



Muscle damage in response to a single bout of high intensity concentric exercise in patients with Pompe disease

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Background: In Pompe disease, resistance exercise could be an effective treatment to delay motor function impairment, however, the acute effects of this exercise modality are unclear.

Methods: In a prospective cohort study, we compared responses to a single bout of resistance exercise by serum markers of muscle damage and quantitative muscle magnetic resonance imaging (MRI) in patients (n=12) and age- and gender-matched healthy controls (n=12). Participants performed 50 maximal effort concentric knee flexions on a dynamometer.

Results: Twenty-four hours after exercise, levels of serum creatine kinase, lactate dehydrogenase and myoglobin increased in controls. In contrast, only myoglobin level increased in patients. All elevated serum markers declined by 48 hours after exercise in both groups. Mild soreness developed at 24 hours, which disappeared at 48 hours in both groups. In controls, MRI R2* relaxation rate reduced immediately and 24 hours after exercise, indicating increased water content and muscle perfusion. In patients, exercise had no effect on R2* values. The resistance exercise did not induce acute strength deficit in patients, rather, patients increased their strength by 24 hours. When serum marker changes were normalized to the magnitude of knee flexor tension developed during exercise, lactate dehydrogenase response was greater in patients.

Conclusions: Late-onset Pompe disease did not exacerbate exercise-induced muscle damage, however, lactate dehydrogenase may be monitored to screen high responders during high intensity resistance exercise interventions.

Keywords: Hamstring muscle; dynamometer; muscle microinjury; muscle magnetic resonance imaging (muscle MRI); Pompe disease

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Introduction

Late-onset Pompe disease (LOPD) is a rare inherited metabolic myopathy with deficiency of acid alpha-glucosidase (GAA) that results in glycogen accumulation in lysosomes. LOPD is characterized by a gradual decline in muscle size and strength, which eventually leads to impairments in motor function and mobility (1).

Enzyme replacement therapy (ERT) with recombinant human acid α -glucosidase has been introduced and proved to be efficient in either stabilizing or improving strength and functional abilities (2). Exercise intervention as a potential add-on therapy has also been recommended in LOPD (3). Previous studies that applied combinations of aerobic and resistance exercise to avoid muscle wasting and maintain functionality, showed inconsistent results (3-5). This may primarily originate from moderate or uncontrolled exercise intensities, small sample size, uncontrolled experimental design, the lack of quantitative strength tests, and because exercise mode-specificity was not considered. The superiority of resistance versus aerobic exercise in the development of muscle strength has been shown in healthy humans regardless of gender, age, and training status (6). Furthermore, the magnitude of strength gain is sensitive to the tension developed in muscles during a particular resistance exercise training (7). Therefore, high-intensity/load resistance exercise could potentially improve muscle weakness in LOPD patients.

There are concerns about the safety of resistance exercise in LOPD, because in healthy humans resistive (especially eccentric) muscle contractions induce myofibrillar disruptions, elevation of muscle protein and enzyme levels in serum [creatine kinase (CK), lactate dehydrogenase (LDH), myoglobin (Mb)], muscle soreness, and strength deficit, commonly named as direct and indirect markers of exercise-induced muscle damage (EIMD) (8). In healthy humans, changes in these markers usually peak at 24 h post-exercise. Evidences indicate that EIMD is less severe, when muscle contractions are performed concentrically (8,9).

Limited data are available, how resistance exercise changes EIMD markers in LOPD patients. Although serum CK activity was monitored in one study during a 24-month enzyme replacement therapy in two patients, no exercise was performed (10). In a 12-week-long combined resistance and endurance exercise intervention, CK was measured every 2 weeks (5). However, measurements were taken at unspecified times with respect to the actual exercise bouts: yet CK changes are sensitive within 12 to 48 hours post-

exercise (11).

