

Reviewer 1. ID Number: 00504406.

Response: Thank you for the review of our work.

Reviewer 2. ID Number: 00506397.

Response: Thank you for the detailed review of our work, we hope that our edits adequately address each of your comments below.

1. Poor expression and grammar are recorded below: 1. “However, from a recent review, discrepancies in the literature are reported with respect to the depth of pain perception threshold, which raise questions as to the extent of tissue disruption in DPN, which the authors demand further study is needed.”

Response: We have restructured this sentence. The sentence now reads. However, from a recent review, discrepancies in the literature are reported with respect to the extent of pain perception threshold [1]. These discrepancies raise questions as to the range of tissue disruption, where previously DPN was thought to include superficial anatomy such as the skin, but recent data suggests deeper structures, including muscle may be affected [1]. (Line 109)

2. “Furthermore, T2D generally exhibit worse balance during activity than non-diabetics, which may account for the high frequency of ER visits due to falls.” Don’t you mean patients with T2DM?

Response: We have gone through the entire document and have changed all instances of T2D to include T2DM. Additionally, Mellitus was added to the definition of T2DM. (Line 100)

3. “Knee proprioception has been commonly measured using joint position sense tasks for a number of populations including ACL, knee arthroplasty and osteoarthritis to name a few”. Do you mean populations of patients with ACL, knee arthroplasty and osteoarthritis, to name a few?

Response: “of patients” was added, punctuation also added. (Line 131)

4. “In studies examining laboratory based induced ischemia; afferent nerves are more commonly affected than efferent nerves due to the greater size and oxidative demands of the afferent nerve.” Need to write in complete sentences.

Response: The word “based” was removed. We have added some wordage to make the sentence more complete: in studies examining physiologic responses during laboratory induced ischemia. (line 292)

5. “Both ankle and hip strength and proprioceptive thresholds were successfully used a predictor variables to determine the number of falls in this population.” Why use of “a” for plural (variables)?

Response: this was a typo. We have changed the word to **as** predictor variables. (Line 124)

6. “Although DPN has been historically characterized as superficial loss of nociception in the feet involving A-delta and C-fibers, others have suggested factors such as age can cause afferents in adjacent subcutaneous tissues which may include A-alpha proprioceptive nerve fibers in muscle to become disrupted as well.” Break this run-on sentence into 2 or 3 to clearly express what you mean.

Response: we have significantly restructured this sentence. It now reads: **However, outside of DPN, factors such as age have been found to disrupt larger diameter afferents such as A-alpha proprioceptive nerve fibers which are found in the deeper tissues such as muscle [2]. To the author’s knowledge, no studies have investigated the effect of DPN on large diameter afferent nerve fibers.** (Line 127)

7. “We hypothesize that patients with T2D will have greater proprioceptive errors than healthy controls, further we hypothesize that patients will not respond with linear improvements to proprioception by target angle of elevation.” Again, need to break this sentence to say what you mean more accurately.

Response: we have restructured the hypothesis statement to include two clear and separate hypothesis. It now reads: **We hypothesize that patients with T2DM will have a greater magnitude of proprioceptive errors than healthy controls. Our secondary hypothesis predicts that patients with T2DM will not have linear improvements to proprioceptive acuity by target angle of elevation.** (Line 145)

8. “All JPS data were downloaded from the iPod using iTunes software. Three dimensional accelerometer data were converted into angular data in a custom Labview program following equations previously validated.” Need to hyphenate 3-D and expand these sentences to express them more precisely (using previously validated equations?).

Response: We have included a bit more explanation behind the equations used. The sentence is now phrased: **...using the second integral function and Pythagorean theorem, which has been validated and described in the literature for accelerometers when estimating humeral elevation angles [3].** (Line 210).

9. Our data suggest that our hypothesis were supported for accuracy but not for precision (Figures 2 and 3). Need to use plural since you started with two hypotheses!!!!

Response: We have changed the word “were” to **was**. We think this fixes the problem of plurality? (Line 247)

10. “We previously reported that patients with pain syndromes have large proprioceptive deficits to both accuracy and precision to a degree that are consistent with the present study.” Should you not say “in both accuracy and precision”? What does “to a degree” mean?

