Molecular Genetics and Metabolism Reports 6 (2016) 16–20

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

# Analysis of body composition and nutritional status in Brazilian phenylketonuria patients

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ARTICLE INFO

*Article history:*
Received 20 November 2015
Received in revised form 15 December 2015
Accepted 15 December 2015
Available online 9 January 2016

*Keywords:*
Inborn errors of metabolism
Phenylketonuria
Nutritional status
Body composition
Bioelectrical impedance

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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http://dx.doi.org/10.1016/j.ymgmr.2015.12.003

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.

**Table 2**
Anthropometrics and bioelectrical impedance parameters of phenylketonuria (PKU) patients and controls.

| | PKU | Controls | p value |
|---|---|---|---|
| Weight (kg) | 47.93 ± 15.99 | 51.52 ± 18.15 | NS |
| Height (m) | 1.52 ± 0.14 | 1.54 ± 0.17 | NS |
| BMI (kg/m$^2$) | 20 ± 4 | 21 ± 4 | NS |
| BMI classification[a] (n) | | | NS |
| Underweight | 1 (4%) | 0 (0%) | |
| Normal weight | 20 (74%) | 18 (67%) | |
| Overweight | 4 (15%) | 6 (22%) | |
| Obese | 2 (7%) | 3 (11%) | |
| Fat mass (%) | 20 ± 7 | 22 ± 9 | NS |
| Free-fat mass (%) | 80 ± 7 | 78 ± 9 | NS |
| ECM/BCM ratio | 1.05 ± 0.08 | 1.04 ± 0.10 | NS |
| Phase angle (°) | 6.22 ± 0.86 | 6.33 ± 1.05 | NS |

BMI, body mass index; ECM/BCM, extracellular mass/body cell mass; NS, non-significant. Fat mass and fat-free mass are expressed as percentage of total body weight. Data are expressed as mean ± SD or frequency (percentage); n = 27/group.
[a] According to WHO 2009. See the text for details on statistics.

## 3. Results

Each group of patients and controls had 27 participants (14 males and 13 females); patients originated from 26 nonrelated families. Concerning PKU type, 14 (52%) patients were mild PKU and 13 (48%) were classical PKU (Table 1). Eleven (41%) patients were early diagnosed and 16 (59%) patients were late diagnosed. Current Phe levels ranged between 102 and 1660 μmol/L while historical Phe levels ranged between 258 and 1482 μmol/L. Regarding treatment adherence, 13 (48%) patients had good metabolic control and 14 (51%) patients had poor metabolic control. The cofactors type of PKU, time of diagnosis, and metabolic control did not affect the anthropometric and BIA-derived measurements; thereby all patients were grouped in a single PKU group for further analyses.

No differences were found between PKU patients and controls regarding body composition, including the BIA-derived parameters FM, FFM, ECM/BCM ratio, and PA (Table 2). Three patients and three controls were below the cutoff values for PA (−3.2%, −14.3%, −17.4%, and −2.4%, −2.8%, −4.4%, respectively) according to Bosy-Westphal et al. [27] and Barbosa-Silva and Barros [18].

## 4. Discussion

This is the first study evaluating the body composition of Brazilian PKU patients, which represent a heterogeneous cohort of patients that differs from those from Europe and USA in terms of diagnosis, treatment, and ethnicity. First, the proportion of late-diagnosed patients in Brazil is still high, since the mandatory Neonatal Screening Program was implemented in 2001 in Brazil. Moreover, Brazilian PKU patients, although having access to the L-amino acid mixture, do not have access to protein-enriched low-Phe food, a fact that could compromise their nutritional status. Finally, Brazil is essentially a mixed country with several ethnic backgrounds. In this way, patients with different PKU types, time of diagnosis, and treatment adherence were included in our study, therefore these factors were also taken into account in the analysis of our results. Even though BIA analysis gives more accurate values on body composition than overall measurements such as BMI [16], our study did not find differences between patients and controls regarding anthropometric features evaluated by both methods. Therefore, our main findings pointed out that patients and controls were similar in body composition parameters, despite PKU type, time of diagnosis, and metabolic control. To the best of our knowledge, this is the first study that evaluated several markers on body composition in a heterogeneous group of PKU patients using BIA analysis.

Overweight has been pointed out as an issue for PKU patients, although this is not a consensus in the literature (Table 3). This disagreement in the literature may be caused by a lack of control for the puberty status of patients, since most studies, including ours, evaluate pre- and post-pubertal patients in a single group. In this way, some studies have found that PKU patients, especially females, show higher BMI and fat mass than controls [11,12]. On the other hand, several authors have not found differences in body composition between patients and age-matched controls [14,15,28–30] as well as comparing patients' outcomes to reference values [31–34]. In our study, the majority of patients

