Body composition in children with sickle cell disease[1–3]

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ABSTRACT

Background: Impaired growth, poor nutritional status, and delayed skeletal and sexual maturation are common in children with sickle cell disease (SCD), yet the nature of associated body-composition deficits has not been fully described.

Objective: The objective was to assess growth, nutritional status, and body composition in 36 African American children with type SS SCD (20 females and 16 males) and 30 healthy control children (15 females and 15 males) of similar age (5–18 y) and ethnicity.

Design: Height, weight, bone age, pubertal status, skinfold thickness, and arm circumference were assessed. Height and weight were converted to *z* scores by comparison with national reference data and skinfold-thickness measurements were converted to *z* scores by comparison with African American–specific reference data. Fat-free mass (FFM) and fat mass (FM) were estimated by using 4 methods. Prepubertal children, pubertal males, and pubertal females were analyzed separately.

Results: Relative to the control subjects and to a national sample, children with SCD had significantly lower *z* scores for weight, height, arm circumference, and upper arm fat and muscle areas. Relative skeletal maturation was significantly delayed. After adjustment for age, children with SCD had significantly lower FM (prepubertal children and pubertal males only) and FFM (all 3 groups).

Conclusions: Children with SCD have impaired growth, delayed puberty, and poor nutritional status. Low *z* scores for upper arm fat area indicate deficits in fat (energy) stores, and low FFM coupled with low upper arm muscle area indicate muscle wasting and low protein stores. These body-composition abnormalities suggest that the nutritional needs of the African American children with SCD were not being met. *Am J Clin Nutr* 2002;76:218–25.

KEY WORDS Sickle cell disease, growth, nutritional status, body composition, children, African Americans

INTRODUCTION

Poor growth and nutritional status in combination with delayed sexual and skeletal maturation are common clinical features of sickle cell disease (SCD), particularly in persons with type SS SCD. Accordingly, the growth of tissue compartments is likely to be altered in children with SCD and has not been fully described. In addition, metabolic studies have indicated elevated resting energy expenditure and elevated protein turnover associated with SCD (1–6), both of which may have negative effects on the accretion of body weight, particularly fat-free mass (FFM). The nature and magnitude of body-compartment deficits are important in understanding the nutritional needs of children with SCD and for monitoring the outcomes of nutrition interventions.

Body composition in children and adolescents traditionally has been difficult to measure with accuracy, partly because of age-associated differences in the composition of body compartments, such as the bone mineral component of FFM, or in the distribution of total body water (TBW). The most commonly used methods use a 2-compartment model that divides the body into FFM and fat mass (FM). Inherent in these models are systematic biases because of varying assumptions about the composition of FFM. Possible sources of bias include altered tissue composition in children with SCD (eg, lower bone density; 7), ethnic differences between the study population and the populations from whom the prediction equations were developed, and problems inherent in measuring body composition in children (eg, variations in the timing of sexual maturation). These sources of bias are particularly important in children with chronic disease, for whom several sources of bias may operate simultaneously (eg, delayed puberty associated with deficiencies of gonadal secretion of steroids in combination with low bone density). Therefore, measurements are somewhat method dependent (8). In the present study, body composition was measured with the use of 4 different methods to avoid the bias from a single method.

SUBJECTS AND METHODS

Subjects

Subjects with SCD were recruited from among the children and adolescents aged 5–18 y cared for at the Comprehensive

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Sickle Cell Center at The Children's Hospital of Philadelphia. All children with SCD who were seen in the clinic and who met the following criteria were invited to participate: type SS SCD, no history of stroke, no hydroxyurea or long-term transfusion therapy, and no hospitalizations or intercurrent illnesses within 2 wk of the study. Healthy control subjects were recruited from community sources and were mainly referred by subjects with SCD and hospital clerical staff; were of comparable age, sex, and ethnicity; had negative sickle cell trait status; and had weights and heights above the 5th and below the 95th percentiles compared with the National Center for Health Statistics (NCHS) reference. None of the children were taking medications known to affect growth or nutritional status. All subjects were of African or African American ancestry on the basis of parental report or self-report. The protocol was approved by the Committee for the Protection of Human Subjects Internal Review Board at The Children's Hospital of Philadelphia. Informed, written consent was obtained from the parent or guardian of each subject, and assent was obtained from the subject. Data were collected during a 24-h overnight admission to the General Clinical Research Center.