In LOPD patients, aerobic or submaximal resistance exercise or their combinations are recommended and excessive resistance exercises are contraindicated (12,13). Despite of these recommendations, no evidence-based consensus exists whether high force resistance exercise exacerbates muscle damage in LOPD patients. Information on the acute effects of such exercise modality is needed and would contribute to proper exercise prescription. EIMD is considered as a normal response after high intensity unaccustomed exercise in healthy humans, which is moderate after concentric muscle contractions, but the responsiveness of LOPD patients is unknown. A well-known technique to measure acute muscle responsiveness to exercise is quantitative magnetic resonance imaging (MRI) (14). Besides the most commonly used metrics (T1 and T2 relaxation times), previous studies have shown that T2* relaxation time may be sensitive to pathological tissue changes and functional impairment in skeletal muscles after exercise (15). Although, T2* relaxation time or R2* ($R2^* = 1/T2^*$) relaxation rate is typically used to measure muscle perfusion after exercise, EIMD may affect R2* value due to magnetic field inhomogeneity caused by microtrauma.

Therefore, the purpose of the present study was to investigate the acute changes of serum and muscle MRI markers of EIMD in LOPD patients after maximal effort concentric contractions. We used isokinetic dynamometry to exercise and test the hamstring muscle, and compared the changes in LOPD patients to an age- and gender-matched healthy control group.

We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-3114>).

Methods

Participants

Seventeen Hungarian LOPD patients from different regions of Hungary were screened for eligibility in this prospective single-center cohort study, which was conducted during four consecutive years. Five patients were excluded because of the use of ventilation assistance, disability (wheelchair dependency), and acute or chronic knee pain, or their combination. Therefore, twelve LOPD patients were found eligible and enrolled. LOPD was confirmed in all patients by typical symptoms and reduced activity of acid alpha-glycosidase (GAA) in the blood. Previous exercise

Table 1 Experimental design: investigation of the acute effects of high force concentric hamstring exercise on the indirect muscle damage markers

Variables in order of tests	Baseline	Immediately (post-exercise)	24 h (post-exercise)	48 h (post-exercise)
CK, LDH, Mb	+	-	+	+
Muscle MRI	+	+	+	-
MVC torque	+	+	+	-
Muscle soreness	+	-	+	+

MVC, maximal voluntary contraction; CK, creatine kinase; LDH, lactate dehydrogenase; Mb, myoglobin; MRI, magnetic resonance imaging.

intervention studies demonstrated cases (3) or used smaller (n=5) samples (4). All patients (five men, seven women; mean age: 42.8±11.0 years, age range: 19–58 years, mean age at diagnosis: 38.2±9.9 years, age range at diagnosis: 18–56 years) were treated according to a standardized scheme with 20 mg alglucosidase alpha (Myozyme®, Sanofi-Genzyme) per kilogram of body weight every 2 weeks. At the time of the investigation patients had been on ERT for 4.0±2.0 years (range, 1–7 years).

In order to reduce the number of confounding factors, age- and sex-matched healthy volunteers (five men, seven women; mean age: 42.7±11.2 years, age range: 19–59 years), without a history of regular physical activity and any illness were also enrolled. Individuals were instructed to maintain their normal physical activity and to avoid any exercise one week before and during the study. The experimental protocol was approved by the Regional Ethics Committee (approval No. 4597) and performed in accordance with the ethical standards described in the provisions of the Declaration of Helsinki (as revised in 2013). Every participant was informed about the procedure and signed their written informed consent before the examination.

Experimental design

Patients were hospitalized for three days in the study center. The investigation consisted of three consecutive days (Table 1), and took place in a biomechanics laboratory (for strength tests and exercise) and in a diagnostic center (for MRI measurements and blood analyses). On day 1, first blood was taken for serum markers; then quantitative muscle MRI was performed followed by measurement of maximal voluntary contraction (MVC) torque and muscle soreness, and finally by dynamometric exercise. Immediately after exercise, another MVC and quantitative muscle

MRI were performed. On day 2 (at 24 h post-exercise), all measurements were repeated in the same order. On day 3 (at 48 h post-exercise), only serum markers and soreness were measured.

