Energy intake and resting metabolic rate in preschool Jamaican children with homozygous sickle cell disease

Atul Singhal, Stephany Parker, Louise Linsell, and Graham Serjeant

ABSTRACT

Background: A relative energy deficiency consequent to a high resting metabolic rate (RMR) may contribute to growth impairment in persons with homozygous (SS genotype) sickle cell disease (SCD). The growth deficit in SCD emerges at an early age, but few studies have addressed the adequacy of energy intake relative to RMR in young children.

Objective: Our objective was to test the hypothesis that energy intake relative to RMR is lower in children with SCD than in control subjects.

Design: The dietary intake of 41 children with SCD and 31 control subjects with a normal hemoglobin genotype (AA) aged 3–6 y was assessed by weighing all food consumed during 3 d. RMR was determined with the use of indirect calorimetry.

Results: The RMR in the children with SCD (x̄ ± SD: 5.47 ± 0.93 MJ/d) was higher than that in the control subjects (5.19 ± 1.3 MJ/d) after adjustment for sex and weight (P = 0.04). Energy intake did not differ significantly between the 2 genotype groups. The ratio of energy intake to RMR was lower in the children with SCD (x̄ ± SD: 1.13 ± 0.33) than in the control subjects (1.35 ± 0.38) after adjustment for sex and weight (P = 0.005).

Conclusions: Prepubertal children with SCD fail to compensate for their higher RMR by increasing their energy intake. This observation is consistent with a hypothesis of a relative energy deficiency in SCD. Am J Clin Nutr 2002;75:1093–7.

KEY WORDS Energy intake, resting metabolic rate, sickle cell disease, children, Jamaica, weighed food intake

INTRODUCTION

Children with homozygous (SS genotype) sickle cell disease (SCD) exhibit deficits in height and weight and in sexual and skeletal maturation (1, 2). The resting metabolic rate (RMR) is elevated in SCD (3–9) and if energy intake is not increased to compensate for this elevation, an energy deficiency arises that could contribute to these growth abnormalities. However, only limited data are available on the adequacy of energy intake relative to RMR in young children with SCD, for whom optimal energy balance may be critical for normal growth (10).

Energy intake and basal energy expenditure in prepubertal children with SCD were compared with those in control subjects in 2 studies (4, 6), which reached conflicting conclusions. One study found higher protein and energy intakes in children with SCD (4), and the other study found no difference in macronutrient intake (6). These studies were limited by small sample sizes and by the use of food diaries (4) or dietary history (6) to estimate dietary intake; those techniques may have a large systematic error of measurement (11). The present study used the more accurate weighed food intake (11) to test the hypothesis that energy intake relative to RMR is lower in young children with SCD than in control subjects of similar age, sex, and socioeconomic status.

SUBJECTS AND METHODS

Subjects

There were 72 children with SCD aged 3–6 y who were living in the Kingston metropolitan area and attending the Sickle Cell Clinic of the University of the West Indies. All children from families willing to participate were recruited (n = 41). Children <3 y of age were excluded because of the difficulties they often have in cooperating during measurements of RMR, and children >6 y of age were also excluded because of their school attendance and the possible disruption in their school activities caused by having to weigh the food they consumed. A group of 32 control subjects with a normal hemoglobin genotype (AA), representing all consenting subjects that fulfilled the eligibility criteria, were also recruited. These control subjects were from the same households as the children with SCD (11 were siblings of children with SCD). Children with a chronic disorder other than SCD and control subjects with a hemoglobin concentration >2 SD below the normal range for Jamaican children were excluded and treated if necessary. All subjects were clinically well when the study began and had been well for 2 wk before the start of the study (one control subject failed to complete the study because of illness at the time of the dietary measurement). The study was approved by the...
Ethical Committee of the University of the West Indies and by the Oklahoma State University Institutional Review Board, and informed consent was obtained from all parents.

Sample size
Because the RMR in children with SCD is ≈20% higher than that in control subjects (5, 6), the study required the power to detect at least a 20% difference in energy intake between genotype groups. On the basis of the variance in energy intakes in hematologically healthy children aged 1–4 y (7 ± SD: 6.2 ± 1.2 MJ/d) (12) and the need to detect a 1 SD (1.2 MJ, or 20%) difference in energy intake between genotypes with 80% power and at 5% significance (13), the study required ≈16 subjects in each group.

