Alterations in basal nutrient metabolism increase resting energy expenditure in sickle cell disease

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Borel, Myfanwy J., Maciej S. Buchowski, Ernest A. Turner, Benjamin B. Peeler, Richard E. Goldstein, and Paul J. Flakoll. Alterations in basal nutrient metabolism increase resting energy expenditure in sickle cell disease. Am. J. Physiol. 274 (Endocrinol. Metab. 37): E357–E364, 1998.—Basal rates of whole body protein, glucose, and lipid metabolism and resting energy expenditure (REE) were measured in eight African-American sickle cell disease (SCD) patients and in six African-American controls. Catheters were placed 1) in an antecubital vein for stable isotope infusion and 2) in a heated hand vein for arterialized venous blood. Breath and blood were collected during the last 30 min of the 2.5-h study, and REE was measured by indirect calorimetry. REE [128 ± 5 vs. 111 ± 1 kJ·kg-fafree mass (FFM)−1·day−1; P < 0.05 vs. controls] was 15% greater in the SCD patients. Whole body protein breakdown (5.0 ± 0.3 vs. 3.8 ± 0.2 mg·kg FFM−1·min−1; P < 0.05 vs. controls) and protein synthesis (4.4 ± 0.3 vs. 3.2 ± 0.2 mg·kg FFM−1·min−1; P < 0.05 vs. controls) were 32 and 38% greater, respectively, in the SCD patients, but whole body amino acid oxidation was similar (0.58 ± 0.03 vs. 0.66 ± 0.03 mg·kg FFM−1·min−1). Measures of whole body glucose and lipid metabolism were not significantly different between the groups. The additional energy required for the greater rates of whole body protein breakdown and synthesis caused by SCD contributes significantly to the observed increase in REE, suggesting that dietary energy and protein requirements are enhanced in SCD patients.

sickle cell anemia; protein metabolism; carbohydrate metabolism; lipolysis; amino acids

SICKLE CELL DISEASE (SCD) is a genetic disorder in which abnormal hemoglobin (Hb), known as sickle Hb or Hbs, is produced due to the replacement of glutamic acid with valine in position six on the β-chains of Hb (28). On deoxygenation in peripheral tissues and organs, red blood cells (RBCs) containing Hbs become rigid and sickled in shape and can obstruct blood flow through small vessels, thereby causing painful vaso-occlusive events that lead to bone, tissue, and organ damage (50). Because of the structural change to the RBC caused by Hbs, the RBC lifespan is greatly reduced from the normal 120 days to 10 days, resulting in a chronic hemolytic anemia (50). Due to the accelerated synthesis of new RBCs and the enhanced catabolism of irreversibly sickled RBCs, increased rates of RBC protein turnover are obligatory in SCD patients. However, the impact of this increase in RBC turnover on whole body protein homeostasis as well as on whole body carbohydrate and lipid homeostasis is not well established. Furthermore, previous research has demonstrated that resting energy expenditure is elevated in adults, adolescents, and children who have homozygous SCD (10, 24, 45, 51, 52). However, the contribution of changes in whole body protein, carbohydrate, and lipid metabolism to this increase in metabolic rate is not completely understood. The breakdown and synthesis of protein, carbohydrate, and lipid are essential metabolic processes that consume considerable energy. For example, the formation of each peptide bond during protein synthesis requires the energy equivalent to ~5 molecules of ATP (41, 42). Thus the purpose of the present study was to identify the metabolic consequences of SCD on protein, carbohydrate, and lipid homeostasis and to ascertain how these alterations affect resting energy expenditure. To accomplish this goal, we measured basal rates of whole body protein synthesis and breakdown, whole body glucose utilization and production, whole body lipolysis, energy expenditure, and whole body oxidation of individual nutrients (amino acid, carbohydrate, lipid) in a group of SCD patients and in a group of control subjects having a normal Hb phenotype.

