Response to the referees' comments

Reviewer #1:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Answer: Thank you for your careful review and hard work. We sincerely hope that our manuscript can provide valuable information to potential patients with T1D.

Specific Comments to Authors:

1- The abstract was organised and summarize the finding however, there were a lot of abbreviation in the abstract: - try to minimize the abbreviation - Mention full word for the abbreviation when first time you were writing.

Answer: Thank you for your careful review. According to your valuable suggestion, we have minimized and standardized the abbreviations in the abstract of our revised manuscript. Please refer to our revised manuscript.

2- Need specific guideline to list the reference

Answer: Thank you for your valuable suggestion. We have changed the format of the references based on the journal's requirements. Please refer to our revised manuscript.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Answer: Thank you for your careful review and hard work. We have made substantial improvements based on your valuable suggestions and hope that our revised manuscript meets your high standards and provides valuable information to readers.

Specific Comments to Authors:

This manuscript by Sun et al. shows that MenSC are able to promote pancreas regeneration and angiogenesis, reduce inflammation, improve glycogen synthesis, and increase area of white pulp in spleens of STZ-induced type 1 diabetes mice, to the same degree as UCMSC. This is an interesting paper, using a novel source of stem cells that may become an effective treatment for T1D. However, the quality of the manuscript can be improved if the authors considered and addressed the following concerns:

Major points:

1. I would recommend changing the title to "Therapeutic effects of menstrual blood-derived endometrial stem cells in mouse models of STZ-induced type 1 diabetes" in order to place the focus on MenSC, since that is the new type of SC being tested. Throughout the paper, I think you should rephrase the parts where you say that MenSC and UCMSC help improve type 1 diabetes to instead place the focus on the therapeutic ability of MenSC as compared to UMSC, as information is already known about UCMSC.

Answer: Thank you for your valuable suggestion. To highlight the focus of our study, all the authors agreed to change the title to "Therapeutic effects of menstrual blood-derived endometrial stem cells in mouse models of STZ-induced type 1 diabetes" according to your valuable suggestion. Additionally, in our manuscript, the UcMSC-treated group was used as the positive control because of the extensive application of UcMSC clinically for diabetes. We have focused on the therapeutic ability of MenSC throughout the manuscript based on your suggestion. As expected, our results also demonstrate that both MenSC and UcMSC transplantation can

significantly improve symptoms in T1D model mice and exhibit protective effects on their main organs, and MSC-mediated angiogenesis, antiapoptosis and immunomodulation likely contribute to the above improvements. Therefore, the application of MenSC can offer more choices for MSC-based therapy for diabetes and enrich MSC products. Please refer to our revised manuscript.

2. Subheadings for the results section need to be improved and made more detailed. For the third subheading, only inflammation is mentioned, but the figures discussed here also show data about anti-apoptosis and angiogenesis, so this should be added to the subheading. The last three subheadings all say “morphology” and/or “function.” Try to be more specific using the results to come up with better subheadings.

Answer: Thank you for your valuable suggestion. To better exhibit the experimental results, we have improved the third subheading to "MenSC transplantation effectively improves inflammation and angiogenesis in T1D mice" and have provided more specific information in the last three subheadings. Please refer to our revised manuscript.

3. The introduction section lacks crucial information. First, information about the usage of UCMSC in the clinic must be added. How/where are they being transplanted? Specifically, what improvements do patients see? Merely stating that their usage is limited is not sufficient. Furthermore, it is crucial to differentiate between T1D and T2D, and it is unclear whether MENSC are to be used for one or both. In addition, information about the STZ model is required.

Answer: Thank you for your careful review. Based on your valuable suggestion, we have supplemented the application and therapeutic effects of UcMSC transplantation on diabetes treatment. Additionally, the similarities and differences between T1D and T2D and information about the STZ-induced T1D model were added. Until now, MenSC-based therapy for T2D has not been reported, but we reasonably postulate that MenSC transplantation likely exhibits good therapeutic effects for patients with T2D based on published reports of MSC-based therapy for T2D. The related references were cited in our manuscript. Please refer to our revised manuscript.

