Sulfur amino acid metabolism in children with severe childhood undernutrition: methionine kinetics1–3

Farook Jahoor, Asha Badaloo, Marvin Reid, and Terrence Forrester

ABSTRACT
Background: Children with edematous but not nonedematous severe childhood undernutrition (SCU) have lower plasma and erythrocyte-free concentrations of cysteine and methionine, which suggests a decreased availability of methionine for cysteine synthesis. We propose that methionine production and metabolism will be slower in children with edematous SCU than in those with nonedematous SCU. 
Objective: We aimed to measure methionine flux, its transmethylation and its transsulfuration, and homocysteine remethylation in children with SCU.
Design: Methionine kinetics were measured in 2 groups of children with edematous (n = 11) and nonedematous (n = 11) SCU when they were infected and malnourished (clinical phase 1), when they were still severely malnourished but no longer infected (clinical phase 2), and when they had recovered (clinical phase 3).
Results: At clinical phase 1, children with edematous SCU had rates of total methionine flux, flux from protein breakdown, and flux to protein synthesis that were slower than the rates of the nonedematous group. There were no significant differences in homocysteine remethylation or methionine transsulfuration and transmethylation between the groups at clinical phase 1.
Conclusion: These findings suggest that, in the acutely malnourished and infected state, children with edematous SCU have slower methionine production than do children with nonedematous SCU because of a slower rate of release from protein breakdown. This slower methionine production is not, however, associated with slower rates of methionine transsulfuration and transmethylation or homocysteine remethylation.

KEY WORDS Methionine kinetics, edematous severe childhood undernutrition, nonedematous severe childhood undernutrition

INTRODUCTION
In studies of glutathione (GSH) metabolism in children with severe childhood undernutrition (SCU), we found that slower erythrocyte GSH synthesis in the edematous group than in the nonedematous group was associated with lower concentrations of cysteine, the rate-limiting precursor of GSH synthesis (1, 2). This finding suggested a shortage in the supply of cysteine for GSH synthesis in children with edematous SCU. The plasma concentration of methionine, the sulfur donor for cysteine synthesis, is also lower in children with edematous SCU (1–3), which suggests decreased methionine availability for cysteine synthesis. It is possible that reduced methionine availability will result in decreased formation of S-adenosylmethionine (SAMe), which could lead to an overall defect in methylation reactions. SAMe is the universal methyl-group donor, and its deficiency has been associated with demyelination of the spinal cord and brain and with vacuolar myelopathy in HIV-infected patients (4–6). Some of these neurologic changes are similar to those seen in kwashiorkor (7), which suggests that methionine deficiency may underlie this disorder.

Methionine is an indispensable amino acid whose production consists of intake from the diet, release from protein breakdown, and methionine resynthesized from the methylation of homocysteine. Because there does not seem to be a difference between the diets of children with edematous SCU and the diets of children with nonedematous SCU (8), it is unlikely that dietary intake is a significant contributor to any difference in methionine production between children with edematous SCU and those with nonedematous SCU. On the other hand, our finding that the whole-body protein breakdown rate is slower in children with the edematous forms of SCU than in those with nonedematous SCU (3) suggests that a more severe shortage of methionine will exist in children with edematous SCU. The possible involvement of impaired homocysteine remethylation is unknown, but a slower protein breakdown could in theory result in decreased serine production and hence a shortage of methyl group donors to facilitate homocysteine remethylation to methionine.

The primary aim of this study was to test the hypothesis that at the time of admission to the hospital for treatment, methionine kinetics will be slower in children with edematous SCU than in those with nonedematous SCU. A secondary aim was to compare the response to treatment by the 2 groups. Stable isotope-tracer methods were used to determine methionine flux, its rate of

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release from protein breakdown, its transmethylation, its synthesis from homocysteine remethylation, and its transsulfuration to cysteine in children with edematous and nonedematous SCU. Production of serine, a primary methyl group donor for methylation reactions, was also measured. The methionine transsulfuration data are reported in another article in this issue of the Journal as “de novo cysteine synthesis” (9).

SUBJECTS AND METHODS

Subjects

Twenty-two children who were admitted to the Tropical Metabolism Research Unit, University of the West Indies, for treatment of SCU participated in the study. These are the same children described in the preceding article (9). During their hospitalization, the children were managed according to a standard treatment protocol as previously described by us (1–3). The rehabilitation diets are as described in the preceding article. Each subject had a deficit in body weight—for age of >20%, indicating severe undernutrition. Details of the physical and clinical characteristics of the subjects are presented in Tables 1 and 2 of the preceding article.

