

# Equation to estimate resting energy expenditure in adolescents with sickle cell anemia<sup>1-3</sup>

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## ABSTRACT

**Background:** Basal energy requirements are higher in adolescents with sickle cell anemia (SCA) than in healthy control subjects. However, no equation is available to accurately predict their energy needs.

**Objective:** Our objective was to develop a clinically useful equation to estimate resting energy expenditure (REE) in adolescents with SCA.

**Design:** REE and other components of total energy expenditure were measured in adolescents with SCA ( $n = 37$ ) and in control subjects ( $n = 23$ ) for 24 h in a whole-room indirect calorimeter. Multiple linear regression analysis was used to describe the relations of REE with independent variables such as sex, weight, height, fat-free mass, fat mass, age, and hemoglobin concentration in adolescents with SCA. The Bland-Altman comparison technique was used to compare values predicted by existing equations with measured REE values.

**Results:** Mean ( $\pm$ SD) measured REEs were  $7746 \pm 974$  and  $6332 \pm 869$  kJ/d in the male and female subjects with SCA, respectively, and these values were 16% higher than those in the healthy control subjects. Standard equations underestimated REE by 12% ( $P \leq 0.001$ ) in adolescents with SCA and overestimated REE by 4% in control subjects ( $P = 0.01-0.29$ ). Several REE regression equations for SCA were developed. The most parsimonious equation for males was  $REE \text{ (kJ/d)} = 5461 + 77.7 \cdot \text{weight (kg)} - 233.2 \cdot \text{hemoglobin (g/dL)}$ , or  $REE \text{ (kcal/d)} = 1305 + 18.6 \cdot \text{weight (kg)} - 55.7 \cdot \text{hemoglobin (g/dL)}$ . For females, the most parsimonious equation was  $REE \text{ (kJ/d)} = 4603 + 55.6 \cdot \text{weight (kg)} - 126.2 \cdot \text{hemoglobin (g/dL)}$ , or  $REE \text{ (kcal/d)} = 1100 + 13.3 \cdot \text{weight (kg)} - 30.2 \cdot \text{hemoglobin (g/dL)}$ .

**Conclusion:** The new equations have better agreement with the basal metabolic needs of adolescents with SCA than do standard predictive equations. *Am J Clin Nutr* 2002;76:1335-44.

**KEY WORDS** Resting energy expenditure, sickle cell anemia, prediction equations, adolescents, African Americans

## INTRODUCTION

Defining and then meeting requirements for energy and nutrients are important for the optimal clinical management of growing adolescents with sickle cell anemia (SCA). Previously we (1, 2) and others (3-6) reported that resting energy expenditure (REE) is higher in persons with sickle cell disease than in healthy control subjects. Higher rates of whole-body protein breakdown and synthesis and higher cardiac output in adolescents with SCA than

in healthy subjects probably contribute to this finding. We showed that  $\approx 50\%$  of the higher resting metabolic rate in patients with SCA could be accounted for by the enhanced energy cost of total protein turnover (7), including 20% caused by higher bone protein turnover (2). The clinical consequences of this hypermetabolic state are the slower growth rate and delayed sexual development often seen in children and adolescents with SCA (8). Therefore, it is important that individual requirements are determined and that an optimal amount of energy is provided to children and adolescents with SCA.

In 1981, the FAO/WHO/UNU Committee on Protein and Energy Requirements recommended that daily energy requirements be estimated by using measurements of energy expenditure (9). This recommendation substantially underscores the importance of measuring REE, which is defined as the energy required to sustain the body's functions at rest and which accounts for  $\approx 65\%$  of total daily energy expenditure (10). REE is calculated from the resting metabolic rate, which equals the basal metabolic rate only if the measurement is performed in the postabsorptive state and under precisely specified conditions, which include the position of the subject during measurement, temperature, humidity, and degree of light and sound in the room at the time of measurement, duration and quality of sleep or rest interval before the measurement period, and duration of the measurement (10). Such rigorous conditions are not required in the measurement of REE, which is adequate in most clinical applications. Moreover, as pointed out by others, accurate measurement of total daily energy requirements requires that REE be

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recorded over a protracted period (11–13). Nevertheless, measurement of REE requires specialized equipment, and it is not practical to obtain an REE measurement on every patient. Therefore, several equations and modified equations were developed to predict age- and sex-adjusted basal or resting energy expenditure for children and adolescents by using variables such as sex, age, height, weight, and body surface area (14–17). Numerous studies showed that the major factor explaining the variation in metabolic rate in humans is fat-free mass (FFM), a heterogeneous component that can be partitioned into muscle mass and non-muscle mass (10). It was also shown that FFM is lower in children and adolescents with sickle cell disease than in healthy control subjects (4, 6). Because the predictive equations commonly used in clinical practice were generated by using healthy populations and did not take into consideration the hypermetabolic state observed in SCA and differences in body composition, it is reasonable to assume that these equations would not precisely predict REE in subjects with SCA. Kopp-Hoolihan et al (18) showed that standard equations are unreliable in patients with SCA and proposed that clinically useful formulas for predicting REE in patients with SCA should be developed.

