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Acute exercise in treated phenylketonuria patients: Physical activity and biochemical response

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ABSTRACT

Background: In phenylketonuria, dietary treatment prevents most of the severe brain disease. However, patients have to follow a diet restricted in several natural components, what may cause decreased bone density and obesity. Exercise is known to improve both mental functioning and bone density also avoiding obesity, and could optimize aspects of central and peripheral outcome, regardless changes in phenylalanine (Phe) levels. However, the acute effects of exercise on metabolic parameters in phenylketonuria patients are unknown and thereby long-term adaptations are unclear. Therefore, this study aimed to evaluate patients' basal metabolic rate (BMR), and their acute response to an aerobic exercise session on plasma concentrations of Phe, tyrosine (Tyr), and branched-chain amino acids (BCAA), as well as metabolic and hormonal responses.

Methods: Five early- and four late diagnosed phenylketonuria patients aged 21 ± 4 years and 17 sex-, age-, and BMI-matched controls were evaluated for BMR, peak oxygen consumption (VO_{2peak}) and plasma amino acid, glucose, lipid profile and hormonal levels. At least one week later, participants performed a 30-min aerobic exercise session (intensities individually calculated using the VO_{2peak} results). Blood samples were collected in fasted state (moment 1, M1) and immediately after a small breakfast, which included the metabolic formula for patients but not for controls, and the exercise session (moment 2, M2).

Results: Phenylketonuria patients and controls showed similar BMR and physical capacities. At M1, patients presented higher Phe concentration and Phe/Tyr ratio; and lower levels of BCAA and total cholesterol than controls. Besides that, poorly controlled patients tended to stay slightly below the prescribed VO_2 during exercise. Both patients and controls showed increased levels of total cholesterol and LDL at M2 compared with M1. Only controls showed increased levels of Tyr, lactate, and HDL; and decreased Phe/Tyr ratio and glucose levels at M2 compared to values at M1.

Conclusions: Acute aerobic exercise followed by a Phe-restricted breakfast did not change Phe concentrations in treated phenylketonuria patients, but it was associated with decreased Phe/Tyr only in controls. Further studies are necessary to confirm our results in a higher number of patients.

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1. Introduction

Phenylketonuria (PKU, MIM 261600) is an autosomal recessive disease characterized by high levels of phenylalanine (Phe) in plasma and brain, due to the low activity of Phe hydroxylase (PAH, EC 1.14.16.1), which converts Phe into tyrosine (Tyr). Currently, patients are diagnosed by newborn screening programs and are treated with a Phe-restricted diet. Although mental retardation can be prevented with early diagnosis and dietary treatment, some peripheral and neurological problems remain. Regarding brain status, patients have shown non-optimal neuropsychological outcome with decreased capacity especially in executive

Abbreviations: BCAA, branched-chain amino acids; BMI, body mass index; BMR, basal metabolic rate; CTL, control; HDL, high-density lipoprotein; LDL, low-density lipoprotein; N/A, not applicable; NS, non-significant; Phe, phenylalanine; PKU, phenylketonuria; RER, respiratory exchange ratio; Tyr, tyrosine; VCO_2, carbon dioxide production; VO_2, oxygen consumption; VO_{2peak}, peak oxygen consumption.

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functions [1,2], increased risk of depression [3,4], anxiety, and mood disturbances [5,6]. On the peripheral level, decreased bone density [7–9] and increased risk of overweight [10,11] are also reported in treated PKU patients. As yet, it is not clear whether these problems are due to the high blood Phe concentrations or to the dietary treatment restricting not only Phe, but also other important micronutrients. Moreover, a wide range of protein-rich foods are forbidden thus daily caloric needs are fulfilled with carbohydrates and lipids [10].

Exercise may represent a treatment strategy in PKU since it has been proven to enhance overall health in different populations. In healthy individuals, regular exercise improves mood and cognition [12], decreases depressive symptoms [13], decreases the risk of obesity [14], and improves bone density [15,16]. Moreover, physical training leads to better neurological outcomes in patients with neurodegenerative diseases [17,18], and mild cognitive impaired elderly [19]. Therefore, PKU patients might also benefit from the exercise-induced adaptations.

High plasma Phe along with the Phe-restricted diet may lead to different metabolic responses to exercise in continuously treated PKU, what could affect training adaptations [20]. Acutely, exercise increases the metabolic demand and protein turnover, which can affect amino acid levels [21]. In addition, different dietary composition can alter the metabolic response to exercise, leading to specific long-term adaptations [22]. So far, only the study by Grünert et al. [23] has reported the effects of exercise in PKU patients, suggesting aerobic exercise does not importantly affect peripheral Phe levels in these patients. However, that study was not controlled and had evaluated the pre- and post-exercise Phe and Tyr levels as secondary objectives and in a relatively fasted state.

Therefore, the aim of this study was to investigate the acute effects of an aerobic exercise in PKU patients regarding changes in metabolic parameters.