METHODS

Subject selection. Eight African-American SCD patients (6 male and 2 female), 18–50 yr of age and within 25% of ideal body weight based on Metropolitan Life Insurance tables (33), were identified and screened for participation in the study at the Sickle Cell Clinic of the Comprehensive Sickle Cell Center at Meharry Medical College (Nashville, TN) and at the Vanderbilt University Medical Center (Nashville, TN). Additionally, six African-American subjects (3 male and 3 female) who did not carry the sickle cell (Hbs) gene were selected as control subjects for the study. Each subject’s Hb phenotype was determined using standard electrophoretic methods (2) to confirm the presence of either 1) homozygous sickle cell disease (HbsS; n = 2), in which both genes coding for the β-chains of Hb produce Hbs; 2) sickle cell Hb C disease (HbsC; n = 3), in which one gene codes for Hbs and the other for Hbc; 3) sickle cell-β thalassemia disease (Hbsβthal; n = 3), in which one gene codes for Hbs and the other for reduced or no production of normal Hb (HbA); or 4) normal Hb (HbAα; n = 6), in which both genes code for HbA (50). Subjects eligible for participation in the study were provided with an explanation of the study, and informed consent (approved by both Vanderbilt University Medical School and Meharry Medical College) was obtained for procedures to be performed at the Vanderbilt University General Clinical Research Center (GCRC). Before participation in the study, subjects underwent a complete history and physical examination, including metabolic, hematologic, hepatic, and renal function tests. Female subjects were not pregnant as determined by a pregnancy test, were menopausal with regular menstrual...
cycles, and were studied between 1 and 14 days after the onset of menses (follicular phase) to reduce experimental variability.

Body composition measurements. Each subject's body density was measured by hydrostatic weighing (6), and percent body fat was calculated using an equation specific for African Americans (46). Fat mass was calculated by multiplying body weight and percent body fat, and fat-free mass (FFM) was calculated by subtracting fat mass from body weight. Body mass index (BMI) was calculated as the ratio of body weight (kg) to height squared (m²).

Experimental protocol. On the day of the metabolic study, subjects reported to the GCRC after a 12-h overnight fast so that they were studied in the postabsorptive state. Indwelling catheters were placed in a superficial hand vein for arterialized blood sampling and in an antecubital vein for the infusion of stable isotopic tracers. The catheterized hand was placed in a heated Plexiglas box with the temperature automatically adjusted to 55°C for complete arterialization of venous blood samples (1). In two subjects, placement of the blood-sampling catheter in a hand vein was not possible; therefore, blood samples were collected via a Port-A-Cath providing mixed venous blood. In addition, catheter placement in the antecubital vein was not possible in one subject; thus the external jugular vein was catheterized to allow for the tracer infusions. At the beginning of the metabolic study, each subject received a bolus infusion of NaH13CO3 (0.12 mg/kg), L-[1-13C]leucine (7.2 µmol/kg), and D-[6,6-2H2]glucose (3.6 mg/kg) to prime the CO2, leucine, and glucose pools, respectively. A continuous infusion of the leucine (0.12 µmol·kg⁻¹·min⁻¹) and glucose (0.06 mg·kg⁻¹·min⁻¹) iso- topes as well as of [2H2]glycerol (0.12 µmol·kg⁻¹·min⁻¹) was then started and continued throughout the remainder of the study (13, 20, 56). Each study consisted of a 2-h tracer equilibration period followed by a 30-min basal sampling period.

Blood samples were collected every 10 min during the basal period for determination of plasma glucose, hormone, and amino acid concentrations as well as isotopic enrichments. Simultaneous to the blood sampling, breath samples were collected from each subject via a Douglas bag with duplicate 20-ml samples placed in 20-ml nonsiliconized glass vacutainer tubes for measurement of breath 13CO2 enrichment. For the 45 min before the basal sampling period, total CO2 production, O2 consumption, and resting energy expenditure were measured by indirect calorimetry using a Sensormedics 2900 metabolic cart (Yorba Linda, CA). At the conclusion of the study, the catheters were removed and the subject was fed a meal and discharged from the GCRC.

