

Name of journal: World Journal of Gastroenterology

ESPS Manuscript NO: 29343

Manuscript Type: Review

Title: Fatty liver is associated with an increased risk of diabetes and cardiovascular disease. Evidence from three different disease models: NAFLD, HCV and HIV

Reviewer 1

1. The manuscript is too lengthy for reader to review.

Re: We would like to thank Referee 1 for his/her suggestion which we readily accepted. The manuscript has been re-written and is now more than 2,000 word shorter.

2. The Tables are well organized.

Re: We thank Referee 1 for this comment.

3. Should the authors cite the paper which they published in NEJM in 2010: Risk of Cardiovascular Disease in Patients with Nonalcoholic Fatty Liver Disease. N Engl J Med 2010; 363:1341-1350.

Re: We agree with this suggestion, which has been fully accepted .

Reviewer 2

Excellent review with a very important concept.

Re: We thank Referee 2 for this comment.

I advise that the introduction to each disease be shortened to few informative summary sentences, there is no need to go into the details as this is not the concept of the article on one side and will be a repetition of what is known to professionals with few benefits as to the message to be delivered.

Re: We thank Referee 2 for his/her suggestion which agrees with Reviewer 1's suggestion and was readily accepted. We highlight that our R1 manuscript is more than 2,000 words shorter than the original submission.

Reviewer 3

Lonardo Amedeo et al. performed a narrative review, in which authors focused on the relationship among three types of fatty liver, such as NAFLD, HCV and HIV, and the risk of type 2 DM and cardiovascular disease. This review manuscript encompasses an interesting topic and may be worthwhile publishing, however it needs a minor revision, scientific and stylistic.

Re: We thank Referee 3 for this comment.

Language needs minor corrections.

Re: We thank Referee 3 for this comment. English has been checked by Ms. Jacqueline Mole, a native English speaker who also certified English of our R1.

Major comments:

1. Summary has to be rewritten to tell the specific goal of the review and major conclusions made.

Re: We thank Referee 3 for this comment. Summary has been fully reworked.

2. The information presented by Figure 1 is small. In spite of this figure, I would like to see three figures that indicate the pathogenic mechanisms of liver steatosis in three condition, such as NAFLD, HCV and HIV, and/or to see schema of mechanisms underlying the development of T2D and CVD in these three conditions.

Re: Again, we thank Referee 3 for this comment. Figure 1 has been reworked by expanding, as suggested, the specific pathophysiologic mechanisms underlying the development of T2D and CVD in the three conditions discussed here: NAFLD, HCV and HIV.

Specific comments:

1. In several sentences, author wrote "sentence.(ref)". Please revised them as "sentence (ref)."

Re: We appreciate this comment and we revised the manuscript as suggested..

2. I couldn't understand the following sentences; "Worryial liver biopsies (49, 51, 59, 62). Moreover, T2D is an independent risk factor of both HCC development (63, 64) and increased all-ca ngly, patients with T2D often exhibit advanced histological disease without elevated serum transaminase levels and may also develop HCC even in the absence of cirrhosis (40, 63, 67). A recent large study showed that NAFLD-related HCC was associated with more advanced tumor staging, shorter survival time and lower possibility of receiving liver transplantation (39).

Re: We thank Referee 3 for reporting this mistake. This section was carefully reworked.

3. Some sentences lack references; e.g. "Very recently, however, Targher et al. published a systematic review and meta-analysis, involving 16 observational prospective and retrospective studies with 34,043 adult individuals (36.3% with NAFLD) and approximately 2,600 CVD outcomes (>70% CVD deaths) over a median period of 6.9 years."

4. "Traditional risk factors for HCV infection are: assumption of intravenous and intranasal illicit drugs; hemodialysis; cancer; paid blood donations; having received blood products or anti-D immunoglobulin immunization prior to 1990; high-risk sexual behavior, tattoos or body piercings, working in heath care." →"health care".

5. "In a small clinical trial Pavone et al. identified 29 patients with T2D, who were receiving different interferon-free regimens."

6. "HbA1c levels occurred irrespective of the DAA used, HCV genotype, body weight and HIV status(169)." → "status space (169)."

7. "(i) HIV disease has changed. Once a nearly uniformly fatal disease, HIV has evolved into a chronic manageable disease with substantial variability in the patterns of long-term clinical outcomes, in part due to diversity in the course of the immuno-pathogenesis of the disease, including the levels of potentially adverse immune activation."

8. "(ii) ART has changed. Drug potency, genetic barriers to the emergence of drug resistance as well as short- and long-term drug-related toxicities have been regarded as major determinants of the "success" of the early highly active ART. Scale-up of the ART is on a fast-track trajectory that has surpassed expectations. Global coverage of ART has reached approximately 46% at the end of 2015

(with the greatest gains in the world's most affected region, Eastern and Southern Africa). As ART regimens have become more effective and less toxic, and more patients start ART at earlier in the course of HIV infection, it is possible that risks for morbidity and mortality will continue to decline among older HIV-infected individuals in the near future. ” No reference.

9. “A recent study from the ICONA cohort addressed the issue as to whether HCV co-infection favors T2D development in HIV-infected patients.” No reference.

10. “Evidence supports the notion that the burden of subclinical and clinical CVD is significantly increased in HIV-infected patients. ” No reference. “Monocytes are readily infected by HIV (243) and can adhere to the endothelial surface and event.

Points 3-10 Re: [We thank Referee 3 for reporting these issues, all of which were carefully reworked.](#)