Variable dietary management of methylmalonic acidemia: metabolic and energetic correlations[1–4]

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ABSTRACT

Background: Isolated methylmalonic acidemia (MMA) is managed by dietary protein restriction and medical food supplementation. Resting energy expenditure (REE) can be depressed in affected individuals for undefined reasons.

Objective: The objective was to document the spectrum of nutritional approaches used to treat patients with MMA, measure REE, and analyze the dependence of REE on body composition, biochemical, and nutritional variables.

Design: Twenty-nine patients with isolated MMA (22 *mut*, 5 *cblA*, 2 *cblB*; 15 males, 14 females; age range: 2–35 y) underwent evaluation. REE was measured with open-circuit calorimetry and compared with predicted values by using age-appropriate equations.

Results: Nutritional regimens were as follows: protein restriction with medical food ($n = 17$ of 29), protein restriction with medical food and supplemental isoleucine or valine ($n = 5$ of 29), or the use of natural protein alone for dietary needs ($n = 7$ of 29). Most *mut* patients had short stature and higher percentage fat mass compared with reference controls. Measured REE decreased to $74 \pm 13.6\%$ of predicted ($P < 0.001$) in the ≤ 18-y group ($n = 22$) and to $83 \pm 11.1\%$ ($P = 0.004$) in patients aged >18 y ($n = 7$). Linear regression modeling suggested that age ($P = 0.001$), creatinine clearance ($P = 0.01$), and height z score ($P = 0.04$) accounted for part of the variance of measured REE per kilogram of fat-free mass (model $R^2 = 0.66$, $P < 0.0001$).

Conclusions: There is wide variation in the dietary treatment of MMA. Standard predictive equations overestimate REE in this population primarily due to their altered body composition and decreased renal function. Defining actual energy needs will help optimize nutrition and protect individuals from overfeeding. This trial is registered at clinicaltrials.gov as NCT00078078. *Am J Clin Nutr* 2011;93:47–56.

INTRODUCTION

Isolated methylmalonic acidemias (MMAs) are a group of autosomal recessive inborn errors of metabolism representative of metabolic disorders that feature a block near the terminal oxidation step of substrates feeding into the propionate pathway, primarily the branched chain amino acids, isoleucine and valine, but also threonine, methionine, odd chain fatty acids, and cholesterol. They are predominantly caused by deficiency of methylmalonyl-coenzyme A (-CoA) mutase (MUT), an enzyme that uses 5′-deoxyadenosylcobalamin as a cofactor to catalyze the conversion of methylmalonyl-CoA into succinyl-CoA in the mitochondrial matrix (1). Genetic defects that impair cofactor

transport and metabolism (*cblD variant2*, *cblA*, *cblB*) also cause isolated methylmalonic acidemia. Reduced MUT activity results in the production of methylmalonic acid as well as the accretion of upstream propionyl-CoA–derived metabolites, such as 3-OH-propionic acid and 2-methylcitrate. Affected individuals display massive elevation of methylmalonic acid in the blood, urine, and other bodily fluids. Despite aggressive management of patients with MMA, mortality remains high, and survivors suffer from multisystemic disease, including poor growth, recurrent metabolic crises, chronic renal disease, neurologic problems, pancreatitis, and osteopenia (2–4).

Although nutritional management is the mainstay of therapy for MMA, clear guidelines do not exist. Conventional dietary therapy revolves around limiting the intake of propiogenic precursors—particularly isoleucine, valine, methionine, and threonine—and the provision of a high-energy diet to prevent fasting and catabolism. Supplemental amino acids, such as alanine, have been supplied in an attempt to improve growth, and, rarely, growth hormone has been administered (5–8). To date, very few studies have examined optimum dietary therapy for patients or assessed whether differing dietary regimens have effected significant outcome changes (9, 10).

In this study, we documented the nutritional approaches used to treat a cohort of well-characterized patients with isolated MMA; assessed correlations between clinical and biochemical variables, particularly resting energy expenditure (REE); and searched for treatment-related effects by using regression analysis. In addition to presenting an evidence-based overview of current dietary therapy for MMA, our investigations define the factors influencing basal energy requirements in this population and provide new insights into the underlying cause of the depressed REE that is present in most affected individuals.

SUBJECTS AND METHODS

Subjects

Patient studies were approved by the National Human Genome Research Institute Institutional Review Board as part of the National Institutes of Health (NIH) study 04-HG-0127 "Clinical and Basic Investigations of Methylmalonic Acidemia and Related Disorders" and performed in compliance with the Helsinki Declaration (clinicaltrials.gov identifier: NCT00078078; recruitment start date February 2004). Adult participants or parents of the younger patients signed written informed consent for participation. Patients were evaluated between 2004 and 2009 and were primarily self-referred with no significant overrepresentation from a particular center. There was no recruitment strategy on the basis of race, sex, nutritional status, or disease severity. Ongoing care and dietary management were provided by regional metabolic centers.

Neurologic assessment by a pediatric neurologist was included in the evaluation of every participant. All subjects were ambulatory; 14 of 29 patients had clinical or neuroradiographic evidence of a metabolic stroke. Study participants were evaluated at steady state and were without clinical symptoms of metabolic instability or evidence of ketosis or lactic acidosis. Those with a history of thyroid disease were excluded from the analysis. One patient (patient 18; age: 11 y) was on growth hormone treatment at the time of the study, whereas another (patient 25; age: 24 y) had received growth hormone between the ages of 8 and 14 y.

