ANSWERING REVIEWERS (Manuscript No. 24895)

Response to Reviewer 1 (Reviewer's code: 00058872)

1. Authors are requested to quote the pertinent paper about the link between MS and NAFLD, i.e., World J Gastroenterol. 2013 Jun 14;19(22):3375-84. doi: 10.3748/wjg.v19.i22.3375.
2. What about non-alcoholic fatty liver disease as a new criterion to define metabolic syndrome

Authors' Answer: (1 & 2):

This is a very pertinent and welcome suggestion. We have incorporated a chapter on NAFLD and discussed the Effects of GLP-1RA Liraglutide on NAFLD. (Page#17, Line#12-29) and (Page#18, Line# 01-11)

We have cited the article "What about non-alcoholic fatty liver disease as a new criterion to define metabolic syndrome?" as suggested by Reviewer-1. (Page# 17 , Line#14-17. Reference # 30)

Response to Reviewer-2 (Reviewer's code: 01196818)

1. All products of GLP-1RA belonged to the peptide that cannot be applied through oral adminstration. This point was not mentioned in clear.

Author's Response: We have included this point now. (Page 8, Line#11-13)

2. One table summarized all GLP-1RA with comparison of specificity in each disorder concerned in this article from hyperglycemia, blood pressure, to coronary heart disease. Additionally, is it obtained due to the activation of GLP-1R only?

Author's Response: We have discussed effects of GLP-1RA on hyperglycemia, blood pressure and on coronary heart disease under separate headings. Our job was to present the recent scientific data and we have given the comparison as the outcome in head-to-head trials.

The cardio-metabolic effects of GLP-1RA are both receptor dependent & independent and we have incorporated one paragraph as suggested. (Page#21, Line#14-26, Page# 22, Line#1-2)

3.Adverse effects of GLP-1RA were not conducted. What is the possible reason for each peptide to induce such side effect(s)?

Author's Response: Adverse effects/events (AE) and Serious Adverse Events (SAE) were studied in all GLP-1RA trials conducted. We given a list of GLP-1RA(s) and mentioned the FDA or, EU approval(s) which denotes a reasonably safety standard for their clinical use. We have also mentioned the G.I. side effects of different GLP-1RAs while discussing different trials. Certain controversial issues like risk of pancreatitis or pancreatic cancer were not discussed to avoid long discussions and deviations from the "topic" of our article. We have also mentioned that, in the ELIXA trial, there was no higher incidence of pancreatitis or, pancreatic cancer. Since it was a mini review, we decided to stick to the topic of impact of this class of molecules on the metabolic parameters only. (Page 19, Line# 19-24)

4. Oral agonist for GLP-1R is expected but how to develop it? Please add one perspective.

Author's Response: We have included a paragraph on oral semaglutide and explained how this route was made possible. (Page 8, Line# 16-21)

5. Combination of GLP-1RA with others will be applied in clinics. Please take the reference(s) into this report.

Author's Response: We have included one paragraph on combination of GLP-1RA and basal insulin. Since it is a mini-review, we avoided bringing in other agents that can be used in combination with GLP-1RA. (Page#9, Line#16-29) and (Page# 10, Line# 1-3)

6. What is the most reliable one of GLP-1AR at this moment? It can be included in the conclusion.

Author's Response: We have discussed the effects of various GLP-1RAs on different metabolic parameters. We have also given results of head-to-head comparison trials. We do not want to suggest any particular molecule/brand being the <u>most</u> reliable GLP-1RAs, as we feel that such suggestion may be taken as biased and may be challenged/criticized. We want to leave this decision to our learned readers.

Response to Reviewer-3 (Reviewer's code 00506397)

1. Authors should format the Manuscript so that every Reference that they describe is given a separate paragraph. For example, Introduction can be consolidated into THREE PARAGRAPHS

Authors' Response: We have formatted the manuscript as suggested by Reviewer-3 and made separate paragraphs for each reference as far as possible.

2. The Manuscript should be carefully edited so that the names of drugs are uniformly stated (either ALL of them begin with an Uppercase in their names or ALL of them in Lowercase).
*Auth*ors' *Response: We welcome the suggestion. We have mentioned the names of all drugs in Lower Case, unless a name appears as the first word in a sentence.*

The last line of the ABSTRACT should have a CONCLUDING statement.

Authors' Response: We have added one sentence as "concluding statement" in our Abstract (last sentence – highlighted.(Page# 4, Line# 16-18)

Authors' Response: We have also added one line (in CONCLUSION section) as a concluding statement. (Page# 22, Line# 15-17)

The last sentence of the Abstract should be incorporated earlier as an AIM of the Review.

We have created an "Aim of the Review" as suggested by Reviewer-3.
(Page# 6, Line# 1-3)

Response to Reviewr-4 (Reviewer's code 00506390)

General Comments:

- The review has a very interesting and relevant topic, especially with the prevalence of MetS. The manuscript is generally well written with only a few issues that should be addressed to strengthen this review.
- Please review for grammatical/punctuation errors. There were several punctuation issues throughout the review.
- Please review for formatting issues. There were several formatting issues (i.e., spacing within sentences, spacing between paragraphs, etc.) throughout the manuscript and references.

Authors' Response: Thanks for the comments. We have noted the punctuation, grammatical and formatting errors/inconsistencies and we have thoroughly edited the manuscript to rectify them.

Introduction:

- Page 2: Para 4: The authors state “Recent figures in the USA….”, but refer to statistics from 2010. Please confirm these are the most current statistics. NHANES has data through 2012.

- *Authors’ Response: We quoted the figures from an article published in J Am Coll Cardiol in 2013. However, we have added the NHANES’ obesity data of 2012, as suggested.* (Page# 7 , Line# 20-26)

- Page 2: Para 4: The authors reference the 2009 Joint Scientific Statement. Please provide a formal, in-text reference.

Authors’ Response: We have provided the reference. (Reference5). (Page# 7, Line#6)

- Page 4: Para 1: The authors state “reduction of 0·78% in the albiglutide group and 0·99% in the liraglutide group; treatment difference was 0·21%.” Please clarify the numbers used (i.e., does 0 ·78% mean 78% or 0.78% or 0 to 78%?).

Authors’ Response: We have checked the article. The figures are correct. There was HbA1c reduction of 0.78% (from baseline) in albiglutide group and HbA1c reduction (from baseline) of 0.99% in liraglutide group. The difference of treatment between the two groups was (0.99 – 0.78 = 0.21). (Page# 11, Line# 7-13)

- Page 6: Para 1: The authors state “increase in HDL-cholesterol (18% increment from baseline)”. Does “increment” refer to the type of increase observed? If so, please clarify why an incremental increase is significant.

Authors’ Response: The study endpoints were (1) Reduction in CIMT and (2) Changes in Lipid subfractions. As HDL-cholesterol is cardio-protective, its increase in the study was taken as significant (and favorable for patients) by the authors. (Page# 14, Line# 15-17)