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ΕΡΕΥΝΗΤΙΚΗ ΕΡΓΑΣΙΑ

Correlation between bile reflux gastropathy and therapeutic biliary interventions

OBJECTIVE **To determine whether therapeutic biliary procedures induce bile reflux gastropathy, to estimate its prevalence and risk factors and to assess the endoscopic and histopathological changes in the gastric mucosa.** METHOD **Study was made of 62 patients with epigastric pain and or dyspeptic symptoms following biliary intervention, who were divided into two groups: Group 1, the post-cholecystectomy group, consisted of 34 patients who had undergone cholecystectomy, and group 2, the biliary intervention group, of 28 patients who had undergone endoscopic retrograde cholangiopancreatography (ERCP) for treatment of benign pathology.** RESULTS **The prevalence of bile reflux gastropathy was 21.34% after therapeutic biliary interventions (p=0.00). Diabetes mellitus (DM), obesity, high gastric bilirubin level and increased gastric pH were all risk factors for bile reflux gastropathy in both groups (r=0.27, 0.31, 0.68, and 0.59, respectively). No correlation was demonstrated between age, sex, epigastric pain, heartburn, vomiting, and bile reflux gastropathy.** CONCLUSIONS **Bile reflux gastropathy is common after therapeutic biliary interventions and is more frequent in patients with obesity and DM.**

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2022, 39(6):819–826

A. Othman,[1]
A. Dwedar,[2]
H. El Sadek,[2]
H. Abd El Aziz,[3]
A. Abdelrahman[4]

[1]Department of Internal Medicine, Faculty of Medicine, Suez University, Suez
[2]Department of Internal Medicine, Faculty of Medicine, Zagazig University, Zagazig
[3]Department of Pathology, Faculty of Medicine, Zagazig University, Zagazig
[4]Department of Clinical Pathology, Faculty of Medicine, Zagazig University, Zagazig, Egypt

Σχέση μεταξύ γαστροπάθειας από παλινδρόμηση της χολής και θεραπευτικών διαδικασιών των χοληφόρων

Περίληψη στο τέλος του άρθρου

Key words

Bile reflux
Bilirubin
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ERCP
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Bile reflux gastropathy is a pathological condition characterized by backward flow of duodenal fluid, consisting of bile, pancreatic juices and intestinal mucosal secretions, into the stomach and esophagus,[1] causing mucosal lesions.[2] Bile acids, in combination with gastric acid, have been shown to cause bile reflux gastropathy symptoms, such as heartburn, regurgitation, epigastric pain, etc.[3]

Bile reflux gastropathy frequently occurs after gastric surgical procedures that damage the pyloric sphincter,[2] and after biliary procedures, such as cholecystectomy, endoscopic sphincterotomy (EST), endoscopic stenting and choledochoduodenostomy, which cause malfunction of the sphincter of Oddi.[4] Bile gastropathy is also a normal physiological event in a prolonged period of fasting (primary bile reflux gastropathy).[5] In individuals non-responsive to proton-pump inhibitor (PPI) medication, the overall prevalence of biliary reflux is reported to be 68.7%. These people have acid and bile reflux at the same time and have never had biliary surgery.[6]

Endoscopic retrograde cholangiopancreatography (ERCP) is an increasingly popular modality for both the diagnosis and the treatment of biliary tract disorders.[7] It is one of the most demanding and technically challenging procedures in gastrointestinal endoscopy, which must be

performed by operators with substantial training and experience to maximize success and safety.[8] Cholecystectomy is a surgical operation of gallbladder removal, which can be performed either laparoscopically, using a video camera, or via open surgical technique. Pain and complications caused by gallstones are the most common reasons for cholecystectomy.[9] This study was conducted to determine whether therapeutic biliary procedures induce bile reflux gastropathy, to estimate its prevalence and risk factors and to assess the endoscopic and histopathological changes in the gastric mucosa.

