Evaluation of formulas for calculating total energy requirements of preadolescent children with cystic fibrosis1–3

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ABSTRACT

Background: To support age-appropriate growth and to prevent and treat malnutrition in children with cystic fibrosis (CF), energy requirements for those children are often set above the requirements for healthy children. Care providers use one of several empirically derived formulas to calculate energy requirements, yet the validity of these formulas has seldom been tested.

Objective: We evaluated 6 proposed formulas for calculating energy requirements in children with CF from measured total energy expenditure, fecal fat energy loss, and the theoretic energy requirement for age-appropriate tissue accretion.

Design: Subjects were children aged 6–8 y who had CF and pancreatic insufficiency. Calculated TERs from each formula were evaluated against TER-CF by using summary statistics, regression analysis, and residual plots.

Results: Subjects (n = 53) had suboptimal nutrition and growth status and mild-to-moderate lung disease. The formula that most closely (within 2%) approximated TER-CF was the estimated energy requirement (EER) formula at the active level (EERact). Regression analysis of TER-CF onto calculated TER from each formula yielded the best indexes of model fit for the EERact formula; residual plots of the EERact formula were tightly and normally distributed around zero.

Conclusions: The EERact formula should be used to establish TER-CF in children in this age group who have mild-to-moderate CF. Changes in weight, height, and other indicators of nutritional status must be monitored to modify TER-CF as needed to support individual patient care goals.

KEY WORDS Doubly labeled water, validation, energy expenditure, energy requirement, cystic fibrosis

INTRODUCTION

Malnutrition in children with cystic fibrosis (CF) has long been observed (1–8). In the United States, of persons with CF who are <20 y old, 16% and 15% currently fall below the 5th percentile for weight and height, respectively (9), according to US growth charts (10). Obtaining or maintaining optimal nutrition and growth status is important because malnutrition has been shown to have a negative effect on morbidity and mortality (3, 6, 11–13).

In seeking to prevent or treat malnutrition in children with CF, clinicians often assess energy balance, which at its most basic is the relation between total energy expenditure (TEE) and energy intake (EI). If TEE is measured or calculated, total energy requirements (TER) can be derived for weight maintenance, loss, or gain. In healthy children, age-appropriate growth requires that daily EI exceed TEE by 20–25 kcal/d (14), and the term estimated energy requirement (EER) refers to the TEE plus energy required for tissue deposition and growth. In children with CF, energy requirements must also account for fecal loss of energy due to malabsorption, and thus the TER for children with CF (TER-CF) may be derived by summing TEE + energy for tissue deposition and growth + energy lost in stool.

The gold standard for measurement of TEE is the doubly labeled water (DLW) method; however the cost of this method prohibits its clinical use. Thus, clinicians rely on empirically derived equations for estimating TEE and subsequently EER or TER-CF. Several formulas have been proposed for measuring TER-CF (15, 16), but the validity of these formulas has seldom been tested. Only one study assessed the adequacy of 2 commonly used formulas for calculating TER-CF that included the measurement of TEE by DLW (17). Although the difference between calculated energy requirements and TEE for one formula resulted in a mean (paired) difference of 124 kcal/d at the group level, both formulas tested were associated with large error (400–600 kcal/d) at the individual level. Moreover, conclusions from this study were hampered by the small sample size and the inclusion of only 2 CF-specific formulas for testing.

The purpose of this study was to establish the formula most suited for measuring TER-CF in children. We compared the

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energy requirements calculated from 6 proposed formulas with a total energy requirement composed of measured TEE, fecal energy loss, and the energy required for growth (TER-CF). The 6 formulas were divided into 2 general categories: those developed for use in healthy children, such as the Dietary Reference Intake (18) and the Recommended Dietary Allowance (RDA; 19), and those developed specifically for use in children with CF, such as the RDA multiplied by 1.2 and the Cystic Fibrosis Consensus Report (CFCR) formulas (15, 16).

SUBJECTS AND METHODS

Subjects

Subjects (aged 6–8 y) were recruited from 13 CF centers in the United States, and the study protocol was conducted at the General Clinical Research Center (GCRC) of the Children’s Hospital of Philadelphia (CHOP). The diagnosis of CF was based on clinical symptoms and duplicate quantitative pilocarpine iontophoresis sweat tests with sodium and chloride values >60 mEq/L that were conducted at each subject’s local CF center. Exclusion criteria included a forced expiratory volume in 1 s (FEV₁) <40% predicted, significant liver disease, insulin-dependent diabetes mellitus, and *Burkholderia cepacia* sputum colonization.

