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Safety and effectiveness of resistance training in patients with late onset Pompe disease - a pilot study

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Abstract

Pompe disease is a progressive myopathy resulting from deficiency in lysosomal enzyme acid α -glucosidase (GAA), which leads to glycogen accumulation in lysosomes primarily in skeletal and cardiac muscle. Enzyme replacement therapy (ERT) with recombinant human (rh) GAA works well in alleviating the cardiomyopathy; however, many patients continue to have progressive muscle weakness. The purpose of this study was to evaluate the effectiveness of a respiratory training combined with 24-week supervised resistance training program on muscle strength (measured by Biodex)), and respiratory function including maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP) in subjects with late onset Pompe disease receiving ERT. Ten subjects participated in a 24-week resistance exercise program, three times per week, in addition to respiratory muscle exercise training six days per week. Overall, at the end of the resistance training program, as measured by Biodex dynamometry, the leg extensor strength improved by 10.5 ± 3.2 Nm. ($p < 0.01$), leg flexors improved by 12.1 ± 4.1 Nm ($p < 0.01$), the elbow flexors improved by 5.1 ± 2.3 Nm ($p = 0.03$), and the elbow extensor strength improved by a mean of 4.5 ± 1.9 Nm ($p = 0.02$). MIP improved by 8.5 ± 3.7 cm H₂O ($p = 0.03$) and the MEP by 6.4 ± 4.4 ($p = 0.16$). The exercise training significantly improved the trajectories of MIP and 6 MWT outcomes but not FVC when compared with the natural history data available in 6 individuals. These pilot results indicate that resistance training combined with respiratory training and ERT had a positive effect on muscular strength, functional capacity, and respiratory function in patients with late-onset Pompe disease and might be considered as a potential adjunct therapy in this population.

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Keywords: Exercise; Resistance; Neuromuscular; Pompe disease.

1. Introduction

Pompe disease is a rare inherited progressive autosomal recessive neuromuscular disorder associated with muscle

weakness and respiratory insufficiency that can affect all ages, ethnicities, and sexes [1]. Deficiency of the enzyme acid alpha-glucosidase results in accumulation of glycogen within lysosomes and in cytoplasm eventually leading to muscle degeneration and loss of strength. While initial improvement or stabilization has been seen in the majority of subjects with late onset Pompe disease (LOPD) with enzyme replacement therapy (ERT) [2], patients continue to develop progressive deterioration of their muscle strength and pathology [3,4]. We previously reported results in 18 adult patients with

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LOPD who were monitored over several years as part of the Pompe disease registry [4]. We observed significant heterogeneity in the range of clinical features, and variability in the responses to ERT. We found ERT to have a beneficial effect in stabilizing respiratory function, however, after initial improvement, patients continued to show deterioration in their functional capacity, as measured by the 6 min walk test (6 MWT). We proposed that we could slow the progression of Pompe disease, by combining ERT with physical activity in the form of resistance training, which has a known anabolic stimulus. We were interested in ascertaining if the combination could produce an additive effect or even a synergistic effect.

Slonim et al [5], the first to treat Pompe patients, prior to the availability of ERT, with a combined high-protein and low-carbohydrate nutrition and submaximal aerobic exercise therapy (NET), found significant differences in the pre-NET slope of muscle deterioration to the post-NET slope in compliant patients. A recent review of nutrition and exercise in Pompe disease [6] in humans and mice suggested that benefits from exercise are considered to come from enhanced autophagy and mitochondrial biogenesis, and not an increase in the delivery or uptake of ERT.

Limited information was available on the effectiveness of resistance training in reverting and/or attenuating the progression of Pompe disease in this population. Terzis et al. (2011) reported results of a 20-week exercise combined aerobic and resistance training program in five patients with LOPD on ERT. They found improvements in the muscular strength which was measurably improved both in upper and lower extremities [7]. The authors also evaluated the effects of combined aerobic training (30 min of bicycling at 65–75% of max heart rate) and progressive resistance training (10 repetitions at 80% of 10 Repetitive Maximum (RM) semi squat, standing leg curl, hip abduction and adduction for 3 sets) during their ERT infusions in five patients for a 6 month period (3 sessions per week) and reported no significant changes in 6 min walk test (6 MWT), isometric lower body muscle strength and body composition (fat mass and lean body mass), measured by Dual X-ray absorptiometry (DXA) [8]. A 12-week aerobic exercise intervention found improvements in pain and fatigue [9], and improvement in the 6 MWT, maximum workload capacity and functional improvement were noted in another cohort [10]. These results suggest that exercise training has a positive effect on muscular strength and functional capacity in patients on ERT with late-onset Pompe disease. There were no prior studies combining the effects of respiratory training in combination with resistance training when we started this study, providing the rationale for our study.

Morbidity and mortality in adults with late-onset Pompe disease (LOPD) results primarily from persistent progressive respiratory muscle weakness. Respiratory muscle strength training (RMST) had been studied previously in two LOPD patients on long term ERT with severe respiratory weakness and was shown to result in increased inspiratory and expiratory strength [11]. Jones et al. (2011,2016,2020)

[11–13] provided inspiratory and expiratory muscle strength training in small groups of patients with LOPD and showed that RMT in LOPD is safe and well-tolerated and increases respiratory muscle strength. Recently inspiratory muscle training was shown to improve MIP and thereby stabilize and decelerate the decline of the diaphragm strength and was recommended to be offered to all LOPD patients, especially those who demonstrate a progressive decline in respiratory muscle function or are unable to receive ERT [14–16].

There were no prior studies combining the effects of respiratory training in combination with resistance training when we started this study, providing the rationale for our study. The current study was undertaken to investigate whether a resistance training program, known to be anabolic, can improve muscle strength and function. The primary objective of this study was to evaluate the effectiveness of a supervised resistance training program on improving muscle strength (dynamometry) and functional capacity (6 MWT); and the effectiveness of respiratory muscle training on respiratory function in LOPD patients receiving ERT. To our knowledge, this is the first study to examine the therapeutic efficacy of combined resistance training and respiratory training as an adjunct therapy to ERT in subjects with LOPD to prevent the loss of muscle mass and function.