The study was approved by the Medical Ethics Committee of the University Hospital of the West Indies and the Baylor Affiliates Review Board for Human Subject Research of Baylor College of Medicine. Written informed consent was obtained from at least one parent of each child enrolled.

Study design

Whole-body methionine flux—its rate of release from protein breakdown, its transsulfuration to cysteine, its transmethylation to S-adenosylhomocysteine, and its resynthesis via homocysteine remethylation—and serine flux were measured in children with edematous (n = 11) and nonedematous (n = 11) SCU 3 times during their hospitalization by using constant, intravenous infusions of stable isotopes of methionine and serine at +2 d after admission, when the subjects were both infected and malnourished but clinically stable as indicated by blood pressure, pulse, and respiration rates (clinical phase 1); at +14 d after admission, when the subjects were still severely malnourished (anthropometrically) but no longer infected (ie, all clinical features of the infective episode had resolved), had lost edema, and had improved affect and appetite (clinical phase 2); and at +57 d after admission, when the rate of catch-up growth had reached a plateau and weight-for-length was ≥90% of expected (clinical phase 3).

A diet providing maintenance quantities of energy and protein (417 kJ · kg⁻¹ · d⁻¹ and 1.2 g · kg⁻¹ · d⁻¹) was fed during each isotope-infusion protocol as described in the preceding article. The subjects had been receiving this therapeutic diet for 9 d at the clinical phase 1 measurement and for 13 d before the clinical phase 2 measurement. For the clinical phase 3 measurement, the subjects were taken off their regular high-energy diet (which provided 625–750 kJ · kg⁻¹ · d⁻¹ and 3 g · kg⁻¹ · d⁻¹ protein) and were placed on this maintenance diet for 3 d before the infusion protocol. To ensure that the same amount of energy and protein was given during the course of the isotope infusions, 33% of the child’s daily intake was given by continuous intragastric infusion over an 8-h period starting 2 h before the isotope infusions. This provided 17.4 kJ · kg⁻¹ · h⁻¹ and 0.05 g · kg⁻¹ · h⁻¹ protein. Weight and length were monitored throughout hospitalization, the former daily with an electronic balance (model FL105S; Sartorius, Göttingen, Germany) and the latter weekly with a horizontally mounted stadiometer (Holtain Ltd, Crymych, United Kingdom).

Infusion protocol

The infusion and blood sampling protocol was as described in the previous article. In addition to the 3 tracers reported in the preceding article, there was a simultaneous, primed-continuous intravenous infusion of 1-¹³C1, 5-¹⁵N1-methionine (prime = 2.5 μmol/kg, infusion rate = 2.5 μmol · kg⁻¹ · h⁻¹) for 6 h. The infusion and blood sampling protocols were the same for the 2 subsequent experiments performed in the subjects at clinical phases 2 and 3.

Sample analyses

The blood samples were centrifuged immediately at 1000 × g for 15 min at 4 °C, and the plasma was removed and stored immediately at −70 °C for later analyses. Plasma amino acids were isolated from 0.2 mL plasma by ion-exchange (Dowex 200x) chromatography and were converted to the n-propyl ester, heptafluorobutyramide derivative. Dithiothreitol, 0.075 mL of a 10-mmol/L solution, was added to the derivatization mixture to convert homocysteine to homocysteine. The tracer-tracer ratios of plasma methionine and homocysteine were determined by negative chemical ionization gas chromatography–mass spectrometric analysis by selectively monitoring ions at mass-to-charge (m/z) ratios of 367 to 371 (methionine) and 549 to 550 (homocysteine) with a Hewlett-Packard 5890 quadrupole mass spectrometer (Hewlett-Packard, Palo Alto, CA).

Calculations

The total flux (Q) of methionine and serine were calculated by using their plasma plateau tracer-tracer ratios in the steady state equation described in the preceding article. Endogenous serine flux was obtained by subtracting dietary intake plus the serine tracer infused.