The objective of our study was to develop clinically useful equations for the estimation of REE in adolescents with SCA. The null hypothesis was that in adolescents with SCA, REE calculated by using existing standard equations would not differ from REE measured in a previously validated whole-room indirect calorimeter under strictly controlled conditions. To test this hypothesis, we measured REE and other components of total energy expenditure in 37 adolescents with SCA and in 23 control subjects during a 24-h stay in a room calorimeter and compared the results with basal energy expenditure values calculated from standard equations (9, 19, 20). Furthermore, we assumed that if the null hypothesis were incorrect, our experimental data would be sufficient to generate a new simple equation for predicting REE in adolescents with SCA. Simple potential predictive factors such as weight, FFM, fat mass, height, age, and hemoglobin concentration were chosen for testing in this study.

## SUBJECTS AND METHODS

### Subjects

A group of 37 African American adolescents (14–18 y of age) with homozygous SCA were identified and screened for participation in the study at the sickle cell clinics of the Comprehensive Sickle Cell Center at Meharry Medical College in Nashville, TN, and of the Pediatric Hematology Center of Memphis. The group included 18 males and 19 females. Each participant's hemoglobin genotype was determined by using standard electrophoretic methods (21) to confirm the diagnosis of SCA, in which both  $\beta$  globin genes code for hemoglobin S (22). Additionally, 23 African American adolescents who did not carry the hemoglobin S gene or have any other hemoglobinopathy were matched for sex, age, FFM, and fat mass.

Before participating in the study, subjects provided a medical history and underwent a complete physical examination. The participants were free of any metabolic, skeletal, hepatic, or renal dysfunction as confirmed by blood tests. They were not taking drugs known to affect energy metabolism and were nonsmokers. Female subjects were not pregnant as determined by a serum

pregnancy test and were studied between days 3 and 12 after the onset of menses (follicular phase) to eliminate the influence of menstrual function on energy expenditure (23, 24). Subjects with SCA were studied in the steady state; ie, they were not experiencing a sickle cell crisis during the study and had not experienced a painful crisis for 28 d before the study.

Prospective participants received written and verbal information about the nature and purpose of the study, and those who agreed to participate signed an informed consent form. The consent form was approved by the Institutional Review Boards of both Meharry Medical College and Vanderbilt University School of Medicine for procedures to be performed at the Vanderbilt University General Clinical Research Center.

### Study protocol

All participants reported to the General Clinical Research Center after a 10-h overnight fast. After initial admission, they were transferred to the whole-room indirect calorimeter, where they were asked to engage in a 24-h protocol involving standard daily activities and a 2-h nonintensive exercise protocol. Oxygen consumption ( $\dot{V}O_2$ ) and carbon dioxide production ( $\dot{V}CO_2$ ) and the flow rate, temperature (inside and ambient), barometric pressure, and humidity of the air were sampled 60 times/s and integrated at the end of each minute to calculate energy expenditure (25). The participants were free to view television, read, write, walk, and perform personal care activities and to exercise by using the stationary bicycle, step platform, and aerobic tapes as much as they would in their normal daily routine. They received 5 meals but were not allowed to eat or drink after 2100 and were asked to go to bed between 2130 and 2200.

### Methods

#### Anthropometry

Body weight was measured to the nearest 0.05 kg with a digital scale. Height was measured to the nearest 1 cm with a stadiometer. All anthropometric measurements were performed by one investigator (MSB).

#### Body composition

Fat mass and FFM were determined by hydrodensitometry. The subjects were weighed underwater, and their residual lung volumes were measured by using the nitrogen dilution technique while the subjects were submerged in water to chest level (26). Percentage of body fat was calculated from body density by using Schutte's equation (27), and fat mass and FFM were calculated from body mass.

#### Resting energy expenditure

REE (kJ/min) was defined as the average baseline energy expenditure excluding physical activity and sleeping during a 24-h stay in a room calorimeter. Physical activity was detected by a large precision force platform, and energy expenditure above baseline during periods of physical activity was subtracted for REE calculation (28). An automatic algorithm in data processing was used to detect the baseline level of energy expenditure during these non-sleeping, nonexercising, and nonmoving periods. The lowest 60-min period selected by a computer program by sorting was used to obtain the REE. The detailed methodology of the room calorimeter was previously reported (25, 28). Regression models of REE based on the predictors FFM and fat mass were used rather than division of REE by FFM because division by FFM



**TABLE 1**  
Equations for prediction of basal metabolic rate (BMR)

Reference	Age of subjects	Equation
FAO/WHO/UNU (9)	10–18 y	BMR = 12.1 [weight (kg)] + 499
FAO/WHO/UNU (9)	3–18 y	BMR = 7.4 [weight (kg)] + 482 [height (cm)] + 217
Harris and Benedict (19)	All ages	BMR = 9.6 [weight (kg)] + 1.9 [height (cm)] – 4.7 [age (y)] + 655
Schofield (20)	10–18 y	BMR = 13.4 [weight (kg)] + 693
Schofield (20)	10–18 y	BMR = 8.4 [weight (kg)] + 4.7 [height (cm)] + 200

does not account for nonzero intercepts typically observed in these regressions (29).

#### Prediction equations for basal metabolic rate

The equations formulated by Harris and Benedict (19), FAO/WHO/UNU (9), and Schofield (20) were used to predict the REE of the subjects (Table 1). The predictive power of existing equations was assessed by comparing measured and predicted REE values.