Growth, maturation, and assessment of nutritional status

Growth was assessed with the use of standard methods (9, 10) as previously described (4). Height and weight measurements were compared with NCHS reference standards for age and sex (11). Standardized scores (*z* scores) were calculated by using a computerized program (12); *z* scores were calculated as the difference between the observed value and the median value for the reference population, divided by the SD of the population, with the use of age- and sex-specific values for the reference population.

Skeletal maturation was assessed by one observer (BSZ) from a radiograph of the left hand and wrist and scored according to the method of Tanner et al (13). Skeletal age was based on the 20 bone score, and relative skeletal maturation was calculated as skeletal age minus chronologic age. Sexual maturation was evaluated by a self-assessment pictorial questionnaire (14) illustrating the 5 stages of development as described by Tanner (15). In a previous study, this self-assessment questionnaire showed excellent agreement with physician assessment in children with Crohn disease (16). A composite pubertal score was calculated as the mean of individual scores for breast and pubic hair development in females and for genital and pubic hair development in males.

The assessment of nutritional status was based on triceps and subscapular skinfold thicknesses and midupper arm circumference (MUAC). Measures of MUAC were combined with the triceps skinfold thickness to calculate upper arm fat area (UAFA) and upper arm muscle area (UAMA) (17, 18). Elbow breadth was measured as an indicator of frame size. We computed *z* scores for these nutritional status indexes (elbow breadth, MUAC, triceps skinfold thickness, subscapular skinfold thickness, UAMA, and UAFA) on the basis of African American reference data collected in the first and second National Health and Nutrition Examination Surveys (18).

Body composition

Whole-body measures of FFM, FM, and percentage body fat (%BF) were estimated from published age- and sex-specific prediction equations that use skinfold-thickness measurements at 2 (2SF) (19) or 4 (4SF) (20, 21) sites. Body composition was also measured by using the method of total-body electrical conductivity (TOBEC, HA-2 instrument; EM-Scan, Springfield, IL; 22–24). The TOBEC estimates whole-body FFM, FM, and %BF based on the conductive properties of the water and electrolytes in the body. Subjects were measured in a fasted state in the morning in light clothing and socks. Five replicate measurements were taken and the average was used in the analysis. Measurements for which motion artifact or poor cooperation were noted were excluded from the average (24).

In addition, body composition was calculated from TBW (25) with the isotope-dilution method (26). A urine sample was collected from each subject on admission for a baseline measurement of the enrichment of the naturally occurring stables isotopes ^{2}H and ^{18}O. The subjects were administered 0.3 g $H_2{}^{18}O$/kg and 0.14 g $^{2}H_2O$/kg estimated body water, respectively. After an overnight equilibration period during which the subjects fasted, samples from the second urine void on the following day (time 0) were portioned, and the abundances of ^{2}H and ^{18}O were measured by isotope ratio mass spectrometry (Metabolic Solutions Corporation, Merrimack, NH). The pool size of body water was estimated from the change in isotopic dilution from baseline to time 0 as described by Speakman et al (27). The TBW values based on ^{2}H and ^{18}O were averaged and used in the analyses. FFM was estimated by using age-appropriate hydration factors (28) that estimate the fraction of the TBW in FFM.

Data analysis

Student's unpaired *t* test, assuming equal variances, was used to compare the SCD and control groups for differences in growth, bone age delay, nutritional status, and body composition. The pubertal status between groups was compared by using Fisher's exact test. Because of the extensive changes in body composition associated with puberty, separate analyses were performed for prepubertal children and pubertal children. Prepubertal children were defined as children who had not yet achieved stage 2 for their composite pubertal score. The pubertal group included all children with pubertal scores of 2–5 because there was an insufficient number of children in stage 5 to separate postpubertal from peripubertal children. In further analyses, multiple linear regression was used to test for differences between the SCD and control groups after adjustment for the effects of age on FFM, FM, and %BF. Data were analyzed by using SYSTAT for WINDOWS (version 6.0, 1997; SPSS Inc, Chicago). The results were considered statistically significant at a P value ≤ 0.05.

