Zinc supplementation and stunted infants in Ethiopia: a randomised controlled trial

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Summary

Background Stunting is highly prevalent in Ethiopia and many other developing countries but the reason for it is poorly understood. Zinc is essential for growth but diets in such countries often do not contain zinc in sufficient quantity or of sufficient bioavailability. Thus zinc deficiency may play a major role in stunting. The aim of the study was to investigate whether the low rate of linear growth of apparently healthy breastfed infants in a rural village in Ethiopia could be improved by zinc supplementation.

Methods A randomised, double-blind, placebo-controlled trial was done on apparently healthy breastfed infants aged 6–12 months. 100 non-stunted (length-for-age, Z score <−2) were matched for age and sex with 100 randomly selected stunted (>−2) infants. Infants, both stunted and non stunted, were matched by sex, age (within 2 months) and recumbent length (within 3 cm) for random assignment, to receive a zinc supplement (10 mg zinc per day, as zinc sulphate) or placebo, 6 days a week for 6 months. Anthropometric measurements were taken monthly, data on illness and appetite were collected daily, and samples of serum and hair were taken at the end of the intervention for the analysis of zinc.

Findings The length of stunted infants increased significantly more ($p<0·001$) when supplemented with zinc (7·0 cm [SE 1·1]) than with placebo (2·8 cm [0·9]); and the effect was greater ($p<0·01$) than in non-stunted infants (6·6 [0·9] *vs* 5·0 [0·8] cm for the zinc and placebo groups respectively, $p<0·01$). Zinc supplementation also increased the weight of stunted children (1·73 [0·39] *vs* 0·95 [0·39] kg for the corresponding placebo group, $p<0·001$) and of non-stunted children (1·19 [0·39] *vs* 1·02 [0·32] kg for the corresponding placebo group, $p<0·05$). Zinc supplementation resulted in a markedly lower incidence of anorexia and morbidity from cough, diarrhoea, fever, and vomiting in the stunted children. The total number of these conditions per child was 1·56 and 1·11 in the stunted and non-stunted zinc supplemented children versus 3·38 and 1·64 in the stunted and non-stunted placebo-treated children, respectively. At the end of the intervention period, the concentrations of zinc in serum and hair of stunted infants, who had not been supplemented with zinc, were lower than the respective concentrations of zinc in serum and hair of their non-stunted counterparts.

Interpretation Combating zinc deficiency can increase the growth rate of stunted children to that of non-stunted infants in rural Ethiopia. This would appear to be due, at least in part, to reduction in morbidity from infection and increased appetite.

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Introduction

Zinc has long been recognised as an essential micronutrient for health and normal growth, but only in the past 20 years has the manifestation of mild zinc deficiency been documented in man.[1] Zinc is a constituent of a number of enzymes and as such is involved in a large number of metabolic processes. Mild-to-severe zinc deficiency disturbs several biological functions such as gene expression, protein synthesis, immunity, skeletal growth and maturation, gonad development and pregnancy outcomes, and taste perception and appetite.[2] It has been suggested that zinc deficiency may have a role in stunting, especially in developing countries.[3] The assessment of zinc status is hampered by the lack of a single sensitive and specific biochemical factor. At present, the most reliable method to assess zinc status in children would appear to be to measure increase in growth velocity in response to zinc supplementation in physiological amounts.

The early studies in which adolescents with nutritional dwarfism in Egypt[4] and Iran[5] were supplemented with zinc did not show any consistent effect of zinc on linear growth. However, increased growth with zinc supplementation was found in malnourished infants and children.[6–8] Controlled studies in apparently healthy infants and children from developing and affluent countries have shown a positive effect of zinc supplementation on linear growth,[9,10] and also on lean body mass.[11,12]

