Effect of zinc supplementation on growth and body composition in children with sickle cell disease[1-3]

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ABSTRACT

Background: Poor growth and delayed maturation in children with sickle cell disease (SCD) may be due, in part, to mild zinc deficiency.
Objective: The objective was to determine the effects of zinc supplementation on growth and body composition in children with SCD.
Design: Forty-two prepubertal children (20 girls and 22 boys) aged 4–10 y with SCD-SS were randomly assigned to receive 10 mg elemental Zn/d in cherry syrup (zinc group) or cherry syrup alone (control group). The 2 groups were stratified by sex and initial height status. Dietary intakes were evaluated and anthropometric, high-precision knee-height, and plasma zinc measurements were made at baseline and at 3, 6, and 12 mo. Body composition was determined every 6 mo with dual-energy X-ray absorptiometry, and z scores for anthropometric variables were computed from national reference data. Longitudinal-mixed-effects analysis was used to test for differences between the groups over the 12-mo observation period.
Results: Thirty-eight children completed the study. No significant differences were observed at baseline. After 12 mo, the zinc group had significantly greater mean ($\pm$SE) increases in height (0.66 ± 0.29 cm/y), sitting height (0.97 ± 0.40 cm/y), knee height (3.8 ± 1.2 mm/y), and arm circumference z scores (0.27 ± 0.12 cm/y). Height-for-age and weight-for-age z scores decreased significantly by 0.11 ± 0.04 and 0.13 ± 0.05, respectively, in the control group but did not change significantly in the zinc group.
Conclusions: Prepubertal children with SCD-SS may have zinc deficiency and may benefit from zinc supplementation to improve linear growth and weight gain.   *Am J Clin Nutr* 2002;75:300–7.

KEY WORDS   Sickle cell disease, zinc supplementation, growth, body composition, children

INTRODUCTION

It has been recognized for several decades that children with sickle cell disease (SCD), especially those with SCD-SS, have poor growth and delayed maturation (1). Increased nutrient requirements, poor nutritional status, or both have been documented in children with SCD (2–6). These findings suggest that chronic undernutrition contributes to growth failure and delayed development. Nevertheless, there have been virtually no nutrition intervention studies in children with SCD to address this poten-

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tially remediable problem. Zinc deficiency has been suggested as a contributing factor to growth failure in SCD on the basis of case reports and cross-sectional studies (6–10). In a large cross-sectional survey of plasma zinc status in children with SCD-SS, low growth status, low fat-free mass, and delayed skeletal maturation were associated with low plasma zinc concentrations (6). Zinc supplementation has improved linear growth in otherwise healthy non-SCD children with mild growth failure (11–14). In adults with SCD given zinc supplements, improved immune function (fewer illnesses and increased natural killer cell activity) and red blood cell integrity (reduced number of irreversibly sickled cells and increased RBC survival) were also observed (15–18). The purpose of this study was to determine the effect of zinc supplementation on growth and body composition in prepubertal children with SCD-SS over 12 mo.

SUBJECTS AND METHODS

Subjects

Forty-two children (20 girls and 22 boys) with a mean ($\pm$SD) age of 7.1 ± 1.6 y and SCD-SS were recruited from the Comprehensive Sickle Cell Center at The Children's Hospital of Philadelphia (CHOP). Subjects were considered eligible if they were aged 4.0–10.9 y, had no history of stroke or long-term transfusion therapy, and had a stature <2 SDs above the median for age and sex according to the growth charts of the National Center for Health Statistics (NCHS) (19). Children were excluded

if they had chronic medical conditions other than SCD, had a recent history of poor clinic attendance (missed >3 clinic appointments in the previous year), or were taking hydroxyurea or dietary supplements containing zinc.

Potential subjects from the Comprehensive Sickle Cell Center's patient list who met the eligibility criteria were assigned a random number to establish an unbiased order of contacting and recruiting subjects. Families were initially contacted by a member of the Hematology Care Team and then by a member of the Research Study Team for final determination of eligibility and enrollment. Children who wished to participate but were taking zinc-containing dietary supplements had to agree to refrain from taking the dietary supplements for the duration of the study. These children were considered eligible 1 mo after discontinuing the zinc-containing dietary supplement. None of the children were taking medications known to adversely affect growth, dietary intake, or nutritional status. Children at the Comprehensive Sickle Cell Center are routinely prescribed penicillin prophylaxis and folate supplements.