2. Materials & methods

Ethical approval was obtained from the institutional review board at University of California Irvine (UCI, IRB HS# 2013–9365). Inclusion criteria included a confirmed diagnosis of Pompe disease, age between 16 and 75 years, ability to perform resistance exercises for the duration of the study, and ERT for at least one year. Exclusion criteria included unconfirmed diagnosis of Pompe disease by molecular testing, inability to walk or cycle, and individuals who were on a ventilator. At the baseline visit, written informed consent was obtained from all subjects. Subjects received information on the overall design and expectations of the resistance training program and performed the baseline evaluations. At visit 2, subjects learned how to use the exercise machines from a staff trainer at the local gym, who ensured that subjects were training adequately and were not overexerting themselves. The trainers were provided training on the exercise protocol and instructed on how to use the Borg scale to monitor relative perceived exertion and muscle pain.

Eight male and two female adults with confirmed diagnosis of LOPD participated in the study. Subjects had a confirmed diagnosis of Pompe disease and biallelic pathogenic variants of the GAA gene (Table 1). Seven subjects previously participated in the Pompe Registry, a long-term, observational program and repository of data (IRB #2008–6631) sponsored by Sanofi Genzyme (Cambridge, MA). Measurements of their pulmonary function and 6 MWT post ERT was available in these subjects and were previously reported [4].

Muscle strength and functional capacity were evaluated in the Pediatric Exercise and Genomics Research Center Human Performance Laboratory (HPL), UC Irvine. Each subject

Table 1
Demographic details and baseline measurements of 10 subjects with late onset Pompe disease who participated in a 24-week exercise study.

Subject	Age (y.)	Sex	Age Dx. Y.	Age onset ERT Y.	Mutation 1	Mutation 2	6 MWT (m.)	MIP-cm. H ₂ O	MEPcm. H ₂ O	FVCcm. H ₂ O	FVC% Predicted
1	66	M	55	61	c.-33-13T>G	c.1935C>A, p.Asp645Glu	408	49	57	3.43	79
2	71	F	62	63	c.-32-13T>G	c.2655_2656delCG p.Val886Glufs*2	241.5	57	59	2.86	98
3	55	F	31	46	c.-33-13T>G	C.925G>A, p.Gly309Arg	290	42	43	1.88	49
4	50	M	38	38	c.-32-13T>G	C.925G>A, p.Gly309Arg	442	46	70	2.65	46
5	63	M	62	62	c.-32-13T>G	c.1051delG, p.Val351C*41	430.5	68	110	2.06	53
6	47	M	43	44	c.1594G>A, p.Gly532Ser	c.1935C>A, p.Asp645Glu	487.7	63	80	2.87	59
7	41	M	30	30	c.-32-13T>G	c.258dupC, p.Asn87Glnfs*9	548.6	64	89	3.38	64
8	49	M	45	45	c.-32-13T>G	c.525_526delITG, p.Asn177Profs*11	453.4	40	60	2.04	42
9	54	M	53	53	c.-32-13T>G	c.525delIT, p.Glu176ArgfsX45	457.2	38	106	2.83	54
10	54	M	53	NA	c.-32-13T>G	c.525delT, p.Glu176ArgfsX45	594	56	137	3.29	63
Mean	55.9	8M/2F	47.2	49.1			435.3	52.3	56.8	2.73	60.7

M=male, F=female, 6 MWT=6 min walk test in meters, FVC=forced vital capacity in cm H₂O (upright), FVC predicted=FVC expected according to sex and height in cm H₂O.

served as their own controls, with two baseline measurements obtained approximately 8 weeks apart following enrollment with no exercise intervention. We used visit 2 data as the baseline to increase rigor for the study, to avoid improvements resulting from familiarity with the training. Following the baseline period, a 24-week specifically designed resistance training program was prescribed for each subject, depending on his or her functional abilities. The subjects attended the HPL at 8-week intervals for repeat testing to monitor their progress according to the protocol (Fig. 1).

The resistance-training program used in this study was modified from the standards established for healthy controls. The two muscle groups included in the training program were the quadriceps (knee extensors) and biceps brachia (elbow flexors), and exercise included both concentric and eccentric contractions. We recorded the weight lifted during each trial and determined the maximum weight the subject lifted 5 times (the 5-repetition maximum or 5-RM). The 5-RM was used to determine the parameters of the resistance training program for the duration of the study. Training took place under supervision of a trainer during the exercise period. The subjects were trained 3 times/week for entire 24 weeks of the training period, with mandatory trainings at every escalation of the exercise protocol in all subjects. The weights lifted during knee extension and elbow flexion were initiated at 40% of 5-RM, 3 sets of 10 repetitions three times per week, and was increased every 8 weeks to 50% and 60% of the subject's 5-RM, respectively. If the subject was not able to tolerate the increased load, the weight was reduced to a tolerated load for that subject.

Subjects were provided pressure-threshold respiratory trainers, the Threshold IMT Inspiratory Muscle

Trainer (Respironics) in nine subjects and POWERbreathe Resistance Breathing Muscle Trainer (Gaiam Ltd) in one subject. The inspiratory muscle trainers were individually calibrated to provide an inspiratory resistance load and were incrementally adjusted to progress to higher resistance levels to increase ventilatory exercise training. The Respironics threshold IMT device includes calibration markings up to a maximum resistance of 42cm H₂O, and 2 additional subjects exceeded this resistance and transitioned to the POWERbreathe trainer which offers up to 98cm H₂O of IMT resistance. The POWERbreathe devices were calibrated with a pressure gage. Trainings were initiated at 25 repetitions twice daily of inspiratory muscle training (IMT) starting with a resistance setting of 50% of the maximum inspiratory pressure (MIP). Subjects were advised to perform 25 repetitions of IMT twice daily at home, 6 days per week starting at visit 2, with a progressive increase to 60% resistance setting of the MIP at visit 3 and 70% at visit 4 for a total training period of 24 weeks.

