Chapter 7

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 PKU 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.
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 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.

Methods

Study design

Participants performed two days of interventions (Figure 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.
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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.

Figure 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$_{2\text{peak}}$) 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.

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 metabolic formula).

**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...
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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), $[(3.9 \times \text{VO}_2) + (1.1 \times \text{VCO}_2)]$, 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$_2$.

Standard breakfasts

All participants received a standard breakfast (day 0) after the BMR test and, at day 1, 30 min before the exercise session (Figure 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).

Peak VO$_2$ (VO$_{2\text{peak}}$) test

VO$_{2\text{peak}}$ (mL/kg/min) was determined by an incremental
stationary cycling exercise test to the point of exhaustion (25, 26), using the gas analyzer described to the BMR test. This test was performed at day 0 of evaluations, 30 min after the standard breakfast.

Regarding standard safety procedures, we monitored for headaches, dizziness, altered vision, heart rate and hematocrit levels during and after exercise bouts (maximum test and aerobic session). A stationary bicycle was used due to its safety even for those who were not used to exercise. A cardiologist followed all the procedures.

**Acute exercise protocol**

Using the same ventilatory analyzer described to the BMR and VO\textsubscript{2peak} tests, all participants performed 30 min of cycling exercise at a prescribed VO\textsubscript{2}. The prescribed aerobic intensity was calculated for each participant representing the VO\textsubscript{2} value at 10% below the second ventilatory threshold, which was assessed by the VO\textsubscript{2peak} test at least one week earlier. The one-week interval was chosen to avoid possible interferences of the maximum test on the submaximal exercise session, especially for sedentary individuals.

The VO\textsubscript{2} was tracked throughout the exercise bout and the participant was asked to keep his/her VO\textsubscript{2} within the target zone (prescribed VO\textsubscript{2} ± 2 mL/kg/min). When the participant was below or above it, he/she was encouraged to either increase or decrease the load or speed to stay in his/her calculated aerobic zone. Values of prescribed- and averaged actual VO\textsubscript{2} during the exercise session were compared and expressed as percentage of the prescribed VO\textsubscript{2}. 138
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Since executive function of early and late diagnosed patients has shown to be affected by current levels of Phe (2, 27), the actual VO$_2$ values were analyzed with regard to Phe control in the group of patients.

**Blood sampling**

Blood collections were performed at day 0 after the BMR test in a 10-12 h fasted state (for evaluation of Phe levels only), at day 1 in a 10-12 h fasted condition, i.e. at moment 1 (M1), and immediately after the aerobic exercise bout, i.e. at moment 2 (M2) also having had the light breakfast. The number of samples varied in some evaluations because it was not possible to collect the same amount of blood from all participants.

**Biochemical measurements**

Quantitative analysis of Phe, Tyr, and branched-chain amino acid (BCAA, isoleucine, leucine, and valine) levels in plasma was carried out by HPLC with fluorescence detector (28) with an internal variation coefficient less than 3%.

Serum glucose, total cholesterol, HDL and triacylglycerol were determined by specific commercial kits for the automated analyzer Cobas C111. The LDL value was estimated by the difference of total cholesterol and HDL minus triacylglycerol divided by five.

Plasma adiponectin was evaluated using a commercial kit for human adiponectin (Invitrogen KHP0041) ELISA immunoassay. The catecholamines dopamine, noradrenaline and adrenaline were
analyzed in plasma by HPLC with electrochemical detection.

Statistical analysis

Data normality was tested by Shapiro-Wilk test. Control and PKU groups were compared using the independent Student’s t-test for basal and M1 analyses, and with two-sided paired t-test for comparisons between M1 versus M2 in each group. Correlations were performed using Spearman’s correlation. Categorical variables were compared by Fisher’s Exact Test. SPSS 22.0 was employed for all statistical analyses and a p<0.002 was considered statically significant after applying Bonferroni correction.

Results

Sample characterization

The data of the nine PKU patients and 17 controls are described in the Table 1. Five patients were early diagnosed and four patients were late diagnosed. At day 0, Patients’ current Phe concentrations varied between 323 and 761 µmol/L.

