Response to reviewers

Reviewer # 02520738.
Authors' answer. We are glad the reviewer enjoyed our manuscript and we are grateful for his appreciation.

Reviewer # 00607642

Major comments: 1. "This review is comprehensive in collecting data published in the literature. Of note, this paper is not a systematic review. The authors may decide with their own judgment whether to include published information. This limitation may create data selection bias in the current review."

Authors answer. We agree with the reviewer that this limitation may create selection bias, as well as in all published articles of this type (minireviews). We also thank the reviewer for acknowledging we conducted a comprehensive search of data published in the literature. Indeed, to limit the intrinsic bias of articles of this type we carefully searched throughout PubMed and tried to avoid a selection bias by including all recent human studies testing CCM for the diagnosis of neuropathies in diabetes, as specified in the introduction. As well we included both positive and negative studies and highlighted both strength and limitations of these studies.
Finally, to make readers aware of this limit, we have now specified in the section "conclusions" that: "*We acknowledge our conclusions may be limited by the fact this manuscript is not a systematic review. However, to limit a possible selection bias, we carefully search throughout the literature for human studies testing IVCCM in people with diabetes and reported both positive and negative results, strength and limitations*".

Minor comments:
1. Introduction: It is not necessary to introduce DM in the first paragraph of the Introduction because readers of this Journal are all familiar with the disease. I suggest the authors to focus on diabetic neuropathy in the Introduction.

Authors answer. We thank the reviewer for his suggestion. We removed from the main text the general introduction about diabetes and focused more on neuropathies.

2. I suggest the authors to add a figure to demonstrate how to perform the in vivo corneal confocal microscopy (CCM).
Authors answer. According to the reviewer suggestion we have now added a figure showing a patient undergoing IVCCM (Figure 1).

3. I suggest the authors to be cautious about using CCM for the diagnosis of autonomic neuropathy. As you mentioned, corneal nerve fibers have only sensitive function but not autonomic function. The CGM at most is a surrogate of autonomic function. However, patients with diabetic autonomic neuropathy (DAN) do not necessarily have peripheral sensorimotor neuropathy, especially those in very early stages of DAN. Patients with abnormal results in cardiovascular autonomic reflex (CVR) tests are probably in a moderate-to-advanced stage of DAN. The association between CGM and DAN-CVR (+), as discussed in this review, cannot cover a full spectrum of patients with DAN. I hope you can move this section to the CGM as research tool section.

Authors' answer. We thank the reviewer for his comment and we agree that CCM is a surrogate marker of autonomic function, as well as current recommended diagnostic tests that only measures

reflex responses that can be biased by other factors such as myocardial ischemia and others. To balance our position as suggested by the reviewer and to acknowledge his comment, we modified the main text replacing the following sentence "*can be a potential easy and non-invasive tool for the clinical diagnosis of autonomic dysfunction*" with "*is a surrogate easy and non-invasive marker of autonomic dysfunction*". Moreover, at the end of the section we specify that "*these promising findings have still to be tested for their usefulness for cardiovascular risk-stratification in larger and homogenous populations*". We also modified the title of the section from "*IVCCM for the diagnosis of autonomic neuropathy*" to "*IVCCM and diabetic autonomic neuropathy*". Finally, as suggested by the reviewer, we have now acknowledged the association between CCM and DAN in the research tool section.

Of note, results published by our and other groups show that the association between CCM and autonomic neuropathy is independent by the presence of peripheral neuropathy and we have now specified this in the text. Finally, in the study published by our group (Maddaloni E et al., *Diabet Med* 2015;**32**:262–6) 72.7% of the case subjects were affected by early stage cardiac autonomic neuropathy, suggesting that the association between CAN and DAN can be eventually extended also to these patients.

Reviewer #02446522

Authors' answer. Our manuscript is not about gestational diabetes