MATERIAL AND METHOD

Subjects

The study started with 288 patients admitted to the university hospitals with inclusion criteria of refractory epigastric pain and dyspeptic symptoms after therapeutic biliary interventions, with a history of poor response to prokinetics, mucosa-protective medicines, H_2-blockers, and or PPIs. The university hospital ethics committee approved this study protocol and ensured that the research was in keeping with the declaration of Helsinki 1975 (approval date: 1.1.2018 and approval number 4238). Because of the study exclusion criteria or because they declined to participate in the study, 96 patients were eliminated. The exclusion criteria included unstable cardiopulmonary, neurological or cardiovascular status, other causes of biliary diseases, such as common bile duct (CBD) stricture and hepatolithiasis, structural abnormalities of the esophagus, stomach or small intestine, patients who had undergone bariatric surgery beyond the scope of the study, patients taking long-term non-steroidal analgesics or oral contraceptive drugs, and patients with a positive stool antigen test for *Helicobacter pylori*.

Gastroscopy was performed on 192 patients who met the study inclusion criteria and gave informed consent. The presence of findings other than bile gastritis, including hiatus hernia and biliary dyskinesia, and psychosomatic symptoms, eliminated another 130 patients. Hence, the final study was performed on 62 patients with a gross diagnosis of gastritis, who underwent full assessment of the cause of gastritis. Their age ranged from 24 to 67 years, with a mean age±standard deviation (SD) of 41.6±10.01 years, and 35 were female (56.5%) and 27 male (43.5%). The study patients were classified into two groups. Group 1, the post-cholecystectomy group, consisted of 34 patients who had undergone cholecystectomy, and group 2, the biliary intervention group, included 28 patients who had undergone at least one of the following procedures for the treatment of benign pathology: endoscopic sphincterotomy (ES) and endoscopic stenting.

Diagnostic techniques of bile reflux gastropathy

Gastroscopy: Gastroscopy was performed using an Olympus single-channel CLK-4 gastroscope. Esophageal mucosal alterations, including erythema, presence of bile in the esophagus, edema, gastroesophageal reflux disease (GERD), incompetent cardia, and petechiae were recorded. Gastric mucosal alterations, including erythema, presence of bile in the stomach, thickening of the gastric folds, erosions, and petechiae were also recorded.

Histopathology: For the histopathological study, multiple biopsies were taken from the gastric mucosa via disposable flexible endoscopic biopsy forceps, 2 cup-shaped jaws with a central spike (Boston Scientific®).

Gastric aspirate analysis: Via a triple lumen ERCP cannula, 5.5 F (Boston Scientific®), immediately after insertion of the scope into the stomach, 5 mL of gastric fluid was aspirated through the suction channel of the endoscope and collected in a sterile trap placed in the suction line. Quantitative determination of gastric aspirate total bilirubin level was performed (Gen.3® kit and Cobas 8,000 analyzer). The pH of the gastric aspirate was measured during the gastroscopy, immediately after collection with a glass electrode pH meter (Adwa®).

Statistical analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS) program, version 22 (IBM Corporation, Armonk, NY, USA). Values were expressed as mean±SD for quantitative variables, and as numbers and percentages for qualitative variables. Independent-sample T testing was used to compare the means of quantitative variables of the two groups. Chi-square test (x^2) was used to compare qualitative variable means. The results were considered statistically significant if the p-value was <0.05. Correlation between variables was explored using the Person correlation coefficient (r).

RESULTS

The age of the 34 group 1 patients ranged from 24 to 67 years with a mean age of 43.53±11.45 years; 20 were female (58.8%) and 14 male (41.2%). Bile reflux gastropathy was observed in 14 males (41.2%) and 20 females (58.8%). The age of the 28 group 2 patients ranged from 27 to 59 years, with a mean age 39.25±7.47 years. Bile reflux gastropathy was noted in 13 males (46%) and in 15 females (53.6%).

