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# Factor to consider in gastroesophageal reflux disease refractory to proton pump inhibitor therapy: Bile reflux

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## ABSTRACT

**Introduction:** We aimed to investigate the effect of bile reflux (BR) in patients whose symptoms did not improve despite proton pump inhibitor (PPI) treatment.

**Materials and Methods:** In our retrospective study, patients who were refractory to PPI treatment were divided into two groups as BR and non-BR patients based on the upper gastrointestinal endoscopy and endoscopic biopsy data. Age, sex, and endoscopic biopsy data of the patients were analyzed statistically.

**Results:** A total of 154 patients were included in the study. BR was detected in 107 of the patients, while BR was not observed in 47. While, 53% (n=81) of the patients were male and 47% (n=73) were female. There was no statistically significant difference between the two groups in terms of age, sex, and endoscopic biopsy data. When BR and the presence of *Helicobacter pylori* were compared, it was found that BR was higher in patients who were refractory to PPI therapy.

**Conclusion:** We believe that BR is a more effective factor than *H. pylori* in PPI-refractory gastroesophageal reflux patients.

**Keywords:** Bile reflux, GERD, *Helicobacter pylori*, PPI refractory

## Introduction

Gastroesophageal reflux disease (GERD) is a common disease in the community. Numerous symptoms occur because of histopathological changes responsible for the passage of gastric acid to the esophagus at a pathological level. It has been reported that 45–62% of these symptoms disappear with proton pump inhibitor (PPI) treatment. Stress, intestinal disorders, presence of *Helicobacter pylori*, and lack of adherence to treatment have been reported to be effective in patients with symptoms refractory to PPI therapy.[1,2] In a multicenter, prospective study, it was revealed that in addition to reflux symptoms, dyspeptic complaints such as epigastric pain and indigestion after meals were statistically significantly higher in patients who were refractory to PPI treatment. In the same study, it was shown that dyspeptic complaints increased despite the fact that PPI treatment in the patient group with full compliance with PPI treatment. In treatment-refractory cases, some treatment methods such as high-dose PPI administration, a combination of PPI and prokinetic agents have been suggested.[3,4] We observed that these studies focused on esophageal reflux symptoms refractory to PPI therapy, but did not consider the presence and effect of duodenogastric reflux.

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Bile reflux (BR) was defined as the reflux of duodenal contents into the stomach and esophagus. BR causes damage to the gastric and esophageal mucosa. As a clinical presentation of mucosal damage, dyspeptic complaints occur. Even when PPI therapy is administered at high doses, improvement in these symptoms is not sufficient. There are studies reporting an increase in the risk of gastric, esophageal, and even laryngopharyngeal malignancies because of some histopathological changes.[5-9]

In our literature review, we found several studies on the effect of BR in patients with esophageal reflux symptoms refractory to PPI therapy. In one of these studies, it was observed that the presence of BR reduced the response to PPI treatment. In a study, in which cases with esophageal reflux symptoms refractory to PPI treatment were examined and pH monitoring was used; it was determined that 38% of the patients had isolated BR, and 28% of the patients had both gastric acid and BR.[10]

Considering all this information, we planned a retrospective study to investigate the efficacy of BR in patients with PPI-refractory esophageal reflux symptoms.

## Materials and Methods

Approval was obtained from the Clinical Research Ethics Committee of Tokat Gaziosmanpaşa University Faculty of Medicine (21-KAEK-179). The status and duration of PPI treatment of patients who routinely undergo upper gastrointestinal endoscopy in our clinic are questioned and recorded in the hospital data system. Patients who underwent endoscopy by a single endoscopist in the endoscopy unit of our clinic due to esophageal reflux symptoms refractory to PPI treatment approximately 2018–2019 were scanned from the hospital data system. During the endoscopy, the gastric mucosa was stained with bile/the presence of bile residues in the stomach was evaluated as pathological BR. Observation of the pylorus open throughout the procedure and its failure to close despite peristalsis was recorded as pyloric dysfunction. The status and duration of PPI treatment used by each patient before the upper gastrointestinal endoscopy procedure were recorded from the hospital data system. Patients who were found to have received PPI treatment for at least 8 weeks before the procedure were included in the study.

