Round 1

Dear editor and reviewer,

First, we thank you for the great comments and suggestions. We revised the manuscript (Manuscript NO.: 89962, Minireviews) according to the editor and reviewer's comments. Please check the following point-by-point revision.

All the revised parts in the manuscript were highlighted and listed in the following section for answering reviewers' comments.

Hopefully, all revisions have addressed all the comments.

Thank you.

Sincerely,

Ming Yang, PhD

Department of Surgery

University of Missouri

Comments

Reviewer #1:
Scientific Quality: Grade B (Very good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Major revision
Specific Comments to Authors: 1. The results and discussion section is very weak and no emphasis is given on the discussion of the results like why certain effects are coming in to existence and what could be the possible reason behind them? 2. Conclusion: not properly written. 3. Results and conclusion: The section devoted to the explanation of the results suffers from the same problems revealed so far. Your storyline in the results section (and conclusion) is hard to follow. Moreover, the conclusions reached are really far from what one can infer from the empirical results.

Response: We first thank the reviewer for the great comments and efforts for reviewing this manuscript. The comments were addressed point-by-point. All the changes in the manuscript were highlighted yellow in the revised manuscript. Please see the following points. 1. The results were analyzed to make the conclusion with the possible reasons to get the conclusion. 2. The conclusion was re-written. 3. The conclusion was summarized on the basis of the results reported from literature studies, which is reached by experimental studies and based on the potential underlying mechanisms.

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:

The manuscript has been peer-reviewed, and it is ready for the first decision.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Diabetes, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2023. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable.

Response: The figure is original and provided in PPT, and tables are provided with a three-line format.

7 STEPS FOR SUBMITTING THE REVISED MANUSCRIPT

(1) 89962-Answering Reviewers
(2) 89962-Audio Core Tip
(3) 89962-Conflict-of-Interest Disclosure Form
(4) 89962-Copyright License Agreement
(5) 89962-Approved Grant Application Form(s) or Funding Agency Copy of any Approval Document(s)
(6) 89962-Non-Native Speakers of English Editing Certificate
(7) 89962-Video
(8) 89962-Image File

(9) 89962-Table File
(10) 89962-Supplementary Material
Response: All the documents submitted.

8 COPYRIGHT LICENSE AGREEMENT

Response: Submitted.

9 CONFLICT-OF-INTEREST DISCLOSURE FORM

Response: Submitted.

Best regards,

Ming Yang

Round 2

Dear editor and reviewer,

Thank you for the comments. The comments were addressed and highlighted in the revised manuscript and added the response to reviewer comment document.

SPECIFIC COMMENTS TO AUTHORS

The discussion should be rather organized around arguments avoiding simply describing details without providing much meaning. A real discussion should also link the findings of the study to theory and/or literature.

Response: Authors thank the reviewer for this comment. The discussion of the manuscript was revised to compare current conclusions with literature reports. All the changes are highlighted in the manuscript and listed below: “In addition, FGF-mediated therapies have been applied to treat obesity and obesity-associated metabolic disorders, such as hepatic steatosis and insulin resistance, which are commonly associated with the development of diabetes. For example, adeno-associated virus serotype 8 (AAV8)-mediated liver overexpression of FGF21 reduced HFD-induced obesity, adipose tissue inflammation, hepatic steatosis, and insulin resistance[89]. Furthermore, surgical treatments such as Roux-en-Y gastric bypass (RYGB) surgery can increase the levels of FGF-19 and bile acids in patients with uncontrolled T2DM to improve glycemic control[90]. Another study also showed that the expression of FGF-21 was increased in obese patients with RYGB therapy[91], resulting in weight loss (https://clinicaltrials.gov, numbers including NCT00981500).”. Please see the attached revised manuscript and the response. Best regards, Ming Yang

JOURNAL EDITORIAL BOARD COMMENTS TO AUTHORS

This narrow review has many issues before being considered for publication in WJD. See attached comments. Although previous reviewer has pointed out several similar concerns, the revised version did not well address these issues. I wonder whether the revision has been reviewed by previous reviewer. If not, we should, or someone in the editorial office should send back the revision to previous reviewers to evaluate whether the authors did a good job or not. The manuscript was prepared too rough and not acceptable for publication in the current status. The following major issues should be addressed.