In group 1, the endoscopic findings in the esophageal mucosa included GERD in 22 cases (64.7%), incompetent cardia in 12 (35.3%), and mucosal changes in 10 cases (29.4%). The endoscopic findings in the gastric mucosa included erythema in 18 cases (52.9%), the presence of bile in 17 (50%), thickening of the gastric folds in 12 (35.3%), erosions in 8 (23.5%), edema in 8 (23.5%), and petechiae in 7 cases (20.6%). In group 2, the endoscopic findings in the esophageal mucosa included GERD in 12 cases (42.9%),

mucosal changes in 11 (39.3%), and incompetent cardia in 7 cases (25%). The endoscopic findings in the gastric mucosa included erythema in 18 cases (64.3%), the presence of bile in 16 (57.1%), thickening of the gastric fold in 13 (46.4%), petechiae in 8 (28.6%), erosions in 6 (21.4%), and edema in 5 cases (17.9%) (tab. 1). Typical endoscopic findings are shown in figure 1a–c.

The bilirubin levels in the gastric aspirate in group 1 ranged from 0.15 to 10.4 mg/dL (mean 3.6±3.55 mg/dL). The gastric aspirate pH in this group ranged from 5.5 to 8 (mean 6.94±0.78). In group 2, the bilirubin levels in gastric aspirate ranged from 0.45 to 19.15 mg/dL (mean 7.43±5.70 mg/dL), and the gastric aspirate pH ranged from 5.5 to 8 (mean 7.17±0.88).

Table 1. Endoscopic findings in patients with epigastric pain and or dyspeptic symptoms following cholecystectomy or biliary intervention.

Parameter		Group			
		Group 1		Group 2	
		n	%	n	%
Esophageal	GERD	22	64.7	12	42.9
	Incompetent cardia	12	35.3	7	25.0
	Fluid regurgitation	15	44.1	8	28.6
	Mucosal changes	10	29.4	11	39.3
Gastric	Erythema of gastric mucosa	18	52.9	18	64.3
	Presence of bile	17	50.0	16	57.1
	Thickened gastric fold	12	35.3	13	46.4
	Erosions	8	23.5	6	21.4
	Petechiae	7	20.6	8	28.6
	Edema	8	23.5	5	17.9

Group 1: Post-cholecystectomy group; Group 2: Biliary intervention group
GERD: Gastroesophageal reflux disease

The histopathological findings on the gastric mucosal biopsies in group 1 included chronic inflammation in 18 cases (52.9%), foveolar hyperplasia in 11 (32.3%), chronic atrophic gastritis in 9 (26.4%), bile stasis in 8 (23.5%), interstitial inflammation in 8 (23.5%), edema in 7 (20.6%), intestinal metaplasia in 6 (17.6%) and acute inflammation in 2 cases (5.9%). The histopathological finding on the gastric mucosa biopsies in group 2 included chronic inflammation in 18 cases (64.3%), foveolar hyperplasia in 13 (46.4%), bile stasis in 9 (32.1%), intestinal metaplasia in 8 (28.6%), chronic atrophic gastritis in 6 (21.4%), interstitial inflammation in 6 (21.4%), edema in 6 (21.4%), and acute inflammation in 2 cases (7.1%) (tab. 2). Typical histopathological findings are shown in figure 2a–d.

Bile reflux gastropathy was present in 21 cases (61.76%) in group 1 and in 20 cases (71.43%) in group 2 (tab. 3).

The possible risk factors for bile reflux gastropathy in group 1 included increased gastric bilirubin (17 cases),

Table 2. Gastric mucosal histopathological findings in patients with epigastric pain and or dyspeptic symptoms following cholecystectomy or biliary intervention.

