

DETAILED ANSWERS TO THE EDITOR AND REVIEWERS' COMMENT

Dear Editor,

We would like to use this opportunity to sincerely thank you and the reviewers for your detailed and helpful comments. In the revised manuscript, we carefully addressed the issues raised and we have tried to do our best to provide a point-by-point reply.

Following, all reviewer's comments are in black; our answers are in red.

All modifications we made are highlighted in yellow in the revised manuscript

❖ Editor suggestions – SPECIFIC COMMENTS TO AUTHORS

Comment: Please provide language certificate letter by professional English language editing companies (Classification of manuscript language quality evaluation is B). For manuscripts submitted by non-native speakers of English, please provided language certificate by professional English language editing companies mentioned in 'The Revision Policies of BPG for Article'.

Answer: The revised manuscript was completely reviewed by highly qualified professional native English editors in terms of: presentation style, logic and clarity, consistency and terminology, detailed language and grammar check. We provided the editing certificate.

Comment: Add author's post code.

Answer: Done. See pages 1-2 of the revised manuscript

Comment: In order to attract readers to read your full-text article, we request that the author make an audio file describing your final core tip, it is necessary for final acceptance.

Answer: Done.

Comment: Please add some figures and tables, or we cannot accept it.

Answer: Thanks for your suggestion. Done. See Figure 1, Figure 2, Table 1 and Table 2 of the revised manuscript.

Comment: Please check and confirm that there are no repeated references!

Answer: We confirm that there is not repeated reference in the revised manuscript

Comment: Please add PubMed citation numbers and DOI citation to the reference list and list all authors.

Answer: Done. See references list of the revised manuscript

❖ **Reviewer's code: 00068273 - SPECIFIC COMMENTS TO AUTHORS**

Comment: No particular observations. Very interesting and time-consuming paper. Any limitation in publishing this review.

Answer: Thanks on behalf of all the authors

❖ **Reviewer's code: 00008736 - SPECIFIC COMMENTS TO AUTHORS**

Comment: The authors present a comprehensive Review on the Topic of obesity and Nutrition in patients with liver cirrhosis. The manuscript is very well written, and all relevant aspects are fully covered. To further improve the manuscript, Graphs highlighting the Impact of Body weight, Nutrition and other factors on cirrhosis and liver capacity would be highly welcome. A tabular summary of relevant findings might also be helpful.

Answer: Thanks for your suggestion. Done. See Figure 1, Figure 2, Table 1 and Table 2 of the revised manuscript.

Comment: The section on Vitamin D is very Long and may be shortened.

Answer: Thanks for your suggestion. We cut short the introduction of this section. See pages 12-13 of the revised manuscript.

❖ **Reviewer's code: 00054275 - SPECIFIC COMMENTS TO AUTHORS**

Comment: Nice and exhaustive review: it earns to be published

Answer: Thanks on behalf of all the authors

❖ **Reviewer's code: 02520359 - SPECIFIC COMMENTS TO AUTHORS**

Comment: In the first section it is better to state that NAFLD is the hepatic manifestation of metabolic syndrome, instead of obesity.

Answer: I modified my statement. See page 5 of the revised manuscript

Comment: The authors have to present any data regarding the degree of obesity and its impact to the severity of the liver disease.

Answer: I think that there is a mistake, we have never told that NAFLD severity alone is correlated to the different obesity degree. Since definition of NAFLD and determining the degree of obesity is controversial, literature is not clear about this correlation (CORDEIRO L Arq Bras Cir Dig. 2013, Ms OH Pediatr Gastroenterol Hepatol Nutr. 2016, PATTON HM Am J Gastroenterol. 2010, MACHADO MJ HEPATOL 2006).

Comment: Regarding the role of sarcopenic obesity in cirrhosis the authors have to speculate about the pathophysiologic mechanisms explaining the higher morbidity in these patients. They have also to comment whether the studies conducted in Korean population can be extrapolated in western populations.

Answer: Done. See page 9 of the revised manuscript.

Comment: This sentence, in page 21, is written in duplicate “The recommended dietary pattern is for small, frequent meals evenly distributed throughout the day (every 3–6 h) with a late evening snack containing at least 50 g of complex carbohydrate [117].