RESULTS

Subject characteristics

Thirty-six children with SCD (20 females and 16 males) and 30 control children (15 females and 15 males) were enrolled. Age, bone age, and height were not significantly different between the SCD and the control groups (**Table 1**). Weight, weight-for-age *z* scores, and height-for-age *z* scores were significantly lower in the SCD group. The mean score for sexual development was not significantly different between the SCD and control groups; however, the age range of children who were prepubertal was 5–10.5 y for the control group and was 5.1–14.3 y for the SCD group (**Table 2**), although the difference was not significant.

Bone age was not significantly different between the SCD and control groups, but the SCD group had significantly delayed

TABLE 1
Comparison of growth status between children with sickle cell disease (SCD) and healthy control children[1]

	SCD group (n = 16 M, 20 F)	Control group (n = 15 M, 15 F)
Age (y)	11.3 ± 3.8 (5.1–17.2)	11.2 ± 3.2 (5.0–18.5)
Bone age (y)	10.9 ± 3.7[2] (4.5–18.0)	11.8 ± 3.2 (5.6–18.5)
Height (cm)	140.9 ± 18.5 (110.6–172.3)	147.2 ± 17.6 (109.5–175.4)
Height-for-age z score	−0.4 ± 1.1 (−2.6–1.5)	0.5 ± 1.0 (−2.1–2.9)[3]
Weight (kg)	33.9 ± 13.3 (17.2–71.3)	41.6 ± 15.5 (16.9–75.2)[4]
Weight-for-age z score	−0.8 ± 1.1 (−3.3–1.2)	0.3 ± 1.0 (−1.6–2.4)[3]

[1] $\bar{x}$ ± SD; range in parentheses.
[2] n = 34.
[3,4] Significantly different from the SCD group: [3] P = 0.001, [4] P = 0.038.

skeletal maturation (P = 0.001). Relative skeletal maturation for the SCD group was −0.5 ± 1.4 y compared with 0.6 ± 1.2 y for the control group, representing a delay of ≈1 y in the SCD group (**Figures 1** and **2**). The largest delays in bone age were in older children, primarily males with SCD aged 8.0–14.5 y who had not yet achieved pubertal stage 2. In contrast, the healthy control group had advanced skeletal maturity in the pubertal age range.

Females with SCD had significantly lower z scores for elbow breadth, MUAC, UAMA, and UAFA than did the female control group (**Table 3**). These same z scores and MUAC, subscapular skinfold thickness, UAMA, and UAFA were significantly lower in males with SCD than in the male control group.

Body composition

Prepubertal children

There were no significant group differences in FFM, FM, or %BF between groups, except when TOBEC was used. With the use of TOBEC, the prepubertal SCD group had significantly lower FM and %BF than did the control group (**Table 4**). Subsequent analysis used multiple regression analysis to adjust for the effects of age on body composition in this prepubertal group (**Table 5**). Age was significantly associated with FFM by all methods, and age was significantly associated with FM by 2 methods (TOBEC and 4SF). After adjustment for the effects of age, the SCD group had significantly lower FFM (4SF, 2SF, and TBW) and FM (TOBEC, 4SF, and 2 SF) than did the control group. The age-adjusted group differences in FFM ranged from 0.6 to 2.0 kg depending on the body-composition-assessment method used; for FM the differences ranged from 1.6 to 2.5 kg. Significant age-adjusted differences in %BF were detected only with the use of the TOBEC and 4SF methods (data not shown). There was no significant effect of relative skeletal maturation on these body-composition differences.

Pubertal males

For pubertal males, mean FFM, FM, and %BF were lower in the SCD group than in the control group regardless of the body-composition-assessment method used, although the differences were not significant (Table 4). After adjustment for age, FFM and FM with all methods (except TBW) were significantly lower in males with SCD (**Table 6**). The age-adjusted group differences in FFM ranged from 8.4 to 14.0 kg depending on the method used; for FM the differences ranged from 5.5 to 6.7 kg. %BF did not increase significantly with age in males in either group but was significantly lower in the SCD group by 5.7% and 5.1%, respectively, with the 2SF and 4SF methods. There was no significant effect of relative skeletal maturation on these body-composition differences.

Pubertal females

For pubertal females, there were no significant group differences in FFM, FM, or %BF, although for each measure, females with SCD had lower mean values than did the control females (Table 4). After adjustment for age, FFM was significantly lower by 5.6–5.9 kg in females with SCD than in the control females by the TBW, 2SF, and 4SF methods (**Table 7**). There was no significant effect of age on and no group differences in FM or %BF and no significant effect of relative skeletal maturation on any of the body-composition measures.