Maximal voluntary contraction

Before any strength evaluation, participants warmed-up by cycling for 5 minutes at a self-selected speed on a stationary cycle ergometer, and then by stretching the hamstring muscle. MVC torque of the hamstring was measured using Multicont II isokinetic device (Mediagnost Ltd, Budapest, and Mechatronic Ltd, Szeged, Hungary). Participants were seated on the dynamometer's seat. The shin of the tested lower extremity was fastened with a strap to the lever of the dynamometer above the ankle. Before any testing, gravitation compensation was performed for the tested leg to avoid inaccurate data collection originating from limb weight. Then three concentric knee flexions were executed between 10° and 80° range of motion, with 1 minute rest between repetitions. The threshold trigger torque in these contractions to initiate the movement was 5 Nm. As participants reached this torque the dynamometer rotated to permit the knee flexion, and participants had to flex their knee with maximal effort. The MVC's were performed at 60°/s constant angular velocity. Data giving the torque-time curve were exported, and average torque was calculated offline and was considered as MVC torque.

Blood sampling and analyses

Ten ml blood was drawn from an antecubital vein. After clotting, the blood sample was centrifuged at 1,500 g for 10 min to obtain serum. Serum samples were stored at -70°C until being analysed. CK and LDH activities were determined by kinetic optimized UV method (COBAS

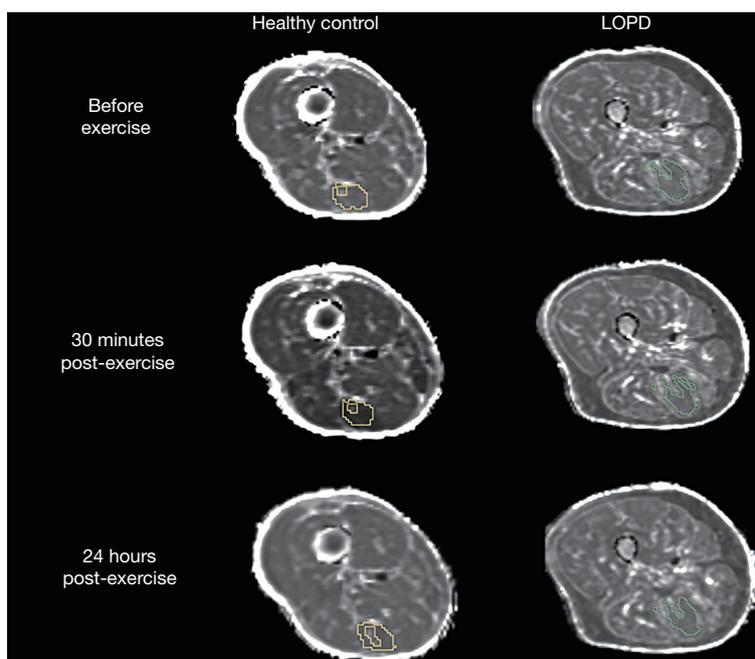


Figure 1 A representative image of muscle MRI ($R2^*$ map). Image of the semitendinosus muscle MRI ($R2^*$ map) in a patient with LOPD and in a healthy control are shown before and after exercise at different time points. LOPD, late-onset Pompe disease.

INTEGRA[®] 400 plus, Roche Diagnostics GmbH, Mannheim, Germany). The reference range was 0–200 IU/L for CK and 240–480 IU/L for LDH. Mb was measured by chemiluminescence automated immunoassay (Immulite 1000, Siemens Healthcare Diagnostics GmbH, Marburg, Germany). The upper reference limit at 97.5 percentile for Mb was 70 $\mu\text{g/L}$ and the median value was 25 $\mu\text{g/L}$.

