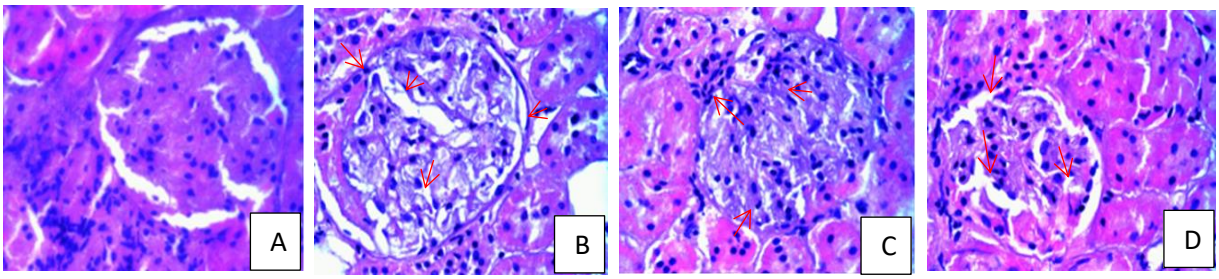
Thank you very much for your valuable comments. Accordingly, we revised the language of the manuscript and corrected all typing errors. In addition we added some information.

Reviewer #1

1-The authors attributed the beneficial effects of liraglutide to its modulatory effect on endoplasmic reticulum stress, please clarify whether endoplasmic reticulum expresses GLP-1 receptors or it may be an indirect effect.
Response: Through our experimental results, we infer that liraglutide may have a therapeutic effect on diabetic nephropathy by reducing the stress level of the renal endoplasmic reticulum. But this experiment did not make further study of the mechanism, this effect may only be an indirect effect.

2- It is better to use Periodic Acid Schiff (PAS) or Masson trichrome stain to determine the degree of collagen deposition and basement membrane thickening.
Response: The PAS staining has been completed during the experiment. The relevant steps and results are reflected in the text. Here is a brief statement: the structure of the kidney glomeruli and tubules in the normal control group is clear; the extra mesangial matrix in the kidney of the model group Increased, the basement membrane thickened significantly. After the intervention of liraglutide, the glomerular basement membrane and mesangial proliferation of rats in the model group were reduced, and the above changes were more obvious in the high-dose group. The drawings are as follows: (A normal group B model group C low-dose liraglutide group D high-dose liraglutide group)



3- In order to verify the effect of liraglutide on podocytes, the expression of their proteins (nephrin and podocin) should be measured.
Response: Unfortunately, this experiment did not further analyze the expression of nephrin and podocin in podocytes, and failed to explain the endoplasmic reticulum stress level of podocytes. The main purpose of the experiment was to clarify whether the role of liraglutide in protecting the kidney is the same Endoplasmic reticulum stress related to this general issue, the details of the mechanism will be further studied in the future.

4- Mention the post-hoc test used following one-way ANOVA to determine the significance difference between groups.

Response: The statistical analysis part has been explained in detail, which has been changed in the article. These methods are used: normality test, t test, one-way analysis of variance, Homogeneity of variance test and SNK method.

5- Please clarify when liraglutide treatment has been started.
Response: After the successful modelling of type 2 diabetic rats, they continued to feed for a week to observe the blood glucose changes, and then began to intervene with liraglutide.

6- Add the references of doses of liraglutide and anaesthetic agent in material and method section.
Response: Reference for determining the dose of liraglutide: Shi Xinyou. Experimental Zoology of Modern Medicine[M]. People's Military Medical Publishing House, 2000.

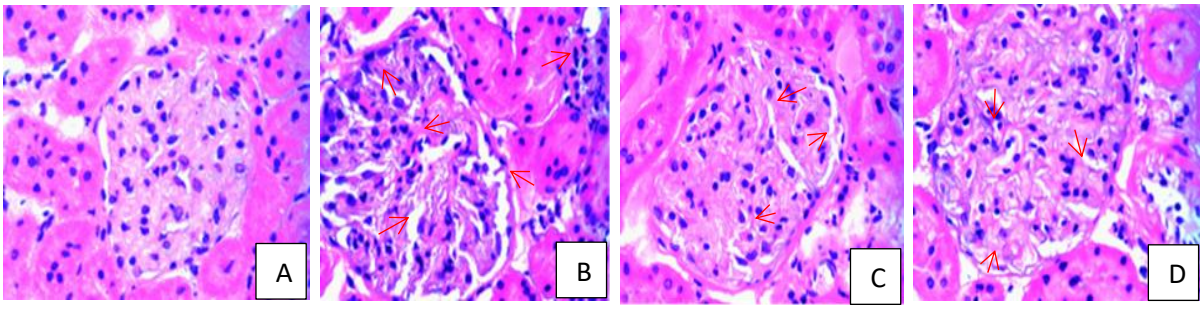
Reference for Dosing of Anesthetics: Gu Xueqiu. Notes on Pharmaceutical Preparations[M]. People's Medical Publishing House, 1983.