3. Muscle strength and function measurement

Subjects were evaluated at the UC Irvine Exercise and Genomics Research Center to undergo testing every 8 weeks from enrollment (week -8) through the end of the program (visit 5, week 24) (Fig. 1) for determination of the following measurements:

3.1. Dynamometry

Strength of knee extensors and elbow flexors was measured using the Biodex System 4 isokinetic(Biodex

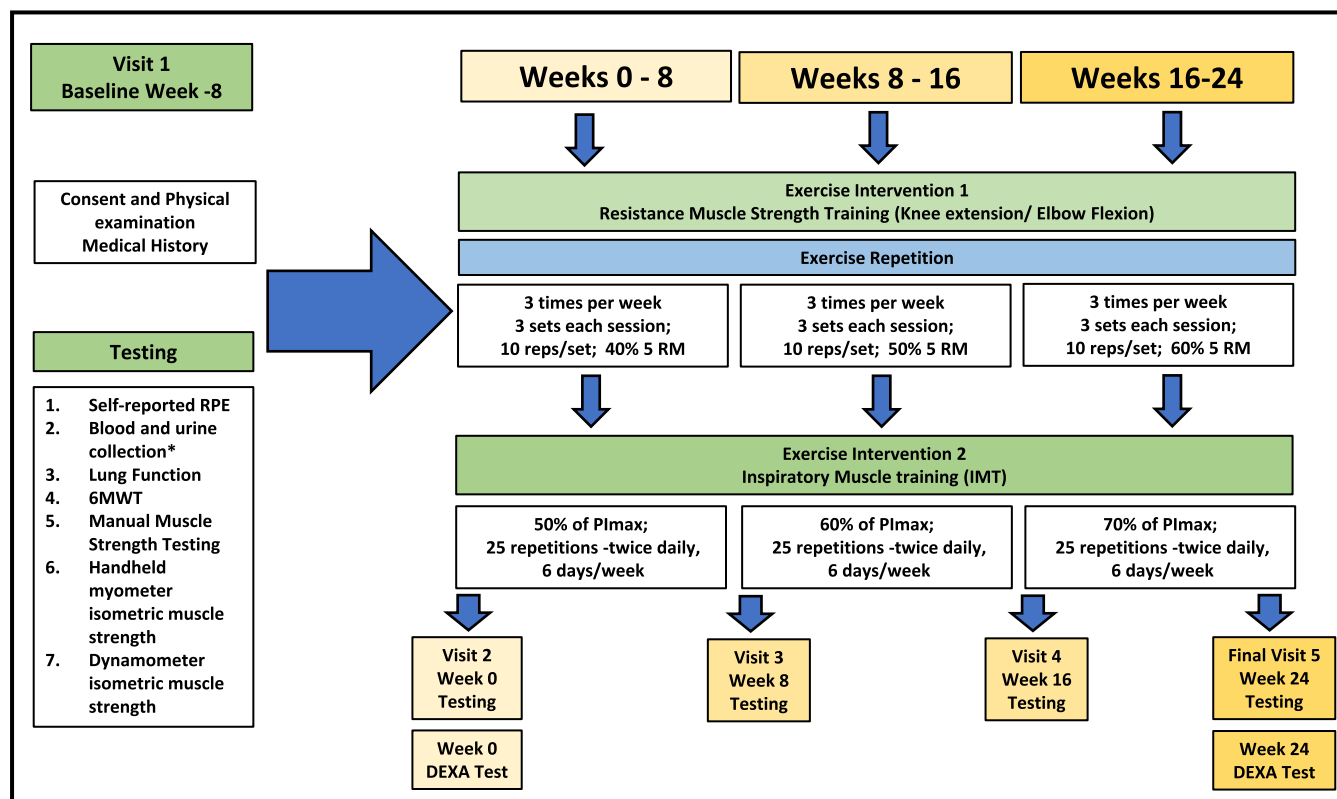


Fig. 1. Schematic of the exercise training protocol.

Medical Systems, Inc, Shirley, New York) dynamometer. In addition, the JAMAR hand-held medical dynamometer and MicroFET@2 (Hoggan Scientific, LLC, Salt Lake City, UT) were used to measure muscle strength in other muscle groups. On the Biodex, subjects performed 2 sets in 2 different speeds (60 and 180deg/sec) of 5 repetitions for each limb and peak torque was recorded. Subjects could rest for one minute between sets. Prior to each assessment, subjects warmed up by performing every exercise/speed at a low level of effort. The dynamometer seat position and attachment length were optimized for each subject and recorded so that the same position was used for each subsequent test. Subjects were verbally encouraged to produce maximal efforts throughout each test session [17].

3.2. Six-minute walk test (6 MWT)

The 6 MWT is the distance walked in 6 min and is a useful measure of functional capacity, has been widely used for measuring the response to therapeutic interventions for pulmonary and cardiac disease and was performed according to the guidelines of the American Thoracic Society [18].

3.3. Pulmonary function studies

The American Thoracic Society guidelines and standards were used for spirometry measurements of the forced vital

capacity (FVC). The Vyaire Vmax® 229 comprehensive pulmonary function testing (PFT) system was used with the Vyaire Biomed #773,470 sensormedics freeflow™ mouthpiece. Each subject was asked to inhale as much air as they could and then exhale the air out as quickly as possible and continue exhaling until the test criteria has been met, roughly 6 s. Maximal inspiratory pressure (MIP) and the maximal expiratory pressure (MEP) more specifically measure diaphragm strength, intercostal strength, and abdominal strength [19]. The MIP was measured from the residual volume and MEP was measured from the total lung capacity [19]. A minimum of 3 acceptable maneuvers were performed and the peak value was utilized [20]. Quality assurance checks informs the technician if the next best MIP or MEP is not within 10% of the best measurement.

