

March 10, 2020

Editorial Office

World Journal of Gastroenterology

Baishideng Publishing Group Inc

Dear Sirs

we would like to sincerely thank you and the Reviewers for your very useful comments which allowed us to significantly improve our work. We have prepared a point to point reply to the comments of Reviewers:

REVIWER ID 03674832: The review study paper 54404-Manuscript “Association between non-alcoholic fatty liver disease and obstructive sleep apnea” has relevance to the audience of this journal. The aim of the present study was to investigate the association of obstructive sleep apnea (OSA) with the pathogenesis and the severity of NAFLD. The authors report that showed an increased prevalence of NAFLD in patients with the diagnosis of OSA, even in the absence of coexisting comorbidities such as obesity or metabolic syndrome. Also, the severity of NAFLD is associated with an increase in OSA severity. Effective CPAP treatment, although not always decisive, may stabilize or slow NAFLD progression with benefits on metabolic and cardiovascular functions. Therefore, in NAFLD patients, although asymptomatic, it is recommended to systematically perform polysomnography. Comments 1. The manuscript is a review paper on an interesting issue: OSA and pathogenesis-severity of NAFLD. 2. It is well written; the text and the table is suitable and informative. 3. References are up to date. 4. There are practical implications of the results of this study in the effort to improve the treatment of both NAFLD and OSA.

Reply: We thank the reviewer for the valuable and extremely positive comments.

REVIEWER ID 00030389: The authors reviewed 13 articles for the assessment of the association between NAFLD and OSA. The results showed four findings. The 1st one is an increased prevalence of NAFLD in patients with diagnosis of OSA. The 2nd one is that this association is observed in the absence of coexisting comorbidities such as obesity or

metabolic syndrome. The 3rd one is that the severity of NAFLD is associated with the increase in OSA severity. The 4th one is that the effective CPAP treatment may stabilize or slow NAFLD progression. This review is informative. I have a few comments. #1. Please separate the conclusion into 4 sections according to the findings. #2. The authors did not describe 6 articles (ref. 34, 37, 39, 41, 52 and 53). Please describe which of 4 findings are observed in these 6 articles.

Reply: The Reviewer is right. We had described these 6 articles only in the table.

According to Reviewer's comments, the "Conclusion" section has been divided into 2 new sections, "Discussion" and "Conclusion".

In the new "Discussion" section we have created 4 different paragraphs according to the 4 different and important findings:

1- *Increased prevalence of NAFLD in patients with diagnosis of OSA*, in which we have described the references 52-53 (Agrawal et al and Qi et al) as follows: "Furthermore, Agrawal et al^[49] described a prevalence of 91.3% of NAFLD in a small group of patients with OSA and abdominal obesity whereas Qi et al^[50] found a prevalence of 64% in 149 non-obese OSA patients."

2- *Association between NAFLD and OSA in the absence of coexisting comorbidities*

3- *The severity of NAFLD is associated with the increase in OSA severity*, in which we have described the references 34, 41, 37, 39 (Petta et al, Arisoy et al, Chen et al and Trzepizur et al) as follows: "Similarly, Petta et al^[34] showed an association between the severity of liver damage with high risk of OSA and lower oxygen saturation. Arisoy et al^[41] observed that BMI and hepatosteatosis grade progressively and significantly increased from patients without OSA to those with severe OSA. Chen et al^[37] found a positive association between the severity of OSA and NAFLD. In particular, the prevalence of NAFLD was 20.4% in patients with AHI<15 whereas it reached 52.1% in patients with AHI≥15. Trzepizur et al^[39] demonstrated an association between increasing OSA severity and liver fibrosis; patients with severe OSA and metabolic comorbidities are at higher risk of significant liver disease and advanced liver fibrosis."

4- Effective CPAP treatment may stabilize or slow NAFLD progression

REVIEWER ID 00049727: Umbro et al. collected the data regarding NAFLD and OSA and found that NAFLD severity is associated with OSA severity. They also suggested that CPAP slowed NAFLD progression. While this study is important, there are some points to be corrected. 1. The sections of Results and Discussion are quite short and are included in the Conclusion in part. 2. The authors should discuss the possible mechanism on how OSA worsens NAFLD activity independently of metabolic syndrome and adiposity in more details.

Reply: Following the Reviewer's suggestion we have moved into the new "Discussion" section some data previously reported in the "Conclusion" section.

Furthermore, in the "Discussion" section we have created 4 different paragraphs according to the 4 different and important findings:

- 1- Increased prevalence of NAFLD in patients with diagnosis of OSA
- 2- Association between NAFLD and OSA in the absence of coexisting comorbidities
- 3- The severity of NAFLD is associated with the increase in OSA severity
- 4- Effective CPAP treatment may stabilize or slow NAFLD progression

In the second paragraph we have discussed more in details the association between NAFLD and OSA in the absence of coexisting comorbidities as follows: "Furthermore, the results of this review showed that the association between OSA and NAFLD seems to be independent of coexisting comorbidities such as visceral fat or MetS.

Yu et al[36] showed an association between OSA and NAFLD independently from visceral fat level in subjects with mean BMI of 24.7 kg/m², particularly in those with short sleep duration or excessive daytime sleepiness. Benotti et al^[40] reported that, in patients with OSA without MetS, as the severity of AHI and hypoxia increased, the prevalence of more severe NAFLD significantly increased as well. However, the exact mechanisms involved in this association in the absence of visceral fat and MetS is still unclear. Certainly the effects of chronic intermittent hypoxia on liver may involve increased lipogenesis, formation of reactive oxygen species and proinflammatory cytokines which cause lipid

peroxidation and hepatocyte injury^[45]. Therefore, lipid metabolism, inflammation and OSA hypoxic environment may be of key importance in reducing the risk of NAFLD in OSA patients.”

EDITORIAL OFFICE: Verify the accuracy of general information for your manuscript

Name of journal: World Journal of Gastroenterology

Manuscript NO.: 54404

Column: Systematic Review

Title: Association between non-alcoholic fatty liver disease and obstructive sleep apnea

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Reviewer code: 00030389, 00049727, and 03674832

First decision: 2020-03-06

Science editor: AI Technique

Reply: We have submitted the manuscript as an “Invited Review” and not as a “Systematic Review”. I, along with my coauthors, would be grateful if you could change the Column from “Systematic Review” to “Invited Review”.

Probably the use of systematic in the manuscript caused confusion. Therefore, we have removed all the “systematic” written in the text. In the “Abstract” section we have replaced “The results of this systematic review showed an increased prevalence of NAFLD in patients with diagnosis of OSA, even in the absence of coexisting comorbidities such as obesity or metabolic syndrome.” with “The results of this review showed an increased prevalence of NAFLD in patients with diagnosis of OSA, even in the absence of coexisting comorbidities such as obesity or metabolic syndrome.”

In the “Introduction” section we have replaced “The aim of this systematic review is to provide a more comprehensive overview of the association between NAFLD and OSA considering also the efficacy of CPAP treatment.” with “The aim of this review is to

provide a more comprehensive overview of the association between NAFLD and OSA considering also the efficacy of CPAP treatment.”

In the “Discussion” section we replaced “The results of this systematic review showed an increased prevalence of NAFLD in patients with diagnosis of OSA.” With “The results of this review showed an increased prevalence of NAFLD in patients with diagnosis of OSA.” Therefore, since our manuscript is an “Invited Review”, the Biostatistics Review Certificate and the PRISMA 2009 Checklist are not required.

I, along with my coauthors, would like to thank you for your comprehension.

I look forward to hearing from you at your earliest convenience.

Yours sincerely,

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