4. The figures need a lot of improvement. In Figure 1, the labels (letters) do not match the letters in the legend or in the text. In Fig. 1A, it needs to be clearly stated what * and # refer to. Most of the images (1D, 1E, 4A, 5C) need better labeling. For example, in 1E and 4A, what is shown in the top row and the bottom row? In 1D and 5C, what is shown in the left column and the right column? You should indicate it in the figure legend and also can add the labels to your figures. Also, utilize arrows to label these images. For example, in 1D, point to the islets. Figure 1G needs a better label for the y axis: I would suggest "%CD31+." Overall, your legends can be more detailed.

Answer: Thank you for your careful review. We apologize for the inconsistent and unclear expression between the labels and legends for all the figures. Corrections have been made accordingly in our revised manuscript to avoid misleading readers. Arrows were used to indicate the position of islets in Figure 1D, and "% $CD31^+$ cells" was used to indicate the y axis in Figure 1G. Please refer to our revised manuscript.

Minor points

1. In the text description about Fig 1A, the authors mention day 43, but in the graph, it appears that it is actually day 42. In Figure 1, what is the significance of increased body weight or food consumption? The text mentions that serum insulin levels were upregulated and it references Fig 1D, E, F, but none of those figures show insulin. Actually, figure 2C is about plasma insulin and that is not even mentioned in the text. I think the insulin figure should be part of Fig 1 not Fig 2. In Fig 1, CD31 is mentioned, but the significance of this marker is never stated.

Answer: Thank you for your careful review. We apologize for the errors and confusing descriptions. We have changed the day to "day 42" and have clarified the text for the results in Fig 1 and Fig 2. We have systemically checked and modified improper expressions in the revised manuscript. The significance of CD31, a typical marker of endothelial cells, has been described in our manuscript. Please refer to our revised manuscript. Regarding the significance of increased body weight or food consumption, because of the absolute insulin deficiency in T1D mice, the body cannot fully use, leading to accelerated decomposition of fat and protein to supply the energy

and heat requirement in vivo, and finally weight loss. Therefore, we believe the increase in body weight and food intake is an important index in the recovery of T1D mice.

2. In terms of new experiments, it would be interesting to see the effect of the two types of MSC on WT mice, and include the histology images in each figure. Apart from this, it would be interesting to see the immune cell populations infiltrating the pancreas in normal mice vs T1D mice in the 3 treatment groups, which can be achieved by immunofluorescence experiments. Apart from this, it was mentioned that the UCMSC transplantation is well tolerated by humans, but do they not have MHC molecules that can pose a threat to the recipient? Overall, I think this study is interesting and may pave the path towards using MenSC as treatment for T1D. This paper will be enhanced by the changes mentioned above.

Answer: Thank you for your valuable suggestion and positive evaluation. In our new experimental design, we will fully consider your valuable suggestions and hope our future results will be approved. Additionally, through the absence or low expression of typical immunological antigens, such as MHC II (< 2%), UcMSC can suppress immune rejection and curb the inflammatory response, which may allow the development of allogeneic MSC therapy [1, 2]. Simultaneously, the safety of UcMSC transplantation in vivo has been extensively confirmed clinically [3, 4].

[1] Ryan JM, Barry FP, Murphy JM et al. Mesenchymal stem cells avoid allogeneic rejection. J Inflamm. 2005; 2(1): 8.

[2] Strauer BE, Brehm M, Zeus T et al. Regeneration of human infarcted heart muscle by intracoronary autologous bone marrow cell transplantation in chronic coronary artery disease: the IACT Study. J Am Coll Cardiol. 2005; 46(9): 1651-1658.

[3] Kassem DH, Kamal MM. Therapeutic efficacy of umbilical cord-derived stem cells for diabetes mellitus: a meta-analysis study. Stem Cell Res Ther. 2020;11(1):484.

[4] Li Y, Wang F, Liang H, et al. Efficacy of mesenchymal stem cell transplantation therapy for type 1 and type 2 diabetes mellitus: a meta-analysis. Stem Cell Res Ther. 2021;12(1):273.

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Answer: Thank you for your careful review and hard work. We have made substantial improvements based on your valuable suggestions and hope our manuscript meets your high standards and provides useful information to readers.

