Total and resting energy expenditure in children with sickle cell disease

Elizabeth M. Barden, PhD, Babette S. Zemel, PhD, Deborah A. Kawchak, MS, RD, Michael I. Goran, PhD, Kwaku Obene-Frempong, MD, and Virginia A. Stallings, MD

Objective: To investigate energy balance in children with sickle cell disease (SCD) as the possible cause of impaired growth and undernutrition.

Study design: Growth, resting (REE), total (TEE), and activity-related (AEE) energy expenditure and dietary intake were examined in 36 African American children with SCD (20 girls and 16 boys) and 30 control subjects (15 girls and 15 boys) of similar age (mean, 11.2 years) and ethnicity. TEE was measured by means of the doubly labeled water technique and REE by indirect calorimetry. AEE was calculated as TEE minus REE. Fat free mass (FFM) was calculated from skinfold prediction equations.

Results: REE was significantly increased (131 kcal/d) in children with SCD (P = .001), after adjusting for sex and FFM. Children with SCD tended to have lower TEE (214 kcal/d) than control subjects, but there was no difference after adjusting for FFM and sex (P = .57). Children with SCD had significantly (P = .025) lower AEE (268 kcal/d) but only marginally (P = .08) lower AEE after adjusting for FFM and sex.

Conclusions: The elevated REE and lower AEE, in combination with poor growth status, indicate chronic energy deficiency in children with SCD. Further studies are needed to determine the best approaches to the treatment and prevention of undernutrition in children with SCD. (J Pediatr 2000;136:73-9)

Sickle cell disease is a chronic hemolytic disease that is frequently associated with delayed growth and maturation and poor nutritional status.1-5 The etiology of impaired growth and altered body composition in SCD has not been clearly established, although nutritional factors have been implicated. These factors include increased energy requirements associated with an increased resting energy expenditure, inadequate dietary intake, elevated

Several studies have documented an increased REE in children and adults with SCD,6,8-11,13 This may contribute to impaired growth because of increased energy demands without concomitant increased caloric intake. However, studies that have focused solely on REE represent only a part of the energy balance equation. Energy balance is reflected as dietary intake minus the sum of all components of energy expenditure, namely REE, physical activity, the thermic effect of food, and growth. With increased REE, alterations in other components of total energy expenditure or energy balance may occur, such as increased dietary intake, reduced physical activity, or poor growth.

To better understand the relationship between energy expenditure and nutritional status in children with SCD, this study examined the pattern of REE, TEE, and activity-related energy expenditure, dietary intake, and growth in a
group of children with SCD compared with a control group of healthy children.

**METHODS**

**Subjects**

Subjects with SCD were recruited from among the children and adolescents from 5 to 18 years of age cared for at the Comprehensive Sickle Cell Center at the Children’s Hospital of Philadelphia. The subjects with SCD met the following criteria: homozygous HbSS-type disease (hemoglobin status confirmed by hemoglobin electrophoresis of subject and parents), no history of stroke or long-term transfusion therapy, no hospitalization or intercurrent illness within 2 weeks of the study, and no other chronic disorder or prescribed medications known to affect growth or nutritional status. Control subjects were of comparable age, sex, and ethnicity (all of African ancestry); had negative sickle cell trait status and weight and height above the 5th percentile compared with National Center for Health Statistics standards; were not taking any medications known to affect growth or nutritional status; and had no chronic disease. They were recruited from the friends and unaffected family members of the subjects with SCD and from the local community. Both groups were evaluated during their usual state of good health, and post-menarcheal female subjects were evaluated within the first 2 weeks of a menstrual cycle.

The protocol was approved by the Committee for the Protection of Human Subjects Internal Review Board. Informed consent was obtained from the parent or guardian of each subject, and assent was obtained from subjects. Data were collected during a 20-hour overnight admission to the General Clinical Research Center.

**Anthropometric Assessment, Maturation, and Body Composition**

Growth and body composition were assessed by measuring standing height (to 0.1 cm) with a Holtain (Crymych, UK) stadiometer, body weight (to 0.1 kg) with a Scaletronix (White Plains, NY) electronic digital scale, mid-upper arm circumference (to 0.1 cm) with a flexible, non-stretchable plastic tape (Ross Laboratories, Columbus, Ohio), and skinfold thicknesses (to 0.2 mm) with Holtain skinfold calipers at the triceps, biceps, subscapular, and suprailiac sites. All measurements were taken by 2 well-trained anthropometrists (B.S.Z. and D.A.K.) using standard anthropometric procedures and recorded in triplicate, with the mean used for analysis.

