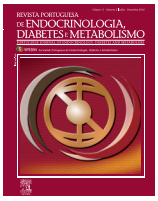
Rev Port Endocrinol Diabetes Metab. 2017;**12(1)**:22-28

Revista Portuguesa
de Endocrinologia, Diabetes e Metabolismo

www.spedmjournal.com



Artigo Original

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

Luciana Monteiro[a], Maria Cristina Foss-Freitas[a], Júlio Crescêncio[b], Lourenço Gallo Júnior[b], Fernanda Coelis[a], Francisco Pereira[a], Estela Carneseca[c], Renan Montenegro Júnior[d], Milton Foss[a]

[a] *Division of Endocrinology, Department of Internal Medicine, Medical School of Ribeirão Preto, University of São Paulo, São Paulo, Brazil*
[b] *Laboratory of Exercise Physiology - Division of Cardiology, Department of Internal Medicine, Medical School of Ribeirão Preto, University of São Paulo, São Paulo, Brazil*
[c] *Institute of Education and Research, Foundation Institution Pio XII - Cancer Hospital of Barretos, Barretos, Brazil*
[d] *Department of Community Health, Service of Endocrinology and Diabetes, University Hospital Walter Cantídio, Fortaleza Medical School, Ceará University, Fortaleza, Brazil*

INFORMAÇÃO SOBRE O ARTIGO

Historial do artigo:
Recebido a 01 de maio de 2016
Aceite a 17 de novembro de 2016
Online a 30 de junho de 2017

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

A B S T R A C T

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 in the 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.

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

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

R E S U M O

Introdução: O objectivo do estudo foi comparar a aptidão física relacionada a saúde em mulheres com lipodistrofia parcial familiar tipo 2 (LPFD2) com mulheres controles sem LPFD2.
Métodos: Foram selecionadas 14 pacientes com quadro clínico de LPFD2 e com mutação no gene LMNA, e 14 pacientes controlos, 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.

* Autores para correspondência.
Correio eletrónico: lucianazaranza@hotmail.com (Luciana Zaranza Monteiro)
Serviço de Endocrinologia, Diabetes e Metabolismo
Hospital Curry Cabral, Centro Hospitalar de Lisboa Central
Rua da Beneficiência, Nº 8
1069-166 Lisboa
Portugal

http://dx.doi.org/10.1016/j.rpedm.2015.10.014

Resultados: Das 14 mulheres com LPFD2, nove (64,3%) tinham diabetes *mellitus* tipo 2 e hipertensão, e 13 (92,8%) hipertrigliceridemia. Na aptidão física, as mulheres com LPFD2, apresentaram uma diminuição na amplitude da articulação do tornozelo ($p < 0,040$), diminuição na resistência muscular abdominal ($p < 0,012$) e na frequência cardíaca ($p = 0,032$) e na potência aeróbia ($p = 0,045$) no pico de esforço. Em relação aos exames laboratoriais, verificamos que as mulheres com LPFD2 tiveram um aumento no ácido úrico, glicemia, Hb1AC, insulina, triglicerídeos, PCR, TGO e TGP e uma diminuição do HDL-c ($p < 0,017$) quando comparadas ao grupo de controlo.
Conclusão: As mulheres com LPFD2 apresentaram níveis de AF diminuído quando comparado ao GC. Futuros estudos devem ser estimulados para a investigação da atividade física e de incentivo para medidas preventivas.

Introduction

Dunnigan type familial partial lipodystrophy (FPLD2) is a rare autosomal dominant caused by mutant *LMNA*, which encodes nuclear lamin A/C, a structural component of the nuclear envelope.[1] FPLD2 is characterized by the gradual appearance at puberty of 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.[5-8] 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,[10,11] hypertension, and type 2 diabetes mellitus (T2DM), as well as mortality from cardiovascular disease, cancer, and all causes of mortality.[12]

On physical health-related fitness, Pate[13] defines as the ability to realizer 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 in women with FPLD2 with healthy without FPLD2 control subjects.