Specific Comments to Authors:

Authors of the manuscript investigated streptozotocin (STZ)-induced diabetic mice to compare the effects of menstrual blood-derived endometrial stem cells (MenSC) and umbilical cord-derived mesenchymal stem cells (UCMSC) transplantation. The following issues should be addressed:

1. Please upload and fill a correct ARRIVE Checklist from https://f6publishing.blob.core.windows.net/customuploadedfiles/The_ARRIVE_Guidelines_English.pdf

Answer: Thank you for your careful review. We have uploaded the updated ARRIVE Checklist in the online submission system.

2. Within the abstract please, resolve UCMSC

Answer: Thank you for your careful review. We have provided the full name of UCMSC in the abstract and have systemically checked and modified the abbreviations in our manuscripts. Please refer to our revised manuscript.

3. Should TNFa be TNFα?

Answer: Thank you for your careful review. We have systemically checked and modified this error. Please refer to our revised manuscript.

4. In core tip: The article is not a review, but an original article.

Answer: Thank you for your valuable suggestion. We have rephrased the core tip of our manuscript; please refer to our revised manuscript.

5. Biochemical and protein assays: Was it n = 5 / group?

Answer: Thank you for your careful review. We meant n = 5/group, and we have revised it accordingly in the manuscript.

6. In methods, I recommend moving the sentence about insulin ELISA to biochemical assays. One-sentence paragraphs should be avoided.

Answer: Thank you for your valuable suggestion. We have rephrased and adjusted the associated paragraphs in our revised manuscript accordingly.

7. Please correct sample sizes within the first sentence of Results.

Answer: Thank you for your careful review. We apologize for these errors, which have been corrected in our revised manuscript accordingly.

8. Repeating the STZ- and measurement procedures at the beginning of Result is unnecessary.

Answer: Thank you for your careful review. We have removed the repeated description of the STZ induction and measurement procedures at the beginning of the Results section. Please refer to our revised manuscript.

9. Figure 2E-F, please correct TNFa and IFNg to TNFα and IFNγ, respectively.

Answer: Thank you for your careful review. We have systemically checked and modified these errors. Please refer to our revised manuscript.

10. Figures suggest large SDs, which with the small sample sizes indicate to use non-parametric tests. What was the rationale behind using parametric tests?

Answer: Thank you for your careful review and valuable suggestion. After careful consideration, we redone the statistics using the nonparametric Mann-Whitney *U* test because of the small sample size in our study and have supplied the precise values of significance for each comparison based on the new statistical analysis. Please refer to our revised manuscript.

11. Was IL-6 and VEGF of control mice measured? Elevated levels of both of these cytokines are associated with several diseases (diabetes, various autoimmune diseases and cancers, etc.). Authors also discussed that “a low dose of IL-6 can counteract the cytotoxicity of IL-1β”, furthermore, the elevation of these markers are usually bad prognostic signs in every conditions. What do authors think, what could be the source of these elevated levels?

Answer: Thank you for your careful review. We measured the expression of IL-6 and VEGF in the control group (STZ-induced T1D mice without treatment only received PBS), but not in normal mice. As you mentioned, many diseases can cause elevated IL-6 and VEGF, but these diseases have mainly been the focus of cancer studies. The rise in the IL-6 and VEGF levels in diabetes treatment is beneficial to relieve diabetes symptoms. In 1989, Campbell et al. first reported that IL-6 could be detected in the culture supernatant of mouse islets cultured in vitro without stimulation. When a mouse anti-IL-6 monoclonal antibody was added, the biological activity of IL-6 was blocked [1]. Subsequently, Vara et al. found that isolated human islets produced IL-6. Additionally, IL-6 plays an essential role in diabetes [2]. Recently, IL-6 was demonstrated to not only affect the transport of sugar [3, 4] but also antagonize the cytotoxic effect of IL-1 on islets [5]. Although few studies have focused on the effects of IL-6 on diabetes treatment, the elevated expression of IL-6 in this study was at least partly produced by regenerative pancreatic islets. Simultaneously, our previous study demonstrated that MenSC release IL-6 [6], which is another potential source of elevated IL-6. Therefore, in our future studies, we will focus on the effect of IL-6 on the improvement of diabetes, particularly in MenSC-based therapy for diabetes. Additionally, MSC improve various diseases by promoting angiogenesis, and published reports have confirmed that MSC can secrete VEGF [6-8]. Angiogenesis is beneficial to relieve symptoms of diabetes, and the regeneration of blood vessels provides support for recovery after injury to the pancreas [9].

