Subrata Ghosh

Andrzej S Tarnawski

Editors-in-Chief

World Journal of Gastroenterology

Dear Drs. Ghosh and Tarnawski:

RE : 70510

Title : **Inverse correlation between gastroesophageal reflux disease and atrophic gastritis assessed by endoscopy and serology**

coauthored by Yoo Min Han, Seokha Yoo, Jong In Yang, Ji Min Choi, Jooyoung Lee, Joo Sung Kim.

Thank you for your kind e-mail, which informed us that our manuscript mentioned above will be re-reviewed after suitable revision. We have tried to emend and improve the paper according to the reviewer's comments. The point-by-point responses to each comment suggested by the reviewer are enclosed on separate pages. Accurate and kind comments by the reviewer- have been addressed in the manuscript. Changes have been made by track change in the revised manuscript and figure to avoid any confusion.

We hope that the revised version will fulfill the requirements for publication in the ***World Journal of Gastroenterology*** and give you satisfaction.

We really appreciated the reviewer's comments and the opportunity to improve the manuscript.

Thank you very much.

Sincerely,

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Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Major revision

Specific Comments to Authors: Han et al. systematically showed that atrophic gastritis, in both endoscopically and serologically, could be an independent protective factor against GERD. Their review was retrospective but it was a very large study in the general population, and very significant in terms of the prevalence and severity of GERD were shown according to the extent of atrophic gastritis. Their article has been well elaborated and of sufficient quality to be reported. Although the study seemed to have conducted in a well-organized manner, further revisions are desirable for publication.

Major comments:

1. The authors conclude that atrophic gastritis is an independent protective factor for GERD and that the cost of maintenance anti-reflux therapy should be taken into account when considering the cost-effectiveness of H. pylori eradication therapy. The primary goal of H. pylori eradication therapy is to improve atrophic gastritis and to reduce carcinogenic risk and associated mortality, and it is clear from previous studies that eradication therapy can reduce cancer deaths (ref 1,2). As the authors mentioned, it is a well-known fact that eradication therapy carries the risk of exacerbation of GERD, while this is a benign disorder, and in most cases, it can be sufficiently controlled by acid secretion inhibitors. It seems clear which is the higher priority, controlling cancer death with eradication therapy or avoiding the risk of exacerbation of benign disease. The author declared that eradication interventions should be cautious given the risk of GERD, but I think this is a dangerous claim to readers. With or without GERD, I believe that the advantages of eradication therapy and to improve mucosal atrophy take precedence over the disadvantages, but what do authors think? It is desirable to specify the author's view on eradication therapy. Ref. 1) Li WQ, et al.

BMJ. 2019; 366:l5016. 2) Take S, et al. J Gastroenterol. 2020; 55: 281- 288.

***Reply*:**

Thank you very much for your helpful comments. We totally agree with you in that point and have tried to comply with your suggestion. Accordingly, the following sentences were deleted from the section of DISCUSSION: "At present, the incidence of *H. pylori* infection is decreasing in Korea, and the number of patients with chronic atrophic gastritis is expected to decrease in the future. The prevalence of GERD may also increase because GERD exhibited an inverse correlation with EAG in our study. The trend of an increasing prevalence of GERD has already been observed in Asian countries. Therefore, the potential costs of maintenance anti-reflux therapy may need to be considered when evaluating the cost-effectiveness of anti-*H. pylori* therapy." (line 26 on page 17 in our previous manuscript)

"The timing of *H. pylori* eradication therapy should be carefully calibrated based on the status of *H. pylori* infection and extent of EAG. Furthermore, the cost–benefit analysis of maintenance anti-reflux therapy over *H. pylori* eradication therapy should be considered in further studies."(line 25 on page 18 in our previous manuscript)

Focusing on the main important point of your recommendation, we further mentioned our perspective on *H. pylori* eradication treatment in the DISCUSSION as follows (underlined): "The primary goal of *H. pylori* eradication therapy is to improve atrophic gastritis and reduce carcinogenic risk and associated mortality as it is clear from previous studies that eradication therapy can reduce cancer deaths[44, 45]. Although eradication therapy is likely to exacerbate the symptoms and clinical course

of GERD, it seems clear that eradication therapy should be prioritized over GERD prevention." (line 18 on page 19)

Also, we added the following two articles (#44 and #45) to the REFERENCES.

REFERENCES

44. **Li W,** Zhang J, Ma J, *et al*. Effects of Helicobacter pylori treatment and vitamin and garlic supplementation on gastric cancer incidence and mortality: follow-up of a randomized intervention trial. *BMJ* 2079;**366**: l5016.

