Author's response to reviews

Title: Bile Reflux Index After Theurapeutic Biliary Procedures

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Author's response to reviews: see over
Dear Editor,

Re: “Bile Reflux Index After Therapeutic Biliary Procedures” MS: 1756586337166087.

We are grateful for your helpful and constructive comments and for those of the reviewers, and have made the appropriate corrections to our manuscript as requested by the reviewers and the editorial board.

Our itemized responses to the reviewers’ comments are provided hereunder.

**Response to first reviewer’s comments:**

**Introduction**

1.- The bile reflux index is a very indirect way to measure or determine duodeno-gastric reflux. The proper way is to measure this reflux directly by different techniques.

* The comment is correct, and we discussed this point in the Discussion section. The BRI was introduced by Sobola et al., who defined the method as a BRI above 14 indicating DGR (defined as bile acid level > 1 mmol/L [the upper limit of physiological reflux]), with 70% sensitivity and 85% specificity. Although the Bilitec is the gold standard in esophagogastroduodenal reflux, it has some shortcomings in the stomach and is also quite expensive, especially in a developing country like us. Thus, in the Introduction part, we have explained our aim as “The aim of this study was to investigate how therapeutic biliary procedures, which disrupt the function of the sphincter of Oddi, affect the gastric histology according to BRI.” Our aim was not to determine DGR accoring to BRI.

**Methods**

1.- What do you mean by “other issues”?

*The phrase was deleted and the sentence revised to read:

“The reasons for visiting the unit included cholangitis, need for stent exchange, common bile duct stones, and benign biliary stricture.”

2.- IM must be intestinal metaplasia. Describe it.

*IM does indicate intestinal metaplasia, and this was added as follows.

“However, Sobal et al. developed a histologic index that identifies DGR based on several findings: edema in the lamina propria, intestinal metaplasia (IM), chronic inflammation, and gastric *Helicobacter pylori* (*Hp*) infection (5). In this system, a histological bile reflux index (BRI) value above 14 indicates the presence of DGR.”
3.- How are you sure that this index truly represents duodenogastric reflux? This point is crucial.

*As explained above, it is not correct to say this index totally represents DGR. But its sensitivity and specificity were defined by the authors who defined it; we only used the values they gave, and do not defend that BRI directly reflects the DGR. However, we accept the BRI as a valuable tool for indicating DGR according to their results.

Results

1.- Table 1 can be eliminated and incorporated in the text.

*In view of the large number of groups, we thought the Table was a better way to summarize the groups for the readers. We have grouped Tables 1 and 2 together as you advised in your third suggestion below.

2.- It is absolutely strange that no patients with Billroth II had HP(+) . This reviewer has studied this point in over 60 patients and 1/3 have HP (+). Your group is too small for any conclusion.

*We agree that this group was too small to make any firm conclusions. As Billroth II operation is a known factor for DGR, and our aim was to determine the effect of the endoscopic therapeutic procedures on the gastric mucosa, we did not try to increase the number in the Billroth II group. As you pointed out, if the group was expanded we may have found Hp(+) patients, but in this small group no patient was Hp (+).

3.- Table 1 and 2 can be grouped together: Eliminate gender, and leave only age and HP.

*We corrected the tables according to your advise.

4.- Your study is very strange. Billroth II gastrectomy is the maximal representant of duodenogastric reflux and none has HP (+).

*As you pointed out before, the group is too small to make any conclusion about Hp.

5.- Table 5 can be eliminated and incorporated in the text. Table 6 similar.

* Tables 5 and 6 were incorporated into the text as requested.

Discussion

Complete

References

13,14,19,20,21,22,23,24,25,26,28,31,32 = numbers in parenthesis should be eliminated.
*13,14,19,20,21,22,23,24,25,26,28,31,32 = numbers in parenthesis were eliminated.

Figure 1 can be eliminated, because it adds nothing relevant.

* Figure 1 was eliminated.

Response to second reviewer’s comments:

1) It is better for you to describe patient’s background factor in detail (for example, functional gastrointestinal disorders, peptic ulcer, and so on).

* Background of patients has been clarified as follows:

For the first 3 groups of patients: first paragraph in the Methods section:
“The reasons for visiting the unit included cholangitis, need for stent exchange, common bile duct stones, and benign biliary stricture.”

For the control group:
The sentence “…had no history of cholecystectomy but had undergone upper endoscopy (for any indication) with normal findings (Group 4, controls; n = 39)”
(For “any indication”, we mean dyspepsia and reflux-like symptoms)

has been corrected to read “…had no history of cholecystectomy but had undergone upper endoscopy for dyspepsia or reflux-like symptoms and had normal findings.”

