Physical Exercise in Patients with Fabry Disease – a Pilot Study

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Physical Exercise in Patients with Fabry Disease – a Pilot Study

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Key words
- rare disease
- lysosome
- α-Galactosidase A
- globotriaosylceramide

Abstract

The aim of this study was to assess the extent of exercise intolerance in Fabry disease (FD) patients and to report individual effects of physical exercise. Exercise capacity and strength of 14 patients (mean age 46 years, 6 females) were determined using cycle ergometry and isokinetic measurements. Patients performed a strength/circuit exercise training protocol for 12 months. The mean relative maximum performance of the group was low at baseline and increased by 12.1 % (baseline: 1.9 [0.9–3.4] $W \cdot kg^{-1}$ vs. re-test: 2.1 [1.1–3.8] $W \cdot kg^{-1}$; $p = 0.035$) during the study. Patients' mean baseline maximum performance blood lactate of 5.4 [1.3–9.9] $mmol \cdot L^{-1}$ increased to a mean of 7.2 (2.4–10.2) $mmol \cdot L^{-1}$ ($p = 0.038$). Mean strength of the lower limbs (left/right extensors and flexors, total work of 5 sets) changed from 2269 (1017–2913) $kg \cdot m^2 \cdot s^{-2}$ to 2325 (1359–3107) $kg \cdot m^2 \cdot s^{-2}$ (not significant). Patients reported increased well-being, daily activity and reduced fatigue during the study. Our results indicate that exercise intolerance in FD patients often results from physical inactivity. FD patients may perform exercise training to improve exercise capacity and muscle strength. Future studies will address the clinical benefits of exercise in FD.

Introduction

Fabry disease (FD) [OMIM 301500] is a rare X-linked inborn error of glycosphingolipid catabolism resulting from deficient α-galactosidase A activity (GLA; 300644) due to mutations in the *GLA* gene (for a comprehensive review see [11]). Progressive systemic accumulation of globotriaoslyceramide (Gb3) within the cellular lysosomes results in macro- and microangiopathic alterations, leading to Fabry-specific manifestations such as early stroke/transient ischemic attack (TIA), malignant arrhythmia, myocardial infarction as well as progressive renal and cardiac failure [30]. Due to the X-linked inheritance, hemizygous male patients can be severely affected, while females display much more variability in disease onset and progression [6]. FD can also be distinguished in a classical form and a non-classical, less severe form often observed in males with residual enzyme activity [1]. Subclinical cardiovascular manifestations of FD involve abnormal blood flow and vessel architecture, endothelial dysfunction, and cardiomyocyte proliferation [15,23]. FD manifestations and early death may be partly avoided or delayed by enzyme replacement therapy (ERT, available since 2001) [16,22,30], however, a large number of patients still suffer from clinically relevant events during ERT [12,27]. The most prominent symptoms in pediatric FD patients are gastrointestinal complaints, recurrent pain attacks and acroparesthesia in hands and feet potentially due to small fiber neuropathy [11]. Physical exertion of FD patients has been suggested to trigger episodes of pain and may result in heat intolerance or heat illnesses as hypohydrosis is often observed in FD [4]. A comprehensive analysis on quality of life in FD by Bouwman et al. reported that FD patients, especially males, are less likely to play competitive sports or engage in a sports club during elementary school compared to controls [4]. While clinicians involved in FD patient treatment report 'general physical weakness' of these patients, data on physical activity, exercise capacity, and strength in FD patients is scarce [3,5,17,28]. The aim of the current study was to assess the extent of exercise intolerance in a heterogeneous group of FD patients. In addition, we assessed the individual response of FD patients to physical exercise in a prospective interventional study.