57% of infants aged 6–11 months in Ethiopia are stunted.[13] Moreover, the dietary pattern is largely cereal and tubers and is low in animal products. Thus suboptimal zinc status is likely to exist in the population. Three earlier studies in subSaharan Africa found no effect of zinc supplementation in linear growth in infants and young children.[12,14,15] Therefore, we decided to test whether zinc deficiency is responsible for the low rate of growth of stunted children in Ethiopia. We did a randomised, double-blind, placebo-controlled study in which stunted and non-stunted infants aged 6–12 months were supplemented with zinc (10 mg/day) or a placebo, 6 days a week) for 6 months. Length and other anthropometric factors were measured monthly and the concentrations of zinc in serum and hair was measured at the end of the intervention. Because their incidence has been reported to be reduced by zinc supplementation, information was collected on anorexia[16] and morbidity six days each week.[17–20]

Before deciding on the design of this study, it was important to address the question of whether or not it would be ethical to include a placebo group. Stunting is a serious problem in Ethiopia but its cause is poorly understood. We regarded zinc deficiency as a possible major contributing factor but there were no data on the extent of severity of the problem in the country when the study was being conceived in 1994 and 1995. As stated above, other studies in Africa, both before and after the present study was done, have not shown any effect on growth[12,14,15] although evidence was building up for a role of zinc in growth[9] that was later confirmed.[10] In Ethiopia, no programmes have ever provided zinc supplements to infants or to any other group of the population. The double-blind placebo-controlled trial is probably the most powerful tool we have to examine whether or not a nutrient deficiency is present that is affecting the health or nutritional status of a group of individuals. It is generally agreed that it is ethical to use a design including a placebo group when there is insufficient evidence to accept or reject the proposed hypothesis and when the individuals enrolled in the study are not being deprived of prophylaxis or treatment.Thus, we regarded the proposed study as ethical and the ethical committee was of the same opinion.

Patients and methods

Study individuals

The study area was in the Dodota Sire district, Arsi zone, central Ethiopia, which is about 150 km east of the capital, Addis Ababa. In this district two working centres, Dheera and Hamude, about 40 km apart with available health facilities and access to all-weather road, were selected. The area lies in the Great Rift Valley of Africa with hot weather and a short rainy season. The staple crops are wheat, maize, sorghum, barley, and tef, which are grown for subsistence not profit. Traditional rearing of animals, mainly cattle and goats, is commonly practised mainly for income generation.

To select the study individuals, a census of all breastfed infants aged 6–12 months and their parents living within 15 km of the working centres was made. Demographic information was gathered using a pretested structured questionnaire to produce a list of target households. Date of birth of children was established by a local event calendar with information such as anniversaries, festivals, fasting periods, and farming seasons. No clinic cards were available from which dates of birth could be established. All infants were born at home with the assistance of traditional birth attendants, which is usual practice in rural Ethiopia.

The study design was explained to the Zonal Health Department of Arsi, the Administrative Officials of Dodota Sire district, community and religious leaders, and the peasant association leaders. The nature of the study was also fully explained to mothers and oral consent was obtained. Permission for the study was obtained from the ethics committee of the Ethiopian Health and Nutrition Research Institute. Before the study, a clinical examination was done by a physician and stool samples were checked for intestinal parasites, specifically ascaris, amoeba, and hookworm. None of those enrolled in the study had intestinal parasites nor were they dewormed. Although there is some malaria in the area, the few clinical cases of malaria proved negative by microscopic examination of blood smears.