DISCUSSION

This is the first study with a large sample size and control group that examined body composition in children with SCD in the United States. Previous studies showed that children with SCD have delayed sexual and skeletal maturation, fat and muscle wasting, and impaired growth (29–41). Consistent with these

TABLE 2
Comparison of pubertal status between children with sickle cell disease (SCD) and healthy control children

	SCD group				Control group			
	Male		Female		Male		Female	
Pubertal stage[1]	Subjects	Age	Subjects	Age	Subjects	Age	Subjects	Age
	n	y	n	y	n	y	n	y
1	10	5.2–14.3	9	5.1–10.6	5	7.0–10.5	5	5.0–10.0
2	1	13.8	4	10.8–16.3	3	10.3–12.9	2	9.1–10.0
3	1	14.4	2	13.0–14.3	4	11.1–13.8	3	9.7–12.8
4	4	14.0–17.2	3	12.3–16.6	3	13.0–15.1	3	12.9–15.8
5	0	—	2	15.9–17.0	0	—	2	15.4–18.5

[1] Based on Tanner (15).

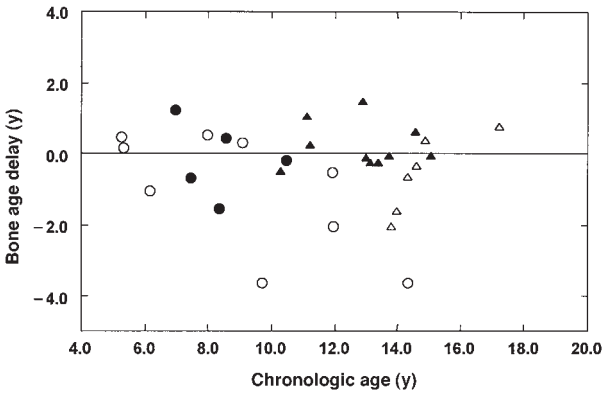

FIGURE 1. Relative skeletal maturation in males with sickle cell disease (SCD) and in healthy control males, by pubertal stage. Control group: ●, Tanner stage 1; ▲, Tanner stages 2–4. SCD group: ○, Tanner stage 1; △, Tanner stages 2–4. Skeletal age was not available for one subject.

earlier studies, our study indicated poor growth and nutritional status in children with SCD compared with national reference data and with a contemporary healthy African American control group. The control group in this study was of similar age and ethnicity, which is important because of reported differences in growth, maturation, and fat patterning between healthy African Americans and healthy white Americans on whom the growth reference data are largely based (19, 42–47). Some of the multiple factors that have been suggested to account for the growth deficit in SCD include tissue hypoxia caused by severe anemia, the chronic and acute effects of vasoocclusion, endocrine dysfunction associated with anemia, chronic organ damage caused by sickling, low dietary intake or elevated energy requirements, and low socioeconomic status (37).

In the present sample of children there was an overlap between the SCD and control groups in unadjusted measures of growth and nutritional status. This was expected because of the broad SDs that occur in growing children over this large age range (5–18 y). When these measures were converted to *z* scores, which are more sensitive indicators of growth and nutritional status relative to a subject's age and sex peers, children with SCD showed marked deficits in *z* scores for weight-for-age, height, elbow breadth, MUAC, triceps skinfold thickness, subscapular skinfold thickness, UAMA, and UAFA. These findings indicate global deficits in growth and energy reserves. Among the children with SCD, the anthropometric *z* scores were lower for males than for females, suggesting that relative to the NCHS reference from which the *z* scores were computed, muscle and FM depletion were more severe in males with SCD. However, relative to the healthy control subjects, males and females with SCD had deficits of similar magnitude.

Relative skeletal maturation was delayed in the SCD group, similar to the findings reported by Stevens et al (35) and by Olambiwonnu et al (48), who proposed transient impairment in gonadal function to account for the variation in sexual maturation. In contrast, relative skeletal maturation was advanced in the control group, which was likely due to the current trend of earlier maturation among healthy African American females (43, 45, 49). This underscores the importance of comparing children with SCD with a contemporary group of similar ethnicity and geographic origin.