3.4. Dual-energy X-ray absorptiometry (DXA)

DXA scans obtained before the training program, and the final visit measured bone mineral density, fat mass and lean mass and was utilized to supplement muscle strength analysis because changes in lean mass can indicate severity of muscle atrophy from Pompe disease. To assess BMD, we obtained T-scores, a statistical value that compares the patient's BMD to a healthy adult of the same sex. T scores between -1 and -2.5 are considered osteopenia, and scores less than -2.5

are considered osteoporosis associated with an increased risk of fractures.

3.5. Primary and secondary endpoints

The primary endpoints were 1) Isometric muscle strength (Biodex) change from week 0, before the beginning of the resistance exercise intervention, through week 24, at the end of the resistance exercise intervention, MIP change from week 0 through week 24. Secondary/exploratory endpoints included MicroFET@2 dynamometer measurements of all muscle groups, grip strength, MEP and FVC change, 6 MWT change and DXA measurements of bone mineral density, fat mass and lean mass from week 0 through week 24.

3.6. Assessment of adverse events

Safety laboratory testing included blood creatinine kinase (CK), and lactate dehydrogenase (LDH) levels, indices of muscle damage were evaluated at each visit and taken into consideration when prescribing each increase in the weight lift exercise program based on the results of the 5-RM.

Subjects completed a Borg scale [21] to monitor relative perceived exertion and muscle pain after each exercise training session and reported any adverse events to the study team immediately if serious or at their routine visits.

3.7. Statistical analysis

We fit linear mixed effect regression models to estimate the effect of the training program and 95% confidence intervals (CI) on each outcome over the 24-week intervention period. We accounted for multiple comparisons using the Benjamini-Hochberg false discovery rate p -value correction.

Comparison of the slopes of 6 MWT and respiratory outcomes during the 24-week exercise therapy study versus natural history period: Data on MIP, 6 MWT and FVC upright were available for a subset of $n = 6$ participants from both the natural history study and the exercise study. In order to test whether the change in each outcome over time was altered by the exercise program, we re-fit the linear mixed effect regression models with the pooled data from both periods and a spline knot fixed at the start of the exercise program. This model allows the slope of the regression line to change at the start of the exercise program. Statistical significance for the slope during the natural history period indicates whether the slope is significantly different from 0 (no change), whereas during the exercise study period indicates whether the slope differed significantly from the slope during the natural history period. $^{\text{§}}p < 0.10$, $^{**}p < 0.05$. Models include time (years) from the start of the exercise program and include age at the start of the exercise program as a covariate.

4. Results

Nine subjects were Caucasian, and one was of Asian ethnic origin. All subjects had enzymatic and molecular confirmation

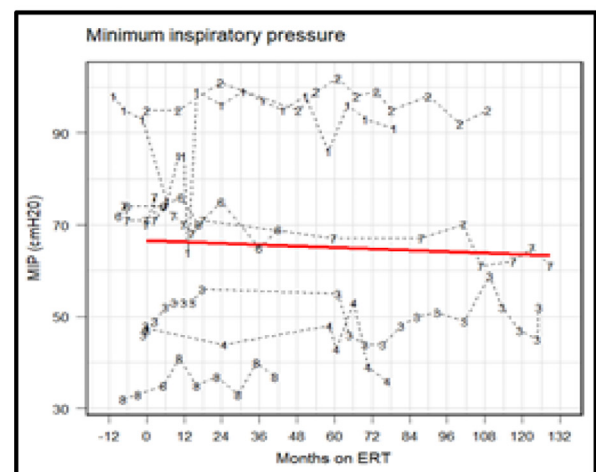
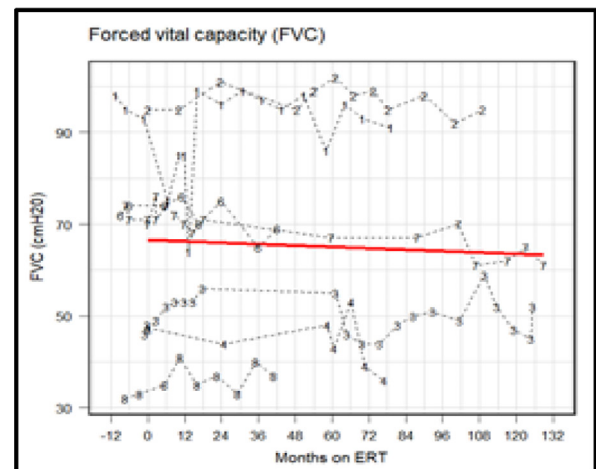
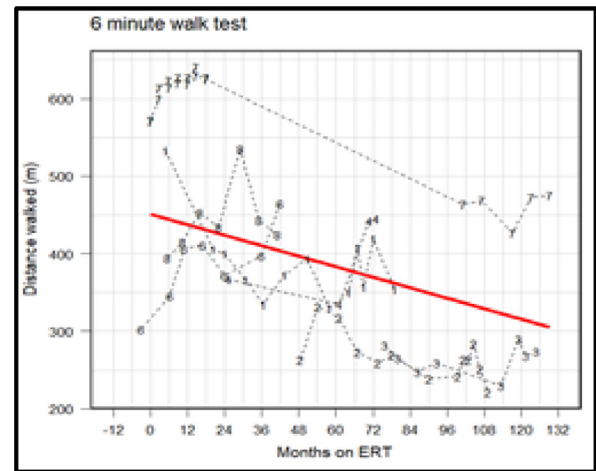


Fig. 2. Natural history data of 6 min walk test, forced vital capacity and maximum inspiratory pressure in 7 subjects after initiation of ERT. a) There was an initial improvement after initiation of ERT followed by a decline in the 6 min walk test; b) relative stabilization of the forced vital capacity, and (c) maximum inspiratory pressure over a period ranging from 3 to 10 years after start of ERT.

of Pompe disease. They enrolled at a mean age of 55.9 y. (range 41–71y.) and were diagnosed at a mean age of 47.2 y. (range 30–62 y.). Nine subjects started treatment ERT at a mean age of 49.1 y (range 30–63 y.), after a mean lag period of 2.6 y. (range 0–15 y.) from diagnosis. Subject 10, the twin brother of subject 9 was not receiving ERT at the time of enrollment in the study. All subjects had baseline proximal muscle weakness that was overall similar, with MRC scores of 3- to 4+/5 except subject 10 who had MRC scores of 5 in all muscle groups. All subjects except subject 6, had the common GAA splice site allele associated with LOPD (Table 1).

