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Does endoscopic retrograde cholangiopancreatography procedures for benign pathology treatment cause biliary reflux?

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Abstract

Bile reflux is caused by the backward flow of duodenal fluid into the stomach. A retrospective cohort study was performed to estimate the prevalence and risk factors of bile reflux gastritis post-ERCP, and its endoscopic and histopathologic consequences on gastric mucosa. The study enclosed 58 patients with refractory epigastric pain and dyspeptic symptoms. They were split into two categories.; the control group (CG): 30 subjects who had never undergone any biliary interventions, and the post-ERCP group (PEG): 28 subjects who have had at least one of the following procedures for benign pathology treatment: endoscopic sphincterotomy (ES) or endoscopic stenting. In CG, the ages ranged from 25 to 68 years with a mean age ± SD of 42.1±12.42. In PEG: the ages ranged from 27 to 59 years with mean age ± SD of 39.25 ± 7.47. All participants had undergone clinical and laboratory assessment and gastroscopy for gastric aspirate analysis as well as gastric mucosa biopsy for histopathological examination. The study showed that the prevalence of bile reflux gastritis was found to be (16.7 %) in CG and (71.43 %) in PEG with a P value of 0.000. In both groups, diabetes, obesity, increased gastric bilirubin, and increased gastric pH were risk factors for bile reflux gastritis (r= 0.28, 0.42, 0.84, 0.66 respectively). However, there were no correlations between age, sex, epigastric pain, heartburn, vomiting, and the occurrence of bile reflux gastritis. In Conclusion, bile reflux gastritis is common post-ERCP being more among obese and diabetic patients.

Keywords: bile reflux, bilirubin, ERCP, endoscopy

1. Introduction

Biliary reflux, bile reflux, biliary gastropathy, duodenogastric reflux (DGR), or duodenogastroesophageal reflux (DGER) is a pathological condition in the form of the backward flow of duodenal fluid that consists of bile, pancreatic juices, and secretions of the intestinal mucosa into the stomach and esophagus (1). Stomach pH is increased when bile pours in it and its bile acids cause mucosal lesions (2). Bile acids, in combination with gastric acid, have been shown to cause bile reflux gastritis symptoms (heartburn, regurgitation, epigastric pain, etc.) (3).

Bile reflux gastritis frequently occurs after gastric surgeries that that damages the pyloric sphincter (2), and after biliary surgeries and procedures as cholecystectomy, endoscopic sphincterotomy (EST), endoscopic stenting, or choledochoduodenostomy that cause the sphincter of Oddi malfunction (secondary bile reflux gastritis) (4). Sometimes it can occur spontaneously without former surgeries. Bile gastritis is a normal physiological event in a prolonged fasting period (primary bile reflux gastritis) (5). In non-responsive individuals to PPI medication, the total prevalence of biliary reflux was 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 interventional technique that combines an upper gastrointestinal endoscope (a thin, lighted flexible tube) and x-ray fluoroscopy, allowing other equipment to enter through the main duodenal papilla into the biliary and pancreatic ducts, to examine and treat diseases of the bile and pancreatic ducts (7). It represents one of the most demanding and technically challenging procedures in gastrointestinal endoscopy, which must be performed effectively and safely by operators with substantial training and experience to maximize success and safety (8).

2. Subjects and methods

1.1. Subjects:

The study started with 288 patients who were admitted to the

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university hospitals with inclusion criteria of refractory epigastric pain and dyspeptic symptoms. Informed consent was obtained, and the Zagazig university hospital ethics committee approved this study protocol (Approval Date: 1.1.2018 and Approval Number 4238). A total of 96 patients were eliminated because of the study exclusion criteria or because they refused to participate in the study. Exclusion criteria included unstable cardiopulmonary, neurologic, or cardiovascular status, other causes of biliary diseases (CBD strictures, and hepatolithiasis), structural abnormalities of the esophagus, stomach, or small intestine, patients who underwent bariatric surgery out of the scope of the study, patients who underwent cholecystectomy, patients on long-term non-steroidal analgesics, patients on oral contraceptive drugs and antigen stool positive patient for H. Pylori. Gastroscopy was performed on 192 patients who met the study inclusion criteria and accepted to participate in the study. Another 134 patients were eliminated because of the presence of findings other than bile gastritis such as hiatus hernia, biliary dyskinesia, and psychosomatic patients. Hence, the study was performed on 58 patients who were split into two groups; the control group (CG) which included 30 patients who had never undergone any biliary interventions, and the post-ERCP group (PEG) which included 28 patients who had undergone at least one of the following procedures for the treatment of benign pathology: endoscopic sphincterotomy (ES) or endoscopic stenting. In CG, the ages ranged from 25 to 68 years with a mean age ± SD of 41.1±12.42. They were 17 Female (56.6%) and 13 Male (43.3%). In PEG: the ages ranged from 27 to 59 years with mean age ± SD of 39.25 ± 7.47. They were 15 Female (53.6%) and 13 Male (46.4%). Such cross-sectional analytical study was conducted at Internal Medicine Department, of the university hospitals.