The protocol was approved by the Committee for the Protection of Human Subjects of the Institutional Review Board at CHOP. Informed, written consent was obtained from the parent or guardian of each subject, and assent was obtained from each subject. Data were collected during an outpatient visit to the General Clinical Research Center and the Nutrition and Growth Laboratory at CHOP.

Study design

The trial was designed as a 12-mo, randomized, placebo-controlled study of zinc supplementation in children aged 4–10 y with SCD-SS. After eligibility was determined, subjects were randomly assigned to receive a formulation providing 10 mg elemental Zn/d in 5 mL cherry syrup (zinc group; $n = 20$) or 5 mL cherry syrup alone (control group; $n = 22$) prepared by the research pharmacy at CHOP. This dose was based on the recommended dietary allowance (20) for zinc at the time the study began. Randomization was stratified according to age group [younger (aged 4.0–6.9 y) compared with older (aged 7.0–10.9 y) children], sex, and initial height status [taller (height-for-age z score ≥ -0.15) compared with shorter (height-for-age z score < -0.15) children] to ensure comparability of groups in these important baseline characteristics. Because of the limited number of children at the CHOP Comprehensive Sickle Cell Center who met the inclusion criteria for certain strata (eg, for age and height), there was an overrepresentation of younger, taller girls and younger, shorter boys available for randomization. The children were evaluated 3, 6, and 12 mo after initiation of zinc supplementation.

Methods

The subjects underwent a complete anthropometric examination at each visit (baseline and 3, 6, and 12 mo) with the use of research-quality anthropometric equipment that was calibrated daily. Height and sitting height (both accurate to within 0.1 cm) were measured with a stadiometer (Holtain, Crymych, United Kingdom), weight (within 0.1 kg) was measured with a digital electronic scale (Scaletronix, Wheaton, IL), upper arm circumference (within 0.1 cm) was measured with the use of nonstretchable tape, and skinfold thicknesses (within 0.1 mm) were measured at the biceps, triceps, subscapular, and suprailiac sites with the use of a skinfold caliper (Holtain). All measurements were made by a highly trained research anthropometrist in triplicate according to the methods described by Lohman et al (21), and the mean values were used in the analysis. Knee height (to within 0.01 mm) was measured with a knee-height measuring device (22) that measures the length of the lower leg from the heel to the superior surface of the knee. Five replicate measures were obtained and the SD was checked to ensure compliance with the technique. If the SD was >0.5 mm, the 5 measures were repeated. The mean of the best set of measurements was used in the analysis.

Height, weight, and body mass index [BMI; weight (kg)/height (m)^2] were compared with data from the newly revised US growth charts (23) for computation of z scores (SD scores). Upper arm fat area (UAFA) and upper arm muscle area (UAMA) were calculated from arm circumferences and triceps skinfold thicknesses; z scores for these anthropometric measures were calculated with the use of NCHS reference data (24, 25).

Sexual maturation was assessed at each visit with a self-assessment questionnaire (26) by children aged ≥ 9 y. The questionnaire consisted of pictorial representations and written descriptions of the Tanner stages of sexual maturation (27). The questionnaire was explained to the children, and the children (sometimes with parental assistance) completed the questionnaire in a private examination room while changing clothes for the anthropometric examination.

Body composition was assessed with the use of 2 methods. Whole-body fat-free mass (FFM), bone mineral content, bone mineral density, fat mass (FM), and percentage body fat (%BF) were measured by dual-energy X-ray absorptiometry (DXA) with the use of a QDR2000 bone densitometer (Hologic, Inc, Bedford, MA). Scans were performed at baseline and 6 and 12 mo after supplementation began with the use of standard positioning techniques in the array mode; enhanced whole-body software version 5.73A (Hologic Inc) was used to analyze the results. Subjects wore standard hospital scrubs at all times to eliminate any possible effect of clothing on the body-composition assessments. Body composition was also assessed on the basis of anthropometric measures obtained at each visit. FFM, FM, and %BF were estimated from skinfold thicknesses with the use of the equations of Brook (28).

