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Predictive equations underestimate resting energy expenditure in female adolescents with phenylketonuria

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Abstract

Resting energy expenditure (REE) is often used to estimate total energy needs. The Schofield equation based on weight and height has been reported to underestimate REE in female children with phenylketonuria (PKU). The objective of this observational, cross-sectional study was to evaluate the agreement of measured REE with predicted REE for female adolescents with PKU. A total of 36 females (aged 11.5–18.7 years) with PKU attending Emory University's Metabolic Camp (June 2002 – June 2008) underwent indirect calorimetry. Measured REE was compared to six predictive equations using paired Student's *t*-tests, regression-based analysis, and assessment of clinical accuracy. The differences between measured and predicted REE were modeled against clinical parameters to determine if a relationship existed. All six selected equations significantly under predicted measured REE ($P < 0.005$). The Schofield equation based on weight had the greatest level of agreement, with the lowest mean prediction bias (144 kcal) and highest concordance correlation coefficient (0.626). However, the Schofield equation based on weight lacked clinical accuracy, predicting measured REE within $\pm 10\%$ in only 14 of 36 participants. Clinical parameters were not associated with bias for any of the equations. Predictive equations underestimated measured REE in this group of female adolescents with PKU. Currently, there is no accurate and precise alternative for indirect calorimetry in this population.

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Keywords

phenylketonuria; resting energy expenditure; indirect calorimetry

INTRODUCTION

Phenylketonuria (PKU) is an autosomal recessive disorder of phenylalanine (Phe) metabolism. Untreated PKU can lead to a toxic accumulation of Phe in the body, impairing neurocognitive function (1-3). To avoid negative outcomes, patients are advised to adhere to a lifelong, low-Phe diet supplemented with medical foods (also known as formula) (4). Despite the benefits of diet therapy, compliance may diminish during adolescence (5).

Nutrition management of patients with PKU primarily focuses on the restriction of phenylalanine consumption. Less of an emphasis is placed on energy intake, despite the critical role it can play in the disorder. The adequacy of energy intake and the distribution of medical food over the course a day can help prevent muscle catabolism and stabilize plasma Phe concentrations (6,7); an excess of energy intake can lead to weight gain. Previous studies report children and adolescents with PKU have a tendency to become overweight (8-10), suggesting energy balance is not being achieved. Assessment of how to approximate energy needs would be of clinical value for this population.

Total energy needs can be estimated from resting energy expenditure (REE) by multiplying REE by an activity factor (11). REE is typically measured by indirect calorimetry which is expensive, time-consuming and unfeasible for widespread use. Clinicians are therefore reliant on predictive equations to estimate REE. In a previous study (12), measured REE in female PKU children (mean age 8.9 ± 3.2 years) was statistically higher than predicted REE when using the Schofield equation based on height and weight (13). No other published research has explored the relationship between measured and predicted REE for PKU patients. The aim of this study was to determine level of agreement between indirect calorimetry-measured REE and commonly used predictive equations for a group of female adolescents with PKU.

METHODS

Participants

Participants for this observational, cross-sectional study were females with PKU attending Emory University's Division of Medical Genetics Annual Metabolic Camp from June 2002 – June 2008. Inclusion criteria were having a diagnosis of PKU after a positive newborn screen, being between the ages of 10-18 years, and having height, weight, and indirect calorimetry measurements taken in a single camp session. Participants were excluded if they were experiencing an acute illness. After explanation of the protocol, guardians of children <18 years gave formal written consent. Assent or consent, dependent on age of subject, was obtained from all participants. This study was approved by Emory University's Institutional Review Board.

Anthropometrics

Measurements were made with participants wearing light clothing and no shoes. Heights were measured to the nearest 0.1 cm using a wall-mounted stadiometer (Heightronic, Measurement Concepts, Snoqualmie, WA). Weights were measured to the nearest 0.1 kg using a digital scale (Scale-Tronix 5005, Scale-Tronix, White Plains, NY). Body mass index (BMI) was calculated from the weight and height measurements (kg/m^2). Height, weight, and BMI percentiles were calculated using the 2000 Centers for Disease Control Growth Charts (14).

Plasma Phenylalanine Concentrations

Metabolic control was assessed using plasma Phe concentrations. Fasting plasma samples (2-3 ml) were collected in heparinized tubes and analyzed on a Beckman 6300 Amino Acid Analyzer using a previously reported technique (15). While a plasma Phe concentration of 2.0 mg/dL (120 μ mol/L) is accepted as the minimum of the therapeutic range for treated PKU patients, no consensus exists for an optimal maximum concentration (4). Suggested maximal therapeutic plasma Phe concentrations range from strict to relaxed: 6.0 mg/dL (365 μ mol/L) to 10 mg/dL (605 μ mol/L), respectively (4).