Answer: Sorry for the mistake. Corrected. See page 20 of the revised manuscript.

Comment: Some minor English language polishing is needed.

Answer: The revised manuscript was completely reviewed by highly qualified professional native English editors in terms of: presentation style, logic and clarity, consistency and terminology, detailed language and grammar check. We provided the editing certificate.

❖ **Reviewer’s code:** 03473431 - **SPECIFIC COMMENTS TO AUTHORS**

Comment: The following changes are needed:

Pag 7, line 4: please specify that the relative risk of cirrhosis increased more than six-fold in women with obesity and alcohol consumption (>150 g/week) vs non-obese and drinking < 70 g/week women.

Answer: Done. See page 6 of the revised manuscript.

Comment: Pag 7, line 13: reference number 13 and 14 (Berzigotti et al) please report inserted in the text.

Answer: Answer: Done. See page 6 of the revised manuscript.

Comment: Pag 7, line: please specify that obesity increase “substantially” (HR 13.1), “independently” but also “significantly” (p= 0.016) the risk of portal thrombosis.

Answer: Done. See page 7 of the revised manuscript.

Comment: Pag 10: line 24 “hospital stay” could be more appropriate than simply “stay”

Answer: Done. See page 9 of the revised manuscript.

Comment: Pag 12: the sarcopenic obesity observed after organ transplantation is well-described, anyway a reference to the possible cause of these condition such as insufficient physical exercise or drugs (calcineurin inhibitor, steroid and rarely mycophenolate) is not done.

Answer: Done. See page 11 of the revised manuscript.

Comment: Pag 14: line 5 “(VDD, <20 ng/mL)” should be “(DDD, <50nmol/L; <20 ng/mL)” since in line 9 the measure is “(<75 nmol/L, <30 mg/mL).

Answer: The sentence was corrected. See page 12 of the revised manuscript.

Comment: Pag 14 line 12: the severity of VDD is “directly” and non “inversely” related to the severity of liver disease and in cirrhotic patient the presence of HbsAg and HbcAg for me could be misunderstood in: HBV infection is not a risk factor for mortality.

Answer: Thank you for this comment we made corrections accordingly. See page 12 of the revised manuscript.

Comment: Pag 15 line 19: the abbreviation “MRS” should be “Magnetic Resonance Spectroscopy”

Answer: The abbreviation was replaced with the full name. See page 13 of the revised manuscript.

Comment: Pag 16: vitamin D deficiency is discussed; what about disbiosis in cirrhosis as a cause and an effect of VDD?

Answer: We agree it’s an interesting topic, although not fully studied and we feel that it is beyond the scope of the manuscript. We could not find evidence for an association with vitamins or vitamin D in cirrhosis, only a general statement of reduced absorption with bacterial overgrowth.

Comment: Pag 17 line 17: Please clarify that the guidelines (reference n° 81) recommend calcium and vitamin D as a general preventive treatment in patients with cirrhosis and severe cholestatic disease and not in all patients with chronic liver disease.

Answer: We thank you for the comment, and we have now added “(especially in patients with cirrhosis or severe cholestasis)”. See page 15 of the revised manuscript. We just would like to clarify that in the guidelines mentioned it is a recommended supplement to all patients with chronic liver disease: “Page 7, “10.3 **General measures for all patients with chronic liver disease:** (1) Lifestyle measures (recommendation grade C) • Reduction in alcohol intake if excessive. • Regular weight bearing exercise. • Stop smoking. (2) Dietary (recommendation grade C) • Ensure adequate nutrition as low body mass index is an independent risk factor. • **Supplementation with calcium (1 g/day) + vitamin D3 (800 U/day).** There is no risk of hypercalcaemia except in patients with sarcoidosis where calcium levels should be monitored.”

Comment: Pag 18 line 25: It should report “primary biliary cholangitis” and not “primary biliary cirrhosis” even the reference should be updated.

Answer: Thank you for highlighting the new definition for PBC. It was properly updated in the relevant places. See page 16 of the revised manuscript.

Comment: Pag 19 line 15: ADL is “advanced liver disease”

Answer: The abbreviation was replaced with the full name. See page 17 of the revised

manuscript.