Methods

Among infants who were apparently healthy, looked well, and were free from intestinal parasites and whose mothers were willing to participate in the study, 100 stunted (length-for-asf Z score [LAZ]<−2) infants were randomly selected and matched for age and sex with 100 non-stunted (>−2) infants for inclusion in the randomised, double-blind, placebo-controlled study, with ran from August, 1996, to February, 1997. The infants, both stunted and non-stunted, were matched by sex, age (within 2 months), and recumbent length (within 3 cm) and randomly assigned to receive the zinc supplement or placebo (figure 1). The zinc-supplement groups received 10 mg zinc as zinc sulphate in 3 mL syrup and the placebo groups received 3 mL of a syrup without zinc, both prepared by the Pharmacy Department of the Gelderse Vallei Ziekenhuis (Ede, Netherlands). The supplement and placebo were indistinguishable in colour and the slight metallic taste of the supplement was acceptable to the infants. The syrup comprised zinc sulphate heptahydrate (4400 mg), citric acid monohydrate (450 mg), saccharin sodium (300 mg), vanilla-coconut essence (15 drops), methylparaben concentrate (2 mL), sorbitol, 70% w/v (180 mL), and water to 300 mL. Trained field assistants gave the supplement and the placebo 6 days a week for 6 months. The supplement was given between 07.00 h and 11.00 h after breastfeeding but before any weaning foods were fed. Mothers complied well with this instruction. The field supervisor made spot checks of the field workers and of the households. In addition, information was gathered via the local peasant associations and community leaders as well as from the mothers during the monthly visit of one of the investigators. Neither the field assistants nor the investigator knew the codes. The codes were revealed only after the study was completed and the data analysis was finalised.

All anthropometric measurements were taken at monthly intervals for 6 months by the same investigator. Recumbent length was measured to the nearest 0·1 cm using a length board with an upright wooden base and a moveable headpiece designed by the Division of Human Nutrition and Epidemiology, Wageningen University. Weight was measured to the nearest 10 g by a metal-beam seat balance (Seca, model 725/424, Lamerus, Utrecht, Netherlands) in light clothes. The knee-heel length was measured to the nearest 0·1 mm by an electronic kneemometer (model BK5, Force Institute DK-2605 Brondby, Denmark). Mid-upper-arm circumference (MUAC) was measured to the nearest 0·1 cm with a flexible non-stretch measuring tape, midway between the acromion and the olecranon of the left arm with the arm hanging relaxed, without compressing the tissue. Triceps skinfold was measured to the nearest 0·1 mm with a Harpenden calliper at the same site. For all anthropometric measurements, three independent measurements were taken except knee-heel length, for which five independent measurements were taken. Three measurements on each of two occasions within 1 h from each of 20 infants were taken to measure the reliability of recumbent length, weight, MUAC, and triceps skinfold. The means of the first series of measurements were higher, but not significantly, than the second series of measurements (technical error=$d^2/2n$ where d=difference between measurements; coefficient of variation of all measurements in parentheses): recumbent length, 0·21 cm (0·51 cm, 0·31%); weight, 0·05 kg (0·08 kg, 0·17%); MUAC, 0·04 cm (0·07 cm, 0·14%); triceps skinfold, 0·13 mm (0·22 mm, 0·18%). For the measurements of knee-heel length, five independent measurements were taken and within each series of measurements, the technical error was as high as 14 mm. During the time of knee-heel measurements, the infants were very uncooperative, crying, moving their legs and hands, and were very unstable. It is difficult to keep them lying or sitting quietly even with the help of their mothers. Thus, the reliability could not be assessed. The SD scores for length for age (LAZ), weight-for-age (WAZ), and weight-for-length (WLZ) were calculated using the CASP program, version 3 (CDC, Atlanta, GA, USA). Stunting, underweight, and wasting were defined as LAZ less than –2, WAZ less than –2, and WLZ less than –2 compared with the standards laid down by the National Center for Health Statistics,[21] respectively.

During each daily visit by the field assistants, information was obtained from the child's mother about the presence or absence of symptoms of illness and on the child's appetite. Any child reported to have any symptom of illness was referred to the health centre for clinical examination and, if necessary, for treatment. All clinical examinations and treatments were recorded. Data on

the consistency and frequency of the passage of stools were first obtained from the mothers and then from observation of the stool samples by the field assistants. The mothers were well informed about keeping stool samples for examination during the field assistants' visits. Diarrhoea was defined as the passage of three or more liquid or semi-liquid stools in a 24 h period. Fever was defined as body temperature over 38·5°C at least once in a 24 h period. Data on appetite were collected by asking the mothers whether the child refused to breastfeed, whether the frequency, duration or intensity of breastfeeding was reduced, or whether the frequency or amount of weaning foods consumed was reduced.

