Abstract

Introduction: The objective of this study was to compare health-related physical fitness in women with familial partial lipodystrophy type 2 (FPLD2) with healthy without FPLD2 control subjects.

Methods: We selected 14 patients with clinical signs and symptoms of FPLD2 and with mutation of LMNA gene and 14 control patients, who were evaluated for anthropometric variables and body composition by dual-energy X-ray absorptiometry and physical fitness (cardiopulmonary, flexibility, grip strength and abdominal muscular strength). There were no differences in weight, height or body mass index.

Results: Of the 14 women with FPLD2, nine (64.3%) reported type 2 diabetes mellitus and hypertension, and 13 (92.8%) hypertriglyceridemia. Regarding physical fitness, women with FPLD2 presented decreased amplitude of the ankle joint \( (p < 0.04) \), and reduced abdominal muscle resistance \( (p < 0.012) \), heart rate \( (p = 0.032) \) and peak effort power \( (p = 0.045) \). Laboratory tests showed that women with FPLD2 had increased levels of uric acid, glycemia, HbA1c, insulin, triglycerides, CRP, ALT and AST and reduced levels of HDL-c \( (p < 0.017) \) compared to CG.

Conclusion: The women with LPFD2 showed physical fitness levels decreased when compared to the control group. Future studies are needed to investigate the physical activity and to encourage preventive measures in this population.

Health-Related Physical Fitness in Women with Dunnigan Lipodystrophy with Mutation in LMNA Gene

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Keywords: Lamin Type A, Lipodystrophy, Familial Partial, Physical Fitness, Women

Introduction: O objectivo do estudo foi comparar aptidão física relacionada a saúde em mulheres com lipodistrofia parcial familial tipo 2 (FPLD2) com mulheres sem FPLD2 controles. 

Métodos: Foram selecionadas 14 pacientes com quadro clínico de LPFD2 e com mutação no gene LMNA, e 14 pacientes controles, onde foram verificadas as variáveis antropométricas e de composição corporal pelo DXA, a aptidão física (capacidade cardiopulmonar, flexibilidade, força manual de preensão e força muscular abdominal). Não foram encontradas diferenças no peso, estatura e índice de massa corporal.

Aptidão Física Relacionada a Saúde em Mulheres com Lipodistrofia Tipo Dunnigan com Mutação no Gene LMNA

Palavras-chave: Aptidão Física, Lamin Tipo A, Lipodistrofia Parcial Familiar, Mulher

