

Dear Dr. Ma,

We would like to thank the editors and reviewers for their careful assessment of our study; their suggestions have strengthened the manuscript. We hope that our responses and modifications to the manuscript will render our study acceptable for publication in

this excellent journal. Our-point-by point response is appended; specific changes in the revised manuscript text are indicated by red font.

Sincerely yours,

Xiaodong Sun

Response to Reviewer's comments:

Q1. Language and style: There are a huge lot of language errors (grammar, syntax and even spellings) in the entire manuscript. Without rewriting the paper with the help of an English language expert or medical writer the reading of this paper is difficult.

Response: Thank you very much for your review with valuable suggestions and remarks. We greatly appreciate the time you have contributed to the review process. We hope that amending the manuscript according to your suggestions would meet your acceptance and enable publishing of our study in this excellent Journal.

We are sorry for the language errors. We have checked the whole manuscript carefully. Additionally, the manuscript has been revised by the Ryan Chastain-Gross, Ph.D., Edanz group China (www.liwenbianji.cn/ac) for providing language editing

assistance.

Q2 Abstract: The first sentence in the abstract “Diabetic kidney disease... unclear pathogenesis” is not fully correct although the putative mechanisms are not fully elucidated.

Response: Thank you very much for your review with valuable suggestions and remarks. We revised the “unclear” to “complex”.

Q3. Introduction: A brief description of what is dickkopf-1 is important in this section to enable readers how the embryokine acts in cellular signaling mechanisms.

Response: Thank you for the valuable suggestions. We added a brief introduction about dickkopf-1 in the Introduction section.

Q4. Materials and Methods: This section should section should be grossly modified to explain the logics for inclusion and exclusion criteria. There is no point in mentioning other form of diabetes as exclusion criteria again after mentioning study on type 2 diabetes patients. As type 1 diabetes is another big risk factor for DKD, authors should clearly explain the justification for excluding that cohort from the study.

Response: Thank you very much for your valuable suggestions and remarks. We have revised the inclusion criteria and the exclusion criteria. We deleted other forms of diabetes as exclusion criteria. Considering that most individuals with diabetes are type 2 diabetes with complicated pathophysiological mechanism, herein, we aimed to

assess the serum dickkopf-1 levels in type 2 diabetic individuals with different albuminuria stages, and further explored the potential relationship between them.

Q5. *Authors should describe how they calculated the insulin resistance index.*

Response: We have added it in the methods section.

Following formulas were used to calculate: $\text{HOMA-IR} = \text{FPG (mmol/L)} \times \text{FINS (uIU/ml)} / 22.5$.

Q6. *Authors should have ideally mentioned how they calculated the sample size in the study for optimal statistical significance.*

Response: Thank you for the professional statistical guidance. The sample size was calculated by using G. Power 3.1.Ink application power analyses with the accepted minimum level of $\alpha=0.05$ and $\beta=0.2$ (power=0.8). We added it in the statistical analysis section.

Q7. *Statistical analysis: This section is quite short.*

Response: We detailed the statistical analysis part.

Parametric variables were presented as mean (SE), and nonparametric variables (HOMA IR, triglycerides) expressed as median (IQR). Logarithmic transformations were applied to the nonparametric variables prior to analysis. One-way analysis of variance (ANOVA) was performed for multiple comparisons, followed by Tukey post hoc comparison. Pearson's correlation was used to examine relationships between

variables. Multivariate linear regression models were used to estimate the determinants of dickkopf-1. Logistic regression analyses indicated the risk factors in diabetic patients with proteinuria. The sample size was calculated by using G. Power 3.1 (Germany) with the accepted minimum level of $\alpha=0.05$ and $\beta=0.2$ (power=0.8). IBM SPSS Statistics, version 20.0 (IBM Corp., Armonk, NY, USA) was used to perform for data analysis. The value of $P<0.05$ was accepted as statistically significant.

Q8. *Results: It's not as astonishing to see high triglycerides among type 2 diabetic individuals to the readers as the authors do!!!. However, it may interesting to know whether this observation has any correlation to serum dickkopf-1 levels.*

Response: We appreciate the comments. This is really an interesting question. According to our analysis, there is no significant difference between triglycerides and dickkopf-1 ($r=-0.058$, $p=0.625$). We showed the result in table 2. We have added the result in the Results part.

Q9. *Discussion: The first sentence in this section refutes the authors' own statement in the second paragraph of results "No significantly difference in serum dickkopf-1 levels between healthy individuals and all diabetic individuals were found (6.63 ± 0.29 ng/mL vs. 6.13 ± 0.23 ng/mL; $P=0.2598$)." "*

Response: We are sorry for the error. We have revised it.

Q10. Most of the other paragraphs of the section talks about pathophysiology of DKD and the potential role of dickkopf-1 in its causation rather than comparing and contrasting the current evidence on this topic and how the authors' research helps us to improve our knowledge about the research questions they raised. A concise version of the discussion might have been mentioned in a couple of paragraphs in the introduction.

The authors also should have briefly mentioned the merits and limitations of their work before concluding this section.

Response: Thank you for the valuable comments. We have deleted the pathophysiology of DKD and revised the discussion section. In addition, we have mentioned our limitations at the end of the article.

Response to issues raised by Science editor:

Q1. The language classification is Grade C. Please visit the following website for the professional English language editing companies we recommend:
<https://www.wjgnet.com/bpg/gerinfo/240;>

Response: We are sorry for the language errors. We have checked the whole manuscript carefully. Additionally, the manuscript has been revised by the Ryan Chastain-Gross, Ph.D., Edanz group China (www.liwenbianji.cn/ac) for providing language editing assistance.

Q2. The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);

Response: *We have provided all the approved grant application forms.*

Q3. *The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text.*

Response: *We have added it at the end of the main text.*