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Spatio-temporal gait differences in Facioscapulohumeral muscular dystrophy during single and dual task overground walking - A pilot study

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Dear Dr. Alphonsa,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below for reviewer 2 and attached to the email for reviewer 1.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Dec 31, 2021.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #2: The authors report on the effect of dual task gait activity for individuals with FSHD. Gait metrics have been reported on previously and may be useful as outcome measures for studies in FSHD. This current study investigates the impact that dual- task activity have on gait metrics. While this may be of interest to the field, there are some clarifications needed.

Intro

Lines 33-37; consider rewording/breaking up into more than 1 sentence. Hard to put all of those measures together with subjective, lack sensitivity, provide qualitative information, do not emphasize functional capacity or insufficient in detecting mild changes in annual progression. The reference used here only speaks to the sensitivity of strength and functional measures.

Line 53-56 are not clear to me.

Line 57-59- Lack of "control group"?

Page 4 consider reference for line 15-17. Is this also 17? Consider adding an additional sentence to support your choice of using cadence and gait velocity over stride length and stride velocity- the measures that were found to change over 20 months.

Page 4 paragraph 2: DT assessments have been used in other groups---but these groups are mainly groups with cognitive involvement- why do the authors think it will impact gait metrics in a muscle disease where there isn't cognitive involvement?

ST needs to be spelled out at first use. If abbreviating ST and DT- use throughout manuscript.

Consider additional background information re: methylation in introduction.

Methods:
Paragraph 1; exclusion criteria A) inability to walk and stand on both feet for 1 minute. Did individuals have to do both? There are individuals who can stand, but can't walk. Please clarify.

Why was physical activity readiness assessed? Information from this was not reported in the results.

Consider providing more information re: MMT - 0-6 and 7-15 is not standard scoring for MMT.

Consider providing an example of the pseudo randomized order that is referred to in line 46-47.

Results:

It is not clear if cadence and gait velocity were chosen apriori or after comparing those with FSHD and controls- per lines 17-20. Please clarify.

The clinical severity score (CSS) comes up in the results; however, this should also be included in the methods.

Discussion:
Please consider expanding on the similarities to the Statland study as the cadence in the current study is lower than what Statland reported and the velocity is higher than previous report. Maybe both are lower than healthy controls?

Good hypothesis regarding why DT did not impact gait- individuals with FSHD may be doing this routinely in their day to day experiences.

What is the relevance of performance errors? I am not sure that I have read much about the errors in other populations where DT has been evaluated.

The authors may want to consider referencing the statement in lines 51-54 on page 12.

Conclusions:
The authors may want to consider the findings in light of the small sample size. Consider rewording to more accurately reflect results.

There is additional documentation related to this decision letter. To access the file(s), please click the link below. You may also login to the system and click the 'View Attachments' link in the Action column.

Authors' rebuttal

Response to reviewer 1

Spatio-temporal gait differences in Facioscapulohumeral muscular dystrophy during single and dual task overground walking- A pilot study

The authors describe an interesting study on the study and quantification of spatio-temporal gait characteristics of people with FSHD. This study and its results look promising and may lead to several clinical applications. However, I am concerned about the fact that the novelty of this study is not properly highlighted and in some cases even questionable.

General Comments

1) In my opinion the paper could benefit from a section called data analysis that will explain all the variables and motivate the analysis needed to process them properly. as it is now, the authors only present information about what they used for the analysis but no motivation. Also to this point it is very vague which parameters are used, how they look like and why this analysis is used for those parameters. It is also vague which comparisons are made. Everything becomes more clear in the results, but the materials and methods section could maybe benefit from a picture of the test set-up and figures that help with the visualization of the parameters

Response: The demographic variables are first introduced and explained in the procedure section and later the statistical analysis section explains in detail how these variables were further used for statistical analyses. To have another "data analysis" section would be redundant. Hence, the authors have decided to add an experimental design figure in the procedure section that explains the gait and behavioral outcome variable obtained.

Graphical Abstract

1) The graphical abstract (the same way as a textual abstract) should summarize the whole paper. As it stand now, it is focused on the results and it is also difficult to understand without the caption. I would suggest to the authors to make a graphical abstract that reflects the complete paper.

Response: The author has deleted the first graphical abstract and introduced a new one. If this satisfies the reviewers, this can be used for the final draft. If it does not, we would like to move forward without a graphical abstract.

Abstract

1) Do you have any hypothesis? research objective or question? This should already be highlighted in the abstract. The aim offered here is very narrow and in the introduction more objectives are given that are not mentioned in the abstract

Response: New aims have been updated in the abstract. Hypotheses are now included in the introduction.

2) The methods section is a bit too brief and does not describe the methodology. Maybe a bit more on the single and the dual tasks? What about data analysis? parameters?