#### Statistical analysis

Sample size was calculated by using data from our preliminary studies showing that REE was 170 and 136 kJ/kg FFM in adolescents with SCA and control adolescents, respectively. Using a two-sided *t* test with an  $\alpha$  level of 0.005, we calculated that 10 participants in each sex subgroup would provide 90% statistical power to detect differences between the adolescents with SCA and the control adolescents within each sex. We used a conservative number of  $\geq 12$  adolescents in each SCA sex subgroup because of uncertainty regarding the effect of other variables.

The Bland and Altman method (30) was used to assess agreement between the REE values predicted by the equations and the REE values measured by whole-body indirect calorimetry. Differences between predicted and measured REE were plotted against the averages of predicted and measured REE. Regression analysis was used to test the relation between these differences and means. If the slope relating the differences and means was significant, the 95% limits of agreement were estimated as 2 SD of the estimate around the regression line. Differences between subjects in continuous variables were evaluated by using independent-sample, two-tailed *t* tests. Multiple linear regression

analysis was performed on REE by using a backward elimination approach. The covariates that were considered for inclusion in the modeling were SCA status (0 = healthy control subject, 1 = subject with SCA), sex (0 = male, 1 = female), FFM, fat mass, age, hemoglobin concentration, and plausible interactions among these. A multiple linear model (analysis of variance) was used to test for differences between estimated and measured REE values. Plots of REE estimated from the new equations against measured REE were used to assess the general agreement between paired values of estimated and measured REE. The constancy of estimation across the range of predicted REE values was assessed by plotting these values against residuals. A *P* value < 0.05 was used for inclusion of terms in the regression and to indicate statistical significance. Statistical analyses were performed with SPSS version 10.0 (SPSS Inc, Chicago).

## RESULTS

### Subject characteristics

Descriptive data for the study participants are shown in Table 2. Body weight, age, FFM, and fat mass were not significantly different between the adolescents with SCA and the control adolescents. Mean ( $\pm$ SD) hemoglobin concentrations were significantly (*P* < 0.001) lower in the subjects with SCA than in the control subjects ( $8.9 \pm 1.8$  compared with  $13.3 \pm 1.1$  g/dL). Plasma concentrations of albumin and thyroid-stimulating hormone and red blood cell concentrations of folate were not significantly different between the subjects with SCA and the control subjects. There were no significant differences between the subjects with SCA

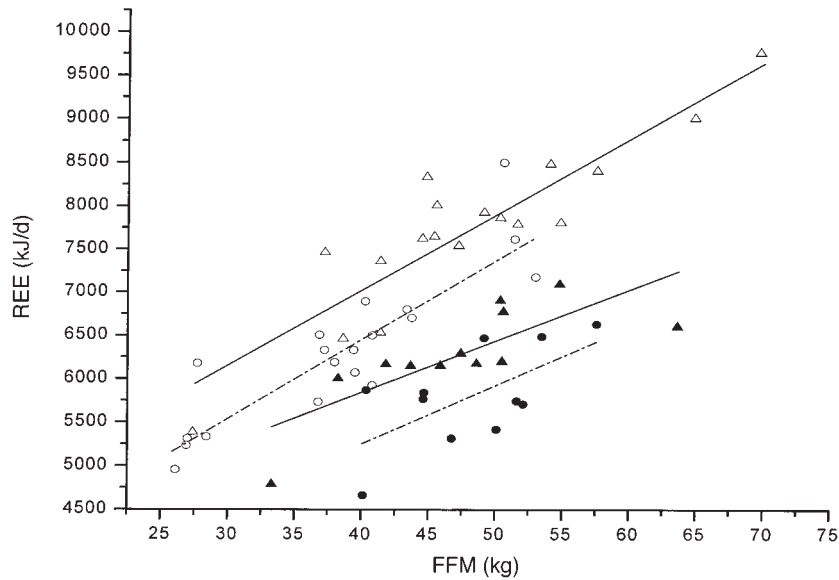
**TABLE 2**  
Subject characteristics<sup>1</sup>

	Subjects with SCA		Control subjects	
	Males ( <i>n</i> = 18)	Females ( <i>n</i> = 19)	Males ( <i>n</i> = 12)	Females ( <i>n</i> = 11)
Age (y)	15.8 $\pm$ 1.5	15.5 $\pm$ 1.3	14.8 $\pm$ 1.3	14.5 $\pm$ 1.4
Weight (kg)	55.8 $\pm$ 13.7	50.8 $\pm$ 16.6	53.1 $\pm$ 12.3	59.2 $\pm$ 7.6
Height (cm)	167.0 $\pm$ 12.2	154.4 $\pm$ 9.6	163.8 $\pm$ 9.9	163.8 $\pm$ 6.2
Fat-free mass (kg)	48.3 $\pm$ 10.0	40.0 $\pm$ 8.1	47.4 $\pm$ 7.8	48.2 $\pm$ 5.4
Fat mass (kg)	7.7 $\pm$ 5.4	12.4 $\pm$ 9.4	5.8 $\pm$ 2.1	11.5 $\pm$ 4.6
Body fat (%)	13.1 $\pm$ 5.6	21.6 $\pm$ 10.8	10.8 $\pm$ 2.6	20.6 $\pm$ 9.4
REE (kJ/min) <sup>2</sup>	5.38 $\pm$ 0.68 <sup>3</sup>	4.40 $\pm$ 0.60 <sup>3</sup>	4.36 $\pm$ 0.41	4.03 $\pm$ 0.40
Hemoglobin (g/dL)	9.38 $\pm$ 1.88 <sup>3</sup>	8.50 $\pm$ 1.72 <sup>3</sup>	13.98 $\pm$ 2.04	12.53 $\pm$ 1.36
RBC folate (nmol/L)	384 $\pm$ 159	386 $\pm$ 144	337 $\pm$ 181	332 $\pm$ 73.7
Albumin (g/L)	43.5 $\pm$ 4.1	42.7 $\pm$ 2.6	41.0 $\pm$ 1.07	40.7 $\pm$ 2.4
TSH ( $\mu$ U/mL) <sup>2</sup>	2.05 $\pm$ 1.12	1.97 $\pm$ 1.09	1.52 $\pm$ 0.67	1.51 $\pm$ 0.59
Estradiol (pmol/L)	—	63.5 $\pm$ 45.6	—	89.4 $\pm$ 48.6
Testosterone (nmol/L)	16.7 $\pm$ 6.58	—	20.9 $\pm$ 7.83	—

