

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Major revision

Specific Comments to Authors: Nonalcoholic fatty liver disease (NAFLD) and diabetes mellitus (DM) are prevalent in the world, It is known that they frequently co-exist and act synergistically to increase the risk of adverse clinical outcomes. The topic of this article is interesting, this review aims to investigate the relationship between NAFLD and DM, the authors expertly describe the pathogenesis and treatment of NAFLD, as well as cardiovascular risk and the relationship with COVID-19.

We thank the reviewer for the appreciation of the work and the time spent to assess our manuscript.

However, this article has a few of shortcomings. 1. It is less well conceived and thematically focused - "Nonalcoholic fatty liver disease and diabetes ", including the abstract, and especially the section on " NAFLD diagnosis via radiological imaging" doesn't seem to have anything to do with DM.

We thank the reviewer for the constructive criticism; we have significantly shortened the length of the section on imaging and added more information on the links between diabetes and NAFLD. We expanded the section on the pathogenesis and implemented with graphical representations; we also added a paragraph on conclusion and future research.

2. The article provides some descriptions of the connection between NAFLD and DM, but these are somewhat superficial, the intensive relationship is recommended, including the putative pathophysiological mechanisms linking NAFLD and DM, as well as the description of how they interact.

Thank you, we have followed your valuable suggestion and implemented accordingly, as specified in point 2.

3. The authors lack insight into the problems with the current research on NAFLD and DM, and it is suggested to add their own insights.

Thank you, we added the conclusion paragraph with our own insights and implemented our thoughts throughout the text on what is the current state of the art.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: General comments 1. Lack of line numbers make reviewing very difficult.

We thank the reviewer for the time spent to assess our manuscript, despite the difficulty encountered.

2. Major English check needed.

Thank you for the suggestion, this has been done with a native English speaker.

3. I strongly suggest the topic of these review is modified because the paper is more centered on the pro and cons of diagnostic technologies. It can be changed to “Nonalcoholic fatty liver disease and diabetes; Pros and cons of diagnostic technologies”

Thank you for the suggestion, we have shortened the section on radiological imaging, so that it will better suit the rest of the review and expanded the other sections to match the title and plan of the review.

4. The review lacks a solid conclusion and authors new finding which relates to the topic.

Thank you for the suggestion; we added a deeper insight into the current research on NAFLD and T2D. Furthermore, we implemented a section on conclusions.

Abstract 1. ... and represents a clinical-histopathologic entity where the steatosis component may vary in degree and have or have not a fibrotic component, Please this sentence not so clear. Rewrite it for clarity.

Thank you, we have clarified it: “that may or may not have associated fibrosis”.

2. The purpose and importance of this review to the readership was not stated in the abstract.

Thank you for the suggestion. We added this in the abstract: “This review offers a comprehensive multidisciplinary approach to NAFLD, highlighting its connection with diabetes”.

3. Authors should include new results from the review in the abstract.

Thank you for the suggestion. We better clarified main body of the review in the abstract.

Introduction 1. Nonalcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease in the world. Please can authors include some data on the distribution of NAFLD around the world to validate the above statement.

Thank you for the suggestion. We added the relevant information regarding prevalence: 25-30% of the worldwide population, estimated in about 2 million of individuals being affected.

2. The aim in the last paragraph of the introduction section does not match the topic of the review. Please, rethink about it.

Thank you for the suggestion. We have restructured the review and the sentence accordingly.

Pathogenesis 1. The association of liver steatosis and metabolic dysfunction is so strict- Please what do authors mean by this statement? Please clarify.

Thank you, we have explicated the interrelation by implementing the texts and the relevant references, as well as drawing summarising diagrams.

2. I also think oxidative stress and inflammation are also key pathogenesis of NAFLD, authors should elaborate on it as well in this section.

Thank you, we have implemented the text, adding references to the mitochondria role and exemplifying with figures the text, particularly regarding the presence of fatty free acids and reactive oxygen species.

3. I suggest the authors include a diagram to show each key factors pathway in causing NAFLD.

Thank you, we have added them: Figures 2 and 3.

Diabetes and NAFLD: a well-established relationship 1. I suggest the authors include a diagram to show the relationship between diabetes and NAFLD or give examples of such studies in a tabular form.

Thank you, please kindly see figures 2 and 3 as mentioned.

Diabetes, NAFLD and cardiovascular risk and Diabetes, NAFLD and COVID-19 1. I do not think these sub topics are in line with the topic of the review. I suggest if it should be included the title of the review should be modified eg. Nonalcoholic fatty liver disease, diabetes, cardiovascular disease and COVID-19.

Thank you for the suggestion, although we think it is a demonstration of the systemic and metabolic disease NAFLD represents, so, in accordance with the other reviewers, we decided to leave it.

Treatment 1. Please change this topic to “Prevention and treatment”

Thank you, we changed as suggested.