Parameter	Group			
	Group 1		Group 2	
	n	%	n	%
Chronic inflammation	18	52.9	18	64.3
Acute inflammation	2	5.9	2	7.1
Chronic atrophic gastritis	9	26.4	6	21.4
Intestinal metaplasia	6	17.6	8	28.6
Bile stasis	8	23.5	9	32.1
Interstitial inflammation	8	23.5	6	21.4
Foveolar hyperplasia	11	32.3	13	46.4
Edema	7	20.6	6	21.4

Group 1: Post-cholecystectomy group; Group 2: Biliary intervention group

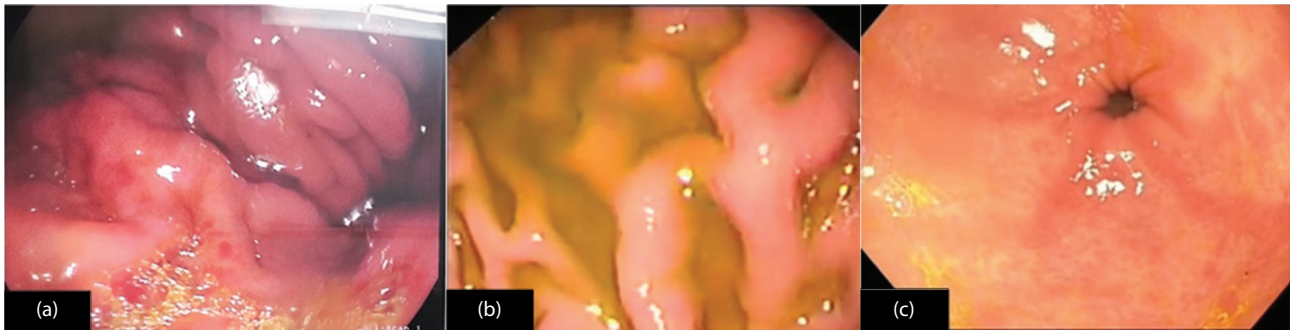

Figure 1. Bile reflux gastropathy: Upper gastrointestinal endoscopic photographs showing (a) gastric petechiae and presence of bile in the stomach, (b) thickening of the gastric folds and presence of bile in the stomach, and (c) antral gastritis with mucosal erythema and erosions, with the presence of bile in the stomach