<sup>1</sup> $\bar{x} \pm$  SD. SCA, sickle cell anemia; REE, resting energy expenditure; RBC, red blood cell; TSH, thyroid-stimulating hormone.

<sup>2</sup>Baseline energy expenditure excluding physical activity and sleeping during a 24-h stay in the whole-room indirect calorimeter (lowest 60-min period).

<sup>3</sup>Significantly different from control subjects, *P* < 0.05 (independent-sample *t* test).



**FIGURE 1.** Relation between resting energy expenditure (REE) and fat-free mass (FFM) in male ( $\Delta$ ;  $n = 18$ ;  $R^2 = 0.82$ ) and female ( $\circ$ ;  $n = 19$ ;  $R^2 = 0.77$ ) adolescents with sickle cell anemia (SCA) and in healthy male ( $\blacktriangle$ ;  $n = 12$ ;  $R^2 = 0.60$ ) and female ( $\bullet$ ;  $n = 11$ ;  $R^2 = 0.41$ ) control adolescents. On average, REE was 1377 kJ/d higher in the adolescents with SCA than in the control adolescents after adjustment for sex and FFM ( $P < 0.001$ ). On average, REE was 576 kJ/d lower in the females than in the males after adjustment for SCA status and FFM. No interactions involving sex were significant. A positive relation between REE and FFM was observed in both the adolescents with SCA and the healthy control adolescents after adjustment for sex. The overall regression equation ( $R^2 = 0.846$ ) was  $REE \text{ (kJ/d)} = 2366 + 82.94 \cdot FFM - 576 \cdot \text{sex} + 1377 \cdot \text{SCA}$ . The relation between REE and FFM in the male adolescents with SCA (upper solid line) was significantly greater than that in the male control adolescents (lower solid line) ( $P < 0.001$ ). The relation between REE and FFM in the female adolescents with SCA (upper dashed line) was significantly greater than that in the female control adolescents (lower dashed line) ( $P < 0.001$ ).

and the control subjects in plasma concentrations of testosterone in the males and of estradiol in the females.

### Measured resting energy expenditure

Multiple regression analysis of REE showed that FFM was an important predictor of REE, as expected ( $P < 0.001$ ). After adjustment for FFM and sex, the subjects with SCA had, on average, a higher REE than did the healthy control subjects (difference: 1377 kJ/d;  $P < 0.0001$ ). Both the males with SCA and the control males had higher REE than did the girls after adjustment for FFM and SCA (difference: 576 kJ/d;  $P = 0.001$ ). These results are shown in **Figure 1**.

### Resting energy expenditure by prediction equations

Absolute differences between predicted and measured REE in the subjects with SCA and in the control subjects are shown in **Table 3**. The prediction equations underestimated measured REE in the SCA group and overestimated it in the control group. Detailed comparisons between values predicted by using 3 standard equations and measured values are shown in **Figure 2**. The mean ( $\pm$  SD) bias in REE in adolescents with SCA was negative for all equations and ranged from  $-771 \pm 479$  kJ/d for the FAO/WHO/UNU equation by weight (**Figure 2A**) to  $-930 \pm 521$  kJ/d for the Harris-Benedict equation (**Figure 2B**). For the FAO/WHO/UNU equation by weight and height and the Schofield equation by weight, the mean biases were  $-834 \pm 467$  kJ/d ( $P = 0.101$ ,  $r = -0.274$ ) and  $-724 \pm 482$  kJ/d ( $P = 0.627$ ,  $r = -0.083$ ), respectively. In the control subjects, the mean bias was positive for all equations and ranged from  $171 \pm 367$  kJ/d for the FAO/WHO/UNU equation by weight to  $82 \pm 360$  kJ/d for the

Harris-Benedict equation. Ratios of predicted to measured REE expressed in percentages are shown in **Table 4**. On average, the prediction equations underestimated the measured values for adolescents with SCA by 11.30%, and the differences in REE values were significant ( $P < 0.001$ ) in both the males and the females for all equations. A comparison between measured REE and REE obtained by using the FAO/WHO/UNU equation by weight is shown in **Figure 3** (top). Overestimation of REE in the control subjects ranged from 1.8% in the Harris-Benedict equation to 5.4% in the Schofield equation by weight. Detailed analysis showed that the bias was significant in the female control subjects for the FAO/WHO/UNU equation by weight ( $P = 0.008$ ;  $t$  test), the Schofield equation by weight ( $P = 0.003$ ;  $t$  test), the Schofield equation by weight and height ( $P = 0.035$ ;  $t$  test), and the Harris-Benedict equation by weight ( $P = 0.036$ ;  $t$  test). No significant bias was found in the male control subjects ( $P > 0.05$  for all;  $t$  test).