7-Please indicate the number of animals used in the legend of the figures of each parameter.
Response: The animals were divided into 4 groups, 6 rats in each group.

8-Mention the volume of collected blood and method of plasma preparation
Response: Take 2ml of blood from the apex of the heart, and use serum for the test items. The extraction method is: after the blood is collected, the blood is poured into a clean and dry glass test tube, and immediately placed in a centrifuge at 2500rpm/min and centrifuged for 2min. Take out the test tube and place it in a 37℃ water bath for 4 to 5 minutes. Take out the test tube and use a glass rod to peel the upper layer of fibrin to the side of the tube, and then centrifuge to precipitate at 2500 rpm/min for 1 to 2 minutes to obtain a serum sample. No chemical reagents are added in the process of separating serum, which can keep the original composition of blood as much as possible and reduce interference to measurement items.

9-Photomicrographs of histopathological features must show salient changes with arrows. In addition, figure legends should describe the gross morphological and histopathological changes.
Response: Changes have been made in the paper. The results of HE staining are as follows: A normal group B model group C low-dose liraglutide group D high-dose liraglutide group)

The kidney glomeruli and tubules of the normal control group have clear structures without obvious inflammatory cell infiltration and fibrosis; the kidneys of the model group have increased glomerular volume and increased cell number. After the intervention of liraglutide, the glomerular volume of rats in the model group was slightly reduced, and the infiltration of inflammatory



cells in the interstitium was improved, and the above changes were more obvious in the high-dose group.

10-The methods of measuring plasma creatinine and urea as well as protein in urine were not mentioned. In addition, the mortality rate should be stated.

Response： After centrifugal separation of serum, an automatic biochemical analyzer was used to determine blood creatinine and blood urea nitrogen levels. The glucose oxidase membrane electrode method was used to measure blood glucose. The BCA kit was used to determine the 24h urine protein content. After the successful modeling, 5 rats died, all of which showed that the hair was erect and dry, the wheezing was obvious, the random blood glucose value was increased, and some blood glucose meters could not measure it. Considering that the cause of death was high blood sugar leading to acute complications of diabetes; observation after successful modeling During this period, 1 rat was excluded from the group due to the blood glucose drop lower than the modeling standard, and the modeling efficiency was about 75%.

11- In the abstract, the authors stated that Western blotting showed that GRP78 and caspase12 protein expression in kidney tissue was significantly lower in model rats than normal rats, while these proteins showed a higher level in the model group, please revise it.

Response： Sorry for the typo，GRP78 and Caspase12 protein expressions in rat kidney tissues of model group were significantly increased compared with that of normal control group ($P<0.05$).GRP78 and Caspase12 proteins in renal tissue of the lilarutide intervention group were lower than those of the model group ($P<0.05$), and the decrease was more significant in the high-dose intervention group ($P<0.05$)。

Reviewer #2

1- How do researchers define low dose Liraglutide as 100 μg/kg and high dose Liraglutide as 200 μg/kg? Please add a reference if available.

Response: According to Shi Xinyou. Modern Medical Experimental Zoology [M]. People's Military Medical Publishing House, the literature mentions that the dosage ratio of human to mouse and rat is 1:25-50, and the rat is calculated as 25 here. The initial dose of liraglutide is 0.6 mg/d, and the increased dose is 1.2 mg/d after 1 week. According to the average human weight of 60kg and the average weight of the rat after the model is 450g, it is calculated that the

starting dose of the rat is 112.5ug/d, increase the dose to 225ug/d, and roughly take 100ug/d and 200ug for ease of operation /d to intervene.

2- To be clear to readers please provide the number of rats in each group in the 'Liraglutide administration and grouping.' Section.
Response: A total of 30 rats were randomly selected as the normal control group. The remaining 24 were modeled with type 2 diabetes. The modelling rate was 75%. The 18 successfully modeled were randomly divided into three groups: model group and low liraglutide. There were 6 rats in each group in the dose group and high-dose liraglutide group.

