Milan, 2023-04-14

Dear Editor,

Thank you for your interest in considering a revised version of our manuscript.

Please find herewith enclosed a copy of our revised manuscript entitled “The paradoxical association between dyspepsia and autoimmune chronic atrophic gastritis: Insights into Mechanisms, Pathophysiology, and Treatment Options”

Thank you very much for going into depth with our paper and for your constructive criticism that substantially improved the paper. We believe that all concerns have been successfully rebutted.

All changes have been highlighted in the text, as requested in the instructions for the authors.

We hope the revised version will now be suitable for publication in the *World Journal of Gastroenterology*.

Here is our point-by-point response to your comments:

Reviewer #1:

Specific Comments to Authors: Thanks a lot for the manuscript, there is a small remarks. You write about autoimmune gastritis, but in the diagnostic algorithm there is no indication for the estimation of antiparietal antibodies, pepsinogen 1 and 2, and also not cases when a histological conclusion is necessary. Please expand the algorithm or describe these situations in the text. It would also be great to present the results (graphs or equations) of correlation analysis of symptoms among themselves and with the levels of pepsinogen levels 1 and 2).

We thank the reviewer for this interesting observation. It would be very interesting to include the test of APCA in a flow chart of dyspepsia in an original paper, but this is beyond the scope of this literature review, which only evaluated papers in which patients have already been diagnosed with AIG. Therefore, we created an algorithm based on the differential diagnosis of different clinical manifestations of dyspepsia in AIG patients without further specifying the tools required for the diagnosis of AIG.

Regarding symptoms, we have added a graph (Figure 2) explaining the frequency of upper GI symptoms in AIG

Reviewer #2:

Specific Comments to Authors: This review summarized the pathological mechanisms, clinical implications, and the current management strategies of AIG. It is of valuable information for the clinical and fundamental research. However, it would be better if the data could be shown as bar or other figures in the several publications referred to in "Dyspepsia in autoimmune gastritis: clinical manifestations and pathophysiological mechanisms " of "Results" section.

Many thanks for this comment. For the convenience of the reader', we have summarized the most common upper GI symptoms reported by AIG patients, together with the underlying pathophysiological mechanisms, according to the findings in the literature, in Table 1 and in the new Figure 2.

Reviewer #3:

Specific Comments to Authors: 1. The number of cases analyzed should be expanded. 2. The relationship with Helicobacter pylori should be analyzed in more detail, and the process of chronic development should be more accurate.

We thank the reviewer for this interesting observation.

Regarding comment 1, it is important to emphasize that the manuscript being evaluated is a systematic review of the literature that includes papers selected according to the topic and scope of the review and does not include patients.

As for comment 2, the points suggested are very interesting, but that is beyond the scope of this literature review.

Reviewer #4:

Specific Comments to Authors: Patients with autoimmune gastritis can exhibit various symptoms of dyspepsia, and currently there are no fully effective clinical methods for the treatment of dyspepsia in such patients. In this review, the authors proposed innovative treatments for the possible pathophysiological mechanisms of autoimmune gastritis. They recommended a multidisciplinary approach for the management of dyspepsia in AIG. Prokinetic agents, antidepressant drugs, and non-pharmacological treatments may be helpful, and targeting dyspepsia in AIG based on changes in the microbiota and advanced endoscopic techniques to treat severe dyspeptic symptoms might be an area of ongoing research. There are some questions: For patients with nutritional deficiencies such as vitamin B12 and iron, does nutritional support therapy help improve the symptoms of indigestion? Patients with autoimmune gastritis often have concomitant autoimmune thyroid diseases. Does abnormal thyroid function also play a role in the occurrence and development of dyspepsia in patients with AIG?

We thank the Reviewer for these kind observations. Regarding the specific questions:

Nutritional support. The treatment section states, "Initial management of dyspepsia in AIG may involve dietary modifications, such as avoiding trigger foods or eating smaller, more frequent meals. Patients may also benefit from lifestyle modifications, such as weight loss or stress reduction techniques, even if these interventions are not supported by studies." Nutritional support could help in treating dyspepsia in these patients, even if there is no clear evidence of a direct effect on dyspeptic symptoms.

Abnormal thyroid function. This is an interesting observation. Indeed, abnormal thyroid function, which is very common in patients with autoimmune gastritis, has been associated with gastric dysmotility [PMID: 19533804]. However, it is difficult to understand whether dyspepsia in AIG patients directly results from abnormal thyroid function or is due to AIG or a combination of both. A commentary has been added with an appropriate reference (see the

section “Dyspepsia in autoimmune gastritis: clinical manifestations and pathophysiological mechanisms”; ref # 29).

Your valuable comments and suggestions were of great help in the completion of this paper.

I confirm that the paper has not been submitted nor published in another journal.

Please feel free to approach us for any questions or further clarifications

Thank you.

Sincerely,

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