Magnetic resonance imaging

Imaging was performed using a 3T Magnetom TIM Trio whole-body MRI scanner (Siemens AG, Erlangen, Germany) with a body matrix coil combined with the spine matrix coil. For $R2^*$ mapping, a multi-echo 3D FLASH sequence with 10 equally spaced echoes (TR/TE₁=36/2.28 ms; inter-echo spacing =3.43 ms; Flip Angle =16°; 208 sagittal slices; slice thickness =2 mm; FOV =250 ×250 mm²; matrix size =128×128; receiver bandwidth = 300 Hz/pixel) was used. The shortest echo time was limited by the resolution selected. Multi-echo 3D FLASH sequence was positioned according to the following: the top of the field of view was shifted from the right head of the femur distally to properly cover the hamstring muscles. This distance was measured individually and used during

the repeated MR examinations to ensure appropriate repositioning. MRI examination of the hamstring complex was performed before exercise, 30 min and 24 h post-exercise. MRI data analysis was performed only in 8 patients with LOPD and in their matched control subjects due to disease related intramuscular fatty infiltration.

Matlab[®] and a self-written program code were used for quantitative MR data analysis (The Math Works, Inc., Natick, MA, USA). $R2^*$ maps were calculated by voxel-wise nonlinear least-squares fitting of the mono-exponential signal decay over echo time for each voxel where the goodness of fit (r-square) was greater than 0.9 [Eq. [1]].

$$S_{TE} = S_0 \times e^{(-TE \times R2^*)} \quad [1]$$

Hamstring muscles i.e., semitendinosus (ST) and semimembranosus (SM) muscles, and long head of biceps femoris (BF) were manually delineated (with FSL software, <https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>) by an experienced observer on $R2^*$ maps excluding subcutaneous and inter-muscular fat, vessels, nerves, and fasciae (Figure 1). To increase the reliability, $R2^*$ maps of the three time points were linearly registered to each other using the FSL Linear Image Registration Tool Version 4.1 (16). $R2^*$ values were then derived separately from each muscle in the control

group, while only ST muscle was evaluated in patients with LODP due to significant intramuscular fatty infiltration in BF and SM muscles.

Delayed onset muscle soreness

After performing the MVCs, subjects were asked to report their perceived delayed onset muscle soreness in the hamstring muscle. Soreness was assessed by a 50 mm visual analogue scale (0= no pain, 50= very sore) (17).

Concentric hamstring exercise

Subjects exercised the hamstring in a sitting position using the same dynamometer as described previously. The concentric contraction started at a knee angle of 10° and ended at 80°. A trigger threshold of 5 Nm was set for the contractions, which the participants had to achieve to initiate the dynamometer's lever arm to move into the direction of concentric contraction. The contraction velocity was 30°/s. Subjects were encouraged to maximally execute the knee flexions. When the lever reached the 80° position, it automatically returned to the 30° position with the same velocity, while subjects relaxed their muscles. There were 5 sets of 10 repetitions hamstring contractions with 2 minutes rest between sets. Average torque of each exercise contraction was calculated and further averaged in each set (set torque) and in the entire exercise (exercise torque) given by the five sets. Visual feedback on effort and verbal encouragement was given to participants during both the MVC tests and the exercise.

Data analysis

Data analyses were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). Means and standard error of the means (SEM) were calculated. Between-group differences in the baseline values were determined using independent *t*-tests (in LDH) or Mann-Whitney U-tests (in MVC torque, CK, Mb, and soreness), depending on the Shapiro-Wilk normality test results. Exercise torque was compared between groups using independent *t*-test.

Except R²*, we determined the exercise effect across time in every measured variable using nonparametric Friedman ANOVA. This was performed because of the results of the normality tests and/or because the baseline values were significantly different between groups. To test differences in

means among the different test times, Wilcoxon Matched Pairs tests were used for post-hoc analysis. One-way repeated measures ANOVA was performed with a post-hoc test including Bonferroni pairwise comparisons to compare changes in R²* values among the time points. The assumptions of that were satisfied as judged by testing for normality, outliers, and sphericity.