Response: authors have included a new figure describing the experimental design and provided more details in the methods section.

3) What means nearly matched in this context? It is unclear

Response: anthropometric matched as one cannot have a perfect matched control unless it is the individuals own baseline.

4) The methylation analysis for example could have been explained in methods. Now it appears a bit out of the blue as part of the results section

Response: this has been addressed

5) Most of the conclusion section is about results. But does not conclude much. Also it does not reflect on the aim of the study as described in the abstract. Where is the quantification of spatio-temporal gait characteristics?

Response: We believe the explanation of each hypothesis (mentioned in the introduction) in the discussion should flow well in the entire manuscript.

Introduction

1) The intro feels a bit like a disconnected collection if interesting information. However, the authors do not draw any connections to their objectives.

For example it is mentioned that: *However, these tools and measures can be limiting as they are subjective, lack sensitivity, provide only qualitative information, do not emphasize functional capacity, and are insufficient in detecting mild changes occurring in annual disease progression[15].*
Does that mean that what the authors suggest tackles all these issues? Is your approach different/novel from the existing approaches you mention in the introduction? If yes why? Do you tackle all of the problems mentioned in the introduction as limitations of previous approaches?
Response: Although these tasks are a good measure to understand affected abilities in FSHD, they can increase the risks of falls. Safer alternatives, such as the effects of performing a cognitive secondary task using a dual task paradigm, have not yet been explored on FSHD patient gait function. This is already in the introduction and should answer the authors questions.

2) Maybe interesting to mention the prevalence and incidence of the disorder? is it rare or not?

Response: This information has been updated in the introduction

3) The introduction mentions 2 objectives, while the abstract only one. Additionally, there is a hidden objective in the introduction that maybe should be objective C) (*Further, we investigated the correlation between the gait parameters and the methylation status in FSHD.*)?

Response: this has been corrected

4) It is also unclear why this last part about the methylation is necessary as an objective. To what end? What is the ultimate purpose of this analysis?

Response: the rationale for the use of methylation is now included.

Materials & Methods

1) How much time did your participants have to think about and inform you if they would like to participate or not?

Response: This was variable as recruitment of FSHD participants was through a joint effort from the School of Medicine and other research groups and availability of FSHD participants. Recruitment of controls was based on each FSHD participant as the controls were anthropometric matched.

2) You matched the healthy and the FSHD participants based on anthropometric characteristics. This is a very interesting point. Could you please describe why this was necessary?

Response: To account for variability in the FSHD group (mainly age). This is also an important factor that has not been very well addressed in other studies and makes our study stronger.

3) It would have been interesting to share the demographics of your participants (healthy and not). It may be that age (since it is progressive) and gender play a role in the results. Maybe better to share this info here, rather than in the results section.

Response: This was submitted as supplemental table 3 during the initial submission. The reviewer may have missed checking it.

4) Why was pseudo-randomization necessary? Could you elaborate on that?

Response: Randomization is a powerful and commonly used technique and makes a lot of sense when one randomly assigns participants to a control or treatment group. In our study since we already had predetermined control and FSHD groups, we wanted to account for the effects of single and dual task equally on all participants. By randomizing we face the challenge of not controlling for this effect. Hence, the use of pseudorandomized trial order. Please note that the number assigned where participant had to serially subtract seven was still randomized therefore preserving the novelty of the dual task.

5) The section called *Relevant 4q35A methylation*, only describes the process but not why this was necessary. What is the purpose of this analysis?

Response: The fundamental epigenetic dysregulation of the chromosome 4q35 D4Z4 locus leads to the pathogenic gene expression causing FSHD. It is an important piece of information that ties biomechanical/ gait characteristics with the epigenetics therefore bridging two important fields. We have included this in the last paragraph of the procedures section.

6) In the *Statistical Analyses* section, it is not clear if the data were pre-analyzed to see if they fulfill the assumptions of the statistical tests used (homogeneity, normality, and independence for example). Could you elaborate on that?
7) *DRA RQA,* is mentioned here as an abbreviation for the first time without any explanation as to what it is, how it is calculated and how is it relevant for this analysis

Results

1) Did the authors decide to exclude other parameters because they did not show a change between healthy and FSHD? Is it maybe interesting to mention which were those?

Response: Table 1 reports all participant mean demographic data consistent with the literature. We additionally provide all participant individual data in the supplemental table 3.

2) **Table 2:** Mean and SD makes more sense for data that are normally distributed. Is that the case here?

Response: Our intention to provide the Mean and SD was to highlight the range in the data. It is also consistent with how the data are reported in past FSHD studies and important for a clinician to understand the FSHD population we studied. It is understandable that a similar amount of variance would be seen in the controls as they were matched to each FSHD participant.

3) Is it not important for cadence and velocity to also see if there is difference between the ST and the DT within a specific group? This way you can show that the DT really impacted performance per variable. Or is this not relevant?