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Methods

Subjects

14 subjects were recruited out of registered FD patients at the interdisciplinary Fabry center of the University Hospital Muenster (IFAZ) in 2014 by random selection. *GLA* mutations were identified as described (A. Rolfs, Centogene AG, Rostock, Germany) [26] and GLA enzyme activity measurements as reported previously [7,21]. Mildly to severely affected FD patients ≥ 18 years were included in the study. A comprehensive diagnostic work-up was performed in all patients, including medical history, laboratory testing and cardiac (ECG, ultrasound), renal (ultrasound), and neurologic (MRI where indicated) evaluation. Only patients with a stable disease course defined as a maximum Disease Severity Score (DS3) [13] change of < 8 points/year during the past 2–3 years were enrolled. Patients with most severe FD manifestations such as acute cardiovascular disease manifestations or heart/renal transplantation were excluded from the study. All subjects were free of any acute orthopedic diseases that may have limited their participation in the study. All investigations were performed after the approval of the Ethical Committee of the Medical Faculty of the University of Muenster (project-no. 2013–559-f-S, date of report: 08.04.2014) according to the IJSM ethical standards [14]. Written informed consent of patients was obtained prior to the subjects' participation in the study. During the study, 4 patients (#1, #5, #10 and #13) retired due to aversion to the training and/or lack of time to perform the training.

Ergometry

Aerobic (endurance) exercise capacity was determined according to the American Heart Associations' Exercise Standards for Testing and Training [9]. Prior to ergometry exercise testing, patients were seen by a clinician and a resting ECG (AT-10 plus, Schiller, München, Germany) was performed to identify major cardiac abnormalities. Patients maximum exercise capacity was tested on a cycle ergometer (ec3000, Custo med, Ottobrunn, Germany) after adaptation of optimal sitting position by an experienced operator at ambient temperature. Initial examination at baseline was performed starting at 25 W with an increase every 2 min by 10 W to determine patient's exercise capacity and to obtain a cardiac stress test to exclude any acute coronary abnormalities such as prolonged QRS, ventricular extra systoles, left or right bundle branch block and brady- or tachyarrhythmias [9]. Patients were re-tested after initial examination starting at 25 W with an increase every 2 min by 25 W. Female patients #6 and #11 remained on the 25 + 10 W interval setting due to severe FD manifestations associated with weak physical constitution. Exercise blood pressure was measured manually at every step and a capillary blood sample was drawn for blood lactate (LA) measurement (Biosen S-line, EKF Diagnostics, Magdeburg, Germany). Performance at LA thresholds (2, 3, 4 $mmol \cdot L^{-1}$ and individual anaerobic threshold [IAT]) were approximated using Winlactat software version 5.0.0.54 (Mesics, Muenster, Germany). ECG was continuously documented during exercise testing (cardio 110 BT, Custo med). Verbal encouragement was provided to all subjects throughout the test to achieve maximum performance. Ergometry was performed until exhaustion or if clinically indicated.

Isometric and isokinetic measurement

Isometric and isokinetic measurements were performed subsequent to patients' ergometry after a 30 min break on a NORM isokinetic dynometer (Cybex, Ronkonkoma, USA) using established test protocols [8]. Each subject sat in the chair and the dynamometer was adjusted to align the axis of rotation of the dynamometer with the knee axis of rotation by an experienced operator. Velcro straps secured the subject's thigh and torso to prevent excessive upper extremity motion. Isometric strength testing was done in a 60° flexed position in knee extension as well as knee flexion during a 20 s period of time. The angular velocity for isokinetic measurement was set to $60° \cdot s^{-1}$. Subjects performed 3 easy repetitions for initial accommodation to the given speed, followed by a set of 5 maximum contractions. 3 parameters were determined to investigate changes in patients' leg strength during the study. 1) the mean combined total isokinetic workload during 5 repetitions of right and left leg flexors and extensors given as spend energy ($kg \cdot m^2 \cdot s^{-2}$) as well as the mean best work of lower leg (left/right combined) 2) extensors and 3) flexors at $60° \cdot s^{-1}$ given as torque ($N \cdot m^{-1}$).
Measurements were performed without gravity correction. The whole isokinetic measurement was repeated after a 2 min break. Verbal encouragement was provided to all subjects throughout all contractions to achieve maximum performance. The order of tested leg was randomized.