2) What time did you carry out these examinations?

The subjects for this prospective study were the patients who presented to our endoscopic retrograde cholangiopancreatography (ERCP) and endoscopy unit for investigation/treatment of various benign pathologies between April 2003 and October 2003.

3) What kind of methods should you perform to clarify the etiologies of DGR in future?

* If possible, we will try to perform Bilitec.

4) Remove M/F% in Tables 1 and 2.

* Female and male ratios were removed.

According to Editorial comments:

We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns.
Please can you also address the following editorial concerns:

1) Document in the methods section, the full name of the ethics committee that approved your study.

* The full name of the approving ethics committee was added at the end of the first paragraph of the Methods section:

“All patients provided informed consent for the procedures and those who agreed to enter the study were enrolled; the Gastroenterology Clinical Council approved the study.”

2) Include a title page in the main manuscript file - this should list the title of the article. The full names, institutional addresses, and e-mail addresses for all authors must be included on the title page. The corresponding author should also be indicated.

* The full names, institutional addresses, and e-mail addresses for all authors were provided in a title page in the main manuscript file, and the corresponding author was indicated.

3) Include an abstract in the main manuscript file- The abstract of the manuscript should not exceed 350 words and must be structured into separate sections: Background, the context and purpose of the study; Methods, how the study was performed and statistical tests used; Results, the main findings; Conclusions, brief summary and potential implications. Please minimize the use of abbreviations and do not cite references in the abstract.

*An abstract was added in the main manuscript file according to the above guidelines.

4) Please include a 'Competing interests' section-

A competing interest exists when your interpretation of data or presentation of information may be influenced by your personal or financial relationship with other people or organizations. Authors should disclose any financial competing interests but also any non-financial competing interests that may cause them embarrassment were they to become public after the publication of the manuscript.

Authors are required to complete a declaration of competing interests. All competing interests that are declared will be listed at the end of published articles. Where an author gives no competing interests, the listing will read 'The author(s) declare that they have no competing interests'.

When completing your declaration, please consider the following questions:

Financial competing interests

* In the past five years have you received reimbursements, fees, funding, or salary from an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? Is such an organization financing this manuscript (including the article-processing charge)? If so, please specify.
* Do you hold any stocks or shares in an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? If so, please specify.
* Do you hold or are you currently applying for any patents relating to the content of the manuscript? Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript? If so, please specify.
* Do you have any other financial competing interests? If so, please specify.

Non-financial competing interests

Are there any non-financial competing interests (political, personal, religious, ideological, academic, intellectual, commercial or any other) to declare in relation to this manuscript? If so, please specify.

If you are unsure as to whether you, or one your co-authors, has a competing interest please discuss it with the editorial office.

*A "Competing interests" section was added at the end of the manuscript as follows:

"The author(s) declare that they have no financial or non-financial competing interests."

5) Please include an 'Authors' contributions' section-

In order to give appropriate credit to each author of a paper, the individual contributions of authors to the manuscript should be specified in this section.

An "author" is generally considered to be someone who has made substantive intellectual contributions to a published study. To qualify as an author one should 1) have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) have been involved in drafting the manuscript or revising it critically for important intellectual content; and 3) have given final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

We suggest the following kind of format (please use initials to refer to each author's contribution): AB carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. JY carried out the immunoassays. MT participated in the sequence alignment. ES participated in the design of the study and performed the statistical analysis. FG conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

All contributors who do not meet the criteria for authorship should be listed in an acknowledgements section. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chair who provided only general support.

*An "Authors’ contributions” part was added at the end of manuscript (After the "Competing interests" section):

AUTHORS’ CONTRIBUTIONS:

S Kuran made substantial contributions to conception and design of the study, and acquisition, analysis and interpretation of data, and was also involved in drafting the manuscript.
E Parlak made substantial contributions to conception and design of the study, acquisition of data, and revision of the manuscript.

G Aydog conducted pathological reporting and contributed to conception and design.

S Kacar made substantial contributions to conception and design, was involved in drafting the manuscript, and provided critical revision of the scientific content.

N Sasmaz was involved in providing critical revision of scientific content.

A Ozden was involved in providing critical revision of scientific content.

B Sahin was involved in providing critical revision of scientific content, and gave final approval of the version to be published.

Thank you again for your helpful comments and advice.

Best regards,

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