Consistent with our findings, others have reported deficits in nutritional status among subjects with SCD. Singhal et al (5) reported significantly lower weight, MUAC, and body mass index (BMI) in 20 Jamaican children with SCD between the ages of 15.0 and 17.4 y. Another study of adults with SCD aged 17–35 y from Nigeria reported significant differences in weight, BMI, skinfold thicknesses, and MUAC for males but not for females with SCD compared with control subjects (38), illustrating possible sex-related differences. The authors suggested that hormonal causes may have been associated with the different degree of growth retardation found among males because males with SCD often have severe hypogonadism and females with SCD have no comparable hormonal deficiency.

A previous study of children (aged 3–17 y) in Philadelphia also reported, in 1976, delayed skeletal maturation at all chronologic ages, coupled with lower weight, biacromial breadth, and smaller body measurements in males (sitting height, MUAC, calf circumference, bicondylar femur breadth, and triceps skinfold thickness) and females (all body measurements except for triceps skinfold thickness) with SCD than in a healthy control group (31). These authors suggested that the delay in skeletal maturation was associated with smaller body dimensions in the children with SCD, who also had significantly leaner body extremities than did sex-matched control subjects.

Previously, we reported a significantly greater (10.5%) resting energy expenditure (adjusted for FFM and sex) and a significantly lower activity energy expenditure in this sample of children with SCD than in a control group (4). Total energy expenditure was not different between groups because of the opposing effects of resting energy expenditure and activity energy expenditure, and voluntary physical activity was significantly lower in the children with SCD. Others found similar patterns with respect to resting (1, 3, 5) and total (6) energy expenditure in subjects with SCD. In addition, elevated protein turnover was reported in children and adults with SCD (1–3). These studies suggest that children with SCD have increased protein requirements and are at risk of protein-energy malnutrition, which is consistent with our finding of significantly lower UAMA *z* scores and FFM in these children (50). Micronutrient deficiencies, such as zinc, also are associated with reduced lean or fat tissue stores in SCD (51).

Our findings of low FFM in the entire sample and lower FM in prepubertal males and females and pubertal males provide further evidence that the nutritional needs of children with SCD

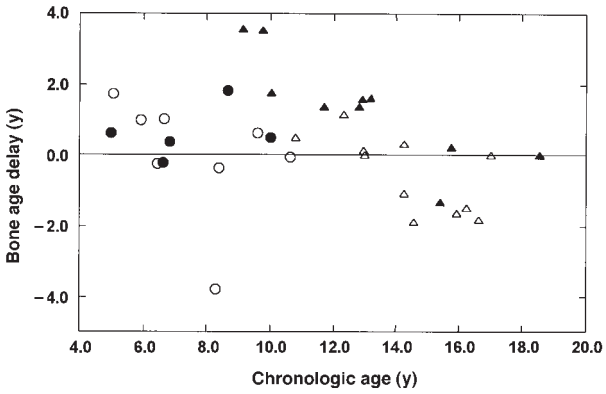

FIGURE 2. Relative skeletal maturation in females with sickle cell disease (SCD) and in healthy control females, by pubertal stage. Control group: ●, Tanner stage 1; ▲, Tanner stages 2–5. SCD group: ○, Tanner stage 1; △, Tanner stages 2–5. Skeletal age was not available for one subject.

TABLE 3
Comparison of nutritional status between children with sickle cell disease (SCD) and healthy control children[1]

	Female		Male	
	SCD group (n = 20)	Control group (n = 15)	SCD group (n = 16)	Control group (n = 15)
Anthropometric measure				
Elbow breadth (mm)	5.5 ± 0.6	5.9 ± 0.6	5.6 ± 0.6	6.1 ± 0.8
MUAC (cm)	20.8 ± 4.2	23.5 ± 4.5	19.1 ± 3.4	22.4 ± 3.8[2]
Skinfold thickness (mm)				
Triceps	10.3 ± 4.6	12.9 ± 5.9	6.4 ± 1.5	8.6 ± 4.0
Biceps	5.3 ± 2.4	6.4 ± 4.0	3.5 ± 0.8	5.0 ± 2.8
Subscapular	8.9 ± 5.2	10.6 ± 5.7	5.4 ± 1.4	7.8 ± 4.1[2]
Suprailiac	6.5 ± 3.5	9.8 ± 5.9	4.7 ± 1.6	6.9 ± 4.1
UAMA (mm^2)	25.1 ± 8.8	30.7 ± 9.5	24.0 ± 9.1	31.7 ± 11.1[2]
UAFA (mm^2)	10.5 ± 6.8	14.7 ± 9.3	5.9 ± 2.1	9.4 ± 5.5[2]
z Scores				
Elbow breadth	−0.2 ± 1.0	0.4 ± 0.8[3]	−0.9 ± 0.6	0.1 ± 1.2[2]
MUAC	−0.5 ± 0.8	0.4 ± 0.8[3]	−1.1 ± 0.5	0.1 ± 1.0[3]
Skinfold thickness				
Triceps	−0.5 ± 0.6	0.0 ± 0.7	−0.4 ± 0.4	0.1 ± 1.0
Subscapular	−0.2 ± 0.6	0.0 ± 0.6	−0.3 ± 0.3	0.3 ± 1.2
UAMA	−0.4 ± 0.9	0.8 ± 0.9[3]	−1.0 ± 0.5	0.1 ± 0.9[3]
UAFA	−0.5 ± 0.6	0.1 ± 0.7[2]	−0.5 ± 0.3	0.1 ± 1.0[2]