Written informed consent was obtained from the parent or legal guardian of each subject, and assent was obtained from each subject. The protocol was approved by the Committee for the Protection of Human Subjects of the Institutional Review Board at both CHOP and each subject’s home institution.

Clinical status, pulmonary, stool, and genotype evaluation

Clinical status was rated by using the method of Shwachman and Kulczycki (20). Pulmonary function was evaluated by using standard methods for spirometry and plethysmography, and it was compared with reference values (21). A 72-h stool sample was collected; subjects were given standardized instructions and kits for collecting stool and were instructed to maintain their usual enzyme regimen. Stool specimens were stored in a frozen state until they were analyzed, and fat content was measured by using a gravimetric method (Mayo Medical Laboratories, Rochester, MN). The coefficient of absorption (%COA) was calculated from a 7-d weighed food record and 72-h stool collection (22). Genotype was obtained from the subjects’ medical record when available. When the genotype was not known, a blood sample was submitted for genotype analysis (Genzyme Genetics, Pittsburgh, PA). For the purposes of this study, subjects were categorized as either homozygous, heterozygous for ΔF508 mutation, or other. Other mutations included both identified non-ΔF508 mutations and unknown mutations.

Anthropometric measures

Weight and height were measured by using standard techniques (23) and a scale accurate to 0.1 kg (Sacletronix, White Plain, NY) and a stadiometer accurate to 0.1 cm (Holtain, Crymych, United Kingdom), respectively; body mass index (in kg/m²) was calculated. The height of each biologic parent was obtained by measurement or recall; those values were combined and divided by 2 to obtain a mid-parent height (24). The mid-parent height and the subject’s height were then used to calculate an adjusted height. Weight, adjusted height, and body mass indexes were compared with National Center for Health Statistics reference standards, and z scores for weight-for-age, adjusted height-for-age, and body mass index were computed (10). Upper arm circumference was measured by using a flexible plastic measuring tape (Ross Laboratories, Columbus, OH), and a skinfold caliper (Holtain, Crymych, United Kingdom) was used to measure tricep, bicep, subscapular, and suprailiac skinfold thicknesses on the right side. Total upper-arm muscle and fat areas were calculated (25), and z scores for upper arm muscle area and upper arm fat area were computed (26).

Total energy expenditure measures

TEE was measured by using the DLW technique (27). After collection of a baseline urine sample, subjects received a DLW dose consisting of 0.14 g ²H₂O (99.8 atom % excess; Sigma Aldrich, Milwaukee, WI) and 0.3 g H₁³⁰O/kg estimated TBW (10 atom % excess; ICON Services, Summit, NJ). A previously weighed absorbent cloth was used to collect any spillage of the dose, which was reweighed to quantify dose loss. Subjects collected the 2nd and 3rd daily voids on days 1, 7, 10, and 14 after the dose. Samples were stored in a frozen state until they were analyzed in the CHOP Mass Spectrometry Core Laboratory.

Isotopic enrichment of urine specimens was measured by using a Plus Isotope Ratio mass spectrometer (ThermoQuest Finnigan, San Jose, CA). Before mass spectrometer analysis, urine samples were treated with 20 mg activated charcoal and filtered through a 0.45-micron filter (Millipore Corporation, Billerica, MA). For deuterium analysis, water was reduced to hydrogen gas via the automated injection of 1.0 μL sample into a quartz tube packed with chromium metal (100–200 mesh) maintained at 850 °C. For each specimen, 5 measurements of isotopic enrichment and 5 measurements of a standard reference gas of hydrogen were obtained. All measurements were expressed as the mean ± SD of the 5 analyses. The within-sample CV was <0.5%. After correction for triprotium ion, the data were expressed as parts per mil (‰) relative to standard mean oceanic water. For ¹⁸O analysis, the sample was placed in the gas bench analyzer, and a defined volume of gas (0.3% CO₂/99.7% He) was injected into the sample vial. A period of 18 h was allowed for equilibration of the water and carbon dioxide at room temperature (≈22 °C). The sample was then injected into a gas chromatography column held isothermally at 28 °C. For each specimen, a total of 13 measurements was made, of which 9 pertained to the unknown urine specimen and 4 pertained to the reference gas. All measurements were expressed as the mean of the 9 analyses as parts per mil (‰) relative to standard mean oceanic water.

