Cover letter for Point-By-Point response

7th September. 2022

Amin A; Hettiarachchi P; Jovandaric M

P-Reviewer, World Journal of Diabetes

Manuscript NO: 79128

Advances in neovascularization after diabetic ischemia

Authors: Yue Cai, Guang-Yao Zang, Yan Huang, Zhen Sun, Li-Li Zhang, Yong-Jiang Qian, Wei Yuan, Zhong-Qun Wang

The detailed point-by-point responses to the reviewers' comments are listed below.

We take this opportunity to express our gratitude to the editor and reviewers for their constructive and useful remarks. We hope that our responses are suitable and intriguing for further consideration in World Journal of Diabetes.

Sincerely yours,

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Point-by-point responses to the reviewers' comments.

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Major revision

Specific Comments to Authors: The manuscript entitled "Advances in neovascularization after diabetic ischemia" authored by Cai et al reviewed the mechanisms of neovascularization after diabetic ischemia to increase the current knowledge of diabetic ischemic complications and their therapies, provide more treatment options for clinical practice, and to effectively relieve patients' pain. Data from the following studies provides broader insights into the inflammatory and oxidative stress mechanisms in different ailments not just diabetes and should be integrated in the introduction: https://doi.org/10.3844/ajptsp.2006.21.25, PMID: 29959408, PMID: 17151319, PMID: 17151316, http://dx.doi.org/10.4236/jdm.2011.13006, PMID: 15362483. One major concern that should be addressed: What time range of publication did this review article cover, what keywords did the search for literature include, what were the inclusion criteria, how many studies did the search find and how many were primary research vs review articles, of those, how many were selected for evaluation in this study, and finally what criteria were used for selecting the articles that were reviewed (was it the subject of the study, its novelty or both). It would also be useful to integrate in-depth discussion of clinical trials of potential treatments. Other comments • Proofreading is absolutely required. • The list of references needs to be more inclusive. If considered, the following studies would help addressing that concern and provide useful molecular discussion points on inflammatory and oxidative stress mechanisms: PMID: 35517830, PMID: 35740022, PMID: 35177980, PMID: 33255507, https://doi.org/10.1039/D0NA00958J, 10.1097/HM9.0000000000000008, https://doi.org/10.1186/s41936-020-00177-9, https://doi.org/10.1186/s41936-021-00251-w, PMID: 32460808, PMID: 33255507.

>First of all, I would like to thank the reviewer for providing us with rich data, which enabled us to have a broader understanding of oxidative stress, and improved the content of this part in the paper, making its content richer and the reference more comprehensive.

Secondly, regarding the main concern raised to be addressed, our responses are as follows: With neovascularization after diabetic ischemia as the theme, we selected the articles in recent years, namely 2017-2022, to learn from the mechanism, complications research, treatment

and other aspects, understand the views and grasp the research hotspots in recent years. During the literature retrieval, we always focused on the keywords "diabetes" and "angiogenesis" or " arteriogenesis" to understand their background, definitions, pathogenesis, etc. In order to have a deeper understanding of their pathogenesis, we would separately use "glycolysis" or "lactation" or "oxidative stress" as the keywords for literature search. According to the data provided by reviewers, we have a more perfect complementary study of "oxidative stress". Because the ischemic complications of diabetes involve various systems in the body, we have a better understanding of the system by taking "diabetic cardiovascular disease, diabetic retinopathy, diabetic nephropathy, diabetic foot ulcer" as the keywords. Thirdly, we studied a total of about 135 articles, and finally selected 101 articles to be cited in this paper by taking into consideration both subject of the study and novelty, among which review articles accounted for the majority and research articles accounted for a minority. Finally, we sincerely thank you for your valuable advice and hope that our answers will be satisfactory to you.

The revised section on "*Oxidative stress*" is attached below:

Oxidative stress

When the body is subjected to various diabetic stimuli, the mitochondria is stimulated to produce superoxide, leading to the formation of the powerful oxidant nitrite, which damages DNA and depletes intracellular NAD(+)[89], resulting a pathological state. Two common mechanisms[88] contribute to increased oxidative stress[97] in diabetes: one is an increase in free radical production and the other is a decrease in the levels of protective endogenous antioxidants. Also, natural antioxidants include dandelion[101], saffron[92-93], hawthorn[90], vitamin C, vitamin E[95], however, rhizoma polygonate in traditional Chinese medicine can dephosphorylate DNA to damage DNA[96]. In addition, hyperglycemia activates NF-κB, which can lead to changes in the inflammatory response, upregulation of COX-2, iNOS[91], TNF-α, and IL-1, promotion of cell proliferation and inhibition of cell death. The increased expression of iNOS catalyzes the production of large amounts of NO[98]. The inhibition of TLR2/4 signaling can avoid NF- κ B translocation, ultimately reducing cell apoptosis[94]. The hyperglycemic environment can stimulate the mitochondrial respiratory chain to produce a large number of oxygen free radicals, activate protein kinases C[87], and promote the NADPH-related processes of oxidative stress, leading to endothelial cell apoptosis. A small number of ROS can maintain normal physiological function[54]; however, an excess of ROS cause oxidative stress[99], which can activate multiple stress kinases and related proteases and affect

their activities[100], aggravates cytotoxicity, and attacks cells, leading to endothelial progenitor cell senescence, apoptosis, and inhibition of migration and proliferation. Superoxide anions and H2O2 in the ROS family play a major role in this process. In addition, the activity of endodermal nitric oxide synthase is reduced, the metabolism of tetrahydrobiopurine (BH4) is abnormal, and BH2 cannot be recovered in diabetes, resulting in a lower level of BH4[55]. Nitric oxide synthase (NOS) induces the formation of many superoxide anions instead of NO, aggravating oxidative stress. Advanced glycation end products lead to an imbalance in ROS production and clearance and increased endothelial permeability[56]. Oxidative stress impairs angiogenesis through multiple mechanisms.

Reviewer #2:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: very nice

> We gratefully thanks for the precious time the reviewer spent making encouraging and positive comments remarks.

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Include few figures to make it more readable

> Thanks for your valuable comments. Based on your suggestions and consideration of the layout of our manuscript, after discussion, we decided to delete the original Fig.1. We believe that it plays a limited role in the manuscript, and can be deleted to obtain better readability.