

To World Journal of Diabetes,

Name of journal: *World Journal of Diabetes*

ESPS Manuscript NO: 12195

4 September, 2014

Dear Editor,

We would like to thank to editors and reviewers of 'World Journal of Diabetes' for their valuable comments on our manuscript entitled 'Sirtuins as Novel Players in the Pathogenesis of Diabetes Mellitus'. We responded the comments of the reviewer and editor and made the changes in red font in the manuscript. Our responses are as follows;

Reviewer 02639698

Comments to the Author

The topic is interesting and well discussed. A few comments:

a) recent papers should be cited and discussed: Bible E. Nat Rev Nephrol 2013; Hasegawa et al Nat Med 2013; Song YS et al Diabetes Res Clin Pract 2013; Polak-Jonkisz et al J Physiol Biochem 2013; Chong ZZ. Nat Rev Endocrinol 2013, Kitada et al Curr Drug Targets 2013

Authors Response: We would like to thank to reviewer for his/her valuable comments. We cited and discussed the paper that you mentioned.

b) tables summarizing key elements may be useful

Authors Response: We added a table in the manuscript that summarizing the effects of sirtuins.

c) typo and grammatical errors are to be corrected.

Authors Response: We corrected the grammatical and spelling errors.

Reviewer 00467221

Comments to the Author

Correct following spells and sentences.

Page 1. abstract NAD⁺ dependent protein -> dependent enzyme

Authors Response: We appreciated about the valuable comments of the reviewer. We corrected the sentence as 'dependent enzymes' in red font.

page 3. It is unlogical -> "unlogical" this is not English word.

Authors Response: We are very sorry for this error. We corrected unlogical as 'illogical'

Page 4. 2'-()acetyl-ADP ribose -> (?)

Authors Response: We corrected 2'-()acetyl-ADP ribose as 2'-O-acetyl-ADP.

Page 7. Moynihan et. al.transgenic mice exhibit insulin secretion -> exhibit (enhanced?)
insulin secretion

Authors Response: We corrected the sentence as 'Moynihan et al. (23) firstly demonstrated that increased dosage of mammalian Sir2 in pancreatic beta cells enhanced glucose-stimulated insulin secretion in mice'.

Page 11. Recently, Marampon et al. demonstrated that an angiotensin converting enzyme inhibitor, zofenoprilat, induced SIRT1 downregulation via p38 activation. -> this sentence is not clear.

Authors Response: We rewrote the sentence as ‘Recently, Marampon et al. (67) demonstrated that an angiotensin converting enzyme inhibitor, zofenoprilat, triggered SIRT1 downregulation via p38 activation.’

The author have discussed how SIRT1 upregulation might be beneficial now saying downregulation is beneficial.

Authors Response: The reviewer is correct. There are conflicting results regarding the role of SIRT1 related pathways. Hence, we added a paragraph in the manuscript as ‘In contrast to data mentioned above regarding the beneficial effects of SIRT1 activation, recently, Marampon et al. (67) demonstrated that an angiotensin converting enzyme inhibitor, zofenoprilat, triggered SIRT1 downregulation via p38 activation. They concluded that zofenoprilat negatively controlled angiotensin I receptor protein expression through SIRT 1 and this would be associated with improved cardiovascular morbidity and mortality especially in hypertensive and diabetic patients. Hence, further researches are needed to clarify the exact role of SIRT1 related pathways in the pathogenesis of diabetes and hypertension.’

Reviewer 00505646

Comments to the Author

Page 2 Introduction: "Pathogenesis of diabetes" probably you mean "Pathogenesis of diabetes complications" From page 4 a number of spelling and grammar mistakes

Authors Response: We would like to thank to reviewer for his/her valuable comments to improve our manuscript. We corrected the grammatical and spelling errors and corrected the sentence as ‘Hyperglycemia and related metabolic alterations including advanced glycation end products, polyol, hexosamine and protein kinase C pathways collectively contribute the classical pathogenesis of diabetes complications.’

Dr Adem Kucuk participated in the review process and he signed copyright form. We added his name in the manuscript.

We hope that we satisfactorily responded the comments of the reviewers. We would like to thank to both editors and the reviewer for their valuable supports. Please let us know if any revision needed.

Yours sincerely,

Kultigin Turkmen, MD

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