Relative changes in serum markers and muscle soreness were also determined. This was performed by using the peak values, which were expressed as percent of the baseline values, except muscle soreness, in which the peak values were considered as relative change. The relative changes in the above variables were then normalized to exercise torque. This was necessary because the magnitude of muscle tension influences EIMD, and with this procedure we were able to differentiate group responses relative to their muscle tension, and to reduce the confounding effect of fitness status. Relative changes and normalized changes were compared between groups using Mann-Whitney U tests. Results were considered significant at P<0.05 for all statistical tests.

Results

All participants (n=24) executed the measurement tests. There were neither dropouts nor missing data.

Effect of concentric exercise on maximal voluntary contraction torque

At baseline, MVC torque was significantly smaller in LODP patients than in controls (P=0.0001). Exercise torque was significantly lower in LODP patients (53±5 Nm) compared to controls (73±8 Nm) (P=0.015).

Friedman ANOVA revealed significant time effect for MVC torque in both groups (P=0.0001 for LODP patients, P=0.003 for controls) (*Figure 2*). The post-hoc analyses showed that MVC torque reduced significantly immediately after exercise (P=0.003), and then recovered to baseline at 24 h post-exercise in controls. The reduction in LODP patients immediately after exercise only approached the significance level (P=0.06). However, MVC torque was greater at 24 h post-exercise compared to the baseline (P=0.028).