[1] $\bar{x}$ ± SD. MUAC, midupper arm circumference; UAMA, upper arm muscle area; UAFA, upper arm fat area.
[2,3] Significantly different from the SCD group of the same sex: [2] $P < 0.05$, [3] $P < 0.01$.

were not being met. The magnitude of these deficits was most pronounced in pubertal males, in whom FFM was ≈14 kg less and FM was 6 kg less than in control males. A study using bioelectrical impedance analysis in 48 Nigerian children aged 3–20 y reported no significant differences in FFM, FM, or %BF between children aged <10 y with SCD and a control group, but significantly lower weight, BMI, and FFM in males and %FFM in females with SCD aged >10 y (41). These authors also reported greater FM and %BF in males and females aged >10 y with SCD than in a control group, which they suggested may have been due to differences in activity levels between the children with SCD and the healthy control subjects.

The findings reported here may be somewhat limited by the use of 2-compartment models to assess body composition, because these models cannot distinguish between lean body mass and skeletal mass in the FFM component, and by interindividual and developmental differences in the hydration of FFM (52). Differences in fat distribution and skinfold compressibility vary by age, sex, and ethnicity (46, 47) and may limit the applicability of generalized skinfold-thickness equations (45). The 2SF method has the advantage of including pubertal status and ethnicity (for either white American or African American children) in the calculation. The 4SF method is not ethnic-specific, but has been validated in the younger age range (1–11 y). Because of the

TABLE 4
Group differences in fat mass (FM), fat-free mass (FFM), and percentage body fat determined with 4 body-composition-assessment methods in children with sickle cell disease (SCD) and in healthy control children[1]

	Prepubertal children		Pubertal males		Pubertal females	
	SCD group	Control group	SCD group	Control group	SCD group	Control group
TOBEC						
FFM (kg)	21.2 ± 4.5 [18]	21.1 ± 3.8 [10]	31.4 ± 3.3 [5]	36.2 ± 11.1 [10]	34.5 ± 6.7 [11]	36.7 ± 4.6 [9]
FM (kg)	3.5 ± 2.5 [18]	5.7 ± 2.8[2] [10]	6.7 ± 3.0 [5]	9.5 ± 5.3 [10]	11.9 ± 5.9 [11]	14.0 ± 7.5 [9]
Percentage body fat (%)	13.0 ± 6.7 [18]	20.6 ± 6.8[3] [10]	17.0 ± 6.4 [5]	20.0 ± 6.2 [10]	24.7 ± 7.0 [11]	26.3 ± 8.5 [9]
2SF						
FFM (kg)	21.7 ± 5.5 [19]	22.7 ± 4.2 [10]	37.4 ± 7.5 [6]	39. 5 ± 11.3 [10]	36.0 ± 6.6 [11]	39.5 ± 6.1 [10]
FM (kg)	2.7 ± 1.3 [19]	4.1 ± 2.8 [10]	3.6 ± 1.2 [6]	6.3 ± 4.8 [10]	10.4 ± 6.0 [11]	12.5 ± 6.9 [10]
Percentage body fat (%)	10.7 ± 3.6 [19]	14.6 ± 7.5 [10]	8.7 ± 2.2 [6]	12.6 ± 5.2 [10]	21.4 ± 6.6 [11]	22.9 ± 8.0 [10]
4SF						
FFM (kg)	21.4 ± 5.2 [19]	22.3 ± 3.8 [10]	35.6 ± 7.5 [6]	37.6 ± 10.9 [10]	35.1 ± 7.2 [11]	38.7 ± 6.5 [10]
FM (kg)	2.9 ± 1.6 [19]	4.6 ± 2.9 [10]	5.4 ± 1.6 [6]	8.1 ± 4.6 [10]	11.3 ± 4.8 [11]	13.3 ± 6.0 [10]
Percentage body fat (%)	11.5 ± 3.9 [19]	16.0 ± 7.9 [10]	13.2 ± 3.1 [6]	16.9 ± 3.8 [10]	23.6 ± 4.4 [11]	24.7 ± 6.3 [10]
TBW						
FFM (kg)	20.2 ± 3.4 [14]	22.3 ± 2.2 [6]	33.4 ± 6.6 [6]	31.6 ± 7.8 [8]	32.1 ± 5.9 [9]	36.2 ± 5.6 [8]
FM (kg)	4.8 ± 2.5 [14]	7.1 ± 3.1 [6]	7.6 ± 2.7 [6]	10.6 ± 6.4 [8]	12.5 ± 4.0 [9]	15.3 ± 8.4 [8]
Percentage body fat (%)	18.2 ± 6.1 [14]	23.8 ± 8.3 [6]	18.2 ± 4.8 [6]	23.9 ± 7.0 [8]	27.6 ± 5.3 [9]	28.2 ± 9.1 [8]