### New regression equations

Our data were used to derive new equations for predicting REE in adolescents with SCA aged 14–18 y. A regression matrix between REE and simple, potentially predictive factors for REE such as sex, weight, height, FFM, fat mass, and age is shown in **Table 5**. FFM and body weight were the most important alternative variables in developing regression equations for calculation of REE in males ( $R^2 = 0.805$  and  $0.702$ , respectively) and females ( $R^2 = 0.757$  and  $0.825$ , respectively).

Multiple regression analyses with independent variables such as sex, weight, height, FFM, fat mass, age, and hemoglobin concentration allowed several REE regression equations for SCA to

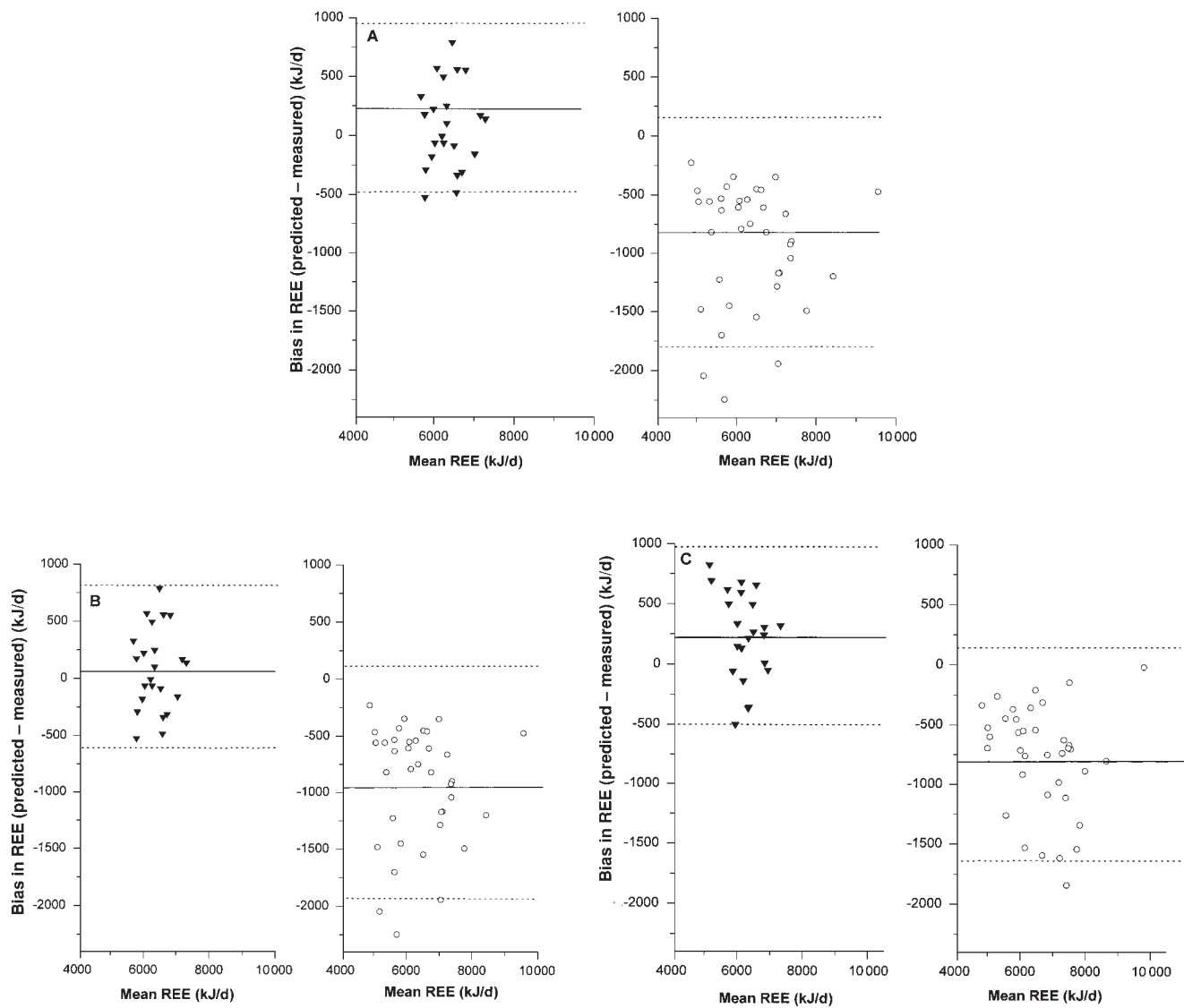


**TABLE 3**  
Absolute differences between resting energy expenditure (REE) predicted by standard equations and measured REE in adolescents with sickle cell anemia (SCA) and in control adolescents<sup>1</sup>

