Reviewer 1

Dear Authors in your Manuscript entitled The relationship between GCKR rs780094 gene polymorphism and type 2 diabetes mellitus with proteinuria you investigated the role of rs780094 SNP in the GCKR gene and susceptibility to develop diabetic kidney disease diagnosed as different level of albuminuria/proteinuria. I would suggest to correlate the results according to albuminira category (A1-A3). In addition, medications (antidiabetic, lipid lowering and antihypertensive) should be presented while they all can alter the albuminuria level. Moreover, it would be better to use the term control group instead of "normal" people.

1、I would suggest to correlate the results according to albuminira category (A1-A3).

My answer：The discussion of relevant content has been added to the discussion.

2、medications (antidiabetic, lipid lowering and antihypertensive) should be presented while they all can alter the albuminuria level

My answer：The shortcomings of the article have been explained: the article ignores the influence of drugs on the level of proteinuria, which will be further studied in the future

3、it would be better to use the term control group instead of "normal" people.

My answer：In all articles, "normal" people are changed to control group

Reviewer 2

Title: The term diabetes mellitus is only accepted to gestational diabetes. The authors must use type 2 diabetes. Abstract: Please use the correct abbreviation for type 2 diabetes (T2D). Please define UACR. If authors quantified urinary albumin, they should use the term albuminuria, not proteinuria (this implicates other detection techniques and other proteins plus albumin). Also, the microalbuminuria is disused. Please use mild, moderate, and severe to classify the albuminuria. In the introduction, it is recommended that the authors explain more and better about GCKR. - Section 2.2: Please double-check abbreviations (Kg, M) to facilitate the reading and define TG, TC, HDL-C, LDL-C, BUN, and SUA. - Sections 2.3 and 2.4: Please explain the methodology aspect of these sections. Results: Please avoid incorrect terms, such as simple type 2 diabetes, which means T2D without albuminuria. The authors quantified UACR; they must use this term, not proteinuria. - The authors forgot to mention the 2-hour postprandial blood glucose in the methodology section. - Please homologate SUA or UA. - Please define urine protein/creatinine or urinary albumin/creatinine. These are different, and they are not clinically the same. - Please homologate HDL or HDL-C; LDL or LDL-C. Discussion section: Please use ESRD for end-stage renal disease in the manuscript; it was previously defined. Please avoid the term flora and use urobioma to refer to bacteria nonpathogenic in the urinary tract. The information provided by the authors in the second paragraph, Glucokinase (GCK)

is... it is general information that could used in the introduction. In this section, the authors must discuss the protein's changes, modifications, and mutations and the causes and consequences at the kidney level. Besides, it must be compared and contrasted with other works or hypothesize about this in the tissue interest. Please define IS previous to contraction or use of the abbreviation. The authors say... "This may be due to the increased expression of GCKR accompanied by insulin resistance, and high insulin levels may stimulate the brush-like edge of the proximal convoluted tubules, promote the exchange of uric acid and sodium ions, increase uric acid reabsorption, and thus increase uric acid levels"... In this part exist multiple concerns. E.g., the subjects analyzed in the present study do not present hyperinsulinemia; thereby, they have no insulin resistance. This can be quickly corroborated whether the authors calculate and include the HOMA calculation. Besides, their assays do not have the scope to ensure or discard the environment in the proximal tubules, and a lot less to know sodium ions behavior in this region. The conceptual asseveration of managing uric acid in tubules is wrong. First, the kidney manages hippurate in the cortex, and the renal medulla is in charge of managing urates (UT and UTA transporters), but not uric acid; this molecular form only exists in urine, and if happens in the kidney, the problem is lithiasis. Therefore, the following assumptions on RAAS, VSMCs, and proteinuria are wrong, too, or at least low supported.

1、Title: The term diabetes mellitus is only accepted to gestational diabetes. The authors must use type 2 diabetes. Abstract: Please use the correct abbreviation for type 2 diabetes (T2D).

My answer：The title has been revised according to the requirements。

2、Please define UACR

My answer：urinary albumin/creatinine ratio

3、If authors quantified urinary albumin, they should use the term albuminuria, not proteinuria (this implicates other detection techniques and other proteins plus albumin). Also, the microalbuminuria is disused. Please use mild, moderate, and severe to classify the albuminuria.

My answer：proteinuria has been replaced with albuminuria。ll subjects were divided into Group I (control group), Group II [diabetes with normoalbuminuria, urinary albumin/creatinine ratio (UACR) < 30 μg/mg], Group III (diabetes with microalbuminuria group, 30–299 μg/mg), Group IV (diabetes with albuminuria, UACR ≥ 300 μg/mg), Group M (normal group) and Group N (albuminuria group).