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Exclusion criteria adopted were: age under 18 years, DL and low HDL-cholesterol level was < 50 mg/dL. hypertriglyceridemia was diagnosed with triglycerides ≥ 150 mg/dL. T2DM was identified as two fasting glucose ≥ 126 mg/dL and/or low high-density-lipoprotein (HDL)-cholesterol and T2DM. and muscularity, acanthosis nigricans, hypertriglyceridemia and/ or peripheral fat loss, excess accumulation of fat around the neck and chin, perivisceral adiposity and muscular hypertrophy predominant in the lower limbs. Approximately one third of affected women develop acanthosis nigricans, hirsutism, menstrual abnormalities and polycystic ovaries.2,3 The severity of FPLD2 is due to its association with metabolic alterations: insulin resistance, diabetes, hypertriglyceridemia that can lead to acute pancreatitis and hepatic steatosis, reduced HDL – cholesterol and adiponectin.4 A sedentary life style represents a behavior clearly identified to involve an unfavorable lipid profile.5,6 The association between insufficient practice of physical exercise and dyslipidemia may explain in part the lower risk predisposing to the onset and the development of cardiovascular diseases in more physically active individuals.9 Physical fitness is known to be a powerful predictor of chronic disease morbidity and mortality. Prospective observational studies in adults have shown that low physical fitness is strongly associated with risk for developing coronary heart disease,8 hypertension, and type 2 diabetes mellitus (T2DM), as well as mortality from cardiovascular disease, cancer, and all causes of mortality.10 On physical health-related fitness, Pate13 defines as the ability to realize daily tasks vigorously and demonstrate traits and characteristics that are associated with a low risk of premature development of hypokinetic diseases. Since FPLD2 is a rare disease, to date there is no study dealing with the physical fitness in women with this condition. The purpose of this article is to compare health-related physical fitness (auto-immune or related to HIV infection or use of highly active antiretroviral therapy), severe renal or hepatic diseases, depression and alcoholism. A control group with 14 healthy volunteers was matched for age, sex and body mass index (BMI) with lipodystrophic group. This group was recruited from outpatient clinic and hospital employees and was not related to the patients. These subjects had a normal fat distribution, belong to the same ethnic origin and did not show a family history of lipodystrophy. Diagnosis of Dunnigan-type FPL (FPLD2) was confirmed by molecular analysis of LMNA gene provided by the Molecular Endocrinology Laboratory of Medical School of Ribeirão Preto, University of São Paulo, Brazil. Fourteen women confirmed diagnosis of Dunnigan-type FPL (FPLD2) and were included for statistical analysis. The study was approved by the Research Ethics Committee of the Medical School of Ribeirão Preto according to the norms of Resolution 196/96 of the National Health Council regarding research on human beings, and all subjects gave written informed consent to participate. Genetic and Mutational analysis DNA extraction and LMNA genotyping were performed as described using sequence-proven DNA standards. Mutational analysis of LMNA was performed on all the patients by direct sequencing of the coding region and the splice-site junctions, as described previously.14 Screening for mutations of LMNA through direct sequencing. Genomic DNA was extracted from peripheral blood, with the kit QIAamp DNA blood (Qiagen CA, USA). The amplification of LMNA gene was designed to include the exon-intron junction allowing the screening for mutations at alternative splicing sites. The primers used to amplify exons 8 and 9 were previously described.11 Primers used in exon 11 analysis were designed as follows: primer forward 5’ GTAGCTAGAACAGATGCAGTCATC 3’, primer reverse 5’ AGAGAGAAAACAGAGGAGAGG 3’. DNA sequencing was performed on ABI3130 genetic analyzer (PE Applied Biosystems, Foster City, California, USA), using BigDye® terminator cycle sequencing kit V3.1 Ready Reaction (ABI PRISM/PE Biosystems, Foster City, CA, USA). Results were analyzed using the Condon code aligner software (Li-COR, Inc), following manufacturer’s instructions. Body composition Weight (kg) was measured once using a portable Filizola digital scale with a maximum capacity of 150 kg and accurate to 0.1 kg. Height (cm) was measured once using an inextensible measuring tape. Body mass index (BMI) was determined as body weight (kg)/height (m²). Waist-to-hip ratio (WHR) was measured. Flexible, non-stretch fiberglass tape was used for measurements. Fat mass (FM), percent fat mass (%) and fat-free mass (FFM)
were determined using dual-energy X-ray absorptiometry (DXA) (Hologic 4500 W, USA).

**Flexibility**

Passive joint motion was evaluated in 20 body movements (ankle, knee, hip, trunk, wrist, elbow, and shoulder) using Flexitest and three laxity tests. Eight movements are of the lower limbs, three are related to the trunk, and the remaining nine are of the upper limbs. The movements are listed according to roman numbers, from a distal to a proximal sense. Flexit index individual movements (0 to 4) and overall Flexindex scores were obtained in all subjects by the same investigator. The level of flexibility has been classified in accordance with the overall score for each movement: < 20 = level of flexibility, very small; 21-30 = small level; 31-40 = average negative; 41-50 = middle positive; 51-60 = large level, and > 60 = very high level (hypermobility). 15

**Grip strength**

The test was measured with a JAMAR dynamometer/once with each elbow in flexion, once with each elbow in extension. Each measurement was repeated twice and the higher score was recorded.

**Abdominal muscular strength and endurance: timed bent-leg sit-ups**

The test was scored as the number of sit-ups performed in 1 minute. Each subject lay supine on the mat, with knees bent at right angles and hands crossed on the chest. The technician held the subject’s ankles firmly for support and maintained the count. The subject’s elbows had to touch the knee with the same side (i.e., right elbow to right knee). After each upward movement, the two sides of scapular returned to touch the mat, but the head did not have to touch it.

**Cardiopulmonary Fitness**

All subjects were submitted to a cardiopulmonary exercise testing. The protocol consisted of dynamic physical exercise in a seated position on an electronically-braked cycle ergometer (Corival 400, Quinton). The power applied in the cycle ergometer was ramp type with intensity determined by the formula developed by Wasserman et al16 based on anthropometric characteristics, age and gender. Patients were encouraged to make the effort applied by Wasserman et al was ramp type with intensity determined by the formula developed (Corival 400, Quinton). The power applied in the cycle ergometer in a seated position on an electronically-braked cycle ergometer was ramp type with intensity determined by the formula developed by Wasserman et al based on anthropometric characteristics, age and gender. Patients were encouraged to make the effort applied by Wasserman et al. The ventilatory variables were obtained in this protocol using an ergospirometer (CPX/D MedGraphics) calibrated before each test, which allows the acquisition, processing and storage of data from breath-by-breath. The VO2peak and heart rate - HRpeak values were expressed as an average over the last 30 seconds of effort.

**Biochemical assessment**

Blood was drawn after a 12 hours overnight fast. Total cholesterol, HDL cholesterol, triglycerides, uric acid, basal insulin, alanine aminotransferase (ALT), Aspartate aminotransferase (AST), C-reactive protein (CRP) and glucose were measured by Konelab 60i Thermo scientific apparatus using standard reagent kits and the glycated hemoglobin (HbA1c) test by an ion-exchange high-performance liquid chromatography procedure (D-10 Biocad hemoglobin testing system, France, Marnes-la-Coqaut, reference range 4.7–6.0%). Glucose was measured by enzymatic method (hexokinase).

**Statistical analysis**

Statistical analysis was performed with SAS/STATA® 9.0. The Wilcoxon-Mann-Whitney test was used to compare of physical fitness measurements between the two groups. Biochemical parameters were compared between groups by analysis of variance (ANOVA). Tracking of anthropometric characteristics, biochemical parameters and physical fitness was assessed with Spearman’s rank order correlations between measurements in women with FPLD2, and control group. To verify the difference between the groups that make physical activity on biochemical parameters, we used multiple linear regression. Results are presented as means ± SD, unless otherwise noted. The 95% confidence limit was calculated and the level of significance was set at p value of 0.05 or less.

**Results**

The characteristics of the participants are presented in Table 1. Genetic studies were carried out in the 14 female patients with partial lipodystrophy phenotype. All patients had a missense mutation in LMNA gene: thirteen patients harbored the heterozygous variation p. R482W (exon 8) and one patient the mutation identified was p.R644C (exon 11). When questioned about the presence of comorbidities, nine (64.3%) women with FPLD2 reported T2DM and hypertension, and 13 (92.8%) hypertriglyceridemia. About exercise habits (walking, per 30-60 minute), five women with FPLD2, and four group control walk.

BMI was similar in the two groups, whereas women with FPLD2 had a reduction of fat mass and percent fat, and an

<table>
<thead>
<tr>
<th>Table 1. Subject characteristics, means (±SD)</th>
<th>Women with FPLD2 (n = 14)</th>
<th>Control (n = 14)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35.8 ± 13.9</td>
<td>35.9 ± 13.8</td>
<td>0.99</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.6 ± 0.1</td>
<td>1.6 ± 0.1</td>
<td>0.91</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>58.6 ± 5.9</td>
<td>63.9 ± 6.7</td>
<td>0.99</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23 ± 2.1</td>
<td>23.2 ± 2.4</td>
<td>0.82</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>10 ± 2.3</td>
<td>19.1 ± 4.1</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>41.4 ± 4.5</td>
<td>34.1 ± 3.9</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Percent fat mass (%)</td>
<td>19.1 ± 4.2</td>
<td>34.8 ± 5.0</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>77.4 ± 5.1</td>
<td>74.1 ± 5.5</td>
<td>0.10</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
<td>88.5 ± 3.6</td>
<td>94.8 ± 5.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Waist-to-hip ratio (cm)</td>
<td>0.87 ± 0.05</td>
<td>0.78 ± 0.05</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

* statistically significant p < 0.05; BMI: body mass index
increase of lean mass. They also differed significantly in the waist/hip ratio.