Methods

A cross-sectional study was conducted on 14 women with FPLD2 followed at the Clinic of Diabetes and Metabolism, University Hospital, Medical School of Ribeirão Preto, University of São Paulo, Brazil.

All of them presented at least three of the following features: postpuberal loss of adipose tissue affecting lower limbs and sparing face and neck (essential criteria) with prominent veins and muscularity, acanthosis nigricans, hypertriglyceridemia and/or low high-density-lipoprotein (HDL)-cholesterol and T2DM.

T2DM was identified as two fasting glucose ≥ 126 mg/dL and hypertriglyceridemia was diagnosed with triglycerides ≥ 150 mg/dL and low HDL-cholesterol level was < 50 mg/dL.

Exclusion criteria adopted were: age under 18 years, pregnancy or breastfeeding, presence of acquired lipodistrophy (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.[14] Primers used in exon 11 analysis were designed as follows: primer forward 5'GTAGCTAGAACAGAGTCAGAGTC 3', primer reverse 5'AGAGAGAAAACAGAGGAGAGAGG 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 (m^2). 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. Flexitest 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 al*[16] based on anthropometric characteristics, age and gender. Patients were encouraged to make the effort applied to the power at which they reached cardiorespiratory exhaustion. In all patients studied, the onset of the ramp was preceded by an effort at minimum workload (3-4 watts) at a constant speed of 60 revolutions per minute, with the aim of obtaining a steady-state of the physiological systems involved in carrying the oxygen. 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 VO_{2peak} and heart rate - HR_{peak} 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-Coquete, 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 1. Subject characteristics, means (±SD)

	Women with FPLD2 (n = 14)	Control (n = 14)	*p*
Age (years)	35.8 ± 13.9	35.9 ± 13.8	0.99
Height (m)	1.6 ± 0.1	1.6 ± 0.1	0.91
Weight (kg)	58.6 ± 5.9	63.9 ± 6.7	0.99
BMI (kg/m^2)	23 ± 2.1	23.2 ± 2.4	0.82
Fat mass (kg)	10 ± 2.3	19.1 ± 4.1	< 0.05
Fat-free mass (kg)	41.4 ± 4.5	34.1 ± 3.9	< 0.05
Percent fat mass (%)	19.1 ± 4.2	34.8 ± 5.0	< 0.01
Waist circumference (cm)	77.4 ± 5.1	74.1 ± 5.5	0.10
Hip circumference (cm)	88.5 ± 3.6	94.8 ± 5.3	0.03
Waist-to hip ratio (cm)	0.87 ± 0.05	0.78 ± 0.05	< 0.01

* 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 Flexitest. 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 ($p < 0.016$) (Table 3).

There was correlation of glucose with waist circumference ($r_{s = 0.60;} p < 0.024$); VO_2 PE ($r_s = -0.54$; $p = 0.042$); HR PE ($r_s = -0.52$; $p = 0.051$) and POT PE ($r_s = -0.61$; $p = 0.026$) the group of women with FPLD2.

There were not found correlations of glucose with hip circumference, waist-to hip ratio, flexibility test, grip strength, abdominal muscular strength, peak oxygen uptake in the anaerobic threshold; heart rate at anaerobic threshold and power on the anaerobic threshold.

There was correlation of HbA1c with waist circumference ($r_{s = 0.73;} p < 0.001$), waist-to hip ratio ($r_s = 0.62$; $p = 0.022$), HR PE ($r_s = -0.52$; $p = 0.054$) and POT PE ($r_s = -0.58$; $p = 0.033$) the group of women with FPLD2.