Majors:

1. Under the 2nd section, "FGFS PLAY AN IMPORTANT ROLE IN DIABETES AND RELATED DISEASES", the introduction "Each FGF plays a variety of roles in diabetes and relative metabolic disorders in patients. In this section, we summarize the current research findings in this field." needs to rewrite. Since the authors did not well introduce all FGF member of 23 evenly, instead of only very briefly introducing each of them with a focus only on their metabolic syndrome (obese, insulin resistance), diabetes, diabetic complications. Therefore, the author should mention this here, some sentences like
   "It is known that there are 23 FGFs recognized, some of which have been extensively investigated such as FGF21, and some of which have not been such as XX. In addition, although these FGFs belong a same family with some similar principle functions, their functions remain significantly distinct. Therefore, the below section will very briefly introduce each member and also focus on the function related to metabolic syndrome, diabetes and diabetic complications."
   Response: Thanks for pointing this out. This section was rewritten to "Of the recognized 23 FGFs, some of them have been extensively investigated such as FGF-21 in diabetes, and some of which have not been well studied such as FGF-8. Although the same family of FGFs has similar principle functions, the functions of each member remain distinct in diabetes. Therefore, the following section will briefly introduce the function of each member and mainly focus on the function related to metabolic syndrome, diabetes, and diabetic complications.".

2. To introduce clinical trials is a good idea, which can indicate the potential importance of FGFs in clinics. However, its current status in the conclusion without any detail summary or descriptive information is equal to nothing. Therefore, since the trials mainly for FGF21, and also includes 1 or 2 for FGF19, and FGF23, the authors may make a same section between second (introducing each FGF) and Conclusion, to very briefly introduce these trials or add the trial information at end of each FGF introduction under the second.
   Response: Thank editors for this comment. Another section of CLINICAL TRIALS was added in the revision to introduce the trials very briefly. A section was added before the Conclusion. "POTENTIAL ROLES OF FGF IN DIABETES AND DIABETIC COMPLICATIONS IN CLINICALS
   In this section, we briefly introduce several clinical trials about the roles of FGF in diabetes and diabetic complications. Several trials (https://clinicaltrials.gov, numbers including NCT02667964, NCT01858597 or NCT03816605, NCT00491322, NCT04012983, and NCT05937737) have been performed to investigate the roles of FGFs in insulin secretion, insulin resistance, regulation in the expression of insulin receptor substrate 1 and glucose transporter 1 in gestational diabetes mellitus, and function as biomarkers for periodontal disease in patients with diabetes, as well as the association of FGF expression levels with the intake of phytochemicals in diet and dietary total antioxidant capacity in patients with T2DM.
   The impact of physical activity and diet intake on FGF expression in DM patients has been investigated. For example, the relation of FGF-21 expression and physical activity in regulation of insulin secretion in patients with T1DM or T2DM, and healthy volunteers was investigated in a trial (NCT02667964). Another trial (NCT05937737) investigated the impact of phytochemical intake from the diet and total dietary antioxidant capacity measured by different methods on the expression of serum FGF-21 in patients with T2DM. Given the regulatory effect of vitamin D on insulin secretion in the pancreas, ergocalciferol (vitamin D2) was applied to treat vitamin D deficiency-related insulin resistance and regulate FGF-23 expression in patients (NCT00491322). In addition, the functions of FGFs have been

investigated in diabetic complications. Gestational diabetes mellitus (GDM) is the most common complication in pregnant women. The roles of FGF-19 and FGF-21 in regulating insulin resistance, dyslipidemia, and glucose intolerance in GDM (NCT01858597 and NCT03816605), due to their effects on the expression of insulin receptor substrate-1 and glucose transporter-1 in placenta. Moreover, an observational study (NCT04012983) was conducted to investigate the diagnostic role of FGF-21 from gingival crevicular fluid in periodontal disease in diabetic and nondiabetic patients, in combination with an adipokine chemerin. However, the therapeutic roles of FGF in diabetes remain unknown. More clinical trials are expected to validate pre-clinical findings of FGFs such as FGF-19 and FGF-21 in diabetes."

Minors

Appreciate the following details and all of them were revised as suggested.