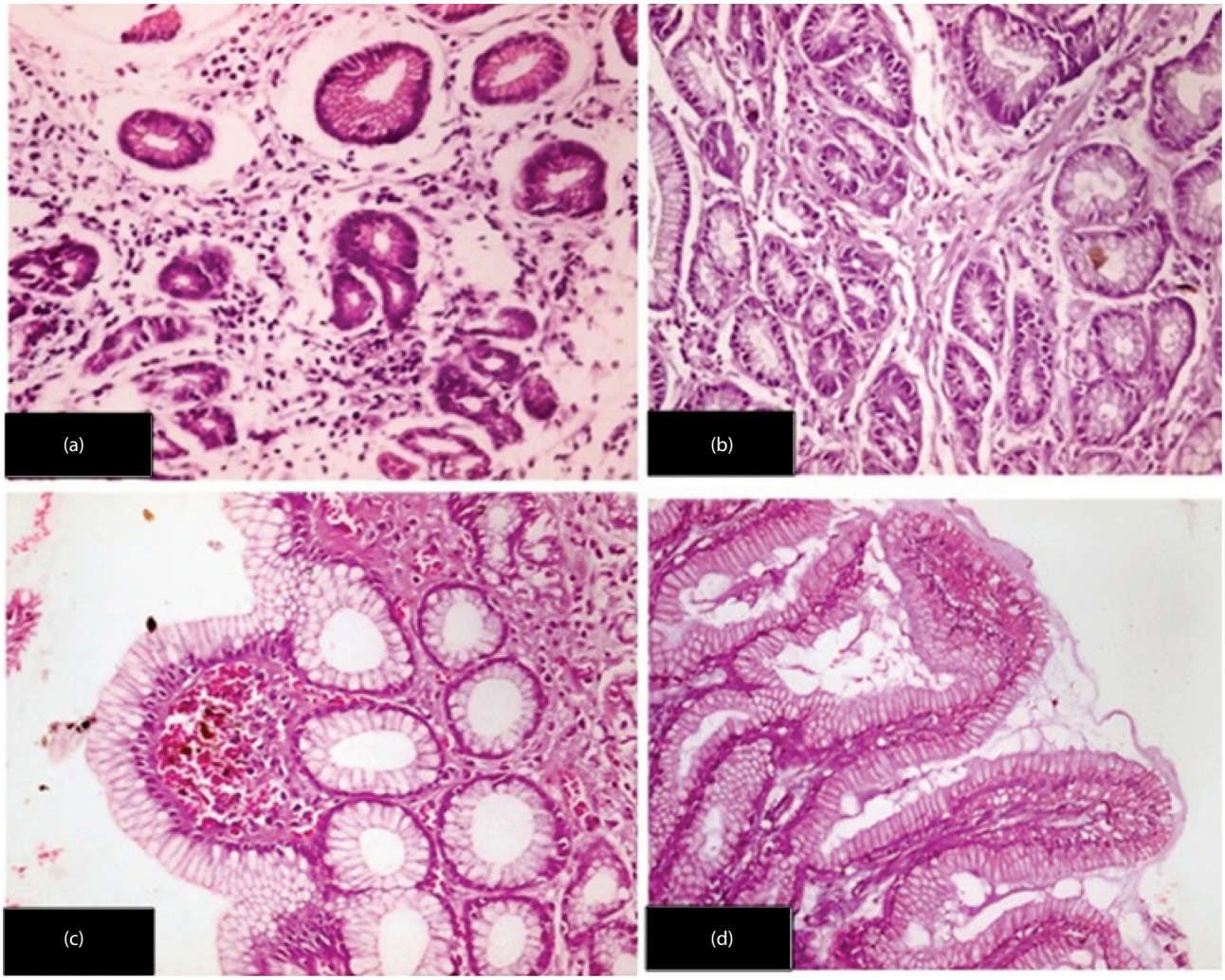

Figure 2. Bile reflux gastropathy: Photomicrograph, showing (a) chronic atrophic gastritis with periglandular fibrosis, chronic inflammatory infiltrate, and mild dysplasia (H&E ×400), (b) chronic gastritis with periglandular fibrosis and mild chronic inflammatory infiltrate (H&E ×400), (c) chronic gastritis with focal bile stasis (H&E ×400), (d) chronic gastritis with diffuse intestinal metaplasia and interstitial inflammation (H&E ×400)

Table 3. Bile reflux gastropathy and non-bile reflux gastropathy in patients with epigastric pain and or dyspeptic symptoms following cholecystectomy or biliary intervention.

Parameter	Group 1		Group 2		X^2	p
	n=34	%	n=28	%		
Bile reflux gastropathy	21	61.76	20	71.4	0.64	0.59
Non-bile reflux gastropathy	13	38.24	8	28.6		

Group 1: Post-cholecystectomy group; Group 2: Biliary intervention group

and alkaline gastric pH (20 cases), diabetes mellitus (DM) (14 cases), obesity, defined as body mass index (BMI) ≥30 kg/m^2 (17 cases), and *H. pylori* infection (3 cases), and in group 2 increased gastric bilirubin (19 cases), and alkaline gastric pH (20 cases), DM (13 cases), obesity (17 cases), and *H. pylori* infection (4 cases).

The analysis revealed statistically significant positive correlation between the presence of bile reflux gastropathy and increased gastric bilirubin, increased gastric aspirate pH, DM and obesity in both study groups (r=0.68, 0.59, 0.27, 0.31, respectively). No correlation was found between age, sex, epigastric pain, heartburn, vomiting, and the presence of bile reflux gastropathy in either study group (tab. 4).

DISCUSSION

Bile reflux gastropathy is a condition characterized by upper abdominal pain, frequent heartburn, nausea, and vomiting of bile, which appears to be caused by the

Table 4. Correlation between risk factors and presence of bile reflux gastropathy in patients with epigastric pain and or dyspeptic symptoms following cholecystectomy or biliary intervention.

