Peer Review File

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Reviewer A

Comment 1: This manuscript is dedicated to endoscopic diagnosis for celiac disease. While the subject matter is intriguing, it requires revision in several aspects.
Reply 1: Thank you for the time devoted to the review and the constructive comments. We have tried to address these and hope that it is acceptable. The changes are highlighted in bold.
Comment 2: In the Methods section, the author refers to Table 1, but the corresponding results are not presented in the text. This inconsistency needs to be addressed.
Reply 2: Thank you for this comment. We have now addressed this by adding more details to the methods section as follows **"We searched two electronic databases from their inception to December 2023 for relevant articles on the role of endoscopy in CD. Two authors (MGS & AY) reviewed these references and relevant studies were included in the discussion section of this review."**. The literature search was for a narrative review, and we did not follow a systematic review methodology. All the relevant studies retrieved from the literature were discussed in the discussion section.
Comment 3: In the Discussion, the author asserts, "Currently, endoscopic markers of CD such as scalloping, mosaic pattern, loss of duodenal folds, fissuring, nodularity, and erosions, are well described (Figure 1)." However, it is advisable for the author to provide supporting references for these statements.
Reply 3: Thank you for this comment. Reference added **"Dickey W. Endoscopic markers for celiac disease. Nat Clin Pract Gastroenterol Hepatol. 2006;3(10):546–51."**
Comment 4: Regarding Dye-based chromoendoscopy, the mention of methylene blue is noted, but there is no reference to indigo carmine, as discussed in Bonatto MW et al.'s study titled "Endoscopic evaluation of celiac disease severity and its correlation with histopathological aspects of the duodenal mucosa" (Endosc Int Open. 2016 Jul;4(7):E767-77).
Reply 4: Thank you for highlighting this study which we have now included as follows **"Another study by Bonatto et al. proposed an endoscopic classification incorporating chromoendoscopy, using 0.5% indigo carmine, with zoom magnification to confirm the presence of villous atrophy during endoscopy. The authors showed that this classification increased the agreement between endoscopy and histopathology. However, the agreement remained weak in less severe cases (32)."**
Comment 5: Concerning magnified endoscopy, the author cites a study by Raju et al., reporting a sensitivity of 86.4% and a specificity of 74.4%. However, caution should be exercised in drawing conclusive recommendations based solely on one study. Furthermore, the manuscript lacks guidance on defining satisfactory values for sensitivity and specificity.
Reply 5: Thank you for this comment. We completely agree that recommendations should not based on a single study. We have now changed the wording as follows **"The high cost of the high-magnification endoscopes and the lack of added diagnostic benefit over conventional endoscopy, hindered their routine use in clinical practice." We did not define satisfactory values for sensitivity and specificity as there is no current consensus on such values.**
Comment 6:While data on NBI are presented, the evaluation of these findings is not described. It is crucial for the authors to clarify whether they recommend performing NBI based on the results or in conjunction with magnification endoscopy.
Reply 6: Thank you for this insightful comment. While the data showed impressive results for NBI alone and in conjunction with magnification/water immersion, we have refrained from making any specific recommendations as the studies are still limited. Instead, we proposed that more studies with clinical validation of the NF-NBI classification should be conducted.
Comment 7: As for capsule endoscopy, the manuscript should specify the recommended sensitivity and specificity values. The rationale for these recommendations must be clearly stated.
Reply 7: Thank you for this comment. The recommendation is based on the cited European guidelines for the study of coeliac disease. To the best of our knowledge, no other international guidelines recommend the routine use of capsule endoscopy for coeliac disease diagnosis. There is currently no consensus on recommended sensitivity and specificity values for capsule endoscopy regarding the diagnosis of coeliac disease. Also, no studies have addressed this topic since 2012.

Reviewer B

Comment 1: In the present narrative review article Shiha et al discussed about the role of endoscopy in the diagnosis of celiac disease (CD). Main comments:

Reply 1: Thank you for the time devoted to the review and the constructive comments. We have tried to address these and hope that it is acceptable. The changes are highlighted in bold.

Comment 2: A linguistic revision is necessary, see for instance page 2 line 88 charactarized - - > characterized.

Reply 2: Thank you for highlighting this typo which has now been corrected.

Comment 3: Since a no-endoscopy approach may be adopted nowadays for some kind of patients (see Husby S et al, J Pediatr Gastroenterol Nutr 2020; Losurdo G et al, World J Gastroenterol 2021), a short paragraph discussing about this issue may make the article more complete.

Reply 3: Thank you very much for this excellent suggestion. We have now added a paragraph on the role of endoscopy in the no-biopsy era as follows "**Although endoscopy and biopsy has been long considered as the gold standard test to diagnose CD, recent evidence suggests that serology-based diagnosis in selected adult patients with markedly high tissue transglutaminase antibody levels (≥10 times the upper limit of normal) is highly accurate (51). This no-biopsy approach has been used in the paediatric population for over a decade (52). Yet, following the same approach to diagnose adults with CD has been a matter of an ongoing debate (53)(54). Avoiding unnecessary endoscopy could lead to significant reductions in both the healthcare costs and the carbon footprint of endoscopy (55). However, it is important to recognise that less than a third of patients with suspected CD would fulfill the criteria for a serology-based diagnosis, and that most patients will still need endoscopy and biopsy to confirm the diagnosis. Furthermore, many patients may still want to have a histological confirmation of CD before adhering to a life-long gluten-free diet. Therefore, the decision to pursue endoscopy- versus serology-based diagnosis for CD should be tailored to individual patient preferences, clinical presentation, and risk factors. Future studies on the accuracy of endoscopic tools for the detection of villous atrophy in CD may yield different results if they only included patients with low and intermediate tissue transglutaminase antibody levels.**"

Comment 4: In the "optimal biopsy strategy" paragraph, please discuss about the usefulness of biopsy correct orientation on paper.

Reply 4: Thank you for this excellent comment. We have incorporated this in the "optimal biopsy strategy paragraph" as follows **"Another important factor to optimise the diagnosis is the correct orientation of the biopsy specimens. Non-oriented biopsies could lead to false-positive diagnosis of CD, even by expert pathologists (28). The correct orientation of biopsies begin in the endoscopy suite, with placing the biopsy specimens on a strip of paper in a straight line, with the luminal surface upwards (28). This technique aids the pathologists in making a more accurate diagnosis."**

Comment 5: Page 5 lines 153-155: a more in depth analysis about the role of enteroscopy in CD is important (see Tomba C et al, J Clin Gastroenterol 2016).

Reply 5: Thank you for this comment, we have now expanded on this as follows **"A sequential approach of CE as a first-line investigation, followed by device-assisted enteroscopy if CE detected complications, has been shown to have a high diagnostic yield in patients with suspected refractory CD (50)(51). In a meta-analysis of 3 studies, the pooled diagnostic yield of push endoscopy and double-balloon enteroscopy for the diagnosis of small bowel malignancy and ulcerative jejunitis in patients with complicated CD was 27% (95% CI, 14.8% - 42.6%) (49)."**

Comment 6: Since this is a narrative review, the Checklist may be deleted.

Reply 6: We agree that the checklist may not be necessary, but this was an editorial requirement.

Comment 7: The Summary final paragraph should be more analytical and discuss possible perspectives and the point of view of the Authors.

Reply 7: Thank you for this excellent comment. We have expressed all our perspectives in the discussion section. The decision to conclude our review with a broader and open-ended summary was deliberate to encourage readers to reflect on the evidence provided throughout the manuscript and develop their own perspectives and points of view.