Analytical procedures. During the metabolic study, plasma glucose concentrations were measured enzymatically using a Model II glucose analyzer (Beckman Instruments, Fullerton, CA). Whole blood hemoglobin concentrations were measured colorimetrically using the cyanmethemoglobin method (Procedure no. 525, Sigma, St. Louis, MO). Blood samples were collected into separate Venoject tubes (Terumo Medical, Elkton, MD) containing 15 mg Na2EDTA. In addition, 3 ml of blood were transferred to a tube containing ethylene glycol-bis(N,N'-aminoethyl ether)-N,N',N'-tetraacetic acid and reduced glutathione, with the plasma stored at −80°C for later measurement of plasma epinephrine and norepinephrine concentrations by high-performance liquid chromatography (HPLC) (23). The remaining blood was spun in a Beckman desktop centrifuge at 3,000 revolutions/min and 4°C for 10 min, and the plasma was collected and stored at −80°C for later analysis. Plasma for glucagon analysis was collected in tubes containing 50 µl of 500 kIU/ml apronitin (Trasyrol, FBA Pharmaceutical, New York, NY) and was analyzed by radioimmunoassay (5) using Unger’s 30K antiserum (University of Texas Southwestern Medical School, Dallas, TX). Immunoreactive insulin was determined using the Sephadex-bound antibody (Pharmacia, Piscataway, NJ) method (55). Clinical Assays Gammacoat radioimmunoassay kit (Travenol-Gentech, Cambridge, MA) was used to measure plasma cortisol concentrations. Plasma amino acid concentrations were determined by reverse-phase HPLC after derivatization with phenylisothiocyanate (25).

After deproteinization with Ba(OH)2 and ZnSO4 and elution over cation and anion resins, plasma [3H]glucose enrichment was determined by gas chromatography-mass spectrometry (GC-MS) according to the method of Bier et al. (13). Plasma enrichments of [13C]leucine and α-[13C]ketoscaprone (KIC) were determined using GC-MS. Plasma was deproteinized with 4% perchloric acid, and the supernatant was passed over a cation exchange resin to separate the keto and amino acids. The keto acids were further extracted with methylene chloride and 0.5 M ammonium hydroxide (34). After drying under nitrogen gas, both the keto and amino acid fractions were derivatized (47) with N-methyl- N-(t-butyldimethylsilyl)-trifluoroacetic amide containing 1% t-butyldimethyl-ylchlororosilane (MTBSTFA +1% t-BDMCS; Regis Technologies, Morton Grove, IL). The derivatized samples were then analyzed via GC-MS (Hewlett-Packard 5890A GC and 5970 MS, San Fernando, CA) for plasma leucine and KIC enrichments. For determination of [3H]glycerol enrichment, plasma was deproteinized with 4% perchloric acid, and the supernatant was passed over cation and anion exchange resins. The eluate was dried overnight at 50°C, the glycerol fraction was derivatized with MTBSTFA + 1% t-BDMCS, and the derivatized samples were injected into the GC-MS for determination of plasma glycerol enrichment. Breath 13CO2 enrichment was measured by isotope ratio-mass spectrometry (Metabolic Solutions, Merrimack, NH) (48).

