Dear Yuan Qi,

Re: Manipulation of dietary advanced glycation end-product content influences the progression of non-alcoholic fatty liver disease (Manuscript Number 27036)

Thank you for inviting us to resubmit our manuscript (ID 02539423) for publication in the *World Journal of Gastroenterology.* It describes original, unpublished work which shows that increased advanced glycation end-product (AGE) consumption increases liver injury, inflammation and liver fibrosis in NAFLD via RAGE dependent proinflammatory and profibrotic effects.

This manuscript builds substantially on our previous work on AGEs and liver fibrosis[1] by studying the effects of dietary AGEs in a novel, long term dietary model which mimics human NASH. We have complemented our work by using RAGE KO animals and isolated Kupffer cells to explore mechanistic pathways.

These findings suggest potential new pharmacological and dietary strategies to slow the progression of fatty liver disease. We feel that the *World Journal of Gastroenterology* is a highly appropriate forum for these novel findings to be disseminated and discussed.

We found your comments and those of the reviewers very helpful and have made a number of changes to the text. We believe these changes significantly strengthen the manuscript and hope it will now be acceptable for publication in the *World Journal of Gastroenterology*.

Our detailed responses are listed below.

Yours sincerely,

Christopher Leung

Reviewer #1: Reviewer's comment: Manuscript Number 27036

The exact pathophysiology of NASH remains unknown and this paper studies the role of AGEs in NAFLD progression. Some data support dietary AGEs as a cause of oxidative stress in the liver (including paper published by the authors in J Hepatol 2014, reference #21 in the manuscript). Therefore, it was postulated that high dietary AGEs intake may play a role in liver inflammation and NASH. This study is commendable in that it explores the influence of increased dietary AGEs intake. Although the study was performed in mice, by modulating dietary intake, it brings this concept one step closer to a human model. It also tried to pinpoint the specific role of AGEs by modulating AGEs levels (i.e. having one group marinated in vinegar), and a second experiment

with RAGE KO models. Unfortunately, correlation does not imply causation. There was no increased inflammatory infiltration of the liver or cytokine expression, which was disappointing. Nonetheless, the pathogenesis of NASH is complex and I believe this is an insightful effort in trying to elucidate this complex process.

Classification Grade B (Very Good)

Language evaluation Grade B (minor language polishing)

Conclusion (High priority for publication)

Response to Reviewer #1:

Thank-you for the review and we agree that the pathogenesis of NASH is complex and the findings are important despite no increased inflammatory infiltration of the liver or cytokine expression. We discuss this further on page 18, paragraph 2. We also highlight the important findings in comments section on page 21.

We have also read and edited the manuscript carefully and performed the minor language polishing as requested.

Reviewer #2: Reviewer's comment: Manuscript Number 27036

A well designed and organized study. But a little bit long paper. My only suggestion is deleting some sentences from introduction and conclusion part.

Classification Grade C (Good)

Language evaluation Grade A (priority publishing)

Conclusion (Minor revision)

Response to Reviewer #2:

Thank-you for the review. As suggested, we have deleted some sentences from the introduction and conclusions.

References

1 Leung C, Herath CB, Jia Z, Goodwin M, Mak KY, Watt MJ, Forbes JM, Angus PW. Dietary glycotoxins exacerbate progression of experimental fatty liver disease. *Journal of Hepatology* 2014; **60**(4): 832-838 [PMID: 24316518 DOI: http://dx.doi.org/10.1016/j.jhep.2013.11.033]