Indirect Calorimetry

REE was measured using a Vmax Spectra 29 indirect calorimeter (Sensormedics, Yorba Linda, CA, USA). After an overnight fast (10-12 h), participants were transported to the Clinical Interactions Site. Participants were instructed to lie supine, still, and awake during the test. Once comfortable, the participant's head was covered with a clear plastic canopy to sample oxygen consumption (VO_2) and carbon dioxide production (VCO_2). Participants were tested for a minimum of 15 minutes, with steady state as the endpoint. Steady state was defined as a period of at least 5 consecutive minutes where VO_2 and VCO_2 each varied by <10%. Measured REE was calculated using the modified Weir equation (16). Respiratory quotient was calculated by dividing mean VCO_2 production by mean VO_2 consumption while in steady state. A respiratory quotient below 0.7 or above 1.0 indicated an abnormal fasting state or measurement error; only measurements with a respiratory quotient inside the expected range were analyzed.

Predictive Equations

Six female-specific equations with variables easily obtained in the clinical setting (height, weight, and/or age) were selected for comparison: Harris Benedict (17), Food and Agriculture Organization/World Health Organization/United Nations University (FAO/WHO/UNU) based on weight (11), FAO/WHO/UNU based on weight and height (11), Molnár (18), Schofield based on weight (13), and Schofield based on height and weight (13). The selected equations were developed using an adolescent source population with the exception of the Harris Benedict equation, which was selected due to its pervasive clinical use.

Statistical Analysis

Analyses were performed using Statistical Analysis Software version 9.2 (SAS Institute Inc, Cary, NC). Descriptive data is presented as mean $\pm$ standard deviation for continuous variables and as counts for categorical variables. A P -value < 0.05 was considered statistically significant. Bias in the predictive equations as compared with measured REE was assessed using paired Student's t -tests. In a regression-based analysis, measured REE was plotted against predicted REE. A Pearson's correlation coefficient (r) and a concordance correlation coefficient (CCC) were calculated for each comparison. CCC is a measure of precision and bias, with values closer to one indicating a higher level of agreement. Each predicted REE value was expressed as a percentage of measured REE. Values within $\pm 10\%$ of measured REE were regarded as a clinically relevant estimation, while estimations below 90% or above 110% of measured REE were considered to exceed clinical utility (19). Finally, age, weight, height, and plasma Phe regression models were fit with "measured REE minus predicted REE" as the response to determine if participants' covariates could account for the observed differences between measured and predicted REE.

RESULTS AND DISCUSSION

Thirty-six female adolescents (11.5 – 18.7 years) with PKU were evaluated. Weight and heights ranged from 30.4 – 120.0 kg and 134.6 – 166.9 cm, respectively. Descriptive characteristics of the participants are outlined in Table 1. Of the 36 participants, 17 had a BMI above the 85th percentile. The majority of participants (21 of 33 participants with Phe measurements) were considered out of metabolic control, even by the less restrictive standard of 10 mg/dL.

Table 2 summarizes the agreement of measured REE with the six selected predictive equations. Each predictive equation significantly ($P < 0.005$) underestimated measured REE. The Schofield equation based on weight had the smallest mean prediction bias (144 kcal) and the Molnár equation had the largest (308 kcal). While each equation had a similar correlation coefficient with measured REE, the CCC suggests wide variations in the precision and bias of the equations. The Schofield equation based on weight had the largest CCC (0.626), while the FAO/WHO/UNU equation based on weight and height had the lowest CCC (0.423). Clinical accuracy of predicted REE was low, with at least half of the measured values being underestimated by more than 10% for all equations. The differences between measured and predicted REE were not associated with any clinical parameter ($P > 0.05$).

Predictive equations served as poor surrogates for measured REE in this group of female adolescents with PKU. This finding extends the previous report that predictive equations, on average, underestimate REE in female children with PKU (12). Thus, indirect calorimetry may be merited for female PKU patients to accurately establish energy prescriptions that promote energy balance.

Several factors may contribute to the significant predictive biases. In addition to becoming overweight, PKU children and adolescents may have impaired linear growth (20,21). Deviations in height and weight distribution as compared to the equation's source population may bias predictive REE. In the Schofield data, the heaviest participant was 11.1 kg lighter than the heaviest participant in the current study. Limitations in the Schofield data are also seen in the FAO/WHO/UNU, since the Schofield equations were formulated as extensions of the FAO/WHO/UNU data. Thus it is no surprise that the corresponding equations performed similarly, with the updated Schofield equations faring slightly better. The Harris Benedict equation, despite pervasive use, is intended for adults which inherently suppresses REE estimations for adolescents due to differences in lean body mass (22). Additionally, the shortest participant in the Harris Benedict dataset was approximately 15.4 cm taller than the shortest participant in the current study. Previous studies have also reported that the Harris Benedict equation underestimates REE in pediatric populations (23-25). Bias in the Molnár equation, which is intended for obese and non-obese adolescents, may be attributable to the current study's slightly older and slightly shorter participants, or differences in REE measurement technique.