4、In the introduction, it is recommended that the authors explain more and better about GCKR

My answer：I put the explanation of ECKR more in the discussion section

5、Section 2.2: Please double-check abbreviations (Kg, M) to facilitate the reading and define TG, TC, HDL-C, LDL-C, BUN, and SUA.

My answer：The section has been carefully examined and rewritten。

6、Sections 2.3 and 2.4: Please explain the methodology aspect of these sections.

My answer：This method has been described in detail in the article。

7、Results: Please avoid incorrect terms, such as simple type 2 diabetes, which means T2D without albuminuria.

My answer：All relevant descriptions have been modified

8、The authors forgot to mention the 2-hour postprandial blood glucose in the methodology section

My answer：Thank you for your reminder, I have added in the article.

9、Please homologate SUA or UA. - Please define urine protein/creatinine or urinary albumin/creatinine. These are different, and they are not clinically the same. - Please homologate HDL or HDL-C; LDL or LDL-C

My answer：I have corrected these errors.

10、Discussion section: Please use ESRD for end-stage renal disease in the manuscript; it was previously defined。

My answer：I have corrected these errors.

11、Please avoid the term flora and use urobioma to refer to bacteria nonpathogenic in the urinary tract.

My answer：I have corrected these errors.

12、The information provided by the authors in the second paragraph, Glucokinase (GCK) is... it is general information that could used in the introduction.

My answer：In the discussion section, you can avoid being top-heavy, and you can better connect with the article. If you think it is wrong, I can modify it again

13、In this section, the authors must discuss the protein's changes, modifications, and mutations and the causes and consequences at the kidney level. Besides, it must be compared and contrasted with other works or hypothesize about this in the tissue interest.

My answer：This difference existed in the control group and T2D patients, but was not related to whether the patients had albuminuria, nor to the degree of albuminuria in the patients. It is speculated that the change in C→T gene can cause the substitution of amino acids, thus affecting the activity of GCKR, but how GCKR acts on urinary protein warrant further study.

14、Please define IS previous to contraction or use of the abbreviation

My answer：It has been modified in the text

15、The authors say... "This may be due to the increased expression of GCKR accompanied by insulin resistance, and high insulin levels may stimulate the brush-like edge of the proximal convoluted tubules, promote the exchange of uric acid and sodium ions, increase uric acid reabsorption, and thus increase uric acid levels"... In this part exist multiple concerns. E.g., the subjects analyzed in the present study do not present hyperinsulinemia; thereby, they have no insulin resistance. This can be quickly corroborated whether the authors calculate and include the HOMA calculation.

My answer：At that time, insulin resistance was not calculated for data reasons, and this deficiency will be remedied in subsequent studies

16、The conceptual asseveration of managing uric acid in tubules is wrong. First, the kidney manages hippurate in the cortex, and the renal medulla is in charge of managing urates (UT and UTA transporters), but not uric acid; this molecular form only exists in urine, and if happens in the kidney, the problem is lithiasis. Therefore, the following assumptions on RAAS, VSMCs, and proteinuria are wrong, too, or at least low supported.

My answer：It has been modified in the text

1. Abstract methodology is missing the method of genetic analysis

It has been added in the text:

Genome-wide association study（GWAS） is a method of studying the association between a specific gene and a disease, using a large number of DNA samples for high density of single nucleotide polymorphisms (SNPS) genetic markers to find out the presence of sequence variations.

2. Introduction seems incomplete to correlate the hypothesis of research work especially studies to support it

According to the requirement, some description is given in the preface. In order to avoid excessive introduction, the content of this part is mainly expounded in the discussion part.

3. Methodology is incomplete to define the genetic analysis in detail which is the core of study and statistical analysis accordingly

In this paper, "DNA extraction and detection of gene polymorphism with TaqMan probe" is described in detail

4. Results to define clearly HW table for genetic analysis

Thank you for your reminding. This study conforms to Hardy-weinberg balanced heredity law, and P> 0.05

5. It would add value if genetic analysis outcome to be correlate with chemical tests to prove the hypotheis

That's good advice! A subgroup analysis could be added to explore the association between genetic variation and chemical test results. This helps to further confirm the hypothesis and increase the depth of the study.In the future research, I will take your suggestions and further study and explore

6.Conclusion to be re written in-view of specific genetic target and outcome and its clinical correlation and utility

Thank you for your suggestion. I have revised the content as required

7.Grammatical mistakes to be corrected

Couldn't agree more! It is recommended to review the entire draft carefully and use a syntax checker to help correct grammar errors. These errors may include spelling errors, punctuation errors, sentence structure errors, etc. At the same time, I use a retouching company to retouch the article and provide proof of retouching.