	Bile reflux gastropathy	
	r	P
BMI	0.31*	0.16
Gastric pH	0.59**	0.00
Gastric bilirubin	0.68**	0.00
RBS	0.27*	0.03
Epigastric pain	0.07	0.57
Heartburn	-0.10	0.43
Vomiting	-0.007	0.96
Age	0.16	0.21
Sex	0.15	0.25

* Correlation significant at the 0.05 level (2-tailed)

** Correlation significant at the 0.01 level (2-tailed)

BMI: Body mass index, RBS: Random blood sugar, GERD: Gastroesophageal reflux disease

backward flow of duodenal fluid into the stomach and esophagus. This fluid contains bile, pancreatic juices, and duodenal mucosal secretions.[1] The diagnosis is based on clinical findings, pH of aspirated gastric juice (on the assumption that the reflux would cause an increase of pH over 7 due to the alkaline nature of duodenal juice),[10] and the endoscopic and histopathological findings.[11]

The esophageal endoscopic findings in this study were GERD, incompetent cardia, fluid regurgitation, and mucosal changes. In both groups 1 and 2, GERD was the most common esophageal endoscopic finding, at a percentage of 64.7% and 42.9%, respectively. The gastric endoscopic findings were erythema of the gastric mucosa, the presence of bile, thickening of the gastric folds, erosions, petechiae, and edema. In both groups 1 and 2, the most common gastric endoscopic finding was erythema of the gastric mucosa, 52.9% and 64.3%, respectively. Because of the prolonged fasting state required before the endoscopy procedure, no bile should be found in the stomach when the gastroscopy is performed, meaning that the presence of bile in the stomach should put bile reflux on the differential diagnosis list. These findings were similar to those of previous studies, which relied on endoscopic findings for the diagnosis of bile reflux, based on the presence of bile in the stomach, with adhesion of bile crusts on the gastric mucous membrane, and changes in the mucous membrane, that becomes hyperemic, frail and erosive.[12] In a Romanian endoscopic study of bile reflux gastropathy, the endoscopic gastric mucosal changes were erythema, presence of bile in the stomach, overthickening of the gastric folds, erosions, atrophic mucosa, petechiae, intestinal metaplasia, and polyps.[2] All of the patients had bile in the stomach.[11]

The alkaline gastric aspirate in both groups 1 and 2 (6.94±0.78 and 7.17±0.88, respectively) with a high level of gastric bilirubin (3.6±3.57 and 7.43±5.7, respectively) were thought to be the cause of the esophageal and gastric mucosal damage in our study. The normal mean bilirubin level in gastric aspirate is 1.3 mg/dL,[13] and the normal pH of gastric juice is 1.5 to 3.5.[14] Although the exact mechanism of the mucus membrane alterations are still unknown,[15] some studies have indicated that interaction of bile acid, a component of bile, with M3 muscarinic receptor subtype expressed in the chief cells might contribute to mucosal damage, manifested as active inflammation, intestinal metaplasia, glandular atrophy and focal hyperplasia, and other pathophysiological consequences of bile reflux.[16] Apoptosis and redox reactions had been reported to be associated with bile acid-induced gastritis.[17] Some reports suggest that bile acids and other duodenal contents act synergistically with gastric acid and *H. pylori* infection in the development of chronic gastritis.[15]

Chronic inflammation was the most common histopathological finding in both groups 1 and 2, at percentages of 52.9% and 64.3%, respectively, and the least frequent histopathological finding was acute inflammation, at percentages of 5.9% and 7.1%, in groups 1 and 2, respectively. Our results are in agreement with a previous study that reported histopathological evidence of chronic gastritis, namely foveolar hyperplasia, intestinal metaplasia, dysplasia, acute gastritis, chronic atrophic gastritis, polyps, benign ulceration and edema, with chronic inflammation being the most common histopathological finding (84.06%).[2] The histopathological changes due to bile reflux gastropathy in children were characterized by chronic inflammation, with foveolar hyperplasia in both the gastric corpora and antrum, vascular congestion, edema of the lamina propria, and smooth muscle hyperplasia.[18]

