

Peer Review File

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Reviewer A

Reviewer:

This is an important study with a compelling research design that is worthy of publication. The use of age matched healthy controls is nice as is the method of exercise testing.

Response:

Dear Reviewer, thank you for your positive opinion and your insightful comments on our manuscript. We have corrected the manuscript according to your suggestions. Please find our point-by-point responses below:

Reviewer:

I have minor comments which include the following:

Page 4, paragraph 3, line 100-103: "There are concerns about the safety of resistance exercise, because resistive (especially eccentric) muscle contractions induce myofibrillar disruptions, elevation of muscle protein and enzyme levels in serum [creatinine 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)." It is not clear to me about the population that needs to be concerned about resistance exercise. Does this refer to LOPD or the general population? Seems like this refers to LOPD and this should be stated. Either way, it seems like references are needed.

Response:

The sentence is now corrected to refer to LOPD. Furthermore, we provided reference for EIMD markers.

Reviewer:

Page 6, line 142: "The study was conducted during four consecutive years." this line is awkward and should be incorporated in the first 1-2 sentences of the paragraph. Also, the word "Finally" in line 136 should be deleted.

Response:

We corrected.

Reviewer:

The study measures delayed onset muscle soreness at baseline, 24 hrs, and 48 hrs. I am not sure the baseline measure really reflects DOMS as the exercise intervention has not yet been applied.

Response:

You are absolutely right. However, as none of the patients reported any soreness, the source of pain seems not to be a question here. Indeed, we aimed to ask patients to report their pre-exercise pain because pain can develop even from everyday activities such as extensive walking or stair descending.

Reviewer:

Discussion: "Furthermore, seven out of the twelve patients did not report muscle soreness at all at any time points, suggesting little damage or no damage at all." please clarify this refers to LOPD subjects.

Response:

Corrected.

Reviewer:

Discussion "In conclusion, our complex approach (serum biomarkers, MCV torque and quantitative muscle MRI) did not indicate additional muscle damage in LOPD patients after standardized single bout of high intensity concentric exercise: they showed similar or less severe responsiveness in EIMD markers, except LDH activity." It seems like the intent is to say that LOPD subjects did not show evidence of increased (rather than additional) muscle damage compared to healthy controls.

Respond:

It is correct. Now we use your words for clarification.

Reviewer B

Reviewer

Summary

Muscle Damage in response to a single bout of high intensity concentric exercise in patients with Pompe disease by Vaczi et al. describes changes in serum CK, LDH, and Mb and MRI in response to resistance exercise in patients with late-onset Pompe disease. Authors concluded that high intensity concentric exercise does not incur additional muscle damage in patients with LOPD and monitor of LDH can guide the training efforts.

Response

Dear Reviewer:

Thank you very much for revising our paper and for your insightful comments. We thoroughly checked the paper and edited it by incorporating your suggestions and requests. Please find our point-by-point responses bellow:

Reviewer:

Authors state “Late-onset Pompe disease (LOPD) is a rare inherited metabolic myopathy with acid maltase deficiency that results in glycogen accumulation in lysosomes.” Although, acid maltase deficiency will be right, this terminology is outdated and rarely used nowadays when describing Pompe disease.

Response:

Thank you very much for the comment. We have changed the terminology: “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.”

Reviewer:

Line 136 – Authors should consider moving the details on their cohort including number of patients and age to results section.

Response:

Thank you for your suggestion. It is a normal practice that subject information is positioned in the methods section. We checked ATM and we found the same practice, see examples in Pompe studies: Alandy-dy et al. 2019, Meinke 2019. Therefore, we kindly request the reviewer to accept subject information kept in its original place.

Reviewer:

Line 138 – Correct terminology is acid alpha-glucosidase (GAA).

Response:

Corrected

Reviewer:

Line 137 – Diagnosis of Pompe disease is generally based on enzyme activity and variant analysis. EMG is not routinely used for confirmation of diagnosis.

Response:

Thank you for your notice, we have corrected the sentence.

Reviewer:

Line 141 – acid alpha-glucosidase is not the correct term for describing Myozyme. Correct term here would be alglucosidase alfa (Myozyme).

Response:

Corrected.

Reviewer:

Figure 1 detailing enrolled patients each year out of total patient in Hungary is not adding any scientific details and author should consider removing that or moving it to supplementary material.