[1] Campbell I L, Cutri A, Wilson A, et al. Evidence for IL-6 production by and effects on the pancreatic beta-cell[J]. The Journal of Immunology, 1989, 143(4): 1188-1191.

[2] Vara E, Arias-Diaz J, Garcia C, et al. Production of TNF alpha, IL-1, IL-6 and nitric oxide by isolated human islets[C]//Transplantation proceedings. 1995, 27(6): 3367-3371.

[3] SANDLER S, BENDTZEN K, Eizirik D L, et al. Interleukin-6 affects insulin secretion and glucose metabolism of rat pancreatic islets in vitro[J]. Endocrinology, 1990, 126(2): 1288-1294.

[4] Kitade H, Kanemaki T, Sakitani K, et al. Regulation of energy metabolism by interleukin-1 β, but not by interleukin-6, is mediated by nitric oxide in primary cultured rat hepatocytes[J]. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research, 1996, 1311(1): 20-26.

[5] Buschard K, Aaen K, Horn T, et al. Interleukin 6: a functional and structural in vitro modulator of beta-cells from islets of Langerhans[J]. Autoimmunity, 1990, 5(3): 185-194.

[6] Liu Y, Niu R, Yang F, et al. Biological characteristics of human menstrual blood‐derived endometrial stem cells[J]. Journal of Cellular and Molecular Medicine, 2018, 22(3): 1627-1639.

[7] Borlongan CV, Kaneko Y, Maki M, Yu SJ, Ali M, Allickson JG, Sanberg CD, Kuzmin-Nichols N, Sanberg PR. Menstrual blood cells display stem cell-like phenotypic markers and exert neuroprotection following transplantation in experimental stroke. Stem cells and development 19, 439-452, (2010)

[8] Jiang Z, Hu X, Yu H, Xu Y, Wang L, Chen H, Chen H, Wu R, Zhang Z, Xiang C, Webster KA, Wang JA. Human endometrial stem cells confer enhanced myocardial salvage and regeneration by paracrine mechanisms. Journal of cellular and molecular medicine 17, 1247-1260, (2013)

[9] Fadini G P, Rigato M, Boscari F, et al. Short-term statin discontinuation increases endothelial progenitor cells without inflammatory rebound in type 2 diabetic patients[J]. Vascular pharmacology, 2015, 67: 21-29.

Reviewer #4:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Answer: Thank you for your careful review and hard work. We have made substantial improvements based on your valuable suggestions and hope our manuscript meets your high standards and provides valuable information to readers.

Specific Comments to Authors:

Point 01 In the results section: "C57BL/6N mice (n = 40) were adaptively fed for one week and randomly divided into 2 groups: the normal group (n = 10) and the STZ-induced T1D group (n = 40)." The number of mice in each group (10 and 40) do not add up to the total number of mice in the study (n=40).

Answer: Thank you for your careful review. We apologize for this error. The accurate sample sizes have been provided in our revised manuscript.

Point 02 How come the authors, already from the start, have chosen to use parametric statistical tests? This is wrong, as the number of mice in each group was so small (n=10), which directly calls for the non-parametric tests, regardless of normality (which, by the way, was not even performed, even though it was not even necessary, due to the small number of samples in each group). Therefore, the authors will have to redo the statistics, now with non-parametric tests.

Answer: Thank you for your careful review and valuable suggestion. After careful consideration, we have redone the statistics using the nonparametric Mann-Whitney *U* test because of the small sample size in our study. Please refer to our revised manuscript.

Point 03 I would like to see the precise values of significance for each comparison. $P<0.05$ and $P>0.05$ are not enough.

Answer: Thank you for your valuable suggestion. We have supplied the precise significance values for each comparison based on the new statistical analysis; please refer to our revised manuscript.

EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor:

General Information of the Manuscript Name of journal: World Journal of Stem Cells Manuscript NO.: 67752 Title: Therapeutic effect of two promising types of mesenchymal stem cells in mouse models of STZ-induced type 1 diabetes

Authors: Yu-liang Sun, Ling-rui Shang, Rui-hong Liu, Xin-yi Li, Sheng-hui Zhang, Ya-kun Ren, Kang fu, Hong-bin Cheng, Yahaya B, Yan-li Liu, Jun-tang Lin

Academic Editor code: 05823102

Academic Editor Country: Egypt

Science Editor: Recommend for potential acceptance.