Effect of concentric exercise on serum biomarkers of muscle microinjury

All baseline serum biomarker mean levels were within the

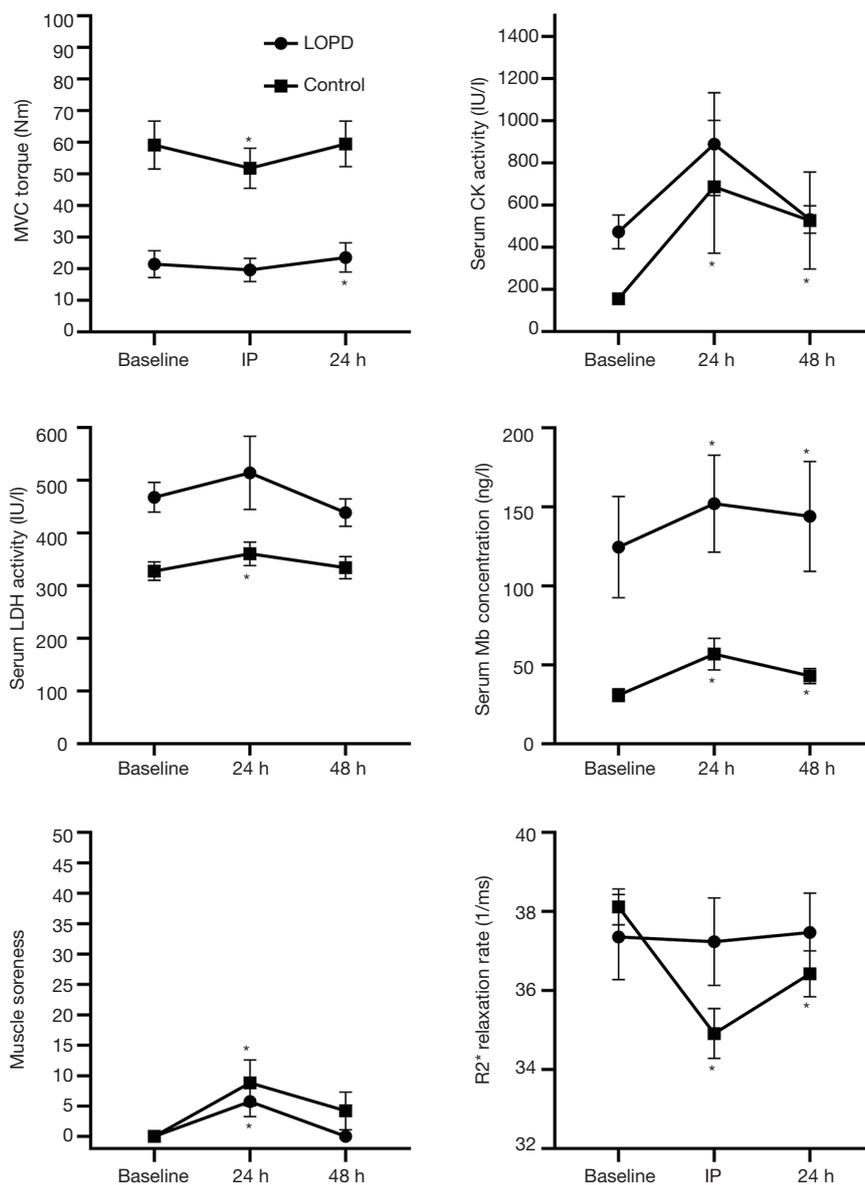


Figure 2 Acute effect of concentric hamstring exercise on indirect skeletal muscle damage indicators. Effects on MVC torque, serum biomarkers, muscle soreness and quantitative muscle MRI are shown in patients with LOPD and healthy controls. *, significant difference from baseline ($P < 0.05$). mean \pm SEM is shown. IP, immediately post-exercise; 24 h, 24 hours after exercise; MVC, maximal voluntary contraction; CK, serum creatine kinase activity; LDH, lactate dehydrogenase activity; Mb, serum myoglobin concentration; LOPD, late-onset Pompe disease.

normal reference range in both groups, though few outliers were found among LOPD patients (Figure 2). At baseline, levels of CK ($P = 0.0001$), LDH ($P = 0.0001$), and Mb ($P = 0.006$) were significantly higher in LOPD patients than in controls.

In controls, all biomarker levels increased significantly

at 24 h post-exercise ($P < 0.05$), and then started to recover at 48 h post-exercise (Figure 2). However, this recovery was incomplete ($P < 0.05$), except LDH activity. In LOPD patients, Mb increased significantly at 24 h ($P = 0.010$), and remained elevated at 48 h (Figure 2). The tendency of increase in the CK activity at 24 h only approached the

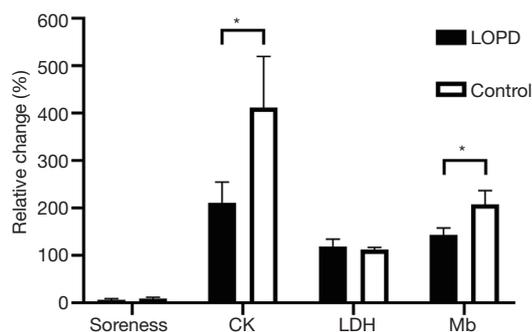


Figure 3 Exercise-induced relative changes in serum markers and hamstring soreness. Peak values as percent of the baseline values (mean \pm SEM) are shown. *, significant difference between groups ($P < 0.05$).

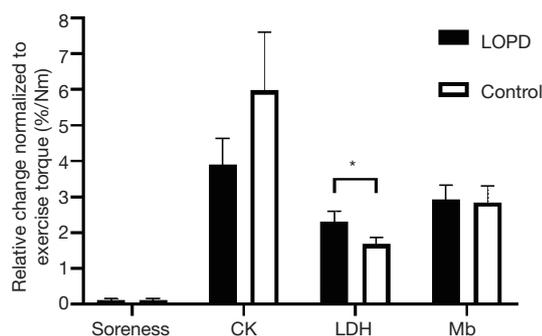


Figure 4 Exercise-induced changes in serum markers and hamstring soreness normalized to exercise torque. Mean \pm SEM are shown. *, significant difference between groups ($P < 0.05$).

significance level ($P = 0.078$) (Figure 2). The time effect in LDH was significant ($P = 0.020$), however, the post-hoc test revealed only a significant reduction from 24 to 48 h post-exercise ($P = 0.012$) (Figure 2).