Response: Yes, we looked into all of the within group differences and these are highlighted in the supplemental tables 1 and 2.

4) Figures appear pixelated. Maybe the authors could use vector images, instead of bitmaps?

Response: The corresponding author provided all tiff images as well. These may have lost its quality when embedded in the manuscript and were generated by the editorial manager. We hope the final manuscript will incorporate the original high quality tiff images and account for this issue. We will emphasize this to the editors again.

5) What is the difference between figures 1A and 1B?

*Response: **1A** shows pairwise comparisons of cadence (steps/min) for **each** FSHD participant with the specific matched control are represented as individual lines. **The data are matched for each individual pair separately for ST and DT**. Individual pairwise test results for each*

task are reported as p values. ***1B is the*** *MLM model fit for cadence (steps/min) is shown as estimated marginal mean cadence for ST and DT for Control and FSHD groups.*

6) For the section *Relationship of DRA RQA methylation percentage vs Gait*, how did you decide which controls to remove? those that were genetically matched?

Response: Two of the FSHD patients and corresponding controls were removed from this data as their contracted allele was 4q35A-L which may have an altered epigenetic environment. Each paired matched control was removed without any bias. Each FSHD participant has their own matched control. No two matched controls were same or reused.

Discussion

1) The discussion does not discuss the limitations of this study

Response: The authors have added a limitations section

2) In the *Discussion* section the hypotheses appear for the first time. Where were these hypotheses described previously? Shouldn't those be also in the introduction and abstract?

Response: this has been addressed

3) The authors mention that *We provide preliminary evidence to indicate that FSHD gait may not be affected by secondary task demands to the same extent as it affects healthy participants.* isn't that reasonable since you excluded people with cognitive decline? What would happen if you included other people with FSHD?

Response: The authors did not intend to have a third group of people with cognitive decline as there is plenty evidence to indicate this in the literature (comparisons between healthy and individuals with cognitive decline). Our study findings didn't reflect any effects of DT on FSHD gait. The FSHD group did not have cognitive decline- which was not intentional.

4) It would be interesting in your discussion to discuss how variability in FSHD is accounted for in this research and if you can make any conclusive remarks about the majority of people with FSHD or only for the specific group you have tested.

Response: The variability is pertaining to the group of FSHD participants we recruited. Researchers are aware of this problem with respect to the FSHD population. There are many groups of researchers trying to gather data with bigger sample size to combat the variability issue. We tried to account for the variability by using a powerful multilevel modeling analysis. Recruitment of a large FSHD population comes with financial, time of recruitment and location-based limitations. This limitation was added after the conclusion.

5) Surprisingly, we observed that FSHD patients outperformed controls in DT, as indicated by a low number of subtraction errors. There are several potential explanations for this observed paradigm. The first is that FSHD patients may have greater real-world experience with cognitive tasks during locomotion due to necessity for fall prevention. Constant DT would be unnecessary or easier for healthy controls and might include tasks like environmental mapping, obstacle recognition, terrain optimization, and locating ramps or handrails. Alternatively, this lack of DT percentage cost could be a manifestation of lower ST gait function present in FSHD patients, and the ability to easily perform cognitive DT while walking at lower speeds. It will be interesting to see which of these DT paradigms is correct with further experimentation. Finally, it is possible that this ST/DT paradigm could be useful in the detection of mild FSHD outcome measures, but a much larger and more diverse sample is required for this expansion research.

This is quite an interesting section with interesting speculation. Were there any of these assumptions you make to justify the observations found in other studies?
Response: Future studies could answer these questions but for now the authors don't plan on adding any new studies to this gait protocol.

6) Are your results, (namely: *In this study we have provided new evidence to demonstrate gait as a clinical assessment tool for FSHD patients.)* novel? Is this the first study that does that?

Response: It is novel in the sense of using a gait mat system and with the use of the dual task paradigm to assess any dual task effects of FSHD gait.

Conclusions

1) Lastly, our study provides preliminary evidence with ST and DT protocols that researchers can incorporate into clinical trials to understand the effectiveness of drugs on muscle degeneration in FSHD.
This sentence should have been also in the introduction and abstract and not appear here for the first time
Response: The incorporation on the effects of ST and DT are upto clinicians based on their hypothesis. Hence, we conclude that our findings pertaining to ST and DT can be used by clinicians to incorporate in their FSHD clinical trials. We believe this fits well in the conclusion as an implication of our findings.

Reviewer #2: The authors report on the effect of dual task gait activity for individuals with FSHD. Gait metrics have been reported on previously and may be useful as outcome measures for studies in FSHD. This current study investigates the impact that dual- task activity have on gait metrics. While this may be of interest to the field, there are some clarifications needed.