TEE was measured over a period of 9.3 ± 0.6 d. Isotope dilution spaces (in kg) were measured by using the slope intercept method and equations of Cole and Coward (28), and the mean isotope dilution ratio was 1.036 ± 0.026. Total body water was calculated as the average of the deuterium and ¹⁸O dilution spaces corrected for in vivo isotope exchange (29). The rate of carbon dioxide production was computed from the difference in elimination rate of the isotopes (27) by using the 2-point method with urine samples from day 1 (2nd and 3rd void) and day 7 or 10 (2nd and 3rd voids). The mean food quotient for the cohort (0.86) was used to calculate energy expenditure according to the modified equation of Weir (30). The analytic error for TEE measures in our laboratory is 4.7%.
Resting energy expenditure measures

Resting energy expenditure (REE) was measured by using open-circuit indirect calorimetry during a GCRC admission. Participants fasted for 12 h before REE measurement, and they were brought from the GCRC to the Nutrition and Growth Laboratory in a wheelchair. A computerized metabolic cart (Sensor medics 2900 Z; Sensor Medics, Yorba Linda, CA) was used to measure REE for 60 min in a quiet, thermoneutral room. Subjects rested in a supine position while under a large, clear, ventilated hood. Expiratory gases were sampled and analyzed every second, and 1-min averages were recorded. The first 10 min of the measurement period was devoted to environmental acclimation of the participant, and that period was not used in calculations. In addition, periods of significant movement or coughing were documented and, if associated with changes in REE, those periods were not used in calculations. The remaining data points were averaged, and REE was calculated from oxygen consumption and carbon dioxide production by using the equations of Weir (30).

Total energy requirements for children with cystic fibrosis

In healthy preadolescent children, an EI that exceeds TEE by 20–25 kcal/d (14) is required for age-appropriate tissue deposition and growth. In children with CF, chronic fecal energy loss must also be taken into account. Thus TER-CF was defined as TEE (kcal/d) + fecal fat energy loss (kcal/d) + energy required for tissue deposition and growth (kcal/d). TEE was measured in each subject by using DLW; energy for growth was 20 kcal/d for those aged 3–8 y (14), and fecal fat energy loss was determined for each subject from a 72-h stool collection, as described above. Grams of fecal fat loss were multiplied by 9 kcal/g to determine fecal fat energy loss (kcal/d).

Formulas for calculating energy requirements

The formulas proposed for calculating energy requirements in healthy children and children with CF are outlined in Table 1. The EER formulas calculate energy requirements according to weight, age, height, and physical activity level (PAL), and PAL is defined as the TEE/REE. There are 4 PALs from which to choose: “sedentary,” “low active,” “active,” and “very active.” The mean PAL for our cohort was 1.56 (reference 16), which is defined as the TEE/REE. There are 4 PALs from which to choose: “sedentary,” “low active,” “active,” and “very active.” The mean PAL for our cohort was 1.56 (reference 16).

Statistical analysis

Data analysis occurred in 5 distinct phases. Phase 1 consisted of generating descriptive statistics for the entire cohort of children, including data on nutrition, growth, and disease status. In phase 2, bivariate plots were generated in which calculated TER from each formula was plotted against the TER-CF for each subject.
TABLE 2
Characteristics of study participants