Seven subjects who participated in the exercise study also had participated in the ongoing natural history study. It is noted that ERT had a more beneficial effect on preserving respiratory function, in particular respiratory measurements FVC and MIP compared to the 6 MWT from the natural history study (Fig. 2b,c). Their natural history data for the 6 MWT, indicated progressive deterioration over the course of 3–11 years while taking ERT. These findings were the rationale for undertaking the exercise and IMT study.

In contrast to the deterioration in the 6 MWT (–6.8 m. loss) as measured during the natural history study (Fig. 2a), there was no significant change in the 6 MWT (–1.7 m.) (Fig. 3a) over the same course of 24 weeks with exercise. We found that respiratory function was preserved with the respiratory resistance training study. There was a marked improvement in the MIP respiratory pressure which increased on average by 8.5 ± 3.7 cm H₂O ($p=0.03$, Fig. 3b). As expected, both MEP and FVC were not significantly improved from the start to the end of the respiratory intervention.

Comparison of the slopes using linear mixed effect model of 6 MWT and respiratory outcomes among subjects ($n=6$) during the natural history versus the 24-week exercise therapy study are shown in Table 3. These findings suggest that the 6 MWT distance and FVC in upright position diminished significantly over time during the natural history period, and the exercise study significantly improved the trajectories of MIP and 6 MWT outcomes but as expected, not the FVC. Results differ from the main analysis due to restricting analysis to the subset of 6 participants who had data from both timepoints as well as the procedure modeling the slopes in both periods simultaneously.

The subject's muscle strength as measured by Biodex dynamometry was reported at 60deg/sec only, because the subjects had difficulty with performing at the faster velocity of 180deg/sec. There was a significant improvement in the muscle groups that were exercised in this study; the elbow flexors improved by 5.1 ± 2.3 Nm. ($p=0.03$), and the elbow extensor strength improved by a mean of 4.5 ± 1.9 Nm. ($p=0.02$). The leg extensor strength improved by 10.5 ± 3.2 Nm. ($p < 0.01$), leg flexors improved by 12.1 ± 4.1 Nm. ($p < 0.01$), (Table 2) (Fig. 4a–d).

Results from the linear mixed regression models showed modest improvements in the other outcomes over the 24-week exercise period (Table 2). Muscle strength measurement using the MicroFET@2 dynamometer that reflects all the muscle

Table 2

Linear mixed effect model for selected strength and respiratory outcomes among late onset Pompe disease subjects ($n=10$) in the 24-week exercise therapy study.

Primary Outcomes	Estimated change over 24 weeks	SE	p-value
6 min walk test distance walked (m)	-1.69	10.65	0.88
Maximum inspiratory pressure (cmH2O)	8.47	3.66	0.03
Biodex dynamometry			
Leg flexion (lbs.)	12.13	4.11	<0.01
Leg extension (lbs.)	10.49	3.22	<0.01
Elbow flexion (lbs.)	5.11	2.26	0.03
Elbow extension (lbs.)	4.54	1.88	0.02
Secondary Outcomes			
Maximum expiratory pressure (cmH2O)	6.35	4.38	0.16
Forced vital capacity	-0.32	0.28	0.26
MicroFET@2 Dynamometry			
Knee extensors (lbs.)	4.97	1.94	0.02
Knee flexors (lbs.)	2.34	2.41	0.34
Elbow extensors (lbs.)	-0.12	1.47	0.94
Elbow flexors (lbs.)	1.58	1.17	0.19
Jamar hand held dynamometer			
Grip strength (lbs.)	2.62	2.31	0.27

Table 3

Comparison of the slopes of 6 MWT and respiratory outcomes among late onset Pompe disease subjects ($n=6$) during the natural history versus the 24-week exercise therapy study using linear mixed effect model.

	The slope (unit change in outcome per 1 year)	
	Natural history period	Exercise study period
6 MWT (m)	-7.67**	77.36**
MIP (cmH2O)	-0.13	28.21**
FVC upright (%)	-0.70**	-5.34

groups, showed improvement of the knee extensors, (the primary muscle group that was exercised) by 5.0 ± 1.9 lbs. ($p 0.02$), and trends for improvements in the measurements of the knee flexors, elbow extensors and flexors. Grip strength as measured with the Jamar handheld dynamometer showed an increase of 2.62 lbs., although this change was not significant (Fig. 4i).

We compared findings of body composition (bone density, lean body mass and fat mass) with DXA scans between the baseline at week 0, before exercise and final measurements at week 24. The lean mass showed an increase after the exercise program (paired t -test $p=0.04$, one-tail, $p=0.08$ for two tail). No correlation was found between the lean mass gained and the age of the subject. We found that all individuals had osteopenia, and one female had osteoporosis, with a prior history of a pelvic fracture after a fall. Paired t -tests for femur and lumbar t scores, total bone mineral content and fat mass showed no significant differences pre- and post-exercise.