At the end of the study, samples of venous blood (5 mL) were collected from those infants whose mothers gave permission, from the cubital vein between 08.00 h and 11.00 h in the non-fasting state. Samples were taken without anticoagulant into Vacutainer tubes (Venojet, Terumo, Belgium), stored in a cool place for 45 min, and then centrifuged at room temperature for 15 min at 1500 *g*. The serum was then transferred to vials and stored at –20°C in the health centre before being transferred frozen to the Ethiopian Health and Nutrition Research Institute where they were also stored at –20°C. Scalp-hair samples (50–100 mg) were collected from close to the capital portion of the scalp at the end of the study. Only the proximal 1–2 cm of the hair shaft, which reflects the zinc uptake by the follicles during the intervention, was used for the analysis. Serum zinc was analysed[22] by flame atomic absorption spectrometry (Varian Spectra AA 10/20 Plus, Varian Techtron Pty, Mulgrave, Victoria, Australia). Hair samples were washed with non-ionic detergent, rinsed several times with deionised water, dried, and a sample (40–70 mg) digested with trichloroacetic acid and zinc was analysed by flame atomic absorption spectrophotometry.[23] All glassware used for analysis was washed with acid and rinsed with deionised water. Accuracy and precision of the analyses were monitored by replicate analysis of quality control reference material SRM 1598 bovine serum (National Institute of Standards and Technology, Gaithersburg, MD, USA).

Statistical analysis

Before deciding to use parametric tests, we examined the data to ensure that they were not skewed. Descriptive data are expressed as mean (SD) and the results of the intervention as mean (SE). Significance was set at p less than 0·05. All factors, except incidence of anorexia and morbidity, were compared by ANOVA with "whether or not zinc supplemented" or "whether or not stunted" as dependent variables to test for differences among groups and, if significant, by independent *t* test. The significance of the difference in the effect of zinc between the stunted and non-stunted infants was also tested by independent *t* test. χ^2 analysis was used to test for differences in anorexia and morbidity among the groups. Anthropometric and biochemical indices were correlated with Pearson product-moment correlation and, if one of the indices was not normally distributed, also by rank-order correlation. All analyses were done with SPSS version 7.5.

Results

The number of children recruited in the census was 305 and, of the 50 individuals in each group, complete results over the 6-month period were obtained from 45–47 individuals per group (figure 1). All children in the study were exclusively breastfed for the first 4 months of life. When the intervention commenced, some mothers had begun to provide traditional cereal-based weaning foods. The practice was observed throughout the study period and, among those children who completed the study, 11 (6%) were weaned because of the mother's lack of breast milk. During the study, information on the health of the infants collected by the field assistants was passed to the health centres where diagnoses were confirmed and recorded and where treatment was done without reference to whether the infant was receiving the zinc supplement or not. No cases of malaria, based on examination of thick blood films, were recorded and no antimalarials were issued. Medicines prescribed included oral antibiotics (ampicillin), antihelminthics (piperazine), aspirin, and chloramphenicol eye drops. There were no differences between the groups in age or between the zinc and placebo groups of the stunted and non-stunted groups with respect to all the factors listed in table 1. Compared with non-stunted infants, the stunted infants were shorter (about 5 cm), lighter (about 1 kg), had smaller mid-upper-arm circumference (about 1 cm) indicating less muscle and fat mass, and had smaller triceps skinfold thickness (about 0·3 mm) indicating less body fat. This was reflected in lower WAZ and higher WLZ. There were no differences between the mothers of stunted and of non-stunted infants (table 1). The proportion of mothers with desirable body weight (body mass index >18·5 kg/m^2) was 66·3% while those with mild (18·4–17·0 kg/m^2), moderate (16·9–16·0 kg/m^2 and severe (<15·9 kg/m^2) chronic energy deficiency were 21·7%, 3·8%, and 8·2%, respectively.