Dietary intake was assessed by conducting three 24-h dietary recall interviews at baseline and 3, 6, and 12 mo after the supplementation began. The interviews were conducted by a trained interviewer at the time of each visit and then twice by telephone within a 2-wk period. A food-portion booklet was provided to each family to assist in estimating portion sizes. Dietary information was collected on 2 weekdays and 1 weekend day at each time point and analyzed by a research nutritionist at the CHOP General Clinical Research Center using the MINNESOTA NUTRITION DATA SYSTEM (version 4.01/29; University of Minnesota, Minneapolis). The results of the three 24-h dietary recalls from each visit were averaged.

Fasting blood samples were collected at each visit for measurement of plasma zinc concentrations. Children were instructed to not take their supplement on the morning of the study visit so that the blood values would not be influenced by absorption of a recent dose of supplement. All specimens were collected in the morning in trace element–free evacuated tubes, stored in zinc-free Eppendorf tubes, and frozen at $-70°$C until analyzed. Frozen specimens were shipped on dry ice to the Pediatric Nutrition

Laboratory at the University of Colorado Health Sciences Center for measurement of zinc concentrations. All longitudinal samples for an individual subject were analyzed in the same batch with the use of a model 2380 atomic absorption spectrometer fitted with a background deuterium lamp (Perkin-Elmer, Norwalk, CT) (29). A separate blood sample was drawn at baseline for measurement of serum copper to ensure that the children were not copper deficient.

Compliance with the study protocol was assessed with the use of several techniques. First, all subjects were provided with monthly calendars and child-friendly stickers to place on the calendar to denote the days on which the supplement was actually taken. Second, the families were asked to return the cherry-syrup containers every 3 mo in exchange for new bottles for the next 3 mo; residual volumes in the used bottles were measured. Last, information about the frequency of supplement use was obtained by interview during each visit. This information was reviewed by the research team and the level of compliance was ranked as follows: supplement taken ≥75% of the time, supplement taken <75% of the time, or uncertain of the level of compliance.

Statistical analysis

Statistical analyses were conducted with the use of STATA 6.0 (Stata, Inc, College Station, TX). Baseline comparisons of continuous variables were performed with Student's t test and of categorical variables with the chi-square test. Longitudinal-mixed-effects (LME) analysis (30) was used to determine differences in longitudinal data between the zinc and control groups over time. These analyses were made with the use of the intention-to-treat model, so all subjects were included regardless of adherence to the study protocol. LME analysis is similar to multiple linear regression analysis in that it allows for multiple observations per subject. The approach has several additional advantages; it allows for unequal intervals between visits, uses data from all subjects (even when some study visits were missed), and accommodates both random and fixed effects. LME analysis was used to examine the effect of zinc on growth over the 12-mo study period. Initial age was entered into the model to account for the expected size differences in children. Time (in y) was entered into the model because all children grew over the 12-mo study period. For body size measures such as height, the coefficient for time is expected to be positive and significant. For age-adjusted measures such as height-for-age z score, the coefficient for time is expected to be nonsignificant if children maintain their growth status over time. Models that included sex were examined, and sex was unrelated to the patterns of growth. The interaction term (group × time) was the term of interest because it indicates the difference in the rate of growth between the groups (control group = 0; zinc group = 1) over time.

RESULTS

Sample characteristics

Younger, taller girls and younger, shorter boys were overrepresented in the randomization process. However, none of the baseline measures were significantly different between the sexes (**Table 1**). Of the 42 children enrolled, 38 completed the 12-mo study. Two children moved away from the geographic region, and 2 families refused to complete the study. All available information on all children was used in the analyses conducted. There were a total of 151 observations from the visits at baseline and 3, 6, and 12 mo because not all of the children completed the 4 examinations. Most of the baseline measurements were similar between the 4 children who did not complete the study and the rest of the group; however, the 4 children who did not complete the study had significantly lower height-for-age z scores (−1.52 compared with −0.22; $P = 0.01$). All children were prepubertal at enrollment. One boy and one girl had entered Tanner stage 2 by the end of the study. There were no adverse events related to participation in the study, although 2 children did not like the taste of the cherry syrup.

