

RESPONSE TO REVIEWERS' COMMENTS

Manuscript No.: 86168

Title: Mechanism and recent updates on insulin disorders

Revised Title: Mechanism and recent updates on **insulin-related** disorders

The authors of this manuscript express their sincere thanks to the Editor and the reviewers for the critical assessment of this work. The authors have acted upon the recommendations of the Editor and the reviewers which have resulted in a significant enhancement in the quality of this manuscript. **All modifications suggested by reviewers have been incorporated in the revised manuscript and shown in red colour.**

Response to the comments is outlined below.

REVIEWER 1

Comment 1

The manuscript entitled “Mechanism and recent updates on insulin disorders” and authored by Kumar et al reviewed the insulin disorders and the underlying mechanisms associated with insulin pathophysiology. The following investigations should be integrated to enrich the discussion: PMID: 33255507, <https://doi.org/10.1186/s41936-020-00177-9>, PMID: 34639131, <https://doi.org/10.4236/ajps.2018.96091>, <https://doi.org/10.3844/ajptsp.2007.4.9>, PMID: 29959408, PMID: 17151320, PMID: 35531567, PMID: 36432184, PMID: 35740022, PMID: 35177980, <https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2021009706>, <https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2020174446>, PMID:

36139719, <https://patents.google.com/patent/JP2020132625A/en>, PMID: 35211395, <https://doi.org/10.1186/s12645-022-00144-9>.

Response:

It is my humble submission that the investigations suggested by the reviewer to enrich the discussion are entirely out of scope of the present study and thus cannot be integrated in the present manuscript. Current manuscript deals with insulin-related disorders. Since scope of suggested literature does not match with our topic, hence we could not cite these articles in our manuscript. We have explored the suggested literature and we are providing the theme of the suggested literature in parenthesis. PMID: 33255507 (Hepatic Fibrosis); PMID: 34639131 (Anti-Hepatocellular Carcinoma biomolecules); PMID: 29959408; PMID: 17151320, (articles do not reports any mechanistic view on insulin disorder); PMID: 35531567 (effect of herbal product on Prostate Cancer); PMID: 36432184; PMID: 36139719 (combination therapy for Hepatocellular Carcinoma); PMID: 35740022 (Bioinformatics study); PMID: 35177980 (Liver cancer, oxidative stress and inflammation); PMID: 35211395 (Angiogenesis)

Comment 2

One major concern that should be addressed: What time range of publication did this review article cover, what keywords did the search for literature include, what were the inclusion criteria, how many studies did the search find and how many were primary research vs review articles, of those, how many were selected for evaluation in this study, and finally what criteria were used for selecting the articles that were reviewed (was it the subject of the study, its novelty or both).

Response

The present review is not a “Systematic Review”. That is why we did not mentioned the time range of the literature, inclusion/exclusion criteria, criteria for selecting articles (whether review or articles). We simply provided the basic literature on the topic and

added updates on the basic knowledge using keyword for the respective headings and sub headings.

Comment 3

Other clear setback is lacking in-depth coverage of relevant patents.

Response

We are thankful to reviewer for the suggestion. In-depth coverage of relevant patents is not under the scope of the present review. However, we have enriched the text by incorporating content from latest literature.

Other comments •

Massive proofreading is REQUIRED. • Abbreviations list must be added. • Figures' legends should be more descriptive. • Adding a conclusion figure would be useful. • If integrated, the following studies could enrich the discussion: PMID: 34662244, PMID: 26641660, PMID: 36757420.

Response:

Proofreading has been done thoroughly.

Abbreviations have been explained throughout the manuscript.

Description has been added in most of the Figures legends. To avoid any repetition of the text, the figure legends have been written accordingly. Text material has also been added and discussed in the manuscript.

Adding a conclusion figure is not worth as each heading has its own identity.

The suggested (PMID: 34662244, PMID: 26641660, PMID: 36757420) studies are not in the line of the present review.

REVIEWER 2

Comment 1.

Are there controversies in this field? What are the most recent and important achievements in the field? In my opinion, answers to these questions should be emphasized. Perhaps, in some cases, novelty of the recent achievements should be highlighted by indicating the year of publication in the text of the manuscript.

Response: Controversies have been incorporated in PCOS section. Recent discussion has been mentioned as Ganguly et al. (2022), Zeng et al. (2019) and Armanini et al. (2022) in different sections. Relevant contents have been added during revision process. All additions are shown in red.

Comment 2.

The discussion section is modest.

Response: Thank you for comment. The review is discussed as per the theme of the manuscript. Additional information has also been incorporated under different sections.