In stunted children, growth (increase in length) over the 6 month period was 2·5-fold higher with zinc supplementation than without (7·0 [1·0] *vs* 2·8 [0·9] cm) while in non-stunted children length increased only 20% (6·0 [0·9] *vs* 5·0 [0·8] as shown in table 2 and figure 2. Growth in the zinc-supplemented stunted group was about 6% greater (not significant) than in their non-

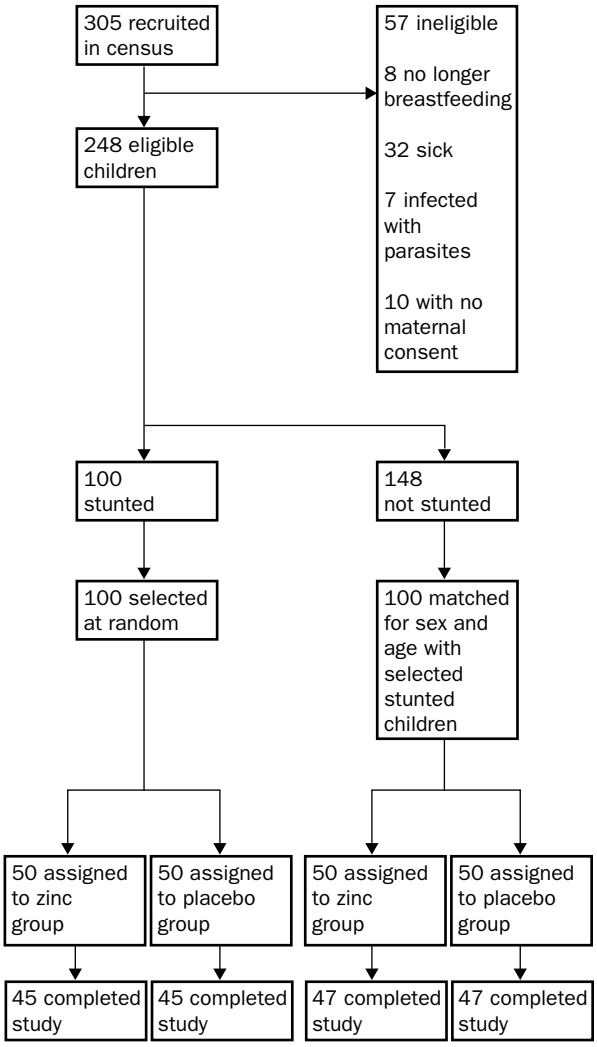

Figure 1: **Trial profile**

	Stunted		Non-stunted	
	Zinc	Placebo	Zinc	Placebo
Infants				
n (M/F)	45 (24/21)	45 (24/21)	47 (22/25)	47 (22/25)
Age (months)	9·5 (2·0)	9·7 (2·0)	9·3 (2·1)	9·2 (2·0)
Length (cm)*	64·6 (3·2)	64·4 (3·2)	69·6 (3·5)	69·9 (3·2)
Knee-heel lenth (mm)*	168 (12)	165 (11)	179 (11)	180 (10)
Weight (kg)*	6·6 (0·9)	6·4 (0·9)	7·5 (0·9)	7·4 (0·8)
Mid-upper-arm circumference (cm)†	12·3 (1·3)	12·1 (1·5)	13·1 (1·1)	12·9 (1·1)
Tricepts skinfold thickness (mm)†	5·3 (0·5)	5·3 (0·7)	5·6 (0·40)	5·6 (0·3)
Z-Scores				
Length-for-age*	−2·74 (0·59)	−2·87 (0·60)	−0·70 (0·76)	−0·57 (0·74)
Weight-for-age*	−2·46 (0·69)	−2·70 (1·01)	−1·35 (0·75)	−1·45 (0·88)
Weight-for-length‡	−0·48 (1·15)	−0·69 (1·24)	−1·00 (0·79)	−1·27 (0·98)
Mothers				
Age (years)	25·8 (5·9)	27·1 (6·4)	26·2 (5·3)	25·4 (5·3)
Length (cm)	154·7 (6·4)	153·3 (6·8)	154·3 (5·4)	153·4 (5·2)
Weight (kg)	47·3 (4·8)	46·4 (5·2)	47·7 (5·8)	44·9 (4·8)
Mid-upper-arm circumference (cm)	23·7 (3·3)	22·8 (1·9)	23·5 (2·3)	22·6 (1·9)
Triceps skinfold thickness (mm)	7·1 (1·8)	6·9 (1·8)	7·0 (1·9)	6·3 (1·8)
Body mass index (kg/m²)	19·8 (1·9)	19·8 (2·0)	20·0 (2·2)	19·1 (2·0)

