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Role of nonalcoholic fatty liver disease as risk factor for drug-induced hepatotoxicity

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Role of nonalcoholic fatty liver disease as risk factor for drug-induced hepatotoxicity
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Dear Dr. Fromenty,

Reviewers have submitted their critical appraisal of your paper. The reviewers' comments are appended below. Based on their comments and evaluation by the editorial board, your work was FOUND SUITABLE FOR PUBLICATION AFTER MINOR REVISION.

If you decide to revise the work, please itemize the reviewers' comments and provide a point-by-point response to every comment. An exemplary rebuttal letter can be found on at http://www.jctres.com/en/author-guidelines/ under "Manuscript preparation." Also, please use the track changes function in the original document so that the reviewers can easily verify your responses.

Your revision is due by Jan 26, 2017.

To submit a revision, go to http://jctres.edmgr.com/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Hartmut Jaeschke, PhD
Associate Editor
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: This is a well written review on a novel, potentially important but under-investigated topic in the area of liver disease study. I just have a few minor comments.
1. In table 1 and Table 2, under comments: It appeared that references are missing, so it is not clear if the comments are based on what existing studies.
2. Page 8, APAP section. In addition to CYP2E1 activity, there are plenty of reports suggesting that NAFLD is associated with lower hepatic GSH. Do authors think that lower GSH at baseline in certain NAFLD patients can also increase the threshold of APAP toxicity?
3. Page 20: Phenobarbital Section. The role of CAR in the development of metabolic syndromes seems to be controversial, but some studies were performed with CAR agonists while others were performed in CAR KO mice. The different model system could be responsible for some existing discrepancy.
4. Page 21, first paragraph. Although hepatotoxicity is the focus here, it may be worthwhile to point out somewhere in the text that, different from troglitazone, the major concern associated with the use of rosiglitazone has been its possible association with increased risk of heart diseases.
5. Page 22. line 4: change "worsened" to "worsen".

Reviewer #2: This is a very nice review of issues surrounding NAFLD and drug-induced liver injury. The authors were very thorough and covered the topic from multiple perspectives. Just a few minor issues could be addressed:
1) Paragraph 2, Page 10: The authors state that therapeutic doses of APAP can cause liver injury and even ALF. The authors need to point out that this is a controversial claim. There is evidence that APAP causes transient aminotransferase elevations in some patients, but no well-controlled study (including a recent RCT by Heard et al. [BMC Pharmacol Toxicol. 2014.]) has reported ALF. The only evidence for ALF at therapeutic doses comes from case reports, which are notoriously unreliable.
2) Although the clinical studies cited on page 10 are useful, the authors should point out that while the studies did adjust for confounding factors like socioeconomic status, they could not adjust for residual bias (e.g. something associated with obesity other than obesity itself that contributes to the greater incidence of ALI among APAP overdose patients, such as dose taken (larger subjects may take larger doses), incidence or severity of depression, genetic factors, etc.).
3) At the top of page 10, the authors could cite Du et al. Expert Opin Drug Metab Toxicol. 2015. as a nice review of the controversy surrounding the significance of JNK in APAP toxicity.
4) Change "participate" on line 13 of page 14 to "contribute."
5) Lines 40-42 on page 23 could be written with a more professional tone. Some readers may feel that "flimsy" is not appropriate in professional writing.

********Authors' rebuttal********

We are grateful to the reviewers for their encouraging comments regarding our manuscript and also for their different remarks that helped us to significantly improve our manuscript. Please, note that all changes are in red in the revised version.

Answers to Reviewer 1:

Comment n°1: References in tables 1 and 2.

Following the remark of Reviewer 1, we have added the missing references in the tables.

Comment n°2: GSH in NAFLD patients and APAP toxicity.

Because this issue was probably not sufficiently addressed in the first version of the manuscript, we have added the following sentences in the revised version: "Finally, variability in hepatic GSH levels might also exist in obese individuals. Indeed, GSH stores could be lower in patients with NASH, as compared to individuals with simple fatty liver, because NASH is consistently associated with higher oxidative stress [8,9]. Consequently, greater oxidative stress and lower liver GSH at baseline could increase the threshold of APAP toxicity in certain obese patients [8]".

Comment n°3. Role of CAR regarding phenobarbital.

We have added the following sentences in order to address this issue: "Alternatively, phenobarbital might have exacerbated fatty liver by activating CAR [6]. However, the role of CAR in drug-induced steatosis is still unclear and could depend on the duration of CAR activation and/or the nature of the activating molecule [6]".

Comment n°4. Rosiglitazone and risk of heart diseases.

We have added the following sentence regarding rosiglitazone-induced cardiotoxicity: "Besides hepatotoxicity, a major concern with the use of rosiglitazone is its possible association with increased risk of cardiac diseases including congestive heart failure [186]. Rosiglitazone-induced cardiotoxicity could also involve mitochondrial dysfunction [186]".

Comment n°5. We have corrected the spelling mistake.

Answers to Reviewer 2:

Comment n°1: Therapeutic doses of APAP and ALF.

Following the remark of Reviewer 2, we have added a sentence and modified the beginning of the next sentence, as follows: “However, it is noteworthy that no well-controlled study has reported ALF in individuals treated with recommended doses of APAP. Hence, such rare therapeutic misadventures..”.

Comment n°2: Clinical studies and confounding factors.

We have added the following sentence regarding this issue: “Although all these clinical studies are very informative, it is noteworthy that some confounding factors were not taken into account, such as different psychological and genetic factors.”

Comment n°3: Reference Du et al., 2015 for the role of JNK in APAP toxicity.

As suggested by Reviewer 2, we have cited this interesting review.

Comments n°4 and 5: The word “participate” has been replaced by “contribute”. We also removed the word “flimsy” in the corresponding sentence.

2nd Editorial decision
Date: 26 Oct, 2016

Ref.: Ms. No. JCTRes-D-16-00029R1
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Dear Dr. Fromenty,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

Comments from the editor and reviewers can be found below.

Thank you for submitting your work to JCTR.

Kindest regards,

Hartmut Jaeschke, PhD

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Associate Editor
Journal of Clinical and Translational Research

Comments from the editors and reviewers:

N/A

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