Energy Expenditure in Chilean Children with Maple Syrup Urine Disease (MSUD)

Karen Campo • Gabriela Castro • Valerie Hamilton •
Juan Francisco Cabello • Erna Raimann •
Carolina Arias • Verónica Cornejo

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Abstract *Introduction:* Maple syrup urine disease (MSUD) is an autosomal recessive disorder caused by a blockage of branched-chain keto acid of BCAA (branched-chain keto acid dehydrogenase, BCKDH) leading to neurological damage induced by accumulation of leucine and metabolites. MSUD expenditure and energy requirement information is limited.

Objective: To determine if basal/total energy expenditure (BEE/TEE) is comparable between different determination methods and if values agree with recommendations of energy in MSUD children, and whether they relate to nutritional status.

Methods: Case-control study between MSUD ($n = 16$) and healthy children ($n = 11$) aged 6–18 years. Current nutritional status, physical activity level, body composition by DEXA and BEE/TEE by indirect calorimetry (BEEr) and predictive equations (FAO/WHO/ONU – WHO – and Schofield) were assessed; STATA 2013 ($p < 0.05$).

Results: When comparing the energy expenditure variables, there was no significant difference between groups. Moreover, compared to BEEr, equations underestimate according to BEE WHO and Schofield, respectively ($P = 0.00$; 0.02). The WHO equation had lower average calorie difference, greater concordance correlation and association with indirect calorimetry compared to the

Schofield equation for both groups, being the best predictor of the BEE for MSUD group.

Conclusion: Energy recommendations for MSUD children are according to energy expenditure; thus the use of WHO equation is a clinically and statistically feasible tool for its determination.

Introduction

Maple syrup urine disease (MSUD) is an autosomal recessive disorder caused by a blockage of branched-chain keto acid of BCAA (branched-chain keto acid dehydrogenase, BCKDH), resulting in the accumulation of branched-chain amino acids: valine, isoleucine, and leucine (VIL). High levels of leucine in the blood and brain and its keto acid (α -ketoisocaproic (α KIC)) cause metabolic decompensation. Worldwide incidence is 1:185,000 and is 1:60,000 in Latin America (Colombo et al. 2010; Kaye et al. 2006; Knerr et al. 2012; Morton et al. 2002; Strauss et al. 2010; Zinnanti and Lazovic 2011; Cornejo 2004; Cremer et al. 1982).

The classic form of MSUD has less than 2% residual enzyme activity. Clinical symptoms begin at the fifth day of life in terms of poor suck, food refusal, unexplained drowsiness, and coma. Later, additional symptoms appear, such as autonomic dysregulation, respiratory distress, apnea, bradycardia, hypothermia, axial hypotonia with episodes of distal hypertonia that could lead to opisthotonus, cerebral edema with bulging fontanelle, and a characteristic odor of burnt sugar. If this disease is not diagnosed and treated early in lifetime, severe neurologic damage or death can occur (Colombo et al. 2010; Kaye et al. 2006; Knerr et al. 2012; Morton et al. 2002; Strauss et al. 2010; Zinnanti and Lazovic 2011; Cornejo 2004; Cremer et al. 1982).

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K. Campo (✉) • G. Castro • V. Hamilton • J.F. Cabello • E. Raimann •
C. Arias • V. Cornejo

INTA – Instituto de Nutrición y Tecnología de Alimentos Doctor
Fernando Monckeberg Barro, University of Chile, Av. El Líbano
5524, Macul, Macul, Santiago, Chile
e-mail: karen.campo@inta.uchile.cl

Treatment consists of a leucine-restricted diet, eliminating all foods of animal origin. Thus, to facilitate proper protein synthesis, prevent protein catabolism, restore energy homeostasis, and promote anabolism, it is necessary to deliver BCAA-free medical foods (Knerr et al. 2012; Robinson and Drumm 2001).

Information about energy supply, energy expenditure (EE), and daily energy requirements in children with MSUD is limited. However, it is an important area of study, as the information is necessary to maintain metabolic balance and proper growth in MSUD children. Some authors have proposed hypercaloric intakes, while others have argued that a relatively low energy intake is required for normal growth and development (Bodamer et al. 1997; Barja 2011; Hauser et al. 2011; Ruiz et al. 2007).

Some clinical studies have evaluated basal and total energy expenditure (BEE and TEE) with indirect calorimetry and estimated using various predictive equations to determine the level of agreement between them and thus improve clinical care. However, the failure of predicting BEE and TEE for children with inborn errors of metabolism (IEM) has been reported, because equations are based on age, weight, and height of healthy reference populations (Bodamer et al. 1997; Barja 2011; Hauser et al. 2011; Ruiz et al. 2007; Quirk et al. 2010). In order to extrapolate to populations with pathology, adjustments are required, illustrating the need for continued study (Hauser et al. 2011).

