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Professor Jin-Lei Wang  
Director, Editorial Office  
Baishideng Publishing Group Co., Limited

May 11, 2014

Dear Professor Jin-Lei Wang:

Thank you very much for considering our original manuscript entitled as " Beneficial effect of an omega-6 PUFA-rich diet against NSAID-induced mucosal damage in the murine small intestine

." by Toshihide Ueda, Ryota Hokari, Masaaki Higashiyama, Chie Kurihara, Kengo Tomita, Yoshikiyo Okada, Chikako Watanabe, Syunsuke Komoto, Shingo Usui, Shigeaki Nagao and Soichiro Miura to your journal " World Journal of Gastroenterology ".

We have attempted to address your and two reviewer's coments and made the appropriate changes according to those comments.

NSAIDs-induced small intestinal lesions are common, but no treatments are established except withdraw of taking NSAIDs. This study will give the very useful clinical information that dietary fat is involved in pathophysiology of NSAIDs-induced small intestinal lesions.

The authors' responses to your comments and each of reviewer's comments are summarized in separate sheets in a point-to-point manner.

Thank you again for considering our manuscript.

Sincerely yours.

With my best regards,  
Yours sincerely,  
Ryota Hokari, M.D.

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We thank the editors and the reviewers for their valuable and constructive comments. Specific responses to each comment are integrated in the text below.

To reviewer1

1. Line 216: The authors state to have shown that the different fat diets alone (without NSAIDs) caused no small intestinal injury. However, no histological data show this to be the case, as Figure 1 only shows the combined effects of diet fats and indomethacin. Histological images documenting the claim by the authors should be included in the study.

: Thank you for your valuable comment. As you suggested, we added the histological figure with different diet without NSAIDs. Figure 1A was changed into new Table 2.

2. Table 2: I am puzzled that all diet groups without IND scored a straight 0 mm<sup>2</sup> (even without a SEM) with regards to lesions. Were these groups analyzed the same way as those with IND?

: Thank you for your valuable comment. As you suggested, we increased the number of experiment concerning effect of dietary fat on area of intestinal lesion without indomethacin. Some mice had small intestinal intestinal lesion in any of the diet although the area of lesions were very small. No significant difference was observed among them. We revised Table 2 (new Table 3).

3. Figure 1: I am puzzled by the big difference in the histology images between the diet groups (C-E), showing either near-complete absence of villi (C, D) or near-intact villus architecture (E). If these images are representative they are hard to reconcile with the modest difference in score shown in the diagram (A) of the same figure.

: Thank you for your valuable comment. Although all the pictures were taken from each group, averaged data were not so big. I agree these pictures were not representative ones. As you suggested, we changed Figure 1.

4. Figures 2-4: The y-axis of the graphs lacks labeling.

: Thank you for your valuable comment. We added them.

To reviewer 2

1. The materials and methods did not fully explained how the experiments were done and not clearly matched with the results.

: Thank you for your valuable comment. We thoroughly checked material method and corrected them properly. We added titles in the results section.

2. Page 7; space error on the top of page

: Thank you for your valuable comment. We corrected it.

3. Page 7, line 99; apace?

: Thank you for your valuable comment. We corrected it.

4. In the results, expression of adhesion-related genes such as MAdCAM-1 was not shown but method for qRT-PCR was described in the materials and methods.

: Thank you for your valuable comment. We showed results section concerning expression of adhesion molecules to match the method and results.

5. The method for "Isolation of monocytes and platelets and labeling with CFSE" was not clearly proposed in the results

: Thank you for your valuable comment. We added isolation of monocytes in the result section. We also added the results of isolation of platelets in the result section.

6. The methods for "preparation for intravital observation" and "analysis of monocyte and platelet dynamics" were hard to match with the associated results. Match the title of methods and results.

: Thank you for your valuable comments. As you suggested, we changed the discription of method to match the results. "Analysis of monocyte and platelet dynamics" were changed into "Analysis of monocyte recruitment to intestinal microvessels" and "Analysis of platelet recruitment to intestinal microvessels". We separated them. We added title in the results section also.

7. Results: the description for the results was not clearly addressed with their Figs or tables. For example, line 154-155, "However, treatment with SO did not aggravate the small intestinal lesions": aggravate what? Ulcer or thickness?

: Thank you for your valuable comment. As you suggested, "However, treatment with SO did not aggravate the small intestinal lesions": was changed into "However, treatment with SO did not increased the area of small intestinal lesions, histological scores nor number of infiltrating cells"

8. Fig legends also not clearly represent their study. "Fig. 1. Histological evaluation" can be replace with "Histological evaluation of impact of IND and fat-rich diets"

: Thank you for your valuable comment. We replaced Fig 1 legends into "Histological evaluation of impact of IND and fat-rich diets"

9. Fig 1; What is histological grade on the y-axis?. Thickness of epithelium?

: Thank you for your valuable comment. We added definition of histological grade used in this study in Table 2 legend.

10. Label Y-axis of the graphs in fig 2, 3, and 4

: Thank you for your valuable comment. We added Y-axis label in graph 2, 3 and 4.

11. Fig 2 and 3: it is not clear where monocytes adhere in the picture.

: Thank you for your valuable comment. We changed the picture into more clear ones.

Thanks to reviewer's comments, we believe that our manuscript has become much strengthened.