Calculations. Regression of the variables of interest with time during the 0.5-h basal sampling period indicated that the slopes were not significantly different from zero, thereby demonstrating that a metabolic steady state was achieved. Thus steady-state values are reported as the means of all time points. Basal steady-state rates of whole body glucose metabolism (32). Breath 13CO2 production was determined by multiplying the total CO2 production rate by breath 13CO2 enrichment (56). The rate of whole body leucine oxidation was calculated by dividing breath 13CO2 production by 0.8 (correction factor for the retention of 13CO2 in the bicarbonate pool) (8) and by the plasma KIC enrichment. The nonoxidative leucine Ra (an estimate of whole body protein synthesis) was determined indirectly by subtracting leucine oxidation from leucine Ra. Rates of whole body protein breakdown, amino acid oxidation, and protein synthesis were calculated from the leucine Ra, the leucine oxidation rate, and the nonoxidative leucine Ra, respectively, assuming that 7.8% of whole body protein is comprised of leucine (22). Because glycerol released during lipolysis cannot be reincorporated into triglycerides in the adipose cell due to a lack of glycerol kinase activity, the Ra of glycerol multiplied by three was used to determine rates of whole body lipolysis (17). Glycerol Ra was
calculated by dividing the \( ^{1}H_{2}O \) glycerol infusion rate by the plasma glycerol enrichment (43, 56). Rates of whole body amino acid, carbohydrate, and lipid oxidation were determined from indirect calorimetry in combination with the leucine oxidation data. The energy expended due to amino acid oxidation was subtracted from the total energy expenditure, and the net rates of carbohydrate and lipid oxidation were calculated based on the nonprotein respiratory quotient (30). The assumptions and limitations of calculating net substrate oxidation based on indirect calorimetry measurements have been reviewed previously (30).

Statistical analysis. Comparisons between the SCD and control groups were made using unpaired t-test analysis, with differences significant at \( P \leq 0.05 \). Values presented in the text, Tables 1 and 2, and Figs. 1 and 2 represent means \( \pm \) SE for each group.

**RESULTS**

Subject characteristics. The SCD (n = 8, 6 male and 2 female) and control (n = 6, 3 male and 3 female) groups of subjects were similar with regard to age, weight, height, BMI, percent body fat, FFM, and fat mass (Table 1). Furthermore, as would be expected, the Hb concentration of the SCD group was significantly lower than that of the control group (Table 1). SCD is a collective term for the various Hb phenotypes, including HbSS, HbSC, and HbSβ thal, in which sickle Hb (HbS) is produced due to the replacement of glutamic acid with valine in position six on the \( \beta \)-chains of Hb (28). All of these Hb phenotypes result in the occurrence of sickled RBCs, hemolytic anemia, and vaso-occlusive events (50). Because results for the three Hb phenotypes in the SCD group vs. the controls were similar, they were pooled and reported as one mean.

Plasma hormone concentrations. Basal plasma insulin (6.4 ± 1.1 vs. 6.3 ± 0.5 µU/ml), glucagon (57 ± 5 vs. 54 ± 4 pg/ml), cortisol (8.7 ± 0.8 vs. 8.4 ± 2.1 µg/dl), epinephrine (26 ± 3 vs. 28 ± 4 pg/ml), and norepinephrine (146 ± 19 vs. 154 ± 16 pg/ml) concentrations were comparable between the SCD and control groups, respectively.

Plasma amino acid concentrations. Although plasma alanine and arginine concentrations were 35 and 28% lower, respectively, in the SCD patients than in the control subjects, concentrations of other individual amino acids were similar between the two groups (Table 2). One exception was plasma histidine concentrations, which were 26% lower in the SCD patients than in the control subjects, a difference that approached statistical significance (\( P = 0.0541 \)). Plasma concentrations of total branched-chain, gluconeogenic, essential, and nonessential amino acids tended to be lower, although not significantly, in the SCD patients than in the control group. However, the plasma concentration of total amino acids was 12% lower in the SCD patients than in the controls.

Resting energy expenditure. Resting energy expenditure normalized to FFM was 15% greater in the SCD patients compared with the controls (128 ± 5 vs. 111 ± 1 kJ · kg FFM \(^{-1} \) · day \(^{-1} \); Fig. 1A).

Whole body protein breakdown and synthesis. Rates of basal whole body protein breakdown (5.0 ± 0.3 vs. 3.8 ± 0.2 mg · kg FFM \(^{-1} \) · min \(^{-1} \)) and synthesis (4.4 ± 0.3 vs. 3.2 ± 0.2 mg · kg FFM \(^{-1} \) · min \(^{-1} \)) were 32 and 38% greater, respectively, in the SCD patients compared with the control subjects (Fig. 2).