Data are mean (SD).
Significant difference between stunted and non-stunted groups by independent *t* test: *p<0·001; †p<0·05; ‡p<0·01.

Table 1: **Characteristics at baseline of infants and mothers who completed the study**

stunted counterparts. The stimulatory effect of zinc in the stunted children was significantly greater than in the non-stunted children (p<0·0001). In fact, growth was sufficient in the zinc-supplemented stunted group to allow the LAZ scores to increase over the intervention period. No other groups could achieve this goal. Growth rates were constant over the 6 months of the study (figure 2). There were no differences in growth between boys and girls in each of the groups (data not shown). In addition, there were no differences between younger (<50th percentile, 9·75 months at the start of the intervention) and older infants except in the non-stunted group where the younger infants grew 10% more than their older counterparts. No differences in the change in knee-heel length over the period of the intervention were seen among the four groups. Zinc supplementation increased the weight gain over the 6 months by about 20% in the non-stunted group and by about 80% in the stunted group. The increase in weight gain in the zinc supplemented stunted group was sufficient to give a positive change in WAZ scores (table 2). The changes in mid-upper-arm circumference and triceps skinfold thickness tended to follow the weight changes but did not reach significance. Thus with those infants given the placebo, the stunted children deteriorated markedly in

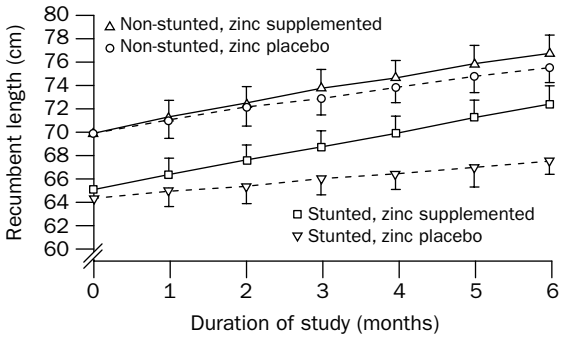

Figure 2: **Recumbent length during the intervention period**
Bars are SE of the mean.

	Stunted		Non-stunted	
	Zinc	Placebo	Zinc	Placebo
n (M/F)	45 (24/21)	45 (24/21)	47 (22/25)	47 (22/25)
Length (cm)	7·0 (1·0)*	2·9 (0·9)	6·6 (0·9)†	5·0 (0·8)§
Knee-heel length (mm)	21·3 (9·6)	21·4 (7·3)	21·9 (6·1)	19·8 (6·3)
Weight (kg)	1·73 (0·39)*	0·95 (0·39)	1·19 (0·39)‡§	1·02 (0·32)
Mid-upper-arm circumference (cm)	0·4 (1·3)	0·3 (1·4)	0·1 (1·2)	0·0 (1·1)
Triceps skinfold thickness (mm)	0·1 (1·3)	0·2 (1·1)	−0·2 (1·2)	−0·5 (0·3)‖
Z-Scores				
Length-for-age	0·14 (0·46)*	−1·24 (0·49)	−0·18 (0·32)*§	−0·74 (0·42)§
Weight-for-age	0·36 (0·49)*	−0·28 (0·56)	−0·31 (0·49)§	−0·46 (0·55)
Weight-for-length	−0·17 (0·55)†	−0·26 (0·54)	−0·43 (0·50)‡‖	−0·17 (0·47)§

Data are mean (SE).
Significant difference by independent *t* test: with comparable placebo group—*p<0·001; †p<0·01; ‡p<0·05; with comparable stunted group—§p<0·001; ‖p<0·05.