Despite measured energy needs being higher than predicted values, nearly half the participants had a BMI greater than the 85th percentile. This finding highlights the need for clinicians and dietitians working with children and adolescents with PKU to emphasize appropriate energy intake over the course of the day, thereby promoting energy balance and metabolic control. Diet prescriptions for PKU patients should be built considering both the weight status and plasma Phe goal of the individual patient, and not rely solely on predictive equations.

While the findings of this study suggest a significant deviation between measured and predicted REE, certain limitations must be noted. Variables that may affect REE, most notably menarche, were not evaluated. Pubertal status does not appear to be a primary determinant of REE in girls (26), although menarche status may be a significant REE predictor for premenarche girls (27). Additionally, this was an uncontrolled evaluation of predictive equations. The predictive

bias may be driven by the weight and height distribution of the participants than the underlying pathogenesis of PKU, as bias was not associated with plasma Phe concentrations. Age-match controls would elucidate the difference in future studies. Another limitation, inherent in the study of rare disorders, is sample size. A larger sample may reduce the large variability seen within the current data. Finally, it is not known whether the differences between measured and predicted energy estimates is large enough to lead to long-term, negative outcomes related to weight and metabolic control.

CONCLUSION

In conclusion, predictive equations significantly underestimate measured REE in this sample of female adolescents with PKU. The Schofield-W equation showed the highest agreement with measured REE. However, due to the significant bias and low clinical accuracy apparent in all equations, predicted REE should be used with caution. Currently, there is no accurate and precise alternative for indirect calorimetry within this population. Future studies comparing PKU patients and unaffected controls are needed to further elucidate the source of the equations' under predictions.

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Table 1

Characteristics of 36 female adolescents with phenylketonuria

Characteristic	Value
Age (y)	14.2 ± 1.9 ^a
Weight (kg)	61.9 ± 22.7
Weight Percentile	66.7 ± 29.3
Height (cm)	156.0 ± 7.0
Height Percentile	40.0 ± 27.5
Body Mass Index ^b	25.0 ± 7.6
Body Mass Index Percentile	73.3 ± 26.3
Plasma Phenylalanine (mg/dL) ^c	13.7 ± 7.5

^a Mean ± standard deviation (all such values)^b Calculated as kg/m²^c n=33; three participants did not have blood samples drawn

Assessment of six predictive equations' agreement with measured resting energy expenditure in 36 female adolescents with phenylketonuria

Table 2

	REE ^a (kcal/day)	Mean Bias (measured – predicted)		CCC ^c	Under Prediction ^d (n)	Accurate Prediction ^e (n)	Over Prediction ^f (n)	
		kcal	p-value					
Measured	1667 ± 406							
FAO/WHO/UNU, weight ^g	1501 ± 276	166	0.0014	0.707	0.589	19	13	4
FAO/WHO/UNU, weight & height ^h	1427 ± 192	240	<0.0001	0.708	0.423	21	12	3
Harris Benedict ⁱ	1469 ± 222	197	0.0003	0.712	0.505	20	12	4
Molnár ^j	1359 ± 280	308	<0.0001	0.711	0.474	26	9	1
Schofield, weight ^k	1522 ± 304	144	0.0048	0.707	0.626	18	14	4
Schofield, weight & height ^l	1443 ± 213	223	<0.0001	0.708	0.468	21	12	3

^aREE, resting energy expenditure

^br, correlation of measured REE with each predictive equation

^cCCC, concordance correlation coefficient

^dNumber of predictions less than 90% of measured REE

^eNumber of predictions between 90 – 110% of measured REE

^fNumber of prediction greater than 110% of measured REE

^gFood and Agriculture Organization/World Health Organization/United Nations University (FAO/WHO/UNU) equation based on weight = 12.2Wt + 746

^hFAO/WHO/UNU equation based on weight and height = 7.4Wt + 4.82Ht + 217

ⁱHarris Benedict equation = 9.56Wt + 1.85Ht - 4.6756A + 655.10

^jMolnár equation = 12.24Wt + 5.86Ht - 49.59Age + 389.53

^kSchofield equation, based on weight = 13.4Wt + 693

^lSchofield equation, based on height and weight = 8.365Wt + 4.65Ht + 200

For all equations: Wt = Weight in kilograms, Ht = Height in centimeters, Age = Age in years