We did not observe 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.[17] 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

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

	Women with FPLD2 (n = 14)	Control (n = 14)	*p*
Flex wrist	39 ± 2.6	40 ± 3.9	0.61
Flex elbow	40 ± 2.3	41 ± 2.6	0.58
Flex shoulder	40 ± 11.3	47 ± 10	0.12
Flex trunk	30 ± 8.9	33 ± 10	0.38
Flex hip	41 ± 12.3	46 ± 12.6	0.21
Flex knee	44 ± 6.4	47 ± 10.6	0.39
Flex ankle	36 ± 7.5	43 ± 10.6	< 0.04
Flexindex	39 ± 7.7	43 ± 7.5	0.20
Right grip strength	21.5 ± 5.4	23.5 ± 4.1	0.34
Left grip strength	18.5 ± 5.3	21.1 ± 4.2	0.17
Abdominal muscular strength	15 ± 7.7	26 ± 5.2	< 0.01
VO_2 AT (mL kg^{-1} min^{-1})	12.3 ± 2.7	11.2 ± 3.0	0.27
HR AT	115.6 ± 16.2	112 ± 17.7	0.51
POT AT (watts)	45.1 ± 14.5	46.4 ± 11.9	0.86
VO_2 PE (mL kg^{-1} min^{-1})	18.9 ± 4.3	20.1 ± 4.5	0.62
HR PE	142.4 ± 22.3	159.2 ± 15.4	0.03
POT PE (watts)	79.2 ± 22.6	96.9 ± 15.1	0.04

* statistically significant $p < 0.05$; Flex - flexibility; VO_2 AT - peak oxygen uptake in the anaerobic threshold; HR AT - heart rate at anaerobic threshold; POT AT - power on the anaerobic threshold; VO_2 PE - peak oxygen uptake at peak exercise; HR PE - heart rate at peak exercise; POT PE - Power at peak exercise.

Table 3. Biochemical parameters values of the study participants, means (± SD)

Variables	Women with FPLD2 (n = 14)	Control (n = 14)	p
Glucose (mg/dL)	147.1 ± 77.1	76.2 ± 3.8	< 0.01
HbA1c (%)	8.1 ± 2.5	5.3 ± 0.4	< 0.01
Insulin (μU/mL)	36.3 ± 29	3.3 ± 1.3	< 0.01
Uric Acid (mg/dL)	5.5 ± 1.4	3.6 ± 0.8	< 0.01
HDL (mg/dL)	38.4 ± 6.0	49.3 ± 10.5	< 0.01
CT (mg/dL)	201.8 ± 51.8	181.3 ± 45.1	0.32
TG (mg/dL)	302.1 ± 177.4	84 ± 27	< 0.01
ALT (mg/dL)	49.1 ± 41.3	15.8 ± 4.7	< 0.01
AST (mg/dL)	42.8 ± 31.1	19.4 ± 3.8	0.01
CRP (mg/dL)	0.5 ± 0.5	0.1 ± 0.2	0.02

statistically significant $p < 0.05$. HbA1c, glycated hemoglobin; HDL - high density lipoproteins; CT - total serum cholesterol; TG - triglycerides; ALT - alanine aminotransferase; AST - aspartate aminotransferase; CRP - C-reactive protein.

LMNA cause the autosomal-dominant FPLD2.[18] 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, insulin, triglycerides, CRP, ALT and ALT and reduced levels of HDL-c ($p < 0.016$). The present results confirm those reported by Hartmut,[14] 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.[19]

In study of Valerio *et al*,[20] 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*[21] 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[22] 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.[23] Hypotheses were formulated about alterations in the structure of cartilages and capsules which might interfere with joint mobility.[24] Studies were also conducted to investigate the role of muscular deficits in patients with diabetes.[25,26]

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*,[27] 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,*[28] 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.[28,29]

Grip strength is a simple and direct isometric method for the assessment of hand and forearm skeletal muscular 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.[30] Sayer *et al*[31] 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,[32] 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.[33] Actually, grip strength in subjects with exercise habits is known to be higher than those without exercise habits.[34] Previous studies have shown that increase in moderate and vigorous activity results in a decrease in fasting insulin level, a marker of insulin resistance,[35] indicating physical activity exerts its action on glucose metabolism in the long term.