Dietary assessment
The study was conducted in the subjects’ homes. All food consumed over 3 consecutive days (2 weekdays and 1 weekend day) was weighed with the use of portable electronic scales (Ohaus LS5000; Ohaus Corp, Florham Park, NJ) accurate to 2 g. A few days before data collection, the mothers received instructions in their homes on how to use the scales and how to record the data. A detailed food diary that included a full description of the food consumed (including food consumed straight from the container and food eaten outside of the house) and recipes for homemade dishes was also kept. The mothers were encouraged to weigh any leftovers and, whenever possible, any food that was spilled or dropped, and particular care was taken to make sure that all caregivers or other household members likely to feed the child were familiar with the procedures. Nutrient intakes were calculated with the use of NUTRITIONIST IV (version 3.5.2; First DataBank Division, Hearst Corp, San Bruno, CA) modified for use in the Caribbean and were adjusted to account for the sweetened condensed milk commonly consumed in Jamaica.

Resting metabolic rate
After fasting overnight (12–14 h), subjects were brought to the metabolic laboratory by car, and their RMR was determined with the use of indirect calorimetry as described previously (5). Measurements were conducted between 1000 and 1200 in an air-conditioned room (22–25°C). After subjects were supine on a couch for 30 min, a hood was placed over their head and shoulders and 10 min was allowed for equilibration of expired gases. Two consecutive 5-min samples of expired gases were then collected in Douglas bags, and the flow rate in the hood was adjusted between 30 and 40 L/min to maintain the CO₂ content of the expired air between 0.5% and 0.7%. Air samples were dried before entrance into the variable area flow meter (Rotameter; Fischer Controls Ltd, Croydon, United Kingdom) and again before measurement of the oxygen (paramagnetic oxygen analyzer; Servomex Ltd, Crowborough, United Kingdom) and carbon dioxide content (infrared CO₂ analyzer; Analytic Development Company Ltd, Hoddesdon, United Kingdom). The analyzers were calibrated daily by using 99.99% nitrogen as a zero calibrator and fresh air and 0.82% CO₂ for the oxygen and carbon dioxide span calibrations, respectively.

The oxygen consumption and carbon dioxide production were measured with the use of a ventilated hood. The flow rates were corrected for the presence of water vapor and were reduced to those at standard temperature and pressure. RMR was calculated by using the method of Weir (14), and the means of RMR calculated from the two 5-min gas collections were used for analysis and were expressed as MJ/d. The methodology and repeatability for the RMR measurements were described previously (5, 7).

Hematologic indexes were measured electronically (Coulter S Plus 4 and MaxM; Coulter Electronics, Hialeah, FL). Height was measured with the use of a wall-mounted stadiometer (Holtain Ltd, Crosswell, Crymych, United Kingdom) accurate to 1 mm. Weight was measured with the use of a beam balance (Detecto Inc, Brooklyn, NY) accurate to 0.1 kg while the subjects wore light clothing and no shoes. Skinfold thickness was measured at the biceps, triceps, subscapular, and suprailliac sites with the use of Harpenden skinfold calipers (British Indicators, Ltd, London) accurate to 0.1 mm, and arm and wrist circumferences were measured with the use of a nonstretchable measuring tape accurate to 1 mm. Equipment was calibrated at weekly intervals, and all anthropometric measurements followed standard protocols and were made by a single observer (SP) trained in the techniques involved.

Socioeconomic status
SOCIOECONOMIC STATUS
Socioeconomic status was determined with the use of an index of overcrowding (persons per room) and a social amenities rating previously used in Jamaica (16), which records the number and types of household appliances, source of water, and type of sanitation. Paternal income as an indicator of socioeconomic status was not used because of the high frequency of single-parent families.

Statistical analyses
Two-factor analysis of variance was used to examine differences in normally distributed variables by sex and genotype. Variables that were not normally distributed were transformed as appropriate. Genotype differences in RMR and the ratio of energy to RMR were examined with the use of two-factor analysis of variance after adjustment for weight. The Wilcoxon signed-rank test was used to investigate whether energy and protein intake was significantly greater than the recommended dietary allowances for the Caribbean (17) (one-sided P value given). Statistical significance was set at P < 0.05 for all analyses. All data were analyzed with the use of STATA version 6 (Stata Corp, College Station, TX).

RESULTS
The children with SCD did not differ significantly from the control children in age, weight, body mass index, or indexes of socioeconomic status (Table 1). As expected, mean hemoglobin concentrations were lower in the children with SCD than in the control children.

RMR was significantly higher in the children with SCD (7 ± SD: 5.47 ± 0.93 MJ/d) than in the control children (5.19 ± 1.3 MJ/d) when adjusted for weight and sex (Table 2). The genotype-by-sex interaction for RMR was not significant.