Table 2: **Changes in anthropometric variables during the intervention**

WLZ scores while with infants given zinc supplements, the stunted children deteriorated somewhat less in WLZ score.

It was not possible to take blood or hair samples before the intervention period but blood samples were obtained from 25 children from each group at the end of the intervention. Then the mean concentration of zinc in serum (p<0·0001) and hair (p=0·02) was lower in the placebo stunted group than in the zinc-supplemented stunted group (table 3). The groups supplemented with zinc had higher concentrations of zinc in serum and hair with the most pronounced differences being seen in serum zinc concentrations and between the stunted groups. The concentrations of zinc in serum and hair were positively associated with increased growth (r=0·59, p<0·0001, and r=0·18, p=0·04, respectively). Because the values for serum zinc concentration were not normally distributed, the rank-order correlation was also calculated for this relationship (r=0·59, p<0·0001). Boys tended to have higher serum zinc concentrations than girls (data not shown). Zinc supplementation reduced the incidence of anorexia, cough, diarrhoea, fever, and vomiting in the stunted children by more than half (p<0·0001) from 3·38 episodes per child in the placebo group to 1·56 episodes per child in the supplemented group (table 4). The incidence in both non-stunted groups was comparable to that of the zinc-supplemented stunted infants.

Discussion

This study clearly shows that zinc supplementation can halt the stunting process in stunted infants in rural Ethiopia (table 2, figure 2). This would appear to be due, at least in part, to improved appetite, as judged by recording episodes of anorexia, and reduced morbidity from gastrointestinal and respiratory disease (table 4).

	Stunted		Non-stunted	
	Zinc	Placebo	Zinc	Placebo
Serum				
n (M/F)	25 (13/12)	25 (13/12)	25 (11/14)	25 (11/14)
Serum zinc (mmol/L)	15·8 (3·7)*	11·0 (1·9)	17·9 (5·0)‡	14·5 (2·1)§
Hair				
n (M/F)	35 (17/18)	35 (17/18)	34 (16/18)	34 (16/18)
Hair zinc (mmol/g)	1·38 (0·42)†	1·16 (0·44)	1·57 (0·51)	1·43 (0·47)‖

Data are mean (SD).
Significant difference using independent *t* test: with comparable placebo group—*p<0·001; †p<0·05; ‡p<0·01; with comparable stunted group—§p<0·001; ‖p<0·05.

Table 3: **Concentration of zinc in serum and hair at the end of the intervention period**

	Stunted		Non-stunted	
	Zinc	Placebo	Zinc	Placebo
Symptoms				
Anorexia	3*	15	0	4
Cough	15*	32	12	21§
Diarrhoea	13†	40	14	19‖
Fever	27†	41	18	21‖
Vomiting	12‡	24	8	12
Total	70†	152	52	77‖
Total/child	1·56†	3·38	1·11	1·64‖

Significant difference by χ^2 analysis: with comparable placebo group—*p<0·05; †p<0·001; ‡p<0·01; with comparable stunted group—§p<0·05; ‖p<0·001.

Table 4: **Incidence of anorexia and selected illnesses during the 6 month intervention period**