Strength/circuit exercise program

The exercise training program was based on the 'Lift Yourself' well-being program for patients with FD drafted by the Directorate of Sport, Exercise and Physiotherapy at the University of Salford, UK (unpublished). The program refers to the 2011 general guidelines for exercise and physical activity by the American College of Sports Medicine [10] and the 2010 British Association of Sport and Exercise Sciences [25], with adaptation for FD patients. Patients were introduced to the exercise program in small groups and performed exercise for ~12 months at home using patient's body weight and a set of dumbbells (2–4 kg). Patients were instructed to perform 3 training sessions per week (30–45 min per session, 90–135 min per week) with one day of rest in-between sessions. The initial exercise program included 3 sets of 6 repetitions of squats, step-ups, assisted push-ups (wall press), heel raises, dumbbell rows, shoulder presses (seated), back extensions, glute bridges, and abdominal crunches with 30 s of rest in-between exercises (also performed as circuit training). 4 weeks after the start of the program, patients were free to intensify the exercise individually up to 3 sets of 15 repetitions advancing to single-leg heel raises, step-up plus knee lift, standard push-ups, standing shoulder press, single-leg glute bridges, modified planks, and increased dumbbell weights if possible. Patients' weekly exercise and potential restrains were interrogated and documented by an assistant. Patients were free to perform any additional activity at own will. Patients' diet was not controlled. 4 patients (#1, #5, #10 and #13) retired from the study for various reasons during the first 3 months and were only included in baseline data analysis.

Statistical data analysis

Statistical analyses were performed using SPSS, version 22.0 (Statistical Package for Social Science, Chicago, USA) and GraphPad PRISM V5.0 software (GraphPad Software Inc., La Jolla, USA). Data are given as mean (range) or *n* (%) and mean differences at

baseline and re-test were compared using 2-sided paired t-test. The longest available observation time was analyzed for each patient as indicated. Statistical significance was considered at a 2-sided $p < 0.05$.

Results

Anthropometric data and participants' characteristics

Patients' baseline characteristics are given in **Table 1** (anthropometric data) and **Table 2** (clinical data). Of the 14 enrolled patients, 12 (85.7%) were on ERT (mean duration = 51 months; individual ERT duration and additional medication is given in the **Supplemental Table**), 4 (28.6%) had suffered from stroke/TIA and 6 (42.9%) presented with left ventricular hypertrophy (LVH, defined as interventricular septal thickness > 13 mm). None of the patients switched ERT product or changed ERT dose during the study. One patient (#5) started treatment with an anticonvulsant while one patient (#13) stopped treatment with a selective serotonin re-uptake inhibitor during the study **Supplemental Table**. 8 patients (57.1%) had plasma lyso-Gb3 levels above the reference value **Supplemental Table**. One patient had an implanted cardioverter defibrillator (ICD). In addition, patients presented with classical FD symptoms such as fatigue, pain attacks, hypo- or hyperhidrosis and gastrointestinal complaints. Patients' initial exercise examination to approve their participation in the program did not indicate any reason for exclusion from the program.

Table 1 Patients' anthropometric data at baseline.

Variable	Value
n	14
Female, *n*	6 (43%)
Age, yrs	46 (18–66)
Height, cm	173 (168–184)
Body mass, kg	71 (59–97)
BMI, $kg \cdot m^{-2}$	24 (19.7–34)

Values are presented as mean (range) or n (%)

FD patients have reduced exercise capacity

Initial exercise examination using cycle ergometry (**Table 3**) revealed significantly reduced exercise capacity in FD patients compared to the normal population in this age and weight range (17). Mean maximum absolute workload was 130 (65–215) W corresponding to a mean 1.8 (0.9–3.1) $W \cdot kg^{-1}$ of maximum relative workload (**Table 3**). No patient presented any ECG abnormalities, lack of increase in systolic blood pressure/heart rate or other contraindications for further exercise testing. The mean maximum LA concentration was 6.0 (1.3–11.1) $mmol \cdot L^{-1}$, and 3 patients (#3, #4 and #11) did not show any significant LA increase ($\leq 2.4\,mmol \cdot L^{-1}$) at maximum performance (**Table 3**). The mean maximum HR of the group was 147 (105–196) $b \cdot m^{-1}$. One female patient (#9) reported acute acroparesthesia in her hands during initial exercise examination, which lasted for about 30 min. Despite present hypohidrosis (patients #5 and #3), no participant reported any exercise intolerance due to increased body temperature or symptoms of heat illness.

