

Response to Reviewers

Reply to comments of Reviewer # 1:

The authors are immensely grateful to the reviewer for detailed examination of the manuscript and his kind suggestions to improve the content and the quality of the manuscript. We have incorporated all the suggestions in the revised manuscript. Following is the point wise statement of action taken by us in response to the reviewer's comments.

Comments:

1. Nitric oxide quenching capacity must be included and discussed in the text.

Reply: As suggested, involvement of AGEs in NO quenching and inactivation of endothelium-derived NO has been discussed in second paragraph of the sub-heading "*AGEs and Endothelial Cell Dysfunction*" under the heading of "**AGES AND DIABETIC-CARDIOVASCULAR-COMPLICATIONS**". Relevant content is highlighted.

2. The role of AGEs on Smooth Muscle Cell contractile phenotype and functions as well as on transdifferentiation to a macrophage-like state, calcification, and so on should be included in reference to CVD development in T2DM.

Reply: We fully agree with the reviewer's comment that modification of smooth muscle cells is crucial in CVD. Effect of AGEs on Smooth Muscle Cell contractile phenotype and functions as well as on transdifferentiation to a macrophage-like state, calcification etc has been extensively discussed under the sub-heading "*AGEs and Vascular Smooth Muscle Cell Modifications*" of "**AGES AND DIABETIC-CARDIOVASCULAR-COMPLICATIONS**". Content has been highlighted in revised manuscript.

3. In regard to the RAGE inhibitors FPS-ZM1, authors must state that this inhibitor, as described by all suppliers as well as in the patent covering its activity, the inhibition capacity is described only for against A β 40, HMGB1 & S100B.

Reply: As suggested by the reviewer, effect of RAGE inhibitor FPS-ZM1, is described only against A β 40, HMGB1 & S100B in the revised manuscript. The content has been highlighted under the sub-heading "*AGE-RAGE signaling blockers/RAGE antagonist*" of "**ANTI-AGE THERAPIES**".

Reply to comments of Reviewer # 2:

The authors are immensely grateful to the reviewer for detailed examination of the manuscript and his kind suggestions to improve the content and the quality of the manuscript. We have incorporated all the suggestions in the revised manuscript. Following is the point wise statement of action taken by us in response to the reviewer's comments.

Comment:

1. The first two parts should be simplified to better highlight the theme.

Reply: As suggested by the reviewer, the first two parts namely "**Introduction and Epidemiology of CVD in diabetes**" have been modified to better highlight the theme in the revised manuscript.

2. Epidemiological data shown in the paper should be updated.

Reply: As suggested, epidemiological data shown in the revised manuscript have been updated under the headings of "**Introduction**" as well as in "**Epidemiology of CVD in diabetes**"

3. More clinical researches should be included for discussion, to compare the impact on AGEs associated CVD complications among different hypoglycemic scheme.

Reply: As suggested by the reviewer, data discussing the impact on AGEs associated CVD complications among different hypoglycemic scheme have been incorporated in the revised manuscript under the sub-heading "*AGEs and Hypoglycemic drugs*" of "**ANTI-AGE THERAPIES**"