

Format for ANSWERING REVIEWERS



Aug 12, 2013

Dear Editor,

We are extremely grateful to all the reviewers' excellent comments and valuable advices about our paper. We have corrected the manuscript follow reviewers' comments. Our replies to the reviewer's comments are as follows:

Please find enclosed the edited manuscript in Word format (file name: 4215-review.doc).

Title: Nonalcoholic Fatty Liver Disease is Associated with Coronary Artery Disease in Koreans

Author: Dae Hee Choi, Sung Joon Lee, Chang Don Kang, Myoung Ok Park, Dong Wook Choi, Tae Suk Kim, Wonho Lee, Byung Ryul Cho, Yong Hoon Kim, Bong-ki Lee, Dong Ryeol Ryu, Ji Won Lee

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 4215

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

To Reviewer 1 (00503546)

Main comments

(1) The patients with fatty liver had more diabetes, authors wrote. Perhaps enrolled patients included some diabetes patients with medication (such as sulfonylurea, glinide and DPP-4 inhibitor). If so, insulin and HOMA-IR may not be evaluated properly.

Answer: The authors greatly thank you for your suggestion and totally agree with your opinion.

Actually, enrolled subjects in two groups (non-CAD vs. CAD groups) included small number of diabetes (12.5% vs. 21.7%), however, subjects with diabetes might have enhanced insulin secretion by drugs (such as sulfonylurea, glinide and DPP-4 inhibitor). In our review, the used drugs were most insulin and small number of those drugs. In addition, the two groups with subjects except diabetes were not significant differences in insulin and HOMA-index. We really benefited from it a lot. Thank you.

(2) [Result] 1st paragraph: 40.9% in group A → 51.1%, maybe.

Answer: The authors greatly thank you for your suggestions. We have recalculated and corrected result.

(3) [Introduction] Many NAFLD studies conducted in Western populations, have found a relationship between NAFLD and CAD in relatively obese patients rather than that in Asians.: Add references.

Answer: As your kind suggestion, we have cited that important 2 literatures in our revised

manuscript. In addition, we proofread our manuscript.

(4) [Figure 1] $P=0.002$ means what? Figure 1 and Table 1 present the same thing.

Answer: As your kind suggestion, we have removed the Table 1 and modified Figure 1. In current manuscript, Figure 1 shows that angiographically proven coronary artery stenosis was strongly associated with NAFLD in a grade-dependent manner by Pearson's correlation analysis ($P=0.002$). Thank you for your keen comment.

To Reviewer 2 (00214311)

Main comments

Needs major revision as specified in the manuscript

Answer: The authors greatly thank for your suggestions. As your important suggestion, we totally reviewed and modified our manuscript. Briefly, we made further characterization of study groups (CAD vs. non-CAD) and specified these two groups in order not to confuse the readers. We also revised Tables and Figures in order to easy understanding of the results. Furthermore, we corrected broad and overreaching expressions.

To Reviewer 3 (02445063)

Main comments

(1) In results section: First couple of paragraphs are written in a confusing manner. --> Of them, 82 (61.2%) had ultrasonographically diagnosed NAFLD. The majority of the subjects had mild fatty liver (46.3%), whereas 52 (38.8%) had no evidence of fatty liver . {This sentence is confusing} --> The following sentence needs further characterization elaboration of CAD population vs non CAD. Needs to be revised/ paragraph 1 and 2 reworked; does not fit where it is placed.

Answer: The authors greatly thank you for your suggestions. As your important suggestion, we totally reviewed and modified our manuscript. We made further characterization of study groups (CAD vs. non-CAD) and specified these two groups in order not to confuse the readers.

(2) In the next sentence-"More diabetes" is confusing- how is this defined?

Answer: As your kind suggestion, we totally reviewed the manuscript and had major revision. The definition of diabetes was described in the method part.

(3) The sentence, "In our results, any factors which we concerned were not found to be related to CAD."- is confusing and needs to be rewritten.

Answer: The authors greatly thank you for your suggestions. That expression had made a deletion.

(4) Under discussion: --> The statements , " In contrast, our study was different from that study because we evaluated not only the presence of fatty liver and CAD but also the degree of fatty liver and severity of CAD. Our results show that angiographically proven coronary artery stenosis was strongly associated with NAFLD in a grade-dependent manner." These are broad and over-reaching- Important to qualify with your results there is no histology/staging of fibrosis or use of elastography/stiffness- which should be included in the discussion.

The sentence, "In the present study, we also find the clue to elucidate precise mechanism of this relationship."- is poorly written and requires revision to clarify.

Answer: As your kind suggestion, we proofread our manuscript. Moreover, we made mention of absence of histology/ staging of fibrosis as an important limitation in our study. We really benefited from it a lot. Thank you.

(5) Tables: Table 2- A comment on the number of post-menopausal women in each group is

warranted. Post-menopause is known influence on NAFLD/NASH.

Answer: The authors greatly thank you for your suggestions. That's very important thing that affecting the results. However, in each group, women were predominant, and all subjects were post-menopausal except for one person in the CAD group. This study was conducted at a single center in a rural area, which increased the chance for selection bias as described in the review part. Old aged women were predominant in the included subject. Thank you for your keen comment.

(6) In addition- There is no definition of diabetes mellitus a known cause of fatty liver disease is not defined?

Answer: As your kind suggestion, the definition of diabetes was described in the method part.

(7) For other pages of tables- you need to include the title of the table for ease of reading/editing.

Answer: The authors greatly thank for your suggestions. As your important suggestion, we had rewritten the title of tables and figures.

(8) Table 2- was diabetes, a known cause of NAFLD controlled in the regression?

Why wasn't there controlling for diabetes/hgbA1c which is a well published association and always controlled for in clinical trials?

Answer: The authors greatly thank you for your suggestions. That's very important thing that affecting the results. An analysis of the relationship between NAFLD and the presence of CAD is shown in Table 2. In addition to the significantly different variables between the 2 groups in Table 1, well-known established risk factors for CAD, such as age, gender, glucose, HbA1c and body mass index, were considered as covariates in conducting the multivariate analysis. In those models, as shown in Table 2, NAFLD was the significant independent predictor for CAD ($P = 0.03$, odds ratio: 1.685; 95% confidence interval: 1.051-2.702).

(9) How is "NAFLD defined- assuming it is fat upon sonography"

Answer: The authors greatly thank you for your suggestions. As you pointed out, it was a main limitation in our study. Our results were not based on a biopsy-proven NAFLD. There is no histology or staging of fibrosis by use of elastography to determine the liver fibrosis. To overcome this, we diagnosed fatty liver using hepatic ultrasonography. In addition, absence of alcohol ingestion history and other chronic liver disease might support the presence of NAFLD. Although this major limitation is present, we are hoping for publication on your journal.

To Reviewer 4 (00053684)

Main comments

There is an interesting retrospective study that demonstrated that CAD is more frequent in NAFLD patients.

Answer: The authors greatly thank for your suggestions. We have corrected the manuscript follow reviewers' comments and have added related papers.

3 References and typesetting were corrected

4 We found to make use of a copyediting service provided by professional English language editing companies as you recommended. We choose following English language editing company: **American Journal Experts: <http://www.journalexperts.com> for accept manuscript.**

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

A handwritten signature in black ink, appearing to be 'Dae Hee Choi' in Korean characters, written in a cursive style.

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