<table>
<thead>
<tr>
<th>Physical variables</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>7.3 ± 0.9 (6.0–8.9)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>22.9 ± 5.7 (16.8–40.0)</td>
</tr>
<tr>
<td>WAZ</td>
<td>−0.53 ± 1.20 (−3.69–2.51)</td>
</tr>
<tr>
<td>AHAZ</td>
<td>−0.63 ± 1.08 (−2.49–2.68)</td>
</tr>
<tr>
<td>BMIZ</td>
<td>−0.30 ± 1.13 (−3.16–2.08)</td>
</tr>
<tr>
<td>Disease variables</td>
<td></td>
</tr>
<tr>
<td>FEV1 (% of prediction)</td>
<td>98 ± 19 (55–133)</td>
</tr>
<tr>
<td>COA (%)</td>
<td>82 ± 16 (30–98)</td>
</tr>
<tr>
<td>SHW</td>
<td>89 ± 5 (77–96)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Energy variables</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>REE (kcal/d)</td>
<td>1022 ± 136 (712–1572)</td>
</tr>
<tr>
<td>TEE (kcal/d)</td>
<td>1590 ± 241 (1061–2300)</td>
</tr>
<tr>
<td>TEE:REE</td>
<td>1.56 ± 0.16 (1.28–1.87)</td>
</tr>
<tr>
<td>TER-CF (kcal/d)</td>
<td>1741 ± 287 (1100–2492)</td>
</tr>
<tr>
<td>Fecal fat energy loss (kcal/d)</td>
<td>130 ± 125 (16–1663)</td>
</tr>
</tbody>
</table>

1 n = 53 except UAMAZ UAFAZ, n = 52, and SHW, n = 49. WAZ, weight-for-age z score; AHAZ, adjusted height-for-age z score; BMIZ, body mass index z score; UAMAZ, upper-arm muscle area z score; UAFAZ, upper-arm fat area z score. FEV1, forced expiratory volume in 1 s; COA, coefficient of absorption of fecal fat; SHW, shwachman score; REE, resting energy expenditure; TEE, total energy expenditure; TER-CF, total energy requirement for children with cystic fibrosis.

2 Measured as TEE + fecal fat energy loss + energy for growth.

In phase 3, summary statistics and 6 different linear regression models were specified and tested, in which TER-CF was regressed onto calculated TER, specifically to obtain information on the performance of each formula within a common framework. Criteria for formula evaluation and model comparison included the difference between calculated TER and TER-CF and the percentage of calculated TER relative to TER-CF (group level agreement), as well as root mean square error (RMSE), Wald-statistic P value, and squared multiple coefficient of determination (R²(individual level agreement)). In phase 4, paired t tests were performed to determine the significance of the difference between TER-CF and calculated TER from each formula. Finally, in phase 5, residual versus predictor plots were generated for each regression model (specified in phase 3) to evaluate the consistency of the error variance. The predictor (calculated TER) was plotted along the x axis, and the model residuals were plotted along the y axis. All analyses were conducted by using STATA software (version 8.0; STATA Corp, College Station, TX).

RESULTS

Descriptive (phase 1) statistics for our cohort of 53 children (51% male) are shown in Table 2. As reflected by the negative Z scores, subjects presented with suboptimal growth and nutrition status values and mild-to-moderate lung disease. The mean TEE: REE (or PAL) was 1.56 ± 0.16, which indicates a low active PAL for the group (14). The PAL distribution in this cohort was 19% sedentary, 41% low active, and 40% active. Finally, 89% of subjects were homozygous or heterozygous for the ΔF508 mutation, and 88% had pancreatic insufficiency (<15 μg Fe/g stool).

Bivariate plots in which the calculated TER from each formula was plotted against the TER-CF for each child (phase 2 statistics) are shown in Figure 1. Inspection of the outliers in Figure 1 indicated that these subjects had low %COA (40–60%). The calculated TER from the EERact formula appeared both closest to and normally distributed around the line of identity. This observation was supported by the data presented in Table 3, which shows the value for calculated TER minus TER-CF, the ratio of calculated TER to TER-CF (%TER-CF), and the results of regression analyses in which TER-CF was regressed separately onto each calculated TER formula (phase 3 statistics). The EERact formula, at the group level, estimated an energy requirement closest to TER-CF (difference = 13 kcal/d and 102% TER-CF). Regression analysis of TER-CF and the proposed formulas yielded the lowest RMSE (221 kcal/d) and the highest R² (R² = 0.42, P = <0.01) for the EERact formula.

A significant difference was observed between TER-CF and calculated TER from the EERlow-act, RDA × 1.2, CFCRact, and CFCRact formulas; no significant difference was observed between TER-CF and calculated TER from the EERact and RDA formulas (paired t test, phase 4 statistics). Residual versus predictor plots (phase 5 statistics), in which the calculated TER of each formula was plotted along the x axis and the regression model residuals (from phase 3) were plotted along the y axis, are shown in Figure 2. The residuals in plots A and B (EERact and EERlow-act, respectively) were normally and tightly distributed around 0. The residuals in plots C and D (RDA and RDA × 1.2, respectively) also were normally distributed around 0 but showed greater scatter than did plots A and B. The residuals in plots E and F (CFCRact and CFCRact, respectively) were not normally distributed around 0, and they varied in a systematic fashion between being positive and negative, which suggests a curvilinear rather than a linear function.