In the case of methionine, the di-labeled 1-¹³C1, 5-¹⁵N1-methionine model described by MacCoss et al (10) was used to calculate kinetic parameters. Two fluxes of methionine were calculated: the flux of the carbon skeleton (Qc) by using the labeled carboxy moiety (1-¹³C1) and the flux of the methyl group (QM) by using the labeled methyl moiety (5-¹⁵N1). Methionine transmethylation and homocysteine remethylation were calculated from these 2 flux measurements, and methionine transsulfuration to cysteine was calculated as de novo cysteine synthesis from serine as described in the preceding article. Briefly, because methionine is transmethylated to homocysteine (Hcy) intracellularly, the plasma homocysteine tracer-tracer ratio more accurately reflects the intracellular transmethylation of the methyl group of methionine. This estimate is obtained by multiplying the plasma tracer-tracer ratio of the methyl group of methionine (measured as the M + 4 isotopomer)
by the ratio of the intracellular to extracellular tracer-tracee ratio of the carboxy methionine. That is,

\[ \frac{\text{Tr}/\text{tr}_\text{IC} \text{ methyl Met}}{\text{Tr}/\text{tr}_\text{M} + 4 \text{ Met}} = \frac{\text{Tr}/\text{tr}_\text{M} + 1 \text{ Hcy}/(\text{Tr}/\text{tr}_\text{M} + 1 \text{ Met} + \text{Tr}/\text{tr}_\text{M} + 4 \text{ Met})} \]

where \( \text{Tr}/\text{tr}_\text{M} + 1 \text{ Hcy} \) represents the intracellular enrichment of the carboxy moiety of methionine, and \( \text{Tr}/\text{tr}_\text{M} + 1 \text{ Met} + \text{Tr}/\text{tr}_\text{M} + 4 \text{ Met} \) represent its total enrichment in plasma.

Because homocysteine formed by transmethylation (TM) is either remethylated (RM) back to methionine or transsulfurated (TS) eventually to a-ketobutyrate and cysteine, then

\[ \text{TM} = \text{RM} + \text{TS} \]

Because the flux of methyl methionine (\( Q_m \)) will be greater than the flux of carboxy methionine (\( Q_c \)) by the rate of homocysteine remethylation

\[ \text{RM} = Q_m - Q_c \]

Because cysteine receives its carbon backbone from serine and its sulfur from methionine, de novo cysteine synthesis calculated from U-\(^{13}\)C-serine (as described in the preceding article) is equivalent to TS. Hence, TM can be calculated.

Furthermore, because flux (\( Q \)) = sum of inflows = sum of outflows, then

\[ Q_c = I + \text{PB}_{\text{MET}} = \text{PS}_{\text{MET}} + \text{TS} \]

Where \( I \) represents dietary methionine plus infused labeled methionine, \( \text{PB}_{\text{MET}} \) is methionine released from protein breakdown, \( \text{PS}_{\text{MET}} \) is methionine utilized for protein synthesis, and TS is methionine transsulfurated to a-ketobutyrate and then oxidized. Because \( I \) is known, methionine derived from protein breakdown is calculated as \( \text{PB}_{\text{MET}} = Q_c - I \), and methionine used for protein synthesis as \( \text{PS}_{\text{MET}} = Q_c - \text{TS} \).

In the children with edematous SCU, body weight measured in the malnourished edematous state (ie, the clinical phase 1 measurement) was corrected by subtracting the contribution of edema fluid. Edema fluid was estimated as the difference between body weight on the day of the clinical phase 1 experiment, \( \approx 2 \) d after admission, and the lowest postexperiment weight observed before the clinical phase 2 measurement. All kinetic data are expressed per kg body wt.

Statistics

Data are expressed as means ± SEMs. Differences between the 2 groups at clinical phase 1 were determined by unpaired, 2-tailed \( t \) tests to test our primary hypothesis that at the time they are admitted to the hospital for treatment, children with edematous SCU have slower methionine kinetics than do children with nonedematous SCU. To determine the response to treatment and whether differences due to the effects of treatment depend on diagnosis, 2-factor repeated-measures analysis of variance (ANOVA) was used with diagnosis as the between factor and clinical phase as the repeated factor. If the repeated-measures ANOVA was significant, pair-wise comparisons were made by the Bonferroni method. Inferential tests were considered statistically significant if \( P < 0.05 \). All data analyses were performed with GRAPHPAD PRISM version 4 software (GraphPad Software, San Diego, CA).

RESULTS

The clinical and physical characteristics of both groups of subjects are presented and described in the preceding article (9).

As shown in Figure 1, the tracer-tracee ratios of the \( M + 4 \) isotope of methionine, derived from the intact di-labeled tracer, and the \( M + 1 \) isotope, derived when the di-labeled tracer loses its labeled methyl group, and the \( M + 1 \) isotope of homocysteine, derived from the \(^{13}\)C-carboxy moiety of the tracer, reached a plateau in plasma during the final 1.5 h of the infusion. This permitted use of the steady state equations described above to calculate all kinetic parameters.

