Author’s response to reviews

Title: The Diagnostic Value of Ultrasonography in Carpal Tunnel Syndrome: A Comparison between Diabetic and Non-Diabetic Patients

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Author’s response to reviews: see over
Dear Professor Deesha Majithia:

Thanks for reviewer’s accept of our response. We have made further revisions for reviewer 4’s comments. The revised manuscript entitled as “MS: 1989849118700162 The Diagnostic Value of Ultrasonography in Carpal Tunnel Syndrome: A Comparison between Diabetic and Non-Diabetic Patients”. All of the changes have been underlined with red color to facilitate your review.

Below are our point-by-point responses to the reviewer 4’s comments.

**Reviewer 4**

**major comments:**

1. only the aim of the study is to describe the comparison between diabetic and non-diabetic patients only in the discussion section I could find one sentence at page 11 that “there is no difference of CSA of the median nerve at the wrist crease or tunnel inlet between DM and non-DM CTS patients.” I think that this is the main conclusion but this is not emphasized in the manuscript or even mentioned in the abstract.

**Answer:** We emphasized this result in the abstract. We further discussed the difference in ultrasound findings between DM and non-DM CTS in the Discussion section as suggested, as follows:

“Several studies have explained the phenomenon of local enlargement of the median nerve in CTS, including nerve constriction at the site of the entrapment with proximal swelling [18], and the presence of Renaut bodies [19]. The biological response to compression seems to be a cascade composed of endoneurial edema, demyelination, inflammation, distal axonal degeneration,
fibrosis, growth of new axons, re-myelination, and thickening of the perineurium and endothelium [20-21]. A recent study has demonstrated focal enlargement of median nerve CSAs in diabetic patients, especially at the level of the inlet. Other additional factors may contribute to the phenomenon, including a reduction in myelinated nerve fibers and capillary density that may predispose DM patients to develop CTS [22], and the polyol pathway, glycation and pro-inflammatory reactions that are known to contribute to diabetic peripheral nerve injuries [23]. The reasons why CSAs between DM and non-DM groups are not significant in the present study may be that the biological response to compression is a more important contributing factor than diabetic peripheral nerve injuries.”

2. The 79 asymptomatic hands of 80 non-DM patients and 21 asymptomatic hands of 40 DM patients were taken as controls. I wonder whether this is correct. Preferably the authors should use hands of healthy controls and not asymptomatic hands. It is known that asymptomatic hands have a larger CSA in comparison to healthy controls and looking at the data this seems also the case in this study. Using the values of the healthy controls will probably change the results and preferable symptomatic hands of DM and non-DM, asymptomatic hands of DM and non-DM and CSA of the median nerve of healthy controls should be compared.

**Answer:** We agree with your comments that the findings in the unaffected hands of non-diabetic CTS patients are not independent observations. In the revised manuscript, we also added 20 healthy volunteers in our study as normal control. The details are described in the Patient and Methods section, as follows: “Twenty healthy volunteers (40 hands) who had no clinical or NCS evidence of CTS and no other neurologic disorders were enrolled as normal control (‘C-hands’).”

The data of C-hands from the 20 health control were re-calculated and presented in Tables 1 and 2. Part of the Results section was also re-written according to the statistical results.

3. It is known that DM patients can have clinical CTS with abnormal electrodiagnostic findings, but also clinically asymptomatic electrodiagnostic CTS can occur. How did the authors handle with this group and what were the sonographic findings?

**Answer:** In order to clarify the sonography findings of CTS, only patients fulfill both the clinical and NCS criteria of CTS were enrolled in our study. We excluded other neurologic disorders, including radiculopathy, musculoskeletal related
disorders, polyneuropathy and plexopathy, that may mimic the CTS in both diabetic and non-diabetic groups.

4. Assessing the predictive factors: "Among the parameters, CSA of the median nerve at the wrist crease is a predictive factor for CTS in diabetic patients". I do not think that this is methodologically correctly done. Sonography is a diagnostic test!

