

Dear Editor,

We resubmit the paper entitled “**The multifaceted relationship between diabetes and kidney diseases: Beyond diabetes**”, after revision.

We provide a point-by-point response to the reviewers’ questions, and additional information was provided where requested: all the changes are written in red. Then, the paper was revised for English. We are confident the recommendations and suggestions from the Reviewers have improved the quality of our manuscript.

We hope our new amended version of the manuscript matches the requirements and that our work could be considered suitable for publication in Your prestigious journal.

The final manuscript has been seen and approved by all the authors, and they have given the necessary attention to ensure the integrity of the work. No conflict of interest, financial or other, exists.

**Reviewer #1:**

I have some concerns about this review: 1. Any different therapeutic strategy between DKD VS NDKD? 2. Whether DM exacerbate NDKD? 3. In different race, gender, age stage, does DKD have any prefer?

*Answer:*

*Dear Reviewer,*

*Thank you for your comments. A point-by-point response follows:*

- 1. The differential diagnosis between DKD and NDKD is essential to guide therapeutic decisions and the long-term management of diabetic patients with kidney disease. In particular, the correct diagnosis may influence the choice to use immunosuppressive drugs. As suggested, these considerations (with proper references) have been added to the paper.*
- 2. It is possible that DM may influence the prognosis of NDKD, even if available data mainly come from secondary analysis of epidemiological studies. Currently, a multicenter prospective study is ongoing to explore this possibility. We added information and updated references in the text.*
- 3. In some studies, it has been observed that, as you suggest, some demographical factors may correlate with the development of DKD. We added these data in the text.*

**Reviewer #2:**

Thank you for the effort that you have put into this paper. The paper underlines novel approaches differentiating DKD from NDKD, and the interplay between DM and kidney disease. I have no remarks, paper can be accepted.

*Answer:*

*Dear Reviewer,*

*Thank you for your positive comments. Our idea was just to provide clinicians with useful information and elements to manage the complex interplay between kidney diseases and diabetes.*

**Reviewer #3:**

The present manuscript reviewed the complex and multifaceted correlation between diabetes and kidney diseases, focusing on the clinical presentation, differential diagnosis, and new therapeutic opportunities. This review concentrated on not only the diabetic kidney disease, but also other forms of kidney disease that are not directly correlated with diabetes. This review showed extended concentration on kidney disease in diabetes, which could attract interests to some extent. However, there are still some concerns or confusions before publication can be considered.

1. In the part of “WHAT ARE THE CAUSES OF CHRONIC KIDNEY DISEASE IN DIABETIC PATIENTS?”, I supposed that the pathogenesis should be fully discussed. However, in the part of “Diabetic kidney disease”, the natural course, the relationship between symptoms and albuminuria were discussed whereas the “oxidative stress” was absent. I suggested that “glomerular hemodynamics, inflammatory responses and oxidative stress” should be fully discussed in this part and in right sequence. In the part of “Nondiabetic kidney disease”, the epidemiology took up a lot of paragraphs. Therefore, I suggested this part (“WHAT ARE THE CAUSES OF CHRONIC KIDNEY DISEASE IN DIABETIC PATIENTS?”) need re-arrangement, combing and summarizing the pathogenesis logically. And the natural course or epidemiology should be discussed in separate parts.

2. The part of “WHAT ELEMENTS MAY GUIDE DIFFERENTIAL DIAGNOSIS BETWEEN DKD AND NDKD?” also need re-arrangement with a sequence from non-invasive indexes to renal biopsy. And “HOW” to use these indexes to distinguish the diagnosis between DKD and NKDK should be discussed.

3. The title of “MAY DIABETES REPRESENT A COMPLICATION OF KIDNEY DISEASES?” was suggested to be revised to better match what has been discussed below.
4. In the part of “MAY ANTIDIABETIC DRUGS INFLUENCE THE COURSE OF KIDNEY DISEASES? THE EXAMPLE OF SGLT2 INHIBITION”, the effects of other antidiabetic drugs (metformin, GLP-1RA) would better to be discussed.
5. CONCLUSIONS would better to be simplified.

*Answer:*

*Dear Reviewer,*

*Thank you for your comments. A point-by-point response follows:*

*1. The pathogenesis of DM and related kidney damage is very complex, and its complete discussion is far from the scope of the present paper. Indeed, here, we briefly exposed the main factors associated with the development of kidney diseases in diabetic patients (with related references).*

*However, as suggested, we tried to rearrange these parts to schematize the different points. Moreover, we synthesized the epidemiology part of the “Nondiabetic kidney disease” section.*

*2. As you can see, the section “WHAT ELEMENTS MAY GUIDE DIFFERENTIAL DIAGNOSIS BETWEEN DKD AND NDKD?” has been fully revised (also following the suggestions of another reviewer).*

*However, in this part, we did not divide the methods to make differential diagnosis according to the invasiveness but rather according to the clinical use. So, while in the first part of this section, we discuss the tools used in the clinical practice (i.e., clinical evaluation and kidney biopsy), in the second part, we discuss the more innovative and speculative approaches which have still not been applied in the clinical setting. Then, in the final part of the section, we underlined that the most effective ways to use these new methods is not defined and still needs validation studies.*

*3. As suggested, we changed the title of that section.*

*4. Analogously with that stated for the pathogenesis of kidney damage in diabetes, the full discussion of the mechanisms and effect of distinct antidiabetic drugs on the kidney is far from the objective of the present manuscript (probably, it would require a separate paper).*

*On the other hand, this is the reason why we entitled this section “MAY ANTIDIABETIC DRUGS INFLUENCE THE COURSE OF KIDNEY DISEASES? THE EXAMPLE OF SGLT2 INHIBITION”, thus indicating that the case of SGT2i is just an example of how complex the characterization of new*

*therapeutic target and drugs may be. However, in the final part of the section, we added references on the nephroprotective effects of metformin and GPL-IRA, trying to emphasize that the development of new therapeutic approaches to kidney disease in diabetic patients is in rapid expansion.*

*5. As suggested, we simplified and abbreviated the conclusions.*

Sincerely,

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