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Name of Journal: *World Journal of Diabetes*

ESPS Manuscript NO: 25002

Manuscript Type: Review

Reply letter to
Scientific editor: Shui Qiu
World Journal of diabetes

Thanks for completing a very efficient and constructive review on our proposed Manuscript 25002, "Assessment of the cardiovascular and gastrointestinal autonomic complications of diabetes".

We are happy to have the possibility of resubmitting, and have answered the highly relevant questions raised by the reviewers below, in a point-to-point manner.

Reviewer nr 01919991

The manuscript by Brock et.al., reviews the use several approaches in the diagnosis and monitoring of diabetic neuropathy and points some putative biomarkers which could be useful in the management of neuropathic complications of diabetes. In general term the manuscript is well written and follows a logical projection. There is lots of information and it would be beneficial to the general audience to have this information summarized on a final table.

Our answer:

We thank the reviewer for this constructive comment. We have actually thoroughly discussed whether a summarizing table will provide the reader with a better overview or not. We believe however, that all protocols are tailored and therefore needs thorough knowledge on assessment limitations. We have already one table covering heart rate variability and one table covering the assessment of GI motility. As biochemical biomarkers are still in their infancy, we feel that it would be more appropriate to avoid the inclusion of such a table until such methods have a proven clinical value as maybe demonstrated in objective clinical trials in the future.

Reviewer 00036318

This is a comprehensive review of the pathogenesis and diagnostic approach of autonomic neuropathy in patients with type 2 diabetes. The review is well-written and useful to the

clinician involved in the management of these patients. I would only recommend a modification of the title so that it more accurately reflects the contents of the review to something like "Assessment of the cardiovascular and gastrointestinal autonomic complications of diabetes".

Our answer:

We thank the reviewer for this constructive comment and have now changed the title to the following: "Assessment of the cardiovascular and gastrointestinal autonomic complications of diabetes"

Reviewer 00506304

In this review article, the authors have reviewed pathophysiology of diabetic autonomic neuropathy, assessment of cardiovascular and gastrointestinal complications in diabetic neuropathy (e.g., heart rate variability analysis and scintigraphic motility analysis, etc.), and related biomarkers. In general, this paper is comprehensive and covers the important topics.

Minor specific comments are as follows. - Please provide a reference for this statement "such impairments in blood flow also result in alterations in Na⁺/K⁺ ATP-ase activity and nitric oxide metabolism, which further contribute to neuronal damage" (Page 8)

Our reply: Encouraged by the reviewer, we have now clarified the text and added two references.

The text now reads: *"In addition, such impairments in blood flow also result in alterations in Na⁺/K⁺ ATP-ase activity and nitric oxide metabolism. Animal studies suggest that altered Na⁺/K⁺ pump function may occur due to C-peptide deficiency, resulting in the shunting of glucose through the polyol pathway, thereby leading to increased levels of sorbitol and alterations of the nerve excitability recovery cycle which further contribute to neuronal damage [15, 16].*

The statement "...hexosamine biosynthesis pathway" is a minor branch of glycolysis, where fructose-6-phosphate is converted to glucosamine-6-phosphate, catalyzed by the rate-limiting enzyme glutamine"; Please check the name of this enzyme (Page 9).

Our reply: We thank the reviewer for this obvious mistake. The name has been corrected to Glutamine:fructose-6-P-amidotransferase.

Regarding the biomarker, tumor necrosis factor-alpha may not be a specific marker for this diabetic complication. It is often produced in many other inflammatory diseases.

Our reply: We certainly agree with the reviewer, and based on their comment we have now rephrased the section.

It now reads: *"Tumour necrosis factor-alpha (TNF-a) is a potent systemic pro-inflammatory cytokine and is a central component of the inflammatory response, in various immune mediated inflammatory diseases. It is a pathophysiological feature of such disorders, such as rheumatoid arthritis, which are characterised by chronic inflammation. TNF-a is produced in Schwann cells and has a role in peripheral nerve regeneration and regulation of apoptosis. Elevated concentrations of TNF-a and heightened disease activity in immune mediated inflammatory disorders is well described, however, more recently a similar association has been reported with neuropathy in diabetes T1DM and T2DM [49]. As such, TNF-a in diabetes may play a role in the pathogenesis*

and development of diabetic neuropathy and therefore could represent a candidate biomarker for the presence, severity and progression of diabetic neuropathy."

Reviewer 00506347

Very good overall review. Important topic. I believe the wording could be better. The sentence structure consists of many long sentences and can be hard to read.

Our reply: thanks very much for the comment. We have now been through the whole manuscript and tried to reword the most complicated sentences, in order to clarify the content and to increase readability. The word count is now 5100.

Reviewer 00674619

This is an interesting and general well assembled paper. The manuscript is very well organized, wrote and the data are well and clear presented. Moreover, the present topic appears timely. 'Biochemical markers of neuroinflammation in diabetes' represent an interesting subject developed very well in this manuscript. The manuscript is state-of-the-art and the presented results are of potential interest for a wide readership regarding the management of patients with diabetes.

There are a few raised points:

1. Along the entire manuscript, it should be corrected errors in spelling by a careful reading of the authors.

Our reply: We have read the manuscript several times now, and agree with the reviewer that there were typos in the text. To the best of our knowledge, these have now been corrected.

2. Also, the authors should pay attention to manuscript format.

Our reply: Thanks for the comment. We believe the manuscript is now formatted according to the journal guidelines.

On behalf of the authors,

Yours sincerely

Christina Brock