Age, sex, endoscopic findings (BR, pyloric dysfunction, and esophagitis), and endoscopic biopsy results of the patients were recorded.

Patients under 18 years of age, patients with malignancy in the upper GI endoscopy, and patients who did not complete 8 weeks of PPI treatment were excluded from the study.

In line with these criteria, 154 patients were included in the study totally. The patients were divided into two groups as Group 1 with BR and Group 2 without non-BR (NBR). Patients' age, gender, BR, pyloric dysfunction, esophagitis, and endoscopic biopsy data (mild, moderate, and severe) were found and recorded in the hospital data system and compared.

### Statistical Analysis

Data were recorded using the Statistical Package for the Social Sciences-version 15. Student's t-test was used to compare the mean age between the two groups. Pearson $\chi^2$ was used to reveal the differences in gender and endoscopic biopsy results (inflammation, activity, atrophy, H. pylori, and intestinal metaplasia) between the two groups. $P < 0.05$ value was considered statistically significant.

## Results

In our study, which included 154 patients, BR was detected in 69% (n=107) of the patients, while BR was not observed in 31% (n=47) of them. While 53% (n=81) of the patients were male, 47% (n=73) were female. While the mean age was 48 SD 17.02 in the BR group, the mean age was 44.74 SD 13.05 in the NBR group. There was no statistically significant difference between the two groups in terms of age and sex (p=0.6 and p=0.62, respectively).

Esophagitis findings were observed in 5% (n=8) patients in the BR group and 2% (n=3) patients in the NBR group. Pyloric dysfunction was detected in <1% (n=1) patients in the BR group and in 1% (n=2) patients in the NBR group. There was no significant difference between the two groups in terms of esophagitis and pyloric dysfunction (p=0.808 and p=0.170, respectively) (Table 1).

When we look at the endoscopic biopsy data, the results of the two groups were similar in terms of activity, inflammation, intestinal metaplasia, H. pylori, and atrophy.

Only BR was detected in 36% (n=56) patients in the BR group. Both BR and *H. pylori* were found together in 33% (n=51) patients. About 18% (n=29) patients were found to have *H. pylori* without BR. BR and *H. pylori* were not detected in 11% (n=18) of the patients. There was no statistically significant difference between the two

**Table 1. Demographic and clinical characteristics of study patients**

| | Bile reflux | Non-bile reflux | p |
|---|---|---|---|
| Population | 107 | 47 | |
| Mean age±SD, years | 48.38±17.02 | 44.74±13.05 | 0.6 |
| Gender (female/male) | 73/34 | 33/14 | 0.62 |
| Disfunction of pylorus | 1 | 2 | 0.808 |
| Esophagitis | 8 | 3 | 0.17 |

SD: Standart deviation.

groups in terms of *H. pylori*. However, when BR and *H. pylori* efficacy were compared in treatment-refractory patients, a statistically significant difference was observed (p=0.046) (Table 2).

## Discussion

In our study, we investigated the presence and effects of BR in patients with dyspeptic symptoms refractory to PPI therapy.

When we examined the demographic data of both groups, the two groups were similar in terms of age and sex. BR was detected in 69% of the patients included in the study. There was no significant difference between the two groups in terms of pyloric dysfunction and esophagitis findings. The results of the two groups were similar in terms of inflammation, activity, intestinal metaplasia, atrophy, and *H. pylori* from endoscopic biopsy data.

When we examined the relationship between BR and H. pylori, only BR was observed in 36% of the patients, while the presence of only *H. pylori* was detected in 18% of the patients. In 33% of the patients, *H. pylori* was detected with BR. Statistically, we found that BR was higher in PPI refractory patients compared to *H. pylori*.