Intro

Lines 33-37; consider rewording/breaking up into more than 1 sentence. Hard to put all of those measures together with subjective, lack sensitivity, provide qualitative information, do not emphasize functional capacity or insufficient in detecting mild changes in annual progression. The reference used here only speaks to the sensitivity of strength and functional measures.

Line 53-56 are not clear to me. & Line 57-59- Lack of "control group"?
Response: the authors need further help to identify these two comments as the lines are not matching with the submission output we have from the editorial manager. We are happy to address this once we identify the exact concern.

Page 4 consider reference for line 15-17. Is this also 17? Consider adding an additional sentence to support your choice of using cadence and gait velocity over stride length and stride velocity- the measures that were found to change over 20 months.
Response to the choice of use of cadence and gait velocity: Statland used a different measuring system, Since Tekscan was a novel system available to us that allowed us to

measure FSHD gait we evaluated several of the outcome variables from Tekscan and provided Cadence and gait velocity in line with the Statland's study.

Page 4 paragraph 2: DT assessments have been used in other groups---but these groups are mainly groups with cognitive involvement- why do the authors think it will impact gait metrics in a muscle disease where there isn't cognitive involvement?
Response: The effect of dual tasks has been well established in healthy, aging and individuals with cognitive decline. The dual task paradigm specifically impacts the primary task since it acts as an interference. We wanted to evaluate this influence in FSHD which makes the study novel. We weren't sure how DT would affect individuals with FSHD as the primary task (gait) is affected due to muscle damage. Our data, although preliminary and with restricted sample size and FSHD variability indicated that there was no difference in ST and DT which provides new evidence. This does not indicate that FSHD did not have cognitive involvement. The MoCA scores showed that the FSHD group we recruited did not have cognitive decline.

ST needs to be spelled out at first use. If abbreviating ST and DT- use throughout manuscript.
Response: this has been addressed

Consider additional background information re: methylation in introduction.
Response: The authors have addressed this in the procedures as methylation analyses was an addition to this study from another project and was not among the primary aims of this study.

Methods:
Paragraph 1; exclusion criteria A) inability to walk and stand on both feet for 1 minute. Did individuals have to do both? There are individuals who can stand, but can't walk. Please clarify.
Response: This was specific to FSHD based on previous studies. As the disease progresses and individuals with FSHD may be wheelchair bound, they continue to have the ability to walk (say 1 minute) but not for a prolonged period of time.

Why was physical activity readiness assessed? Information from this was not reported in the results.
Response: Physical activity readiness was used to evaluate if individuals met the criteria to safely walk across the gait mat. We had everyone pass this assessment. Therefore, this was an inclusion criterion that was satisfied for individuals to be included in the study.

Consider providing more information re: MMT - 0-6 and 7-15 is not standard scoring for MMT.
Response: This was based on the grading scale used by (CITE)

Consider providing an example of the pseudo randomized order that is referred to in line 46-47.
Response: Explained using Figure 1 and additional explanation is now provided in the procedure section.

Results:

It is not clear if cadence and gait velocity were chosen apriori or after comparing those with FSHD and controls- per lines 17-20. Please clarify.

Response: Tekscan allowed us to evaluate several variables however to keep it consistent with previous studies we used cadence and gait velocity as the dependent variables.

The clinical severity score (CSS) comes up in the results; however, this should also be included in the methods.
Response: CSS is calculated from the MMT which is mentioned in the procedures. However, I have added a brief explanation in the procedures and introduced CSS.

Discussion:
Please consider expanding on the similarities to the Statland study as the cadence in the current study is lower than what Statland reported and the velocity is higher than previous report. Maybe both are lower than healthy controls?
Response: The authors were surprised to see this trend. However, on further evaluation we found a few FSHD had rapid uncontrolled walking patterns, but others had slower. This added to the variability, but the low sample size resulted in an average velocity that was still higher compared to Statland. Further investigation with bigger sample size is necessary to understand this trend possibly by dividing the FSHD group into subcategories based on gait velocity. We were unable to separate this due to the already low sample size.

Good hypothesis regarding why DT did not impact gait- individuals with FSHD may be doing this routinely in their day to day experiences.
Response: Thank you

What is the relevance of performance errors? I am not sure that I have read much about the errors in other populations where DT has been evaluated.
Response: It is a common yet important behavioral outcome. It is one way to evaluate the accuracy of performing serial subtraction based on number of errors. Figure 5 is the best representation we have with data points showing the average number of errors for each participant by group.

The authors may want to consider referencing the statement in lines 51-54 on page 12.
Response: this was confusing to find. Can you please clarify?

Conclusions:
The authors may want to consider the findings in light of the small sample size. Consider rewording to more accurately reflect results.
Response: we have now addressed this

2nd Editorial decision
11-Jan-2022

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Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers: