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Analysis of body composition and nutritional status in Brazilian phenylketonuria patients

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ABSTRACT

Background: Phenylketonuria (PKU) is characterized by phenylalanine (Phe) accumulation to toxic levels due to the low activity of phenylalanine-hydroxylase. PKU patients must follow a Phe-restricted diet, which may put them in risk of nutritional disturbances. Therefore, we aimed to characterize body composition parameters and nutritional status in Brazilian PKU patients also considering their metabolic control.
Methods: Twenty-seven treated PKU patients older than 5 years, and 27 age- and gender-matched controls, were analyzed for anthropometric features and body composition by bioelectrical impedance (BIA). Patients' metabolic control was assessed by historical Phe levels.
Results: There was no effect of PKU type, time of diagnosis, or metabolic control for any analyzed parameter. About 75% of patients and controls were eutrophic, according to their BMI values. There were no difference between groups regarding body composition and other BIA-derived parameters.
Conclusions: Brazilian PKU patients do not show differences in body composition and nutritional status in comparison with controls, regardless metabolic control. Although similar to controls, PKU patients may be in risk of disturbed nutritional and metabolic markers as seen for the general population.

1. Introduction

Phenylketonuria (PKU, OMIM: 261600) is an inherited metabolic disorder characterized by deficient (mild PKU) to null (classical PKU) activity of the hepatic enzyme phenylalanine (Phe) hydroxylase (PAH, EC 1.14.16.1), which converts Phe into tyrosine. PKU patients show high levels of Phe in the plasma and, consequently, in the brain [1]. Phe in high levels is toxic to the brain; therefore, untreated PKU patients show severe mental retardation. In order to avoid brain damage, patients must be early diagnosed and follow a lifelong Phe-restricted diet. This diet consists of low-Phe foods along with supplementation of an especial L-amino acid mixture [2]. Besides effective in lowering Phe levels, the Phe-restricted diet is hard to accomplish, so that patients may show high Phe levels in plasma reflecting poor dietary control [3–6].

Both high Phe levels and the dietary treatment may lead to nutritional deficiencies. First, increased levels of Phe have been related to disturbed synthesis of hormones and cytokines, such as catecholamines and adiponectin, thus affecting body metabolism [7,8]. Moreover, the diet restricts several sources of natural protein, thereby impairing the intake of essential micro- and macronutrients [9]. Finally, the L-amino acid mixture is composed by synthetic nutrients, which may compromise biological availability [4]. Because of those above-mentioned reasons, concern has been emerged on nutritional status [2], linear growth [10], body composition [11], and risk of overweight and obesity in PKU children [12,13]. Despite that, some studies did not find differences in the growth and body composition parameters in PKU patients compared with controls [14,15]. Therefore, perhaps the risk of disturbed

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body composition in PKU just reflects the increased rates of nutritional imbalance as well as overweight and obesity seen in the general population and that varies from country to country. In addition, treatment management of PKU in Brazil needs special attention. In Brazil, the metabolic formula is supplied free of charge by the government, but the commercial low-Phe products are neither easily available nor typically reimbursed by insurance policies [5]. Besides that, the Neonatal Screening for PKU has been organized as a National Public Policy only since 2001, still existing many patients in the country diagnosed at a late age.

Bioelectrical impedance (BIA) represents a useful evaluation of overall body composition and nutritional status in PKU patients, in addition to the commonly analyzed body mass index (BMI). In this way, the BIA-derived data such as body fat mass (FM) and fat-free mass (FFM) proportion show more accurate values on real tissue mass than BMI estimations [16]. BIA analysis also provides an overview on metabolism and overall cellular integrity by the ratio between extracellular mass and body cell mass (ECM/BCM) and the phase angle (PA), respectively. These BIA-derived values are described as prognostic markers during hospitalization [17] and conditions like post-operative complications [18], kidney dysfunction [19], classical homocystinuria [20], and cancer [21]. In this way, abnormal values of ECM/BCM ratio and/or PA have been related to increased inflammatory processes [22]. Nutritional disturbances such as unbalanced polyunsaturated fatty acid intake [23] and obesity [24] have been related to increased inflammation. Because the PKU treatment seems to compromise the nutritional status in PKU patients, evaluating ECM/BCM ratio and PA can be of value to evaluate nutritional condition in PKU.

The current literature on body composition in PKU is still inconclusive. However, accurate measurements of peripheral markers in PKU patients are important to evaluate nutritional status which, in turn, can improve individual dietary management. Therefore, this study aimed to characterize body composition parameters and nutritional status in Brazilian PKU patients.

