

ANSWERING REVIEWERS

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Title: Clinical assessment and management of liver fibrosis in non-alcoholic fatty liver disease

Dear Editor and Dear Reviewers,

We appreciate the revision and comments on our study in order to improve the manuscript to be considered for publication in your journal. Below is a point-by-point response for the comments made by each of you.

Best regards,

Ricardo Ulises Macías-Rodríguez

Corresponding to: Ricardo Ulises Macías-Rodríguez, M.D., M.Sc., Ph.D.,
Department of Gastroenterology, Instituto Nacional de Ciencias Médicas y
Nutrición Salvador Zubirán, Vasco de Quiroga 15, Belisario Domínguez Sección
XVI, Tlalpan, Mexico City, 14080, Mexico.

Telephone: +52 55-54-87-09-00, ext. 2711

Fax: +52 55-56-55-22-24

Email address: ricardomacro@yahoo.com.mx

REVIEWER #1:

The manuscript (ID: 02861208) entitled "Clinical assessment and management of liver fibrosis in non-alcoholic fatty liver disease" was by Campos-Murguía A, et al. This is a review paper. Main comments 1. The abstract probably can be organized into the goals, methods and findings in a succinct way. This may help readers to grasp your purposes and findings. 2. Please also discuss the benefits of bariatric surgeries to obesity and type 2 diabetes.

ANSWER:

1. Thank you for this valuable comment, we added the aim of the study to the abstract, our methods and main findings.

2. We appreciate this helpful suggestion. We added the benefits of bariatric surgery in weight loss and the improvements in glycemic control in T2DM patients. This effects of bariatric surgery could be the main reason for the improvement NAFLD. This is discussed in the fourth paragraph of the "Weight loss" section.

REVIEWER #2:

This manuscript is a review of the available methodology to define the extent of hepatic fibrosis in patients with nonalcoholic fatty liver disease. The review places this information in context and reviewed available therapeutic intervention. The analysis of the strength of evidence of each method of fibrosis determination is a valuable combined reference given the many choices available to clinicians. The text has multiple minor grammatical / typing errors, but is well written and thoroughly referenced. This paper helps the clinician decide of the method of defining illness and choosing intervention in this important and growing group of patients. Specific comments: 1. In the discussion of the use of vitamin E for the treatment of fatty liver, there is evidence to more strongly support use in the nondiabetic population. This distinction is not explained in the manuscript and would be a valuable clarifying

note. 2. Most of the agents being proposed or discussed for use in fatty liver therapeutics remain experimental. This fact is discussed at the conclusion of the paper, but adding this information more prominently in the text where the agents are introduced would be valuable to the reader looking for intervention for an individual patient. 3. The use of RAS inhibitors in NAFLD is strongly endorsed and referenced to Goh, et al. The paper referenced is a retrospective cross-sectional study. I question the strength of evidence for the strong recommendation for use given by the authors. This may be best further tempered or explained. 4. The advice given is to use the algorithm to define patients with suspected advanced fibrosis to consider for liver biopsy. There are considerations other than fibrosis to judge need for biopsy that should be mentioned in discussion. These include suspected steatohepatitis and concern about an alternative or additional diagnosis for the etiology of liver disease.

ANSWER:

1. Thank you for pointing this out. The PIVENS study represents the best evidence available for the use of vitamin E in patients with NAFLD, unfortunately, this trial did not include patients with diabetes. We found a recently randomized controlled trial published by Bril et al. on Diabetes care, where there was no improvement in liver histology in patients treated with Vitamin E as monotherapy. We have added this information to the discussion of the use of vitamin E.

2. We appreciate this important comment and we agree that to date, the only two drugs recommended by the guidelines are pioglitazone and vitamin E, and the rest of the drugs discussed are experimental and should be used only under clinical trials. We emphasized this idea in the first paragraph of the “Specific pharmacological management” with the following note: “The current recommended drugs thus far in the guidelines are pioglitazone and vitamin E.^[4] Although there are multiple treatments with different mechanisms of action under development for

the treatment of NASH, and specifically aimed to reduce liver fibrosis, these drugs remain experimental and are considered for their use only in clinical trials.”

3.- Thank you for your observation, we agree with the fact that the evidence given for the use of RAS blockers is not strong. We added the main findings of a cohort in 118 NAFLD patients with paired liver biopsies (PLoS One 2016;11 [DOI: 10.1371/journal.pone.0163069]) Additionally, we added that RAS blockers are recommended as first-line therapy by hypertension guidelines and that these drugs have an excellent security profile. To conclude, given that these drugs could have a beneficial effect on the fibrosis development, their high safety profile, and that are recommended as first-line therapy in hypertension guidelines, we consider that the suggestion on their use as a first-line medication in patients with NAFLD and hypertension can be made.

4.- We agree with the reviewer, there are other indications for liver biopsy, therefore, we added these considerations in the last paragraph of the “Liver Biopsy” section.

Point-to-point response for second-round review

Reviewer:

The manuscript (56823) entitled "Clinical assessment and management of liver fibrosis in non-alcoholic fatty liver disease" is a review by Alejandro Campos-Murguía, et al. The author aimed to propose a practical and stepwise approach to the evaluation and management of liver fibrosis in patients with NAFLD, analyzing the currently available literature. Main comments 1. Some language editing is needed. For example, in the second paragraph of the abstract section, its should be "... take into account...". 2. Please do not define abbreviation when it only appears once. For example, PDFF only appeared once.

Response:

We have revised the manuscript according to the second round of comments. Attached is the final version where spelling mistakes have been corrected and the abbreviations of words appearing only once have been removed.

Thank you for your assistance

Best Astrid Ruiz Margáin