Regular exercise may improve exercise capacity of patients with FD

During the training intervention, patients were contacted every week to interrogate training compliance and potential adverse training effects. Patients initially reported normal muscle soreness subsequent to starting the exercise protocol. Throughout the entire study, no patient reported acroparesthesia or pain attacks during or related to exercise. All patients were able to perform the initial exercise protocol, while some exercises (back extensions, glute bridges) were reported to be more strenuous than others. Patients initially reported the mean level of exertion and the mean level of technical demand to be 4.4 and 3.8 (scale from 1 [low] to 10 [high]), respectively. Patients' relative exercise performance increased significantly from 1.9 (0.9–3.4) $W \cdot kg^{-1}$ to 2.1 (1.1–3.8; $p = 0.035$) $W \cdot kg^{-1}$ during a mean observation range of 30 (24–48) weeks (**Fig. 1a**; $n = 9$). Patients' mean maximum performance LA concentration at baseline was 5.4 (1.3–9.9) $mmol \cdot L^{-1}$ and increased significantly during the study to a mean of 7.2 (2.4–10.2; $p = 0.038$) $mmol \cdot L^{-1}$ (**Fig. 1b**; $n = 10$). In particular, patients #8, #9, #11 and #14 showed considerable improvement of exercise capacity.

Table 2 Patients' clinical characteristics at baseline.

#	Age (yrs)	Sex	GLA mutation	GLA activity < ref.	ERT	Stroke/TIA	LVH	LVEF (%)	ICD	eGFR (ml/min/1.73 m^2)	DS3 Score
1	26	f	p.W340X	yes	no	no	no	71	no	132.3	6
2	54	m	p.D313Y	no	no	no	no	64	no	94.0	0
3	49	m	p.R220X[£]	yes	yes	no	yes	70	no	71.0	20
4	47	m	p.R220X[£]	yes	yes	yes	yes	55	no	102.1	18
5	43	m	p.Tyr365CysfsX5	yes	yes	no	yes	57	no	6.5[$,#]	25
6	63	f	p.L45P	yes	yes	no	yes	61	yes	90.0	4
7	44	m	p.C94S	yes	yes	no	yes	74	no	108.1	16
8	42	f	p.S126G	–	yes	yes	no	64	no	100.9[#]	20
9	45	f	p.R220X	yes	yes	no	yes	72	no	96.6[#]	13
10	18	m	p.A143T[§]	yes	yes	no	no	53	no	132.0	5
11	49	f	p.A143T[§]	yes	yes	yes	no	69	no	108.0	19
12	66	m	p.A143T[*]	yes	yes	no	no	66	no	69.3[#]	2
13	32	f	p.A143T[*]	–	yes	yes	no	58	no	115.8	14
14	64	m	p.A143T[*]	yes	yes	no	no	67	no	89.4	2

DS3: Disease Severity Score (13); eGFR: estimated glomerular filtration rate, CKD-EPI-based; ERT: enzyme replacement therapy; GLA: α-Galactosidase A; ICD: implantable cardioverter defibrillator; LVEF: left ventricular ejection fraction; LVH: left ventricular hypertrophy; TIA: transient ischemic attack; #: micro albuminuria; $: dialysis; *,§,£: related; (–): not determined

Table 3 Patients' exercise data at baseline

#	Preloading				at 2 mmol·L^{-1}		at 3 mmol·L^{-1}		at 4 mmol·L^{-1}		at IAT					at max capacity		
	HR (b·min^{-1})	LA (mmol·L^{-1})	SBP (mmHg)	DBP (mmHg)	Perf. (W·kg^{-1})	HR (b·min^{-1})	Perf. (W·kg^{-1})	HR (b·min^{-1})	Perf. (W·kg^{-1})	HR (b·min^{-1})	Perf. (W·kg^{-1})	LA (mmol·L^{-1})	HR (b·min^{-1})	SBP (mmHg)	DBP (mmHg)	RPE (Borg)	Perf. (W·kg^{-1})	LA (mmol·L^{-1})	HR (b·min^{-1})
1	60	0.9	88	62	1.1	108	1.4	135	1.6	150	1.4	3.1	135	129	72	17	1.6	3.9	146
2	71	0.6	105	77	1.2	140	1.4	150	1.6	158	1.3	2.7	147	155	73	14	2.2	9.9	183
3	66	0.6	140	90	1.0	118	1.2	128	1.3	134	1.1	2.4	122	150	80	17	1.1	2.4	122
4	56	0.6	120	80	na	na	na	na	na	na	na	na	na	150	90	20	1.4	1.4	132
5	–	0.8	125	70	0.9	109	1.1	117	1.3	124	1.1	2.8	114	211	86	16	1.4	4.8	127
6	60	0.6	128	69	0.9	89	1.1	96	1.2	98	1.0	2.6	98	147	60	16	1.3	5.7	105
7	51	1.4	119	68	0.9	88	1.3	106	1.6	113	1.5	3.6	110	157	71	15	2.4	7.9	149
8	67	0.7	130	80	0.9	114	1.1	132	1.3	146	1.1	2.6	126	149	68	14	1.6	6.7	165
9	68	1.6	120	80	0.6	107	0.9	126	1.1	137	1.1	4.1	137	160	80	17	1.4	7.1	154
10	55	0.5	130	80	1.9	143	2.3	162	2.5	175	2.1	2.3	151	170	69	13	3.1	8.4	196
11	59	0.5	130	80	1.0	110	1.1	112	1.1	114	1.0	2.1	110	155	90	20	0.9	1.8	109
12	61	1.3	127	89	1.0	102	1.3	113	1.6	123	1.4	3.2	115	165	79	12	2.1	6.9	149
13	63	1.0	100	70	0.8	111	1.1	125	1.3	137	1.2	3.6	133	116	60	7	2.1	11.1	185
14	52	1.4	120	80	2.0	117	2.4	132	2.7	142	2.4	3.0	132	185	65	18	2.7	4.6	143