3. Last sentence in the Ab: "The mechanisms of action of FGFs include suppression of hepatic glucose production and lipolysis in adipose tissues, activation of glucose-excited neurons, inhibition of renal injury and fibrosis, inhibition of high-fat diet-induced obesity and insulin resistance, regulation of thermogenic gene expression, regulation of extracellular matrix components in cardiac fibroblasts, inhibition of cancer cell proliferation and migration, reduction of levels of fasting blood glucose and triglycerides, and promotion of diabetic wound healing process and bone repair." Is too long, which needs to be broken into 2 or 3 sentences.
   Response: Overall, the roles of FGFs in diabetes and diabetic complications are involved in numerous processes. First, FGF intervention can prevent high-fat diet-induced obesity and insulin resistance and reduce the levels of fasting blood glucose and triglycerides by regulating lipolysis in adipose tissues and hepatic glucose production. Second, modulation of FGF expression can inhibit renal and cardiac fibrosis by regulating the expression of extracellular matrix components, promote diabetic wound healing process and bone repair, and inhibit cancer cell proliferation and migration. Finally, FGFs can regulate the activation of glucose-excited neurons and the expression of thermogenic genes.
4. In the first section: "Currently, new therapies for diabetes are needed to prevent this increasing incidence" does not make sense. Therapy for diabetes is for prevention of increase?
   Response: This sentence was rephrased into "Therefore, new therapies are urgently needed to treat diabetes and diabetes-related complications."
5. "Fibroblast growth factors (FGFs), play important roles in metabolic homeostasis and cell biological processes, consisting of 23 family members (FGF-1-23) in humans[6,7]. Alteration of the expression of FGFs is implicated in many chronic diseases, including obesity[8,9], diabetes[10,11], metabolic-associated fatty liver disease[12,13], nonalcoholic steatohepatitis (NASH)[14,15], hyperthyroidism[16], chronic kidney disease (CKD)[17,18], cardiovascular diseases[19,20], and cancers[21,22]. Accumulating evidence shows that FGFs can function as molecular targets for the treatment of diabetes and diabetes-associated metabolic disorders." Needs to rewrite since these are unclear. Probably something like "Fibroblast growth factors (FGFs), consisting of 23 family members (FGF-1-23) in humans[6,7], play important roles in maintaining metabolic homeostasis and cell biological processes since alteration of the expression of FGFs is implicated in many chronic diseases. These diseases included obesity[8,9], metabolic-associated fatty liver disease[12-15], diabetes[10,11], and diabetic complications (including cancer) [16-22]. Investigation has shown that FGFs can function as molecular targets for the treatment of diabetes and metabolic disorders." may be considered.
   Response: They are rephrased into "Fibroblast growth factors (FGFs), consisting of 23 family members (FGF-1-23) in humans[6,7], play important roles in metabolic homeostasis and cell biological processes since alteration of the expression of FGFs is implicated in many chronic diseases. These diseases include obesity[8,9], metabolic-associated fatty liver disease[10-13], diabetes[14,15], and diabetic complications, such as hyperthyroidism[16], chronic kidney disease (CKD)[17,18], cardiovascular diseases[19,20], and cancers[21,22]. Investigation has shown that FGFs can function as molecular targets for the treatment of diabetes and diabetes-associated metabolic disorders.".
6. For FGF2, the authors mentioned basic FGF, but The authors did not mention FGF-1 also called acidic FGF. For a narrow review, you can do not mention many things, but if you want to mention something, which should be

equally for all FGF, such as “a, b name these two fgf at the beginning, these two were named based on their acidic and basic feature, but not late for too many members.

Response: Here, we removed the basic FGF for FGF2, by focusing on their functions.

7. FGF4: “Intracerebroventricular administration of FGF-4 shows an anti-diabetic function in male db/db mice and DIO mice by activating glucose-excited neurons via FGFR1, while it can also deactivate glucose-inhibited neurons[33].” The authors have tried to copy sentence from previous work even did not understand what “DIO” means, they also simply, directly used the abbreviation used by the originally authors. Here DIO was used for “(high fat) diet induced obesity”. Therefore, the reviewer suggest the authors carefully use the copied sentences from abstract to understand the original means and use your own description to indicate what the original work’s points.

   Response: It is not right to mention a lot about the DIO since the abbreviation of DIO in the above context of the manuscript has already been mentioned (diet-induced obese (DIO) mice that mimic human T2DM[25]), herein, it was used as an abbreviation. Similarly, the DIO was abbreviated in the note of Table 1. This sentence was to summarize the key findings of this research study to show FGF-4 treatment can suppress diabetes by manipulating glucose regulatory neurons.

8. FGF-5: “Overexpression of miR-145-5p can suppress the expression of FGF-5 to increase the cell apoptosis and proinflammation of retinal ganglion cells in diabetic retinopathy by upregulating the expression of cytokines such as tumor necrosis factor-α and interleukin-6[34].” is another example of copy-paste. Under the section to narrow introduction of FGF-5, the reviewer does not understand what the authors tried to state, “miR-145-5 can suppress FGF5 expression …. by up-regulating the expression of cytokines….” Or “FGF-5 is able to suppress apoptosis under certain condition”? The later should be addressed here, rather than whether miR-145-5p can inhibit or not (if you are preparing a conpreshensive review, Yes, what is FGF-5, what function FGF-5 have, and how FGF-5 is regulated, all should be addressed.

   Response: The function of FGF-5 was directly described here. The regulatory function of microRNAs such as miR-145-5p was briefly mentioned in this mini-review as a potential treatment option. The sentence was changed into “FGF-5 can regulate the apoptosis and proinflammation of retinal ganglion cells in diabetic retinopathy by upregulating the expression of cytokines such as tumor necrosis factor-α and interleukin-6[34]. This study also showed that the expression of FGF-5 can be regulated by miR-145-5p, functioning as a potential treatment option.”

9. For all rest FGFs member, the authors should be careful to avoid directly copy and paste without digesting original work’s point in order to make this narrow review reaching to acceptable level.

   Response: All the functions of FGFs in diabetes and its complications were summarized to give audiences the key points that FGFs can be targeted to regulate different biological processes. The key findings of the literature reports are discussed in the manuscript.