Answering Reviewers.

Dear Editor, and dear Reviewers.

I appreciated greatly your comments, criticisms and suggestions because were strongly focused to the possible improvement of the manuscript.

I changed it, accordingly hopefully, with the goal of reaching greater clarity and even simplicity of the concepts and discussion. The main changes were

1. Title
   "NAFLD and Atherosclerosis at a crossroad. The overlap of a theory of change and bioinformatics".
2. Abstract – few refinements -
3. Minimal justification of the few concept in the main text
4. Supporting references

Overall, the length of the manuscript text is slightly increased, about 10%.

Thank you for your valuable help and consideration.

Yours sincerely

Guglielmo Trovato.

***Itemized comments of the reviewers and answers:***

**REVIEWER1**

The second paragraph of the background section has not any references. "Arterial stiffness is deemed…… such as the heart, brain or kidneys ". Unfortunately, Texts without references can be seen in other parts of this section. It should be noted that any statement in scientific papers needs a reference. 2- When someone reads the background section of a paper, he/she needs to get some information for previously performed research projects. I think that the information in this section is not appropriate. 3- I believe that authors need serious action about the writing style of this manuscript. Just consider these sentences in the section of current evidence: "Even in a relatively limited field of knowledge and science……. enhance novel knowledge and information". In my opinion, there is no need for these words and phrases and they are not useful. A more scientific style should be considered. Accordingly, there are also some other parts in this manuscript which needs to be rewritten. 4- We know that Atherosclerosis among NAFLD patients is common. We have much evidence regarding this subject. But we cannot establish a causative effect between them yet. We have many powerful references for these two important facts even in 2019 and authors can use them in their manuscript: https://www.ncbi.nlm.nih.gov/pubmed/31516267 https://www.ncbi.nlm.nih.gov/pubmed/31455011 https://www.ncbi.nlm.nih.gov/pubmed/30094399

ANSWER 1: thank you for your careful comments. Yes, I added the suggested references and implemented as well as possible, and by their pertinence, the sections that were left without supporting references.

Thank you. I am personally greatly indebted with you because you allowed me a better restyling and reappraisal of my manuscript.

**REVIEWER 2**

This is a mini review that comments on the pitfalls of the potential association between NAFLD and atherosclerosis. The text is well written and the author displays an interesting debate that might be taken in consideration. The author states that (page 3 line 15): This notion has some epidemiological support: regretfully, and surprisingly, no PWV measurement is currently recommended for any practical and accepted general use. The author is right to comment on the scarcity of the use of PWV in daily clinics. It is considered the gold standard to evaluate arterial stiffness and have been validated broadly. Maybe he could have emphasized the advantages of the method and cited the studies that have used this methodology in atheroscerosis setting. The author also comments (page 3 line 17): "Imaging measures of fat liver content have considerable weaknesses [2] given that they do not have complete correspondence to histology: nonetheless, they have a key role in medical practice, which is extensive and well appreciated, providing a suitable means for monitoring liver fatty content over time and after therapeutic interventions. The non-invasive methods to evaluate liver fibrosis have a good accuracy to identify advanced fibrosis, mainly liver cirrhosis and also a high negative predictive value to exclude advanced fibrosis. Although liver histology is still the gold standard for liver fibrosis, it also has many pitfalls and is not suitable for routine evaluation of patients with NAFLD due to its high prevalence and invasive profile. The author should also comment on other studies that have investigated the association of atherosclerosis and NAFLD. In fact in this mini review the authors comment only one published which might impact on the aim of the review. One study entitled "Increasing aortic stiffness is predictive of advanced liver fibrosis in patients with type-2 diabetes: the Rio-T2DM cohort study" has been published in Liver international in 2016. This study was an observational study that used transient elastography to prospectively evaluate diabetic patients with interesting results. The author comments on the importance of "omics" methodology, but he does not identify in the review any study that has used this methodology for investigating NAFLD and Atherosclerosis. If there is any study so far, this should be emphasized.

**ANSWER 2**

Thank you very much for your comments. As you may have noticed, I deliberately skipped to quote some of our published articles on transient elastography, such as

Trovato FM, et al Liver and spleen transient elastography and Acoustic Radiation Force Impulse Measurements. Performance and comparison of measurements in the same area concurrently assessed for liver fibrosis by biopsy. Adv Med Sci. 2015 Sep;60(2):300-6.

Because I preferred referring to more comprehensive articles and reviews.

Thank you for your suggestion:

Leite NC, Villela-Nogueira CA, Ferreira MT, Cardoso CR, Salles GF. Increasing aortic stiffness is predictive of advanced liver fibrosis in patients with type 2 diabetes: the Rio-T2DM cohort study. Liver Int. 2016 Jul;36(7):977-85. doi: 10.1111/liv.12994. Epub 2015 Nov 18. PubMed PMID: 26509555.

I added this reference and commented accordingly.
Your appreciation of this small article is a great pleasure for me.
Thank you..