DBP/SBP: diastolic/systolic blood pressure; HR: heart rate; IAT: individual anaerobic threshold; LA: lactate; na: not applicable; Perf.: performance; RPE: rated perceived exertion (Borg scale); (–): not determined

Regular exercise may improve strength of patients with FD

Patients' mean combined (5 sets) total isokinetic workload of right and left leg flexors and extensors changed from 2269 (1017–2913) kg·m^2·s^{-2} at baseline to 2325 (1359–3107) kg·m^2·s^{-2} at follow-up (**Fig. 2a**). Patients' mean best work (i.e., torque, best of 5 sets) for lower leg flexors and extensors (left/right combined) changed during the study from 43.0 (23.8–53.1) N·m^{-1} to 44.5 (28.2–44.5) N·m^{-1} and from 57.8 (22.5–79.9) N·m^{-1} to 62.3 (31.1–81.0) N·m^{-1}, respectively (**Fig. 2b/c**). However, only individual improvement of strength was observed, while no significant effect was seen for the combined group. Mean observational time between baseline and re-test was 6 months (n=7).

Regular exercise may improve general well-being of patients with FD

Overall, patients' compliance to the program was sufficient and some patients were able to continuously increase the number of repeats per set or the overall exercise intensity during the study. During the study, 58% of patients reported decreased levels of fatigue. 67% supposed the program to be appropriate to improve the fitness and general well-being of FD patients (**Fig. 3**).

Discussion

The results of the present study indicate that FD patients often refrain from physical exercise which leads to impaired exercise tolerance. Our data also suggest that FD patients may benefit from regular exercise, as some FD patients in this study improved endurance, muscle strength and overall well-being. Although studies already reported on cardiopulmonary exercise testing [2,3], exercise echocardiography [5] and cardiac response to physical exercise testing [28] and partly severe deficits in exercise tolerance in FD patients, our study is first, to the best of our knowledge, to present data of a prospective training intervention in patients with FD.

Exercise capacity in FD patients

Examination at baseline revealed reduced exercise capacity in FD patients compared to the normal population, in that male FD patients reached ~80% and female FD patients ~83% of age and weight adjusted normal reference values [18]. The mean maximum LA concentration was low (6.0 mmol·L^{-1}) and 3 patients did not show any significant increase in LA during exercise testing. No patient presented contraindications for exercise testing such as ECG abnormalities, lack of increase in systolic blood pressure/heart rate or other. Comprehensive evaluation of quality of life in FD already revealed that FD patients are less likely to engage in physical activities (i.e., sports) than control subjects [4,20]. Our study confirms that FD patients have deficits in exercise tolerance and often refrain from physical activities due to fear of provoked pain attacks and suspected FD-specific cardiovascular contraindications. During our investigation, only one patient reported acroparesthesia during exercise examination and no patient experienced exercise intolerance due to present hypohidrosis and increased body temperature. As we did not determine cardiopulmonary parameters in detail during exercise testing in the present study, no conclusions should be drawn concerning the physiological basis of the observed low exercise capacity in the participating FD patients. Beside overall reduced