**Table 3**
Review of literature on studies regarding body composition in early treated phenylketonuria (PKU) patients.

| Authors/location | Controlled | Number (n)/age | Type of PKU | Method | Body fat mass | Body fat-free mass | ECM/BCM | Phase angle |
|---|---|---|---|---|---|---|---|---|
| Das et al. (2014) Germany [31] | No[a] | 51 27 ± 7 (range 16–44) | Classical | BIA | Normal | Normal | Normal | Normal |
| Doulgeraki et al. (2014) Greece [28] | Yes | 80 10 ± 3 (range 5–18) | Mild, classical | DXA | No difference | No difference | N/E | N/E |
| Rocha et al. (2013); Rocha et al. (2012) Portugal [15,30] | Yes | 89 14 ± 7 | HPA, mild, classical | BIA | No difference | No difference | N/E | No difference |
| Douglas et al. (2013) USA [34] | No[a] | 59 (range 10–19) | Classical | ADP | Normal | N/E | N/E | N/E |
| Adamczyk et al. (2010) Poland [33] | No[a] | 45 14 ± 5 | Classical | DXA | Normal | Normal | N/E | N/E |
| Albersen et al. (2010) The Netherlands [11] | Yes | 20 median 10 (range 6–16) | Classical | ADP | Higher in patients | N/E | N/E | N/E |
| Huemer et al. (2007) Austria [14] | Yes | 34 8.7 ± 3.9 (range 0.2–15) | Classical | TOBEC | No difference | No difference | N/E | N/E |
| Dobbelaere et al. (2003) France [32] | No[a] | 20 4.5 ± 1.6 (range 0.7–7) | Classical | BIA | Normal | Normal | N/E | N/E |
| Allen et al. (1995) Australia [29] | Yes | 30 10 ± 3 | Classical | Skinfold-thickness | No difference | No difference | N/E | N/E |

ECM/BCM, extracellular mass/body cell mass ratio; HPA, hyperphenylalaninemia; DXA, dual energy X-ray absorptiometry; BIA, bioelectrical impedance; ADP, air displacement plethysmography; TOBEC, total body electrical conductivity; N/E, not evaluated. Values of age are shown as mean ± SD if not stated otherwise.
[a] Non-controlled study that compared the results from patients with reference values.

and controls showed to be eutrophic regarding their BMI values. Moreover, no differences in body composition were found between patients and controls. Although not at higher risk of developing obesity, PKU patients may show the same risk of having disturbed body composition as the general population. Then, it is important to highlight that Brazil is undergoing an epidemiological transition associated with demographic and nutritional changes, which has led to high prevalence of obesity especially for the age group and geographic area covered by our study [35,36].

BIA analysis provides a range of data that assesses overall nutritional status such as relative active tissue (ECM/BCM ratio) and cellular integrity (PA), which can be of interest to PKU patients. In our study, values of ECM/BCM ratio and PA were similar between patients and controls. In agreement with our results, Rocha et al. [15] have found similar PA and body cell mass index values between Portuguese PKU patients and controls. In other pathologic conditions, ECM/BCM ratio has positively correlated with risk of death in dialysis patients [19], while PA has been negatively affected by nutritional imbalances, thus used as a prognostic factor in patients with homocystinuria [20] and cancer [21]. Both ECM/BCM ratio and PA values have been related to increased inflammation [17–19,21], which are seen in several pathological processes including in PKU patients [37,38]. Because nutritional imbalances have shown to underlie increased inflammation [23,24], the Phe-restricted diet could represent a threat to the overall health of patients. In addition, Brazilian PKU patients do not have adequate insurance coverage for commercial low-Phe products [2,5,6], which compromises the adherence to the dietary treatment. Despite that, the PKU patients of our study were not in higher risk of nutritional disturbances than the general population.

## 5. Conclusions

Overall, our results pointed to similar values of body composition and nutritional parameters between PKU patients and controls. Moreover, the analyzed values were not affected by the PKU type, time of diagnosis, or metabolic control.

*Abbreviations*

| | |
|---|---|
| ADP | air displacement plethysmography |
| BCM | body cell mass |
| BIA | bioelectrical impedance |
| BMI | body mass index |
| DXA | dual energy X-ray absorptiometry |
| ECM | extracellular mass |
| FFM | fat-free mass |
| FM | fat mass |
| HPA | hyperphenylalaninemia |
| N/E | not evaluated |
| NS | non-significant |
| PA | phase angle |
| PAH | phenylalanine hydroxylase |
| Phe | phenylalanine |
| PKU | phenylketonuria |
| TOBEC | total body electrical conductivity |

## Competing interests

The authors declare that they have no competing interests relevant for this manuscript. In addition, in the last 5 years, TGJD had received speaker's fees from Recordati Rare Diseases, Danone Nutricia and Vitaflo, and research fees from Sigma Tau and Vitaflo.

## Authors' contributions

TN, KC, and ASM collected the data. KC, TN, and IDSP performed the statistical analyses. KC, TN, IDSP, and PNM drafted the manuscript. All authors participated in the study design, contributed to the interpretation of the results and revised the manuscript.

## Acknowledgments

We thank Taika I. Brandorff and Petra M. G. Brusschers for their contribution in collecting the data. This study received financial support from FIPE/HCPA (Research Incentive Fund — Hospital de Clínicas de Porto Alegre, grant number 12-0115) and the UMC Groningen (Mandema Stipend to TGJD, grant number Man-081219-802).

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