Reviewer #3:

Scientific Quality: Grade D (Fair)

Language Quality: Grade A (Priority publishing)

Conclusion: Major revision

Specific Comments to Authors: Diabetes and NAFLD association is widely recognized due to insulin resistance which is the primary pathophysiological derangement in most patients with NAFLD. This review provided a comprehensive perspective on the pathogenesis, diagnosis, comorbidity association and treatment of NAFLD.

We thank the reviewer for the appreciation of the work and the time spent to assess our manuscript.

However, some emphases need to be changed or stated. 1. For NAFLD diagnosis, various non-invasive imaging methods have been utilized to assess NAFLD and reported in many literature, this section can be briefly written.

We thank the reviewer for the comment; we shortened the section on imaging accordingly and separated from the diagnosis via clinical and laboratory tests, i.e. biomarkers and algorithms.

2. For NAFLD treatment, especially for patients with NASH and T2D, insulin-sensitizing agents and other new medicine for NAFLD and Diabetes therapy have been used or being tested in the clinical trial, more introduction should be gave on this section.

We thank the reviewer for the suggestion: in the treatment section we dealt with insulin-sensitizing agents and in the section on future research we highlighted the need to develop new drugs and randomised controlled trials.

Reviewer #4:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: In this review, the authors want to discuss the relationship between NAFLD and diabetes. However, the relationship was too superficial, and most of the description has been well-summarized in other published papers, such as <https://doi.org/10.1038/s41575-021-00448-y> and doi: 10.4103/ijem.IJEM_585_17.

We thank the reviewer for the time to assess our manuscript and the valuable comments that significantly improved the overall quality. We are aware other studies on this topic have been published, as this is very relevant in literature, however we have added our personal insights and the possible future treatments deriving from the ongoing studies, as elements of novelty. We have also acknowledged the presence of this related literature, referencing it.

In addition, a major part was used to discuss the diagnosis of NAFLD.

Thank you for the suggestion; we have significantly shortened the section on diagnosis of NAFLD and conversely extended in particular those on pathogenesis and therapies.

As indicated in the title, the authors should mainly illustrate the underlying link between NAFLD and diabetes and treatment options for both diseases. Abstention from alcohol, a Mediterranean diet and modification of risk factors for (NAFLD patients with) major cardiovascular events are always recommended. Some other minors: FFA: fatty free acids, correct it.

Thank you for the suggestions, we revised accordingly.

Nonalcoholic steato-hepatitis > steatohepatitis; (41,7%) and diabetes (33,8%), correct the numbers.

Thank you, we checked again on the manuscript and the numbers are as we reported. The reference is Richardson S. et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. 2020 May 26;323(20):2052-2059. doi: 10.1001/jama.2020.6775. Erratum in: JAMA. 2020 May 26;323(20):2098. PMID: 32320003; PMCID: PMC7177629.

Abbreviations: ultrasound (US), ultrasonography (US), nonalcoholic steatohepatitis.

Thank you, we revised accordingly.

1) Science editor:

The paper seems mainly focused of NAFLD, rather than on the links between NAFLD and type 2 diabetes. some sections should be significantly shortened, while other (in particular pathogenic links and therapies) should be more comprehensively treated. Please, rethink about it.

We thank the Science Editor for the valuable suggestions; we have significantly shortened the section on imaging and conversely more in depth dealt with the pathogenic links and therapies

Criteria followed for reference selection should be clearly reported.

Thank you for the suggestion. We looked mainly at Pubmed for “NAFLD and diabetes” and then cross-checked references for relevant literature.

Suggestions for future studies should be better discussed by authors. A conclusion section is lacking.

Thank you for the valuable suggestion, we added a section on conclusions and future perspectives.

The relationships between NAFLD and alcohol consumption in subjects with type 2 diabetes should be better discussed.

Thank you, we have revised accordingly, adding relevant references.

The novelty of this review does not emerge. Possible future treatments deriving from ongoing experimental studies should be reported and discussed.

Thank you, we revised as suggested, highlighting for a tailored-made approach that would personalise the treatment, for example by modifying the gut microbiota, but highlighting the need for randomised controlled trials to experiment these new drugs.

Major English check is needed.

Thank you, we asked a native British speaker.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade C (Good)

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Diabetes, and the manuscript is conditionally accepted.

We thank the Company Editor in Chief for the time to assess our manuscript, the valuable comments and the positive feedback.

I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please be sure to use Reference Citation Analysis (RCA) when revising the manuscript. RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. For details on the RCA, please visit the following web site:
<https://www.referencecitationanalysis.com/>.

We thank the Company Editor in Chief for the valuable suggestion; indeed, it was very helpful and we additionally searched within the RCA database for relevant references to our manuscript.

Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Thank you, we have revised the table accordingly.