4.1. Adverse events

The creatinine kinase (CK) and lactic dehydrogenase (LDH) levels did not change in any subject during the

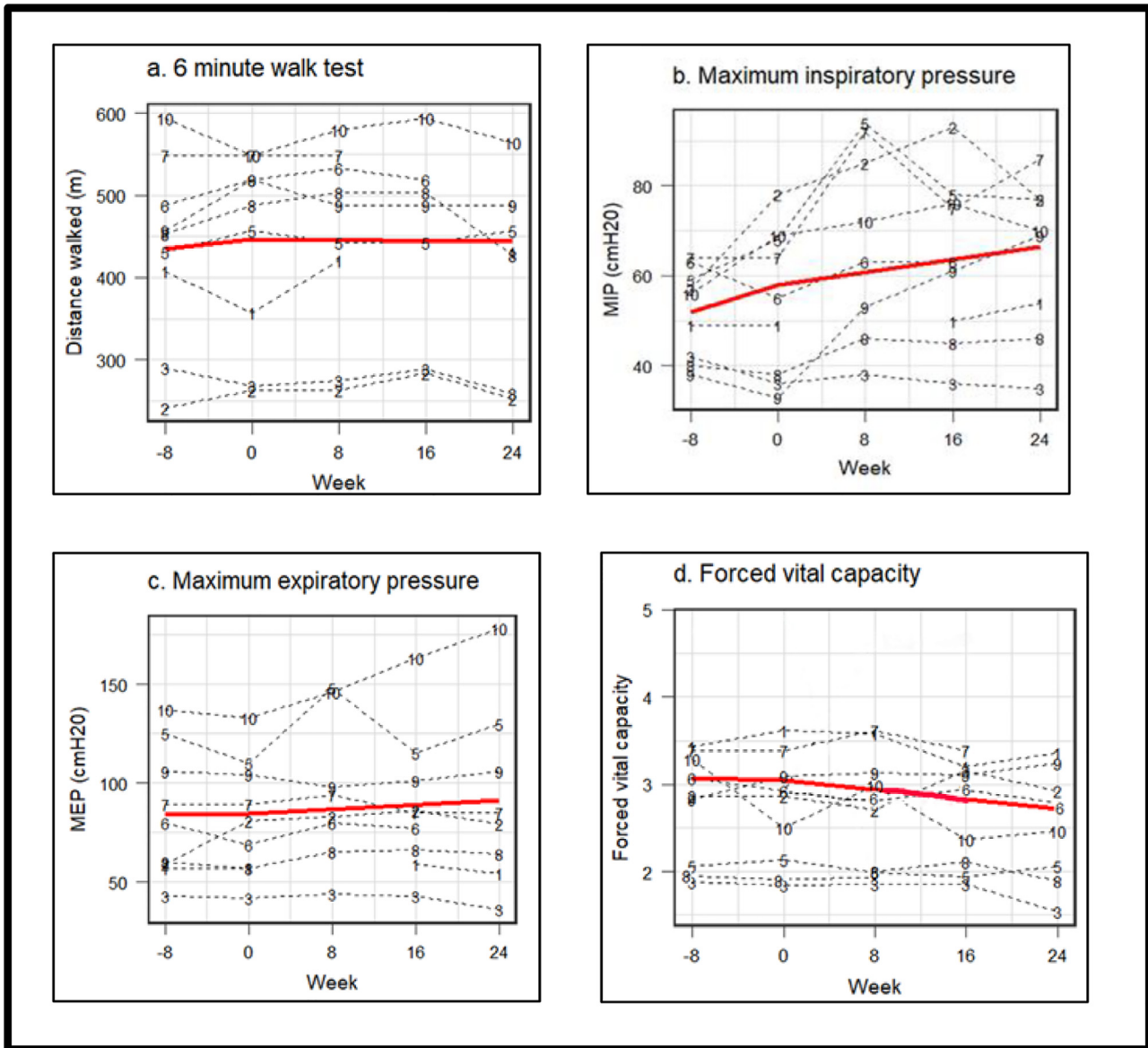


Fig. 3. Respiratory outcome trajectories among patients with late onset Pompe disease participating in a 24-week exercise study using linear mixed effect models. Measurements during exercise treatment compared to baseline (a) of the 6 min walk test showed a -1.69 m change ($p=0.88$); (b). Maximum Inspiratory Pressure (MIP) showed an increase of 8.47 ± 3.66 cm H₂O ($p=0.03$); (c) Maximum Expiratory Pressure (MEP) during showed an increase of 6.35 ± 4.36 H₂O ($p=0.16$); forced vital capacity showed a non-significant change of -0.32 ($p=0.26$)

study. Subjects were questioned about any pain, cramping or other adverse events that occurred in the interim period. Subjects did not score higher than 12 to 14 on the Borg Scale suggesting that physical activity was being performed at a moderate level of intensity. Subject 1 had a fall when getting out of bed one month after the start of the exercise training. One week later he resumed his exercises, however, developed back pain when lifting the weights with his legs. On reviewing his exercise regimen, it was determined that he had independently performed additional exercises daily rather than adhere to the 3 times per week regimen as prescribed. He subsequently made a full recovery from his back pain and continued exercising per protocol. Subject 8 injured his back after lifting a heavy patient during his

nursing job just prior to completing the study. The injury was considered unrelated to the study. Subject 2 discontinued her respiratory treatment one month prior to visit 4 of the exercise training without informing the study team, because she was concerned that the respiratory device might be contributing to the gurgling noises in her epigastric region. Subject 5 did not complete the study because of demands of his job.

Overall, subjects had an improvement in parameters tested, with an adverse event reported in one subject who was exercising excessively, and another who developed back pain from a work-related incident. There was good adherence to the exercise program among those subjects who completed the study.

