Division of Neurology
Dept. of Clinical Neurosciences
Room HMRB 155
3330 Hospital Dr. N.W.
Calgary, Alberta
T2N 4N1
Telephone: (403) 220 - 8831
Fax: (403) 283 - 8731

Dear Drs. Donald Bowden and Lu Qi (Editors-in-Chief)
World Journal of Diabetes

February 28, 2013

Please find enclosed the edited manuscript in Word format (Comorbidities_and_DPN Feb 28 2013 World J Diab resubmitted.doc).

**Title:** Association of comorbidities with increasing severity of peripheral neuropathy in diabetes mellitus

**Author:** Shafina Sachedina and Cory Toth

**Name of Journal:** *World Journal of Diabetes*

**ESPS Manuscript NO:** 1837

The manuscript has been improved according to the suggestions of reviewers and we are appreciative of their suggestions and the time taken to review our paper. In response to this, we have performed the following:

1 Format of the manuscript has been updated as per journal recommendations.

2 Revision has been made according to the suggestions of the reviewer as indicated below. Our answers or responses are provided in italics, with allusion made to changes made to the text of the manuscript where performed.

Thank you again for publishing our manuscript in the *World Journal of Diabetes*.

We look forward to your review of our resubmitted manuscript and thank you for your time and thoughts.

Yours sincerely,

Cory Toth, MD, FRCPC
Associate Professor
Division of Neurology
Department of Clinical Neurosciences
University of Calgary and the Hotchkiss Brain Institute

Response to Reviewers

Reviewer 00506304
Sachedina and Toth determined whether comorbidities, such as dyslipidemia, alcoholism or hypertension, increased the severity of peripheral neuropathy (PN) in patients with type 1 or 2 DM (~300 volunteers). PN was assessed by the Toronto Clinical Scoring System (TCSS), the Utah Early Neuropathy Scale (UENS), and electromyography. They found that lipid disorder was associated with greater PN severity in both type 1 and type 2 DM, while cobalamin deficiency was associated with greater PN severity only in type 2 DM. Some other comorbidities, such as alcoholism, may aggravate PN as evaluated by TCSS. In general, this study is well-performed and provides a better understanding of how comorbidities are associated with PN.

Specific comments 1. Some medications, e.g., sedatives, analgesics, and gabapentin, might interfere with electrophysiological assessment of PN. Have the author ever tried excluding the patients who used these drugs from the analysis? Otherwise, this limitation should be discussed explicitly.

*We did not exclude patients on the basis of medication use - we have included this as a limitation in the Discussion.*

2. Is there any correlation between lipid profile (i.e., the levels of MMA, TG, cholesterol, LDL, or HDL) and plasma glucose (or HbA1C)?

*We performed a post-hoc assessment using linear regression analysis. There were no determined associations between any of these factors with HbA1C levels. This has now been described in the Methods and the Results.*

3. Please check the normal range of red blood cell counts (it should be 10^12/L).

*The reviewer is correct - we only had E12/L listed, and now have corrected this to read as 10E12/L for red blood cell normative intervals.*

Reviewer 00506263
The paper describes that the presence of a lipid disorder is associated with greater peripheral neuropathy severity in patients with type 1 and type 2 diabetes, in addition a cobalamin deficiency is associated with greater peripheral neuropathy severity in patients with type 2 diabetes, but not type 1 diabetes. These results conclude that the presence of specific comorbidities in patients with Type 1 diabetes or type 2 diabetes corresponds with greater severity of peripheral neuropathy. These finding are interesting, however there is some point that should be considered.
Specific comments The present manuscript only show the plasma level of HbA1c, author should show another baseline characteristics such as CBC, lipid levels, fasting glucose and … It would be better to described it as additional new table including normal ranges.

Page 2, line 2; Author should show abbreviation for “PN”.

*The reviewer is correct - peripheral neuropathy has been provided in the first line of the abstract.*

Page 12, line 10; "[6][6][6]….." it must be a misspell.

