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:

Thank you for your valuable suggestions. We have made substantial revisions to improve our original manuscript entitled “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 and in red text in the revised manuscript to facilitate your review.

Below are our point-by-point responses to the reviewers’ comments.

**Reviewer 1**

1. I recommend more discussion about the difference in ultrasonographic findings between non-diabetic CTS and diabetic CTS in the conclusions section of abstract and the discussion.

   **Answer:** We discussed the difference in ultrasound findings between DM and non-DM CTS in the Conclusions section of the Abstract and 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. In page 7, the authors described “the carpal tunnel inlet of the forearm”. In general, carpal tunnel inlet is anatomically located in wrist crease. Therefore, the authors need to describe the exact anatomical location where the CSA and flattening ratio were measured or to add references.

**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.”

3. In page 11, the authors need to more extensively discuss the result that there is no difference in cross sectional area between DM-CTS and non-DM CTS. A previous report (J Ultrasound Med 2009; 28:727-734) shows that cross sectional area of median nerve is increased in diabetic polyneuropathy when compared with normal. So, to explain the reason why there is no difference between DM-CTS and non-DM CTS is important. I also recommend the reference will be added.

**Answer:** We addressed this issue in the Discussion section and added the reference (J Ultrasound Med 2009; 28:727-734) as suggested.

4. I cannot understand the following sentence; “According to ROC analysis, the cut-off value of CSA at the wrist crease for CTS confirmation is more than 12.5mm2 in both DM and non-DM CTS patients. The cause of this variability may be the differences in study design, race, grading severity, or measurement techniques. Nonetheless, patient with DM may not contribute to the CSA of the median nerve for CTS.” Please, re-describe the sentence and add the more detail discussion considering the above-described paper.

**Answer:** We re-wrote the sentences in Discussion section, as follows:

“The cause of this variability may be the differences in study design, race, grading severity, and measurement techniques [7, 25-29]. However, most of these studies exclude DM patients to eliminate possible confounding factors of diabetic
peripheral neuropathy (DPN) in diagnosing CTS. A previous study has demonstrated that the CSA of the median nerve in the carpal tunnel of DPN patients is greater than that of non-DPN patients [30]. However, their study did not exclude asymptomatic CTS in diabetic patients. The present study excluded diabetic patients with DPN (e.g. polyneuropathy or mononeuropathy multiplex) by NCS and clinical presentations in order to focus on the entrapment effects of CTS. The cut-off value of CSA at the wrist crease for CTS confirmation is more than 12.5mm$^2$ in both DM and non-DM CTS patients. There is no statistical difference in the median CSA between DM CTS and idiopathic CTS patients in this study. The results suggest that the entrapment factor may drown out other factors like metabolic and vascular causes of median nerve enlargement in CTS.”

5. In page 12, I guess nerve conduction study is more appropriate than electromyography (EMG).

**Answer:** We changed “electromyography (EMG)” into “nerve conduction study (NCS)” as suggested.

**Reviewer 2**

1. It is not clear how the participants were recruited. Consecutively? At a department of neurology? At a lab for neurophysiology?

**Answer:** The participants were recruited in the out-patient clinic of the Department of Neurology.

2. Were the US and NCS / EMG examiners masked for the status of the patient and his hand, and for each other’s test results?

**Answer:** Both the examiners and interpreters were blind to the status of the patients. For clarity, we added the following sentences in Patients and Method section:

“A neurologist (Dr. Cheng-Hsien Lu) experienced in nerve conduction study (NCS) interpretation and another neurologist (Dr. Shu-Fang Chen) experienced in ultrasound (US) examinations evaluated the study participants. Both were blind to the status of the patients. The musculoskeletal US and NCS examinations were done by standard laboratory methods [14-15].”

3. There are no relevant clinical data: Muscle weakness? MRC scores? Sensory loss? This is important to know the spectrum of patients examined.

**Answer:** In this study, we excluded patients with polyneuropathy. The MRC
scores in all of our patients were equal to five and no glove sticking distributions of sensory loss were found.

4. I have a major problem with the control group (C hands). These are the unaffected hands of CTS patients without DM. However, the findings in the unaffected hands of these patients are not independent observations. In clinical practice we need to discern CTS from other disorders (radiculopathy, musculoskeletal related disorders, plexopathy etc). A separate control group of DM patients with these disorders would have been more appropriate. In my opinion the methodology that the authors have chosen unfortunately undermines the validity of the diagnostic accuracy measured by ROC analysis: they have shown that US can discern CTS in DM from the unaffected hand of a CTS patient without DM, and that is not important in clinical practice.

