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The relationship between dietary intake, growth and body composition in Phenylketonuria

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ABSTRACT

Aim: Phenylketonuria (PKU) is an inborn error of protein metabolism that results from perturbation in phenylalanine hydroxylase activity leading to elevated blood levels of phenylalanine (phe). We aimed to explore the relationships between dietary patterns (total-protein, natural-protein, amino-acid formula), and the ratio of protein to energy intake with growth and body composition.

Method: Longitudinal prospective data (1–6 measurements) of growth, dietary intake and body composition in patients treated with phe-restricted diet only (D-PKU; n = 32), and tetrahydrobiopterin (BH_4) ± phe-restricted diet (BH_4-PKU; n = 5) were collected over a two-year period. Healthy siblings provided control data (n = 21).

Results: There were no significant differences in weight-, height-, BMI z-score or percent body fat mass (% fatmass) between the D-PKU, BH_4-PKU and control groups or between the all-types of PKU combined and controls, which confirmed 'normal' growth in the PKU cohort. Total-protein intake in the all-types of PKU group met or exceeded WHO safe protein recommendations. There were no significant relationships between anthropometric and dietary variables. Significant negative correlations were found in body composition: %fatmass and total-protein intake ($r_s = -0.690$, $p \leq 0.001$), natural-protein intake ($r_s = -0.534$, $p = 0.001$), and AAF intake ($r_s = -0.510$, $p = 0.001$). Age was significantly correlated with %fatmass ($r_s = 0.493$, $p = 0.002$) A total-protein intake of 1.5–2.6 g/kg/day and natural-protein intake > 0.5 g/kg/day were associated with improved body composition. An apparent safe P:E ratio of 3.0–4.5 g protein/100 kcal was strongly associated with appropriate growth outcomes.

Conclusions: Clinical decision-making needs to consider both the enhancement of natural-protein tolerance and the application of an apparent 'safe' protein to energy ratio to support optimal growth and body composition in PKU.

1. Introduction

Phenylketonuria (PKU) is an inborn error of protein metabolism that results from perturbation in phenylalanine hydroxylase activity leading to elevated blood levels of phenylalanine (phe). As elevated phe levels have a toxic effect on the brain, treatment with a diet low in natural protein needs to commence as soon as possible after birth. Lifelong goals of treatment in PKU are to maintain phe levels within the target range to achieve optimal neurocognitive outcomes and maintain normal physical growth and development [1,2]. Recent attention has been directed towards attaining long term ideal body weight and composition in children and adults with PKU [3,4]. There is a recognised spectrum in PKU ranging from 'severe' when individuals have a very low phe tolerance and therefore require a severely restricted natural-protein intake, to milder forms when individuals have a higher phe tolerance.

Consensus exists regarding the need for reduced natural-protein intake and supplementation with precursor free amino acid based formulae (AAF), as natural-protein tolerance is mostly below safe requirements [5,6]. The emergence of cofactor therapy tetrahydrobiopterin (BH_4) [7], has meant that the group of PKU patients who respond to this treatment form a special group in dietary terms, as

Abbreviations: PKU, Phenylketonuria; phe, phenylalanine; %fatmass, percent body fat mass; %FFM, percent fat free mass; P:E ratio, protein to energy ratio; BH_4, tetrahydrobiopterin; AAF, amino acid formula; E%BMR, energy intake as a percentage of basal metabolic rate; BIA, bioelectric impedance analysis; %PE, percentage of dietary energy from protein

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they tolerate a higher natural protein intake which in some cases may result in a normal diet [5]. Currently, published recommendations for 'total-protein intake' in PKU, defined as natural-protein intake plus AAF, are based on healthy population nutritional recommendations with an additional estimated factor to account for the apparent difference in quality between natural-protein and AAF [6]. In addition, consideration is given to the role of AAF in achieving optimal phe levels and micronutrient intake [3,8]. Logically it follows that nutritional outcomes in PKU are likely to be affected by both the quality and quantity of protein consumed and total energy intake, however this needs further documentation.

We have shown previously that the protein:energy ratio (P:E ratio) of the diet has a pivotal role in long term nutritional outcomes, including body composition, in children with inborn errors of intermediary protein metabolism [9] and children on the ketogenic diet [10]. The concept of P:E ratio considers the inter-dependence of protein and energy intakes as it describes the proportion of dietary energy derived from protein. The concept has been incorporated into WHO/FAO/UNU recommendations to consider when describing the risk of protein insufficiency particularly in those consuming marginal diets [11]. We hypothesised that the P:E ratio may have benefit as a clinical monitoring tool in PKU due to the specific features of a PKU diet which include restricted consumption of protein of high biological value and reliance on the use of AAF as a 'protein substitute' to meet nutritional requirements.