At clinical phase 1, when the children were severely malnourished and infected, total methionine flux, flux from protein breakdown, and flux to protein synthesis were slower \( (P < 0.01) \) in the edematous group than in the nonedematous group (Table 1). With respect to these kinetic parameters, there were also significant diagnosis-by–clinical phase interactions between the groups \( (P < 0.05) \). Within the nonedematous group, total methionine flux, flux from protein breakdown, and flux to protein synthesis were faster at clinical phase 1 than at clinical phases 2 and 3 \( (P < 0.05) \). On the other hand, in the edematous group, there were no significant differences in total methionine flux or flux from protein breakdown among the different clinical phases. However, methionine flux to protein synthesis was significantly slower at clinical phase 1 than at clinical phase 3 \( (P < 0.05) \). Also, whereas methionine balance was 54% lower at clinical phase 1 than at clinical phase 3 in the edematous group, it was only 26% lower in the nonedematous group.

As shown in Table 2, at clinical phase 1, both methyl methionine (ie, \( Q_m \)) and carboxyl methionine (ie, \( Q_c \)) fluxes were slower \( (P < 0.05) \) in the edematous group than in the nonedematous group. There were, however, no significant differences in homocysteine remethylation and methionine transsulfuration and transmethylation between the groups. With respect to \( Q_m \) and \( Q_c \), there were also significant diagnosis-by–clinical phase interactions between the groups \( (P < 0.05) \). Within the nonedematous group, \( Q_c \) was faster at clinical phase 1 than at clinical phases
DISCUSSION

The primary aim of this study was to determine whether the rate of production of methionine from protein breakdown, methionine transmethylation, methionine transsulfuration, and homocysteine remethylation was slower in children with edematous SCU than in those with nonedematous SCU at the time of admission for treatment. When acutely malnourished and infected, children with edematous SCU had rates of total methionine flux, flux from protein breakdown, and flux to protein synthesis that were slower than the rates of their nonedematous counterparts. There were no significant differences in homocysteine remethylation, methionine transsulfuration, or methionine transmethylation between the groups at clinical phase 1. These results suggest that in the acutely malnourished and infected state, children with edematous SCU have slower methionine production than do children with nonedematous SCU because of a slower rate of release from protein breakdown. This slower

TABLE 2

Total methionine methyl (Qm) and carboxy (Qc) fluxes, transsulfuration (TS), transmethylation (TM), and homocysteine remethylation (RM) in children with edematous and nonedematous severe undernutrition

<table>
<thead>
<tr>
<th>Kinetic variable</th>
<th>Clinical phase 1</th>
<th>Clinical phase 2</th>
<th>Clinical phase 3</th>
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<tbody>
<tr>
<td>Qm ( \times 10^3 )</td>
<td>( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{h}^{-1} )</td>
<td>( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{h}^{-1} )</td>
<td>( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{h}^{-1} )</td>
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<tr>
<td>Nonedematous</td>
<td>Edematous</td>
<td>Nonedematous</td>
<td>Edematous</td>
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<td>(( n = 11 ))</td>
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<tr>
<td>Qm</td>
<td>Qc</td>
<td>Qm</td>
<td>Qc</td>
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<tr>
<td>84 &amp; 5.6 &amp; 66 &amp; 1.96 &amp; 76 &amp; 2.7 &amp; 76 &amp; 3.3 &amp; 82 &amp; 3.1 &amp; 74 &amp; 3.3</td>
<td></td>
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<tr>
<td>63 &amp; 3.65 &amp; 50 &amp; 0.96 &amp; 53 &amp; 1.8 &amp; 52 &amp; 2.4 &amp; 56 &amp; 2 &amp; 53 &amp; 1.7</td>
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<tr>
<td>21.6 &amp; 3.2 &amp; 15.5 &amp; 1.3 &amp; 23 &amp; 2.3 &amp; 23 &amp; 1.7 &amp; 25.4 &amp; 1.8 &amp; 20.1 &amp; 2</td>
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<tr>
<td>8.6 &amp; 0.4 &amp; 9.4 &amp; 0.8 &amp; 8.7 &amp; 0.2 &amp; 8.4 &amp; 0.4 &amp; 7.9 &amp; 0.4 &amp; 7.6 &amp; 0.3</td>
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<tr>
<td>30.4 &amp; 3.2 &amp; 25 &amp; 1.3 &amp; 32 &amp; 2.2 &amp; 31.4 &amp; 1.8 &amp; 33.8 &amp; 2 &amp; 27.7 &amp; 2.4</td>
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</table>

\(^{1}\) All values are \( \bar{x} \pm \text{SEM}. \) TS, transulfuration; PB, protein breakdown; PS, protein synthesis; clinical phase 1, \( \approx 2 \) d after admission, when the subjects were infected and malnourished; clinical phase 2, \( \approx 14 \) d after admission, when the subjects were still severely malnourished but no longer infected and edematous; clinical phase 3, \( \approx 57 \) d after admission, when the subjects had recovered. Clinical phase 1 (baseline) values were compared by unpaired t test; to determine differential response to treatment, a repeated-measures ANOVA was performed.

\(^{2}\) Diagnosis \( \times \) clinical phase interaction, \( P < 0.05. \)

\(^{3}\) Main effect of diagnosis, \( P < 0.05. \)

\(^{4}\) Significantly different from nonedematous patients in the same clinical phase, \( P < 0.05. \)

\(^{5}\) Significantly different from corresponding clinical phase 2 value, \( P < 0.05. \) (Bonferroni method).

\(^{6}\) Significantly different from corresponding clinical phase 3 value, \( P < 0.001. \)
methionine production was not, however, associated with slower rates of methionine transsulfuration and transmethylation and homocysteine remethylation compared with the rates of the nonedematous children.

Our finding that methionine released from protein breakdown was slower in the edematous group than in the nonedematous group in the malnourished and infected state was not surprising, because it corroborates our earlier findings with leucine kinetics (3) and our current finding with phenylalanine kinetics [see preceding article (9)] that the rate of whole-body protein breakdown is slower in children with edematous SCU. Despite this slower methionine production by the children with edematous SCU, however, methionine transsulfuration to cysteine was maintained at a rate that was not significantly different from that of the nonedematous group. As a consequence, less methionine was available for protein synthesis. These findings indicate that the rates of methionine released from whole-body protein breakdown and available for protein synthesis are slower in children with edematous SCU than in children with nonedematous SCU in the infected and acutely malnourished state.

To explain why children with edematous SCU are sicker and less able to cope and survive chronic food deprivation, Gopalan (11) and Whitehead and Alleyene (12) proposed that impaired muscle protein breakdown may be a contributing factor to the pathogenesis of kwashiorkor. That is, whereas in nonedematous SCU, the breakdown of structural body proteins may be producing enough amino acids to maintain the synthesis of important proteins, peptides, and other biomolecules that are critical for survival, that is not the case in edematous SCU. Our observation that the rate at which methionine is released from protein breakdown is slower in the children with edematous SCU in the malnourished state lends indirect support to this hypothesis. If we are to assume that the slowing down of metabolic processes such as protein turnover is the correct response to food deprivation (13, 14), then the edematous children seem to have the correct response, not the nonedematous children. In the past we reasoned that this ability of children with nonedematous SCU to sustain the protein breakdown rate despite chronic food deprivation enables them to supply enough amino acids to sufficiently maintain the integrity and functional capacities of organ systems critical for survival (3).

Although in the acutely malnourished and infected state, methionine transmethylation and homocysteine remethylation tended to be slower in the edematous group than in the nonedematous group (Table 2), these differences were not statistically significant. Hence, despite slower production rates of both methyl- and carboxy- methionine in children with edematous SCU, flux through the transmethylation-remethylation cycle of methionine metabolism was not impaired. This finding suggests that the production of SAMe, the universal methyl group donor in the body, is not impaired in children with edematous SCU. Hence, impaired methyl group transfer is probably not involved in the pathogenesis of edematous SCU. Interestingly, at clinical phase 2, both transmethylation and remethylation were faster, which may indicate that methylation reactions were proceeding at a rate faster than the clinical phase 1 values. At clinical phase 2, the edematous children have lost edema and their appetite has returned, which indicates that their metabolic capacity has been sufficiently reestablished to permit the initiation of rapid catch-up growth. Hence, more methyl groups will be consumed for new RNA and DNA synthesis and methylation to facilitate a net increase in protein synthesis. Methyl groups will also be consumed in the methylation of new proteins and peptides and in the synthesis of several important biomolecules, such as epinephrine, serotonin, phosphatidylcholine, and creatine, as their pools are replenished.

It is interesting to note that in both groups of subjects, at all 3 clinical phases, methionine transsulfuration to cysteine was slightly more than the dietary intake of methionine of ≈8 μmol·kg⁻¹·h⁻¹. That is, at an intake of ≈1.2 g protein·kg⁻¹·d⁻¹ (80% of the Recommended Dietary Allowance), methionine was being converted to cysteine at a rate equivalent to dietary intake. In fact, the small positive methionine balance at each clinical phase was only possible because of labeled methionine infusion of 2.5 μmol·kg⁻¹·h⁻¹. This finding suggests that the requirement for cysteine is not met by the protein provided by the maintenance diet (1.2 g protein·kg⁻¹·d⁻¹) normally fed during early nutritional rehabilitation, that is, from admission to the end of the maintenance period (clinical phase 2). This may not be the case during the rapid catch-up growth phase, however, when the children are consuming ≈3 g protein·kg⁻¹·d⁻¹. It also suggests that the cysteine requirement, and hence its synthesis from methionine, has a higher priority than the methionine requirement for the early reestablishment of metabolic capacity. It is likely that a high priority for cysteine is necessary to reestablish gut

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>Clinical phase 1</th>
<th>Clinical phase 2</th>
<th>Clinical phase 3</th>
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<tbody>
<tr>
<td></td>
<td>Nonedematous</td>
<td>Edematous</td>
<td>Nonedematous</td>
</tr>
<tr>
<td></td>
<td>(n = 11)</td>
<td>(n = 11)</td>
<td>(n = 11)</td>
</tr>
<tr>
<td>Serine kinetics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total flux</td>
<td>227 ± 9.2</td>
<td>244 ± 17</td>
<td>232 ± 8</td>
</tr>
<tr>
<td>Diet + tracer inflow</td>
<td>36 ± 0.3</td>
<td>35.8 ± 0.1</td>
<td>35.6 ± 0.1</td>
</tr>
<tr>
<td>Endogenous flux</td>
<td>191 ± 9</td>
<td>202 ± 15</td>
<td>197 ± 7.9</td>
</tr>
</tbody>
</table>

All values are ± SEM. Clinical phase 1, ≈2 d after admission, when the subjects were infected and malnourished; clinical phase 2, ≈14 d after admission, when the subjects were still severely malnourished but no longer infected and edematous; clinical phase 3, ≈57 d after admission, when the subjects had recovered. Clinical phase 1 (baseline) values were compared by unpaired t test; to determine differential response to treatment, a repeated-measures ANOVA was performed.
structure and function to facilitate increased digestion of food and absorption of nutrients for rapid catch-up growth.

In severe undernutrition, the gut is marked by reduced secretory mucins (15), mucosal atrophy (16), and reduced activity of the digestive enzymes (17, 18). Mucins are rich in cysteine (19), and gut mucosal and mucin protein turnover proceed at extremely fast rates, 80%–140%/d (20, 21), which suggests a high requirement for amino acids, especially cysteine, to facilitate repair and reestablishment of function. Not surprisingly, it has been shown in piglets that the uptake of dietary methionine is unusually high, 30–40%, and that of cysteine, 80%, by the portal-drained viscera (22). Hence, during the early phase of treatment of children with SCU, the demand for cysteine and methionine by the gut will be unusually high to facilitate repair and restoration of function. Unfortunately, providing more sulfur amino acids by feeding extra protein is not an option during the early phase of nutritional rehabilitation.

Treatment of children with SCU is based on observations that these children have a reduced metabolic capacity related to a chronic reduction in nutrient intake and that immediate administration of nutrients at rates necessary to restore deficits will precipitate metabolic collapse, including further depression of immune capacity, cardiac failure, and death (14, 23). In our center, dietary management during the acute, resuscitative phase of rehabilitation is to restrict energy and protein intakes to near maintenance levels. Adherence to this treatment protocol means that methionine and cysteine intakes cannot be increased during this phase of treatment by simply feeding more protein. On the basis of our past (1, 2) and present findings, we propose that supplementing the resuscitative maintenance diet with extra cysteine will accelerate recovery.

Two of the primary donors of methyl groups in the body are serine and glycine. Our present and past findings (24) that the production of these 2 amino acids is not diminished in children with SCU strongly suggest that these 2 amino acids are still produced in adequate amounts in response to chronic inadequate food intake.

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All 4 authors contributed to all aspects of the production of this article, from the design of the study to data collection, analysis, and interpretation and writing of the manuscript. None of the authors had any conflicts of interest with the funding agencies.

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