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Ying Dou,
Science editor,
World Journal of Nephrology

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Re: Manuscript number: 42343 entitled "Associations of Renal Function with Diabetic Retinopathy and Visual Impairment in Type 2 Diabetes: A Multicenter Nationwide Cross-Sectional Study"

Dear **Prof. Dou,**

Thank you for the thoughtful input and review of our manuscript. We believe as a result of this review, our study will have more value for your readers. We revised the manuscript based on the reviewers' suggestions. We have attached our point by point response.

Thank you for your time and consideration. If you have any additional questions or comments, please let us know.

With many thanks for your attention, I remain.

Sincerely yours,
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Response to Reviewer#1

Comment #1

- In introduction section, 3th paragraph: Please relocate “GFR” abbreviation where was mentioned firstly (2nd paragraph).

Response: We thank you for reviewing our manuscript. We really appreciated your input and found your suggestions very helpful. Thank you for your suggestion. We apologize for these errors. We relocated the “GFR” abbreviation to where it was mentioned firstly (2nd paragraph). The following text has been added in the introduction section.

“If such an association of renal function with DR and visual impairment existed, it would provide further support to the importance for regular monitoring of glomerular filtration rate (GFR) in T2DM patients.”

Comment #2

- In materials and methods section, study design and population subsection, first paragraph, first sentence: In here, I think, you have given incorrect reference as 14. In reference 14, there is an irrelevant correspondence article. Please correct this.

Response: We apologize for the incorrect given reference 14. We have made the following change to the respective reference:

“14. Medical Research Network of the Consortium of Thai Medical Schools: MedResNet (Thailand). Data Archival for Maximum Utilization System (DAMUS). DM/HT study (NHSO Research Project) 2013, http://www.damus.in.th/damus/index.php (Access on 2 September 2018)”.

Comment #3

- In result section, “baseline characteristics” subsection: You has found that finding “Lower GFR was additionally associated with lower smoking rates, waist circumference and medication use of metformin and sulfonylureas”, I wonder that why were an association with smoking and waist circumference? Have you wondered about it? You haven't discussed this topics in the discussion section. Could you address these issues if they can be supported by the literature? I think, the findings about the metformin and sulfonylureas using may be correlated with discontinuation the medication as age progresses or due to detected renal impairment.

Response: Thank you for your comment. We agree with the reviewer regarding to need to discuss the finding of “Lower GFR was additionally associated with lower smoking rates, waist circumference and medication use of metformin and sulfonylureas”. I have added a discussion for these issues in the discussion section:

“The baseline characteristic findings showed lower GFR was associated with lower smoking rates, waist circumference and medication use of metformin and sulfonylureas. These might be from implementation of intervention for slow decline GFR in Thailand suggest smoking cessation and weight reduction in obesity, or anorexia in uremic patients in advanced CKD cases. In addition, the

metformin and sulfonylureas using may be correlated with discontinuation the medication as age progresses or due to detected renal impairment."

Comment #4

- In materials and methods section, data collection subsection: What about the eye examination techniques by the ophthalmologist? Were there any data about techniques? Clinical fundoscopy? or advanced techniques after fundoscopy? I mean that if the ophthalmologists didn't perform or was not able to perform advanced techniques, the study results couldn't be reliable. If such a situation has occurred, most patients may be unnoticed. Are there any detailed data in the case record form? or are there only diagnose information as a result of the examination? Please resolve this confusion. As can be seen in the first paragraph of the discussion section of the study that you have realized this circumstance, however you did not state your eye examination data techniques in "discussion section". I recommend to add this important issue on the "materials and methods" section and to discuss it in the "discussion" section. If there are no qualifiable and adequate data about it, you may give it as a limitation. In spite of you've given it in the limitation section, please consider all of my those approach and suggestions. If you think that you discussed this argument adequately in the limitation section, please just add eye examination techniques and recording data ways in the "materials and methods" section.

Response: We thank you for the valuable and insightful input. We agree with the reviewer regarding the need to clarify the technique for eye examination. They used fundus photography by digital camera and the images were interpreted by an ophthalmologist. We added this information regarding eye examination techniques and data to the "materials and methods" section and discussed it further in the "discussion" section.