*This Endnote-induced error has been corrected.*

Fig. 2B and 2D; solid lines and symbols "*" must be misled us, and author should modify them.

*We have updated both Figure 1 and Figure 2 with separate symbols and lines to demonstrate significant associations.*

Reviewer 00506381
Abstract: 1. The Aim states that this study endeavored to "..determine other comorbid etiologies for PN..." Given the methods, I feel that this statement is misleading.

*We have updated the Abstract AIM and METHODS to improve the message regarding the aim of our study.*

2. Recommend defining "PN" upon first use.

*The reviewer is correct - peripheral neuropathy has been provided in the first line of the abstract.*

Introduction 1. Recommend moving some material from the discussion to the inroduction to set the stage for why the study was conducted (i.e., what are the holes in the literature/knowledge?).

*We have increased the Introduction content to include greater background using concepts from the portions of the second and third paragraphs of the Discussion.*

2. On page 5: "We designed this prospective study to confirm our hypotheses..." This is a concerning statement that implies a lack of objectivity in the conduction of the study.

*We have modified this sentence to state that we are examining our hypotheses.*

Materials and Methods: 1. In the "Subject Recruitment" section recommend stating specifically that a predetermined N was not selected.

*We have added text to mention that no sample size calculation or predetermined n value was set for this study.*

2. Recommend specifically covering all inclusion and exclusion criteria together (the exclusion criteria are spread throughout the manuscript).

*Our inclusion and exclusion criteria were quite simple:*
*Inclusion: 1) provided informed written consent*
*2) established diagnosis of pre-existing type 1 or 2 diabetes based upon laboratory testing (based on Canadian Diabetes Association guidelines).*
*Exclusion:*
1) *Presence of impaired fasting glucose or impaired glucose tolerance*
2) *Absence of discernible PN or with questionable PN*

*We have reformatted the text within the Subject Recruitment portion of the Methods to better represent these inclusion and exclusion criteria.*

3. In the "Clinical Assessment of Peripheral Neuropathy" section, recommend stating here that the clinical examiner was aware of the presence of comorbidities during the evaluation. This was stated in the limitations, but we feel it is important to note in the methods.

4. For "laboratory assessment of peripheral neuropathy" please consider including labs and normal ranges in a table - this section is cumbersome to the reader.

*This has now been performed with creation of a new table.*

5. When abnormal tests were repeated, were they done so with the same blood sample or a new draw? Recommend specifying.

*New blood samples were obtained in each case – this has been added to the Methods.*

6. General comment: The paper jumps between "comorbidities" and "comorbidities known to contribute to PN" - Recommend defining what was used in the study within the methods. Did the authors consider using a validated comorbidity burden tool?

*We have modified the text to remain consistent with statement of comorbidities only.*

*We did not use a validated comorbidity burden tool – we have provided this as a limitation of the study in the Discussion section.*

Results: 1. Page 14: "While these associations are not necessarily causative, they suggest that greater attention should be afforded to potentially correctable comorbid...." Were these cases followed in the present study? The reader is left wondering if any cases in this study were, in fact, correctable (i.e., B12 deficiency etc.). Any follow up data?

*Patient management was performed in cases of potentially treatable comorbidities, but we do not have any data to present for follow-up of time which will require several years of observation. We have provided a comment in the Discussion regarding ongoing treatment in these patient cohorts.*

2. Could more data be included related to individuals with cobalamin-deficiency and metformin use?

*We have provided an additional post-hoc linear regression analysis performed to examine association between neuropathy severity and MMA elevation or cobalamin deficiency. As well, we have provided reference to our prior work examining the relationship between metformin and cobalamin deficiency in patients with type 2 diabetes.*

3. Were any correlations made with glycemic control that could be discussed in the discussion/conclusions?

*We performed a post-hoc assessment using linear regression analysis. There were no determined associations between any of these factors with HbA1C levels. This has now been described in the Methods and the Results.*