It is known that some patients with GERD may continue to have symptoms after PPI treatment. Studies conducted in patients' refractory to PPI therapy have shown that patients' dietary habits, gastrointestinal disorders, and especially the presence of *H. pylori* are effective.[2,11,12] However, it should be considered that BR may also be effective in the formation of symptoms refractory to PPI treatment. In recent studies, different medical and surgical treatment strategies have been tried to be developed. However, in these studies, it was observed that the symptoms continued after the treatments applied in some patients. In a retrospective study investigating the efficacy of Vonoprazan treatment, dose escalation or drug combination was observed in 58% of patients.[13] In a study investigating the efficacy of endoscopic mucosectomy, it was reported that 40–50% of patients could discontinue PPI treatment after the procedure.[14] We saw that patients were not evaluated

**Table 2. Endoscopic biopsy results of patients**

| | Non, n (%) | Mild, n (%) | Moderate, n (%) | Severe, n (%) | Total, n (%) | p |
|---|---|---|---|---|---|---|
| Inflamasyon bile reflux | 2 (2) | 31 (38) | 39 (48) | 9 (12) | 81 (100) | 0.381 |
| Non-bile reflux | 0 (0) | 12 (29) | 21 (51) | 8 (20) | 41 (100) | |
| Activity bile reflux | 48 (60) | 10 (13) | 14 (18) | 7 (9) | 79 (100) | 0.94 |
| Non-bile reflux | 15 (36) | 9 (22) | 11 (27) | 6 (15) | 41 (100) | |
| Atrophy bile reflux | 44 (90) | 5 (10) | 0 (0) | 0 (0) | 49 (100) | 0.59 |
| Non-bile reflux | 16 (94) | 1 (6) | 0 (0) | 0 (0) | 17 (100) | |
| H.Pylori bile reflux | 56 (52) | 23 (22) | 12 (11) | 16 (15) | 107 (100) | 0.108 |
| Non-bile reflux | 18 (38) | 6 (13) | 10 (21) | 13 (28) | 47 (100) | |
| IM bile reflux | 86 (87) | 7 (7) | 4 (4) | 2 (2) | 99 (100) | 0.257 |
| Non-bile reflux | 40 (87) | 6 (13) | 0 (0) | 0 (0) | 46 (100) | |

IM: Intestinal metaplasia.

in terms of BR in both studies, and we think that the reason for the refractoriness to the PPI treatment may be due to BR in the patients. In the 8th statement of the European and American Neurogastroenterology and Motility Society's latest consensus publication, it was reported that reflux symptoms of BR may influence the development of refractory to treatment. Again in the same publication, in the 22nd statement, it was recommended to detect BR with pH monitoring in the diagnosis of symptoms refractory to PPI treatment.[15] In a recent retrospective study, they revealed that BR causes more intense reflux symptoms and that the response to treatment decreases in these patients.[16] In a study including 65 patients who were refractory to PPI treatment, it was revealed that 64% of the patients had BR.[10] In our study, this rate was 69%. In a study, in which H. pylori-positive patients were excluded from the study, BR was detected in 88% of the PPI refractory group.[17] However, this study consisted of a very small patient series and the number of patients in the PPI refractory group was 17. In our study, when we excluded H. pylori-positive patients, this rate was 75%. According to our study, we believe that the higher result is due to the difference in the population included in the study.

The retrospective nature of our study brought some limitations. In some of our patients, we found that endoscopic biopsy materials were insufficient for pathological examination. However, we found that all patients included in the study were examined for H. pylori. In addition, we could not distinguish between pure BR or bile and acid reflux, since the pH monitoring was not used in patients.

## Conclusion

We recommend lifestyle changes, regulation of PPI treatment, investigation of BR without ignoring it, and appropriate treatment when necessary for treating patients with symptoms refractory to PPI treatment. BR is a pathological condition overlooked by clinicians. We think that BR should be considered and followed closely when it is considered that it causes the symptoms to continue despite the fact that the treatment, and that it causes the formation of precancerous lesions in the stomach esophagus and even the laryngopharyngeal region. We believe that BR is a more effective factor than *H. pylori* in patients with symptoms refractory to PPI therapy. We think that the treatment process of these patients should be planned according to BR. However, more efficient results will be obtained as a result of investigating the subject with prospective and larger population series.

### Disclosures

**Ethichs Committee Approval:** Approval was obtained from the Clinical Research Ethics Committee of Tokat Gaziosmanpaşa University Faculty of Medicine (Ethical Committee Aplication Number: 21-KAEK-179 Date: 02.09.2021).

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