Baseline zinc and copper concentrations

Serum copper was measured at baseline to evaluate copper status and to confirm that none of the subjects were copper deficient. None of the subjects had low copper concentrations. At baseline, 6 subjects (15% of the sample) had low plasma zinc concentrations (<10.7 μmol/L). Low plasma zinc was significantly more common in the boys than in the girls ($P = 0.001$, chi-square test) but was not associated with other measures.

Compliance with the study protocol

Sixty-two percent of the subjects complied with the study protocol ≥75% of the time, 17% did not take the supplement regularly or dropped out of the study, and the remaining subjects did not provide enough information to assign a category of compliance status. There were no significant differences in compliance between the zinc and the control groups, nor were there any other characteristics associated with the compliance category (eg, age, sex, and height-for-age, weight-for-age, and BMI-for-age z scores). In the zinc group, full compliance with the study protocol was associated with increased plasma zinc concentrations at the 12-mo visit only (11.0 compared with 13.2 μmol/L; $P = 0.04$). Compliance was included in the LME models described below, but not in the final LME models because it was not a significant predictor.

Growth

Results of the LME models that tested for differences in the rate of growth between the zinc and control groups are shown in **Table 2**. Age at entry to the study and time were significant, as is expected for growing children. The models also showed that initial group differences in growth were not significant. The interaction term (group × time) indicated significantly increased rates of growth in height, sitting height, and knee height in the zinc group. For example, the children in the zinc group grew 0.66 cm more in height than did those in the control group over the 12-mo study period. Group differences in knee height predicted by the LME model are illustrated in **Figure 1**. Zinc supplementation had no significant effect on BMI (data not shown). Within the subgroup of 24 children whose initial height status was low (height-for-age z score < −0.15), the children in the zinc group grew 1.3 cm more in height than did those in the control group ($P < 0.0001$).

Because expected rates of growth vary by age and sex across the age range of our subjects (ie, 4.0–10.9 y), the use of growth z scores provides an indication of how well children maintained their growth status compared with the national growth norms. Height-for-age and weight-for-age z scores were not significantly different between the zinc and control groups ($P = 0.07$ and $P = 0.09$, respectively). When the groups were analyzed separately

TABLE 1
Growth and body-composition characteristics at baseline and 12 mo[1]