45. **Take S,** Mizuno M, Ishiki K, *et al*. Risk of gastric cancer in the second decade of follow-up after Helicobacter pylori eradication. *J Gastroenterol* 2020;**55**:281-8.

2. The authors examined atrophic gastritis in two directions: endoscopic and serological. Did the serological and endoscopic evaluations match in the same case? Previous reports has also pointed out that the Pepsinogen method may result in false negatives especially in cases after eradication, and the accuracy of either method is limited. Whether there was a reliable correlation between these two methods in the cases in this study should be showed in Tables or Figures.

***Reply*:**

We really appreciate your valuable comment. Among 2,857 patients who underwent serologic examination for pepsinogen, 703 patients had the history of *H. pylori* eradication treatment. We analyzed the correlation between serologic and endoscopic method in patients with and without *H. pylori* eradication (Table 1). Among the patients who showed EAG O3, 29 out of 35 (76.319%) had SAG in patients without *H.*

pylori eradication, however, only 7 out of 13 (53.846%) had SAG in patients with *H. pylori* eradication. The correlation between EAG and SAG was higher in cases without *H. pylori* eradication group than cases with *H. pylori* eradication group, which means pepsinogen method may result in false negatives especially in cases after *H. pylori* eradication therapy.

Table1. Correlation between EAG and SAG

	Without *H. pylori* eradication		With *H. pylori* eradication	
	Total patients	Patients with SAG (percentage)	Total patients	Patients with SAG (percentage)
Normal	1000	35 (3.5)	269	8 (3.0)
C1	160	9 (5.6)	86	1 (1.2)
C2	334	32 (9.6)	144	4 (8.0)
C3	315	63 (20.0)	91	12 (13.2)
O1	206	49 (23.7)	70	9 (12.9)
O2	101	48 (47.5)	30	9 (30.0)
O3	38	29 (76.3)	13	7 (53.8)

So, we excluded 703 patients who had the history of *H. pylori* eradication treatment in the analysis. The final results were shown as below and it was not significantly different from initial analysis. We underlined the changed results to clarify the difference. (line 8 on page 14)

"Among 26585 individuals included in this study, 2857 individuals (10.7%) underwent blood examination for pepsinogen test. There were minor and no significant differences in clinical characteristics including the prevalence of GERD between individuals with and without blood examination for pepsinogen test. Among them, 703 patients who underwent H. pylori eradication therapy were excluded and finally 2154 patients were included in the analysis. 358 patients (16.6%) had GERD and the severity of GERD was graded as follows: 78 patients (21.8%) with NERD, 79 patients (22.1%) with LA-M, 154 patients (43.0%) with LA-A, 46 patients (12.8%) with LA-B, and 1 patient (0.3%) with LA-C. Pepsinogen I level showed no significant association with the severity of GERD (P = 0.802). On the other hand, pepsinogen II level was significantly different according to GERD severity (P < 0.001). Post-hoc analysis revealed that LA-A showed significant lower level of pepsinogen II compared with normal group (normal vs LA-A, P < 0.001). In addition, pepsinogen I/II ratio was significantly higher in GERD group compared with normal group (normal *vs* LA-M, P =0.002; normal *vs* LA-A, P < 0.001; and normal *vs* LA-B, P = 0.002). LA-A group also showed significant higher pepsinogen I/II ratio than NERD (NERD vs LA-A, P < 0.001) (Figure 5).

SAG group showed lower prevalence of GERD than normal group (Figure 6). Total 343 out of 1889 individuals without SAG (18.2%) had GERD, in other hands, 15 out of 265 individuals with SAG (5.7%) had GERD. In the multivariate logistic regression analysis, the risk of GERD was adjusted for age, sex, BMI, metabolic syndrome, medication of sedatives or hypnotics, alcohol intake, smoking history, physical activity, dietary factor, and *H. pylori* IgG. Presence of SAG was correlated with reduced risk of GERD (OR = 0.49, 95% CI; 0.28–0.87, P = 0.014). (Figure 7)."