Comment 3.

Abstract: not properly written.

Response: Abstract has been re-written.

Comment 4.

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: Thank you for the comment. We have enriched storyline by addition of content. The corrections have been incorporated in conclusion section. Manuscript has been thoroughly revised.

Comment 5.

The discussion should be rather organized around arguments avoiding simply describing details without providing much meaning.

Response: Thank you for comment. The manuscript has been revised accordingly.

Comment 6.

Spacing, punctuation marks, grammar, and spelling errors should be reviewed thoroughly. I found so many typos throughout the manuscript.

Response: Typographical, grammatical errors, spacing, and punctuation marks have been reviewed thoroughly and corrections have been done throughout the manuscript.

Comment 7.

English is modest. Therefore, the authors need to improve their writing style. In addition, the whole manuscript needs to be checked by native English speakers.

Response: English has been checked thoroughly and corrected as per the requirement. Now manuscript quality has improved considerably. Further, manuscript has been checked by Professor of English language.

REVIEWER 3

Comment

The Manuscript "Mechanism and recent updates on insulin disorders - WJD-No: 86168" was reviewed with interest. Unfortunately, the paper is written in such a manner that it

wouldn't qualify the criteria for publication in a good quality biomedical periodical, especially in the high-quality World Journal of Diabetes with a current impact factor of 4.56. I have just pointed out only some major errors in the paper as almost every paragraph there are several mistakes to point out. General comments: - A narrative review article should elaborate current evidence on a topic with logical arguments procured from existing latest literature in authors view. However, authors have simply gathered some points from literature and presented them in a simple narrative without any contribution from their side in a totally haphazard manner. Authors should have at least read few recent reviews published in the WJD before presenting this paper.

Response: Thank you for the comment. The review has been extensively revised as per the suggestions. Logical arguments have been incorporated under different sections. Unnecessary sentences have been deleted. Text has been enriched.

Comment

- There is no proper order of the presentation e.g., important to less important, common to uncommon, uncertainties in the evidence etc. etc.

Response: Topics covered under different sections are presented appropriately. All the sections are important. Hence equal weightage has been given to various sections. Basic mechanism and recent updates related with the topic have been discussed depending on importance.

Comment

- There are a huge lot of factual errors (some of which I have pointed out below:

Language & style:

- The language quality is horrible with a huge lot of errors throughout the paper which are not salvageable without rewriting the paper with someone who have proficiency in writing a review paper!.

Response: Language has been edited throughout the manuscript. Many paragraphs have been revised and content rewritten. Now manuscript quality has improved.

Comment

Title: - The title is inappropriate as authors are not presenting the recent updates I am afraid. A better title should have been somewhat like "Mechanisms of insulin-related disorders +/- :recent updates" as insulin disorders may convey also convey a faulty impression of abnormalities in the insulin molecule itself.

Response: The title has been modified. Modified title is "Mechanism and recent updates on insulin-related disorders."

Comment

Abstract and Core tip: - Should have given a brief summary of evidence presented in the paper.

- There are several factual errors in these sections themselves.

Response: The abstract has been modified. Errors have been rectified.

Comment

Introduction: - The first sentence itself is wrong regarding the number of amino-acids in insulin. In my knowledge insulin has only 51 amino-acids. Unsure if authors have invented any new insulin.!. - In my knowledge c-peptide is the connecting peptide (not the crucial peptide).

Response: Thanks for suggestion. We are sorry for the factual error. The correction has been incorporated. Manuscript is now error free.

Comment

- A proper introduction of a review should show how the authors are planning to narrate the review with some core ideas of the paper to enhance reader experience with which they will read the entire paper. Authors have described mechanism of insulin secretion and action (??? reaction.!!) and simply narrated the various disorders related to insulin biology & actions.!

Response: Manuscript has been revised thoroughly. The corrections have been incorporated in the introduction section as well as in other sections.

Comment

- I don't understand how authors created new terminologies type 1 IDDM and type 2 IDDM in the next sections. Several abbreviations in the paper are not explained properly and there are errors in these two paragraphs (e.g. juvenile with HLA-DR4-DQ2.....; primary cause of T2DM is progressive progressive impairment of insulin secretion - it is not cause but oftenconsequence.!.)

Response: The terminologies “type 1 IDDM and type 2 IDDM” have been corrected. Abbreviations have been explained. Other errors have been rectified as suggested.

Comment

- GDM section is given more importance with again errors and jargons (e.g., GCK-related diabetes in pregnancy doesn't fall in the category of GDM).