Effect of concentric exercise on muscle soreness

Exercise increased muscle soreness in both LOPD patients ($P = 0.007$) and healthy controls ($P = 0.002$) by 24 hours, which disappeared at 48 h post-exercise (Figure 2).

Effect of concentric exercise on $R2^$ values of muscle MRI*

Significant time effect was found for $R2^*$ values in the semitendinosus (ST) muscle of controls $\{F_{[2,14]} = 16.65; P = 0.0002\}$. Post-hoc test revealed that in controls, concentric muscle exercise elicited a significant reduction

in $R2^*$ values from baseline to IP ($P = 0.006$) and 24 h post-exercise ($P = 0.021$). We observed a trend of recovery, i.e., increase by 24 hours, although it was not significant ($P = 0.072$). BF and SM muscles did not show significant differences in $R2^*$ values over time in the control group. In patients with LOPD, concentric muscle exercise had no statistically significant effect on $R2^*$ values in the ST muscle (Figure 2).

Change of biomarkers relative to exercise torque

The relative change in CK and Mb concentration was significantly greater in healthy individuals than in LOPD patients ($P = 0.047$ and $P = 0.038$, respectively). LDH levels and muscle sore were not different (Figure 3). When the relative changes in serum markers and muscle soreness were normalized to exercise torque, LDH concentration was significantly higher in LOPD patients ($P = 0.039$) (Figure 4).

Discussion

Here we used a complex experimental approach to examine muscle damage after a standardized single bout of high intensity concentric exercise in patients with LOPD. We measured serum biomarkers, MVC torque and quantitative muscle MRI repeatedly at different time-points after the standardized exercise, and compared the outcomes to controls at baseline and sequentially. We found that LOPD subjects did not show evidence of increased muscle damage compared to controls, as they showed similar or less severe responsiveness in EIMD markers, except LDH activity.

In healthy humans, tension developed in muscles induces myofibrillar and membrane ruptures, leading to elevations in serum enzymes and proteins, inflammation, and acute strength deficit (9,17). These responses are considered normal, and microinjury could be an important signal in the induction of hypertrophic changes (18).

At baseline, few LOPD patients demonstrated abnormal CK, LDH, and Mb levels, though the mean values were within the normal reference range. Also, LOPD patients produced 65% less hamstring torque than the healthy controls. Slight elevations in serum markers and muscle wasting are in line with damage of muscle fibres resulting from glycogen accumulation (11,12).

In the control group, all serum markers increased, muscle soreness developed and peaked 24 hours after exercise, similarly other healthy human groups (19). The greatest

increase (4-fold) was found in CK activity, confirming to show the highest sensitivity (20). Smaller increase was found in LDH activity and Mb concentration, and their peak values remained within the normal reference range. Although serum marker changes and dynamics in LOPD were similar to the control group, only Mb concentration was significantly elevated. The lack of statistically significant changes in the other serum markers can be attributed to little tension during the exercise avoiding mechanical stress, and the high variability of responses due to the wide range of strength status. Furthermore, seven out of the twelve LOPD patients did not report muscle soreness at all at any time points, suggesting little or no inflammation caused by EIMD. Though soreness was reported during maximal effort contraction (a sensitive test), data still should be used with caution because soreness sometimes can be overlooked by patients.

