

Responses to reviewers

Reviewer 1

Comments:

This review article is well constructed and the manuscript is well written. I only have some minor comments.

1. In Clinical Implication section, the author recommends the measurement of cIMT for the assessment of CVD risk in patients with NAFLD. However, there are some arguments on the relationship between NAFLD and cIMT. Though a recent systemic review of seven published studies including 3497 subjects reported an increase of 13% of CIMT in NAFLD patients (Sookoian S et al. J Hepatol 2008;49:600-7), some studies failed to demonstrate an association between NAFLD and cIMT, especially conducted in a population of type 2 diabetes mellitus patients (Petit JM et al. Clin Endocrinol Metab 2009;94:4103-4106 and Coracina A et al. Nutr Metab Cardiovasc Dis 2012;22:e11-12). So, some population cannot get any information from cIMT measurement. Could you mention about these discrepant data in your review manuscript?

Reply: Thank you very much for your positive comments and valuable suggestions. According to your advice, I searched related articles again and found that there are really some arguments on the relationship between NAFLD and cIMT in diabetic patients, but the relationship in non-diabetic patients is clear. There isn't any meta-analysis and/or systematic review about NAFLD and cIMT in diabetic patients. So, we just

recommend using the measurement of cIMT in non-diabetic NAFLD patients to assess cardiovascular risk stratification. I have revised this in my manuscript. (Page 10, the sixth line from the bottom in red)

2. Could you add some contents in Classical and New Emerging Risk Factors section? You described several new risk factors for CVD, such as CRP, homocysteine, fibrinogen, and so on. Please add some evidence data and the relationship between inflammatory markers and their origin, if possible.

Reply: Thank you so much for your useful suggestions. After my description of Classical and New Emerging Risk Factors section, I described the inflammatory markers (page 6) and markers of fibrinolytic and homeostatic function (page 9) carefully in Possible Mechanisms Linking NAFLD and CVD. In addition, I added some evidence data such as “A cross-sectional survey of 360 people indicated that an increase in CRP (odds ratio [OR] = 1.37; 95% confidence interval [CI]: 1.06-1.77) per 1 SD (1.48 mg/L) was independent risk factor for NAFLD (page 6 in red)” to elaborate the relationship between CRP and NAFLD. The evidence data about the relationship between homocysteine and NAFLD was also added (page 5 the bottom line 3 in red).

3. Are there any differences in NAFLD epidemiology between Eastern population and Western population? As you know, there are unique characteristics in type 2 diabetes of Asian population compared to

Caucasian. It would be an interesting topic if you summarize typical characteristics of Asian NAFLD patients.

Reply: The main difference in NAFLD epidemiology between Eastern and Western population is the cut-off value of BMI. Only 2%-3% of Asians are classified as obese by current Western criteria (BMI of more than 30 kg/m²), but lots of Eastern population had abdominal obesity even they had normal BMI index. Obesity-related NAFLD commence at much lower levels of BMI in Eastern population. The recommended BMI cut-off values of overweight and obesity for Asians vary from 23 to 25 kg/m² and more than 25 kg/m², respectively, according to the new BMI criteria for Asians by the regional office for the Western Pacific Region of WHO. Our review is mainly about the correlation between NAFLD and CVD, so I didn't elucidate carefully the typical characteristics of Asian NAFLD patients. But I think that your advice is so useful that I searched related articles based on your recommendation. There are several factors as follows. First, both miscarriage and induced abortion are associated with prevalent NAFLD in middle-aged and elderly Chinese women. [Liu, Y. *Ann Epidemiol.* 2013, 23(3): 119-123]. Second, the alleles Ala and T of PPAR γ (Pro12Ala and C161T) polymorphisms, PNPLA3 genetic polymorphisms, genetic variations within FABP1, SREBP-2 1784 G>C genotype are associated with NAFLD in Asian people. [Bhatt, S. P. et al. *Gene*, 2013, 512(1): 143-147; Peng, X. E. et al. *PLoS One*, 2012, 7(11): e50256; Peng, X. E. et

al. Gene, 2012, 500(1): 54-58 and Bhatt, S. P. et al. Dis Markers, 2011, 31(6): 371-377]. Third, Bariatric surgery can achieve a dramatic improvement of NAFLD both biochemically and histologically in morbidly obese Chinese patients. [Tai, C. M. et al. Obes Surg, 2012, 22(7): 1016-1021].

4. I think that it is important to present a summary of various treatment modalities and its outcome for clinicians who are going to read this article.

Reply: I have summarized various treatments modalities and their outcome in red in this review (page10-12). In addition, I also put various treatment modalities into Fig1.

5. There are some technical errors in periods and a capital letter on page 6.
 - (1) possible independent pathophysiologic role between NAFLD and dyslipidemia.(prospective, n=3362, Caucasian, Chinese, African American, Hispanic).
 - (2) significant in either sex.(prospective, n=2756, European-American).
 - (3) showed that In essential hypertensive patients without additional cardiovascular risk.
 - (4) stiffness.(Observational, cross-sectional, n = 68, Italy).
 - (5) with atherosclerosis compared to control subjects.(Observational case-control, n=51, Turkey).

Reply: Thank you so much for your comments and valuable advices. We appreciate for your careful review. We have revised the technical errors

point by point to improve the readability of the text (page 5). We hope that the revision is acceptable.

Reviewer 2

While the subject matter is certainly interesting and timely, this reviewer would ask the author to consider the following suggestions:

(1) A schematic model incorporating the main points listed in the article would be a plus.

Reply: Thank you so much for your valuable suggestions. We have put various treatment modalities for nonalcoholic fatty liver disease into Fig1. I hope that the schematic model could help readers better understand our article.

(2) Instead of listing published data, the author is encouraged to offer his/her own opinion as to how these studies better our understanding of the relationship between NAFLD and CVD.

Reply: We have summarized our own opinion according to the newly published data (Page 5, the eleventh line to the eighth line from the bottom in red). I wish that readers can get a better understanding about our review.

(3) The manuscript suffers from non-idiomatic use of English. The author is encouraged to consult with a native English speaker to improve editing.

Reply: Thank you very much for your valuable advice. We have consulted with

native English speakers about editing before we contribute our review to *World Journal of Gastroenterology*. We hope that this revision is acceptable.