Response:

We have removed figure 1 and re-numbered the rest of the figures.

Reviewer:

Authors should provide details on how many patients were screened for participation in study and if there were any patients that were excluded from the study; reason for the exclusion.

Response:

Thank you for your comment, we have edited the entire paragraph.

Reviewer:

Effect of concentric exercise on serum biomarkers of muscle microinjury – This section is important to understand the result and should be rewritten to make it more clear as it can be confusing to understand the result in its current format. Authors are comparing pre- and post-exercise values within patients and control group and also comparing outcomes in patients to control. Authors should divide this in 2-3 paragraphs – 1) comparison of pre- and post-exercise value within patient and control group and 2) comparison of patients to control.

Response:

Thank you for your insightful comment. We have edited this section by including two paragraphs. 1: baseline data comparison, 2: within group changes. Please note that we found no sense for comparing the groups at specific post-exercise time points (24, 48h) because the baseline values were unequal and such comparisons would mislead us. To present between-group differences in biomarker responsiveness, we used the relative changes as shown in the last paragraph of the methods section, and the results are presented in the last paragraph of the results section.

Reviewer:

What was the baseline level of CK, LDH and Mb in control group? Were these within normal limits?

Response:

We have acknowledged this by including the following sentence into the results section: “All baseline serum biomarker mean levels in both groups were within the normal reference range, though few outliers were found among LOPD patients (Fig 2).”

Reviewer:

Line 273 - Author state that increase in CK activity approached the significance level (p=0.078). This p-value is not statistically significant.

Response:

It is correct. We use the word “approach” to indicate that the value was close to 0.05. This term is commonly used in several articles.

Reviewer:

Line 269 - 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. This is an expected result in a progressive muscle disorder like Pompe disease. Authors should clarify that as well as Authors should consider adding some background on what is expected in terms of serum markers for Pompe disease. This will be beneficial for readers to understand the difference between participant and control at the baseline.

Response:

We have edited this section and also added new reference.

Reviewer:

Authors should provide detailed method of comparison between groups and patient to control – comparison of baseline to 24 hour/48 hours within group, comparison of baseline values in patients to control.

Response:

All required information is presented in the data analysis in paragraph 1-2, see as follows: Baseline between-group comparison was performed as “*Between-group differences in the baseline values were determined using independent t-tests (in LDH) or Mann-Whitney U-tests (in MVC torque, CK, LDH, Mb, and soreness), depending on the Shapiro-Wilk normality test results.*”

The test of within group time effect (baseline to 24/48hrs) was performed as: “*we determined the exercise effect across time in every measured variable using nonparametric Friedman ANOVA*”

The between group comparisons at the specific time points: We found no sense for comparing the groups at specific post-exercise time points (24, 48h) because the baseline values were unequal and such comparisons would mislead us. To present differences in biomarker responsiveness, we used the relative changes as shown in the last paragraph of the methods section.

Reviewer:

Authors state that “Furthermore, seven out of the twelve patients did not report muscle soreness at all at any time points, suggesting little damage or no damage at all.” Soreness is a subjective and in a muscle disease like Pompe where pain, fatigue, and cramps can be present, soreness can be sometime overlooked by patients. Absences of soreness in these patients cannot be extrapolated to be absence of muscle damage. It is reasonable of authors to hypothesize that however, authors may want to be careful with wording.

Response:

You are absolutely right. We have acknowledged this with the following sentence: “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.”

Reviewer:

Authors should provide the basic disease history of the patients such as age at diagnosis, age at symptom onset, time on ERT. In a slowly progressive muscle disease where ongoing irreversible muscle damage can be present from as early as first year of life and patient may have variable degree of muscle damage and loss of muscle tissue. These variables can skew the result, especially when study cohort includes patients ranging from 19 to 58 years of age.

Response:

We edited patient descriptive paragraph by involving the age at diagnosis and time on ERT. Unfortunately, we have no data on symptom onset.

Reviewer:

Authors may find value in bringing the major finding of their study upfront in the discussion so that way it is not lost in the text.

Response:

Thank you very much for the suggestion. We have changed the Discussion accordingly, and summarize the basics and results of the study at the very beginning of the Discussion.