The Relationship between Dietary Intake, Growth, and Body Composition in Inborn Errors of Intermediary Protein Metabolism

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Objectives To examine relationships between dietary intake, growth and body composition patterns in patients with inborn errors of intermediary protein metabolism and to determine a safe protein:energy ratio (P:E ratio) associated with optimal growth outcomes.

Study design Retrospective longitudinal data of growth and dietary intake in patients (n = 75) with isovaleric acidemia (IVA; n = 7), methylmalonic acidemia/propionic acidemia (MMA/PA; n = 14), urea cycle defects (UCD; n = 44), classical maple syrup urine disease (MSUD; n = 10) were collected. Prospective longitudinal data of growth, dietary intake, and body composition from 21 patients: IVA (n = 5), MMA/PA (n = 6), UCD (n = 7), and MSUD (n = 3) were collected at clinic visits.

Results Fifty-two of 75 (66%), 49 of 74 (68%), and 44 of 65 (68%) patients had a *z*-score of 0 (±1) for lifetime weight, height, and body mass index, respectively. Patients with MMA/PA had the lowest median height and weight *z*-scores, and MSUD patients had highest median body mass index *z*-score at all ages. In IVA, MMA/PA, and UCD, total natural protein intake met or exceeded the Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO)/United Nations University (UNU) recommended safe levels. Median percentage fat mass was 17.6% in IVA, 20.7% in MMA/PA, 19.4% in UCD, and 17.8% in MSUD. There was a significant negative correlation between percentage fat mass and total protein intake in IVA, MMA/PA, and UCD (r = –0.737; *P* = .010). The correlation between the P:E ratio and growth variables in IVA, MMA/PA, and UCD suggest a safe P:E ratio (>1.5 to < 2.9) g protein:100 kcal/day.

Conclusion Growth outcomes in inborn errors of intermediary protein metabolism are not always ideal. Most patients with IVA, MMA/PA, and UCD consume sufficient natural protein to meet FAO/WHO/UNU recommendations. A P:E ratio range of (>1.5 to < 2.9)g protein/100 kcal/day correlates with optimal growth outcomes. *(J Pediatr 2017;188:163-72).*

The goals of dietary treatment in inborn errors of intermediary protein metabolism are to secure metabolic stability and promote normal growth. Recently, attention has also been directed toward attaining long-term ideal body composition. However, there is a lack of evidence-based research to inform best practice in the management of inborn errors of intermediary protein metabolism. Therefore, treatment modalities are still reliant on expert opinion rather than large-scale, clinical studies that could inform specific nutrient needs. Indeed, dietary management of patients with inborn errors of intermediary protein metabolism differs worldwide. Consensus exists regarding reduced natural protein intake and for the use of amino acid–based formulas (AAFs) for disorders such as maple syrup urine disease (MSUD), in which natural protein tolerance is below requirements.[1] In contrast, in isovaleric acidemia (IVA), in methyl-malonic acidemia and propionic acidemia (MMA/PA), and urea cycle disorders (UCDs), the consumption of AAF in combination with a lower intake of natural protein is debated. For example, published guidelines for UCD recommend a low natural protein diet without the use of essential amino

%fatmass	Percentage body fat mass
AAF	Amino acid–based formula
BIA	Bioelectrical impedance analysis
BMI	Body mass index
BMR	Basal metabolic rate
E%BMR	Energy intake as a percentage of basal metabolic rate
EAAS	Essential amino acid supplement
FAO	Food and Agriculture Organization of the United Nations
FFM	Fat-free mass
IVA	Isovaleric acidemia
MMA/PA	Methyl-malonic acidemia and propionic acidemia
MSUD	Maple syrup urine disease
P:E ratio	Protein:energy ratio
REE	Resting energy expenditure
UCD	Urea cycle disorders
UNU	United Nations University
WHO	World Health Organization

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acid supplements (EAASs) for those who can adequately meet estimated requirements from foods and are metabolically stable,[2] yet EAASs are still advocated for regular use in some centers.[3] Consequently, studies that compare nutritional outcomes in children with disorders who consume natural protein only versus those requiring natural protein and AAF are required.

Dietary factors that contribute to nutritional outcomes are likely to be multifactorial and include the quality and quantity of protein tolerated, the frequency of further protein restriction and high nonprotein energy intake during metabolic decompensation[1,2,4,5] and the abnormal feeding behaviors and food aversion observed in patients with these disorders.[6,7] Taken together, these protein-restricted regimens may result in short- and long-term nutritional risks.