During the 6-month intervention period, the LAZ score increased 0·14 thus suggesting that the catch-up growth during this period was 7% of the 2·04 LAZ deficit at baseline (LAZ of the non-stunted infants, –0·70 minus LAZ of their non-stunted counterparts, –2·74). Thus, although zinc supplementation can halt the process of stunting, it would take a long time to overcome the length deficit of the stunted infants. Earlier studies of infants and young children in subSaharan Africa[12,14,15] showed no effect of zinc supplementation on linear growth. In fact, the increase in LAZ reported here was greater than that observed in most if not all previous studies.[10] This can be attributed not only to the severity of the zinc deficiency (44% of the non-supplemented stunted group had serum zinc concentrations <10·5 μmol/L) but also to the dose (10 mg/day), frequency of dosing (6 days a week) and age of the infants (6–12 months at onset). In the non-stunted infants, zinc supplementation also resulted in increased linear growth compared with the placebo group, but the effect was less pronounced. This suggests that the beneficial effect of zinc supplementation on growth is related to the degree of stunting, and of zinc deficiency. In those infants not supplemented with zinc, the concentration of zinc in both serum and hair was lower in the stunted children than in their non stunted counterparts. Zinc supplementation of stunted children resulted in higher concentrations of zinc in both serum and hair bringing the concentrations in line with those in the non-stunted infants (table 3).

In this study, zinc supplementation also increased weight gain in the stunted children and, to a lesser extent, in the non-stunted children. In fact, the increase in WAZ over the 6 month intervention period in the stunted children (0·36) was 32% of the initial WAZ deficit (1·11) compared with 7% of the initial LAZ deficit. Such increases in weight have been reported earlier.[9–12]

Earlier studies have also reported changes in body composition after zinc supplementation.[11,12] Triceps skinfold thickness and mid-upper-arm circumference did not change in the present study. It may be that the supplementation period was too short to find any measureable effects on body composition.

No significant difference was observed in knee-heel length among the groups. This was surprising, as knee-heel length has been reported to be a sensitive and precise measurement of short-term linear growth in infants.[24] However, we found it very difficult to measure knee-heel length because the infants were somewhat restless. Thus the low reproducibility of our measurements is a more likely explanation than that the increase in length was restricted to growth in the femur and trunk.

The marked effect of zinc supplementation on reducing morbidity in stunted infants (table 4) has been observed earlier[16–20] and is analogous to the effects observed with vitamin A supplementation.[25] We are now beginning to understand the role of zinc in immune function.[26] Although some of the effects of zinc are related to its interaction with vitamin A,[27] zinc is unique in its affect on appetite.[16] In part, this could be related to taste perception[28] but is probably an adaptation to preventing the adverse effects of cell proliferation in the absence of sufficient zinc.[29]

The serum concentration of zinc is the most commonly used indicator of zinc status[30] although it is influenced by a variety of factors, such as infection, stress, pregnancy, and growth velocity, which limit its diagnostic value. However, as mentioned earlier, about 44% of the non-supplemented stunted group had serum zinc concentrations below 10·5 μmol/L. This proportion was zero in the zinc-supplemented stunted group as it was in both non-stunted groups. The concentration of zinc in hair is generally regarded as a good indicator of zinc status in children providing that care is taken with sampling, washing, and analysis. The effect of confounding factors such as season and age need to be taken into account when interpreting results. The proportion of infants with hair zinc concentrations below 1·07 μmol/g was higher in the non-supplemented stunted infants (43%) than in their non-stunted counterparts (21%). Zinc supplementation reduced these proportions to 26% and 11%, respectively.

That zinc concentration in both serum and hair can be good indicators of status is indicated by the positive association of linear growth with the concentration of zinc in serum and in hair in the supplemented stunted infants. Similar results have been reported earlier[7,31] but not in all studies.[11]

Our results provide clear evidence that stunted infants in rural Ethiopia are in need of zinc supplementation to halt the stunting process. It is also evident that prolonged zinc supplementation would be essential for adequate catch-up growth, but other nutrients may become a growth-limiting factor during supplementation. Zinc supplementation in these stunted infants also improved health possibly by stimulating appetite and reducing morbidity of several infant diseases. This is the first study showing the existence of a serious zinc deficiency in rural Ethiopia and the results ask for an immediate national public-health policy on zinc supplementation.

Contributors

The study was designed jointly by M Umeta, C E West, P Deurenberg, and J G A J Hautvast. The field work was executed under the supervision of M Umeta with a major input by J Haidar and supervisory visits by C E West and P Deurenberg. The data was analysed by M Umeta, C E West, and P Deurenberg. All authors contributed to writing the paper.

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