The timed bent-leg sit-ups test is recommended in the guidelines of the American College of Sports Medicine[36] for measuring abdominal muscle strength and upper extremity strength. Pinet *et al*[37] concluded that cystic fibrosis patients with forced expiratory volume ($FEV_{1)} < 60\%$ predicted had thicker and stronger abdominal muscles than did control subjects, and that this might be due to the heavier respiratory work performed

by these patients.

Diabetic patients have comparatively lower aerobic capacity even in the absence of cardiopulmonary complications. Studies in the literature show that lower VO_{2max} is related to insulin resistance, IGT and magnesium levels.[38-40]

In another study carried out by Katoh *et al*,[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_{2max} 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.[42] In the Kuopio Ischemic Heart Disease Risk Factor Study, higher levels of cardiorespiratory fitness (≥ 31.0 mL of oxygen/kg/min) protected against the development of T2DM after adjusting for age, baseline glucose levels, and other risk factors.[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.[42]

Cardiorespiratory fitness is said to be as informative a predictor for cardiovascular disease as are blood pressure, lipoproteins, or glucose-tolerance tests.[39] 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.[44-50] 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.

Agradecimentos / Acknowledgments

Research funded by the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP - State of São Paulo Research Foundation), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Fundação de Apoio ao Ensino, Pesquisa e Assistência do Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo.

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 Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação dos dados de doentes.

Ethical Disclosures

Conflicts of Interest: The authors report no conflict of interest.

Funding Sources: No subsidies or grants contributed to this work.

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of patient data.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

References

1. Garg A, Subramanyam L, Agarwal AK, Simha V, Levine B. Atypicalprogeroid syndrome due to heterozygous missense *LMNA* mutations. J Clin Endocrinol Metab. 2009;94:4971-83.
2. Agarwal A, Garg A. Genetic disorders of adipose tissue development, differentiation, and death. Annu Rev Genomics Hum Genet. 2006;7:175–99.
3. Capeau J, Magré J, Lascols O, Caron M, Béréziat V, Vigouroux C. Diseases of adipose tissue: genetic and acquired lipodystrophies. Biochem Soc Trans. 2005;33:1073–7.
4. Wong S, Huda M, English P, Bargiotta A, Wilding J, Johnson A. Adipokines and the insulin resistance syndrome in familial partial lipodystrophy caused by a mutation in lamina A/C. Diabetologia. 2005;48:2641–9.
5. Katzmarzyk PT, Church TS, Blair SN. Cardiorespiratory fitness attenuates the effects of the metabolic syndrome on all-cause and cardiovascular disease mortality in men. Arch Intern Med. 2004;164:1092-7.
6. Forrest KY, Bunker CH, Kriska AM. Physical activity and cardiovascular risk factors in a developing population. Med Sci Sports Exerc, 2001;33:1598-604.
7. MacAuley D, McCrum EE, Stott G. Physical activity, lipids, apolipoproteins, and Lp(a) in the Northern Ireland Health and Activity Survey. Med Sci Sports Exerc. 1996;28: 720-36.
8. Guedes DP, Guedes JE. Atividade física, aptidão cardiorrespiratória, composição da dieta e fatores de risco predisponentes às doenças cardiovasculares. Arq Bras Cardiol, 2001;77:243-50.
9. Bassuk SS, Manson JE. Physical activity and cardiovascular disease prevention in women: how much is good enough? Exerc Sport Sci Rev. 2003;31:176-81.
10. Church TS, LaMonte MJ, Barlow CE. Cardiorespiratory fitness and body mass index as predictors of cardiovascular disease mortality among men with diabetes. Arch Intern Med. 2005;165:2114-20.
11. Laukkanen JA, Kurl S, Salonen R. The predictive value of cardiorespiratory fitness for cardiovascular events in men with various risk profiles: a prospective population-based cohort study. Eur Heart J, 2004;25:1428-37.
12. Lohman TG, Ring K, Pfeiffer K, Camhi S, Arredondo E, Pratt C, et al. Relationships among fitness, body composition, and physical activity. Med Sci Sports Exerc. 2008;40:1163-70.
13. Patel RR. The evolving definition of physical fitness. Quest. 1988;40:174.
14. Hartmut S, Janine G, Peter B, Martina S, Johann O, Uwe T. Dyslipemia in familial partial lipodystrophy caused by an R482W mutation in the *LMNA* gene. J Clin Endocrinol Metab. 2001;86:2289–95.
15. Araújo CG. Flexitest: an innovative flexibility assessment method. Champaign: Human Kinetics; 2003.