1.2. Diagnostic techniques of bile reflux gastritis:

Gastroscopy:

Esophageal mucosa alterations as erythema, presence of bile into the esophagus, edema, GERD (Gastroesophageal reflux disease), incompetent cardia, and petechiae were recorded using the gastroscope (Olympus single-channel CLK-4).

Histopathology:

Gastric mucosa alterations as erythema, bile existence in the stomach, gastric folds thickening, erosions, and petechiae were also recorded. Multiple biopsies were taken from gastric mucosa via disposable flexible endoscopic biopsy forceps, 2 cup-shaped jaws with a central spike (Boston Scientific®) for histopathological study.

1.3. Gastric aspirate analysis:

Via 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, to be sent for analysis. Quantitative determination of gastric aspirate total bilirubin level was performed (Gen.3® kit and Cobas 8000 analyzer). The pH monitoring of gastric aspirate was performed during the gastroscopy just after collection with a glass electrode pH meter (Adwa®).

1.4. Statistical Analysis:

The obtained data were statistically analyzed using SPSS program version 22 (IBM Corp., Armonk, NY, USA). Data were expressed as means ± standard deviation ($\bar{X}$ ± SD) in quantitative variables, and numbers and percentages for qualitative variables. Independent-Sample (T) test was used to compare quantitative variables means of two groups. Chi-Square test (X2) was used to compare qualitative variable means. The results were considered statistically significant if the P-value was <0.05. Correlation between variables was done using the Person correlation coefficient (r).

3. Results

The demographic data of the patients with bile reflux gastritis in CG ranged from 30 to 52 years with mean age ± SD of 38.83±7.55 years. Bile reflux gastritis was noted in 2 males (33.3%) and 4 females (66.7%). The demographic data of the patients with bile reflux gastritis in PEG ranged from 27 to 59 years with mean age ± SD of 39.25 ± 7.47. Bile reflux gastritis was noted in 9 males (45%) and 11 females (55%).

In CG, the endoscopic findings of esophageal mucosa included GERD in 16 cases (53.3%), incompetent cardia in 6 cases (20%), and mucosal changes in 5 cases (16.7%). While, the endoscopic findings of gastric mucosa included erythema in 15 cases (50%), presence of bile in 5 cases (16.7%), thick gastric fold in 5 cases (16.7%), erosions in 7 cases (23.3%), edema in 2 cases (6.7%), and petechiae in 4 cases (13.3%) (Table 1). In PEG, the endoscopic findings of esophageal mucosa in PEG included GERD in 21 cases (42.9%), mucosal changes in 11 cases (39.3%), and incompetent cardia in 7 cases (25%). While, the endoscopic findings of gastric mucosa included erythema in 18 cases (64.3%), presence of bile in 16 cases (57.1%), thick gastric fold in 13 cases (46.4%), petechiae in 8 cases (28.6%) erosions in 6 cases (21.4%), and edema in 5 cases (17.9%) (Table 1, Fig. 1a-c).

In our study, Bilirubin level in gastric aspirate in CG was within normal serum range in 24 patients (< 1.3 mg/dl). It ranged from 1.88 to 11.50 mg/dl (mean 7.53±3.63 mg/dl) in the remaining 6 patients. Gastric aspirate pH in the 30 cases of such group ranged from 4 to 8 (mean 6.32±1.29). Meanwhile, bilirubin level in gastric aspirate in PEG was within normal serum range in 9 patients (< 1.3 mg/dl). It ranged from 6.7 to 19.15 mg/dl (mean 10.59±3.97 mg/dl) in the remaining 19 patients. Gastric aspirate pH ranged from 5.50 to 8 (mean 7.72±0.23).