1) Scientific quality: The manuscript is a basic study of therapeutic effect of two promising types of mesenchymal stem cells in mouse models of STZ-induced type 1 diabetes: The topic is within the scope of the WJSC.

(1) Classification: Grade B;

(2) Summary of the Peer-Review Report: The authors show that MenSC are able to promote pancreas regeneration and angiogenesis, reduce inflammation, improve glycogen synthesis, and increase area of white pulp in spleens of STZ-induced type 1 diabetes mice, to the same degree as UCMSC. This is an interesting paper, using a novel source of stem cells that may become an effective treatment for T1D. However, the quality of the manuscript can be improved if the authors considered and addressed the following concerns:

Answer: Thank you for your careful review and hard work. We have made substantial improvements based on your valuable suggestions and hope our manuscript meets your high standards and provides valuable information to readers.

1. change the title to "Therapeutic effects of menstrual blood-derived endometrial stem cells in mouse models of STZ-induced type 1 diabetes" in order to place the focus on MenSC, since that is the new type of SC being tested.

Answer: Thank you for your valuable suggestion. To highlight the focus of our study, all the authors agreed to change the title to “Therapeutic effects of menstrual blood-derived endometrial stem cells in mouse models of STZ-induced type 1 diabetes” according to your valuable suggestion.

2 rephrase the parts where you say that MenSC and UCMSC help improve type 1 diabetes to instead place the focus on the therapeutic ability of MenSC as compared to UMSC, as information is already known about UCMSC.

Answer: Thank you for your valuable suggestion. In our manuscript, the UcMSC-treated group was used as the positive control because of the extensive application of UcMSC clinically for diabetes. We have focused on the therapeutic ability of MenSC throughout the manuscript based on your suggestion. As expected, our results also demonstrate that both MenSC and UcMSC transplantation can significantly improve symptoms in T1D model mice and exhibit protective effects on their main organs, and MSC-mediated angiogenesis, antiapoptosis and immunomodulation likely contribute to the above improvements. Therefore, the application of MenSC can offer more choices for MSC-based therapy for diabetes and enrich MSC products. Please refer to our revised manuscript.

3 Subheadings for the results section need to be improved and made more detailed. For the third subheading, only inflammation is mentioned, but the figures discussed here also show data about anti-apoptosis and angiogenesis, so this should be added to the subheading. The last three subheadings all say “morphology” and/or “function.” Try to be more specific using the results to come up with better subheadings.

Answer: Thank you for your valuable suggestion. To better exhibit the experimental results, we have improved the third subheading to "MenSC transplantation effectively improves inflammation and angiogenesis in T1D mice" and have provided more specific information in the last three subheadings. Please refer to our revised manuscript.

4. The introduction section lacks crucial information. First, information about the usage of UCMSC in the clinic must be added. How/where are they being transplanted? Specifically what improvements do patients see? Merely stating that their usage is limited is not sufficient. Furthermore, it is crucial to differentiate between T1D and T2D, and it is unclear whether MENSC are to be used for one or both. In addition, information about the STZ model is required.

Answer: Thank you for your careful review. Based on your valuable suggestion, we have supplemented the application and therapeutic effects of UcMSC transplantation on diabetes treatment. Additionally, the similarities and differences between T1D and T2D and information about the STZ-induced T1D model were added. Until now, MenSC-based therapy for T2D has not been reported, but we reasonably postulate that MenSC transplantation likely exhibits good therapeutic effects for patients with T2D based on published reports of MSC-based therapy for T2D. The related references were cited in our manuscript. Please refer to our revised manuscript.

5. The figures need a lot of improvement. In Figure 1, the labels (letters) do not match the letters in the legend or in the text. Where image 1F, 1G? In Fig. 1A, it needs to be clearly stated what * and # refer to. Most of the images (1D, 1E, 4A, 5C) need better labeling. For example, in 1E and 4A, what is shown in the top row and the bottom row? In 1D and 5C, what is shown in the left column and the right column? You should indicate it in the figure legend and also can add the labels to your figures. Also, utilize arrows to label these images. For example, in 1D, point to the islets. Figure 1G needs a better label for the y axis: I would suggest "%CD31+." Overall, your legends can be more detailed.