[1] $\bar{x}$ ± SD; n in brackets. TOBEC, total-body electrical conductivity; TBW, total body water; 2SF and 4SF, prediction equations that use skinfold-thickness measurements at 2 (19) or 4 (20, 21) sites, respectively.
[2,3] Significantly different from the SCD group: [2] $P \leq 0.05$, [3] $P \leq 0.01$.

TABLE 5
Regression models testing for differences in fat mass (FM) and fat-free mass (FFM) between prepubertal children with sickle cell disease (SCD) and healthy control children with the use of 4 body-composition-assessment methods after adjustment for age[1]

	FM				FFM			
	β Coefficient	SE	*P*	Adjusted R^2	β Coefficient	SE	*P*	Adjusted R^2
TOBEC								
Constant	0.7	1.6	0.663	0.395	8.0	1.2	<0.001	0.836
Group[2]	−2.5	0.9	0.007		−0.6	0.7	0.373	
Age	0.6	0.2	0.002		1.7	0.1	<0.001	
2SF								
Constant	2.0	1.4	0.152	0.152	6.9	1.6	<0.001	0.813
Group[2]	−1.6	0.7	0.040		−1.9	0.9	0.033	
Age	0.3	0.2	0.097		2.0	0.2	<0.001	
4SF								
Constant	1.5	1.4	0.310	0.226	7.4	1.5	<0.001	0.819
Group[2]	−1.8	0.8	0.027		−1.7	0.8	0.041	
Age	0.4	0.2	0.026		1.9	1.7	<0.001	
TBW								
Constant	2.8	2.7	0.319	0.203	10.8	1.6	<0.001	0.781
Group[2]	−2.4	1.2	0.073		−2.0	0.7	0.012	
Age	0.5	0.3	0.095		1.4	0.2	<0.001	

[1] Regression model: FFM (or FM) = constant + β coefficient (group) + β coefficient (age). TOBEC, total-body electrical conductivity; 2SF and 4SF, prediction equations that use skinfold-thickness measurements at 2 (19) or 4 (20, 21) sites, respectively; TBW, total body water.
[2] Group code: 1 = SCD group; 0 = control group.

extreme leanness of children with SCD, there may be a bias in the TOBEC method associated with increased conductivity at the surface of the bone relative to total conductivity. In addition, the TBW method may involve errors associated with the conversion of TBW to FFM because of low bone density and low FFM in SCD. Because of these limitations, 4 different body-composition methods were used in the present study. Although the absolute levels of FM and FFM differed depending on the method used, the pattern and magnitude of differences were similar between the 2 groups across methods, and the conclusions were based on these consistent findings.

