

Dear Dr. Ji,

Thank you very much for considering our manuscript titled “Insulin resistance is associated with subclinical vascular disease in humans” for publication in the World Journal of Diabetes.

Please, let the reviewer know our gratitude for his/her valuable comments in order to improve the article.

Please, kindly find here the modifications that we have made following the reviewer’s suggestions.

Reviewer #1:

1) The organization is not consistent with a review article. The logical organization for topics is: problems that have been resolved; problems that remain; and future research directions in this area of research. The present format of this review article does not include a core tip; description of the literature search; and conclusion.

We have added the following paragraph trying to outline these concepts:

Cardiovascular disease is a major cause of morbidity and mortality particularly in patients with diabetes. Cardiovascular risk in this population group begins decades prior the clinical diagnosis of the disease and is not fully explained by traditional risk factors such as hypercholesterolemia and smoking.

A core tip and conclusion have been added.

2) The English grammar is rough in areas, which can make it difficult to follow the authors’ logic. The authors should consider having their manuscript reviewed by an English consultant.

We have re-read the article and it has been read and edited by two native English speakers

3) For “functional and structural” consider using the terms “physiological and histopathological”.

The term “functional” refers to “function”, either normal or altered while the term “physiological” refers to “normal function”. The term “structural” refers to form or composition while the term “histopathological” implies the use of a microscope. The terms “functional” and/or “structural” are utilized in many articles concerning vascular disease, including those by Cruickshank et al. 2002, McVeigh et al. 1992, Adams et al. 1998, Brooks et al 2001, Lorusso et al. 2003, Iannuzzi et al. 2004 and 2008, Bjarnegard et al. 2009, Peralta, Adeney et al. 2010, Rask-Madsen et al. 2013, Shah et al. 2015, Jourdan et al. 2005, Ji H et al. 2017

We have revised the use of these terms in the manuscript.

4) “Associated to”; are the authors referring to “related to” or “associated with”?

We have revised and corrected as needed these terms in the document.

5) Introduction, paragraph 1: references are needed.

References have been introduced.

6) “II. Insulin resistance is independently associated”; on pages 5-7. This section can be shortened by omitting descriptions of elementary concepts of cardiovascular physiology.

The section has been shortened as indicated.

7) Major concepts should be referenced as they are introduced rather than providing a brief summary of the conclusion. The authors should provide as needed brief descriptions of the weaknesses of these major references.

We are terribly sorry but after reading this comment several times we are unsure about the specific changes required.

8) Having identical subtitles makes it difficult to follow the logical organization of this topic: i.e. page 10 “II.2 Clinical manifestations of insulin resistance” and page 16 “III.2 Clinical manifestations of insulin resistance”.

Subtitles have been modified.

9) Figure 1: This appears to summarize “A simplified proposed mechanism”.

The sentence has been changed

10) Figure 2: This appears to summarize “Pathophysiological vascular changes”.

The sentence has been modified

11) It is not clear how the authors have incorporated Table 1, Table 2, and Table 3 into this review article.

They can be incorporated in other places of the article as well.

Minor Issues: 1) It should be “hypertriglyceridemia”.

Corrected