2. Methods

2.1. Participants

A cross-sectional study with PKU patients and age- and gender-matched healthy controls was conducted. Patients were recruited at the Medical Genetics Service from the Hospital de Clínicas de Porto Alegre (HCPA), Brazil. Controls were recruited in a routine follow-up at the Pediatric Service from the same hospital. Inclusion criteria included being aged 5 years or older and being able to lie quietly during the BIA test.

The study has been approved by the Research Ethics Committee of HCPA (protocol number 12-0115) and was conducted according to the Declaration of Helsinki guidelines. All subjects or their parents/caregivers signed an informed consent form.

2.2. Patients' characterization

PKU type was defined as mild- or classical PKU according to patients' Phe levels at diagnosis if levels were between 600–1200 μmol/L and >1200 μmol/L, respectively. Time of diagnosis was defined as early when patients were diagnosed before 60 days of life, and late when diagnosed at 60 days or older. Metabolic control was assessed by the median of historical serum Phe concentrations measured in the previous 12 months, with a minimum of three measurements in that period. Thus, patients were classified as having good metabolic control if those Phe levels were ≤360 μmol/L and ≤600 μmol/L for patients aged ≤12 and >12 years, respectively; otherwise, patients were classified as having poor metabolic control. All patients were following treatment since diagnosis, and it consisted of having a low-Phe diet and the L-amino acid mixture. No patient was on tetrahydrobiopterin (BH_4) treatment before or during the study.

2.3. Anthropometric measurements

Height was measured with a wall-mounted stadiometer (Harpenden, Holtain®, Crymych, UK) to the nearest 0.1 cm and weight was obtained using a digital platform scale with a resolution of 0.1 kg (Toledo®, Model 2096PP/2, São Paulo, Brazil), while participants were barefoot and wearing lightweight clothing. BMI was calculated by the quotient between weight (kg) and squared height (m^2), and classified into underweight, normal weight, overweight, or obese according to WHO 2009 [25].

2.4. BIA analysis

Measurements of body composition such as FM, FFM, ECM/BCM ratio, and PA were performed using a BIA device (Biodynamics 450® version 5.1, Biodynamics Corporation, Seattle, WA, USA) and Resting ECG tab electrodes (Conmed Corporation, Utica, NY, USA) according to previously described standards [26]. Briefly, the participants laid in supine position with arms and legs stretched out and kept from touching the body by non-conductor foam objects to prevent from adduction or crossing of the limbs, which would shorten the electrical circuit and reduce the impedance values. One pair of electrodes was placed on the right wrist and hand and the other on the right ankle and foot of the participant.

2.5. Statistical analysis

The Statistical Package for Social Sciences 19.0 (SPSS® Inc., Chicago, IL) was used. Data were described using absolute and relative frequencies. Continuous variables were expressed as mean ± standard deviation (SD). Unpaired and paired Student's *t*-tests were used to compare means of independent variables and to compare means between patients and controls, respectively. Effects of the co-factors were tested by ANOVA. The level of significance was set at 5%.

Table 1
Clinical characteristics of the phenylketonuria (PKU) patients.

Patient	Age (years)	Gender	Time of diagnosis[a]	PKU type[a]	Treatment adherence[a]
#1	6	Male	Late	Mild	Poor
#2	7	Female	Late	Classical	Poor
#3	11	Female	Late	Mild	Poor
#4	11	Female	Early	Mild	Good
#5	11	Male	Early	Classical	Poor
#6	11	Female	Late	Mild	Poor
#7	11	Male	Early	Mild	Poor
#8	11	Female	Early	Mild	Poor
#9	11	Female	Late	Classical	Poor
#10	12	Male	Early	Classical	Poor
#11	12	Male	Early	Mild	Good
#12	12	Female	Late	Mild	Poor
#13	12	Male	Late	Mild	Poor
#14	13	Female	Early	Classical	Poor
#15	13	Female	Late	Mild	Good
#16	14	Male	Late	Classical	Good
#17	14	Female	Early	Classical	Good
#18	14	Female	Late	Mild	Good
#19	15	Male	Late	Classical	Good
#20	16	Female	Late	Classical	Good
#21	16	Male	Late	Mild	Good
#22	16	Male	Early	Classical	Good
#23	17	Male	Early	Classical	Poor
#24	19	Female	Late	Mild	Good
#25	22	Male	Early	Classical	Good
#26	22	Male	Late	Mild	Good
#27	25	Male	Late	Classical	Poor

[a] See the text for details on classification.