron and vitamin A and D or multivitamin supplements as part of the routine care within the PHC system, their nutritional status was supposedly better than that of children in previous studies.[11-13,17,22] This might, at least to some extent, explain the greater effect of zinc supplementation on linear growth of our children compared with these studies. It should be noted that in some studies that reported no significant effect of zinc supplementation on linear growth, the findings however demonstrate a positive effect of supplementation that could become significant in case the sample size would have been greater.[11,12]

Our findings are supported by the fact that the study used a community trial design with a concurrent control group and confirmation that the supplements were successfully delivered to the participants in the intervention group, with a compliance rate, which was found to be literally perfect. Furthermore, the period of supplementation lasted 12 weeks to ensure the detection of any linear growth response, since literature indicates that periods of supplementation less than 8 weeks may be insufficient in this regard.[19] The dropout rate of participants, which was relatively small, does not seem to be a source of attrition bias, since the main reason for drop out in both groups was migration and being locally unavailable for monthly measurements, which is a common phenomenon in disadvantaged rural settings.

The main methodological shortcoming of the current study is the lack of placebo use in the control group, which was primarily due to the technical problems associated with the provision of placebo syrups and also barriers to the logistics for a field trial in a disadvantaged setting. However, except for zinc supplements, children in the control group received exactly the same care in terms of monthly anthropometric measurements and iron and vitamins A and D or multivitamin supplements within the health care system and by Behvarzes.

Our findings are consistent with previous research, which reported limited effect of zinc supplementation on different indices of weight[2,11-13,17] possibly indicating that supplemental zinc is more likely to influence bone and therefore linear growth than accumulation of muscle or fat mass.[10] This can be explained by the fact that zinc is abundant in bone tissue and is needed to maintain bone mineral density and bone metabolism.[23] The organic matrix of bone is comprised of proteins that require adequate amounts of zinc for optimal function.[24] Zinc also acts as a cofactor for osteoblast activity during bone formation and is required for maintaining peak bone density.[25] Evidence demonstrates that zinc may act as a local regulator of bone cell formation by stimulating the proliferation and differentiation of osteoblasts while at the same time inhibiting osteoclast differentiation.[25]

CONCLUSIONS

The effect of zinc supplementation on height achievement in the current study does have important implications for practice within the health care system. National data on food consumption patterns suggest that suboptimal zinc intake is prevalent in many parts of Iran and the problem does not seem to be limited to any one socioeconomic or ethnic group.[5] Our findings suggest that zinc supplementation at the community level and as an integrated part of services provided through PHC can have a remarkable effect on the linear growth of children. However, although zinc supplements are easy to administer, daily supplementation requires commitment from parents and acceptance by children. Further, parents may not link the improvement in linear growth with supplementation. To ensure high compliance, it is therefore important to work closely with the community and to brief parents prior to supplement distribution.

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