Exact nutritional requirements for patients with inborn errors of intermediary protein metabolism have not been studied systematically, partly owing to variability in individual tolerance and, therefore, are not well-defined. Consequently, dietary adequacy is often measured against recommendations for healthy populations. The application of these reference recommendations for children with potentially different requirements is, therefore, problematic. Population-based protein requirements also assume an adequate energy intake to ensure efficient protein use, which presents an additional challenge in children prescribed highly modified diets. The model of how protein and energy requirements are interdependent has evolved over decades of nutritional research,[8-13] and has been incorporated into the 1985 consensus statement from the World Health Organization (WHO), Food and Agriculture Organization of the United Nations (FAO), and United Nations University (UNU).[14] This document summarizes the concept of the protein:energy ratio (P:E ratio), which describes the proportion of dietary energy derived from protein, and has traditionally been used to answer the question: If an individual or group consume this diet, in amounts that will satisfy energy needs, will the concentration (density) of protein also be high enough to meet protein needs?[14] This concept is both relevant and challenging in inborn errors of intermediary protein metabolism, where protein intake may be marginal owing to treatment requirements or protein aversion. Furthermore, the value of AAF as a protein alternative must also be considered given the differences in their absorption and bioavailability compared with natural protein.[15] Consequently, nutritional outcomes, including reduced height, increased incidence of overweight, and abnormal body composition are documented in inborn errors of intermediary protein metabolism.[6,16-19]

Current dietary prescriptions in inborn errors of intermediary protein metabolism do not consider the relationship between protein and energy intake formally. We hypothesized that the use of the P:E ratio in the dietary management of inborn errors of intermediary protein metabolism may have value and provide clinicians with additional guidance when making dietary prescriptions.

The aim of this study was to answer the following questions: Do patients with inborn errors of intermediary protein metabolism consume adequate protein and energy? What relationships exist between dietary intake and growth patterns in patients with inborn errors of intermediary protein metabolism? Finally, can we define a safe P:E ratio to be used as an additional clinical tool in the management of patients with inborn errors of intermediary protein metabolism?

Methods

This study was approved by the Royal Children's Hospital Human Research Ethic Committee (HREC: 30066B).

We collected longitudinal data on dietary intake and growth of patients born between 1976 and December 2014 (n = 75; 30 males, 45 females) with IVA (n = 7), MMA/PA (n = 14), UCD (n = 44), and classical MSUD (n = 10). Data were collected from medical and dietetic clinic records when patients were metabolically stable. Dietary data consisted of dietary recall, food diaries, and dietary history. The data represent reported rather than prescribed intake.

Parents provided written consent for inclusion of their children. We collected longitudinal data on dietary intake and growth, body composition measurements of patients born between January 1995 and December 2014 (n = 21; 8 males, 13 females): IVA (n = 5), MMA/PA (n = 6), UCD (n = 7), and MSUD (n = 3) currently under our care. Data were collected over a 2-year period and included between 1 and 6 separate measurements of body composition and dietary intake for individuals, depending on the age at diagnosis, time to consent, frequency of appointments, metabolic stability, and compliance with data collection requirements.

Weight and length for children under 2 years of age were obtained by standard techniques using digital baby weighing scales and crown-heel length on a scaled length board. Height and weight of children greater than 2 years of age were measured using a combined stadiometer and digital weight measuring station (Seca 284, Seca, Hamburg, Germany). Participants were in light clothing with no shoes. Height to the nearest 0.1 cm and weight to the nearest 0.1 kg were recorded. Body mass index (BMI) was calculated using the equation kg/m^2. Measurements were performed by the dietitian or clinic nurse.

Anthropometric measurements were expressed as age- and sex-specific *z*-scores, using the epidemiological software package Epi Info (version 3.5.1), based on the Centers for Disease Control and Prevention (Atlanta, Georgia) 2002 reference database.

Dietary data collected from 3-day food diaries were analyzed by the same metabolic dietitian using the dietary analysis program Foodworks (Xyris, Version 7.0.3016, Kenmore Hills, Australia). Dietary intake of protein in grams per kilograms per day was compared with FAO/WHO/UNU recommended safe levels.[20] Energy intake was expressed as a percentage of the basal metabolic rate (BMR) calculated using predictive equations according to Schofield,[21] based on age, sex, height, and weight. The P:E ratio was expressed as g protein/100 kcal/day and compared with the P:E ratio calculated from the 1985 FAO/WHO/UNU equation:[14]