Answer: We agree with your comments that the findings in the unaffected hands of non-diabetic CTS patients are not independent observations. In our study, we excluded other neurologic disorders (e.g. radiculopathy, musculoskeletal related disorders, polyneuropathy and plexopathy, etc) in both diabetic and non-diabetic CTS groups. Your concern is quite valid and after much discussion, 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.

5. Patients with clinical and electrophysiological signs of a polyneuropathy were excluded. From the text, I am not convinced that all patients were tested for polyneuropathy. Were all patients clinically screened for polyneuropathy? This may be important.

Answer: We clarified the exclusion criteria further, as follows:

“Diabetic patients with clinical and electrophysiologic diagnosis of diabetic polyneuropathy were excluded. Clinical diagnosis was based on the recommendations of the American Academy of Electrodiagnostic Medicine (AAEM) [13]. An electrodiagnostic abnormality plus at least one sign and one symptom confirmed the presence of polyneuropathy. The neuropathic symptoms included sensory symptoms (e.g., distal numbness, burning, prickling paresthesia,
dysesthesia, and allodynia) and/or motor symptoms (i.e., decreased sensibility on the distal lower extremity, distal muscle weakness or atrophy). Neuropathic signs included absent or decreased ankle deep tendon reflex, decreased or absent distal sensory capacity, distal weakness, and muscle atrophy. Abnormal electrodiagnostic studies included a sural or peroneal and one median or ulnar nerve dysfunction. However, entrapment lesions were excluded. Patients with prior surgery for CTS, and those with gout, rheumatoid arthritis, or abnormal thyroid function related to peripheral neuropathy were also excluded.”

6. The authors state that there are no exact diagnostic ultrasonographic criteria for CTS. However, most investigators readily agree and recommend a CSA measurement at the pisiform bone, a valid and reliable test. **Answer:** We modified the sentence in the Introduction section, as follows: “Most investigators agree that CSA measurement of the median nerve at the pisiform bone is a valid and reliable test for diagnosing CTS [8]. However, the standard criteria of CTS by ultrasonography are not well established, especially in diabetic patients suspected of CTS.”

7. What was the rationale for the study? Why is it important to test the validity of US in the diagnosis of CTS in patients with DM without polyneuropathy (an exclusion criterium for this study)? The answer is given in the discussion but it might be stated more clearly in the introduction. **Answer:** We re-wrote the rationale and aim of this study in the Introduction, as follows: “Although diabetes mellitus (DM) is a risk factor for CTS [9], reports about median nerve CSA measurements between CTS patients with and without DM are scant. The aim of this study was to evaluate whether or not ultrasononographic findings of the median nerve is different between DM and non-DM CTS patients.”

8. The clinical diagnostic criteria for CTS include Tinel’s and Phalen’s tests. However, these tests are not accurate. Lancet 1990;335:393-5. Clin Neurol. Neurosurg 2001;103:178-83. JAMA 2000;283:3110-7. **Answer:** We agree with reviewer that provocative tests (Tinel’s and Phalen’s tests) are not accurate for CTS diagnosis. The statement of the American Academy of Neurology [reference 11] may be the most cited paper for CTS diagnosis. In their criteria, Tinel’s and Phalen’s tests are not indispensable criteria to be fulfilled, but just two of the 3 minor criteria. Furthermore, the CTS
patients enrolled in our study needed to fulfill the clinical and NCS criteria.

9. NCS criteria for CTS: three tests are mentioned here. The “<” signs probably have to be replaced by “>“ signs. Were all three criteria required or just one or two?
   **Answer:** Our apologies. This is our typing mistake. We corrected the NCS criteria for CTS.

10. I recommend meticulous correction of grammar.
    **Answer:** A native English speaker has proofread and revised the language and grammar of the manuscript.

11. EMG (myography) is often used as a synonim for Nerve Conduction Studies which may lead to confusion by some readers.
    **Answer:** We changed EMG to Nerve Conduction Studies (NCS).