16. Wasserman K, Hansen JE, Sue D, Whipp BJ, Casaburi R. Principles of exercise testing and interpretation. 4th ed. Philadelphia: Lippincott Williams and Wilkins; 2004.
17. Garg A. Acquired and inherited lipodystrophies. N Engl J Med, 2004;350: 1220–34.
18. Geiss LS, Pan L, Cadwell B, Gregg EW, Benjamin SM, Engelgau MM. Changes in incidence of diabetes in U.S. adults, 1997-2003. Am J Prev Med. 2006;30:371-7.
19. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract. 2010;87:4-14.
20. Valerio CM, Zajdenverg L, de Oliveira JE, Mory PB, Moyses RS, Godoy-Matos AF. Body composition study by dual-energy x-ray absorptiometry in familial partial lipodystrophy: finding new tools for an objective evaluation. Diabetol Metab Syndr. 2012;4:40.
21. Monteiro LZ, Foss-Freitas MC, Júnior Montenegro RM, Foss MC. Body fat distribution in women with familial partial lipodystrophy caused by mutation in the lamin A/C gene. Indian J Endocrinol Metab, 2012;16:136-8.
22. Araujo C, Chaves C. Adult women with mitral valve prolapse are more flexible. Br J Sports Med. 2005;39:720–4.
23. Hajrasouliha AR, Tavakoli S, Esteki A, Nafisi S. Abnormal viscoelastic behaviour of passive ankle joint movement in diabetic patients: an early or a late complication? Diabetologia. 2005;48:1225-8.
24. Delbridge L, Perry P, Marr S, Arnold N, Yue DK, Turtle JR, et al. Limited jont mobility in the diabetic foot: relationship to neuropathic ulceration. Diabet Med. 1988; 5:333-7.
25. Andersen H, Gjerstad MD, Jakobsen J. Atrophy of foot muscles: A measure of diabetic neuropathy. Diabetes Care. 2004;27:2382-5.
26. Andreassen CS, Jakobsen J, Andersen H. Muscle weakness: a progressive late complication in diabetic distal symmetric polyneuropathy. Diabetes. 2006;55:806-12.
27. Ozdirenç M, Biberoğlu S, Ozcan A. Evaluation of physical fitness in patients with type 2 diabetes mellitus. Diabetes Res Clin Pract. 2003;60:171–6.
28. Sayer AA, Syddall HE, Dennison EM, Martin HJ, Phillips DI, Cooper C, et al. Grip strength and the metabolic syndrome: findings from the Hertfordshire Cohort Study. QJM. 2007;100:707–13.
29. Wijndaele K, Duvigneaud N, Matton L, Duquet W, Thomis M, Beunen G, et al. Muscular strength, aerobic fitness, and metabolic syndrome risk in Flemish adults. Med Sci Sports Exerc. 2007;39:233–40.
30. Rantanen T, Era P, Heikkinen E. Maximal isometric strength and mobility among 75-year-old men and women. Age Ageing. 1994;23:132–7.
31. Sayer AA, Dennison EM, Syddall HE, Gilbody HJ, Phillips DI, Cooper C. Type 2 diabetes, muscle strength, and impaired physical function: the tip of the iceberg? Diabetes Care. 2005;28:2541–2.
32. Lazarus R, Sparrow D, Weiss ST. Handgrip strength and insulin levels: cross-sectional and prospective associations in the Normative Aging Study. Metabolism. 1997; 46:1266–9.