Metabolic and laboratory studies

The diagnosis of MMA was confirmed with cellular biochemical studies including ^{14}C-propionate incorporation and complementation assays (laboratory of David S Rosenblatt, Division of Medical Genetics, McGill University, Montreal, Canada) or molecular genetic analysis of the *MUT*, *MMAA*, and *MMAB* genes (GeneDx, Gaithersburg, MD) (1). (*See* Table 1 footnote for definitions of MMA subtypes.) Because only 2 patients were assigned the *mut*$^-$ subtype, they were included in the *mut*^{0} group for subsequent analysis. Routine laboratory investigations included determination of the complete blood count, serum electrolytes, pancreatic enzymes, thyroid function, lipid panel, iron studies, and numerous serum and urine metabolic measurements. When possible, 24-h urine collections were used to measure creatinine clearance (11) and calculate metabolite output.

Diet and nutritional regimens

Regional metabolic experts at specialized care centers dictated dietary management. The intake used for calculations was based on the prescribed diet and prepared in the NIH metabolic kitchen and administered to patients during the study visit.

Dietary analysis was performed on the basis of formula recipes plus detailed dietary histories and 3-d food records. Five subjects received enteral formula only with negligible oral intake (on average, <100 calories and <1 g protein/d). Of the remaining 23 subjects, 9 completed 2–6-d food records and 14 provided detailed histories of typical dietary intake. Dietary analyses and calculations were performed by using Nutrition Data System for

Research, software versions 2005–2009, developed by the Nutrition Coordinating Center, University of Minnesota.

Anthropometric measurements and body composition analysis

Anthropometric measurements were expressed as age- and sex-specific *z* scores by using the epidemiologic software package Epi Info, version 3.5.1., based on the CDC 2002 reference database (Centers for Disease Control and Prevention, Atlanta, GA). Body mass index (BMI) *z* scores for patients aged >18 y were calculated by using the following equation: BMI – mean/[SEM*(square root of *n*)] (*n* = number of examined persons) (12).

Whole-body composition in grams of fat or fat mass and fat-free (or lean) mass (FFM) was measured by using dual-energy X-ray absorptiometry (DXA; Hologic Delphi A; Hologic, Bedford, MA). Values were compared with mean (±SD) values for the reference child and adolescent models of body composition, matched for age, sex, and ethnicity (13–15).

REE

REE was measured by open-circuit indirect calorimetry (Deltatrac equipment; VIASYS, Yorba Linda, CA) performed with the use of a respiratory metabolic cart. Subjects consumed their habitual diet during the days before the study. Before each test, the calorimeter was calibrated with the use of a reference gas mixture obtained from the manufacturer. Respiratory variables were recorded when steady state had been achieved, typically between 0400 and 0800 while the child was supine in bed. The indirect calorimetry study was performed after 12 h of fasting in adult individuals. However, 17 patients received feedings by gastrostomy tube throughout the night and were not fasted to avoid disruption of their usual regimen.

The modified Weir equation $[3.9(\dot{V}O_2) + 1.1(\dot{V}CO_2)] \times 1.44 =$ REE (kcal/d) was used to calculate energy equivalency from oxygen consumption and carbon dioxide production (16). Predicted values for REE in patients aged ≤18 y were assessed by using the Schofield, WHO/FAO/UNU, and Fleisch equations (*see* Supplemental Table 1 under "Supplemental data" in the online issue). Predicted values for REE in patients >18 y old were assessed by using the Harris-Benedict and Mifflin–St Jeor equations (17–21) (Supplemental Table 1 under "Supplemental data" in the online issue). A correction for amino acid oxidation, using total urine nitrogen from 24-h collections, did not change the calculated respiratory quotient compared with what was measured during indirect calorimetry (not presented).

Data analysis

The results are presented as means ± SDs. Statistical analyses were performed by using SPSS version 17 (SPSS Inc, Chicago, IL) or SAS version 9 (Cary, NC) software. The paired *t* test was used for comparisons of measured REE and predicted REE, and an independent *t* test was used to compare values between females and males. Pearson's correlation coefficient was used to evaluate bivariate correlations. A linear regression was performed with REE and REE per kilogram of FFM as dependent variables by using SPSS (SPSS Inc). A *P* value <0.05 was considered significant.

RESULTS

Demographic, enzymatic, and anthropometric characteristics

Characteristics of the 29 participants (22 *mut*, 5 *cblA*, 2 *cblB*) who completed dietary evaluation and the indirect calorimetry study are presented in **Table 1**. The patient cohort was primarily white, but individual patients were of Native American, Hispanic, Northern European, Middle Eastern, and Asian descent.

The time of diagnosis was highly variable and ranged from the prenatal period up to 39 mo; evaluation at our center was between the ages of 2 and 35 y (mean ± SD: 13.4 ± 9.08 y). Seven patients (5 *mut,* 1 *cblA,* 1 *cblB*) had received organ transplants [combined liver and kidney transplant (*n* = 4), liver transplant (*n* = 2), or kidney transplant (*n* = 1)].

The diversity of the patient group is supported by the spectrum of mutations that is present (Table 1). In the *mut* group (*n* = 22), there were 23 different mutations identified. The majority of *mut* patients had missense mutations [16 of 22 patients (25 of 44

alleles)]. The most common mutation was p.R369H, which was present in 6 individuals. Eleven of 22 *mut* patients harbored at least one nonsense or frameshift mutation (14 of 44 alleles). Seventeen *mut* patients were compound heterozygotes, and none shared an identical genotype with the exception of 2 sisters (patients 4 and 17). Five individuals were apparently homozygous for a single mutation, and, of these, 3 originated from consanguineous unions. Both patients with *cblB* and 3 of 5 patients with *cblA* were homozygous for the common mutations in *MMAB* (p.R186W) and *MMAA* (p.R145X), respectively.

