Author's response to reviews

Title: Mechanosensitivity during lower extremity neurodynamic testing is diminished in individuals with Type 2 Diabetes Mellitus and peripheral neuropathy: a cross sectional study

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Author's response to reviews: see over
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BMC Neurology
Editorial Board

Dear Editorial Board,

Please find enclosed our revised manuscript, "Mechanosensitivity during lower extremity neurodynamic testing is diminished in individuals with Type 2 Diabetes Mellitus and peripheral neuropathy: a cross sectional study" for the BMC Neurology journal. We appreciate the time and effort each reviewer and the editorial board has put into the improvement of this manuscript. We have addressed both reviewers’ comments and have included a point-by-point response below as instructed. Thank you for considering this revised manuscript for publication in the BMC Neurology journal.

Sincerely,

Benjamin S. Boyd, PT, DPTSc
Reviewer 1 comments:

The authors mentioned these findings were compared with healthy controls.

Those results need to be presented.

- The following sentences were modified to specify the source of the comparison group:
  - Page 18, 2nd paragraph: “A comparison to findings in healthy controls in a previous study demonstrates that our sample of people with T2DM had reduced general flexibility during SLR.[12]”
  - Page 20, last paragraph: “Lastly, in contrast to healthy controls, people with T2DM reported symptoms on the dorsal and plantar surfaces of bilateral feet in the START position (16-30%).[12]”

The discussion and conclusion sections are very long. It potentially can be summarized.

- The following modifications were modified to reduce the length of these sections:
  - Page 17, second and third paragraphs were combined and shortened to: “The magnitude of impact that the addition of ankle dorsiflexion has on hip flexion range of motion during SLR testing may reflect the state of mechanosensitivity of the neural structures being tested. Mechanosensitivity is a normal protective response to the stresses applied to nerves during limb movement. Thus, it is reasonable to expect hip flexion range of motion to be reduced when a SLR is performed with the ankle in a position of dorsiflexion. The addition of dorsiflexion has been shown to induce longitudinal gliding and increased strain in the lower extremity posterior neural structures, providing a “sensitized” version of the SLR.[32-34] In previous studies of healthy individuals, the addition of
dorsiflexion to the SLR resulted in between 5.5° and 10.1° reduction in SLR angle depending on the test endpoint.[12, 16] In people with T2DM we found that the addition of ankle dorsiflexion caused a normal 4° reduction in hip flexion range of motion when tested to P1, but only a 5° reduction when tested to P2. This represents a statistically significant 50% reduction in the effect of dorsiflexion on hip flexion range of motion in people with T2DM compared to people without T2DM when tested to P2 (p=0.039).[12] Moreover, in individuals with T2DM and severe DSP the addition of dorsiflexion did not alter hip flexion range of motion at P1 or P2. This represents statistically significant 90% reductions in the effect of dorsiflexion on hip flexion in people with T2DM with severe DSP when tested to P2 compared to people without T2DM (p=0.001).[12] The diminished response to the “sensitized” SLR in people with T2DM and severe DSP may reflect a reduced protective response to neural loading during limb movements due to a diminished mechanosensitivity of the lower extremity nervous system.”

- Page 18, 2nd paragraph: “These findings are in agreement with studies that have documented reduced range of motion in both ankle dorsiflexion, plantar flexion, inversion and eversion and in and hip joints flexion and extension in people with T2DM compared to healthy individuals without DM.[35-37]”

- Page 19, 2nd paragraph: “One possible explanation for the activation of the tibialis anterior is related to the START position for this DF/SLR test which included fixation in a customized brace at 0° ankle dorsiflexion and then passive manual positioning in end of range knee extension.”
Page 21, 2nd paragraph: “It is also important to note that the Michigan Neuropathy Screening Instrument clinical examination includes several of the recommended tests in this recent cluster analysis for identification of pain subtypes.”

Page 22, last paragraph: “Despite strict standardized protocols in this research study, there is potential error in manually controlling hip abduction/adduction using visual inspection during the hip flexion of the SLR. Precisely controlled standardized procedures for clinical neurodynamic testing, as were utilized in this study, are warranted to minimize tester induced variability.”