3-What does model group means? Please clarify this issue in the method section.
Response: The method has been clarified, and here is a brief explanation: the model group of rats is type 2 diabetic rats, given subcutaneous injection of normal saline, and compared with the two groups injected with liraglutide.

4-I can not understand when Liraglutide treatment was started? Please add this info in the method section.
Response: It has been explained in the method section, and here is a brief explanation: liraglutide is injected 1 week after the successful modelling, for a period of 8 weeks.

5-Again in the methods section please verify the methods of measuring glucose with the kit's name and urea and creatinine and proteinuria.
Response: It has been explained in the method part, but here is a brief explanation: after centrifugal separation of the serum, the blood creatinine and blood urea nitrogen levels are determined using an automatic biochemical analyzer. The glucose oxidase membrane electrode method was used to measure blood glucose. The BCA kit was used to determine the 24h urine protein content.

6-What about the tubule-interstitial fibrosis and tubules status in every group? Please add this info if available.
Response: In the pathological section of the kidney, it was observed that the renal tubules in the model group were cystic expansion and the interstitial inflammatory cells infiltrated, which showed the early manifestations of renal interstitial fibrosis. Compared with the model group, the above changes in the liraglutide intervention group alleviated the performance. It can be judged that the use of liraglutide in the early stage of renal tubular interstitial fibrosis may achieve the reversal of renal interstitial. However, because indicators such as PDGF and TGF-β have not been measured, there may be insufficient evidence for whether liraglutide can reverse the late stage of renal fibrosis.

7-In the statistical analyses you should mention all the tests you use. For instance one-way ANOVA test you should mention.

Response: The statistical analysis part has been explained in detail, which has beenchanged in the article. Statistical methods are used: normality test, t test, one-way analysis of variance, Homogeneity of variance test and SNK method.

8-Please add the reference 'doi: 10.4103/0971-5916.200887' and discuss your finding according to this reference.
Response: This document mentions the role of autophagy and endoplasmic reticulum stress in cell survival and apoptosis, and further clarifies that endoplasmic reticulum stress of renal podocytes can lead to diabetic nephropathy. Provided a theoretical basis for our research, we further analyzed the experiment of liraglutide based on the mechanism of reducing endoplasmic reticulum stress to treat diabetic nephropathy. Of course, we will continue to explore the specific molecular mechanism of this effect in the next experiment. This effect of liraglutide on endoplasmic reticulum stress may be an indirect effect.

9-Please summarize your findings in the first paragraph of the discussion for better understanding.
Response: The paper has been modified. In this experiment, we mainly found that liraglutide can reduce blood creatinine and urea nitrogen in type 2 diabetic rats, and reduce 24h urine protein. Liraglutide has a therapeutic effect on diabetic nephropathy, but it has not been clear in the past. Its specific mechanism. We found through experimental results that this effect of liraglutide may be related to the reduction of endoplasmic reticulum stress in the kidneys, so in the future, we can start by reducing the endoplasmic reticulum stress to find new breakthroughs in the treatment of diabetic nephropathy.

10-You should mention and discuss your findings more clearly. I think you give a lots of info regarding ER stress. However you should clearly discuss your findings with others. Please reorganize your discussion part according to these suggestions
Response: The discussion part has been revised, This is the modified part:
The occurrence of diabetic nephropathy is related to endoplasmic reticulum stress, but there are currently no reports about drugs for the treatment of diabetic nephropathy by reducing endoplasmic reticulum stress. Related studies have shown that liraglutide can improve endoplasmic reticulum stress and oxidative stress in in vivo experiments, and may regulate cell proliferation and apoptosis through autotrophic and endoplasmic reticulum stress in vitro [6]. We found through research that liraglutide has a therapeutic effect on diabetic nephropathy, and this effect is related to reducing the stress of the renal endoplasmic reticulum. In previous studies, we found not only the effect of liraglutide in reducing endoplasmic reticulum stress in the kidneys, but also similar findings in the liver of rats, but we have not further studied the molecular mechanism of this effect. it is only indirect effect which may be related to self-addiction and needs further research. But this provides us with

new ideas for the treatment of diabetes and diabetic nephropathy. In the future, we can find new ways to treat type 2 diabetes and diabetic nephropathy by reducing endoplasmic reticulum stress.