fitness due to limited physical activities in FD patients, the progressive systemic accumulation of Gb3 resulting in deleterious micro- and macrovascular alterations [24], impaired endothelial function [19] resulting in reduced NO production and reduced cardiac performance such as limited exercise-induced change in stroke volume must be considered as potential causes [3,5,28]. We detected improved exercise performance shown by increased maximum workload capacity of ~12% during the training intervention. In addition, patients' maximum LA concentration increased significantly by over 50% compared to baseline. Severely affected patients showed lower response to the training, and these patients also reported lower training compliance. Female patients #8, #9, #11 and #14 showed strongest improvement of exercise capacity. Patients #11 and #14 carried the A143T mutation associated with milder FD-typical symptoms, which might explain their better overall response to the training program. However, patients #8 (S126G) and #9 (R220X), bearing more deleterious disease mutations, also responded well to the training. Since we did not directly control changes in patients' daily physical activity associated with participation in the program, observed improvement of exercise capacity or muscle strength may not be the result of the home-based training program. It will have to be the scope of future studies to investigate if severely affected male patients can improve exercise capacity in closely monitored prolonged or intensified training interventions and if clinical benefits can be achieved in these patients using physical exercise.

Notably, training interventions have recently been performed in patients with other lysosomal storage diseases such as Pompe disease with comparable results [29]. Van den Berg [29] reported mean maximum workload of 22 patients with Pompe disease at 110±52 W (mean age 46 years). In these patients, improved endurance was detected over 12 weeks of combined aerobic exercise and strength training in that maximum workload capacity increased by 11%.

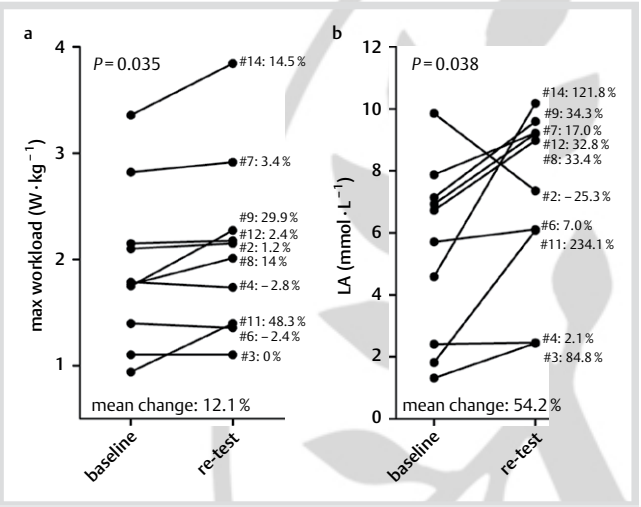

Fig. 1 **a** Change of maximum exercise performance and **b** blood lactate (LA) concentration during the study. The change (slope) in maximum exercise workload of each patient is given in relation to body weight (W · kg^{-1}). Patient number (#) and individual relative change (%) is presented.

Strength and improved well-being

We did not observe a significant increase in lower limb strength over the analyzed patient group. Some of the less severely affected patients, however, were able to improve muscle strength during the training intervention. Since patients were free to perform additional activities besides the main training program, the observed effects might be partly induced by a general increase in physical activities. However, our data provide first evidence that increase in muscle strength can be achieved in FD patients. Severity of disease and individual manifestation have to be considered in future studies to determine which FD patients will benefit from certain training interventions. We also observed increased self-confidence with respect to physical exercise as an additional positive aspect in patients participating in the study. Patients reported that they refrained from physical exercise in the past but they felt encouraged to lead a more

