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Dear Editor,

We have the pleasure to resubmit for your consideration a revised version of our manuscript **"INTRAHEPATIC VASCULAR CHANGES IN NAFLD: POTENTIAL ROLE OF INSULIN-RESISTANCE AND ENDOTHELIAL DYSFUNCTION"**, which has been edited in accordance with the criticisms/suggestions raised by reviewers and the revision of the editorial assistant of WJG. All changes have been highlighted in the new version of the main text. At this point, we would like to thank the reviewers for their constructive observations that undoubtedly have helped us to improve the quality of this manuscript and the potential interest on the vascular hypothesis of NAFLD pursued by our work.

We have also added a native-English speaker in the authorship, Dr. Beverly Kok, UK-fellow at the University of Edmonton, Alberta, Canada, who exhaustively revised the English style to ameliorating the B quality classification achieved with our first submission. Figures are now uploaded in a separate file as ppt images but also present in the main text to facilitate the revision.

Unfortunately, we were not able to subject the title in google scholar as requested by the instructions for authors. We hope to overcome all these editing problems with the help of the editorial assistants if the manuscript will be finally considered of interests for the readers of **WORLD JOURNAL OF GASTROENTEROLOGY**.

Sincerely,

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A point by point response is following listed. The original comments of the reviewers are reported in italics.

Rev. 1

1. *The manuscript `Intrahepatic vascular changes in NAFLD: potential role of insulin-resistance and endothelial dysfunction` by Pasarin M. et al. is an interesting study which poses an intriguing hypothesis of association vascular dysfunction with liver disease development. This provide new insights on metabolic sydrome. MS is well written and elaborated, its clinical relevance is obvious.*

We are very pleased that the hypothesis of NAFLD as a vascular disease of the liver reached the reviewer. Thank you for this comment.

2. *I would give rather minor recommendations to Authos (optional) that might improve manuscript - to consider importnat condition as Flammer sydrome on the NAFLD development, complexity of vascular abnormalities that might develop in liver including portal hypertension, issues like thrombogenesis, vascular malformalities, hypoxia-related mechanisms leading to fibrosis, etc.*

Interesting comment since the impairment of blood supply at the level of several organs, among them, the liver, is the pathophysiological substrate of Flammer syndrome. This would be in line with the importance of vascular changes in determining a chronic liver disease. However, we considered this suggestion off-topic because our review is focused on vascular changes induced by insulin-resistance and, at the best of our knowledge, a link with insulin-resistance/metabolic syndrome has not been demonstrated in patients with Flammer syndrome.

3. *Some illustrations / scheme would be helpful.*

We have added a figure resuming the pathophysiology and the potential strategies of treatment accordingly (please see Fig. 3 in the new version of the manuscript).

Rev. 2

This is a good review of insulin-resistance and vascular changes per NAFLD. The quality of the paper and English worth publishing. I have no specific comment.

Thanks to the reviewer for his/her positive comments.

Rev. 3

The current review addresses an important and timely topic. I therefore found this article interesting and relevant.

Thank you for the interest expressed for the manuscript.

1.The authors summarize very nicely the pathogenic concept of endothelial dysfunction in NAFLD. Many pathways are being described. What is currently lacking is ***a paragraph about biomarkers related to ED – and the potential dysregulation in NAFLD*** *(or, chronic liver diseases in general). I am thinking about tissue factor, thrombomodulin, ADMA, SDMA, CT-proET1, circulating selectins etc. – The authors only mention HVPG measurement, but this would not allow to detect more subtle*

*changes in early diseases. Possibly, a **table summarizing the value of potential biomarkers**, could be stimulating for the field and increase the outreach of the review article.*

We have added a specific subparagraph in the new version of the manuscript (please, see the highlighted text in the paragraph "From bench to bedside: potential clinical consequences"). Unfortunately, we only commented this issue in the main text and not in a specific table because there are not studies that have linked biomarkers with "intrahepatic" vascular changes induced by insulin-resistance. We have tried this limitation to appear clear to promote new adequately designed human studies.

2.Along this line, the therapeutic consequences remain vague. There is a lot of speculation (partially grounded on original data and meta-analyses) on the value of statins for NAFLD, but many other cardiovascular drugs as well as investigational NAFLD drugs (elafibranor, selonsertib etc.) might have an impact on ED. This topic would justify a bit more detailed exploration, possibly also with a figure or table, linking pathogenic observations to current or future therapeutic options.

We thank the reviewer for this important comment. We have finally added a figure depicting our vascular hypothesis of liver damage mediated by IR-induced sinusoidal endothelial dysfunction. In this figure, we have also listed the strategies of treatment with an impact on both IR and sinusoidal endothelial dysfunction. However, not all the drugs quoted have been studied for the effects on intrahepatic endothelial dysfunction and we have opportunely marked those with specific data on this issue. The reviewer will notice that selonsertib was excluded by this list. This was because the known mechanism of action of the drug is against apoptosis and not against IR neither sinusoidal endothelial dysfunction. This does not exclude the potential efficacy of the drug in the downstream pathogenic effects induced by the IR→endothelial dysfunction axis as generally stated in the main text at the end of the review.

*3.It is well described that fibrosis by itself is associated with aberrant vascularization. There are indications of monocyte-derived macrophages promoting angiogenesis in experimental fibrosis. **To which extent are fibrosis and ED linked – or should they be viewed as separate pathogenic events? How will IR affect ED in the context of ongoing fibrogenesis?** – I found these processes not clearly delineated in the current review (the impact of fibrosis is more or less neglected, but is probably relevant in this context).*

We have added a new paragraph targeted on this important issue (please, see the paragraph titled "Endothelial dysfunction and fibrosis"). This has undoubtfully given a more exhaustive view of the pathogenic scenario depicted by the vascular hypothesis o NAFLD. Thank you for this important suggestion.