Intakes of energy, protein, carbohydrate, and fat did not differ significantly between the 2 genotype groups (Table 3). However, there were significant genotype-by-sex interactions for energy...
Comparison of some characteristics of children with homozygous sickle cell disease (SS genotype) and control subjects with normal hemoglobin (AA genotype)

<table>
<thead>
<tr>
<th></th>
<th>SS genotype</th>
<th>AA genotype</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Boys (n = 23)</td>
<td>Girls (n = 18)</td>
<td>Boys (n = 17)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>4.1 ± 0.92</td>
<td>4.2 ± 1.00</td>
<td>4.1 ± 0.80</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>16.3 ± 2.2</td>
<td>16.6 ± 3.7</td>
<td>17.2 ± 2.9</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>105.8 ± 6.9</td>
<td>107.9 ± 10.1</td>
<td>107.9 ± 8.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>14.5 ± 1.0</td>
<td>14.2 ± 1.4</td>
<td>14.7 ± 1.3</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>74.9 ± 10.3</td>
<td>79.0 ± 11.3</td>
<td>118.4 ± 11.4</td>
</tr>
<tr>
<td>Log (persons per room)</td>
<td>0.52 ± 0.66</td>
<td>0.62 ± 0.65</td>
<td>0.81 ± 0.66</td>
</tr>
<tr>
<td>Social amenities rating</td>
<td>232 ± 84.6</td>
<td>242 ± 93.2</td>
<td>246 ± 67.9</td>
</tr>
</tbody>
</table>

1 Two-factor ANOVA.
2 x ± SD.
3 The range of values for the social amenities rating is 0–18.

Comparison of energy intake relative to resting metabolic rate (RMR) in children with homozygous sickle cell disease (SS genotype) and control subjects with normal hemoglobin (AA genotype)

<table>
<thead>
<tr>
<th></th>
<th>SS genotype</th>
<th>AA genotype</th>
<th>P*</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Boys (n = 23)</td>
<td>Girls (n = 18)</td>
<td>Boys (n = 17)</td>
</tr>
<tr>
<td>Respiratory quotient</td>
<td>0.81 ± 0.10</td>
<td>0.77 ± 0.09</td>
<td>0.79 ± 0.10</td>
</tr>
<tr>
<td>RMR (MJ/d)</td>
<td>5.71 ± 0.99</td>
<td>5.13 ± 0.76</td>
<td>5.47 ± 0.93</td>
</tr>
<tr>
<td>Energy intake:RMR</td>
<td>1.04 ± 0.35</td>
<td>1.25 ± 0.27</td>
<td>1.13 ± 0.33</td>
</tr>
</tbody>
</table>

1 Two-factor ANOVA after adjustment for weight.
2 x ± SD.

and carbohydrate intake. The interaction for energy intake was due to the greater energy intake in girls than in boys among the children with SCD but the greater energy intake in boys than in girls among the control children. Similarly, among the children with SCD carbohydrate intake was higher in girls than in boys, whereas among the control children the intake was greater in boys than in girls (Table 3). Post hoc tests were not done because of the small number of subjects in each genotype and sex group. Relative to the recommended dietary allowances for energy (in MJ/d) and protein (in g/d) in the Caribbean (boys aged 1–3 y: 5.8 and 16, respectively; girls aged 1–3 y: 5.4 and 15, respectively; boys aged 4–6 y: 7.5 and 22, respectively; girls aged 4–6 y: 6.8 and 21, respectively), daily energy intake was significantly lower in the children with SCD (median: 93%; interquartile range: 81–99%) than in the control children (96%; 81–105%). Protein intake exceeded the recommended dietary allowance both in the children with SCD (218%; 187–267%) and in the control children (255%; 203–318%) (P < 0.001 for both genotype groups).

The ratio of energy intake to RMR was significantly lower in the children with SCD than in the control children after adjustment for weight and sex (Table 2). The genotype-by-sex interaction for the ratio of energy intake to RMR was not significant (Table 2).

DISCUSSION

This study, which used a technique that is more accurate than food diaries (4) or dietary history (6), confirms that energy intake relative to RMR is markedly lower in children with the SS genotype than in those with the AA genotype. This finding is consistent with the hypothesis of a relative energy deficiency in SCD.