Response: we have replaced “to” with “in.” We have changed “to a degree” to “of similar magnitudes.” (Line 259)

11. “Demographic data from the present study indicate that 60% of the diabetic participants reported some discomfort in the lower extremity during the proprioceptive task; however, we did not separate participants into groups based on pain.” I could not understand by what you meant by demographic data. I could not find mention of “demographic data acquisition” anywhere in the Methods.

Response: The data referred to in this section is with respect to our patient intake form, which included a questionnaire that had several questions with respect to pain. We have changed the word Demographic to Questionnaire. (Line 263).

12. “Together these findings help to explain heightened instability and fall risk in this population, furthermore, the greater errors at smaller angles of elevation could help to explain data on diabetics and small obstacle clearance, which likely occur at similar angles.” Need to break this run-on sentence into more sentences to express more clearly what you mean.

Response: We have restructured this sentence. It now reads: **Together these findings help to explain heightened instability and fall risk in this population. Furthermore, the larger errors we observed at 15 -30 degree target angles could help to explain why patients with T2DM demonstrate poorer obstacle clearance during gait as obstacle clearance is likely to occur within a similar degree of knee angles to our target angle [4, 5].** (Line 283)

13. “Future studies should examine the extent of which joint position sense disruption can be measured in patients with diabetes and within the various stages of DPN in

order to establish a new method for diagnosis, disease and/or treatment progression.” This poorly expressed thought needs revision.

Response: We have restructured this sentence. It now reads: Future studies could examine the extent of which joint position sense is disrupted in diabetic populations. Examining JPS errors by severity of DPN symptoms could help clinicians and researchers diagnose DPN, and could be used as a measurement tool for effectiveness of treatment. (Line 302)

14. “For each of our hypothesis and corresponding results will be discussed below.” Express it more clearly i.e. you have two separate hypotheses and you obtained results that particularly address to each of these hypotheses.

Response: We have added wordage to indicate first and second hypothesis. These hypotheses (1 and 2) are more clearly outlined in the discussion. (Line 241, 244, 248, 271)

15. “Regardless, DPN is the most frequent sequel of diabetes mellitus” Do you mean to say “sequela”?

Response: We did mean sequela, but have changed the sentence to read: Regardless, DPN is the most frequent condition, secondary to diabetes mellitus ^[1]. (Line 105)

16. Use consistent spelling of C-fiber not C-fibre throughout the manuscript.

Response: we have fixed the spelling of fiber throughout.

17. When citing data “figures and tables” in the Text, cite them uniformly as “Figure 1, Figure 2 and Tables etc.

Response: we are a bit unclear as to the reviewer’s comment, our review of the document resulted in only Figures followed by the appropriate numbering. Is there a specific instance the reviewer can point us to?

18. “Funding for this project was partially provided by the Murdock Charitable Trust. “This comes under the heading of Acknowledgements.

Response: We have added the Acknowledgements subheading. (Line 307)

Reviewer 3. ID number: 03699916

Response: Thank you for your review of our work. We hope that our responses to your concerns are sufficiently addressed.

1. Major comment: Authors emphasize the effect of peripheral nerve disorders in the lower extremity on proprioceptive discrepancies in the present study. It is well known that the diabetes also affect central nerve system. Does the disorders of central nerve system in T2D also affect the accuracy and precision of joint position sense in the lower extremity? However the authors can differentiate the effects of central nerve system (brain) and peripheral nerve system (the lower extremity) on proprioceptive discrepancies in the present study?

Response: Our measurements of limb localization are certainly affected by upstream neural centers within the CNS. It is fairly common for research focusing on limb proprioception to ignore what is going on at the brain and spinal cord level (however wrong that may seem). The reviewer is correct that our results could be due to something higher in the CNS, we unfortunately, have no data in the present study to determine if the effects that we measured are a local disruption at the sensor level in the feet/shank or if it is indeed at the higher centers. We have addressed other complications of the CNS under our limitations section : **Limitations**

We acknowledge that proprioception as measured by a joint position sense task does involve a memory component (remembering where your arm was moments ago), further our findings could be influenced by alterations of the central nervous system and small sample size. (line 308)

2. Minor comment: The first paragraph in the Discussion is suggested to delete as this has been mentioned in the end of Introduction.