Flexibility has been evaluated with the Flexitester. Body flexibility was reduced on ankle in the FPLD2 group (p < 0.045) (Table 2). Regarding the level of flexibility classified in accordance with the overall score for each movement, eight (57.1%) women with FPLD2 presented level = 31-40 (average negative) and six (42.9%) = 41-50 (positive middle), while four (28.6%) women in the control group showed level = 31-40 (average negative), eight (57.1%) = 41-50 (positive middle) and two (14.3%) = 51-60 (large level).

Women with FPLD2 showed a decrease in manual strength test when compared to the control group, but no significant difference. Abdominal muscular strength test was significantly lower in the FPLD2 group compared with the control group (p < 0.010) (Table 2). The results of the cardiopulmonary fitness test are given in Table 2. HR PE and POT PE were lower in the FPLD2 group (p < 0.052).

Women with FPLD2 showed a significant increase in glucose, HbA1c, insulin, uric acid, TG, ALT, AST, CRP, and also a reduction of HDL compared to group control (< 0.010) (Table 2). There were not found correlations between the values biochemical (insulin, uric acid, HDL-c, CT, TG, ALT, AST e CRP) and anthropometric characteristics and physical fitness tests in the group of women with and without FPLD2.

Among women with FPLD2, and the control group who do physical activity, observed by multiple linear regression analysis, differences in glucose (102.28, 95% IC = 184.39 – 20.6), A1C (4.27, 95% IC = 7.05 – 1.48), CT (97.03, 95% IC = 177.94 – 16.12), and TG (446.93, 95% IC = 695.41 – 198.44). Women with FPLD2 had higher values than the control group in the variables: glucose, HbA1c, CT and TG.

**Discussion**

A FPLD2 is the most prevalent form, with approximately 200 cases reported and a prevalence of 1 in 15 million persons. The Endocrinology Outpatient Clinic of the University Hospital, Medical School of Ribeirão Preto, University of São Paulo, Brazil, attends a considerably significant sample of families with this disease and thus presents here the first study to describe physical fitness data in women with FPLD2.

There are a few limitations to this study. First, our results can only be generalized to women affected with familial partial lipodystrophy due to LMNA mutations. Because FPLD2 is a rare disorder, we have only been able to report on 14 individuals with LMNA mutations.

The LMNA gene encodes two nuclear proteins, lamin A and C, which are the essential structural components of most differentiated mammalian cells. Rare mutations in exon 8 of

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**Table 2. Comparison of fitness tests, means (±SD)**

<table>
<thead>
<tr>
<th>Test</th>
<th>Women with FPLD2 (n = 14)</th>
<th>Control (n = 14)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flex wrist</td>
<td>39 ± 2.6</td>
<td>40 ± 3.9</td>
<td>0.61</td>
</tr>
<tr>
<td>Flex elbow</td>
<td>40 ± 2.3</td>
<td>41 ± 2.6</td>
<td>0.58</td>
</tr>
<tr>
<td>Flex shoulder</td>
<td>40 ± 11.3</td>
<td>47 ± 10</td>
<td>0.12</td>
</tr>
<tr>
<td>Flex trunk</td>
<td>30 ± 8.9</td>
<td>33 ± 10</td>
<td>0.38</td>
</tr>
<tr>
<td>Flex hip</td>
<td>41 ± 12.3</td>
<td>46 ± 12.6</td>
<td>0.21</td>
</tr>
<tr>
<td>Flex knee</td>
<td>44 ± 6.4</td>
<td>47 ± 10.6</td>
<td>0.39</td>
</tr>
<tr>
<td>Flex ankle</td>
<td>36 ± 7.5</td>
<td>43 ± 10.6</td>
<td>&lt; 0.04</td>
</tr>
<tr>
<td>Flexindex</td>
<td>39 ± 7.7</td>
<td>43 ± 7.5</td>
<td>0.20</td>
</tr>
<tr>
<td>Right grip strength</td>
<td>21.5 ± 5.4</td>
<td>23.5 ± 4.1</td>
<td>0.34</td>
</tr>
<tr>
<td>Left grip strength</td>
<td>18.5 ± 3.3</td>
<td>21.1 ± 4.2</td>
<td>0.17</td>
</tr>
<tr>
<td>Abdominal muscular strength</td>
<td>15 ± 7.7</td>
<td>26 ± 5.2</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>VO₂ AT (mL kg⁻¹ min⁻¹)</td>
<td>12.3 ± 2.7</td>
<td>11.2 ± 3.0</td>
<td>0.27</td>
</tr>
<tr>
<td>HR AT</td>
<td>115.6 ± 16.2</td>
<td>112 ± 17.7</td>
<td>0.51</td>
</tr>
<tr>
<td>POT AT (watts)</td>
<td>45.1 ± 14.5</td>
<td>46.4 ± 11.9</td>
<td>0.86</td>
</tr>
<tr>
<td>VO₂ PE (mL kg⁻¹ min⁻¹)</td>
<td>18.9 ± 4.3</td>
<td>142.4 ± 22.3</td>
<td>0.62</td>
</tr>
<tr>
<td>HR PE</td>
<td>79.2 ± 22.6</td>
<td>159.2 ± 15.4</td>
<td>0.03</td>
</tr>
<tr>
<td>POT PE (watts)</td>
<td>96.9 ± 15.1</td>
<td></td>
<td>0.04</td>
</tr>
</tbody>
</table>