Immediately after exercise, hamstring torque reduced to 85% of the baseline in the healthy group, while there was no change in LOPD. MVC torque represents the maximum contractility, and an immediate drop in MVC torque is commonly named as fatigue. For the acute fatigue in the control group, metabolic changes rather than EIMD might be responsible, considering the full recovery 24 hours later. The acute energy demand is high during pure concentric contraction, and metabolite accumulation is evident shortly after high intensity concentric exercise training (21,22). Because LOPD patients performed less mechanical torque during exercise, the smaller rate of fatigue may be the result of the smaller number of active motor units requiring less energy, inducing less metabolic changes. Greater anaerobic capacity and the selective recruitment of the more fatigable fast fibres may also have led to greater fatigue in the controls. The immediate $R2^*$ reduction in controls confirms this, i.e., increased water content and muscle perfusion could be the result of excessive anaerobic work, while in patients with LOPD absence of effect on $R2^*$ values suggested no significant alteration in water content, perfusion and muscle injury (15).

At 24 hours post-exercise, recovery, i.e., normal MVC torque was seen in the healthy group despite of elevation in biomarkers. In LOPD patients, torque also increased compared to baseline. Normal or even increased contractility after intensive exercise is not unique because early neural adaptation compensates for the acute strength deficit, when EIMD is less severe (23). The early strength recovery/

gain suggests increased neural drive to the muscle or the recruitment of new motor units, indicatives of exercise adaptation in both the controls and LOPD patients. The moderate responses and the quick (48 h) recovery in the serum markers, regardless of health status, are explained by the fact that concentric exercise contractions with less mechanical stress were applied. We can conclude that although soreness and all serum markers show similar dynamics, healthy individuals show higher serum marker response sensitiveness, while LOPD patients demonstrate higher serum marker response variability, smaller acute fatigability, and better strength adaptability at 24 h post-exercise.

Most previous studies used absolute level of markers to quantify EIMD (24,25). We also compared the change in the serum markers normalized to the exercise torque, thus relative to the muscle tension developed in the hamstring muscle. We found that LDH normalized to exercise torque increased more in LOPD patients, and this might be the result of the low fitness status (26). LDH response is also influenced by muscle fiber type composition, which was uncontrolled in our study (27). It is notable, however, that one patient (outlier) responded with very high LDH activity (1,155 IU/L, more than two-fold of the group mean) at 24-h post-exercise. When we removed this data, the statistics showed non-significant change. High LDH responders may show less intracellular energy levels of the muscle fibres, and gene polymorphism of methylenetetrahydrofolate reductase (MTHFR) and paraoxonase 1 (PON1) enzymes might influence the exercise induced release of muscle biomarkers (28). Also, biomarker levels depend on their release kinetics (fastest for Mb), and on the half-life of the tested parameters (LDH the longest).

Limitation of the present study is that we did not measure the hamstring myoelectric activity, therefore we do not know if the source of strength recovery/gain is neural. Furthermore, only the ST muscle could be evaluated by MRI in patients with LOPD due to intramuscular fatty infiltration. However, according to previous MRI studies, ST muscle showed the most significant exercise-induced muscle alterations in the hamstring complex, confirming high sensitiveness of the MRI test in our experiment (29,30). Finally, though exercise-induced responses in our cohort of 12 patients were controlled with gender-and age-matched healthy participants, and were normalized to fitness level, the present data cannot be generalized to the LOPD population

with severe alteration of muscle strength and ventilation.

Conclusions

In conclusion, considering the absolute changes in the serum markers, LOPD did not cause exacerbation of EIMD after a single bout of high intensity concentric exercise compared to controls. However, when the magnitudes of changes in the serum markers were normalized to exercise torque, the LDH response was greater in patients. Therefore, monitoring of LDH in the early phase of a systematic resistance exercise training intervention may help to decide about training effort, and submaximal (80–90%) intensity resistance exercises may limit muscle damage in high LDH responders.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <http://dx.doi.org/10.21037/atm-20-3114>

Data Sharing Statement: Available at <http://dx.doi.org/10.21037/atm-20-3114>

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The experimental protocol was approved by the Regional Ethics Committee (approval no. 4597) and performed in accordance with the ethical standards described in the provisions of the Declaration of Helsinki (as revised in 2013). Every participant was informed about the procedure and signed their written informed consent before the examination.

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