Response: We agree with the reviewer. In the GDM section we used the term only to discuss the relation between women with GDM and mutation in fetal GCK.

Comment

- For authors information: Insulin pump, islet transplantation... are not in the emerging stage (I have been conducting pump clinics over the past one and half decades.!.)

Response: We really appreciate the contribution of the reviewer in the field. We only mentioned the fact already available in the literature with proper citation (Reference No. 26).

Comment

Insulinoma: - This section should have come in the end considering the rarity of the condition but given a lot of importance again with errors (e.g., the 72-hour fasting test is described erroneously).

Response: Thank you for the suggestion. The errors have been corrected.

Comment

- Insulinoma as such is a review topic and authors here just gave some narrative which are probably useful for a medical student or lay man.

Response: Thank you for the comment. The section has been improved.

Comment

Metabolic syndrome: - Again this section should have been earlier and with T2DM or earlier to describe the role of IR in human disease including T2DM, PCOS, MAFLD (not at all mentioned by authors) and cancer biology in relation to it. I haven't wasted time to analyze the errors here as there are so many!!!..

PCOS & mRNA: Again errors and out of context mRNA in a small subsection like this!!!..

Response: Thank you for the comment. We mentioned the update on role of miRNA in insulin signaling implicated in PCOS.

Comment

Neurological disorder: - This is quite vague and irrelevant points too.

Response: Thank you for the comment. The corrections have been incorporated.

Comment

Cancers: - There are 12 different forms of cancers in relation to MS, but unsure why authors limited only to only 3.

Response: We discussed only those cancers which have been studied substantially for insulin association with the disease.

Comment

- No comments about many errors here too,

Figures: Except figure 5 others are substandard quality in the scientific content and 5 is out of context too.

Response: Quality of figures has improved. We have re-structured and redrawn the figures. The quality of figures has improved considerably. Now figure 1, 2, 3, and 4 are better quality figures.. The figure 5 has been incorporated as per suggestion of one of the reviewer.

Comment

Conclusions: - Not succinct as expected Tables: - several points could have been in appropriate tables making lives of the readers easy..!!..

Response: We tried to put information in the figures and incorporated in the manuscript. There is not much information which could be tabulated.

Comment

References: Many are inappropriate as authors have narrated simply some points not relevant for a good quality review.

Response: Relevant references have been added. Major points have been discussed in the text.

Comment

Overall, I am very confused what this paper will add to our knowledge base on insulin-related disorders.!

Response: Thank you for the comment. The review has been extensively revised as per the suggestions.

Response to Reviewer's Comments

Reviewer: 05457585

Comment1:

Are there controversies in this field? What are the most recent and important achievements in the field? In my opinion, answers to these questions should be emphasized. Perhaps, in some cases, novelty of the recent achievements should be highlighted by indicating the year of publication in the text of the manuscript.

Response 1:

Controversies have been incorporated in PCOS section. Discussion has been strengthened by incorporating relevant contents from recent literature viz., Ganguly et

al. (2022), Zeng et al. (2019) and Armanini et al. (2022) under different sections. Relevant contents have been added during revision process. All additions are shown in red/blue.

Comment 2:

The discussion section is modest.

Response 2:

Thank you for comment. The review is discussed as per the theme of the manuscript. Additional information has also been incorporated under different sections.

Comment3:

Abstract: not properly written.

Response 3:

Abstract has been re-written.

Comment4:

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.

Response4:

Thank you for the comment. We have enriched storyline by addition of content. The corrections have been incorporated in conclusion section. Manuscript has been thoroughly revised.

Comment 5:

The discussion should be rather organized around arguments avoiding simply describing details without providing much meaning.

Response 5:

Thank you for comment. The manuscript has been revised accordingly.

Comment 6:

Spacing, punctuation marks, grammar, and spelling errors should be reviewed thoroughly. I found so many typos throughout the manuscript.

Response 6:

Typographical, grammatical errors, spacing, and punctuation marks have been reviewed thoroughly and corrections have been done throughout the manuscript.

Comment 7:

English is modest. Therefore, the authors need to improve their writing style. In addition, the whole manuscript needs to be checked by native English speakers.

Response 7:

English has been checked thoroughly and corrected as per the requirement. Now manuscript quality has improved considerably. Further, manuscript has been checked by Professor of English language.

Reviewer: 02461627**Comment 1:**

Some of the comments were not sufficiently addressed.

Response 1: The whole manuscript has been revised as per the comments.

Some of the relevant suggested literature (PMID: 34639131; PMID: 29959408) have been cited and shown in blue colour.

The source of data used in the study has been mentioned in the end of introduction section.