The aim of this study was to answer the following questions: Does the intake of protein, impact on the growth and body composition trajectory in children with PKU? Is there an optimal P:E ratio for prescribing dietary intake for children with PKU?

2. Methods

This study was approved by the RCH Human Research Ethic Committee (HREC: 32056A) Written consent was provided by parents for the additional measure of body composition to be completed at routine clinic visits.

We collected prospective longitudinal data of growth, dietary intake and body composition in patients born between January 1996 and December 2014 who attend our specialist treatment centre in Melbourne Australia over a 2-year period. The initial measurement being denoted as the 'baseline' measurement.

Data were analysed in patients with: PKU treated with phe restricted diet D-PKU (n = 32; 10 males, 22 females), PKU treated with tetrahydrobiopterin (BH_4) ± phe restricted diet (BH_4-PKU) (n = 5; 3 males, 2 females). D-PKU patients were not categorised by type based on newborn peak phenylalanine levels. Data have also been combined and denoted as all-PKU which represent the spectrum of PKU and the range of protein tolerance. To incorporate every available measurement (all-measurements), the mean of each growth and dietary variable was calculated for each individual patient and the median then calculated for the group. The mean value was compared to the baseline measurement of each patient.

Controls: a single height, weight and body composition measurement was collected from healthy sex and aged matched sibling controls (n = 21; males 8, females 13).

Weight and length for children < 2 years of age were obtained by standard operating procedures using digital baby weighing scales and crown-heel length on a scaled length board. Height and weight of children > 2 years of age were measured using a combined stadiometer and digital weight measuring station (Seca 284). 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 (ME) or clinic nurse.

All anthropometric measurements were expressed as age and gender-specific z-scores, using the epidemiological software package Epi Info (version 3.5.1), based on the Centres for Disease Control and Prevention (Atlanta, GA) 2002 reference database.

Dietary data from food diaries were analysed by a single metabolic dietitian (ME) using the dietary analysis program Foodworks (Xyris, Version 7.0.3016, Kenmore Hills, Australia). Food diaries were reviewed with parents to clarify content for analysis [12]. A subset of diaries was independently analysed by two dietitians for energy intake to ensure reliability. Dietary intake of protein in g/kg/d was compared with FAO/WHO/UNU recommended safe levels [11]. One gram of natural-protein was considered equivalent to 50 mg phenylalanine. This included all phe containing foods and 'uncounted' foods that contain small amounts of phenylalanine such as fruits and vegetables that are allowed freely, yet may increase natural-protein intake by up to 49% [13]. Energy intake was expressed as a percentage of basal metabolic rate (E%BMR) calculated for each patient using the BMR predictive equations of Schofield [14]. This calculation considered a physical activity level (PAL) defined by number of sessions undertaken per week of formal exercise activity, and classified as low, medium and high PAL. Mean energy intake was calculated for individual patients and median energy intake was calculated for the group. P:E ratio was expressed as gram protein/100 kcal/d.

Body composition was measured by Bioelectrical Impedance Analysis (BIA) using the QuadScan 400, Bodystat® (Isle of White LTD) as per the manufacturer's instructions. Participants were instructed to fast for at least 90 min and to not exercise prior to the BIA assessment. Percent fat-free mass (%FFM) and percent fat mass (%fatmass) were estimated using raw impedance values using the equation of Houtkooper [15].

3. Statistical analysis

Statistical analyses were performed using SPSS for Windows software version 23 (IBM, Illinois, Chicago, IL). Significance was set at $p < 0.05$. Continuous variables including z-scores for weight, height and BMI, protein and energy intake and P:E ratio are presented as median and range. Non-parametric tests included: Kruskal-Wallis test for one-way between-group analysis of variance; Mann-Whitney *U* test for differences between two independent groups on a continuous measure; Friedman test for variance between multiple measures in the same subjects. Spearman correlation coefficient Rho (r_s) was used to evaluate associations between categorical variables. Stepwise multiple linear regression analysis was performed with anthropometric parameters and body composition as the dependent variable and dietary parameters as the independent variables.

4. Results

There was no difference in age or gender distribution between PKU and control groups (Table 1).

4.1. Growth and body composition

There was no significant difference in weight-, height-, BMI z-score or %fatmass between the D-PKU, BH_4-PKU and control groups or between the all-PKU group and control group (Table 1). Low numbers of BH_4-PKU patients precluded comparisons with D-PKU patients.

4.2. Dietary intake

Median total-protein intake exceeded the FAO/WHO/UNU recommended safe levels, (data not shown). As expected, natural-protein intake was higher for BH_4-PKU patients. Diaries were independently analysed by two dietitians for energy intake and the maximum variation in energy was 10% with 34% having only 1–2% variation. Validity of energy intake was calculated as a % BMR, with valid records being defined as those with a reported energy intake between 2.1 and