In relation to IEM, studies were performed in children with methylmalonic acidemia (MMA), propionic acidemia (PA), and phenylketonuria (PKU) measuring BEE via indirect calorimetry and using standard predictive equations (Quirk et al. 2010; Feillet et al. 2000). Overall, there is great variability in the results since in organic acidemia different predictive equations overestimate BEE, in contrast to PKU children in which BEE is underestimated (Quirk et al. 2010; Feillet et al. 2000).

Inconsistent results were found when using standard predictive equations for estimating BEE of some diseases. Equations may not be reliable enough to determine the expenditure and energy requirements in children with MSUD. Assessment of BEE and TEE requires using indirect calorimetry and estimating with predictive equations to establish the degree of agreement between these two methods and to accurately adjust energy intake of children. The aims of this study were to determine whether the recommended daily energy intake for children with MSUD is in line relative to basal and total energy expenditure evaluated using different methods and if energy expenditure is related to nutritional status.

Methods

We conducted a case–control study among a group of Chilean children between 6 and 18 years of age with MSUD ($n = 16$)

and a control group ($n = 11$) matched by age, gender, and nutritional status. All participants signed informed consent, approved by the Ethics Committee of Instituto de Nutrición y Tecnología de Alimentos (INTA), University of Chile.

The study group was composed of MSUD children in medical and nutritional follow-up at INTA and able to follow directions. The control group was composed of healthy children of workers of this center who had no acute or chronic illnesses.

Nutritional status was assessed using WHO 2007 growth standards (WHO 2006).

Weight and height were measured in the Frankfurt position in light clothing with no shoes, using a digital scale and stadiometer (Seca), precision 0.1 kg and 0.1 cm, respectively.

Waist circumference (WC) was measured using an automatic adjustable tape (maximum of 182 cm) with a sensitivity of 0.1 cm (Fernández et al. 2004; Barrera 2013).

Indicators: Body mass index (BMI) z -score, height-for-age (H/A) z -score, and WC percentile (PCTL) were determined (Pizarro et al. 2004).

Body composition: Fat mass (FM) and fat-free mass (FFM) were evaluated using Lunar Prodigy Encore 2007 X-ray absorptiometry (DEXA) (software version 11,30,062).

Intake assessment: We conducted 24-h dietary recalls for 2 weekdays and 1 weekend day. Daily energy intake was assessed using the amino acid analyzer program, averaging respondent's days.

Assessment of physical activity (PA) was determined using a validated questionnaire that assessed usual PA for a child or adolescent during the week (Monday through Friday), consisting of five categories: (1) daily hours lying down, (2) daily hours of sedentary activities, (3) number of blocks walked per day, (4) daily hours of recreational outdoor activities, and (5) weekly hours of scheduled exercise or sports. Each category has a score of 0–2, so that the total score ranges from 0 to 10. Sedentary/light PA was considered less than 5 points; moderate activity 5–6 and vigorous was defined as 7 or more points. Physical activity factor (PAF) was identified by gender and age (Godard et al. 2008; Burrows et al. 2008; OMS 2010; FAO/WHO/UNU Expert 2001, 2005).

BEE was measured with indirect calorimetry (BEER) and estimated by two standard predictive equations. The TEE was calculated from data obtained from BEE by applying the PAF (FAO/WHO/UNU Expert Consultation 2001). A canopy indirect calorimetry (SM-2900, model 2900, Sensormedics Metabolic cart, Yorba Linda, CA, USA) was used after participants fasted for 8–10 h and 30 min of mental and physical rest in a comfortable atmosphere and temperature (Bodamer et al. 1997; Ferrannini 1988; Rodríguez et al. 2002). We also determined BEE using two standard predictive equations. The FAO/WHO/UNU 2001 by age, gender, and actual body weight (BEE WHO) and Schofield 1985 based on height and weight were used (BEE Schofield) (Table 1) (FAO/WHO/UNU Expert 2001,

Table 1 Standard predictive equations for children ages 3–18 years

Basal energy expenditure	Standard predictive equations	
	FAO/WHO/UNU 2001	Schofield based on weight and height, 1985
<i>Men</i>		
3–10	$22.706 \times W + 504.3$	$19.59 \times W + 1,303^* H + 414.9$
10–18	$17.686 \times W + 658.2$	$16.25 \times W + 1,372^* H + 515.5$
<i>Women</i>		
3–10	$20.315 \times W + 485.9$	$16.969 \times W + 1,618^* H + 371.2$
10–18	$13.384 \times W + 692.6$	$8.365 \times W + 4,65^* H + 200.0$