Table 1. Endoscopic findings of our study

Parameter		Control Group (CG)		Post-ERCP Group (PEG)		X^2	P
		n= 30		n= 28			
		No. of case	%	No. of case	%		
Esophageal	GERD	16	53.3	12	42.9	0.64	0.43
	incompetent cardia	6	20	8	28.6	0.58	0.45
	Mucosal changes	5	16.7	7	25	0.61	0.43
Gastric	Erythema of gastric mucosa	15	50	18	64.3	1.21	0.27
	Presence of bile	5	16.7	16	57.1	10.27	0.001
	Thick gastric fold	5	16.7	13	46.4	5.99	0.01
	Erosions	7	23.3	8	28.6	0.21	0.65
	Edema	2	6.7	6	21.4	2.65	0.11
	Petechiae	4	13.3	5	17.9	0.23	0.63

GERD; *Gastroesophageal reflux disease*

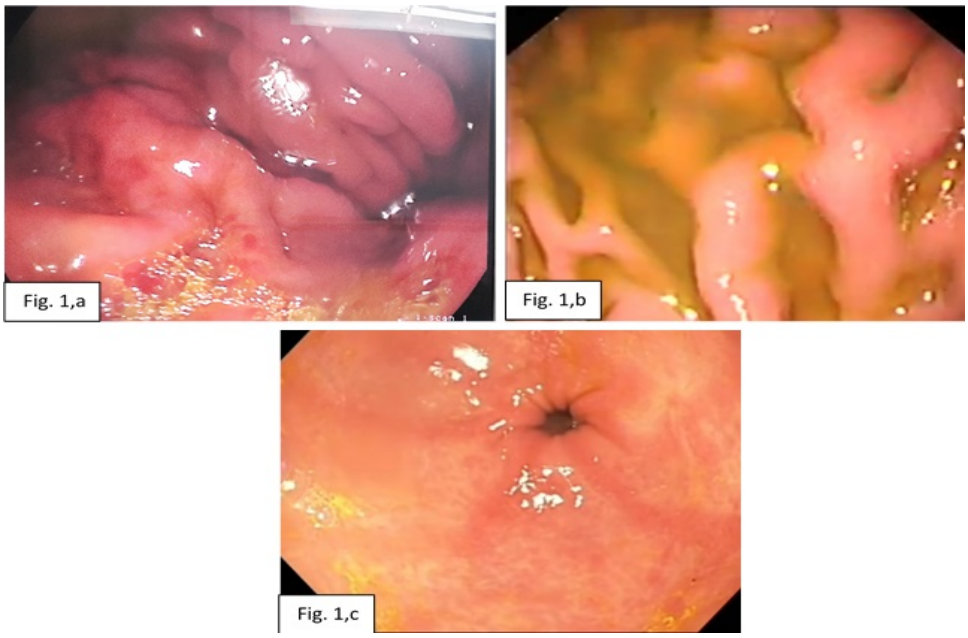

Fig. 1. Upper GIT endoscopic picture showing (a): gastric petechiae and presence of bile in the stomach, (b): thinking of gastric folds and presence of bile in the stomach, (c): antral gastritis with mucosal erythema and erosions with the presence of bile in the stomach

The histopathological finding of gastric mucosa biopsies in CG included chronic inflammation in 5 cases (16.7%), foveolar hyperplasia in 3 cases (10%), chronic Atrophic gastritis in 3 cases (10%), bile stasis in 6 cases (20%), interstitial inflammation in 7 cases (23.3%), edema in 2 cases (6.7%), intestinal metaplasia in 1 case (3.3%), and acute inflammation in 0 cases (0%) (Table 2). The histopathological finding of gastric mucosa biopsies in PEG included chronic inflammation in 18 cases (64.3%), foveolar hyperplasia in 13 cases (46.4%), bile stasis in 9 cases (32.1%), intestinal metaplasia in 8 cases (28.6%), chronic atrophic gastritis in 6 cases (21.4%), interstitial inflammation in 6 cases (21.4%), edema in 6 cases (21.4%), and acute inflammation in 2 cases (7.1%) (Table 2, Fig. 2 a-d).

As regards the presence of bile reflux gastritis, it was present in (6) cases in CG patients with a percentage of 20%. However, it was present in (20) cases in PEG patients with a percentage of 71.43 % (Table 3).

The risk factors for bile reflux gastritis in CG included increased gastric bilirubin (6 cases with a percentage of 100%), and alkaline gastric pH (6 cases with a percentage of 100%), diabetes (4 cases with a percentage of 66.6%), and obesity (5 cases with a percentage of 83.3%). However, the risk factors in PEG included increased gastric bilirubin (19 cases with a percentage of 95%), and alkaline gastric pH (19 cases with a percentage of 95%), diabetes (9 cases with a percentage of 45%), and obesity (8 cases with a percentage of 40%).