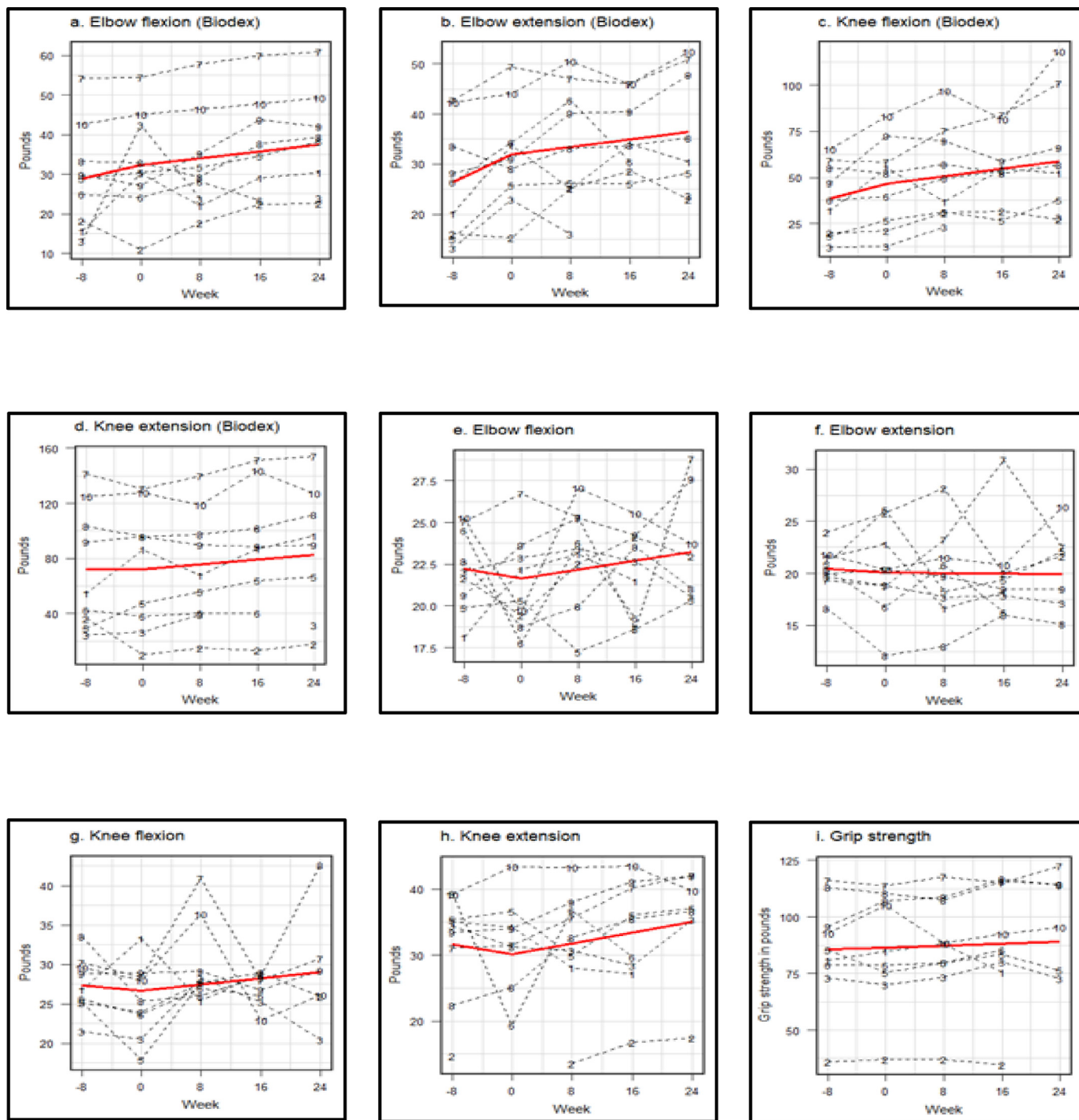


Fig. 4. Strength outcome trajectories among patients with late onset Pompe disease participating in a 24-week exercise study using linear mixed effect models. Biodes dynamometry measurements during the exercise study compared to the baseline of the: (a) elbow flexion showed an increase of 5.11 ± 2.26 Nm. ($p=0.03$); (b) elbow extension showed an increase of 4.54 ± 1.88 Nm. ($p=0.02$), (c) knee flexion showed an increase of 12.12 ± 4.11 Nm. ($p < 0.01$); (d) knee extension showed an increase of 10.49 ± 3.22 lbs. ($p < 0.01$). Changes in the same muscle groups as measured by microFET2 dynamometry showed (e) elbow flexor strength increased by 1.58 ± 1.17 lbs. ($p=0.19$); (f) elbow extensors showed a change of 0.12 ± 1.47 lbs. ($p=0.94$), (g) knee flexors showed a change of 2.34 ± 2.41 lbs. ($p=0.34$); (h) knee extensors showed an increase of 4.97 ± 1.94 lbs. ($p=0.02$); (i) grip strength increased by 2.62 ± 2.31 lbs. ($p=0.27$) compared to baseline.

5. Discussion

Patients with LOPD continue to have progressive muscle weakness, and respiratory dysfunction despite ERT [3,4]. The purpose of this pilot study was to evaluate the effectiveness and safety of a 24-week supervised resistance and respiratory training program on physical strength evaluated by Biodex, stamina evaluated by 6 MWT, and respiratory function evaluated by pulmonary function studies in ten subjects with LOPD. At the end of the 24-week resistance exercise training, the 6 MWT rate of decline was 1.7m compared to a decline of 11.6m per year (equivalent to 6.8m over 24 weeks) from the natural history data in seven subjects from this cohort [4]. There was a significant improvement in the leg extensors and elbow flexors muscle strength, the muscle groups that were targeted in this study, and improvement of the knee flexors and elbow extensors, as measured by Biodex dynamometer. Additional assessment using the MicroFET®2 handheld dynamometer performed because it offers ease of use, also showed improvements of muscle strength of the knee extensors, and modest improvements in other parameters.