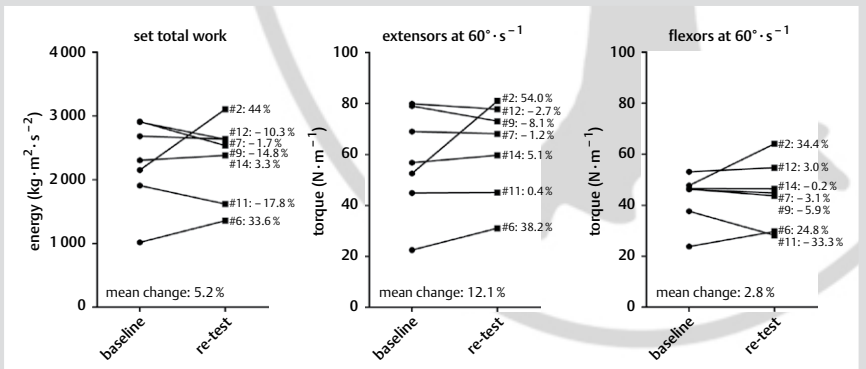

Fig. 2 Change of lower limb isokinetic strength parameters during the study. Patients' strength was determined for left and right flexors and extensors given as **a** total isokinetic workload of 5 repetitions and maximum isokinetic torque of 5 sets for **b** extensors and **c** flexors at 60° · s^{-1}. Mean change of the analyzed parameters was not significant. Patient number (#) and individual relative change (%) is presented.

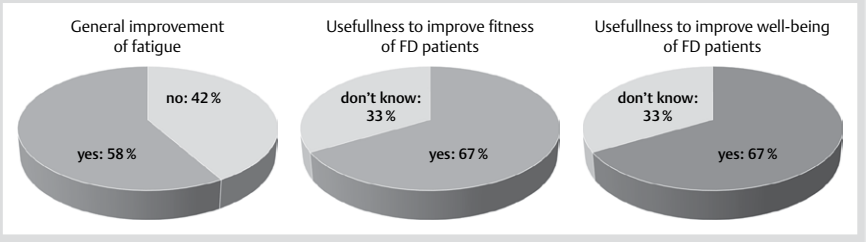

Fig. 3 Results of patients' questionnaire.

active lifestyle. Patients who were able to intensify their training program reported decreased fatigue and suggested the program to be useful to improve well-being of FD patients. This aspect may be an important therapeutic effect since FD patients suffer from considerably impaired quality of life compared to the general population [1].

Limitations

The observed effects in individual patients reported in the present study may not exclusively depend on the described exercise program. Before initiation of our program, most FD patients reported to have refrained from physical exercise and were encouraged to begin physical exercise in general after inclusion in the study. However, our data suggest that FD patients can perform physical exercise to some extend and improvement of exercise capacity, strength and well-being in FD is feasible in a real-life setting. Our study was designed to enroll a selection of different FD patients concerning age, sex and the level of disease severity to access exercise feasibility in the heterogeneous group of FD patients. Our data suggest that mildly affected individuals (i.e., individuals with non-classical FD mutations such as D313Y and A143T) may improve their physical fitness to a greater extend in shorter time intervals and that outcomes not only depend on training compliance but particularly on disease severity and individual disease-specific impairment. Future studies including larger patient groups and controls will have to demonstrate the general benefit of physical exercise in FD and potentially beneficial effects on clinical manifestations.

Conclusion

Our study shows that refraining from physical exercise often parallels FD evolution finally resulting in exercise intolerance. Physical exercise may help to improve endurance capacity, muscle strength and overall well-being in FD patients. We therefore strongly recommend an initial sports medical examination in these patients followed by a physical exercise protocol supporting FD therapy.

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Conflict of interest: None.

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Supplementary Material

Table 4 Patients' enzyme replacement therapy (ERT) duration and additional medication.

Patient #	ERT duration at baseline (months)	lyso-Gb3 at baseline (ng/ml)	Additional medication
1	no ERT	7.2	none
2	no ERT	0.6	none
3	156	25.7	ASA, NSAID
4	156	66.0	P2Y12-blocker
5	36	55.0	Uricostatic, AT-1 blocker, beta blocker, diuretic, anticonvulsant *
6	45	11.6	ACE inhibitor, diuretic, beta blocker, SSRI
7	108	54.1	SSRI
8	2	1.6	ASA, statin, SSRI
9	Started with inclusion	9.5	NSAID
10	24	0.7	none
11	36	0.7	ASA, statin, AT-1 blocker, beta blocker, SSRI
12	14	0.7	Calcium channel blocker, AT-1 blocker
13	19	0.5	ASA, statin, SSRI#
14	14	0.8	Calcium channel blocker

ACE: angiotensin-converting enzyme; ASA: acetylsalicylic acid; AT-1: angiotensin II subtype 1 receptor; lyso-Gb3: plasma globotriaosylsphingosine (marker for disease progression and treatment efficacy) at baseline, reference < 1.0 ng/ml; NSAID: nonsteroidal anti-inflammatory drug; SSRI: selective serotonin re-uptake inhibitor; * started during the study; #stopped during the study