BMR and VO\textsubscript{2}peak tests

Two controls, but no PKU patient, experienced discomfort during the protocols. Concerning basal status, PKU patients and controls showed similar values of BMR and RER during the BMR test. In the same way, patients showed similar aerobic capacity and workload peak in the VO\textsubscript{2}peak test in comparison to controls (Table 1).
Exercise session
Baseline values at M1
In rest and fasted state, patients showed higher Phe levels and Phe/Tyr ratio, and lower levels of BCAA and total cholesterol in comparison to controls (Table 2). Phe levels ranged between 583 and 1029 µmol/L in the PKU group. Regarding Phe control at M1, five patients showed good control. All early-diagnosed patients had good control of Phe levels, while all late diagnosed patients had poor Phe control. Accordingly, patients showed positive correlation between the age at diagnosis and the Phe levels at M1 (r=0.97; p<0.001).

Ventilatory measurements during exercise
PKU patients and controls showed similar values of prescribed VO₂ (21 ± 6 versus 22 ± 4 mL/kg/min, respectively), and actual VO₂ during exercise (18 ± 5 versus 22 ± 4 mL/kg/min, respectively). Despite not statistically different, poorly controlled patients showed the lowest percentage of actual VO₂ during exercise in relation to the prescribed value (Figure 2). Mean RER values during exercise were similar between PKU and controls (0.99 ± 0.09 versus 0.96 ± 0.05, respectively).
### Table 1. Clinical characteristics from control (CTL) and phenylketonuria (PKU) groups at day 0.

<table>
<thead>
<tr>
<th></th>
<th>CTL (n=17)</th>
<th>PKU (n=9)</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Gender (male:female)</td>
<td>12:5</td>
<td>7:2</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>22 ± 4</td>
<td>21 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23 ± 2</td>
<td>24 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Current Phe (µmol/L)</td>
<td>57 ± 14</td>
<td>562 ± 141</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMR (kcal/kg/day)</td>
<td>21 ± 4</td>
<td>23 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>RER during BMR</td>
<td>0.87 ± 0.07</td>
<td>0.82 ± 0.07</td>
<td>NS</td>
</tr>
<tr>
<td>VO₂peak (mL/kg/min)</td>
<td>31 ± 6</td>
<td>28 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>Workload peak (W)</td>
<td>216 ± 49</td>
<td>203 ± 31</td>
<td>NS</td>
</tr>
</tbody>
</table>

BMI, body mass index, BMR, basal metabolic rate, RER, respiratory exchange ratio, VO₂peak, peak oxygen consumption, NS, non-significant. Data for numeric variables are expressed as mean ± SD. See methodology for details on the statistical analysis.

Biochemical values at M2

Phe concentrations were not different between M1 and M2 in the PKU as well as in the control group. In the PKU group, Phe concentrations ranged between 490 and 984 µmol/L at M2. Phe/Tyr ratio was lower at M2 than at M1 only in controls (Table 2). Total cholesterol, LDL levels were increased at M2 in both PKU patients.
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and controls in comparison with M1 (Table 2). Only in controls, Tyr, lactate, and HDL levels were higher, while glucose levels were lower at M2 in comparison with values at M1. Levels of BCAA, triacylglycerol, dopamine, noradrenaline, adrenaline, and adiponectin were not modified between M1 and M2 in patients and controls.