Page 24, last paragraph: “Neurodynamic testing is usually utilized to examine for focal nerve changes in mechanosensitivity due to mononeuropathies.”

Tables 1 and 2 can merge.

- Tables 1 and 2 were combined and table numbering throughout the manuscript were updated to reflect this change.

It seems the selected group of patients had relatively high BMI considering the duration of diabetes which was just 7 years. Does physical activity during life effect mechanosensitivity? Probably a group of patients with lower BMI and a control group are needed for comparison.

- The authors agree that BMI may be a confounding variable that has influenced the outcome. This is addressed in the discussion section as a limitation and would be an excellent follow up study for further investigation. Based on the following suggestion of
the associate editor, no additional action has been taken at this time; “Further work in patients with lower BMI is not necessary.”

*The average VPT in this group of patients was 30 volts which is high. This can be as a limitation of study.*

- The authors feel that while the mean was 30 volts for VPT, the standard deviation was 15 volts, which indicates that there was a great deal of variability amongst the participants in this study. This is actually ideal when trying to examine a phenomenon that is likely correlated to the severity of sensory loss. The 30 volt average is very close to the middle of the scale for the VPT measurement (0-50 volts) where normal is considered to be between 0-15 volts. Contrary to the reviewer comments, we feel that our sample represents the whole spectrum of individuals with sensory deficits, from mild to severe and is therefore more generalizable.

**Reviewer 2 Comments:**

**Major Compulsory Revisions**

1. Page 5: methods section- Was any previous history obtained of intra-vertebral disc disease. If so was this an exclusion criterion.

- Disc disease was not part of the exclusion criteria but a history of sciatica was part of the exclusion criteria. The following addition was made to the methods section to make this clearer:
  - Page 5, 2nd paragraph: “Exclusion criteria included low back or leg pain lasting >3 consecutive days in the past 6 months, complex regional pain syndrome, lumbar
spine surgeries, chemical dependence or alcohol abuse, a history of sciatica or trauma to the nerves of the lower extremity, or chemotherapy in the past year.”

2. There is a relatively small sample size- however this limitation is discussed. What was the rational behind the sample size that was chosen.

- The rationale for the sample size is based on the power calculation discussed below.

3. Was a sample size analysis undertaken? Please document if this was undertaken.

- The following discussion of the sample size and power calculations were added to address this point:
  - Page 5, 2nd paragraph: “Sample size was based on power calculations for a multiple linear regression model with 5 predictor variables, alpha = 0.05, power of 0.8, and an effect size = 0.35.”

4. Vitamin B12 deficiency is relatively common in diabetic populations. This may be potential confounder.

- The following additions were made to the discussion section to address this comment:
  - Page 23, 1st paragraph: “We did not measure nutritional deficits in our study such as vitamin B12 deficiencies which may be a potential confounding variable. Future studies should investigate neurodynamic testing in stratified BMI groups, BMI matched groups and vitamin B12 deficiencies to further explore the effects of body mass and nutritional status on mechanosensitivity of peripheral nerves.
5. There is no documentation that Good Clinical Practice guidelines or their there equivalents were adhered to.

- The following addition was made to the methods section:
  - Page 5, 2nd paragraph: “Institutional review boards at UCSF, SFSU and the General Clinical Research Center’s Advisory Committee at UCSF approved the study and assured compliance with the ethical treatment of human subjects.”

**Minor Essential Revisions**

1. Review references and format

- The references were reviewed and alterations were made to correct the format.
  - The issue number was removed from all journal citations.
  - Citations # 11, 14 and 31 were corrected to appropriate format.

**Discretionary Revisions**

1. Is there any significant difference in the HbA1c with the different groups classified by VPT? Suboptimal glycaemic control may have an acute impact on c-fibres.

- There was no significant difference in HbA1c between the different groups classified by VPT (p=0.331). This finding was omitted from the manuscript to reduce the length of the discussion section.
2. It is probably important to detail in the abstract that a single examiner preformed all examinations.

- Since this is not a reliability/validity study, the authors feel it is sufficient to detail this in the methods section. The following statement addresses this point:
  - Page 5, last paragraph: “One examiner (BB) performed all physical examinations.”