Height-for-age, weight-for-age, and BMI-for-age, expressed as *z* scores (mean ± SD), are presented for the *mut* patients in **Figure 1**A and in more detail for all subtypes in Supplemental Table 2 under "Supplemental data" in the online issue. Patients aged ≤20 y in the *mut* group had a mean *z* score of 0.01 ± 1.2 for weight, −1.04 ± 1.2 for height, and 0.77 ± 1.1 for BMI (*n* = 18). Four females and 3 males aged ≤20 y had a BMI-for-age in the 85th–95th percentile (classified as overweight), and 1 female and 3 males aged ≤20 y had a BMI-for-age above the 95th

TABLE 1
Patient characteristics[1]

Patient no.	Age	Age at DX	Sex	Class	Transplant	Mutation 1	Mutation 2
	y	*mo*					
1	2	23	M	*cblA*		p.Y129X	p.T198SfsX6
2	3	0.25	F	*mut⁰*		p.R228X	p.R369H
3	4	0.25	F	*mut⁰*		p.G670R	p.R403X
4	6	Prenatal	F	*mut⁰*		p.R108H	p.G623R
5	6	0.3	M	*mut⁰*	L&K	p.E224X	p.R228X
6	6	0.25	M	*mut⁰*		c.753+2T→A, splice	p.R581X
7	7	0.3	F	*mut⁰*		p.G642R	p.G642R[2]
8	7	3	M	*mut⁰*		p.P615R	p.L434HfsX3
9	7	0.25	M	*mut⁰*	L	p.R369H	p.S594RfsX11
10	8	11	F	*cblB*		p.R186W	p.R186W[2]
11	8	Prenatal	F	*mut⁻*		p.M186V	p.R369H
12	9	0.75	M	*mut⁰*		p.R369C	p.R403X
13	10	0.13	F	*mut⁰*		p.L11TfsX38	p.V553GfsX17
14	10	0.1	F	*mut⁰*		p.A191E	N/A
15	10	12	M	*mut⁰*		p.R108C[3]	p.R108C[3]
16	10	0.25	M	*mut⁰*		p.R228X	c.1332+1delG, splice
17	11	0.5	F	*mut⁰*		p.R108H	p.G623R
18	11	0.06	M	*mut⁰*	L	p.R369H	p.R369H[3]
19	13	12	M	*cblA*		p.R145X	p.R145X[2]
20	17	6	M	*cblA*		p.E147G	p.P151AfsX19
21	18	0.1	M	*mut⁰*		p.A191E	p.N219Y
22	18	39	F	*cblB*	L&K	p.R186W	p.R186W[2]
23	20	6	M	*mut⁰*		p.R581X	p.R581X[3]
24	21	0.06	F	*mut⁰*	L&K	p.R369H	p.R369H[2]
25	24	0.3	M	*mut⁰*		p.N219Y	p.H350Y
26	25	0.25	F	*mut⁰*		N/A	N/A
27	31	0.25	F	*mut⁻*	L&K	p.E276X	p.R369H
28	33	36	F	*cblA*	K	p.R145X	p.R145X[2]
29	35	13	M	*cblA*		p.R145X	p.R145X[3]

[1] Demographic characteristics and enzymatic and mutation information for the 29 patients studied are listed by age. The class of methylmalonic acidemia is assigned on the basis of the results of the ^{14}C-propionate incorporation assay, which indirectly measures the activity of the MUT (methylmalonyl-coenzyme A) enzyme. *mut⁰* was assigned if enzymatic activity was nondetectable, and *mut⁻* was assigned if residual enzymatic activity was present. Designation of the enzymatic block to a particular complementation group (*cblA*, *B*) was made with heterokaryon rescue, in which the cell line from the affected individual is mixed with a panel of established cell lines of known status (eg, *cblA*, *cblB*). DX, diagnosis; L, liver-only transplant; K, kidney-only transplant; L&K, liver and kidney transplant; N/A: not available.
[2] No known consanguinity.
[3] Known consanguinity.
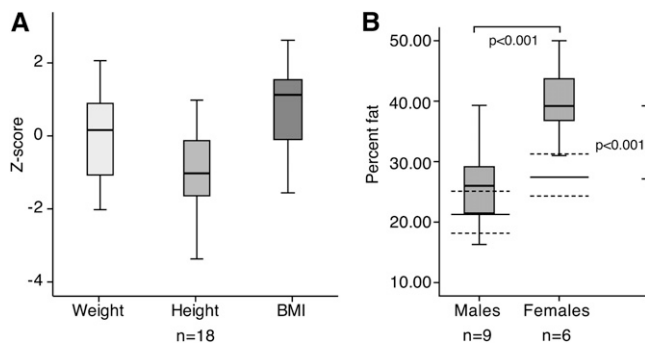
FIGURE 1. A: Weight-, height-, and BMI-for-age *z* scores for patients in the *mut* (methylmalonyl-coenzyme A) group of methylmalonic acidemia aged ≤20 y (*n* = 18) are depicted. Boxes represent the middle 50% of all cases per variable, whereas the remaining 50% is contained between the box and whiskers on each side. The single line inside each box represents the median of the entire data set. The location of this line suggests the skewness in the distribution, when noticeably shifted away from the center, as is the case particularly for the BMI-for-age *z* score in the *mut* subgroup. B: Percentage fat mass in males and females aged ≤18 y with the *mut* subtype of methylmalonic acidemia is depicted. Percentage fat mass was significantly higher in female patients with the *mut* subtype than in males (*P* < 0.001, *t* test). Female patients also had significantly higher percentage fat mass compared with the highest value for white females in the reference population [27.6 ± 6.1% (*n* = 46), depicted as solid lines ± dotted lines (*P* < 0.001, *t* test)] (14). Statistical analyses were performed by using SPSS version 17 (SPSS Inc, Chicago, IL).