	Baseline		12 mo	
	Control group (n = 22)	Zinc group (n = 20)	Control group (n = 20)	Zinc group (n = 18)
Age (y)	7.4 ± 1.8	6.8 ± 1.5	8.5 ± 1.8	7.8 ± 1.5
Weight (kg)	22.5 ± 5.7	20.6 ± 4.2	25.0 ± 6.2	23.5 ± 5.0
Height (cm)	121.9 ± 11.4	117.4 ± 10.8	128.4 ± 11.0	124.4 ± 10.7
BMI (kg/m^2)	14.9 ± 2.2	14.8 ± 0.8	15.0 ± 2.3	15.0 ± 1.1
z Scores				
Height-for-age	−0.28 ± 1.04	−0.42 ± 1.02	−0.23 ± 1.14	−0.35 ± 1.03
Weight-for-age	−0.74 ± 1.22	−0.71 ± 0.86	−0.77 ± 1.21	−0.68 ± 1.00
BMI-for-age	−0.91 ± 1.31	−0.57 ± 0.62	−1.03 ± 4.5	−0.65 ± 0.76
Sitting height (cm)	63.2 ± 4.8	60.4 ± 4.6	66.0 ± 2.5	64.3 ± 4.3
Knee height (mm)	205.9 ± 43.6	193.4 ± 43.9	206.3 ± 43.2	195.9 ± 43.1
Arm circumference (cm)	17.0 ± 2.4	16.5 ± 1.2	17.6 ± 3.1	17.5 ± 1.4
Triceps skinfold thickness (mm)	6.9 ± 3.1	7.8 ± 3.1	6.6 ± 5.0	7.2 ± 2.4
Arm muscle area (cm^2)	17.8 ± 3.9	15.9 ± 3.3	19.5 ± 3.7	18.6 ± 2.9
Arm fat area (cm^2)	5.8 ± 3.7	5.9 ± 2.2	5.6 ± 1.16	5.9 ± 2.3
z Scores				
Arm circumference	−1.12 ± 1.19	−1.19 ± 0.70	−1.18 ± 1.16	−0.93 ± 0.77
Triceps skinfold thickness	−1.05 ± 0.92	−0.67 ± 1.11	−1.15 ± 0.78	−0.86 ± 0.75
Upper arm muscle area	−0.66 ± 1.04	−0.97 ± 0.77	−0.62 ± 1.14	−0.54 ± 0.62
Upper arm fat area	−1.05 ± 1.00	−0.80 ± 0.90	−1.17 ± 0.81	−0.92 ± 0.75
Body composition derived from skinfold thicknesses				
Percentage body fat (%)	12.5 ± 5.6	15.0 ± 6.0	11.5 ± 5.4	12.4 ± 4.1
Fat-free mass (kg)	19.5 ± 4.0	17.6 ± 4.0	21.9 ± 4.5	20.5 ± 4.0
Fat mass (kg)	3.0 ± 2.4	3.1 ± 1.3	3.1 ± 2.5	3.0 ± 1.4
Body composition determined by DXA				
Percentage body fat (%)	14.8 ± 5.1	16.0 ± 3.9	15.5 ± 5.7	17.0 ± 4.9
Fat-free mass (kg)	18.7 ± 4.4	17.0 ± 3.4	20.6 ± 4.5	19.0 ± 3.8
Fat mass (kg)	3.4 ± 2.1	3.3 ± 1.2	4.0 ± 2.7	4.0 ± 1.8

[1] $\bar{x}$ ± SD. Differences between groups were not significant. DXA, dual-energy X-ray absorptiometry.

(**Figure 2**), height-for-age and weight-for-age z scores declined significantly in the control group (P = 0.004 and P = 0.005, respectively) but did not change significantly in the zinc group over the 12-mo study period.

Nutritional status and body composition

Zinc supplementation had no significant effect on the fat-related measures triceps skinfold thickness, UAFA, FM, and %BF (**Table 3**). The change in arm circumference z score was significantly greater and in the UAMA z score was marginally significantly greater in the zinc group than in the control group. The effect of zinc supplementation on FFM derived from skinfold thicknesses was not significant in the entire sample; however, when girls were analyzed separately, zinc supplementation was shown to significantly increase FFM by 0.87 kg (P = 0.008). The effect of zinc supplementation on FFM measured by DXA was not significant, but the trend was similar to that for FFM estimated from skinfold thicknesses. Note that there were fewer DXA than anthropometric measurements as per the study protocol.

Dietary intake

Baseline dietary intakes were not significantly different between the zinc and control groups. Mean dietary intakes of energy, protein, and zinc for the entire sample are shown in **Table 4**. The mean dietary zinc intake for children with SCD was less than the 1989 recommended dietary allowance (20) of 10 mg/d but exceeded the newly established dietary reference intakes (31) for zinc of 5 mg/d for 4–6-y-olds and 8 mg/d for 7–10-y-olds. The

LME analysis showed no significant trends over time in changes in energy, protein, or zinc intakes or in differences between the zinc and control groups (results not shown).

DISCUSSION

The etiology of zinc deficiency in SCD is not known. Possible mechanisms include increased requirements secondary to erythrocyte hemolysis, chronic inflammation, increased protein turnover and urinary zinc losses, inadequate zinc intake because of a poor diet, and inadequate net intestinal absorption. Possible zinc deficiency is suggested by the poor growth and delayed skeletal and sexual maturation commonly observed in children with SCD (1, 32–36).