Whole body glucose utilization and production. Basal plasma glucose concentrations were similar between the SCD and control groups (91 ± 2 vs. 92 ± 3 mg/dl, respectively). Likewise, basal rates of whole body glucose utilization and endogenous glucose production, which are equivalent under the steady-state conditions

### Table 1. Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Sickle Cell Disease</th>
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<tbody>
<tr>
<td>n/Gender</td>
<td>3 Male/3 Female</td>
<td>6 Male/2 Female</td>
</tr>
<tr>
<td>Age, yr</td>
<td>26 ± 2</td>
<td>30 ± 3</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>72.8 ± 5.8</td>
<td>68.3 ± 5.2</td>
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<tr>
<td>Height, cm</td>
<td>175.5 ± 4.3</td>
<td>173.7 ± 4.2</td>
</tr>
<tr>
<td>BMI, kg/m(^{2} )</td>
<td>23.4 ± 1.4</td>
<td>22.4 ± 1.2</td>
</tr>
<tr>
<td>%Body fat</td>
<td>21.7 ± 4.1</td>
<td>21.2 ± 3.1</td>
</tr>
<tr>
<td>Fat-free mass, kg</td>
<td>56.1 ± 3.1</td>
<td>53.5 ± 4.1</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>16.6 ± 4.0</td>
<td>14.8 ± 2.6</td>
</tr>
<tr>
<td>Hemoglobin, g/l</td>
<td>137 ± 7</td>
<td>99 ± 10*</td>
</tr>
</tbody>
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Values are means ± SE. BMI, body mass index. *\( P \leq 0.05 \) vs. Control.
Fig. 1. Resting energy expenditure (A) and estimated energy cost of protein synthesis (B) for control subjects and sickle cell disease (SCD) patients. *Significant difference (P ≤ 0.05) vs. control group. For SCD patients, their greater energy cost of protein synthesis [±8 kJ·kg fat-free mass (FFM)⁻¹·day⁻¹ above control mean] accounted for −50% of their enhanced resting energy expenditure [±17 kJ·kg FFM⁻¹·day⁻¹ above control mean].

of the study, were similar between the SCD patients (2.5 ± 0.2 mg·kg body wt⁻¹·min⁻¹) and the controls (2.4 ± 0.2 mg·kg body wt⁻¹·min⁻¹).

Whole body lipolysis. Although basal rates of whole body lipolysis were 55% greater in the SCD patients than in the controls (36.2 ± 7.0 vs. 23.5 ± 4.2 µmol·kg fat⁻¹·min⁻¹, respectively), the difference did not reach statistical significance.

Nutrient oxidation. Basal rates of whole body nutrient oxidation were comparable between the SCD and control groups as follows: amino acid oxidation (0.58 ± 0.03 vs. 0.66 ± 0.03 mg·kg FFM⁻¹·min⁻¹; SCD vs. control, respectively), carbohydrate oxidation (1.18 ± 0.16 vs. 1.40 ± 0.31 mg·kg body wt⁻¹·min⁻¹), and lipid oxidation (5.88 ± 1.32 vs. 3.38 ± 0.51 mg·kg fat⁻¹·min⁻¹). The percentage of resting energy expenditure derived from carbohydrate was 29 ± 3 vs. 39 ± 7% (SCD vs. control, respectively), from protein was 13 ± 1 vs. 17 ± 1% (P ≤ 0.05), and from fat was 58 ± 3 vs. 44 ± 7%.

Fig. 2. Basal rates of whole body protein breakdown and protein synthesis for the control subjects and SCD patients. *Significant difference (P ≤ 0.05) vs. control group.