Answer: Thank you for your careful review. We apologize for the inconsistent and unclear expression between the labels and legends for all the figures. Corrections have been made accordingly in our revised manuscript to avoid misleading readers. Arrows were used to indicate the position of islets in Figure 1D, and "% $CD31^+$ cells" was used to indicate the y axis in Figure 1G. Please refer to our revised manuscript.

Minor points

1. In the text description about Fig 1A, the authors mention day 43, but in the graph, it appears that it is actually day 42. In Figure 1, what is the significance of increased body weight or food consumption? The text mentions that serum insulin levels were upregulated and it references Fig 1D, E, F, but none of those figures show insulin. Actually, figure 2C is about plasma insulin and that is not even mentioned in the text. I think the insulin figure should be part of Fig 1 not Fig 2. In Fig 1, CD31 is mentioned, but the significance of this marker is never stated.

Answer: Thank you for your careful review. We apologize for the errors and confusing descriptions. We have changed the day to "day 42" and have clarified the text for the results in Fig 1 and Fig 2. We have systemically checked and modified improper expressions in the revised manuscript. The significance of CD31, a typical marker of endothelial cells, has been described in our manuscript. Please refer to our revised manuscript. Regarding the significance of increased body weight or food consumption, because of the absolute insulin deficiency in T1D mice, the body cannot fully use, leading to accelerated decomposition of fat and protein to supply the energy and heat requirement in vivo, and finally weight loss. Therefore, we believe the increase in body weight and food intake is an important index in the recovery of T1D mice.

(3) Format: There are 5 figures, no tables; Thirteen references were cited, including sixteen references published in the last three years.

1 self-citation.

2 Language evaluation: B. Language editing certificate was provided by AJE.

3 Academic norms and rules: The authors provided biostatistics review certificate. The authors signed the conflict-of-interest disclosure form and copyright license agreement. The institutional review board approval form was uploaded. The written informed consent was waived. No academic misconduct was found in the Cross Check investigation and the Bing search.

4 Supplementary comments:

(1) Invited manuscript.

(2) Supported by Henan Province Foundation of China, NO.202300410307 and NO.212102310611; Xinxiang City Foundation of China, NO.GG2020009. /No financial support was obtained for the study.) The topic has not previously been published in the WJSC.

5 Issues raised:

1) Within the abstract please, minimize the abbreviation-

Answer: Thank you for your careful review. According to your valuable suggestion, we have minimized and standardized the abbreviations in the abstract of our revised manuscript. Please refer to our revised manuscript.

2) Mention full word for the abbreviation when first time you were writing.

Answer: Thank you for your careful review. According to your valuable suggestion, we have minimized and standardized the abbreviations in the abstract of our revised manuscript. Please refer to our revised manuscript.

3) Resolve UCMSC.

Answer: Thank you for your careful review. We have provided the full name of UCMSC in the abstract and have systemically checked and modified the abbreviations in our manuscripts. Please refer to our revised manuscript.

4) Should TNFa be TNFα?

Answer: Thank you for your careful review. We have systemically checked and modified this error. Please refer to our revised manuscript.

4) Delete core tip.

Answer: Thank you for your valuable suggestion. We have rephrased the core tip of our manuscript; please refer to our revised manuscript. I can delete the core tip if necessary

5) In methods, moving the sentence about insulin ELISA to biochemical assays.

Answer: Thank you for your valuable suggestion. We have rephrased and adjusted the associated paragraphs in our revised manuscript accordingly.

6) In HE staining: remove (as described before) and put the reference.

Answer: Thank you for your careful review. According to your valuable suggestion, we have removed "as described before" in the Materials and Methods of our revised manuscript. Please refer to our revised manuscript.

7) In Result: Repeating the STZ-and measurement procedures at the beginning of Result is unnecessary.

Answer: Thank you for your careful review. We have removed the repeated description of the STZ induction and measurement procedures at the beginning of the Results section. Please refer to our revised manuscript.

8) Figure 2E-F, please correct TNFa and IFNg to TNFα and IFNγ, respectively.

Answer: Thank you for your careful review. We have systemically checked and modified these errors. Please refer to our revised manuscript.

9) Was IL-6 and VEGF of control mice measured? Elevated levels of both of these cytokines are associated with several diseases (diabetes, various autoimmune diseases and cancers, etc.). Authors also discussed that "a low dose of IL-6 can counteract the cytotoxicity of IL-1β", furthermore, the elevation of these markers are usually bad prognostic signs in every conditions. What do authors think, what could be the source of these elevated levels?