Anthropometric measurements of growth and nutritional status were compared with National Center for Health Statistics reference standards for age and sex, and standardized scores (z-scores) were calculated. Z-scores for height and weight were computed by means of the Centers for Disease Control Anthropometric Software Program, version 3.1. Triceps z-scores were calculated by using African American reference data. Age- and sex-specific prediction equations were used to estimate body composition on the basis of 4 skinfolds. Skeletal maturation and bone age were determined by radiologic examination of the left hand and wrist. Bone age was determined according to standard methods by a single observer (B.S.Z.). Bone age delay was calculated as bone age minus chronological age. Pubertal status was determined by self-assessment (with parental assistance when age-appropriate) with a pictorial form and classified according to the method of Tanner.

Complete blood cell count, reticulocyte counts, and hemoglobin F levels (for children with SCD only) were measured (Clinical Laboratories, Children’s Hospital of Philadelphia). Number of hospitalizations during the year before evaluation (none, 1 to 2, 3 or more) and sickle cell-related admission diagnoses (pain, acute chest, priapism) were considered as indicators of disease severity.

**REE**

REE was measured by open circuit indirect calorimetry by means of a computerized metabolic cart (SensorMedics 2900Z, Yorba Linda, Calif) in a quiet, thermoneutral room between 7:00 and 10:00 AM. While admitted to the General Clinical Research Center, each subject was given a standardized evening meal with a subsequent 12- to 14-hour overnight fast from food and medication. In the morning, each child was awakened, a normal axillary temperature was documented, and physical activity was restricted to bedrest. Subjects were evaluated after being transported by wheelchair to the Nutrition and Growth Laboratory, where they rested quietly in a supine position while wearing a large, clear, ventilated plastic hood used to collect the expired and ambient air for 60 minutes. Each subject was allowed to watch a movie during the procedure. The modified Weir equation was used to calculate REE from analysis of the expired and inspired respiratory gases (oxygen consumption and carbon dioxide production). Data collection began after allowing 10 minutes for equilibration to the technique. Significant movement events were recorded, and those corresponding data points of elevated REE were removed, with the remaining averaged for analysis. REE is presented both as kilocalories per day and as a percent of the predicted values derived from World Health Organization equations (%pred WHO) to facilitate comparison of children of different age, weight, and sex.

**TEE**

TEE expended over the 10-day period after REE assessment was measured by means of the doubly labeled water technique, which allowed the children to engage in free-living activities during the measurement period. A urine sample was collected on admission for baseline measurement of isotopic enrichment. At 8:00 PM on the...
night of admission, each subject received the oral dose of stable isotopes. \(^{18}\)O and \(^{2}\)H were given at doses of 0.3 g \(^{18}\)O/kg and 0.14 g \(^{2}\)H/O/kg estimated total body water, respectively. Enrichments of \(^{18}\)O and \(^{2}\)H were determined in \(^{18}\)O/H/O from the second urine void of day 1 and from a urine sample collected at home first thing in the morning on day 10 after the dosing. Samples were aliquoted, and urinary \(^{2}\)H and \(^{18}\)O abundances were measured by isotope ratio mass spectrometry (Metabolic Solutions Corporation, Merrimack, NH). Carbon dioxide production rate was calculated as described by Speakman, Nair, and Goran\(^{27}\) and was converted to TEE by a research dietitian, using a follow-up phone call for clarification when necessary. Dietary intake was analyzed by means of a nutrient database program (Food Processor Plus version 5.05, ESHA Research, Inc, Salem, Ore) and averaged over the 3 days of records. Mean daily energy intake was calculated and compared with both the 1989 Recommended Dietary Allowances for age and sex\(^{30}\) and the Third National Health and Nutrition Examination Survey.\(^{31}\) The NHANES III dietary intake data are based on a large, contemporary sample of healthy children in the United States and provide age-, sex-, and ethnic-specific values. A caloric intake ratio was computed as TEE/MDEI.