The present study confirms that preschool children with SCD have a greater RMR than do healthy preschool children, similar to observations in older patients (3–9). The young age at which a higher RMR is demonstrable in SCD precedes the age at which large differences in anthropometric measures and body composition become evident (most marked after puberty), and therefore, a higher RMR is presumed to reflect the disease process rather than genotype differences in body composition. Because RMR is the major determinant of total daily energy expenditure, children with SCD should either increase their energy intake or reduce their physical activity. The similarity in energy intakes between the 2 genotype groups in the present study, which is consistent with findings in older patients (18–20), suggests that young children with SCD fail to compensate for their higher energy demands by increasing their energy intake.

Systematic underreporting of energy intake is unlikely to account for our observations. The energy consumption values estimated by weighed food intake of both the children with SCD and the control children were similar to published values (12, 21, 22) in healthy children of a similar age and were close to the recommended dietary allowances in the Caribbean (17). The energy intake of young children estimated from this technique is also more often overreported than underreported (21, 22) and, in small groups, compares favorably to energy expenditure determined with the use of doubly labeled water (21, 22). Moreover, the weighed dietary intake of young children is likely to be more accurate than that of self-reporting older subjects because the committed caregivers of the children comply better in weighing the food than do the older subjects and because preschool children have less unsupervised access to foods outside of the home and are less likely to alter their habitual intake during dietary assessment. Although our decision to collect dietary intake data for only 3 d rather than for 7 d could be criticized, the shorter collection period is unlikely to invalidate our observations because a shorter collection period is associated with better compliance and less disruption of the normal dietary pattern and may
be sufficient to detect large differences between genotype groups in energy intake. Finally, although factors such as underreporting, diurnal variation in RMR, and irritability in fasting children could account for the apparent negative energy balance in some subjects, these sources of error apply equally to both the children with SCD and the control children and therefore do not invalidate the genotype comparisons. The weighed intake method lacks precision for individuals, which could explain the apparent negative energy balance in some subjects. However, the technique is accurate for small groups (21, 22).

Failing to detect a difference in energy intake between the SS and AA genotype groups because of a type II error was unlikely because, with at least 31 subjects in each group, the present study had the power to detect a 0.7 SD (=0.7 MJ) difference in energy intake with 80% power and at 5% significance. This is much less than the 1.3-MJ increase in energy intake required by the children with SCD to compensate for their higher RMR.

Among the children with SCD, the trend for greater energy and carbohydrate intakes in girls than in boys (opposite to the trend seen in the control children) raises the possibility that boys with SCD could be more susceptible to an energy deficiency. However, these observations require confirmation because the present study did not have the design or power necessary to investigate sex-by-genotype interactions in nutrient intake. Furthermore, the sex-by-genotype interaction for the ratio of energy intake with 80% power and at 5% significance. This is much less than the 1.3-MJ increase in energy intake required by the children with SCD to compensate for their higher RMR.

Weighed intake dietary assessment in SCD was performed in one previous study in subjects with a mean age of 11.2 y (range: 5–18 y; 8). In that study, the similar dietary intake in SCD despite a 10.5% greater energy expenditure suggested an energy deficiency. We have reached similar conclusions but in children at a younger age, when an energy deficiency is more likely to compromise early growth. Failure to increase energy intake may reflect fluctuating food availability in poor communities or be influenced by anorexia associated with painful crises and infection (23). Compensation for such a deficiency appears to be achieved by reducing physical activity (7, 8).

Several mechanisms may contribute to the elevated RMR in SCD. These include a high protein turnover secondary to accelerated hemoglobin synthesis (6, 24), inefficient protein utilization consequent to specific amino acid deficiencies (18, 25), and a chronic inflammatory response (26). The decrease in RMR, erythropoietic rate, and protein turnover (27) after splenectomy for hypersplenism in patients with SCD may be explained by a reduction in metabolic demands after alleviation of erythropoietic stress, although RMR remains elevated despite the reduced erythropoietic activity associated with transfusion (28). With this increased protein turnover in SCD, protein intake is apparently no higher than that in control subjects (18–20), suggesting that a relative protein deficiency may occur in SCD. This suggestion is supported by findings in subjects with SCD of abnormal urea kinetics (29) and increased excretion of orotic acid (18), which are reminiscent of normal subjects on low-protein diets.

Although the energy requirements for growth are small, growth is an early casualty of an energy deficiency in young children (10). A relative energy deficiency in SCD may therefore retard growth, and the acceleration in the growth of children with SCD with nutrient supplementation supports this hypothesis (30). The association of lower intelligence quotients with deficits in height in subjects with SCD suggests that suboptimal nutrition may also affect cognitive function (31). The hypothesis that nutritional supplementation may improve physical and mental development in young children with SCD now merits urgent consideration.

REFERENCES