Table 2 Biochemical parameters at moments 1 (M1) and 2 (M2) in controls (CTL) and phenylketonuria (PKU) patients. Phe, phenylalanine; Tyr, tyrosine; BCAA, branched chain amino acids (isoleucine, leucine, and valine); TGA, triacylglycerol, t-cholesterol, total cholesterol; NS, non-significant; N/A, not applicable. Results are expressed as mean ± SD (n), two-sided paired t-test. After applying Bonferroni correction, only results with p<0.002 were considered significant (see methodology). n=17 for CTL and n=8 for PKU at M1 and M2 except for adiponectin values, where n=14 for CTL and n=7 for PKU. Phe, Tyr, tryptophan, and BCAA are expressed as µmol/L; glucose, lactate, TGA, t-cholesterol, HDL, and LDL are expressed in mg/dL; dopamine, noradrenaline, and adrenaline are in pg/mL; adiponectin is expressed in ng/mL.
<table>
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<th>M1</th>
<th>CTL</th>
<th>PKU</th>
<th>p value</th>
<th>M1</th>
<th>CTL</th>
<th>PKU</th>
<th>p value</th>
<th>M1</th>
<th>CTL</th>
<th>PKU</th>
<th>p value</th>
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<tbody>
<tr>
<td>Phe</td>
<td>81 ± 24</td>
<td>773 ± 190</td>
<td>&lt;0.001</td>
<td>73 ± 15</td>
<td>723 ± 139</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Tyr</td>
<td>57 ± 15</td>
<td>62 ± 9</td>
<td>NS</td>
<td></td>
<td>79 ± 20</td>
<td>90 ± 24</td>
<td>&lt;0.001</td>
<td>NS</td>
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<td>Phe/Tyr ratio</td>
<td>1.4 ± 0.2</td>
<td>12.4 ± 2.4</td>
<td>&lt;0.001</td>
<td>1.0 ± 0.2</td>
<td>8.3 ± 1.8</td>
<td>&lt;0.001</td>
<td>NS</td>
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<tr>
<td>Tryptophan</td>
<td>35 ± 9</td>
<td>29 ± 6</td>
<td>NS</td>
<td></td>
<td>35 ± 8</td>
<td>36 ± 12</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>BCAA</td>
<td>456 ± 86</td>
<td>332 ± 50</td>
<td>0.001</td>
<td>403 ± 63</td>
<td>478 ± 132</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Glucose</td>
<td>89 ± 8</td>
<td>83 ± 7</td>
<td>NS</td>
<td></td>
<td>77 ± 9</td>
<td>78 ± 11</td>
<td>0.001</td>
<td>NS</td>
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<tr>
<td>Lactate</td>
<td>1.3 ± 0.5</td>
<td>1.3 ± 0.3</td>
<td>NS</td>
<td></td>
<td>3.7 ± 1.6</td>
<td>3.6 ± 1.8</td>
<td>&lt;0.001</td>
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<td>TGA</td>
<td>89 ± 33</td>
<td>76 ± 27</td>
<td>NS</td>
<td></td>
<td>100 ± 39</td>
<td>77 ± 27</td>
<td>NS</td>
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<tr>
<td>T-cholesterol</td>
<td>168 ± 31</td>
<td>121 ± 26</td>
<td>0.001</td>
<td>181 ± 34</td>
<td>129 ± 26</td>
<td>&lt;0.001</td>
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<td>CTL M1 vs PKU M1</td>
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<td>HDL</td>
<td>54 ± 12</td>
<td>42 ± 6</td>
<td>NS</td>
<td>57 ± 11</td>
<td>45 ± 7</td>
<td>&lt;0.001</td>
<td>NS</td>
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<td>LDL</td>
<td>97 ± 28</td>
<td>63 ± 19</td>
<td>NS</td>
<td>103 ± 28</td>
<td>68 ± 19</td>
<td>0.001</td>
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<tr>
<td>Dopamine</td>
<td>56 ± 15</td>
<td>58 ± 17</td>
<td>NS</td>
<td>57 ± 13</td>
<td>57 ± 11</td>
<td>NS</td>
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<tr>
<td>Noradrenaline</td>
<td>228 ± 77</td>
<td>220 ± 52</td>
<td>NS</td>
<td>229 ± 85</td>
<td>217 ± 53</td>
<td>NS</td>
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<tr>
<td>Adrenaline</td>
<td>49 ± 15</td>
<td>45 ± 12</td>
<td>NS</td>
<td>52 ± 15</td>
<td>43 ± 11</td>
<td>NS</td>
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<tr>
<td>Adiponectin</td>
<td>28 ± 6</td>
<td>37 ± 8</td>
<td>NS</td>
<td>30 ± 9</td>
<td>39 ± 4</td>
<td>NS</td>
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**Figure 2** Actual oxygen consumption ($\text{VO}_2$) during the 30-min exercise in controls (CTL) and well and poorly controlled phenylketonuria (PKU) patients. Data are expressed as mean ± SD of percentage of prescribed $\text{VO}_2$, $n=16$ for controls, $n=5$ and $n=3$ for well and poorly controlled PKU subgroups, respectively.

