

Dear Editor,

Thankyou for considering our manuscript NO: 57306 “**Motility index measured by MR enterography is associated with sex and mural thickness**” for publication in World Journal of Gastroenterology. We have tried to answer to all the reviewers and the editor’s questions, and we think that the manuscript has been improved after revision. All changes are marked in yellow. Please reconsider this revised manuscript for publication in the journal.

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This is an observational, cross-sectional study to assess the use of the MI for assessment of the small bowel motility in the patients with IBD or other intestinal disorders. Of particular note, the study examined the association between the MI and basal characteristics and gastrointestinal symptoms independent of the diagnosis. The data presenting in this study showed that there was a negative association between MI of the terminal ileum measured by MR enterography and mural thickness, especially in men. The observations indicate that MI is useful for determining altered motility patterns in addition to morphological MRE changes and clinical characteristics. Generally, this is an interesting study that presents valuable findings on the use of MR in assessing small bowel motility in clinical practice. Major concerns: (1) In the current version, no information on the disease activity of the patients (CD and UC) was provided. It is encouraged to identify whether MI measured by MR is associated with the disease activity of the patients (CDAI, etc.) (2) Except for CD, the case number of several other diseases, for example UC and dysmotility, was very small. (3) An additional paragraph should be add in the last of the "Discussion" section to present the conclusion of this study.

Reply: 1) You are right that no information about activity was provided in this manuscript. We have previously published a manuscript about Crohn’s disease, ref no 10, referred to on page 3, line 18-21, and then we have in detail calculated the differences between the disease status regarding the degree of disease activity, treatment given, results of laboratory analyses and so on. Crohn’s disease was categorized as active UC when there were signs of actual inflammation on endoscopy or MRE, i.e. increased mural thickness, inflammatory lesions or ulcers, and/or signs of inflammatory activity in blood, plasma or feces. Patients without any signs of active inflammation on endoscopy or MRE and with blood and feces analyses within reference values were classified as inactive disease. We also calculated the Harvey-Bradshaw activity index (HBI) and the magnetic resonance index of activity (MaRIA) from the MR images. There was a complete agreement between the clinical assessment of activity from the data in the medical records and the calculated indeces. We could only find weak

differences regarding MI between active and inactive Crohn's disease, with lower MI of terminal ileum in active disease than in inactive disease. The MI showed strong inverse correlation between mural thickness and MI in the terminal ileum. Those with a swollen or increased mural thickness by fibrosis had a lower MI. Thus, local factors in the bowel wall affect the MI. Treatment given or laboratory analyses did not influence the MI at all. We therefore wanted to look further on basal characteristics, since it seems important to assess a true motility, not dependent on a local edema or fibrosis in the bowel wall. An enteric neuropathy should affect the overall MI and not only be found where the bowel wall has an increased thickness. Due to these findings, and that they are calculated in the published manuscript, we have excluded those calculations in this manuscript, because the message could else have been overloaded. Further, we have an article in press regarding ulcerative colitis, ref no 17, where we in detail tried to identify differences between active and inactive ulcerative colitis, treatment options, laboratory analyses and so on. We could not identify any differences at all regarding these parameters in ulcerative colitis. Thus, we think that it is in order just to assess the differences between the whole disease groups in the present paper which is more focused on to discover true motility differences between patients and controls. The aim of the present study was to evaluate the usefulness and potential of the MI in a large cohort of unselected patients and healthy controls to examine whether the MI could be helpful to identify altered motility patterns in addition to morphological MRE changes and clinical characteristics. **In particular, the aim was to examine the association between the MI and basal characteristics and gastrointestinal symptoms, independent of the diagnosis.** By inclusion of a larger cohort, we could identify influence on MI from basic characteristics such as weight, sex and so on, which could not be identified in the smaller cohorts. The description of how activity was estimated is given on page 7, first section. The number of patients with active disease are given on page 11, line 21-24 and this is further discussed in the discussion, page 14, line 21-25 and page 17, line 7-9.

2) We agree that some of the groups are rather small. It is rather natural that most patients referred to MR are patients with IBD. Since we tried to include all consecutive patients during 2 years, we could not influence the cohort size further. The risk to continue with a study for several years is that the staff get tired and are not as keen on to try to include all. Thus, the inclusion rate may fall if the study continues for several years.

3) A conclusion paragraph is added as a last section in the discussion, page 18, line 1-3.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: The authors hypothesized that MI (Motility index) could be used to identify enteric neuromuscular pathology in patients with gastrointestinal symptoms. To test this hypothesis, they consecutively included all patients undergoing MRE during a 2-year period and evaluated the use of MRI to assess motility. Consecutive adult patients who were referred for MRE during a 2-year period were included as cases while healthy volunteers were included as controls. MI of the terminal ileum measured by MR enterography was found to be inversely associated with mural thickness, especially in males. In females, diarrhea was inversely associated with MI of jejunum, while constipation was positively associated with MI of terminal ileum. The research is well crafted and executed. Also, the manuscript is well written and follows a logical sequence. The study limitations include the single center setting

and the failure to consider the influence of medical treatment on the disease. The study can act as a basis for future research in this field.

Reply: You are right that the single center examination may be a weakness. This is therefore mentioned as a limitation, page 17, line 22. We have previously written two manuscripts regarding different factors in Crohn's disease and ulcerative colitis which might influence the MI, ref no 10 and 17. We could find a weakly lower MI in active Crohn's disease than in inactive, but no difference at all regarding disease activity in ulcerative colitis. Further, no treatment given, laboratory analyses etc had any influence on MI in either disease. We therefore aimed in the present study only to focus on the whole disease groups, and focus more on symptoms and basal characteristics, to try to identify any possible associations between symptoms and a true dysmotility. This is further discussed in the discussion page 14, line 21-25 and page 17, line 7-9.

Science Editor: 1 Scientific quality: The manuscript describes an observational study of the motility index measured by MR enterography. The topic is within the scope of the WJG. (1) Classification: Grade B and Grade B; (2) Summary of the Peer-Review Report: The manuscript is well written and follows a logical sequence. The study limitations include the single center setting and the failure to consider the influence of medical treatment on the disease. This study can act as a basis for future research in this field. Except for CD, the case number of several other diseases, for example UC and dysmotility, was very small. An additional paragraph should be added in the last of the "Discussion" section to present the conclusion of this study. The questions raised by the reviewers should be answered;

Reply: All questions are answered, see above

and (3) Format: There are 3 tables and 2 figures. A total of 31 references are cited, including 8 references published in the last 3 years. There are 7 self-citations. 2 Language evaluation: Classification: Grade A and Grade B. A language editing certificate issued by AJE was provided. 3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement, the Institutional Review Board Approval Form, the informed consent, and the STROBE checklist. No academic misconduct was found in the CrossCheck detection and Bing search. 4 Supplementary comments: This is an unsolicited manuscript. The study was supported by Development Foundation of Region Skåne; Foundation of Skåne University Hospital; and Dir Albert Pålsson's Foundation. The topic has not previously been published in the WJG. The corresponding author has published 1 article in the BPG. 5 Issues raised: (1) I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);

Reply: This has now been done

(2) I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

Reply: Figure 2 a and 2b are provided, but figure 1 is original performed as a word document.

(3) I found the authors did not add the PMID and DOI in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout;

Reply: PMID and DOI are now added

and (4) I found the authors did not write the “article highlight” section. Please write the “article highlights” section at the end of the main text.

Reply: The article highlight is now written and added at the end of the main text

6 Re-Review: Required. 7 Recommendation: Conditionally accepted.

Sincerely

Bodil Ohlsson, professor