Source: (Shimizu-Fujiwara et al. 2012; Rodríguez and Pizarro 2006)

*Actual weight (kg) and height (cm)

Table 2 Characteristics of study groups

Description	MSUD (<i>n</i> = 16)	CONTROL (<i>n</i> = 11)	<i>P</i> *
Age (years)	12.8 (±3.3)	13.0 (±3.5)	0.86
<i>Gender</i>			
Men	5 (31%)	3 (27%)	0.82
Women	11 (69%)	8 (73%)	
<i>Anthropometry</i>			
Weight (kg)	37.3 (±10.3)	41.5 (±13.0)	0.36
Height (cm)	140.2 (±13.6)	141.6 (±15.6)	0.81
zBMI	−0.03 (−1.49 to 1.04)	0.42 (±0.52)	0.10
zT/E	−1.58 (−3.42 to 0.04)	−1.4 (−0.21 to −2.33)	0.69
Waist circumference (cm)	66.1 (±7.5)	73 (49.2–73)	0.20
<i>Body composition</i>			
Fat mass (kg)	11.57 (±4.54)	13.97 (±5.73)	0.21
Fat-free mass (kg)	25.2 (±7.45)	26.39 (±7.31)	0.62

**p* < 0.05, *T*-Student/Wilcoxon

2005; Schofield 1985). All measurements and questionnaires were conducted by a nutritionist.

Statistical analysis: The Shapiro–Wilk test was performed to determine whether the variables had normal distributions; if they did, they were presented using parametric tests. Results were expressed as means and standard deviations; otherwise, nonparametric tests were used (medians, interquartile ranges). Comparison tests (*T* test/Mann–Whitney), associations (Pearson/Spearman correlation and logistic regression), and the level of agreement (Bland–Altman test) were performed. A *P* value < 0.05 was

Table 3 MSUD children description

Description	MSUD <7 days diagnosis (<i>n</i> = 5)	MSUD >7 days diagnosis (<i>n</i> = 11)	<i>P</i> *
<i>Gender (n)</i>			
Male	1	4	
Female	4	7	
Leucine at diagnosis (μmol/L)	690 (±207)	1,939 (±884)	0.00
<i>IQ</i>			
Verbal	85 (±11)	69 (±22)	
Motor	81 (±19)	61 (±16)	
Total	82 (±16)	63 (±20)	
<i>Psychometric diagnosis (n)</i>			
High average (111–119)	—	1	
Average (90–110)	2	1	
Low average (80–89)	2		
Borderline (70–79)	—	1	
Mild impaired (55–69)	1	3	
Moderately impaired (40–55)	—	4	
Severe impaired (≤40)	—	1	
Motor disability (<i>n</i>)	0 ^a	6 ^a	
<i>Level of physical activity (n)</i>			
Sedentary/light	4	10	
Moderate	1 ^b	1	
<i>Nutrition</i>			
Oral	5	8	
Gastrostomy	—	1	
Oral + gastrostomy	—	2	

^a One child with mild motor disability

^b Hyperactivity

**p* < 0.05, *T*-Student

considered significant. The database was created in Microsoft Excel 2010, and analyses were performed using STATA 13 (StataCorp 2011 College Station, Texas).

Results

Table 2 describes general characteristics and anthropometric indicators of study groups. Both groups had normal nutritional status according to BMI z-score with a tendency toward lower height (H/A z-score ≤ 0). According to WC, 25% of children with MSUD and 18% of controls had a slight tendency to be underweight (<25 PCTL). We found no significant differences between groups in relation to body composition, FFM and FM. For descriptive purposes only, the study group was divided according to age at

Table 4 Comparison of total and basal energy expenditure between groups

	MSUD (<i>n</i> = 16)	CONTROL (<i>n</i> = 11)	<i>P</i> *
BEEr ^{a,b} (kcal/day)	1,353 (185)	1,489 (853–1,678)	0.52
TEEr ^b (kcal/day)	2,032 (351)	2,204 (502)	0.30
BEEe OMS ^{a,b} (kcal/day)	1,269 (866–1,472)	1,261 (181)	0.51
TEEe OMS ^b (kcal/day)	1,809 (298)	2,006 (336)	0.12
BEEe Schofield ^{a,b} (kcal/day)	1,248 (871–1,483)	1,231 (166)	0.49
TEEe Schofield ^b (kcal/day)	1,791 (292)	1,957 (306)	0.17

^a Mann–Whitney test (Wilcoxon rank-sum test)^b *T*-Student**p* < 0.05

diagnosis (before and after 7 days of life), as this determines important features such as IQ, feeding route, and neurological and motor impairments (Table 3).