DISCUSSION

This research examined the impact of SCD on whole body nutrient and energy metabolism in a comprehensive manner. We sought to identify the consequences of SCD on basal whole body protein, carbohydrate, and lipid metabolism and to ascertain how these changes altered resting energy expenditure. Basal whole body glucose utilization and production, whole body lipolysis, and whole body amino acid, carbohydrate, and fat oxidation were not significantly affected by SCD. In contrast, resting energy expenditure was increased by 15%, and basal rates of whole body protein breakdown and protein synthesis were increased by 32 and 38%, respectively, in the SCD patients vs. the controls. Thus our data support the hypothesis that the dietary energy and protein requirements of SCD patients are increased.

Previous data regarding the impact of SCD on resting energy expenditure are limited. Badaloo et al. (10) observed that resting metabolic rate normalized to body weight or metabolic body size was −20% greater in adult HbSS patients than in controls. A similar magnitude of increase in resting energy expenditure has been found in adolescents (51, 52) and children (24, 45) with HbSS. Our observation of enhanced resting energy expenditure in adult SCD patients confirms these previous findings and suggests that the energy requirements of individuals with SCD may be increased. Although there are limited data examining the influence of increasing energy intake in SCD patients above normal dietary guidelines, two growth-retarded children with HbSS given additional energy via daily nasogastric nutritional supplementation were found to have accelerated rates of growth with a decreased incidence of painful vaso-occlusive crises and infections (27).

The maintenance of protein homeostasis is important for human health and well-being, since the balance between protein synthesis and breakdown influences the function of proteins involved in many physiological activities (e.g., enzymatic, hormonal, immunological, membrane transport). Early studies have suggested that serious abnormalities in protein homeostasis exist in individuals with SCD. Using three different levels of daily N intake (90, 135, and 180 mg·kg⁻¹·day⁻¹), Odonkor et al. (36) demonstrated that daily urinary and fecal N losses were 8–20 and 35–216% greater, respectively, in nine male adolescent HbSS patients compared with five age- and gender-matched controls. Daily N balance tended to be negative in the HbSS patients at all levels of N intake but positive in the controls. However, interpretation of these findings is limited by the fact that energy intake per unit body weight was lower in the HbSS group than in the control group. Although adult HbSS patients consuming adequate protein and energy have been found to have increased urea production, only a small proportion of this urea is excreted in the urine, with a larger proportion hydrolyzed in the bowel, suggesting
the presence of mechanisms for nitrogen conservation (29).

Although negative nitrogen balance is suggestive of poor protein homeostasis, the metabolic mechanisms contributing to this impaired homeostasis in SCD patients remain unestablished. In an early effort to define these events, Waterlow (54) used L-[U-14C]lysine and a limited number of subjects to measure whole body protein turnover. Turnover of whole body protein was approximately twofold greater in two male HbSS patients than in a male control subject. Using primed intermittent oral doses of [15N]glycine, Badaloo et al. (10) found that estimates of whole body nitrogen flux, protein synthesis, and protein breakdown were significantly elevated in six adult male HbSS patients compared with six adult male controls. Whereas the assessment of protein metabolism with [15N]glycine is attractive due to its noninvasive nature, data from these studies must be interpreted with care due to limitations of the methodology (56). Our finding of enhanced basal rates of whole body protein breakdown and protein synthesis in the SCD patients supports the previous findings of Waterlow and Badaloo et al. and supports the hypothesis that dietary protein requirements are increased in SCD patients. In addition, our data demonstrate that, although the basal turnover rate of the body protein pool is increased, whole body amino acid oxidation is not altered in adults with SCD, a finding consistent with that in children with HbSS (45).