33. Paalanne NP, Korpelainen RI, Taimela SP, Auvinen JP, Tammelin TH, Hietikko TM, et al. Muscular fitness in relation to physical activity and television viewing among young adults. Med Sci Sports Exerc. 2009;41:1997–2002.
34. Miyatake N, Saito T, Miyachi M, Tabata I, Numata T. Evaluation of muscle strength and its relation to exercise habits in Japanese. Acta Med Okayama. 2009;63:151–5.
35. Assah FK, Brage S, Ekelund U, Wareham NJ. The association of intensity and overall level of physical activity energy expenditure with a marker of insulin resistance. Diabetologia. 2008;51:1399–1407.
36. Mahler DA, Froelicher VF, Miller NH. ACSM′s guidelines for exercise testing and prescription. 5th ed. Baltimore:Williams & Wilkins;1995.
37. Pinet C, Cassart M, Scillia P. Function and bulk of respiratory and limb muscles in cystic fibrosis. Am J Respir Crit Care Med. 2003;168:989 –94.
38. Colman E, Katzel LI, Sorkin J, Coon PJ, Engelhardt S, Rogus E, et al. The role of obesity and cardiovascular fitness in the impaired glucose tolerance of aging. Exp Gerontol. 1995;30:571-80.
39. Wei M, Gibbons TL, Mitchell JB, Kampert CD, Blair LS. The role of obesity and cardiovascular fitness and impaired fasting glucose and type 2 DM in men. Ann Intern Med. 1999;19:89-96.
40. Kobayashi T. Plasma and erythrocyte magnesium levels are correlated with oxygen uptake in patients with noninsulin-dependent DM. Endocr J. 1998;45:277-83.
41. Katoh J, Hara Y. Cardiorespiratory function as assessed by exercise testing in patients with NIDDM. J Int Med Res. 1996;24:209-13.
42. Hu G, Lakka TA, Barengo NC, Tuomilehto J. Physical activity, physical fitness, and risk of type 2 diabetes mellitus. Metab Syndr Relat Disord. 2005;3:35-44.
43. Lynch J, Helmrich S, Lakka TA. Moderately intense physical activities and high levels of cardiorespiratory fitness reduce the risk of non-insulindependent diabetes mellitus in middle-aged men. Arch Intern Med. 1996;156:1307–14.
44. Pate RR, Pratt M, Blair SN, Haskell WL, Macera CA, Bouchard C, et al. Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. JAMA. 1995;273:402-7.
45. Willett WC, Dietz WH, Colditz GA. Guidelines for healthy weight. N Engl J Med. 1999;341:427–34.
46. Blair SN, Cheng Y, Holder JS. Is physical activity or physical fitness more important in defining health benefits? Med Sci Sports Exerc. 2001;33:S379–S99.
47. Wannamethee SG, Shaper AG. Physical activity in the prevention of cardiovascular disease: an epidemiological perspective. Sports Med. 2001;31:101–14.
48. Dubbert PM, Carithers T, Sumner AE. Obesity, physical inactivity, and risk for cardiovascular disease. Am J Med Sci. 2002;324:116–26.
49. Erlichman J, Kerbey AL, James WP. Physical activity and its impact on health outcomes. Paper 1: The impact of physical activity on cardiovascular disease and all-cause mortality: an historical perspective. Obes Rev. 2002;3:257–71.
50. Katzmarzyk PT, Janssen I, Ardern CI. Physical inactivity, excess adiposity and premature mortality. Obes Rev. 2003;4:257–90.