The average energy and protein intake was calculated, and no significant difference was found between the study group (1,621 kcal/day, 78.9 g/day) and control group (1,512 kcal/day, 54.9 g/day). However, the average uptake of leucine differed significantly by group, with MSUD children having 484 mg/day compared to controls with 4,338 mg/day.

Comparing variables of energy expenditure, no significant differences between groups were found (Table 4). Both predictive equations underestimated the basal energy expenditure as to BEEr in both groups (*P* = 0.00 and 0.02) (Table 5). The BEE WHO and Schofield underestimated the MSUD group by 9.5% and 10.4%, respectively, and 7.5% and 9.4% for the control group, respectively.

Regarding indirect calorimetry, the WHO equation had lower average calorie difference, greater concordance correlation coefficient, and association than the Schofield equation for each group (Table 5; Fig. 1 and 2).

In the study group, real and estimated BEE was significantly correlated with BMI *z*-score, WC, and FFM and TEE related to WC and FFM. The control group had similar associations, except no relationship was found between BEE and BMI *z*-score (*P* < 0.05). Using logistic regression, FFM explained 81% of BEEr for MSUD children (*P* < 0.001), while FFM and WC explained 95% (*P* = <0.001) and 92% (*P* = <0.001) of the BEE computed using the WHO and Schofield equations, respectively. For the control group, FFM explained 87% of BEEr (*P* = 0.05), while FFM and WC explained 94% of the BEE computed using the WHO equation. We found no significant predictors of BEE estimated using the Schofield equation.

The majority of the MSUD children (88%) were sedentary/light PA, with only two children (12%) reporting a moderate level. In the control group, 55% were in the sedentary/light category and 45% in the moderate (*P* = 0.05) (Table 6).

Discussion

Scientific evidence relating expenditure and daily energy requirements in MSUD children is limited, yet there are recommendations on energy intake for long-term monitoring of these children, whereas it is essential to promote energy balance and maintain proper metabolic control in order to avoid metabolic decompensation and promote weight–height growth and normal development (Lewis et al. 2001).

Despite finding inconsistencies between reported energy intake and energy expenditure measured by indirect calorimetry, which could be explained by underreporting and/or weaknesses of the data collection tool used, evaluation and assessment in this study allowed us to determine that for children with MSUD daily energy intake is recommended according to their basal and total energy expenditure.

Calculation of the BEE in children with MSUD would be underestimated by predictive equations used; however, in contrast to the inconsistency of the results reported in other IEM, our results indicate that the WHO equation can be used as an alternative method for BEE determination, if the final value is adjusted in calories (+133 kcal). The equation can provide clinically reliable data and can encourage the promotion and maintenance of energy and metabolic balance in MSUD children (Hauser et al. 2011; Quirk et al. 2010; Feillet et al. 2000).

It has been reported that factors including anthropometric variables such as height, BMI, body composition, and physical activity may contribute to the variation of the BEE in healthy individuals (Marugan de Miguelsanz et al. 2011). Groups were comparable in terms of these variables (*P* < 0.05); thus, it can be noted that the elements that determine BEE in healthy children may similarly affect children with MSUD.

For healthy reference populations, FFM explains 60–80% of the variance in BEE and is closely related to protein intake. This was demonstrated in the fact that no difference was found in body composition (FM and FFM) between the study and control groups and that FFM explained 81% of the variance in BEE for MSUD children.

It was confirmed that intake of high biological value protein (intact) in children with MSUD is restricted and 85.5% of it comes from the BCAA-free medical formula (synthetic protein) (Hauser et al. 2011; Marugan de Miguelsanz et al. 2011; Shimizu-Fujiwara et al. 2012).