percentile (classified as obese). The mean BMI (in kg/m²) for all patients aged >20 y (*n* = 6) was 24.2 ± 6.2, with *z* scores between −1.56 and 0.9 SD (mean = −0.49). Women had higher values than did men (26.5 ± 6.5 compared with 19.5 ± 0.63, respectively; *P* = 0.12); 2 subjects were considered obese with a BMI >30 (22). BMI-for-age *z* score correlated significantly with age (*r* = −0.555, *P* = 0.002), with the highest values observed in the younger age group (Supplemental Figure 1, B and C, under "Supplemental data" in the online issue).

Fat mass (Figure 1B), measured by DXA, ranged between 13% and 50% (mean ± SD: 30.8 ± 10%). Mean values in patients aged ≤18 y were compared with age-, sex-, and ethnicity-matched control reference data (14, 15). Percentage fat mass was significantly higher in females than in males with the *mut* subtype [39.78 ± 7.26 (*n* = 6) compared with 27.3 ± 7.3 (*n* = 9), respectively; *P* < 0.001]. Females with the *mut* subtype had also significantly higher percentage fat mass compared with the highest value for white females in the reference population [27.6 ± 6.1 (*n* = 46), *P* < 0.001] (Figure 1B).

Although patients with the *mut* and *cblB* type had lower mean height *z* scores than did patients with *cblA,* consistent with the milder phenotype of the vitamin B-12–responsive *cblA* patients, and girls in the *mut* group had lower average height (−1.49 ± 1.4 compared with −0.76 ± 0.9) and higher BMI (1.07 ± 0.9 compared with 0.58 ± 1.2) *z* scores compared with males, these differences were not statistically significant (Supplemental Table 2 under "Supplemental data" in the online issue). Transplanted patients had significantly greater height *z* scores than did non-transplanted patients (mean ± SD: −0.006 ± 0.99 compared with −1.028 ± 1.47, respectively; *P* = 0.054) (data not presented). Patient 5 (Table 1), who received a liver and kidney transplant at the age of 5 y, had a height and weight at age 6 y that were greater than the 60th percentile. Patient 18, who received a liver transplant at age 19 mo and who began growth

hormone replacement therapy 1 y before the NIH visit at age 11 y, had a height *z* score of −0.13 and a BMI *z* score of 1.29. Patient 25, who was 24 y old during the NIH evaluation, received growth hormone between 8 and 14 y of age, and his height and BMI *z* scores were −1.7 and −1.4, respectively.

Laboratory and metabolic studies

Biochemical variables are presented in **Table 2**. Plasma methylmalonic acid concentrations ranged between 36 and 6129 μmol/L, plasma glycine between 211 and 1179 μmol/L, and daily urinary output of methylmalonic acid between 21 and 7308 μmol · kg⁻¹ · d⁻¹.

Creatinine clearances ranged between 14 and 132 mL · min⁻¹ · 1.73 m⁻². A progressive decrease in creatinine clearance associated with a decrease in methylmalonic acid urinary output and an increase in plasma methylmalonic acid concentrations was observed in patients with the *mut* subgroup in the different age groups, reflecting the decreasing filtration of methylmalonic acid in patients with progressive renal failure. As expected, plasma concentration of methylmalonic acid correlated negatively with creatinine clearance in the *mut* group (*r* = −0.746, *P* < 0.001). Three patients, >20 y of age, had a creatinine clearance <30 mL · min⁻¹ · 1.73 m⁻²; a liver and kidney transplant recipient had a creatinine clearance of 64 mL · min⁻¹ · 1.73 m⁻² 9 y after transplant. No significant correlations were observed between biochemical variables and any of the dietary indexes.

Dietary and nutritional management

Patients were treated with highly variable dietary regimens (**Table 3**). Five patients received only formula and had negligible oral dietary intake, 18 subjects received a combination of formula and diet, and 6 subjects only received food orally. Energy intake ranged between 23 and 86 kcal · kg⁻¹ · d⁻¹; and total protein intake, expressed as natural (complete) protein plus free amino acids in medical foods, ranged between 0.38 and 2.94 g · kg⁻¹ · d⁻¹. Natural (complete) protein intake ranged between 0.29 and 2.12 g · kg⁻¹ · d⁻¹ [33–265% of Recommended Dietary Allowance (RDA)]. As a subgroup, the transplant recipients had total protein intakes ranging between 0.50 and 1.06 g · kg⁻¹ · d⁻¹ with natural (complete) protein intake accounting for between 0.29 and 0.85 g · kg⁻¹ · d⁻¹ (36–89% of RDA). Eighteen patients were treated with medical foods that provided from 0.21 to 1.95 g · kg⁻¹ · d⁻¹ of synthetic amino acids. Daily propiogenic precursor load from these diets ranged between 0.28 and 2.66 mmol/kg. Five patients received valine supplementation (68–170 mg/d), including one who had received a combined liver and kidney transplantation, and 2 received additional isoleucine (48–340 mg/d).