Source of equation	Subjects with SCA						Control subjects					
	Males (n = 18)		Females (n = 19)		Males (n = 12)		Females (n = 11)		Males (n = 12)		Females (n = 11)	
	Difference	P	Difference	P	Difference	P	Difference	P	Difference	P	Difference	P
Harris and Benedict (19) by weight, height, and age	-1207 ± 527 (-2246 to -469)	≤0.001	-667 ± 361 (-1490 to -227)	≤0.001	-83 ± 266 (-525 to 251)	0.298	262 ± 372 (-309 to 791)	0.041	115 ± 34 (-593 to 647)	0.257	361 ± 364 (-188 to 775)	0.08
FAO/WHO/UNU (9) by weight	-935 ± 545 (-1947 to -43)	≤0.001	-617 ± 357 (-1490 to -161)	≤0.001	115 ± 34 (-593 to 647)	0.257	361 ± 364 (-188 to 775)	0.08	114 ± 36 (-511 to 631)	0.243	232 ± 419 (-434 to 827)	0.096
FAO/WHO/UNU (9) by weight and height	-937 ± 533 (-1941 to -118)	≤0.001	-737 ± 382 (-1692 to -284)	≤0.001	114 ± 36 (-511 to 631)	0.243	232 ± 419 (-434 to 827)	0.096	183 ± 41 (-583 to 703)	0.097	431 ± 360 (-106 to 878)	0.003
Schofield (20) by weight and height	-864 ± 548 (-1881 to 57)	≤0.001	-591 ± 378 (-1494 to -56)	≤0.001	201 ± 342 (-503 to 694)	0.067	288 ± 410 (-367 to 827)	0.042	183 ± 41 (-583 to 703)	0.097	431 ± 360 (-106 to 878)	0.003
Schofield (20) by weight	-837 ± 531 (-1843 to -16)	≤0.001	-711 ± 365 (-1544 to -311)	≤0.001	201 ± 342 (-503 to 694)	0.067	288 ± 410 (-367 to 827)	0.042	201 ± 342 (-503 to 694)	0.067	288 ± 410 (-367 to 827)	0.042

<sup>1</sup> $\bar{x} \pm$  SD; range in parentheses.





**FIGURE 2.** Bias in resting energy expenditure (REE; REE predicted by an equation – REE measured for 24 h with whole-room indirect calorimetry) in control adolescents ( $\blacktriangledown$ ) and adolescents with sickle cell anemia (SCA) ( $\circ$ ) plotted against the mean of predicted and measured REE values. The solid line in each panel represents the mean difference between predicted and measured REE values. The 2 dashed lines in each panel represent the upper and lower limits of agreement, which were calculated as the mean  $\pm$  2 SD. *P* values are for the slope relating the difference between predicted and measured REE values to average REE, and *r* values are Pearson's correlation coefficients between measured and average REE. The equations were A) the FAO/WHO/UNU (9) equation by weight (basal metabolic rate = 12.1[weight (kg)] + 499; *P* = 0.085 (*r* = –0.367) and *P* = 0.264 (*r* = –0.189) in the control adolescents and the adolescents with SCA, respectively), B) the Harris-Benedict (19) equation (basal metabolic rate = 9.6[weight (kg)] + 1.9[height (cm)] – 4.7[age (y)] + 655; *P* = 0.791 (*r* = 0.059) and *P* = 0.869 (*r* = –0.028) in the control adolescents and the adolescents with SCA, respectively), and C) the Schofield (20) equation by weight and height (basal metabolic rate = 8.4[weight (kg)] + 4.7[height (cm)] + 200; *P* = 0.136 (*r* = –0.321) and *P* = 0.287 (*r* = –0.180) in the control adolescents and the adolescents with SCA, respectively).

be developed. The most accurate overall equation (*P*  $\leq$  0.0001, overall *R*<sup>2</sup> = 0.879) was

$$\text{REE (kJ/d)} = 3882 + 101 \cdot \text{FFM (kg)} - 439.8 \cdot \text{sex (female)} - 112.9 \cdot \text{hemoglobin (g/dL)} \quad (1)$$

Although FFM was a slightly better single predictor of REE than was body weight when controlled for sex (*R*<sup>2</sup> = 0.866 and 0.845), the latter was chosen because it is easier to measure body weight than FFM in clinical practice. Therefore, the most parsimonious simple equations (*P*  $\leq$  0.0001, overall *R*<sup>2</sup> = 0.760) for males were

$$\text{REE (kJ/d)} = 5461 + 77.7 \cdot \text{weight (kg)} - 233.2 \cdot \text{hemoglobin (g/dL)} \quad (2)$$

and

$$\text{REE (kcal/d)} = 1305 + 18.6 \cdot \text{weight (kg)} - 55.7 \cdot \text{hemoglobin (g/dL)} \quad (3)$$

For females, the most parsimonious simple equations (*P*  $\leq$  0.0001, overall *R*<sup>2</sup> = 0.855) were

$$\text{REE (kJ/d)} = 4603 + 55.6 \cdot \text{weight (kg)} - 126.2 \cdot \text{hemoglobin (g/dL)} \quad (4)$$



**TABLE 4**

Ratio of resting energy expenditure (REE) predicted by equations to REE measured by using whole-body indirect calorimetry in adolescents with sickle cell anemia (SCA) and in control adolescents<sup>1</sup>