Table 2. Gastric mucosa histopathological findings of our study

Parameter	Control Group (CG) n= 30		Post-ERCP Group (PEG) n= 28		X^2	P
	No. of case	%	No. of case	%		
Chronic inflammation	5	16.7	18	64.3	13.72	0.00
Foveolar hyperplasia	3	10	13	46.4	9.62	0.002
Chronic Atrophic gastritis	3	10	9	32.1	4.33	0.15
Bile stasis	6	20	8	28.6	0.58	0.45
Interstitial inflammation	7	23.3	6	21.4	0.03	0.86
Edema	2	6.7	6	21.4	2.65	0.10
Intestinal metaplasia	1	3.3	6	21.6	4.47	0.04
Acute inflammation	0	0	2	7.1	2.22	0.14

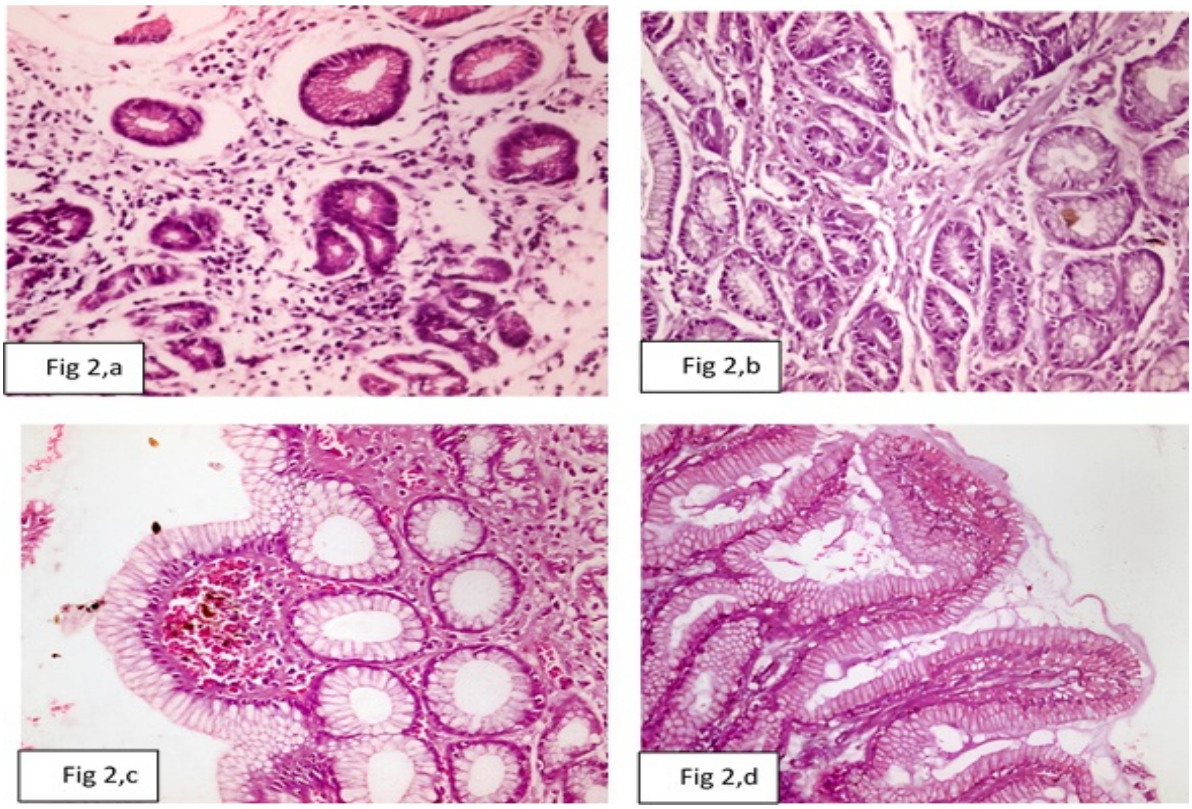

Fig. 2. Photomicrograph of (a): chronic atrophic gastritis with per glandular fibrosis, chronic inflammatory infiltrate, and mild dysplasia (H&E X400), (b): chronic gastritis with per glandular fibrosis and mild chronic inflammatory infiltrate (H&E X400), (c): chronic gastritis with focal bile stasis (H&E X400), (d): chronic gastritis with diffuse intestinal metaplasia and interstitial inflammation (H&E X40)

Table 3. Percentage of bile reflux gastritis and non- bile reflux gastritis post-ERCP

Parameter	Control Group (CG)		Post-ERCP Group (PEG)		X2	P
	N=30	%	N=28	%		
bile reflux gastritis	6	20	20	71.4	15.49	0.000
Non- bile reflux gastritis	24	80	8	28.6		

The study revealed statistically significant positive correlations between increased gastric bilirubin, increased gastric aspirate pH, diabetes, obesity, and the presence of bile reflux gastritis in both studied groups. There were no correlations between age, sex, epigastric pain, heartburn, vomiting, and the presence of bile reflux gastritis in both groups of our study (Table 4).