At birth, infants with SCD-SS are normal in size, but significant growth deficits become apparent by 5 y of age (37). In a recent survey of 63 children with SCD in Baltimore, 25% had height, weight, and weight-for-height values that were less than the 5th percentile of the NCHS standards (38). The frequency of impaired growth increased with age, although no sex differences were found. However, others reported more severe growth deficits in boys than in girls with SCD (35, 39). In the present study, groups were purposely balanced by sex and initial growth status. Although sex was not a significant predictor of zinc-related growth response in the LME models, more boys than girls had clinically low plasma zinc concentrations at baseline.

Zinc supplementation has improved linear growth in otherwise healthy, non-SCD children with mild growth failure in

TABLE 2
Longitudinal-mixed effect models of the effect of zinc supplementation on growth in all subjects[1]

	Coefficient	SE	P	No. of observations
Height (cm)				
Initial age	5.77	0.53	<0.001	151
Group	−0.74	1.73	0.667	151
Time	5.32	0.20	<0.001	151
Group × time	0.66	0.29	0.025	151
Intercept	79.26	4.08	<0.001	151
Weight (kg)				
Initial age	2.30	0.35	<0.001	151
Group	−0.33	1.15	0.773	151
Time	2.11	0.18	<0.001	151
Group × time	0.39	0.26	0.137	151
Intercept	5.45	2.72	0.045	151
Sitting height (cm)				
Initial age	2.18	0.25	<0.001	151
Group	−1.43	0.85	0.090	151
Time	2.41	0.28	<0.001	151
Group × time	0.97	0.40	0.016	151
Intercept	47.12	1.96	<0.001	151
Knee height (mm)				
Initial age	22.88	2.11	<0.001	148
Group	0.99	6.89	0.886	148
Time	18.89	0.83	<0.001	148
Group × time	3.81	1.22	0.002	148
Intercept	34.09	16.28	0.387	148

[1] Control group = 0; zinc group = 1.

FIGURE 1. Illustration of the longitudinal-mixed-effects model for growth in knee height. The model predicts growth in knee height over time [knee height = 34.09 + 22.88 × age + 0.99 × group (0 = control group; 1 = zinc group) + 18.89 × time + 3.81 × group × time] using the variables in Table 2. The mean age of the children in the study (7.1 y) was used in the prediction model to illustrate the difference between groups in knee height growth during the 1 y supplementation period.

North America (11–13), Guatemala (14), Chile (40), Ecuador (41), and Ethiopia (42). A recent meta-analysis of 25 zinc supplementation trials conducted in children between 1969 and 1996 (43) showed a small but significant improvement in height (0.22 SD) with zinc supplementation ($P < 0.0001$), especially in those children with the greatest degree of stunting (−2.0 SD) and the lowest baseline plasma zinc concentrations. Similarly, in the present study, multiple measures of linear growth showed improvements in the zinc group, although the initial plasma zinc concentration was not a significant predictor of growth response. Our sample was too small to determine whether the degree of stunting was associated with growth rates. However, the subgroup of shorter children showed an even larger response to zinc supplementation than did the zinc group as a whole. In children with SCD, nutrition-related growth failure may occur in those who are not stunted (ie, −2.0 SD) but who have not achieved their genetic potential for growth.

Plasma zinc may not be a sensitive indicator of growth-limiting zinc deficiency, especially in patients with SCD for whom hemolyzed red blood cells may contaminate plasma samples. A measurable effect on growth in a controlled study is considered to indicate preexisting growth-limiting zinc deficiency that has been at least partially corrected by the provision of zinc supplements (11, 31). In the present study, there were no differences in growth related to baseline plasma zinc concentrations. However, zinc supplementation was associated with greater linear growth and other indicators of nutritional status. This finding suggests that the gradual growth failure in children with SCD-SS may be preventable with adequate nutritional care, particularly zinc supplementation.