12. A major problem of diagnosing CTS in DM is that the electrophysiologic abnormalities “drown” of “dilute” in a background polyneuropathy. It would be nice to have a study that investigates the role of US in these cases. However, the major problem is that there is no reliable reference test.
    **Answer:** The reviewer’s concern is the pivotal point of clinical practice in diagnosing CTS in DM. Although there is no reliable reference test in these patients, we used both clinical and NCS criteria to fulfill the CTS diagnosis. In this study, we also excluded diabetic patients with peripheral neuropathy by NCS and clinical presentations to focus on the entrapment effects of CTS. We hope to evaluate the value of ultrasound findings of the median nerve between diabetic CTS and idiopathic CTS patients.

**Reviewer 3**

1. While defining the patients and methods of the study, the inclusion and exclusion criteria of both study and control group should be better identified. What is the number of patients excluded from study for each criterion (e.g., Diabetic neuropathy)?
   **Answer:** We re-identified our inclusion and exclusion criteria very clearly in the Patients and Methods section. We enrolled 20 healthy volunteers as normal control as suggested. The 67 diabetic patients with clinical suspicion of CTS and the 40 non-DM patients (after 27 with diabetic neuropathy were excluded) were consecutively enrolled.
2. Intra- and inter-observer (if US had been performed by >1 physician) agreement is required for standard evaluation of musculoskeletal US.

Answer: To clarify, our NCS laboratory and musculoskeletal US had both intra- and inter-observer qualification. We added a paragraph in section of Patients and Methods, as follows:

“A neurologist (Dr. Cheng-Hsien Lu) experienced in nerve conduction study (NCS) interpretation and another neurologist (Dr. Shu-Fang Chen) experienced in ultrasound (US) examinations evaluated the study participants. Both were blind to the status of the patients. The musculoskeletal US and NCS examinations were done by standard laboratory methods [14-15].”

3. Symptom duration of CTS is important for evaluating chronic changes of median nerve. If it is possible, this data could be included. Furthermore, an analysis between symptom duration and sonographic findings might give interesting data.

Answer: Since CTS symptoms may have an insidious onset, the association between symptom duration and ultrasound findings is an interesting finding. It may be difficult to record the duration of symptom and evaluate the association with ultrasound findings. We add the following sentences in the Discussion section as part of the study limitations:

“Finally, the association between symptom duration and US findings is an interesting finding. However, symptoms in most CTS patients here have an insidious onset, the exact duration of symptoms can not be determined for correlation with the severity of US data.”

4. While discussing of effects of diabetes mellitus on median nerve, giving more data about glycemic state of the patients’ strengths the subject. (disease duration of diabetes, medications used for diabetes)

Answer: We provided the HbA1C data and the duration of DM in our diabetic patients as suggested. The results were listed in Table 4 and prescribed in the paragraph of correlation among glycemic state of the patients, CSA, and NCS parameters, as follows:

“The HbA1C and duration of DM were not correlated to the CSA of the median nerve.”

Answer: We added the literature in the Discussion section, as follows:
“A previous study has demonstrated that the CSA of the median nerve in the carpal tunnel of DPN patients is greater than that of non-DPN patients [30]. However, their study did not exclude asymptomatic CTS in diabetic patients. The present study excluded diabetic patients with DPN (e.g. polyneuropathy or mononeuropathy multiplex) by NCS and clinical presentations in order to focus on the entrapment effects of CTS. The cut-off value of CSA at the wrist crease for CTS confirmation is more than 12.5mm² in both DM and non-DM CTS patients. There is no statistical difference in the median CSA between DM CTS and idiopathic CTS patients in this study. The results suggest that the entrapment factor may drown out other factors like metabolic and vascular causes of median nerve enlargement in CTS.”

6. Could the authors discuss the possible differences between CTS in diabetes and CTS in other patients?
Answer: We added a paragraph to discuss the possible differences between CTS in diabetes and idiopathic CTS in the Discussion section:
“Previous reports show that increased CSA of the median nerve is the most predictive parameter for non-DM CTS [24]… The results suggest that the entrapment factor may drown out other factors like metabolic and vascular causes of median nerve enlargement in CTS.”

Reviewer 4
1. Major Compulsory Revisions
Answer: We made substantial revisions on this manuscript as based on the reviewer’s comments.

2. Needs some language corrections before being published
Answer: A native English speaker has proofread and polished the language and grammar of the revised manuscript.