Comment: Pag 20 line 102: in the study by Mousa (Reference n° 102) the treatment group was treated not only with zinc and antioxidant but also with lactulose.

Answer: Thank you for emphasizing this difference between treatment arms. This was amended in the text. See page 18 of the revised manuscript.

Comment: Pag 22 line 5: clarify that magnesium uptake is increased in the condition of magnesium depletion.

Answer: We have made this clarification. See page 19 of the revised manuscript.

Comment: Pag 28 line 10 and 15: "TIPS" is more currently used than "TIPSS"

Answer: Thanks for the suggestion. Corrected. See pages 25-26 of the revised manuscript

Comment: Pag 29 line 6 and 20: in line 6 and not in 20 should be explained the significance of "RYGP"

Answer: Done. See page 25 of the revised manuscript.

Comment: Pag 29 line 20; "LABG" is laparoscopic adjustable gastric banding and SG is "sleeve gastrectomy"

Answer: Done. See page 26 of the revised manuscript.

❖ **Reviewer's code: 00003629 - SPECIFIC COMMENTS TO AUTHORS**

Comment: It would have been useful to make a reference of how body muscle tissue and body mass fat can be estimated clinically.

Answer: Done. See page 8 of the revised manuscript.

Comment: Authors should also consider the following references: Clapp B, et al. Long term (7 or more years) outcomes of the sleeve gastrectomy: a meta-analysis. Surg Obes Relat Dis 2018. [Epub ahead of print] PubMed PMID: 29625744; Lemmens L, et al. Banded Sleeve Gastrectomy: Better Long-Term Results? A Long-Term Cohort Study Until 5 Years Follow-Up in Obese and Superobese Patients. Obes Surg 2018. [Epub ahead of print] PubMed PMID: 29671124; Noel P, et al. What are the long-term results 8 years after sleeve gastrectomy? Surg Obes Relat Dis. 2017; 13:1110-1115; Yemini R, et al. Bariatric surgery in solid organ transplant patients: Long-term follow-up results of outcome, safety, and effect on immunosuppression. Am J Transplant 2018. [Epub ahead of print] PubMed PMID: 29569341; Adams TD, et al. Weight and Metabolic Outcomes 12 Years after Gastric Bypass. N Engl J Med 2017; 377:1143-1155.

Answer: Thanks for your suggestion. We add some of the suggested references. See pages 26-27, and 54-55 of the revised manuscript

Comment: (Page 6 lines 1-4 from top): The ultrasound estimation of steatosis is grossly subjective.

Answer: Thank you for your comment. We totally agree with you: ultrasound had a lot of limitation, but we only reported a large multicentric and recent study.

Comment: (Page 6, line 9 from bottom): Within what interval of observation decompensation of cirrhosis developed?

Answer: Done. See page 6 of the revised manuscript.

Comment: (Page 7, line 11 from top): Please give a reference.

Answer: Done. See page 10 of the revised manuscript

Comment: Authors should follow the format of WJG and make sure that all cited references comply.

Answer: Done. All references were revised accordingly with the WJG author's guidelines.

❖ **Reviewer's code: 03567380 - SPECIFIC COMMENTS TO AUTHORS**

Comment: Overall, the review is well written and encompasses many of the necessary aspects of this field. However, there are a few areas the authors should address to improve this review, which are outlined below: 1) The authors spend a significant portion of the review talking about micronutrient status and supplementation. This section would be improved by discussing alterations, and the subsequent effects, to the microbiome during cirrhosis/obesity.

Answer: Thanks for your interesting suggestion but it's beyond the scope of this manuscript. However, we added that deficiencies can be related also to cholestasis and bacterial overgrowth. See page 12 of the revised manuscript.

Comment: The authors need to include figures or tables to graphically summarize the literature for the major sections of the review (or at minimum a overall summary figure).

Answer: Thanks for your suggestion. Done. See Figure 1, Table 1 and Table 2 of the revised manuscript.

Comment: The sentence "The recommended dietary pattern is for small, frequent meals evenly distributed throughout the day (every 3–6 h) with a late evening snack containing at least 50 g of complex carbohydrate" is repeated twice (once on page 20, and the other on page 21).

Answer: Sorry for the mistake. Corrected. See page 20 of the revised manuscript.