Table 5 Level of agreement for predictive equations regarding actual basal energy expenditure

	CONTROL											
	MSUD											
	Difference BEE			Bland–Altman			Difference BEE			Bland–Altman		
	BEE (kcal/day)	% Adequacy	Kcal	r^a	CCC ^b	X ^c	BEE (kcal/day)	% Adequacy	Kcal	r^a	CCC ^b	X ^c
Indirect calorimetry	1,353						1,489					
OMS	1,269	94.5	74	0.00	0.786	−133	1,261	84.7	228	0.848	0.682	−120
Schofield	1,248	93.4	89		0.780	−145	1,231	82.7	258	0.787	0.563	−150

^a Association level^b Concordance correlation coefficient^c X = average difference in kcal* $p < 0.05$, Mann–Whitney test (Wilcoxon signed-rank test)

Fig. 1 Difference against average data of BEE (actual and estimated by WHO) in MSUD children

Fig. 2 Difference against average data of BEE (actual and estimated by WHO) in control children

Protein restriction and its quality have been described as possible causes of stunting in children with MSUD, and some research has found that this type of diet may affect BEE variability (Lewis et al. 2001; Nishimoto et al. 2012; Sentongo et al. 2000). However, it is important to highlight that in this group, the BEE did not correlate with any of the macronutrients nor did it relate to protein source.

In this study, both groups had stunted children, which suggest that the disease alone is not the decisive factor of linear growth. There may also be a genetic component because the Chilean population, in general, is smaller in size compared to international anthropometric standards. Considering this aspect, and that no association was established with the BEE, no adjustment by this variable was required as discussed in other studies (Rodríguez and Pizarro 2006).

To our knowledge, no previous studies have described PA in this specific group. In our sample of children with MSUD, some are less likely to exercise due to late

Table 6 Level of physical activity by group

	MSUD (<i>n</i> = 16)	CONTROL (<i>n</i> = 11)	<i>P</i> *
<i>Physical activity factor (PAF)^a</i>			0.0531
Sedentary/ light	14 (88%)	6 (55%)	
Moderate	2 (12%)	5 (45%)	

^a *n* (%)

**p* < 0.05, *T*-Student

diagnosis (>7 days old) with metabolic decompensation, which caused motor disabilities. According to the National Survey of Physical Activity and Sport Habits conducted in 2012, Chile's population lacks adequate PA habits. As a country, Chile has the second highest percentages of inactivity at the international level, which is reflected in the study group analyzed in this study (Deportes 2012). In our sample of MSUD and control children, 88% and 55%, respectively, were sedentary.

It is important to mention some limitations of the study that may attenuate the importance of the results obtained. First, sample size determines the variability of the data and our sample was small. Another limitation was the failure to obtain an assessment of pubertal development, a known predictor of BEE in these stages. Regarding the latter, it is noteworthy that the groups split into smaller and older than 10 years (MSUD <10 years, *n* = 4; >10 years, *n* = 12; CONTROL <10 years, *n* = 2; >10 years, *n* = 9) to evaluate energy expenditure in prepubertal and pubertal stage, finding intragroup differences in children with MSUD that would change the results found for children under 10 years; however, the size of these subsamples does not allow for statistical significant conclusions; thus, determining the effects on the BEE of this population is pending for a future study.

The high percentage of children with MSUD in Chile assessed in our sample is a strength of the study (55%) also and that it is pioneering study in the evaluation of these variables and the results obtained. Future studies should be conducted to improve the method of PA evaluation using direct assessment, which has greater validity and precision (Rodríguez and Terrados 2006). Additional studies could also clarify and explore the course of the disease in different stages of life.

Conclusion

For children with MSUD, energy recommendations are in accordance with energy expenditure. Our results indicate

that the predictive equation, FAO/WHO/UNU 2001, reliably estimates energy expenditure for MSUD children between 6 and 18 years and that it provides adequate energy prescription for achieving the goals of treatment of this disease such as promote anabolism, proper growth, and development and maintain energy and metabolic balance in all stages of development.

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Compliance with Ethics Guidelines

Conflict of Interest

Karen Campo, Gabriela Castro, Valerie Hamilton, Juan Francisco Cabello, Erna Raimann, Carolina Arias, and Verónica Cornejo declare that they have no conflict of interest.

Informed Consent

All procedures were in accordance with the ethical standards of the Instituto de Nutrición y Tecnología de Alimentos – INTA – ethics committee and with the Helsinki Declaration, the Nuremberg Code of 1975, and the regulations for ethics committees of the University of Chile. Informed consent was obtained from all participants.

Details of the Contributions of Individual Authors

1. Karen Campo: First author responsible for planning, conducting and executing the study, data analysis, and reporting of the work described in the article.
2. Gabriela Castro: Helped plan the study and reviewed the work described in the article.
3. Valerie Hamilton: Helped plan the study and reviewed the work described in the article.
4. Juan Francisco Cabello: Reviewer.
5. Erna Raimann: Reviewer.
6. Carolina Arias: Reviewer.
7. Verónica Cornejo: Mentor and Chief of Laboratory.

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