We also added detailed explanation for the reason why we excluded the patients who underwent H. pylori eradication therapy in the analysis of SAG in DISCUSSION: (line 27 on page 16)

"We excluded patients who underwent *H. pylori* eradication therapy because pepsinogens normalize after successful *H. pylori* eradication. It would be incorrect to evaluate atrophic gastritis only based on pepsinogens in cases after *H. pylori* eradication therapy. "

3. In Discussion, the authors stated that it may be possible to assess the risk and severity of GERD with only a simple serological test (page 16, line 28-29). As shown in Figure 5, it may be true that patients with SAG tend to have a lower prevalence of GERD, but in the end, GERD can only be diagnosed endoscopically. So picking up patients without SAG as GERD high risk would only increase the burden of excessive endoscopy after all. It seems that there is a limit to picking up patients at risk of GERD serologically, and I think that it may be sufficient to recommend endoscopy to patients with GERD-related symptoms. It is desirable to clearly state the clinical significance of performing a serological risk assessment of GERD.

***Reply*:**

We are very grateful for your advice. According to your proposal, we made further comments on the clinical significance of performing a serological risk assessment of GERD in the DISCUSSION as follows: "However, our findings need to be interpreted carefully considering several aspects. Since GERD can only be diagnosed endoscopically, considering patients without SAG as a high risk for GERD would increase the burden of excessive endoscopy and be unnecessary. It may be sufficient to recommend endoscopy to patients with GERD-related symptoms. To prove the clinical usefulness of serological tests in GERD risk assessment, further studies with

more research data are needed." (line 29 on page 15)

Minor comments: 1) In Figures 3A and 6, it is necessary to show the unit of the vertical axis. Why is the vertical axis of Figure 3A up to 9 and of Figure 6 up to 10?

***Reply*:**

Thank you for your helpful advice. As your comment, we added the unit (%) of the vertical axis in Figure 3A and 6. The range of vertical axis was adjusted to the maximal value of each grade of GERD.

Reviewer #2:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Rejection

Specific Comments to Authors: This is a potentially interesting manuscript describing the associations between reflux esophagitis and gastric atrophy defined by endoscopy as well as serology. However, there are several points that concern me. Major point In evaluating the atrophic status of stomach using serology by using pepsinogens, we must consider the past history of H. pylori eradication. Several studies (APT 20Suppl1:25-32, 2004, JGH doi:10.1111/jgh.15017) reported that pepsinogens normalize after successful eradication, suggesting that evaluation of atrophy status merely by pepsinogens is not always correct if subjects with post eradication are not excluded. I strongly recommend to exclude subjects with successful eradication history. The result of this study seems to be incorrect, and more sharp correlation would be obtained if excluding subjects with past successful eradication history. Correlation between serological atrophy and reflux esophagitis has been already reported by several investigators (J Korean Med Sci 32:796-802, 2017, World J Gastreontestinal Endosc 16;71-7, 2011, Int J Biol Markers 25; 207-12, 2010). Thus, regrettably, this manuscript does not offer any new information to the field.

***Reply*:**

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eradication treatment. We analyzed the correlation between serologic and endoscopic method in patients with and without *H. pylori* eradication (Table 1). Among the patients who showed EAG O3, 29 out of 35 (76.319%) had SAG in patients without *H. pylori* eradication, however, only 7 out of 13 (53.846%) had SAG in patients with *H. pylori* eradication. The correlation between EAG and SAG was higher in cases without *H. pylori* eradication group than cases with *H. pylori* eradication group, which means pepsinogen method may result in false negatives especially in cases after *H. pylori* eradication therapy.

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Reviewer #3:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: This manuscript is very interesting and relevant. Contains very important information on the prevention of gastric and esophageal cancer. To confirm the diagnosis of GERD, the authors used risk factors: age, gender, anthropometric data, metabolic syndrome, smoking and many others. Authors explain regarding causality among H. pylori infection, atrophic gastritis, and GERD. I agree with the authors that their results findings must be confirmed through prospective clinical trials. The Kimura-Takemoto visual endoscopic method used in the manuscript is very subjective. I recommend that the authors continue a similar study using the endoscopic morphological method - Updated Kimura-Takemoto classification of atrophic gastritis. This is important in the second step for the accurate diagnosis of atrophic gastritis after serological screening.

***Reply*:**

We are very grateful your helpful advice. As your perspective, the Kimura-Takemoto visual endoscopic method used in the manuscript is very subjective. According to your advice, it would be very important to continue further study using the endoscopic morphological method - Updated Kimura-Takemoto classification of atrophic gastritis. Thank you for your helpful and constructive advice.

Re-reviewer

Comment: The authors responded appropriately to the reviewers' suggestions, and it seems that all necessary corrections were addressed. This research is now considered to be suitable for publication.

Reply:

Thanks for your comments.