Fang-Fang Ji
Science Editor
World Journal of Hepatology

Re: 41170; Treating NAFLD with antidiabetic drugs: are GLP-1 agonists the end of the struggle?

Dear Dr Ji,

Thank you for your time to review our submission to your journal. Your suggestions and the reviewer's comments have been supportive for the final development of our manuscript. Please find below (underlined) the changes that we have made to our initial submission in response to your suggestions and the reviewer's comments.

Reviewer #1 comments:

This manuscript is submitted as an editorial Authors discuss the role of various anti diabetic agents in treatment of NAFLD and NASH The manuscript is timely in addressing the topic that it does The quality of the manuscript is good Hypothesis, methods, results, Limitations, strengths and ethical standards do not apply to this study Major revisions The Manuscript is submitted as an Editorial - The format does not fit the format provided here https://www.wjgnet.com/bpg/GerInfo/214 There is no perspective section. While the authors provide a brief review of available data, an overarching perspective reviewing any nuances or future directions is missing.

Thank you for this comment. A "perspective" section has been added according to the format provided by the journal, in order to highlight potential areas for future research. The following paragraph has been added:

"GLP-1 agonists have been shown to be effective in improving liver histology and reducing aminotransferase levels in patients with NAFLD. So, the question arises as to whether these agents could serve as a treatment option for these patients. While data are promising, they are still limited. Future large scale randomised controlled trials with complete histological outcomes are warranted to elucidate the efficacy of GLP-1 agonists in treating NAFLD. Another major limitation is the lack of long-term outcomes. Studies of longer duration are required to properly evaluate the histological improvement in NAFLD. What is more, it would be interesting if future trials would include both diabetic and non-diabetic patients, in order to clarify the effect of GLP-1 agonists in NAFLD, regardless of changes in glycemic control. It would be, also, significant to be assessed whether GLP-1 agonists affect NAFLD in a dose dependent manner, searching for preferred doses."

Also while data from multiple studies is provided there are no comments regarding limitations or strengths of studies.

Thank you for this comment. We reported the major limitations of the studies in the "perspective" section along with suggestions for improvement in future research. We, also, added the major strengths and limitations of Armstrong's study : "The authors used histological primary endpoints, being able to evaluate the direct effect of liraglutide on the liver. The study was performed on patients with biopsy-proven NASH, avoiding the inclusion of those without definite NASH. Their findings suggested that liraglutide led to the histological resolution of NASH, with the small sample size being, however, a major limitation."

Perhaps the study would better fit 'Mini Review' Category

This is true. However, our manuscript was an invited Editorial and therefore we suppose that it is upon the Editorial Board to decide which category it fits better.

Small typo on page 4 "either pioglitazon e (30 mg/d) or vitamin E"

It has been corrected.

Sentence on page 4 needs restructuring "The results showed that pioglitazone significantly improved steatosis and lobular inflammation compared to placebo, while the rate of steatohepatitis resolution was higher in the pioglitazone group."

Thank you for your comment. The aforementioned sentence has been changed to: "Pioglitazone was associated with significant reduction in steatosis and lobular inflammation compared to placebo"

Reviewer #2 comments:

The editorial by Maria Kalogirou and Emmanouil Sinakos is written well, and a topic of interest, which could be recommended for publication after some adjustments: Are any systematic meta-analysises available? This should be discussed in the manuscript, respectively the lack of such studies.

Thank you for your comment. We have, already, included the most recent meta-analysis regarding the efficacy and safety of GLP-1 agonists in NAFLD (Dong et al., 2017). The corresponding part in the manuscript is the following: "Lastly, a recent meta-analysis of six studies assessing the efficacy of GLP-1 agonists (liraglutide and exenatide) in NAFLD, revealed that these agents improve liver histology and reduce serum aminotransferase levels, indicating that they might be effective in patients with biopsy-proven NASH." Unfortunately few meta-analyses

have been published up to now. We chose to mention the one conducted by Dong et al., as the most recent meta-analysis on GLP-1 agonists.

If would be of interest to clearly specify which studies for GLP1-based therapies were randomised and double-blinded.

Thank you for this comment. The only randomised and double-blind study for GLP-1 agonists in patients with definite NASH was the one by Armstrong et al. and the on-going trial comparing the efficacy of semaglutide versus placebo in NASH (NCT02970942). The last one is clearly defined as randomised and double-blind in text. We, also mentioned that the LEAN study by Armstrong et al. was randomised and double-blind, by adding the phrase: "a double-blind randomized placebo controlled trial".

Is any data on long-term outcome of GLP1-based therapies available?

A major limitation of the studies assessing the efficacy of GLP-1 agonists in NAFLD is their short-term follow-up. In response to your comment, we have highlighted this fact in the "perspective" section: "Another major limitation is the lack of long-term outcomes. Studies of longer duration are required to properly evaluate the histological improvement in NASH."

Are recommendations from EASL/AASLD for GLP1-based therapies available? This or lack of such recommendations should be discussed in the manuscript

Thank you for your comment. We mentioned the recommendations from EASL/AASLD regarding the use of GLP-1 agonists in NAFLD, based upon their latest guidance. Thus, we added the following part in our manuscript: "GLP-1 agonists are not, currently, recommended by the AASLD and EASL for the treatment of NAFLD. In their latest guidance, it was pointed out that it is still prema-

ture to consider them as a specific treatment for patients with NASH without diabetes, due to inadequate evidence."

Overall, due to the currently available data, the conclusions seem too strong (page 8) "...ultimately bring the struggle to find an effective antidiabetic agent for patients with NAFLD to an end..." and should be tampered down.

Thank you for your comment. We altered the conclusions, according to your suggestions. The modified part is the following: "In conclusion, current evidence suggests that GLP-1 agonists may be an attractive therapeutic option for patients with NAFLD. However, larger studies of longer duration with histological endpoints are still required to establish their exact role in the management of NAFLD."

Period after et al. recommended, for example, Armstrong et al (page 5, line 24)

This has been altered accordingly.

Check spelling: „mid-2019" page 7, line 25

Thank you for this comment. The phrase "during 2019" has been used instead.

Reviewer #3 comments:

This editorial entitled, treating NAFLD with anti diabetic drugs: Are GLP-1 agonists the end of the struggle? The topic is quite interesting as fatty liver disease is one of the major health problems allover the world and lack of an approved medication. Most of the trials included patients with a biopsy-proven NASH. Therefore, I suggest to change the tile into: Treating NASH with anti-diabetic drugs: Are GLP-1 agonists the end of the struggle?

Thank you for your comment. The title was changed, according to your suggestion.

We hope that the above mentioned changes satisfactorily address your comments and that our revised manuscript will now be approved for publication in your journal.

Sincerely,
Maria-Styliani Kalogirou