Source of equation	Subjects with SCA ( <i>n</i> = 37)		Control subjects ( <i>n</i> = 23)	
	Ratio	<i>P</i>	Ratio	<i>P</i>
	%		%	
Harris and Benedict (19)	87.1 ± 6.1 (72.6–95.4)	<0.001	103.8 ± 6.4 (91.5–117.0)	0.287
FAO/WHO/UNU (9) by weight	89.2 ± 6.0 (76.6–99.6)	<0.001	104.3 ± 6.6 (90.4–116.2)	0.005
FAO/WHO/UNU (9) by weight and height	88.3 ± 5.6 (76.7–98.8)	<0.001	103.3 ± 6.7 (91.7–117.7)	0.036
Schofield (20) by weight and height	89.8 ± 6.2 (76.8–100.6)	<0.001	105.4 ± 6.7 (90.5–116.2)	0.001
Schofield (20) by weight	89.1 ± 5.6 (77.8–99.8)	<0.001	104.4 ± 6.7 (91.8–117.7)	0.005

<sup>1</sup> $\bar{x} \pm SD$ ; range in parentheses.

and

$$\text{REE (kcal/d)} = 1100 + 13.3 \cdot \text{weight (kg)} - 30.2 \cdot \text{hemoglobin (g/dL)} \quad (5)$$

The comparison between measured REE and REE obtained by these equations is shown in Figure 3 (bottom).

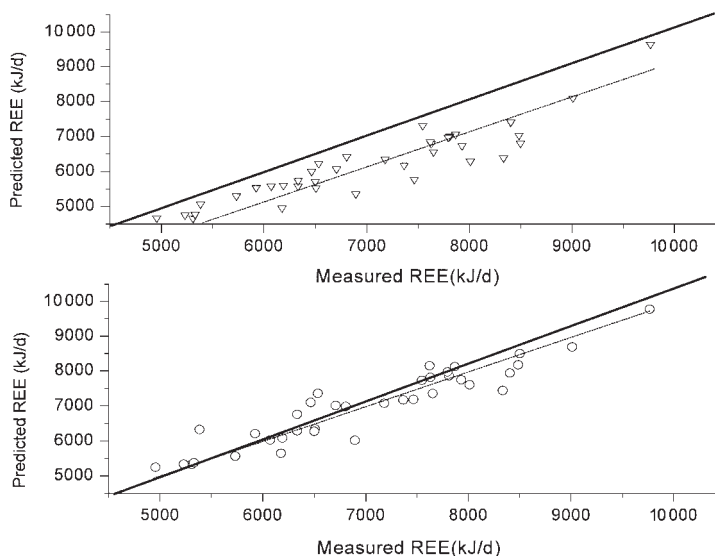
## DISCUSSION

In this study, we examined the validity of standard equations used in clinical practice to predict REE in adolescents with SCA and found that these equations underestimated REE by 10–15%. We propose new, practical, simple equations based on 24-h measurements of REE in a whole-room indirect calorimeter.

We chose to evaluate the prediction equations of Harris and Benedict (19) and of FAO/WHO/UNU (9) because they are the most commonly used equations in clinical settings. We also examined the equations of Schofield (20) because they were developed for adolescents of similar age to that of our study population. These equations were examined previously in independent samples (31–35). For example, the Harris-Benedict equations were

shown to overestimate the basal metabolic rate in healthy female adolescents by 12% and to underestimate it by 12% in healthy male adolescents (31). Dietz et al (16) reported good agreement between the results predicted by FAO/WHO/UNU equations and the measured REE values of 54 adolescents. Finan et al (32) concluded that the FAO/WHO/UNU equations are reasonably accurate for predicting REE in healthy children. In contrast, these and other prediction equations overestimated REE in 33 Italian children (17). Also, Stallings and Pencharz (31) showed that the FAO/WHO/UNU equation underestimated REE by  $9 \pm 13\%$  ( $\bar{x} \pm SD$ ) in obese adolescents.

On the basis of the comparisons shown in Tables 3 and 4, it appears that none of the equations are appropriate for estimation of REE in adolescents with SCA. Although some of these equations predicted average REE values in the control subjects similar to the measured values, detailed analysis in adolescents with SCA indicated a significant underestimation of 9–13% with the FAO/WHO/UNU equation and of 11–15% with the Harris-Benedict equation. Previously, we (1, 2, 7) and others (3, 4) showed that REE is 15–20% higher in patients with SCA than in healthy control subjects. In the present study, the difference in



**FIGURE 3.** Comparison between measured resting energy expenditure (REE) and REE predicted either with the FAO/WHO/UNU (9) equation by weight (top) or with the new proposed equations (bottom) in adolescents with sickle cell anemia (*n* = 37). The solid line in each panel is the line of identity (ie, measured REE = predicted REE), and the dashed line in each panel represents the relation between measured REE and predicted REE.  $R^2 = 0.828$  for the FAO/WHO/UNU equation by weight, and  $R^2 = 0.893$  for the new equations.

**TABLE 5**  
Multiple regression model results for resting energy expenditure in adolescents with sickle cell anemia

	Coefficient $\pm$ SE	P	Overall adjusted $R^2$
<b>Males and females</b>			
Intercept (kJ/d)	3882.0 $\pm$ 424.7		0.879
Fat-free mass (kg)	100.9 $\pm$ 9.17	<0.001	
Sex (female = 0, male = 1)	-439.8 $\pm$ 158.1	0.009	
Hemoglobin concentration (g/dL)	-112.9 $\pm$ 53.2	0.041	
<b>Males</b>			
Intercept (kJ/d)	5460.8 $\pm$ 689.2		0.788
Body mass (kg)	77.73 $\pm$ 11.56	<0.001	
Hemoglobin concentration (g/dL)	-233.2 $\pm$ 105.6	0.043	
<b>Females</b>			
Intercept (kJ/d)	4603.1 $\pm$ 414.4		0.855
Body mass (kg)	55.6 $\pm$ 5.95	<0.001	
Hemoglobin concentration (g/dL)	-126.2 $\pm$ 59.5	0.047	

REE between the adolescents with SCA and healthy control adolescents (adjusted for sex, FFM, fat mass, and age) averaged 21%. Therefore, it was not surprising that the concurrently used prediction equations underestimated measured REE. Detailed comparisons (Figure 2) indicated that REE in individual adolescents with SCA could be underestimated by as much as 1700 kJ/d with the Harris-Benedict equation and 1410 kJ/d with the FAO/WHO/UNU equation.