In our study, bile reflux gastropathy was found in 21/34 cases (61.76%) and 20/28 cases (61.76) in groups 1 and 2, respectively. According to previous research, the prevalence of bile reflux after therapeutic biliary interventions was 60%.[19]

Obesity, increased pH in gastric aspirate, increased gastric bilirubin and random blood sugar (RBS) all showed statistically significant positive correlation with bile reflux gastropathy in both study groups. These findings corroborate previous studies where obesity was identified as a risk factor for bile reflux gastropathy.[20] A significantly

higher rate of post-ERCP complications has been reported in obese patients (BMI ≥30 kg/m^2) in comparison to those who were overweight (BMI 25–30 kg/m^2), normal weight (BMI 18.5–25 kg/m^2), and underweight (BMI <18.5 kg/m^2).[21] Increased bilirubin level and pH in the gastric aspirate were confirmatory tools in the diagnosis of biliary gastropathy, with a significant relationship between the level of gastric bilirubin and the degree of inflammation.[13] A gastric bilirubin level of above 20 mg/dL could indicate severe esophagitis, erosive gastritis or gastroesophageal metaplastic changes. More severe biliary gastritis was associated with higher bilirubin levels in the gastric aspirates.[22]

DM is considered to be a risk factor for bile gastritis,[2,5] and type 2 DM has been associated with gastroduodenal dysmotility.[23] Diabetes gastroparesis is a condition where persistent hyperglycemia, in either type 1 or type 2 DM, causes damage to the vagus nerve, which is responsible for proper gastric movement, resulting in delayed gastric emptying without mechanical obstruction.[24] Severe bile reflux gastropathy was reported to be a consequence of diabetic gastroparesis.[25,26]

We found no correlation between age, sex, epigastric pain, heartburn, vomiting, and the presence of bile reflux gastropathy in our study. Previous studies that looked into the relationship between age and biliary gastritis found no significant connection between age and bile reflux gastropathy.[27,28]

In our study, histopathological examination of gastric mucosa revealed chronic atrophic gastritis, with periglandular fibrosis, chronic inflammatory infiltrate, and mild dysplasia (fig. 2a), and chronic gastritis with periglandular fibrosis and mild chronic inflammatory infiltrate (fig. 2b), focal bile stasis (fig. 2c), and diffuse intestinal metaplasia and interstitial inflammation (fig. 2d). Earlier studies reported histopathological alterations from bile gastritis similar to our findings, namely chronic gastric mucosal inflammation, lamina propria edema, foveolar hyperplasia, antral atrophy and intestinal metaplasia.[2,29] The histological alterations from bile reflux gastritis in the form of foveolar hyperplasia, edema, smooth muscle fibers in the lamina propria, and paucity of acute or chronic inflammatory cells were similar to those seen in chemical (reactive) gastritis.[23]

Recommendations: The patients diagnosed with bile reflux gastropathy were advised on lifestyle changes, including weight loss, avoiding GERD triggers, waiting at least 3 hours after eating before lying down, elevation of the head of the bed, and smoking cessation. Medications such as PPIs and histamine type 2 receptor blockers (H2RBs) might be prescribed if the symptoms persist. Patients with bile reflux gastropathy are often treated as those with classic GERD, because there are no formal guidelines. PPIs, H2RBs, prokinetics (metoclopramide), and baclofen (to reduce relaxation of the lower esophageal sphincter) are some of the treatment possibilities. It is also important to review the patient's medication list and minimize drugs such as opioids and anticholinergics that decrease gastroduodenal motility. Ursodeoxycholic acid (UDCA), cholestyramine, misoprostol, and sucralfate have been investigated, but there is not enough evidence to recommend them.[23]

In conclusion, therapeutic biliary interventions, cholecystectomy and ERCP were shown to be associated with bile reflux gastropathy at a rate of 61.76% and 71.43%, respectively. DM, obesity, high gastric bilirubin level, and increased gastric pH were risk factors for bile reflux gastropathy in both groups of patients, but no correlation was observed with age, sex, epigastric pain, heartburn or vomiting.