The requirements for specific individual amino acids during SCD have not been established. Hb is a structurally imbalanced protein, totally devoid of isoleucine but rich in valine, leucine, glycine, and histidine (18). Additionally, the pool of sulfur-containing amino acids may be limited in SCD due to an increased loss of taurine-conjugated bile salts. Thus individual amino acid pools may be limiting in the formation of various body proteins. Previously, Enwonwu et al. (18) observed that plasma concentrations of valine, isoleucine, leucine, tyrosine, phenylalanine, histidine, arginine, alanine, and total essential amino acids were significantly lower in HbSS patients than in matched control subjects, suggesting that a "metabolic insufficiency" of several amino acids occurs with HbSS. In contrast, plasma amino acid concentrations of children with HbSS were found to be similar to those of control children except for significantly higher asparagine and cysteine concentrations (45). In the present study, plasma concentrations of individual amino acids were similar for the SCD and control groups except for significantly lower concentrations of alanine and arginine in the SCD patients. Furthermore, whereas plasma total branched-chain, gluconeogenic, essential, and non-essential amino acid concentrations were comparable between the two groups, the plasma total amino acid concentration was significantly lower in the SCD patients. The significance of alterations in the amino acid pool to changes in protein synthetic rates in SCD requires further investigation.

Logic suggests that the rapid turnover of RBCs in SCD necessitates an increase in whole body protein turnover due to the accelerated synthesis of new RBCs and to the enhanced breakdown of irreversibly sickled RBCs. Although these events have not been directly measured, Serjeant (49) made theoretical calculations to determine that daily Hb synthesis must be increased by approximately sevenfold in HbSS patients (40 g/day) compared with normal adults (6.25 g/day). On the basis of these calculations, Hb synthesis accounted for ~2.5% of whole body nitrogen flux in the control subjects and for ~12% in the HbSS patients studied by Badaloo et al. (10). Additional evidence supporting the contribution of increased RBC production to the increased protein turnover observed in SCD patients is the finding of a decrease in whole body protein turnover after splenectomy in HbSS children with hypersplenism (9, 11). Whether the synthesis of other body proteins in SCD patients is accelerated has not been directly measured. However, the magnitude of the increase in whole body protein turnover in the HbSS subjects studied by Badaloo et al. was sixfold greater than the estimated increase in RBC protein turnover, suggesting that the turnover of non-RBC proteins, such as skeletal muscle, cardiac muscle, hepatic, or gastrointestinal proteins, also must be increased.

Although the mechanisms responsible for the increased resting energy expenditure observed in SCD patients cannot be completely determined from the present study, our data demonstrate that basal rates of amino acid oxidation, which were unaffected by SCD, did not contribute to the observed increase in resting energy expenditure. In contrast, there appears to be a close relationship between accelerated rates of whole body protein and energy metabolism in SCD. The processes of protein breakdown and protein synthesis consume energy, thereby accounting for a considerable portion of basal energy expenditure (42). Enhanced protein turnover leads to an increase in the energy required for peptide bond formation, amino acid transport, degradation of protein, urea formation, and excetration of protein breakdown waste products. For example, the synthesis of each peptide bond requires the energy equivalent to ~5 molecules of ATP (41, 42). On the basis of this fact, the energy cost of protein synthesis has been estimated to be 4.5 kJ or 1.076 kcal/g protein (41). In the present study, the estimated energy cost of protein synthesis was significantly greater in the HbSS patients (28.6 ± 1.8 kJ·kg FFM⁻¹·day⁻¹) than in the control subjects (20.6 ± 1.2 kJ·kg FFM⁻¹·day⁻¹; Fig. 1B). These estimates of the energy cost of protein synthesis accounted for 22.5 and 18.7% of resting energy expenditure in the SCD patients and the control subjects, respectively. Furthermore, ~50% of the observed increase in resting energy expenditure in the SCD patients could be accounted for by the enhanced energy cost of protein synthesis (Fig. 1).

Although basal protein turnover and resting energy metabolism are altered with SCD, data regarding the effect of SCD on lipid and glucose metabolism are limited. Whereas several studies have demonstrated a
minor impairment of glucose metabolism in HbSS patients after an oral glucose tolerance test (3, 4, 38), Saad et al. (44) found no difference in blood glucose concentrations or glucose disappearance rates between HbSS patients and controls during an intravenous glucose tolerance test (IVGTT). However, C-peptide concentrations were significantly lower in the HbSS patients than in the controls during the IVGTT, thereby suggesting an impairment in insulin secretion in response to an intravenous glucose load in the HbSS patients.

