Author’s response to reviews

Title: Islet transplantation improved penile tissue fibrosis in a rat model of type 1 diabetes

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Reviewer Note for Author:

1. It was asked to authors in the first review if twelve weeks was enough time to induce advantage-stage DMED in the rats since experiments using APO were conducted after the islet transplantation or insulin administration to evaluate the erectile function in the rats but the same were not used before the treatments in order to confirm the establishment of advantage-stage DMED. The authors affirmed that "a large number" of references have mentioned that diabetic rats showed advantage-stage DMED at 12 weeks but cite only one work (Cellek) in their response. Despite the existence of some other possible works showing the effect within de 12 weeks I consider experiments using APO before islet transplantation an essential internal control of the experiment which could reinforce the successful induction of DMED before treatment.
However, since it seems difficult to add this data to the present work I could suggest the authors to mentioned the references where this methodology was used before.

Response: First of all, thank the reviewer for your understanding of us. In accordance with the reviewer valuable suggestions for us, we provide some references to explain the 12-week diabetic rats enough to induce advantage-stage DMED. For example, Jian Wang et al. showed that using APO experiments to detect penile erection function in 8 week diabetic rats, the experimental result is no erection. Yajun Ruan et al. used an APO experiment to detect penile erectile function in 12-week diabetic rats and found that the APO test was negative and used it as DMED. In addition, FENG ZHOU et al. also demonstrated that 12 weeks were sufficient to cause penile erectile dysfunction in diabetic rats. According to the reviewer's comments, we have added a part of the discussion in line 264-268 of Page 11 of our article and identified it in red.

2 In relation to the need of a broad discussion about the factors that could contribute to the reversion of DMED after islet transplantation, besides blood glucose normalization, the authors answer just repeat the information present in the first version of the work about the possible participation of c-peptide. Thus, the discussion remains the same and nothing more was added to improve this topic. In my opinion, it is important discuss more appropriately and show more details about these results.

Response: First of all, thank the reviewer’s comments, In contrast to simple insulin therapy, islet transplantation allows diabetic rats to obtain insulin secretion with a maximum close to physiological state. Islet is mainly composed of five different types of cells: α, β, δ, PP and rarely found ε cells. These cells respectively produce glucagon, insulin, somatostatin, pancreatic polypeptide and auxin. A lot of references show that these hormones can regulate each other, so that blood glucose presents a dynamic equilibrium state, which is one of the reasons why islet transplantation can well improve penile fibrosis in diabetic rats. In addition, islet cells can also secrete some non-classical islet peptides, such as GLP-1, GIP, xenin, oxytocin secreted by pancreatic islet α cells, and PYY, NPY secreted by islet PP cells, and Urocontin3 secreted by islet β cells. These hormones can regulate the function of pancreatic β-cells and the secretion of insulin, and have great potential in the treatment of diabetic facets. Among them, GLP-1 stimulates insulin secretion, inhibits glucagon secretion, reduces food intake, reduces appetite, delays gastric emptying, reduces body weight, and protects β cells from apoptosis. The American Diabetes Association (ADA) and the European Association for Diabetes Study (EASD), recommend GLP1 agonists as adjunctive agents for metformin when monotherapy fails to meet therapeutic goals. Weihao Wang et al.’s meta-analysis also demonstrated that combination therapy with GLP-1 and insulin can achieve ideal therapeutic effects on glycemic control, weight loss, and insulin dose reduction in patients with type 1 diabetes. Therefore, islet transplantation may improve the effect of fibrosis in penile tissue of diabetic rats by secreting these hormones, which is worthy of further study. According to the reviewer's comments, we have added a part of the discussion in line 321-335 of Page 11 of our article and identified it in red.

3 The authors presented some information about islet transplantation and peripheral resistance in type 2 diabetes answering a question asked in the revision. It is clear that authors agree with me
that the results of the present study could address type 2 diabetes models but it is not totally sure and there is need for the development of a similar work in diabetes type 2 models. Thus, I suggest authors a minor alteration in the title of the work highlighting the use of a type 1 diabetic model (Islet transplantation improved penile tissue fibrosis in A RAT MODEL OF TYPE 1 DIABETES)

Response: First, thank the reviewer for your professional advice. We have already changed the title of this article to " Islet transplantation improved penile tissue fibrosis in A RAT MODEL OF TYPE 1 DIABETES "

4 The information in the Figures and in the Legends are poor and superficial. For example, the magnification bar should be in the figure 3. The representation of the statistic show be revised. For example, The difference between ED CTL group is important for the discussion, but the author don't show it in the figures 3 and 4, panels D, E, and F.

Response : Thanks to the reviewer for your valuable suggestions on the pictures and its Legends, We have added the magnification bar in figure 3 and already shown the difference between the ED group and the CTL group in the figures 3 and 4, panels D, E, and F.