### Data Analysis

Unpaired \(t\) tests were used to compare groups for differences in energy expenditure, growth, bone age, nutritional status, dietary intake (kcal/d, %RDA, %NHANES III), and the caloric intake ratio. Further analyses used multiple linear regression to determine the effect of covariates known to influence energy expenditure, such as fat free mass, sex, pubertal status, and weight. Interaction terms were tested in the multiple regression models; if insignificant, they were dropped from final models. Pubertal status between groups was compared by means of Fisher exact test. Paired \(t\) tests were used to test for differences in growth and nutritional status z-scores based on chronologic versus bone age. Paired \(t\) tests were also used to compare MDEI (kcal/d) with TEE (kcal/d). The effect of disease severity variables on growth, nutritional status, and energy expenditure was determined by one-way ANOVA. Data were analyzed by means of SYSTAT for Windows (version 6.0, 1997, Chicago, IL). Results were considered statistically significant at a probability value of \(P < .05\).

## RESULTS

### Subject Characteristics

A total of 36 children with SCD (16 boys and 20 girls) and 30 control children (15 boys and 15 girls) were enrolled. The final study sample was restricted to those subjects for whom REE was available. Results for 2 sub-
Table II. Clinical laboratory values

<table>
<thead>
<tr>
<th></th>
<th>SCD group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>8.0 ± 1.3</td>
<td>12.8 ± 0.8</td>
</tr>
<tr>
<td>Reticulocyte count (%)</td>
<td>14.1 ± 5.5</td>
<td>1.3 ± 0.6</td>
</tr>
<tr>
<td>Hemoglobin F (%)</td>
<td>8.2 ± 4.8</td>
<td>1.0 ± 0.2</td>
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Table III. Energy expenditure of children with SCD compared with healthy control children

<table>
<thead>
<tr>
<th></th>
<th>SCD group</th>
<th>Control group</th>
<th>Adjusted least square means* (kcal/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>REE (kcal/d)</td>
<td>1262 ± 37</td>
<td>1221 ± 45</td>
<td>NS</td>
</tr>
<tr>
<td>TEE (kcal/d)</td>
<td>1725 ± 74</td>
<td>1937 ± 114</td>
<td>NS</td>
</tr>
<tr>
<td>AEE (kcal/d)</td>
<td>455 ± 68</td>
<td>725 ± 97</td>
<td>0.029</td>
</tr>
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Energy Expenditure

REE values were similar between groups on the basis of kilocalories per day (Table III), but children with SCD had significantly higher REE expressed as %pred WHO (108 ± 15% vs 93 ± 13%, respectively, P = .001). Significant group differences (SCD vs control) did not change when z-scores were based on bone age instead of chronologic age, so all further analyses used chronologic age-based measures.

Energy Intake

A total of 55 subjects provided completed diet records. MDEI was similar...
for children with SCD and control subjects (1822 ± 409 kcal/d and 1900 ± 448 kcal/d, respectively). There were no significant group differences when MDEI was compared with the RDA for energy (84% ± 19% for children with SCD vs 89% ± 23% for control subjects) or to NHANES III data on non-Hispanic black children (94% ± 19% for children with SCD vs 98% ± 26% for control subjects). There were no significant differences in either group between TEE and MDEI, and the ratio of TEE/MDEI was similar between children with SCD and control subjects (1.0 ± 0.3 and 1.0 ± 0.3, respectively).

**DISCUSSION**

This study, with a large sample size and an adequate control group, examined the relationship between SCD and multiple components of energy expenditure in a US population. Other investigators have reported that children with SCD were delayed in sexual and skeletal maturation, wasted, and short for their age and that they have elevated REE. Our findings are consistent with earlier reports on children with SCD. In addition, reduced FFMI and percent body fat were evident. Although the SCD and control groups did not differ in their distribution of pubertal stages or bone age, bone age was delayed (bone age minus chronologic age) in the SCD group by over a year compared with the control group.