**Answer:** We delete the sentence "Among the parameters, CSA of the median nerve at the wrist crease is a predictive factor for CTS in diabetic patients" as reviewer’s concerned. We re-wrote the Discussion section of Abstract as follow “The CSA of the median nerve at the outlet and wrist crease are significantly larger in CTS hands in both DM and non-DM patients compared to normal hands. The CSA of the median nerve by ultrasonography may be a diagnostic tool for evaluating CTS in DM and non-DM patients.”

5. I am not sure whether the section of comparing ultrasound with electrodiagnostic finding is useful. The authors mention that” the CSA positively correlated with distal motor latency of median CMAP, distal sensory latency of median SNAP, and latency of median F wave, but negatively correlated with amplitude of median CMAP, amplitude of median SNAP, and sensory NCV of the median nerve”. These data are already well known in the literature.

**Answer:** The consensus of electrodiagnostic study for CTS is not specific for DM patients. The diagnostic criteria are dependent on the distal latency and NCV of the median nerve as the constellation of axonal degeneration is manifested in reduced CMAP amplitude or underestimated SNAP. Although previous literature [ref. 4 and 6] showed the relationship of ultrasound and electrodiagnostic findings, they focus on the non-DM CTS cases. Our participants included DM and non-DM cases, the results further demonstrated the correlation are also exist in DM-CTS patients. As that, the combination of NCS and US may be able to estimate CTS with diabetes mellitus more accurately.

**minor comments:**

1. Abstract and text in manuscript: the use of D in D-hands and the CSA_D is confusing.

**Answer:** We changed D-hands as DM-hands to avoid confusion.

2. The cut off of CSA_W ≥12.5 mm2 is not useful, this should be 13 (because the result will present as either 12 of 13 mm2) and this should be changed in the text
also for the other cut off values.

**Answer:** As reviewer’s comment, we change the cut off of CSA_W \( \geq 13 \text{ mm}^2 \) in the text. We also changed the other cut off values as integer.

3. abstract methods: sentence: "Data were analyzed to determine statistical significance" can be left out.

**Answer:** As reviewer’s commend, we left out the sentence "Data were analyzed to determine statistical significance".

4. in the abstract and discussion section it is written that: any 1 mm2 increase in CSA_W increased the rate of CTS by 28%. I cannot find how the authors came to this result in the result section.

**Answer:** In the result sub-section Predictive factors for CTS in DM patients, we describe that “After analysis, only CSA_W (OR 1.21, 95% CI 1.07-1.38; p=0.003) was independently associated with CTS in DM patients, and any 1 mm2 increase in CSA_W increased the predictive rate of CTS by 28%.”

5. In the methods section it is written that the electrophysiologic test results considered supportive of CTS were the following: 1) median nerve distal sensory latency <3.4 ms; 2) median nerve distal motor latency over the thenar <4.2 ms [12]; and 3) difference between median and ulnar nerve distal sensory latencies <0.4 ms [10]. < is probably a typing error, this should be >

**Answer:** Our apologies. This is our typing mistake. We corrected the NCS criteria for CTS.

6. page 7: FR_D , this abbreviation is used without explanation (only further on and at the abstract).

**Answer:** In the Patient and Methods sub-section ultrasonography assessment, we defined the abbreviation of FR as follow:

“The CSA and flattening ratio (FR, defined as the ratio of the major axis of the median nerve to its minor axis)”.

7. It should be circumference instead of circumfluence of the wrist

**Answer:** This is our typing error, we corrected it.

8. Table 2 and 3. P-values relate to? (which values are being compared)

**Answer:** We identified the statistic analysis of p-value in the annotation of Table 2 and 3.
9. Table 3 and 4: should be electrodiagnostic testing

   **Answer:** As reviewer’s suggestion, we changed to electrodiagnostic testing.

10. Please define CSA at inlet of the carpal tunnel. What is the difference with measurement at the wrist crease?

    **Answer:** We added the definition of both inlet and outlet in the Patient and Methods section as suggested. Further, the abbreviation “CSA_W” and “CSA_D” indicate the inlet and outlet, respectively. The revised text reads:

    “The “tunnel inlet” referred to the level immediately deep to the proximal edge of the flexor retinaculum. The “tunnel outlet” referred to the level immediately deep to the distal edge of the flexor retinaculum.”