In summary, the results of the present study showed that children with SCD, on average, do not grow like contemporary healthy African American children. This finding is supported by the findings of previous studies (31, 53, 54), ie, that delayed skeletal maturation during adolescence may allow for a longer growth period in the long bones of the extremities, resulting in normal adult height among surviving adults with SCD. Importantly, growth in children refers to more than just height and weight patterns but to increases in the body tissue compartments of fat and muscle. Children with SCD show marked reductions in FFM and reduced body fat, indicating reduced energy stores. Because weight is a composite value of the components FFM and FM, weight alone does not fully characterize the growth deficit in children because of the difference in relative proportions of FFM and FM. In addition, because body composition is

TABLE 6
Regression models testing for group differences in fat mass (FM) and fat-free mass (FFM) between pubertal males with sickle cell disease (SCD) and healthy control males with the use of 4 body-composition-assessment methods after adjustment for age[1]

	FM				FFM			
	β Coefficient	SE	*P*	Adjusted R^2	β Coefficient	SE	*P*	Adjusted R^2
TOBEC								
Constant	−17.3	11.1	0.145	0.054	−39.4	15.4	0.025	0.639
Group[2]	−5.9	2.6	0.039		−13.6	3.6	0.002	
Age	2.1	0.9	0.032		5.9	1.2	<0.001	
2SF								
Constant	−11.9	8.3	0.175	0.057	−38.4	12.6	0.01	0.713
Group[2]	−5.5	2.2	0.026		−14.0	3.3	0.001	
Age	1.4	0.6	0.045		6.1	1.0	<0.001	
4SF								
Constant	−12.4	7.7	0.13	0.024	−37.9	12.5	0.01	0.704
Group[2]	−5.9	2.0	0.012		−13.6	3.3	0.001	
Age	1.6	0.6	0.018		5.9	1.0	<0.001	
TBW								
Constant	−9.8	12.7	0.458	0.185	−25.0	1.0	0.029	0.708
Group[2]	−6.7	3.5	0.080		−8.4	2.7	0.011	
Age	1.6	1.0	0.134		4.5	0.8	<0.001	

[1] Regression model: FFM (or FM) = constant + β coefficient (group) + β coefficient (age). TOBEC, total-body electrical conductivity; 2SF and 4SF, prediction equations that use skinfold-thickness measurements at 2 (19) or 4 (20, 21) sites, respectively; TBW, total body water.
[2] Group code: 1 = SCD group; 0 = control group.

TABLE 7
Regression models testing for group differences in fat-free mass (FFM) between pubertal females with sickle cell disease (SCD) and healthy control females with the use of 4 body-composition-assessment methods after adjustment for age[1]

	β Coefficient	SE	*P*	Adjusted R^2
TOBEC				
Constant	20.7	7.3	0.011	0.173
Group[2]	−4.9	2.7	0.082	
Age	1.3	0.6	0.037	
2SF				
Constant	20.8	6.6	0.006	0.305
Group[2]	−5.6	2.5	0.036	
Age	1.4	0.5	0.009	
4SF				
Constant	17.6	7.0	0.021	0.330
Group[2]	−5.9	2.6	0.035	
Age	1.6	0.5	0.006	
TBW				
Constant	22.7	7.1	0.007	0.220
Group[2]	−5.8	2.7	0.05	
Age	1.1	0.5	0.068	

[1] Regression model: FFM = constant + β coefficient (group) + β coefficient (age). TOBEC, total-body electrical conductivity; 2SF and 4SF, prediction equations that use skinfold-thickness measurements at 2 (19) or 4 (20, 21) sites, respectively; TBW, total body water.
[2] Group code: 1 = SCD group; 0 = control group.

altered in many children with SCD, clinical activities that use weight for calculations (eg, estimated energy requirements, transfusion volume, dietary intake, or medication dosage) may deviate from actual requirements because of differences in relative proportions of body compartments.

The clinical and functional implications of the body-composition profile observed in the present study are unclear, and the long-term health implications of low FFM in SCD also are not known. To date, no evidence links FM or FFM to health outcomes in SCD. Longitudinal studies are needed to determine whether improved growth in the FM and FFM compartments will have long-term benefits. The low activity energy expenditure observed in this same sample (4) may have been the cause or consequence of the low FFM in the SCD group; children who are less physically active are less likely to gain as much FFM as are their peers who are more active. The low FFM in this sample may be the most easily quantifiable measure of restricted physical activity in children with SCD. Intervention studies targeting energy and nutrient intakes and physical activity are needed to further define this relation and to potentially improve the quality of life of children with SCD by supporting normal childhood activities.

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