Response: We have streamlined the first paragraph of the discussion to identify the two hypotheses from the introduction; it is our hope that by identifying them as hypothesis 1 and hypothesis 2 we can reduce confusion later on as each paragraph tackles the results of the study with respect to each hypothesis.

Reviewer 4. ID number: 00504150

Response: Thank you for your review of our work, we hope our responses are satisfactory.

1. The authors describe the results of diabetic neuropathy symptom score in the Materials and Methods section. These should go to the Results section as has been done in the Abstract.

Response: we chose to place the symptoms scores under the Subject subheading because the data from the questionnaires pertains specifically to the subjects (and describes the subjects) and not directly to what was measured in our study.

2. In the abstract the authors use an abbreviation T2D whereas T2DM is employed in the main text. Consistency should be considered.

Response: we have gone through the manuscript and have replaced all T2D with T2DM, additionally we have added the word mellitus to the definition of T2DM. (Line 105)

3. Also the authors use an abbreviation ADL, which is not necessary because it is used only once in the abstract.

Response: we have removed the comment regarding ADL from the abstract.

4. Please spell out ACL.

Response: Anterior Cruciate Ligament injury is now included. (Line 133)

5. The authors state “...and significant differences between levels of target angle were also observed ($p < 0.001$).”. However, Table 2 indicates p value of $p = 0.001$.

Response: we have changed the symbol $<$ to be $=$. The statistic now states $p = 0.001$ (Line 231)

6. In legend of Figure 3, it states that asterisks denote significant differences. However, there are no asterisks in Figure 3. The same issue applies to Table 2.

Response: since there were no significant differences noted in Figure 3, we have removed the memo regarding asterisks from Figure 3. The note from Table 2 has also been removed.

7. The bar graphs, so called the "dynamite plots", in Figures 2 and 3 are less than ideal. Given the small N, parallel strip plots could be used - with a dot for each subject so that the distribution of the values can be recognized.

Response: The use of parallel strip plots would be difficult to demonstrate the levels of variability (error bars) from our analysis which are essential to the ANOVA tests used.

Reviewer 5. ID number: 01805500

Response: thank you for reviewing our work.

1. Some typos should be amended, i.e., comparted.

Response: we have carefully double checked our document for typos, may were captured by another reviewer which we have remedied.

2. Some pieces of information about the app in iPod are advisable.

Response: we have included more information regarding how the iPod acceleration data were converted to angles: ...using the second integral function and Pythagorean theorem, which has been validated and described in the literature for accelerometers when estimating humeral elevation angles [3]. (Line 210). Additionally, we have a citation describing the validation of the iPod and app that we used. [6]

3. A limitation to study about the small sample size of diabetics should be emphasized taking into account the high prevalence of T2DM and its neuropathy.

Response: We have addressed the small sample size as a limitation when interpreting our results. (Line 308)

Cited work for reviewer feedback:

1. **Chantelau EA.** Nociception at the diabetic foot, an uncharted territory. *World J Diabetes.* 2015;6(3):391-402.
2. **Lautenbacher S, Kunz M, Strate P, Nielsen J, Arendt-Nielsen L.** Age effects on pain thresholds, temporal summation and spatial summation of heat and pressure pain. *Pain.* 2005;115(3):410-8.
3. **Amasay T ZK, Kincl L, Hess J, Karduna A.** Validation of tri-axial accelerometer for the calculation of elevation angles. *International Journal of Industrial Ergonomics.* 2009;39:783-9.
4. **Liu MW, Hsu WC, Lu TW, Chen HL, Liu HC.** Patients with type II diabetes mellitus display reduced toe-obstacle clearance with altered gait patterns during obstacle-crossing. *Gait Posture.* 2010;31(1):93-9.
5. **Ledin T, Odkvist LM, Vrethem M, Moller C.** Dynamic posturography in assessment of polyneuropathic disease. *J Vestib Res.* 1990;1(2):123-8.
6. **Edwards E. LY, King J., Karduna K.** Joint position sense -There's an app for that. *Journal of Biomechanics.* 2016;7(33).