DISCUSSION

In the current study, we compared 6 formulas using TER-CF to predict energy requirements of preadolescent children with mild-to-moderate CF and pancreatic insufficiency; the TER-CF accounted for measured TEE, fecal energy loss, and energy required for growth. We used summary statistics and regression analysis to evaluate these formulas and found that one formula, EERact, performed better than the others at both the group and individual levels. To understand why the EER formula was a more accurate predictor than were the CF-specific formulas, we explored the derivation and covariates of all the formulas.

In 1992, a consensus report on nutritional assessment and management of persons with CF was published; it recommended 2 formulas for determining energy requirements of children with CF (16). For children with normal growth and good control of steatorrhea, the consensus report advocated the use of the RDA (19) to meet daily energy requirements. At that time, the energy RDA for children aged <10 y was derived from data on EIIs associated with normal growth. These data were compiled by the World Health Organization (WHO) from studies conducted in the United States, United Kingdom, Canada, and Sweden, and actual energy requirements for the RDA were established at 5% greater than reported EI to account for underreporting (18). For children aged <10 y, the RDA for energy was expressed by age and weight. In the current study, we found that the RDA formula underestimated TER-CF by only 4% (57 kcal/d) at the group level, but it performed poorly at the individual level, especially for subjects with higher body weight. We also evaluated the performance of a method we refer to as the RDA × 1.2. This formula has
been cited in the literature (15) and anecdotally supported for use in some age groups (31). The RDA \times 1.2 formula overestimated TER-CF by the largest amount (25%, or 416 kcal/d), and it had the weakest agreement with TER-CF at the individual level.

The second formula, which was advocated by the 1992 CFCR (16), was recommended for use in children who had poor growth despite meeting energy needs according to the RDA. This formula calculates energy requirements on the basis of basal metabolic rate, lung function, level of steatorrhea, and PAL. The basal metabolic rate equations used in this formula were derived by FAO/WHO/UNU (32) from a compilation of studies. In the current study, we found that the CFCR formula at the sedentary

FIGURE 1. Bivariate plots in which the calculated total energy requirement (TER) from each formula was plotted against the TER for cystic fibrosis (TER-CF) for each child. The calculated TER from the formula for the estimated energy requirement in an active level of physical activity (EER_{act}) appears closest to and normally distributed around the line of identity. RDA, Recommended Dietary Allowance; CFCR, Cystic Fibrosis Consensus Report.
(CFCR\textsubscript{sed} and active (CFCR\textsubscript{act}) PALs overestimated the group mean TER-CF by 8% (136 kcal/d) and 22% (380 kcal/d), respectively, and that both formulas showed large variance around the mean. In addition, the CFCR formulas did not perform as well as did other formulas at the individual level. The CFCR formulas differ from other formulas in that they take FEV\textsubscript{1} and %COA into account when calculating energy requirements. In the cohort in the current study, we found that the CFCR formulas overcompensated for energy loss in stool in subjects with a low %COA, whereas the actual energy loss in stool compensated for energy loss in stool in subjects with a low %COA, resulting in a calculated TER of 2576 kcal/d. In other words, the calculated TER was increased by 914 kcal/d to account for %COA, this value was then multiplied by 1.55 (ie, 0.93/0.60), which produced a calculated TER of 2576 kcal/d. In other words, the calculated TER was increased by 914 kcal/d to compensate for energy loss in stool, whereas the actual energy loss in stool for this subject was 306 kcal/d (34 g fat x 9 kcal/g fat). However in a subject with 87% COA and similar FEV\textsubscript{1} and activity level, the correction factor for fecal energy loss was 1.07 (ie, 0.93/0.87), which increased the calculated TER by 112 kcal/d, and the actual fecal energy loss for this subject was 79 kcal/d. Our finding that the 1992 CFCR formulas overestimated energy requirements was contrary to findings of an earlier study that tested the adequacy of these formulas in 15 children aged 10.0 ± 2.4 y (17). The earlier study found that the CFCR formulas underestimated energy requirements, as compared with TEE (by DLW), by 124 kcal/d at the group level. However, the children in that earlier study had poorer lung function (\overline{x} ± SD FEV\textsubscript{1}: 79 ± 22% predicted) than did the children in our cohort (\overline{x} ± SD FEV\textsubscript{1}: 99 ± 20% predicted), and the %COA values of the earlier cohort were not presented.

