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January 22, 2019

Ying Dou
Science Editor
World Journal of Gastrointestinal Endoscopy

Re: Manuscript number 43175

Dear Ying Dou,

Thank you very much for the correspondence of December 6, 2018 regarding our manuscript, "Narrow band imaging evaluation of duodenal villi in patients with and without celiac disease: a prospective study." We are pleased that our manuscript has received favorable reviews and that the Editorial Team has found it to be of merit. We are very happy to provide a revised manuscript and have enclosed herein point-by-point responses to the comments received. We believe our revised manuscript satisfactorily addresses all of the comments and is now considerably stronger thanks to the thoughtfulness and quality of the reviews we received, and we hope you will agree.

Thank you again for your consideration and the opportunity to contribute to *WJGE*.

With best wishes,

A handwritten signature in cursive script, likely belonging to James H. Tabibian.

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Name of journal: World Journal of Gastrointestinal Endoscopy

Manuscript NO: 43175

Title: Narrow band imaging evaluation of duodenal villi in patients with and without celiac disease: a prospective study

Reviewer's code: 02953383

SPECIFIC COMMENTS TO AUTHORS

The authors aim to examine the clinical utility of narrow band imaging (NBI) for evaluating morphology of duodenal villi during routine endoscopy based on a prospective cohort study. The authors concluded that NBI appears to have excellent diagnostic performance and can facilitate targeting of duodenal biopsies. The authors also found NBI had high negative predictive value and therefore was useful in avoiding biopsies that were likely to reveal histopathologically normal mucosa. This study is well written and is based on a tertiary center and the case number was relatively large. The reviewer only has a few suggestions and comments. 1. Please describe in more detail about the classification of duodenal villi pattern on NBI and pathology since this is the most important part of this study. Representative images of NBI and pathology may be helpful for readers to apply in their clinical practice. 2. In the "Scoring of duodenal villi" in the method section, the normal category of NBI included "isolated increased intra-epithelial lymphocytes" but I don't think NBI could show the presence of lymphocytes. 3. How many biopsies did the study obtained in each patient? And why only second portion of duodenum was taken biopsy? 4. Please describe the endoscopic experiences of the GI fellow. 5. Did the experienced advanced endoscopist (CJG) and the GI fellow (JHT) also view the white-light images? I guess the performing endoscopist's decision to biopsy or not to biopsy has been somewhat influenced by the white-light findings. 6. Please explain why experienced endoscopist has lowest sensitivity 56% while the GI fellow has the perfect sensitivity 100%. 7. There were two tables under Table 2 but they seem to be the same content with different arrangements of columns and rows. 8. Figure 1. Suggest change the therapeutic endoscopist to experienced endoscopist as in the main text. In addition, the legend seems too lengthy. 9. I cannot see the figure 2.

Response: We appreciate our Reviewer's kind comments and constructive comments. We have used these to improve our revised manuscript in several regards, as enumerated here:

- 1) We agree that additional details regarding the classification of duodenal villi would be useful. We have thus added methodological details in the Methods section, under the "Scoring of duodenal villi " subsection, as requested.
- 2) We omitted the phrase "isolated increased intra-epithelial lymphocytes" from the methods as suggested and instead comment on this entity in the Discussion section;
- 3) We have included a specific statement ("At least four biopsies were obtained from the second portion of the duodenum using single-use radial jaw 4 forceps (Boston Scientific, Natick, MA) per hospital standard of practice.") regarding duodenal biopsies in the Methods section, as requested, and have also added clarification in this regard to the Discussion section.
- 4) The GI fellow was in year 4-5 of his GI fellowship during the time of this study and had performed approximately 350 EGDs prior to starting the study; we have added

this information as well as additional information regarding the advanced endoscopist to the manuscript.

5) White-light images were not part of the study and did not comprise a basis for biopsies.

6) The fair agreement between advanced endoscopist and GI fellow and the discordance referred to by the Reviewer were driven by the relatively frequent designation of atrophy by the GI fellow (i.e. a tendency to overcall) and the more conservative scoring by the advanced endoscopist. This is supported by their respective negative and positive predictive values (see Table 4), but we believe that with minor coaching/training, both could see performance improvements (a subject pending for future study).

7) We have corrected the issue with the duplicate tables.

8) We have revised Figure 1 and its legend, as recommended.

9) We apologize for the issue with Figure 2; this has been provided to the Editorial Office.

Reviewer's code: 02505493

SPECIFIC COMMENTS TO AUTHORS

The present study was undertaken to examine the applicability of narrow band imaging for evaluating morphology of duodenal villi and avoiding unnecessary biopsies. The authors describe extensively their strategy and the obtained results. They also notice some limitations of the study. However, figure 2 is missing of the m/s, as well as both .tiff files concerning Figures 1 and 2 cannot be found in the initial submission. Nevertheless, the work is very interesting and describes a useful approach for evaluating morphology of duodenal villi, therefore, after the submission of Figures 1 and 2 files, it can be accepted for publication.

Response: We greatly appreciate our Reviewer's kind comments and feedback. We have provided the Figure files to the Editorial office to complete our submission.

Reviewer's code: 01047575

SPECIFIC COMMENTS TO AUTHORS

Mucosal biopsies is considered the gold standard for evaluating duodenal villus morphology, but it is a time- and resource-intensive approach. Therefore, a new method to assess duodenal villus morphology is needed. In this study, assess the diagnostic accuracy of narrow band imaging (NBI) for evaluating morphology of duodenal villi. This is an interesting topic and significant, but the following problems should be addressed.. 1. In the study, the authors included patients who were suspected of celiac disease. That means the diagnosis was not confirmed. So I do not think the title is appropriate. 2. The data which could reflect the diagnostic accuracy of NBI, such as sensitivity, specificity and their 95% confidence interval should be calculated and listed in the part of abstract and results. 3. The three category convention (normal, partial atrophy and complete atrophy) used in NBI should be described

detailed, and representative images should be attached. 4. The manuscript is not prepared. The formal table should be three-lined. Table 2 is repetitive and figure 2 is lost in the manuscript.

Response: We are very grateful for our Reviewer's kind comments and constructive feedback.

We have revised our manuscript according to the suggestions received, as enumerated here:

1) We included patients in the study with known (previously confirmed) Celiac disease as well as patients with no Celiac disease (some of whom had suspected Celiac). Those with known Celiac were referred for repeat EGD with biopsies to assess treatment response, surveillance, and/or other indications. We have clarified this in the "Patients" subsection of the Methods and also in Table 1.

2) Regarding the inclusion of additional data in the abstract, while we agree that having such data is useful, we did not do so in light of abstract length considerations. We have provided these data in the manuscript body/Table 3 but did make minor revisions to the abstract to clarify what metrics of diagnostic performance were evaluated.

3) Figure 2 has been provided to the Editorial office. We have included Table 2 as it presents data that are not presented in any of the other tables or figures.