The following text has been added in the "materials and methods" section.

"The technique of eye examination was fundus photography by digital camera and interpreted by ophthalmologist."

The following text has been added in the "discussion" section.

"…,limitations in the technique of eye examination such as image produced is two-dimensional, unlike 3D in binocular indirect binocular ophthalmoscopy, less magnification and image clarity than indirect ophthalmoscopy,…"

Comment #5

- In discussion section, "the association between GFR and DR, severe DR and severe visual impairment" subsection: What did you mean with "Contrarily, prior studies that report the converse outcome were conducted in participants of non-Asian ethnicity". What is the meaning of "converse outcome". As you stated end of the paragraph that how are you against the

possibility of ethnic differences? How did you get this? Could you explain more understandable? It seems as if there is a ambiguity, isn't there?

Response: We agree with the reviewer regarding the need to explain this sentence in more detail. The following text has been added in the discussion section:

"The present study showed that eGFR by using the CKD-EPI formula is independently associated with DR in adult T2DM patients. This study's results are similar to previous reports from non-asian ethnicity; Penno et al. [27] and Grunwald et al. [28] were studies which found an independent inverse correlation between eGFR and DR."

"Therefore, GFR not only may be an important clinical marker for DN, but could be correlated with DR [33]. It is worth noting that the prior studies that demonstrated a lack of significant independent association between eGFR and DR in T2DM (Chen et al. [12]and Sabanayagam et al. [13]) were conducted among participants of Asian ethnicity. Contrarily, Penno et al. [27] and Grunwald et al. [28] studies had reported an "inverse correlation between eGFR and DR" in a study population of non-Asian ethnicity. Our study is the first study that has shown a significant independent inverse correlation between eGFR and DR in Asian patients, and thus opposes the possibility of ethnic differences as previously suggested in the prior available literature [11, 34]."

Comment #6

- In discussion section, "the association between GFR and DR, severe DR and severe visual impairment" subsection, 2nd paragraph: I guess, you've given inaccurate reference by 38. In 38th reference, there is no data among CKD, diabetes and AGEs. Please correct it.

Response: We thank you for reviewing our manuscript. We really appreciated your input and found your suggestions very helpful. We apologize that our description of levels of stratification were not clear. We described that cataracts, one sight-threatening condition that can cause visual loss had the same pathophysiologic mechanism as with diabetes and CKD via the accumulation of AGEs. The results from Ortwerth BJ study had also demonstrated that one pathogenic mechanism of cataract formation is by AGEs due to UVA light by using analysis of enzymatic digests of [U-14C]ascorbate–labeled proteins technique.

"This could also be explained by the shared common risk factors for ocular and kidney disease (T2DM, age, smoking, HTN, dyslipidemia and obesity) and shared common pathogenic mechanisms of sight-threatening conditions (any retinopathy and cataract) that are also present in persons with diabetes and CKD, such as accumulation of AGEs [37-40],…"

Comment #7

- It has been suitable that you've mentioned about lack of the "urine albümine" data in the limitation section. Thank you. It is very important.

Response: Thank you very much for your comment. We really appreciate your input. We agree it is a very important point.

Response to Reviewer#2

Comment #1

-The paper is well written, and the topic is relevant. The patient group is type-2 diabetes, and the authors analyzed the relationship between renal function on the one hand and diabetic retinopathy and visual disturbances on the other. Many studies are available regarding this relationship in type-1 diabetes. The present study document a relationship also in type 2 diabetes. The main message is that decreased GFR in type-2 diabetes is associated with diabetic nephropathy and severe visual disturbances. The group of patient is very large, 13192 patients. The measurements are relatively simple, but the results are important, and the statistical analyzes are adequate. The presentation is satisfactory, and the tables are informative, although, in the tables, it should be indicated that the values I brackets are percentages, thus the reader does not need to guess. The conclusions are correct, and the discussion balanced with relevant emphasis on strengths and weakness' in the study

Response: Thank you very much for reviewing our manuscript. We really appreciated your input and found your suggestions very helpful. We agree with the reviewer regarding the need to indicate that the values of brackets are percentages. We have added "(%)" following the categorical variables and "mean±*SD"* following the continuous variables in the Table 1 and 2.