REE

Mean measured REE for the ≤18-y group was 78 ± 13.6%, 71 ± 12.2%, and 75 ± 12.7% of the REE predicted based on the Fleisch, WHO/FAO/UNU, and Schofield equations, respectively (*P* < 0.001 for each mean measured compared with predicted REE value by paired *t* test comparisons), as depicted in **Figure 2**A and **Table 4**. Similarly, in the group aged >18 y, measured REE was 78 ± 11% predicted by the Harris-Benedict equation (*P* = 0.004) (Figure 2B).

TABLE 2
Biochemical variables (n = 29)[1]

Subgroups	Plasma methylmalonic acid	Plasma glycine	Cr/Cl	Urine methylmalonic acid	Methylmalonic acid output
	$\mu mol/L$	$\mu mol/L$	$mL \cdot min^{-1} \cdot 1.73\ m^{-2}$	$mmol/mol\ Cr$	$\mu mol \cdot kg^{-1} \cdot d^{-1}$
mut					
All nontransplanted patients (n = 18)	1434 ± 1807 (84–6129)	576 ± 289 (211–1179)	68 ± 30 (14–115)	5232 ± 4843 (559–16,543)	3460 ± 2336 (390–7308)
Age groups					
2–9 y (n = 8)	626 ± 455 (139–1380)	539 ± 261 (211–861)	78 ± 15 (59–103)	5624 ± 6329 (684–16,543)	4165 ± 3064 (996–7308)
10–18 y (n = 6)	2020 ± 2176 (151–5328)	598 ± 352 (288–1179)	66 ± 35 (32–115)	7045 ± 4650 (2970–14,439)	3533 ± 2451 (839–6815)
>18 y (n = 4)	2317 ± 2698 (84–6129)	618 ± 321 (339–1066)	49 ± 43 (14–104)	2478 ± 1893 (559–4391)	2151 ± 1876 (390–4522)
Transplanted patients (n = 4)	120 ± 81 (45–231)	454 ± 111 (364–602)	86 ± 15 (64–96)	1025 ± 616 (314 ± 1401)	375 ± 333 (93–822)
cblA					
All patients (n = 5)	89 ± 77 (36–223)	412 ± 167 (302–702)	97 ± 31 (45–132)	728 ± 459 (180–1206)	684 ± 883 (21–1688)
cblB					
All patients (n = 2)	665 (290–1020)	445 (380–508)	56 (51–61)	3722 (1289–6156)	1618 (1328–1908)

[1] All values are means ± SDs; ranges in parentheses. Reference ranges: plasma methylmalonic acid ($\leq$0.04 $\mu mol/L$), plasma glycine (127–341 $\mu mol/L$), urine methylmalonic acid [<3 mmol/mol creatinine (Cr)]. Cr/Cl, creatinine clearance; *mut*, methylmalonyl-coenzyme A.

Measured REE was also lower than the actual total energy provided in both age groups ($P < 0.0001$ in the $\leq$18-y group, and $P = 0.004$ in the >18-y group), with a mean ratio of total energy provided over measured REE (in kcal) for all patients of 1.91 ± 0.50 (range: 1.29–3.54). Ratios per MMA subgroup are provided in Table 3. The ratio of total energy over the predicted REE was 1.45 ± 0.32 (range: 1.01–2.39).

There was no significant difference between the predicted REE calculated by using Fleisch, WHO/FAO/UNU, or Schofield equations for the $\leq$18-y group ($P = 0.230$, one-factor ANOVA). Mean REE measurements for the patients aged >18 y using the Harris-Benedict (78 ± 11% predicted) and Mifflin–St Jeor (81 ± 10% predicted) equations were likewise very similar ($P = 0.6$). No differences were observed in measured or percentage predicted REE between males and females (Table 4). Similarly, there were no significant differences between transplant recipients (77 ± 6% predicted, $n = 7$) and nontransplanted patients (76 ± 13% predicted) ($P = 0.91$) (data not shown).

We sought to explore the dependency of the REE on biochemical and anthropometric variables. Linear regression analysis was performed for measured REE as well as for REE corrected for FFM as determined by DXA analysis (REE/kg FFM) (Table 4). For measured REE, a model including age, percentage FFM, and total protein intake ($g \cdot kg^{-1} \cdot d^{-1}$) had an R^2 of 0.588 (F statistics, $P < 0.0022$). Correlation coefficient P values in the model were as follows: $P = 0.012$ for age, $P = 0.016$ for percentage FFM, and $P = 0.041$ for total protein intake (**Table 5**).

REE per kilogram of FFM was also examined by using a regression model including age, creatinine clearance, height-for-age z score, and total protein intake ($g \cdot kg^{-1} \cdot d^{-1}$) as dependent variables. This analysis revealed an R^2 of 0.661 (F statistics, $P < 0.0001$) and the following P values: age, $P = 0.001$; creatinine clearance, $P = 0.013$; height-for-age z score, $P = 0.041$; and total protein intake, $P = 0.884$.

Bivariate correlations of REE per kilogram of FFM with variables including creatinine clearance ($r = 0.541$, $P = 0.017$), total protein intake ($r = 0.577$, $P = 0.01$), and height z score ($r = 0.503$, $P = 0.056$) are shown in **Figure 3**, A, B and C, respectively. The difference between total energy provided and measured REE expressed per kilogram of FFM correlated significantly with age ($r = -0.569$, $P = 0.006$) and was highest in the younger patients (Supplemental Figure 1A under "Supplemental data" in the online issue).

