

Dear Editor,

We submit a revised version of our invited editorial titled “The role of sodium-glucose co-transporter-2 inhibitors in the management of nonalcoholic fatty liver disease” for consideration for publication in the World Journal of Gastroenterology. We thank the Reviewers for their comments, which improved our paper. We modified the text according to these comments. All changes are shown in red in the revised text.

Reviewers’ code: 03023823

Several statements are not supported or weakly supported by available reports, which are not critically discussed.

We thank this Reviewer for this comment. However, we would like to emphasize that all the statements in the editorial are supported by references. Moreover, we recognize the limitations of the existing studies and therefore we avoid the use of strong language in our statements and in the conclusions. We also expanded the discussion of the available studies. Finally, since this is an editorial, it is expected or even desirable to express personal opinions, within reason.

Reviewers’ code: 01518946

This is excellent comments as editorial review.

We thank this Reviewer for this positive comment.

Reviewers’ code: 03478516

Please, add in the Discussion also this article that states this review includes a large number of patients with type 2 diabetes and found that SGLT2-i reduces HbA1c with a notable increased risk in non-serious adverse events. The analyses may overestimate the intervention benefit due bias. PLoS One. 2016; 11(11): e0166125. Benefits and Harms of Sodium-Glucose Co-Transporter 2 Inhibitors in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis

We thank this Reviewer for this comment. We added in the Discussion “Moreover, these agents induce a notable increase in non-serious adverse events, particularly urinary and genital tract infections, and their glucose-lowering benefit might have been overestimated.” and we cite this important paper.

Reviewers’ code: 02942902

This is an editorial paper regarding the potential role of SGLT2 inhibitors in NAFLD/NASH patients with diabetes. I consider that the topic is important; however, I have some comments. 1) It has been suggested that pharmacokinetics of SGLT2 inhibitors were unlikely to be affected by the presence of hepatic impairment (Clin Ther. 2018;40:1701-1710; Clin Ther. 2015;37:610-628; Diabetes Obes Metab. 2014;16:118-23; etc). However, careful attention may be required when physicians administrate an SGLT2 inhibitor to the patients with severe liver cirrhosis, because the number of studied patients in each study, particularly those with severe liver dysfunction (e.g., Child-Pugh grade C) was limited. 2) In relation to my comment No1., SGLT2 inhibitors may be carefully administrated to patients with ascites, since such patients are frequently receive diuretic(s). 3) Regarding the basic researches to investigate the effect of SGLT2 inhibitor on NAFLD/NASH, a paper (Shiba K, et al., Sci Rep. 2018;8(1):2362) may be useful for an additional reference.

We thank this Reviewer for these important comments. We added in the Discussion “In addition, even though the pharmacokinetics of SGLT2 inhibitors are unlikely to be affected by the presence of hepatic impairment, there are limited data regarding the safety of these agents in patients with severe liver dysfunction (e.g., Child-Pugh grade C). Therefore, close monitoring is required during the administration of SGLT2 inhibitors in patients with advanced cirrhosis, particularly in patients with ascites who are receiving diuretics.” and we cite these 3 relevant papers. We also added in the discussion “Importantly, a recent preclinical study also showed that canagliflozin reduces the risk for hepatocellular cancer in an animal model of NASH” and we cite the interesting study by Shiba et al.

Reviewers' code: 01436308

This manuscript summarized the role and potential mechanisms of SGLT2 inhibitors in the treatment of NAFLD. The topic is important and the manuscript is well written. I would recommend the publication of this manuscript.

We thank this Reviewer for these positive comments.

We look forward to your decision.

Best regards,

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