

ANSWERING REVIEWERS



February 16, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: MS 8879-R1 Bertolotti AJE Edited 13N33SVJ NO FIG.doc).

Title: NAFLD and aging: epidemiology to management

Invited review

Submission ID: 8879

Authors: Marco Bertolotti, Amedeo Lonardo, Chiara Mussi, Enrica Baldelli, Elisa Pellegrini, Stefano Ballestri, Dante Romagnoli, Paola Loria

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 8879

The manuscript has been improved according to the suggestions of reviewers and revision has been made accordingly.

Unless specified, page and line numbers refer to the **revised** version of the manuscript.

Changes made by the Authors have been highlighted **in red** in the revised version.

The text of the manuscript was revised by a professional editing company, as requested. An electronic copy of the text with the corrections highlighted with the "track change" option is available and can be provided whenever requested.

Attached you will find copy of the Editorial Certificate.

Finally, we attach copy of the Copyright Assignment form, in DOC format. Copy of the original signed document can be faxed or Emailed if necessary.

Comments and responses:

Reviewer 02861134:

We thank the Reviewer for the encouraging and positive comments.

Reviewer 00058872:

We thank the Reviewer for the overall encouraging comments and for the suggestions.

In agreement with these suggestions, we further stressed the role of inflammation in the pathogenesis of NAFLD and the fact that NAFLD cannot be considered an exclusive disease of the liver, but rather a systemic condition.

The latter consideration was recalled at page 6, opening sentence of the paragraph *Cardiovascular disease, metabolic complications, extrahepatic cancer*. The 2011 WJG paper was quoted here, and later on as well. A pertinent paper from our research group, already present in the reference list (n. 206 of the old manuscript), was also quoted here (n. 70 in the revised version).

In particular, the role of IGF, already mentioned as related to insulin resistance, was underlined together with the role of adipokines (Page 8 of the revised manuscript).

Likewise, the other points raised by the Reviewer were addressed: the apoptosis-antiapoptosis balance, as related with Bcl-2 (page 8, last sentence); the ER stress, the unfolded protein response, JNKs (page 8), the liver-spleen axis (page 8) and finally the role of abdominal fat and the potential relevance of its reduction (beginning of Page 10).

The role of hypercortisolism was mentioned (page 8 of the revised version) and a paper from our own research group, along with those suggested by the Reviewer, was quoted (appearing as n. 98 of the new manuscript).

The citations suggested by the Reviewer were added (respectively as n. 71, 99, 107, 108, 111 and 129 in the revised version). Two additional references regarding the role of Bcl-2 were also inserted at page 8 (n. 109 and 110).

Reviewer 00053684:

We thank the Reviewer for the encouraging and positive comments.

Reviewer 00070060:

We thank the Reviewer for the overall encouraging comments and for the suggestions.

The first issue addressed by the Reviewer (the relationship between altered drug metabolism and HCC development) was recalled at page 6 of the revised manuscript, at the end of the *Cryptogenic cirrhosis and HCC* paragraph, and briefly recalled later (page 7, second sentence of the *Liver* paragraph).

The second one, regarding the association between A-FABP and steatosis in the elderly, was addressed at page 8, third sentence.

The two new references suggested by the Reviewer were added, as n. 69 and 104 in the new manuscript.

Reviewer 00187937:

We thank the Reviewer for the overall encouraging comments and for the suggestions.

The first issue regarding vitamin B12 and folate deficiency, and increased homocysteine levels was addressed at page 14 of the revised manuscript, with regards to dementia, and briefly recalled at page 16 concerning the possible cardiovascular implications.

Four new pertinent references were added (n. 190, 191, 192 and 207 in the revised version).

Regarding the second issue: the sentence at page 17 was modified as follows: "However, after careful considerations of the cost/benefit balance of this procedure, liver biopsy might be considered in selected elderly patients^[51]."

Additional changes:

The reference citations in Tables 2 and 3 were modified as requested.

The figure was decomposed as requested.

Old reference 22 was moved to n. 29 in order to be consistent with the order in Table 2.

A new reference from our research group regarding the relationship between NAFLD and insulin resistance was added (ref. 91, end of page 7).

A new reference regarding possible therapeutic approaches involving the microbiota was added in the **Prebiotics and Probiotics** heading (page 19, n. 250).

Thank you again for considering to publish our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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