DISCUSSION

As part of an effort to document the spectrum of nutritional approaches used to manage patients with MMA, we have evaluated affected individuals in the inpatient setting to survey dietary therapy, to study the potential contribution of dietary management on patient phenotype, and to examine whether REE, a critical variable that profoundly influences the individual response to diet, is inherently abnormal in these patients or ascribable to a set of clinical or laboratory variables. The data presented in this article derive from a cohort who have been comprehensively characterized in a research environment and should serve as a valuable resource for future studies on the natural history of MMA and other disorders of organic acid metabolism.

TABLE 3
Dietary characteristics[1]

Subgroups	Total protein	Complete protein	Incomplete protein equivalent	Total energy	Provided kcal/ measured REE
	$g \cdot kg^{-1} \cdot d^{-1}$	$g \cdot kg^{-1} \cdot d^{-1}$	$g \cdot kg^{-1} \cdot d^{-1}$	kcal/d	
mut					
All patients (n = 21)	1.33 ± 0.72[2]	0.75 ± 0.32	0.58 ± 0.57	1725 ± 581	1.98 ± 0.5
Age groups					
2–9 y (n = 10)	1.50 ± 0.67	0.84 ± 0.17	0.72 ± 0.63	1453 ± 263	2.12 ± 0.6
10–18 y (n = 7)	1.46 ± 0.81	0.82 ± 0.46	0.64 ± 0.60	1780 ± 511	1.83 ± 0.4
>18 y (n = 5)	0.69 ± 0.26	0.48 ± 0.18	0.23 ± 0.26	2307 ± 904	1.91 ± 0.4
cblA					
All patients (n = 5)	1.32 ± 0.72	1.0 ± 0.63	0.31 ± 0.52	1665 ± 871	1.68 ± 0.3
cblB					
All patients (n = 1)	0.67	0.67	0	1409	1.49

[1] Dietary characteristics of the 29 patients are grouped by methylmalonic acidemia class and age for the patients in the *mut* (methylmalonyl-coenzyme A) group. REE, resting energy expenditure.

[2] Mean ± SD (all such values).

The subjects who participated in this study were evaluated at a single site but represented multiple treatment centers, mainly in the United States; they had varying ages, anthropometric measurements, nutritional regimens, biochemical variables, and transplant status (Table 1). The largest subgroup consisted of the *mut^o* class (n = 20 of 29), which is in agreement with other survey-based reports on isolated MMA (23, 24). In contrast to other single-center studies, all patients in our cohort were placed into subclasses by enzymology and in almost every instance (28 of 29 patients) causative mutations were identified. Molecular genetic subclassification will be especially important to perform as future cohorts are accrued, because it should allow the inherent heterogeneity of the population to be refined and treatment regimens to be precisely compared between centers.

The nutritional management of the patients evaluated here was very diverse and appeared to follow 3 major approaches: natural protein restriction with medical food use (n = 17 of 29); natural protein restriction with medical food and supplemental isoleucine or valine (n = 5 of 29) and the use of natural protein alone for dietary needs (n = 7 of 29). Restriction of complete (natural) protein to less than the RDA was common (n = 22 of 29) and ranged from 33% to 98% of the RDA, which averaged 70 ± 19% over the entire group. A surprising observation of this study was the administration of large supplemental doses of isoleucine solution, valine solution, or both to a subset of patients (n = 5 of 29) who were also receiving medical foods. Although some nutritional textbooks support the administration of valine and isoleucine to patients with MMA and propionic acidemia (25), older studies firmly established that isoleucine and valine were toxic and induced vomiting and ketosis when given to patients (26, 27). Clearly, the use of supplemental valine and isoleucine in MMA is an area in which further clinical research is required, especially because there have been no studies to prove the efficacy of such an approach.

The diversity of approaches used to treat similar groups of patients provided an ideal opportunity to examine whole-body energetics in MMA. The one consistent finding noted in most patients (26 of 29) was a significantly lower than predicted REE ($P < 0.0001$) (Figure 2, A and B) measured by the well-accepted method of indirect calorimetry and assessed by using appropriate predictive equations (28–30). A methodologic or measurement error in our reported values seems unlikely because *cblC* patients participating in our protocol (data not shown) and several *cblA* patients reported herein showed a normal REE, validating the accuracy of our method.

There have been conflicting reports on the REE in MMA. Feillet et al (31) observed, on average, a 20% reduction as compared with predicted values, with significantly lower values in females. In contrast, Van Hagen et al (32) observed no difference between measured and predicted values of REE in 2 patients with MMA and in 6 patients with propionic acidemia. These authors noted a higher relative BMI than in the patients studied by Feillet et al and suggested that the intake of synthetic amino acid mixtures and a higher energy intake may account for the discrepancy. The results of our study suggest a means to reconcile these findings. By normalizing measured REE to FFM, we predict that both patient groups would show similar results to what we have documented in our cohort.
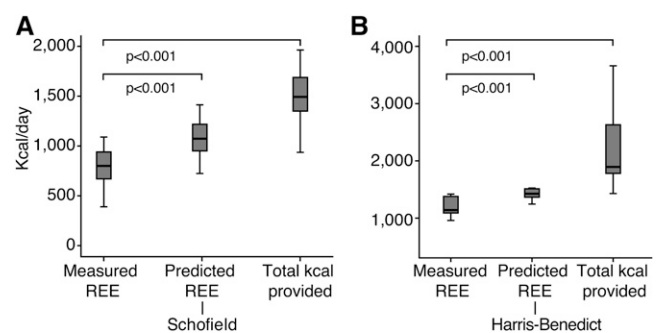
FIGURE 2. Measured and predicted resting energy expenditure (REE) and total kilocalories provided are presented in kilocalories per day for the entire patient population. A: Measured REE compared with predicted REE based on the Schofield equation (17) and total kilocalories per day provided to patients ≤18 y of age (n = 22). B: The same variables for patients >18 y of age in which predicted REE is calculated by the Harris-Benedict equation (20) (n = 7). Measured REE was lower than predicted by any of the equations as well as from the actual total calories provided in both age groups ($P < 0.001$ for both paired comparisons between measured REE and the values derived from each of the predictive equations as well as measured REE compared with total daily kilocalories provided, paired *t* test). Statistical analyses were performed by using SPSS version 17 (SPSS Inc, Chicago, IL).