Answer: Thank you for your careful review. We measured the expression of IL-6 and VEGF in the control group (STZ-induced T1D mice without treatment only received PBS), but not in normal mice. As you mentioned, many diseases can cause elevated IL-6 and VEGF, but these diseases have mainly been the focus of cancer studies. The rise in the IL-6 and VEGF levels in diabetes treatment is beneficial to relieve diabetes symptoms. In 1989, Campbell et al. first reported that IL-6 could be detected in the culture supernatant of mouse islets cultured in vitro without stimulation. When a

mouse anti-IL-6 monoclonal antibody was added, the biological activity of IL-6 was blocked [1]. Subsequently, Vara et al. found that isolated human islets produced IL-6. Additionally, IL-6 plays an essential role in diabetes [2]. Recently, IL-6 was demonstrated to not only affect the transport of sugar [3, 4] but also antagonize the cytotoxic effect of IL-1 on islets [5]. Although few studies have focused on the effects of IL-6 on diabetes treatment, the elevated expression of IL-6 in this study was at least partly produced by regenerative pancreatic islets. Simultaneously, our previous study demonstrated that MenSC release IL-6 [6], which is another potential source of elevated IL-6. Therefore, in our future studies, we will focus on the effect of IL-6 on the improvement of diabetes, particularly in MenSC-based therapy for diabetes. Additionally, MSC improve various diseases by promoting angiogenesis, and published reports have confirmed that MSC can secrete VEGF [6-8]. Angiogenesis is beneficial to relieve symptoms of diabetes, and the regeneration of blood vessels provides support for recovery after injury to the pancreas [9].

[10] Campbell I L, Cutri A, Wilson A, et al. Evidence for IL-6 production by and effects on the pancreatic beta-cell[J]. The Journal of Immunology, 1989, 143(4): 1188-1191.

[11] Vara E, Arias-Diaz J, Garcia C, et al. Production of TNF alpha, IL-1, IL-6 and nitric oxide by isolated human islets[C]//Transplantation proceedings. 1995, 27(6): 3367-3371.

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[13] Kitade H, Kanemaki T, Sakitani K, et al. Regulation of energy metabolism by interleukin-1 β, but not by interleukin-6, is mediated by nitric oxide in primary cultured rat hepatocytes[J]. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research, 1996, 1311(1): 20-26.

[14] Buschard K, Aaen K, Horn T, et al. Interleukin 6: a functional and structural in vitro modulator of beta-cells from islets of Langerhans[J]. Autoimmunity, 1990, 5(3): 185-194.

[15] Liu Y, Niu R, Yang F, et al. Biological characteristics of human menstrual blood‐derived endometrial stem cells[J]. Journal of Cellular and Molecular Medicine, 2018, 22(3): 1627-1639.

[16] Borlongan CV, Kaneko Y, Maki M, Yu SJ, Ali M, Allickson JG, Sanberg CD, Kuzmin-Nichols N, Sanberg PR. Menstrual blood cells display stem cell-like phenotypic

markers and exert neuroprotection following transplantation in experimental stroke. Stem cells and development 19, 439-452, (2010)

[17] Jiang Z, Hu X, Yu H, Xu Y, Wang L, Chen H, Chen H, Wu R, Zhang Z, Xiang C, Webster KA, Wang JA. Human endometrial stem cells confer enhanced myocardial salvage and regeneration by paracrine mechanisms. Journal of cellular and molecular medicine 17, 1247-1260, (2013)

[18] Fadini G P, Rigato M, Boscari F, et al. Short-term statin discontinuation increases endothelial progenitor cells without inflammatory rebound in type 2 diabetic patients[J]. Vascular pharmacology, 2015, 67: 21-29.

10) Write in vivo or in vitro italic

Answer: Thank you for your careful review. According to your valuable suggestion, we have Changed and standardized the typeface in revised manuscript. Please refer to our revised manuscript.

11) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout;

Answer: Thank you for your careful review. According to your valuable suggestion, we have Changed and standardized the reference in our revised manuscript. Please refer to our revised manuscript.

6 Re-Review: required;

7 Recommendation: acceptance