* statistically significant p < 0.05; Flex - flexibility; VO₂ AT - peak oxygen uptake in the anaerobic threshold; HR AT - heart rate at anaerobic threshold; POT AT - power on the anaerobic threshold; VO₂ PE - peak oxygen uptake at peak exercise; HR PE - heart rate at peak exercise; POT PE - Power at peak exercise.
LMNA cause the autosomal-dominant FPLD2. In later life, individuals with FPLD2 often experience severe metabolic derangements, including insulin resistance, dyslipidemia, heart disease, and type 2 diabetes. Mutations elsewhere in the LMNA gene are associated with several additional autosomal-dominant diseases.

According to our study results, nine (64.3%) women with FPLD2 reported T2DM and hypertension, and 13 (92.8%) hypertriglyceridemia. Laboratory tests showed that women with FPLD2 had increased levels of uric acid, glycemia, HbA1c, triglycerides, CRP, ALT and ALD and reduced levels of HDL-c (p < 0.016). The present results confirm those reported by Hartmut, who evaluated a family with FPLD2 and observed that most subjects had elevated serum levels of the components of the metabolic profile, especially glycemia, insulin and triglycerides. Diabetes, hypertension, and hypertriglyceridemia are all established risk factors for total mortality and cardiovascular disease. Diabetes, hypertension, and hypertriglyceridemia are all established risk factors for total mortality and cardiovascular disease.

In study of Valerio et al., thirteen FPLD2-affected women showed hypoleptinemia, insulin resistance and a more aggressive lipid profile when compared to control subjects. In general, there is a direct correlation between adipose mass and plasma leptin concentration.

Monteiro et al. investigated body fat distribution in fourteen women with familial partial lipodystrophy caused by mutation in the lamin A/C gene and found that the FPLD2-affected women showed reduction in total fat (%), total fat mass (kg) and trunk and an increase in total lean mass (kg) and trunk when compared to the control group.

The women investigated in the present study showed a reduced level of flexibility compared to controls without FPLD2, although the difference was significant only for the ankle (p < 0.045). Araujo and Chaves investigated using Flexitest the flexibility in women with mitral valve prolapsed (MVP) and found that Flexindex was significantly higher in the women with MVP.

Several authors have dealt with the impairment of joint motion at the foot-ankle complex in the presence of diabetes. A general decreasing trend was observed in the range of motion, especially in flexion-extension movements. Hypotheses were formulated about alterations in the structure of cartilages and capsules which might interfere with joint mobility. Studies were also conducted to investigate the role of muscular deficits in patients with diabetes.

Few studies to date have examined loss of muscle mass and strength with insulin resistance, although a large number of studies have described the loss of muscle mass and strength with age.