TABLE 4
Measured and percentage predicted resting energy expenditure (REE)[1]

Subgroups	Measured REE[3]	Measured REE/FFM[3]	Percentage predicted REE[2]				
			Fleisch	WHO/FAO/UNU	Schofield	Harris-Benedict	Mifflin–St Jeor
	kcal/d	*kcal/kg FFM*					
mut							
All patients (*n* = 22)	890 ± 248	38.7 ± 10.7	76 ± 10	70 ± 10	73 ± 10	75 ± 10	79 ± 9
Age groups							
2–9 y (*n* = 10)	714 ± 174	43.1 ± 5.3	72 ± 12	67 ± 11	71 ± 11		
10–18 y (*n* = 7)	974 ± 218	41.2 ± 14	81 ± 7	73 ± 7	76 ± 8		
>18 y (*n* = 5)	1124 ± 161	28.7 ± 5				75 ± 10	79 ± 9
Sex							
Males (*n* = 12)	944 ± 259	39.3 ± 9.5	77 ± 8	72 ± 7	75 ± 8	79 ± 14	81 ± 13
Females (*n* = 10)	825 ± 229	38.0 ± 12.4	74 ± 13	66 ± 12	71 ± 13	72 ± 8	78 ± 9
cblA							
All patients (*n* = 5)	1172 ± 459	37.0 ± 9.0	87 ± 18	76 ± 24	80 ± 25	88	90
Age groups							
2–9 y (*n* = 1)	409	41.1	58	48	51		
10–18 y (*n* = 2)	1457	43.3	100	90	94		
>18 y (*n* = 2)	1270	28.5				88	90
Sex							
Males (*n* = 3)	1139 ± 638	35.7 ± 6	87	72	76	97	97
Females (*n* = 2)	1222 ± 144	38.9 ± 15	87	84	88	80	83
cblB							
All patients (*n* = 2)	830 ± 155	36.9 ± 19	75	71	77		

[1] REE scores for all 29 patients are shown. Equations listed in Supplemental Table 1 under "Supplemental data" in the online issue were used to calculate predicted score (17–21). FFM, fat-free mass; *mut*, methylmalonyl-coenzyme A.

[2] Values are measured REE as a percentage of predicted values ± SDs.

[3] Values are means ± SDs.

The failure of predictive equations to accurately estimate REE has been reported in various clinical settings (33–35). Because predictive equations are based on age, weight, and height of normal historical reference populations, adjustments for significant deviations from normal body composition, such as obesity, have been proposed (36–38). FFM represents ≈40% of body weight in nonobese patients (39) and is the major determinant of the REE, explaining ≈60–80% of its variance (40–43). Although lower than predicted in most of our patients, when measured REE was adjusted for FFM in this study group (mean REE/kg FFM = 41.8 ± 9.9 kcal/kg FFM in patients aged <18 y)

(Table 5), it was very similar to values observed by other authors for controls in several pediatric populations (44–46). Because most of our patients had an increased amount of fat and decreased FFM, it is highly unlikely that a control set from the normal population will be identified, and future efforts will need to use patients with obesity (38) or decreased muscle mass syndromes, such as Duchenne muscular dystrophy (47), as comparators.

To examine the dependency of REE on other factors, measured REE, as well as REE adjusted for FFM, were used to query further correlations between clinical variables. Regression

TABLE 5
Contribution of body composition, protein intake, and renal function to resting energy expenditure (REE) in children with methylmalonic acidemia[1]

Variable	Parameter (β)	SE	P (variable)	R^2	P (model)
REE (kcal/d)					
Intercept	208.9	275.1	0.45	0.58	<0.0022
Age	14.2	5.2	0.012		
FFM percentage	11.1	4.2	0.016		
Total protein intake (g · kg^{-1} · d^{-1})	−159.1	73.4	0.041		
REE/kg FFM (kcal/kg FFM)					
Intercept	36.9	5.0	0.001	0.66	<0.0001
Age	−0.642	0.1	0.001		
Creatinine clearance	0.120	0.04	0.013		
Height z score	−2.39	1.09	0.041		
Total protein intake (g · kg^{-1} · d^{-1})	−0.39	2.7	0.884		