In the present study, 10 mg elemental Zn/d was provided as a supplement. Further study is required to determine whether this
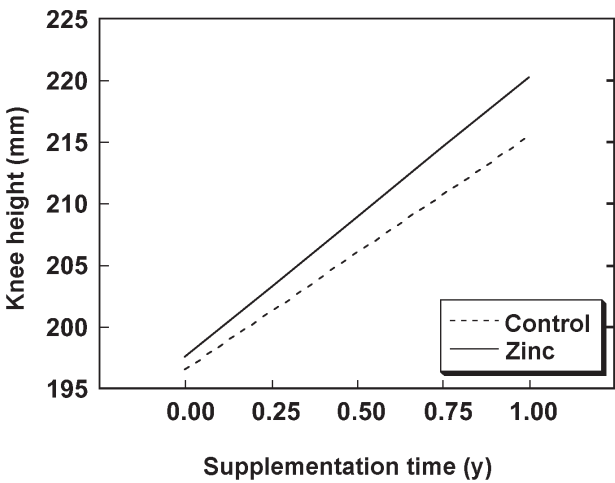
is the optimal amount of supplemental zinc to prevent zinc-related growth failure in prepubertal children with SCD. Although a randomized, placebo-controlled study of zinc supplementation in SCD has not been conducted previously, abnormalities in zinc nutriture in patients with SCD have been reported on the basis of low plasma zinc concentrations (6, 8, 9, 44–48), low red blood cell zinc concentrations, and decreased activity of the zinc-dependent enzyme carbonic anhydrase in the presence of normal plasma zinc concentrations (10, 49). Depressed alkaline phosphatase activity, testosterone concentrations (50), and retinol binding protein (8) reported in patients with SCD suggest alterations in zinc-dependent proteins.
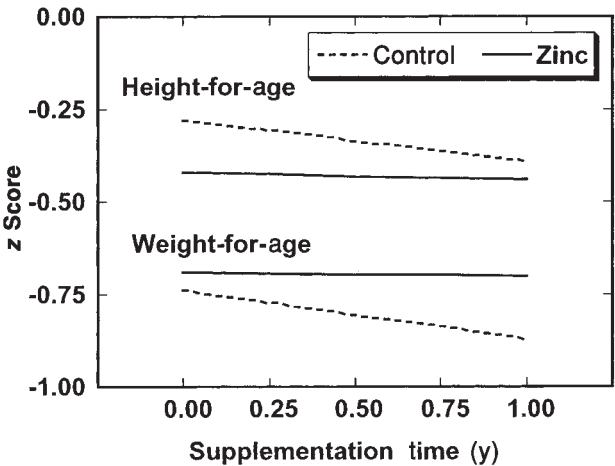

FIGURE 2. Illustration of the changes in growth status in the zinc and control groups. Height ($P = 0.004$) and weight ($P = 0.005$) z scores decreased significantly over time, but did not change significantly in the zinc group.

TABLE 3
Longitudinal-mixed effect models of the effect of zinc supplementation on body composition in all subjects or girls only[1]

	Coefficient	SE	P	No. of observations
Arm circumference z score				
All subjects (n = 42)				
Group	0.00	0.30	0.992	151
Time	−0.03	0.09	0.703	151
Group × time	0.27	0.12	0.030	151
Intercept	−1.17	0.20	<0.001	151
UAMA z score				
All subjects (n = 42)				
Group	−0.19	0.27	0.477	151
Time	0.05	0.11	0.658	151
Group × time	0.29	0.15	0.065	151
Intercept	−0.67	0.19	<0.001	151
FFM_{SF}				
All subjects (n = 42)				
Initial age	1.99	0.24	<0.001	150
Group	−0.46	0.79	0.560	150
Time	2.08	0.17	<0.001	150
Group × time	0.26	0.24	0.291	150
Intercept	4.87	1.85	0.008	150
Girls only (n = 20)				
Initial age	1.96	0.20	<0.001	72
Group	−0.49	0.65	0.451	72
Time	1.70	0.23	<0.001	72
Group × time	0.87	0.32	0.008	72
Intercept	5.23	1.47	<0.001	72
FFM_{DXA}				
All subjects (n = 42)				
Initial age	1.93	0.24	<0.001	113
Group	−0.41	0.80	0.606	113
Time	1.59	0.14	<0.001	113
Group × time	0.15	0.21	0.481	113
Intercept	4.47	1.88	0.017	113
Girls only (n = 20)				
Initial age	1.71	0.19	<0.001	52
Group	−0.54	0.62	0.384	52
Time	1.23	0.14	<0.001	52
Group × time	0.32	0.20	0.118	52
Intercept	5.56	1.42	<0.001	52

[1] UAMA, upper arm muscle area; FFM_{SF}, fat-free mass estimated by using the skinfold-thickness equations of Brook (28); FFM_{DXA}, fat-free mass measured by dual-energy X-ray absorptiometry.