Only 10% of the REE values predicted by standard equations were within 2 SD of the measured values. Several factors may account for these predicted REE values in adolescents with SCA. Some equations are not appropriate for African American adolescents (12, 33). More importantly, however, all standard equations were defined for healthy individuals with normal energy metabolism. Metabolic perturbations in SCA include elevated cardiac output necessitated by the low oxygen carrying capacity of the blood (3, 5) and increased protein turnover (1, 3, 7). We estimated that  $\approx$ 50% of the increase in resting metabolic rate is due to increased protein synthesis (1) and that <20% of this increase is caused by greater hemoglobin synthesis (7). Hemoglobin synthesis is related to the degree of anemia. Our adolescents with SCA had chronic hemolytic anemia, a typical feature of SCA (36). Although the degree of anemia is extremely variable among patients with SCA, the hemoglobin concentration is relatively constant in any given patient. Therefore, it is reasonable to predict that changes in hemoglobin concentration would cause changes in energy requirements. Indeed, including hemoglobin concentration increased the precision of our predictive equations, and hemoglobin concentrations explained 10% and 12% of the variation in REE in males and females, respectively. This inverse relation between REE and hemoglobin concentration in SCA may be related to increased cardiac output with tachycardia, increased myocardial oxygen demand, high protein turnover, and changes in cell metabolism due to hypoxia (37–40).

In the control subjects, REE was overestimated by 100–400 kJ/d depending on the equation. Several explanations have been offered for the lack of concordance between observed and predicted REE. In a study by Wong et al (15), differences in lean body mass, age, and sexual maturation were factors leading to overestimation of REE in healthy African American children and adolescents. A similar conclusion was reached by Morrison et al (33) in a cross-sectional study of 47 African American and 56 white girls aged 6–16 y. Therefore, we can assume that these factors

could have resulted in an overestimation of REE in the control adolescents in the present study.


In the formulation of our new equations, we found that body weight predicted 74% and 80% of the variation in REE in the males and females, respectively. This finding is consistent with those of other studies that reported that weight was the most important variable in predicting REE in girls and boys (11). FFM may be considered a better predictor of REE in adolescents (14, 15, 34), and it explained 83% of the variation in the present study. However, the limited improvement in  $R^2$  and potential problems with the accurate measurement of FFM in clinical practice make weight a more appropriate single variable to estimate REE in adolescents with SCA. In some studies (17, 28, 35), including height improved REE estimation in adolescents. In the present study, however, the addition of height to the equations did not contribute significantly to the accuracy and precision of the predicted REE values. Regression equations derived by combining the 2 sexes were less accurate than were single-sex equations. In particular, the REE of females with SCA was overestimated, probably because of the differences between the sexes shown in Table 2 and Figure 1. Consequently, single-sex equations are recommended.

Our data must be interpreted with caution. The predictions of basal energy expenditure in our new equations are dependent on body weight, which in adolescents with SCA may not be an accurate reflection of metabolically active tissue. Part of the variation in REE cannot be explained by body size or body composition even in healthy adolescents (10, 41, 42). The nutritional status of the subjects with SCA at the time of REE measurement, use of medications and other therapies, and hormonal status may also affect REE. Although we attempted to control for most of these conditions, not all clinically relevant variation could be eliminated. Nevertheless, our proposed prediction equations were examined for both accuracy and precision. Accuracy was assessed by the slope and intercept of the plot of measured REE versus predicted REE (Figure 3). The precision of the equations was assessed by using  $R^2$  values (Table 5). An alternative approach is to use correction factors for existing standard equations. We calculated that the correction factors for the FAO/WHO/UNU and Harris-Benedict equations are 1.14 and 1.19, respectively, for male adolescents with SCA and 1.11 and 1.13, respectively, for female adolescents with SCA. Both these approaches could lead to a valid estimation of energy needs. Using correction factors, however, does not account for individual variation in REE caused by variation in hemoglobin concentrations.





Finally, our study population was limited to 14–18-y-old adolescents. Although including age in our analyses may have explained some of the association between tested variables and REE, including prepubertal and pubertal adolescents in future studies would allow formulation of more a universal predictive equation.

In conclusion, the REE data collected in the present study were used to produce regression equations for the estimation of REE in 14–18-y-old males and females with SCA. Standard prediction equations underestimate REE by 10–15% in adolescents with SCA. On an individual basis, REE may be underestimated by 800–2000 kJ/d (190–525 kcal/d) depending on the equation. Although accurate, measurement of REE by using indirect calorimetry is cumbersome, expensive, and unavailable in many clinical situations. By contrast, body weight and hemoglobin concentration are 2 easily measurable predictive factors of REE. We recommend that these new simple equations be used in clinical practice for predicting energy requirements in adolescents with SCA. 

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