[1] Linear regression models for measured REE and measured REE per kilogram of fat-free mass (FFM) in the whole patient population are shown. The resulting equation for REE was as follows: REE = 208.9 + (14.2 × age) + (11.1 × percentage FFM) − [159.1 × total protein intake (in g · kg^{-1} · d^{-1})]. The equation for REE/kg FFM was as follows: REE/kg FFM = 36.9 − (0.642 × age) + (0.12 × creatinine clearance) − (2.39 × height z score) − [0.39 × total protein intake (in g · kg^{-1} · d^{-1})]. Statistical analysis was performed by using SPSS version 17 (SPSS Inc, Chicago, IL).
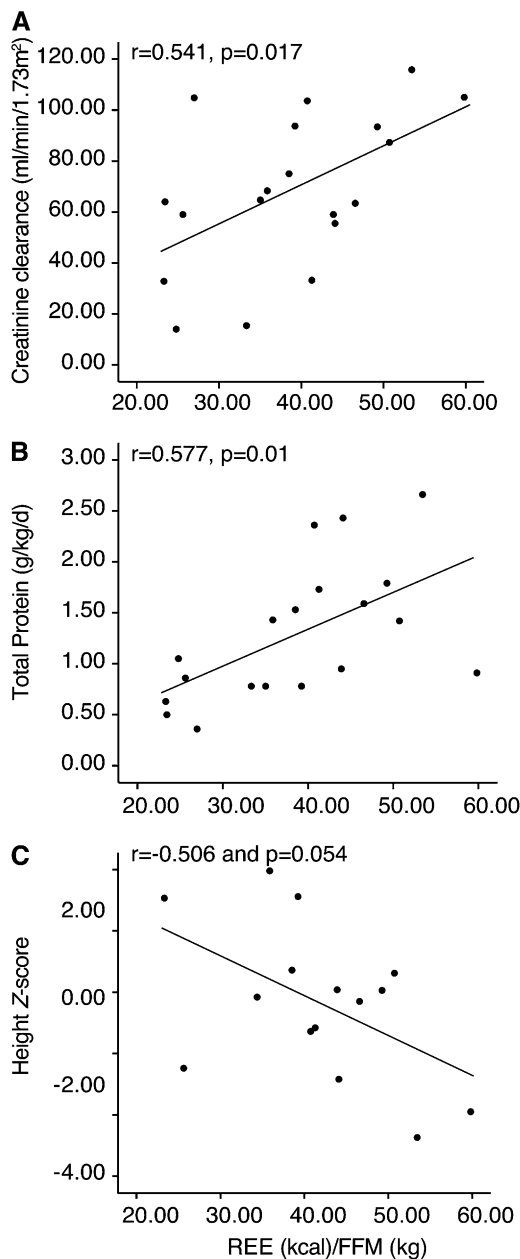
FIGURE 3. Bivariate correlations for patients in the *mut* (methylmalonyl-coenzyme A) subgroup with dual-energy X-ray absorptiometry data are depicted between REE (resting energy expenditure) per kilogram of FFM (fat-free mass) and creatinine clearance (mL $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2}; $n = 19$), total protein intake (g $\cdot$ kg^{-1} $\cdot$ d^{-1}; $n = 19$), and height-for-age z score (age: ≤ 20 y; $n = 15$). Pearson's correlation coefficients and P values for each correlation are shown.

modeling then defined significant associations between FFM-adjusted REE and creatinine clearance, height z score, total protein intake, and age in the *mut* group (Table 5 and Supplemental Figure 1 under "Supplemental data" in the online issue). Whereas a depressed REE is observed in patients with MMA, it can be largely explained by the patients having diminished FFM, with contributions likely from factors known to affect REE, such as impaired renal function and protein intake (48–50). That protein intake may influence the REE in MMA is particularly intriguing because branched-chain amino acid oxidation, a process known to liberate the bulk of circulating metabolite load in

patients (51), occurs largely in the skeletal muscle beds (52, 53), the dominant component of FFM. Examining organ-specific contributions to REE (54) may yield further insight into the mechanisms by which the REE is altered in this patient population.

The increased fat mass and BMI present in several patients in this study agrees with observations made by previous authors (10, 31, 32). The present article and that of Feillet et al (31) provide direct measures of the low basal energy requirements in this patent population and lend support to the observations by Thomas et al (55) that some patients with organic acidemias can achieve normal growth with an energy intake of as low as 53% of the RDA. Although the fat mass percentage was higher in our female population compared with males, this was not associated with a lower measured REE, as was reported by Feillet et al (31). Thus, the depressed REE does not explain the higher than expected fat mass of females in our study and suggests that, in some patients, abnormal body composition may be multifactorial. The total energy provided to patients in this study was $\approx$2-fold greater (mean: 1.91; range: 1.29–3.54; Table 3) than the measured REE. This ratio would correspond to the energy demands of heavy physical activity (56), yet none of the patients had more than mild to moderate activity levels. Whether the higher energy intake (Supplemental Figure 1A under "Supplemental data" in the online issue) and increased BMI in the younger age group (Supplemental Figure 1, B and C, under "Supplemental data" in the online issue) represent a trend toward increased use of gastrostomy tube feeding, supplemental medical food, or both in recent years is uncertain, but these factors are likely contributory to the abnormal body habitus seen in the patient population. Taken together, obesity can be influenced by multiple factors in this disorder, including decreased physical activity, continuous overnight feeding, excess energy intake to avoid catabolic state, and possibly other factors intrinsic to disease-related pathophysiology, such as mitochondrial dysfunction (57).

Until better treatment options become available, optimizing dietary management remains the primary means to improve outcome in patients with MMA. The results of this study show that predictive equations are not a reliable guide to the energy requirements of individuals with MMA, especially because significant deviations from normal growth and body composition are present. Future studies to examine whole-body metabolism with stable isotopes may be useful to delineate the factors determining energy requirements and nutritional needs in this patient population.

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