

ANSWERING REVIEWERS



April 30th, 2014

Dear Editor,

here enclosed you find the revised manuscript according to the Reviewers comments and a letter with a point to point answer to all the comments raised by the Reviewers. (file name: Reviewed manuscript.docx).

Title: NAFLD AND VASCULAR DISEASE: STATE-OF-THE-ART

Author: Silvia Fargion, Marianna Porzio, Anna Ludovica Fracanzani

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 9169

The manuscript has been improved according to the suggestions of reviewers (in-text corrections are underlined):

- Reply to reviewer 1

This is a comprehensive review to emphasize a close relationship between nonalcoholic fatty liver disease (NAFLD) and atherosclerotic cardiovascular disorders. The author indicate the highest point of researches and the current recognitions concerning this issue. I would like to say congratulations to the authors for their perfect work. To raise the scientific value of this review article, I recommend quoting the following paper to the "oxidative stress" section. Ikura Y, et al. Localization of oxidized phosphatidylcholine in nonalcoholic fatty liver disease: impact of disease progression. Hepatology 2006; 43: 506-514.

We thank the referee for his/hers comments. As suggested, we have now added the quoted reference in the appropriate section which surely improves the quality of the paper.

- Reply to the reviewer 2

We thank the Reviewer for the very accurate revision of the paper and we answer point to point to his/her comments.

Fargion and colleagues did a good work. The review gives good information. However, I have some comments:

1-What is the novelty of your work? What is the difference between your review and the following reviews with pubmed ID: 23666091, 23073871, 21987620 and 22596186?

We have systematically analyzed the topics singularly presented in the other reviews you mentioned. For example in review PMID 23073870 the Authors presented data only on brachial artery flow-mediated dilation, endothelial dysfunction and increased carotid intima-media thickness as surrogate markers of atherosclerosis. In addition, we have added some new, topics specifically the relation between NAFLD and impaired left ventricular function, atrial fibrillation and epicardic fat, the linkage between NAFLD, OSAS and vascular disease, the

importance of microangiopathy in NAFLD, the correlation between CVD, NAFLD, vascular disease and coagulation imbalance and increase assumption of fructose. Furthermore, we have emphasized that NAFLD, by itself, is probably an important and independent risk factor for the occurrence and progression of CVD.

2- *The review consists of separate parts. Try to arrange them and make correlations between these items.*

According to the Referee suggestion we have now linked the single topics we present in the introduction (page 3, last 3 lines; page 4 lines 1-4)

3- *What is the relation between vascular disease and the following items: obstructive sleep apnea syndrome, insulin resistance and adipokines imbalance? You made correlations between these items and NAFLD but not with vascular diseases.*

We have more extensively discussed the relationship between OSAS, insulin resistance, and adipokines imbalance and vascular disease by adding in the text a few sentences:

- OSAS, NAFLD and vascular disease: page 10, lines 13-14, lines 19-24
- Insulin resistance, NAFLD and vascular disease: page 13 lines 10-11, 15-16
- Adipokines imbalance, NAFLD and vascular disease: page 15, lines 17-22

4- *Try to add more figures and tables to represent your ideas.*

As suggested we have now added a figure (figure n° 3) in which possible causes and consequences of the procoagulant imbalance in patients with nonalcoholic fatty liver disease are listed and table n°3 that shows studies on the association between non-alcoholic fatty liver disease and carotid intima-media thickness (IMT) in adults and the independent predictors for IMT increase (page 12, lines 29-31)

5- *Arrange studies in table 1*

We have now arranged the studies in table 1 in a chronological sequence

6- *There is no reference for table 2 inside the text.*

We are sorry for our mistake, we have now mentioned in the text table 2 (page 8, line 21).

- References and typesetting were corrected

I hope that now the manuscript is acceptable. Looking forward to hearing from you
Sincerely

Prof. Silvia Fargion

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