Hand grip strength value using a Jamar dynamometer was lower in the FPLD2 group compared with the control group. Ozdirenç et al. investigated physical fitness in T2DM patients and found that the physical functional capacity was lower in T2DM patients than in age-matched healthy control subjects. Sayer et al. demonstrated that lower grip strength as a marker of sarcopenia is associated with individual features of the metabolic syndrome including higher fasting triglycerides, blood pressure and waist circumference.

Previous studies have indicated that muscular strength is a significant predictor of metabolic risk in adults. Grip strength is a simple and direct isometric method for the assessment of hand and forearm skeletal muscle strength, which may be representative of overall muscular strength because it is highly correlated with other muscular strength measures, including elbow flexion, knee extension, trunk flexion, and trunk extension. Sayer et al. have indicated that there is a graded association between increased glucose levels and weaker muscular strength in those with impaired glucose tolerance and normal blood glucose levels. As such, there appears to be a link between muscular strength and glucose metabolism. Because muscular strength is related to skeletal muscle mass, which is a significant site of glucose disposal, muscular strength may be important for glucose metabolism and could be a good target for the treatment of metabolic risk leading to conditions such hyperglycemia and type 2 diabetes mellitus. The amount of physical activity is also found to be related to muscular fitness. Actually, grip strength in subjects with exercise habits is known to be higher than those without exercise habits. Previous studies have shown that increase in moderate and vigorous physical activity is also found to be related to muscular fitness. Grip strength in subjects with exercise habits is known to be higher than those without exercise habits. Previous studies have shown that increase in moderate and vigorous physical activity is also found to be related to muscular fitness. Grip strength in subjects with exercise habits is known to be higher than those without exercise habits. 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Diabetic patients have comparatively lower aerobic capacity even in the absence of cardiopulmonary complications. Studies in the literature show that lower VO$_{2\text{max}}$ is related to insulin resistance, IGT and magnesium levels.\textsuperscript{5,40} 

In another study carried out by Katoh et al.,\textsuperscript{41} T2DM (aged 32-68, BMI 27.8 ± 4.8 kg m$^{-2}$) and 16 healthy subjects (aged 23-57, BMI 22.7 ± 3.2 kg m$^{-2}$) using bicycle ergometry, VO$_{2\text{max}}$ was lower in diabetic patients. 

The Malmö Preventive Trial indicated that poor physical fitness, measured by vital capacity and maximal oxygen uptake, was inversely correlated with the risk of T2DM.\textsuperscript{42} In the Kuopio Ischemic Heart Disease Risk Factor Study, higher levels of cardiorespiratory fitness ($\geq 31.0$ mL of oxygen/kg/min) protected against the development of T2DM after adjusting for age, baseline glucose levels, and other risk factors.\textsuperscript{43} 

Even though the mechanism of association between low cardiorespiratory fitness and the risk of T2DM is unknown, several putative mechanisms can be proposed. Individuals with low cardiorespiratory fitness have high insulin resistance. Individuals with lower cardiorespiratory fitness levels also have fewer glucose transporters compared with those who are more fit.\textsuperscript{44} 

Cardiorespiratory fitness is said to be as informative a predictor for cardiovascular disease as are blood pressure, lipoproteins, or glucose-tolerance tests.\textsuperscript{45} Our results suggest the importance of ascertaining fitness in routine clinical practice and of scientific investigations into the etiology of low fitness beyond inactivity. 

Epidemiologic evidence has shown that physical activity and body fat loss are of medical benefit, not just for preventing diabetes but also for cardiovascular health and quality of life.\textsuperscript{44,45} Regular physical activity is a crucial component of a healthy lifestyle. Healthcare professionals and policy makers should aggressively promote physical activity to improve physical fitness and control of chronic diseases such as diabetes and hypertension. 

FPLD2 is a disease rarely and has been associated with metabolic complications. These aspects are still little studied and further investigation is needed to better identify the metabolic profile and physical fitness. Further studies of physical fitness comparing FPLD2 patients and controls are so warranted. 

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**Responsabilidades Éticas**

**Conflitos de Interesse:** Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

**Fontes de Financiamento:** Não existiram fontes externas de financiamento para a realização deste artigo.

**Proteção de Pessoas e Animais:** Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investiga-

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**References**