The EER formulas performed best in estimating TER-CF at both the group and individual levels. These formulas (14) were designed to replace and expand on the energy requirements of the 1989 RDAs. The Institute of Medicine defined the EER as "the dietary energy intake that is needed to maintain energy balance in a healthy person of a defined age, sex, weight, height, and level of physical activity consistent with good health." In children, the Institute of Medicine says, "The EER includes the needs associated with the deposition of tissues at rates consistent with good health" (14). A major difference between the energy requirement formulas of the RDA and the Dietary Reference Intake is that the former recommendations were derived from reported EI data, whereas the latter were derived from a compilation of TEE data as measured by the DLW method. We found that the EER\textsubscript{act} formula produced a mean closest to the group mean TER-CF and a smaller SD, and when regressed on TER-CF, had the lowest RMSE and the highest \(R^2\) of all of the formulas. Whereas the EER\textsubscript{act} formula most closely approximates TER-CF when PAL is not known, we also explored the accuracy of the EER formulas when PAL is known. We used TEE and REE measurements to calculate the true PAL and appropriate EER formula (sedentary, low active, or active) for each child. The calculated TER using each child's true PAL averaged 92% of the TER-CF, underestimating energy needs by 8%; when the formula was regressed onto TER-CF for each child, the \(R^2\) increased to 0.57. Not surprisingly, this approach yielded the highest individual agreement \(R^2\) between TER-CF and calculated energy needs; however, it must be recalled that the use of EER\textsubscript{act} for all subjects came within 2% of TER-CF, a closer estimate at the group level than was obtained by using the known PAL in the EER formula. It is interesting that the EER\textsubscript{act} formula appeared to be most accurate for children with CF not because it was consistent with their true PAL (recall that the PAL of our cohort was 1.56, indicating the EER\textsubscript{swact} formula), but because the higher physical activity coefficient found in the active than in the low-active formula accounted for fecal energy loss.
The current study had limitations. Energy loss in stool was a factor used to establish TER-CF. Because our measure of fecal energy loss accounted only for fat malabsorption, it is expected that the total energy loss (fat, protein, carbohydrate, and bacteria) in stool was greater, and therefore TER-CF was theoretically greater. In a study of children of similar age who have CF (33), fecal fat represented 61% of the total energy content of the stool, and the remaining 39% was composed mainly of nitrogen and...
bacteria. If we were to increase the fecal energy value for the subjects in our cohort by 39%, the total fecal energy loss would be estimated at 181 kcal/d. That value is close to the group mean difference between the calculated TER from the EERact and EER_{new} formulas (213 kcal/d), which supports our suggestion that the increased physical activity coefficient of the EER_{new} formula reasonably accounts for fecal energy loss. The fact that we studied young children (age 6–8 y) with only mild-to-moderate disease progression was another limitation, and the findings from this study cannot be generalized to older or younger patients with CF or to those with worse lung disease. The energy requirement formulas best suited for children with advanced disease may be different and have yet to be explored.

In summary, this study sought to determine the most accurate formula for determining energy requirements of preadolescent children with CF and pancreatic insufficiency. The summary statistics and regression analyses provided complimentary evidence that the EER_{new} formula was the most accurate method among those studied for predicting energy requirements of preadolescent children with CF. We conclude that the EER_{new} formula, which can easily be calculated in a clinical setting, provides a starting point from which clinicians can establish TER-CF for children in this age group, and that weight gain and nutritional status should be monitored to adjust TER-CF as necessary to support optimal nutritional status and growth goals for the individual patient.

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BSZ and VAS designed the study; BSZ, VAS, and JIS collected the data; MY, YD, JT, IEO, and VAS were responsible for the mass spectrometry and data interpretation; JT, RFI, JIS, and VAS conducted data analysis; JT, RFI, JIS, and VAS wrote the manuscript; and EIO, MY, YD, and BSZ critically reviewed and edited the manuscript. None of the authors had a personal or financial conflict of interest.

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