**Discussion**

To the best of our knowledge, this is the first study to evaluate a controlled aerobic exercise session in PKU patients and healthy individuals. For that, we analyzed patients’ basal metabolic status compared to controls, as well as their immediate responses to an aerobic exercise session at the same relative intensity, which was
calculated for each participant by a previous VO$_2$peak test. Our data corroborate the study by Grünert et al. (23), where exercise did not change Phe concentrations acutely in PKU patients. Moreover, we showed that metabolic responses to exercise are similar between PKU patients and controls, despite different previous meal.

Our results were measured in a small number of patients of both genders immediately after a 30-min exercise session that was performed after a light breakfast. The small sample size is a limitation of the study, thus making comparisons between subgroups of patients very difficult. That possibly contributed to the fact that most analyses were not significant in the group of patients. To counteract that, we have included a greater number of controls, in a compatible ratio to male and female patients. Due to the nature of the disease, PKU patients and controls received distinct breakfasts, which varied in compositions, thereby possibly causing different biochemical responses to exercise (22, 29). The different meals represent real dietary habits of PKU and non-PKU individuals, while studying the patients in fasting condition would have caused other biochemical responses that had to be prevented this way (23, 30, 31).

Regarding basal metabolic status, PKU patients showed similar BMR values in comparison to controls. Some studies have found increased basal metabolism in different diseases (32-35), although the mechanisms are not yet elucidated. Despite that, our results agree with the study by Allen et al. (36), where no differences in BMR were found between early diagnosed PKU children and matched controls.
In rest and fasting (M1), patients showed lower BCAA and total cholesterol levels in comparison with controls. Lower lipoprotein levels and disturbed amino acid concentrations have been already described in PKU children (37, 38), being associated with the composition of the Phe-restricted diet (11).

PKU patients have been encouraged to exercise (11, 39), although its efficacy is not evidence-based. The concern on low physical activity level for PKU patients has risen from data on bone density measurements (7-9), as well as the eminent weight gain associated to consuming Phe-free products, which are often rich in carbohydrates (10, 11). Obesity may become a spreading health issue of this era, and exercising regularly may also prevent overweight and its related disorders. Despite that, the PKU patients of the present study showed normal BMI and were so physically active as the controls, seen by the similar values observed on $VO_{2\text{peak}}$ and workload peak in the $VO_{2\text{peak}}$ test in both groups. However, the three patients who showed the highest Phe values at M1 (poorly controlled), stayed slightly below the prescribed $VO_2$ during the exercise in average. This result did not reach statistical significance probably due to the small sample of patients. However, high Phe levels impair executive functioning (2, 27) that could, in turn, affect exercise performance. In this way, patients that showed bad Phe control before exercise seemed to have difficulties in keeping the prescribed $VO_2$ during cycling, even though being encouraged to do so.

Both patients and controls showed expected responses
regarding higher total cholesterol and LDL levels after exercise, since exercise enhances the availability of energetic substrates (40, 41). Tyr levels were increased after exercise only in the control group. Grünert et al. (23) have shown that Tyr levels increase immediately after aerobic exercise in PKU patients. In that study, patients exercised during 20 min at night (three hours after a dinner) making difficult any comparison with our findings, since in our study patients exercised during 30 min at morning (shortly after a breakfast). Because of the different protein sources of the breakfasts, our patients may have absorbed L-amino acids from the metabolic formula faster than the controls had absorbed casein from the yogurt (42). Therefore, the effects of the breakfast for patients might have been even more important with regard to amino acids levels at M2. Nevertheless, the aerobic exercise in combination with the amino acid-rich formula did not lead to unexpected metabolic responses in PKU patients. In addition, RER levels were similar between groups during basal condition and exercise. This result suggests that high Phe levels and different dietary composition did not modify substrate utilization in a small sample of treated patients with normal BMI.

Conclusions

Acute aerobic exercise followed by a Phe-restricted breakfast did not change Phe concentrations in treated PKU patients, but it is associated to lower Phe/Tyr ratio only in controls. Future studies are needed to confirm our results in a higher number of patients, as well as controlling for dietary intake before exercise.
Chapter 7

References


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