The increase in RBC destruction that occurs with SCD leads to a chronic hemolytic anemia. Because of its adverse effects on oxygen transport by the blood, the chronic anemia experienced by SCD patients may potentially result in alterations in glucose metabolism. Researchers (14–16, 19, 26) have clearly demonstrated that glucose is a preferred metabolic fuel in rats made anemic by dietary iron deficiency, as evidenced by elevated fasting blood glucose and lactate concentrations, 2) enhanced rates of glucose turnover, oxidation, and recycling, 3) increased basal rates of endogenous glucose production, 4) accelerated rates of basal and insulin-stimulated glucose utilization, and 5) greater peripheral insulin responsiveness. Thus one can hypothesize that glucose metabolism may be altered in SCD patients such that glucose becomes a preferred metabolic substrate, since it can be metabolized in the absence of oxygen via glycolysis and since it is a more oxygen-efficient fuel than is fat. However, in the present study, basal rates of whole body glucose utilization and endogenous glucose production were not different between the SCD and control subjects. In addition, although statistical significance was not reached, whole body lipolysis was 55% greater, whole body carbohydrate oxidation was 16% lower, and whole body lipid oxidation was 64% higher in the SCD patients than in the controls. Thus, although it is clear from the present study that basal whole body glucose metabolism did not contribute to the observed increase in resting energy expenditure, our data suggest that greater rates of whole body lipolysis and lipid oxidation may contribute to the increase in resting energy expenditure in the SCD patients.

Information regarding the hormonal milieu present in patients with SCD is limited. Plasma triiodothyronine and thyroxine concentrations were normal in children and adolescents with HbSS (31, 35), but plasma triiodothyronine concentrations were decreased in adult men with HbSS (40). Plasma cortisol concentrations were significantly lower in children with HbSS than in control children (39). Plasma concentrations of growth hormone were lower in adolescents but greater in young adults with HbSS compared with controls (37). In the present study, basal plasma concentrations of insulin, glucagon, cortisol, norepinephrine, and epinephrine were similar for the adult SCD patients and controls. Thus the basal circulating plasma concentrations of these hormones do not appear to play an important role in the basal metabolic profile observed in our SCD patients. However, the potential role that these hormones may play during metabolic conditions such as stress, feeding, or exercise in SCD patients cannot be determined from the present study. Given the nature of SCD, one can speculate that our observed alterations in basal protein and energy metabolism might have been due to an enhanced “steady-state” (free from vaso-occlusive crisis) acute-phase reactant and cytokine response in the SCD patients. However, information in this regard has been contradictory, with some studies demonstrating normal concentrations (7, 12) and others increased concentrations (21, 53) of various acute-phase reactants and cytokines such as C-reactive peptide, fibrinogen, tumor necrosis factor, and interleukin-1 in steady-state SCD patients. Because the measurement of thyroid hormones, growth hormone, and various acute phase reactants and cytokines was not possible in the present study, we cannot make any conclusions regarding their potential influence on the increased whole body protein and energy metabolism observed in the SCD patients.

In conclusion, findings from the present study clearly demonstrate that basal rates of whole body protein breakdown and protein synthesis are significantly increased in SCD patients, thereby contributing to the greater resting energy expenditure observed in these individuals. Furthermore, these data support the hypothesis that dietary energy and protein requirements are greater in SCD patients. In addition, whereas alterations in basal whole body glucose metabolism did not contribute to the observed increase in resting energy expenditure, there was a trend toward increased rates of whole body lipolysis and lipid oxidation in the SCD patients, which may contribute to their greater resting energy expenditure. The knowledge gained from the present research provides a basis for the design of optimal nutritional regimens for SCD patients with the goal of improving their nutritional well-being.

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