Earlier studies of energy metabolism in children with SCD examined REE and possible causes for its elevation. Singhal et al found a 10% greater unadjusted REE and 19% greater REE per kilogram of FFMI in 20 Jamaican teenagers with SCD measured during their usual state of good health compared with age- and sex-matched control subjects. The authors suggested that increased cardiac output and increased protein turnover are possible contributors to the mechanism of increased REE in SCD. Salman et al compared 8 prepubertal children with SCD with 7 healthy control children of similar age and ethnicity. Unadjusted REE was similar between groups, but REE was 19% greater when expressed per kilogram of FFMI. Significant group differences in resting cardiac index, left ventricular mass, and whole body glutamine usage were also reported. These authors proposed that increases in production of erythrocytes, cardiac workload, and rates of protein synthesis and catabolism result in greater energy and protein requirements in children with SCD compared with healthy children. Studies of adults with SCD also have reported elevated REE compared with control subjects (18% and 15% adjusted for FFMI) and suggested elevated energy requirements resulting from increased REE and protein turnover.

Our study demonstrated a 10.5% increase in REE (adjusted for FFMI and sex) that was consistent in both children and adolescents with SCD.
their usual state of health, assessed under strict research conditions. The analysis used a regression-based approach that avoids bias associated with the use of the ratio, REE per kilogram of FFM. This may explain the difference in magnitude of the elevation of REE in children with SCD that we observed compared with previous studies that used REE per kilogram of FFM (~10% vs ~15% to 20%). TEE and MDEI were similar for the SCD and control groups. However, children with SCD had significantly lower uncorrected AEE and marginally lower (P = .08) adjusted AEE. The energy balance pattern that emerges from these findings is that children with SCD have elevated REE, compromised physical activity (lower AEE), and possibly inadequate energy for growth. These children with SCD did not voluntarily increase their energy intake, and thus their TEE, to compensate for elevated REE. It has been suggested that chronic anemia and possibly a lower threshold for anaerobic metabolism may contribute to the lower AEE in children with SCD, although this would unlikely affect REE.

The only other report of TEE in SCD examined 16 post-pubertal Jamaican boys with SCD (mean age, 18 years), TEE, estimated by heart rate monitoring, was significantly lower in subjects with SCD than in control subjects (P = .05), and REE was higher. Energy intake was not measured. Despite this difference in TEE, they reached a conclusion similar to ours, that reduced physical activity may be a compensatory mechanism to high resting energy requirements in children with SCD.

There are no comparable studies of dietary intake and TEE in US children with SCD. Because absorption appears to be normal in children with SCD, we believe MDEI was representative of the metabolizable energy intake in both SCD and control groups. Although all dietary intake measures (kcal/d, %RDA for age, %NHANES III) were similar to those of control subjects, children with SCD had low weight for age, height for age, weight for height, and body fat stores and marginally lower AEE. This profile of nutritional status indicators underscores the energy imbalance and functional sequelae in SCD.

Disease severity measures were evaluated to determine whether differences in energy expenditure, body composition, or growth in the SCD group were influenced by disease. There were no significant associations between disease severity measures and age, energy expenditure (%pred WHO, TEE kcal/d), growth (height z-score), or nutritional status (weight z-score, triceps z-score). Similarly, Singhal et al did not find any additional contribution to their energy expenditure model from age, hemoglobin concentration, hemoglobin F concentration, or absolute reticulocyte concentration. Salman et al reported a significant positive correlation between REE and reticulocyte count (r = 0.756; P < .002), along with a significant negative correlation between REE and hemoglobin concentration (r = -0.585; P = .05).

In sum, our work supports previous studies in demonstrating that REE is unequivocally increased in SCD, but we did not observe a concomitant increase in TEE reflecting the increase in REE. TEE is similar because of opposing effects of the REE and AEE compartments of energy expenditure, with a reduction in voluntary physical activity in children with SCD. The functional childhood and adult consequences (ie, school performance, employment, and quality of life) of this reduction in physical activity require further study. Nevertheless, it is clear that energy requirements to sustain normal growth, physical activity, and basic physiologic functioning (REE) are not being met for this contemporary American sample of children with SCD, as evidenced by growth failure, reduced physical activity, and altered body composition. Further studies need to be conducted to determine the best approaches to treatment and prevention of undernutrition in people with SCD. Nutritional guidelines for this at-risk population should be developed to ensure normal growth and usual childhood activities that currently may be limited by energy intake.

We express our deepest appreciation to the children and their families for their participation and commitment to research. Additionally, we would like to thank the staff of the Comprehensive Sickle Cell Center and the General Clinical Research Center of the Children's Hospital of Philadelphia for their assistance with the project.

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