ΠΕΡΙΛΗΨΗ

Σχέση μεταξύ γαστροπάθειας από παλινδρόμηση της χολής και θεραπευτικών διαδικασιών των χοληφόρων

A. OTHMAN,[1] A. DWEDAR,[2] H. EL SADEK,[2] H. ABD EL AZIZ,[3] A. ABDELRAHMAN[4]

[1]Department of Internal Medicine, Faculty of Medicine, Suez University, Suez, [2]Department of Internal Medicine, Faculty of Medicine, Zagazig University, Zagazig, [3]Department of Pathology, Faculty of Medicine, Zagazig University, Zagazig, [4]Department of Clinical Pathology, Faculty of Medicine, Zagazig University, Zagazig, Αίγυπτος

Αρχεία Ελληνικής Ιατρικής 2022, 39(6):819–826

ΣΚΟΠΟΣ Προσδιορισμός σχετικά με το κατά πόσο οι θεραπευτικές διαδικασίες των χοληφόρων προκαλούν γαστροπάθεια από παλινδρόμηση της χολής, εκτίμηση του επιπολασμού και των παραγόντων κινδύνου, καθώς και αξιολόγηση των ενδοσκοπικών και των ιστολογικών αλλαγών στον γαστρικό βλεννογόνο. **ΥΛΙΚΟ-ΜΕΘΟΔΟΣ** Εξήντα

δύο ασθενείς με επιγαστρικό άλγος ή και δυσπεπτικά συμπτώματα ομαδοποιήθηκαν σε δύο ομάδες: στην ομάδα 1 (ομάδα μετά χολοκυστεκτομή) αποτελούμενη από 34 ασθενείς και στην ομάδα 2 (ομάδα παρέμβασης) αποτελούμενη από 28 ασθενείς που είχαν υποβληθεί σε ενδοσκοπική παλίνδρομη χολαγγειοπαγκρεατογραφία (ERCP). **ΑΠΟΤΕΛΕΣΜΑΤΑ** Ο επιπολασμός της γαστροπάθειας από παλινδρόμηση της χολής ήταν 21,34% μετά από θεραπευτικές παρεμβάσεις στα χοληφόρα (p=0,00). Ο διαβήτης, η παχυσαρκία, η υψηλή γαστρική χολερυθρίνη και το αυξημένο γαστρικό pH ήταν όλοι παράγοντες κινδύνου για γαστροπάθεια από παλινδρόμηση της χολής και στις δύο ομάδες (r=0,27, 0,31, 0,68 και 0,59, αντίστοιχα). Δεν υπήρξαν συσχετίσεις μεταξύ ηλικίας, φύλου, επιγαστρικού πόνου, καύσου, εμέτου και γαστροπάθειας από παλινδρόμηση της χολής. **ΣΥΜΠΕΡΑΣΜΑΤΑ** Η γαστροπάθεια από παλινδρόμηση της χολής είναι συχνή μετά από θεραπευτικές παρεμβάσεις στα χοληφόρα και είναι συχνότερη στους παχύσαρκους και στους διαβητικούς ασθενείς.

Λέξεις ευρετηρίου: Γαστροπάθεια, ERCP, Παλινδρόμηση χολής, Χολερυθρίνη, Χολοκυστεκτομή

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Corresponding author:

A.A. Othman, Department of Internal Medicine, Faculty of Medicine, Suez University, Suez 435 11, Egypt
e-mail: Amira.Othman@med.suezuni.edu.ege