Previous reports have linked zinc to growth abnormalities in children with SCD (6, 8, 10, 46). Relative to normal plasma zinc concentrations, low plasma zinc concentrations are associated with poorer growth status (ie, a height-for-age z score less than the 5th percentile) (8); significantly lower height, weight, elbow breadth, upper arm muscle mass, and FFM; and delayed skeletal age (6). However, one study failed to show an association between low serum zinc concentrations and growth (48). A small, randomized trial of zinc supplementation in 10 male subjects aged 14–17 y with SCD and growth retardation showed significantly improved growth and skeletal maturation over 1 y (51). The effect of zinc supplementation on prepubertal children with SCD has not been evaluated.

The importance of zinc in tissue synthesis also has ramifications for the relative size of body compartments. Induction of zinc deficiency in animal models resulted in reduced skeletal growth and maturation (52), reduced muscle mass (53), and a higher proportion of body weight as fat (54). In zinc supplementation studies in children, increased UAMA has been reported in addition to increased weight or linear growth (14, 55, 56). In the present study, improvements in FFM and related measures (eg, UAMA z score) were not definitively associated with zinc supplementation. A larger sample size and longer observation period may be required to determine the effect of zinc supplementation on body composition in children with SCD. There was no association of zinc supplementation or baseline zinc status with fat stores, which is consistent with the literature from animal models described above.

Inadequate zinc intake is another possible mechanism of zinc malnutrition in SCD. Poor appetite is frequently reported by care providers of children with SCD, and anorexia associated with febrile or painful episodes is common (57, 58). However, the few studies of nutrient intake in children with SCD are based on small sample sizes (59) and, therefore, have limited generalizability. In a comparison of 9 children with SCD and control subjects, lower red blood cell zinc was not associated with differences in zinc intake (59). Similarly, Phebus et al (8) documented lower serum zinc concentrations in 80 children with SCD than in 44 healthy control subjects aged 3–18 y and found no significant differences in dietary zinc intakes. In the present study we found no significant association between reported dietary zinc intake and plasma zinc concentrations at baseline. Children in the zinc group had greater growth rates than did those in the control group, but there were no significant differences in dietary intakes of energy, protein, or zinc between the 2 groups. In contrast, increased appetite and food consumption have been observed in healthy children after zinc supplementation (60).

In summary, this study showed an improved rate of linear growth in prepubertal children with SCD-SS whose diets were supplemented with 10 mg elemental Zn/d as zinc sulfate in a randomized, placebo-controlled study. Although the etiology of mild zinc deficiency in SCD is unknown, the significant declines in height-for-age and weight-for-age z scores observed in the control group, which are typical of the gradual growth failure that occurs in children with SCD, suggest that children with SCD are unable to meet their zinc requirements through diet. Zinc supplementation should be considered in these children. Further

TABLE 4
Mean dietary intakes of energy, protein, and zinc in children with sickle cell disease[1]

	Girls		Boys	
	3–5 y (n = 6)	6–11 y (n = 14)	3–5 y (n = 5)	6–11 y (n = 17)
Energy (kJ /d)	7201 ± 364	6460 ± 490	5837 ± 515	7360 ± 448
Protein (g/d)	60 ± 3	50 ± 6	41 ± 5	53 ± 3
Zinc (mg/d)	10.4 ± 1.5	8.1 ± 1.2	6.0 ± 0.8	9.6 ± 0.8

[1] $\bar{x}$ ± SE. Differences between groups were not significant.

studies are needed to confirm these findings concerning growth and body composition and to determine the long-term effects of zinc supplementation on other aspects of health and well-being (eg, sexual and skeletal maturation, appetite, immune function, SCD-related illness, red blood cell integrity, and cognitive function) in patients with SCD.

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