We compared our data from the resistance training program with studies reported in the literature. One study found a 15–50% increase in muscular strength and 6 min walking distance after a 20 week program of supervised aerobic and progressive resistance exercise training [7]; in a further study the authors noted no additional improvement in LOPD subjects undergoing exercise training whilst receiving ERT [8]. A 12-week aerobic exercise intervention in 23 subjects comprised of 3 components with 3 sets of 15 to 20 repetitions 3 times per week: endurance training on equipment of choice at 60% of patient maximum heart rate, followed by 7 resistance exercises, with an initial training weight of 70% of 4 repetitions maximum, and core stability exercises. The quality of motor function and the amount of physical activity patients engaged in did not change, however levels of pain and fatigue improved [9]. The lack of positive benefit was attributed to the short exercise period. There was an improvement in the 6 MWT by 16 m, hip flexors, and shoulder abductors muscle strength, and timed tests maximum workload capacity and functional improvement were noted [10]. During ERT only patients remained more or less stable indicating that training was the main driver behind the effects. These results suggest that exercise training has a positive effect on muscular strength and functional capacity in patients on ERT with late-onset Pompe disease.

We found in the current study that respiratory resistance training in combination with ERT resulted in a significant improvement in the MIP by a mean of 8.5 cm H₂O and MEP by a mean of 6.4 cm H₂O in the subjects. Retrospectively, the inspiratory exercise load could have been increased to obtain the maximum benefits from the inspiratory muscle training, rather than prescribe the load for the entire study based on the baseline measurements.

Recently inspiratory muscle training was shown to improve MIP and thereby stabilize and decelerate the decline of the diaphragm strength and was recommended

to be offered to all LOPD patients, especially those who demonstrate a progressive decline in respiratory muscle function or are unable to receive ERT [14–16]. Jones et al. (2011,2019,2020) [12,13,22] provided inspiratory and expiratory muscle strength training in small groups of patients with LOPD and showed that RMT in LOPD is safe and well-tolerated and increases respiratory muscle strength. The first study to evaluate respiratory muscle strength training used a device that provided 60% of the maximal inspiratory and expiratory strength with 25 repetitions twice a day six days a week [11]. An 8 week respiratory muscle training study (both inspiratory and expiratory resistance, at 70% of MIP (for inspiratory training) and MEP, 25 repetitions) in eight patients with LOPD who were receiving ERT, was conducted and revealed a significant increase in MIP in all 8 subjects, and 7 of 8 showed significant increases in MEP [12]. The authors next tested the effects of a 12-week RMT in a group of 22 adults with LOPD in an exploratory, double-blind, randomized control trial using a parallel arm pretest- posttest design and sham-RMT as the control condition [13]. Participants performed inspiratory and expiratory RMT repetitions at a calibrated, individualized pressure-threshold equal to 70% of their MIP and MEP. MIP increased 7.6 cmH₂O in the treatment MEP increased 14.0 cmH₂O in the treatment group and 0 cmH₂O in the control group, however these differences did not achieve statistical significance. Interestingly the motor function generally improved after RMT, for e.g., the 6 MWT, improved in the treatment group compared to the control group, however these differences did not achieve statistical significance. It is possible that the sham-RMT did not appear to be an inert control, thus diluting the significance of the RMT.

Since little is known about the effect of inspiratory muscle training (IMT) alone on pulmonary function in subjects with LOPD, an 8-weeks trial of inspiratory muscle training in 8 LOPD participant was performed [16]. MIP increased by 9 cm. H₂O or 30.0% and there were no significant changes in the pulmonary function measurements, in particular the MEP, like the present study [17]. Another study in 11 subjects comprising a 6-week IMT training period, followed by a 6-week non-training, and an optional training period of 40 weeks revealed a significant increase in the MIP within the 6-week period of frequent IMT with a mean of 7.63 cmH₂O or 15.7% and a significant increase was also seen after week 52 by a mean of +26.4%. There was no effect on spirometry tests (FVC, FEV1), capillary blood gas analysis, motor function tests, patient's perceived quality of life or any significant change in dyspnea score [14]. In another pilot study in 8 LOPD subjects the average improvement from baseline in MIP at 3 months was +25.2%, at 6 months +24.9%, at 9 months +23.7%, at 12 months and at 24 months MIP increased by 5.6 cmH₂O or +17.8% [15]. Overall, our results in this trial are largely consistent with the work from other researchers which have shown a 15.7 to 30% increase in MIP in response to RMT.

Interestingly we also did not see significant changes in the FVC measurements. As noted previously, compared to MIP,

FVC has several limitations [13]. FVC is an indirect measure of respiratory muscle strength, and relatively insensitive to changes in respiratory muscle strength [23–25]. Therefore, we believe that measurements of the MIP are more sensitive in detecting early changes in respiratory muscle function [13,26–28], since substantial changes in respiratory muscle strength may be present before changes in lung volume measures like FVC are noted [29].

On reviewing the adverse events, we did not observe an increase in the blood CK or LDH levels indicating that there was no muscle damage occurring because of the exercise. Two individuals had an adverse event (back pain) related to increasing the frequency of the training in one and a work-related injury in the second. As a precaution however, we recommend that subjects more severely affected by the disease may need adjustments and more careful monitoring of the resistance training programs to avoid injuries and falls.

Recently protocols have been developed for adapted physical activity and individual rehabilitation plan focused on therapeutic exercise and respiratory rehabilitation in Pompe disease [13,30,31]. The protocol we used for our resistance and inspiratory muscle training in LOPD can also be utilized for patients with other neuromuscular disorders with supervision.

New therapies currently under development such as gene therapy and next generation ERT hold promise, nevertheless, exercise therapy remains a cheap and effective adjunct treatment to prevent ongoing progression of disease. Our study suggests that resistance exercise training combined with inspiratory muscle training and ERT leads to improved muscle strength and a marked improvement in the respiratory measurements in most subjects with very few adverse side effects. Our findings encourage use of supervised exercise and inspiratory muscle training for improving physical function and health to improve generalized muscle weakness and particularly respiratory weakness which remains the primary cause of morbidity and mortality in LOPD.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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