2. Methods

2.1. Study design

Participants performed two days of interventions (Fig. 1) at the Laboratory of Physical Exercise (LAPEX), Federal University of Rio Grande do Sul (UFRGS), Porto Alegre, Brazil. This study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The local Human Research Ethics Committee has approved the study (N.120292 HCPA-UFRGS), and all participants (or parent/legal tutor for patients younger than 18 years old) signed an informed consent term before starting the tests.

2.2. Participants

Inclusion criteria were: (a) confirmed diagnosis of classical PKU, (b) following treatment regularly in a PKU Center in the south of Brazil, (c) aged >13 years, (d) not engaged in exercise training, and (e) mentally and physically able to perform exercise. From a total of 16 invited patients, five did not agree to participate due to travel issues and two because of personal reasons. Therefore, nine PKU patients from the Medical Genetics Service — Hospital de Clínicas de Porto Alegre, Brazil, were included. One patient did not follow the fasting requirement at day 1, so he was excluded from the exercise session results. Healthy non-PKU subjects were sex- age- and BMI-matched in an approximately 1:2 ratio to patients, and were not engaged in exercise training. The controls were invited through banners and advertisements in the University community.

Patients were classified as being early diagnosed (if the diagnosis was performed before the end of the first month of life) or late diagnosed (if the diagnosis was performed after the end of the first month of life), and were following treatment since diagnosis. Patients were also classified as "well controlled" if their current Phe levels at M1 were below 700 μmol/L, or as "poorly controlled" if these levels were equal or above 700 μmol/L. The treatment consisted of being on the Phe-restricted diet (low Phe intake along with the metabolic formula).

2.3. BMR test

The BMR was determined in a 10–12 h fasted state between 7.00 and 9.00 am at day 0 in order to assess daily basal caloric expenditure. The participants stayed in supine position for 30 min while their expiratory ventilation was analyzed by an automated open-circuit gas analysis system (MedGraphics Cardiorespiratory Diagnostic Systems, model CPX-D, and using the method Breath by Breath). The expired air fractions of oxygen consumption (VO_2) and carbon dioxide production (VCO_2) were measured every minute during the last 20 min of the test. The equation proposed by Weir [24], $[(3.9 \times VO_2) + (1.1 \times VCO_2)]$, was used to obtain the values in kcal/min, which were then transformed into kcal/kg/day. Respiratory exchange ratio (RER) was also calculated by the quotient between VCO_2 and VO_2.

2.4. Standard breakfasts

All participants received a standard breakfast (day 0) after the BMR test and, at day 1, 30 min before the exercise session (Fig. 1). The PKU breakfast consisted of a banana, a rice cookie and 200 mL of water mixed with two tablespoons of the metabolic formula (PKU 2 Secunda, Milupa) and one tablespoon of crystal sugar. The controls also received a banana and a rice cookie, but a regular yogurt (200 mL) instead of the metabolic formula. Regarding nutritional facts, PKU patients received a breakfast of 198 kcal and 40 mg of Phe (67% of carbohydrates, 30% of protein — containing approximately 395 mg of tyrosine, 403 mg of isoleucine, 664 mg of leucine, and 470 mg of valine — and 3% of lipids), while controls received a 157 kcal meal containing 340 mg of Phe (80% of carbohydrates, 17% of proteins and 2% of lipids).

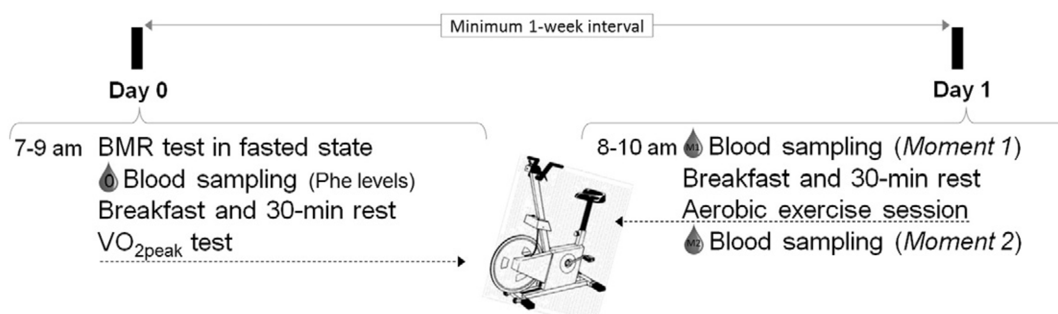

Fig. 1. Experimental design. In fasted state, participants went to the lab twice (at day 0 and day 1). In the day 0, participants performed the basal metabolic rate (BMR) test, followed by blood sampling for plasma phenylalanine (Phe) evaluation (0), breakfast and 30-min rest. Then the peak oxygen consumption (VO_{2peak}) test was performed. In the day 1, blood sampling was collected at moment 1 (M1), then participants received breakfast, waited 30-min in rest and performed the aerobic exercise session. Immediately after exercise (moment 2, M2), the last blood sample was collected.

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