Table 4. Correlation between risk factors and presence of bile reflux gastritis in studied groups

	Bile Reflux Gastritis	
BMI	r	P
Gastric pH	0.42**	0.001
Gastric Bilirubin	0.66**	0.00
RBS	0.84**	0.00
Epigastric pain	0.28*	0.03
Heart burn	1.01	0.45
Vomiting	0.005	0.97

BMI: Body mass index, **RBS:** Random blood sugar**, GERD:** Gastroesophageal reflux disease. **Correlation is significant at the 0.01 level (2-tailed), * Correlation is significant at the 0.05 level (2-tailed)

4. Discussion

Bile reflux gastritis is a disease characterized by upper abdominal pain, frequent heartburn, nausea, and vomiting of bile. Such disease appears to be caused by the backward flow of duodenal fluid into the stomach and esophagus. This fluid contains bile, pancreatic juices, and duodenal secretion (1). The diagnosis was based on clinical findings (9), pH monitoring of the aspirated gastric juice on the assumption that the bile reflux would cause an increase of pH over 7 as a result of the alkaline nature of duodenal juice (9), with the aid of endoscopic and pathologic findings (10).

In this study, the esophageal endoscopic findings were GERD, incompetent cardia, and mucosal changes. The most frequent esophageal endoscopic finding was GERD (42.9%). However, the gastric mucosa endoscopic findings were erythema, presence of bile, thick gastric fold, erosions, edema, and petechiae (Figure 1a-c). The most frequent gastric endoscopic finding was erythema of gastric mucosa with a percentage of (64.3%) (Table 1). Such findings were similar to that of former studies. Martamala and Rani (11) diagnosed bile reflux gastritis endoscopically, based on the presence of bile in the gaster, with adherence of bile on the gastric mucous membrane in the form of crusts and changes in the mucous membrane that becomes hyperemic, frail, and erosive (12). In a Romanian endoscopic study of bile reflux gastritis, the endoscopic gastric mucosa changes were erythema, bile existence in the stomach, over thickening of gastric folds, erosions, atrophic mucosa, petechiae, intestinal metaplasia, and polyp (2). Al-Bayati and Alnajjar conducted that the endoscopic findings were erythema, gastric erosion, thickening of gastric folds, and gastric atrophy. The most common gastric endoscopic finding was erythema of the gastric mucosa (50%). All the patients had bile in the stomach (12).

Shenouda et al. found that mean normal bilirubin levels in gastric aspirate was 1.3 mg/dl (13). The normal pH of gastric juice was 1.5 to 3.5 in the human stomach lumen (14). In our study, the alkaline gastric aspirate (7.72±0.23) with a high level of gastric bilirubin level (10.59±3.97) was supposed to be the cause of esophageal and gastric mucosal damage although the exact mechanisms were still unclear (15). Some studies indicated that interaction of bile acid, a component of bile; with M3 muscarinic receptor subtype expressed in 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 studies reported that bile acids and other contents of the duodenum would act synergistically in the development of chronic gastritis with gastric acid and Helicobacter pylori infection (15).

The most frequent histopathological finding in our study was chronic inflammation with a percentage of (64.3%). However, the least frequent histopathological finding was acute inflammation with a percentage of (7.1%) (Table 2). Our results agreed with a previous study that proved that the histopathological changes of tissues samples were chronic gastritis, foveolar hyperplasia, intestinal metaplasia, dysplasia, acute gastritis, chronic atrophic gastritis, polyps, benign ulcers, and edema. The most frequent histopathological finding was chronic inflammation (84.06%) (2). The histopathologic changes due to bile reflux gastritis in children were characterized by chronic inflammation with foveolar hyperplasia in both the gastric corpora and antrum, vascular congestion, edema of lamina propria, and smooth muscle hyperplasia (18).

In our study, bile reflux gastritis was present in (20) cases out of the 28 cases post-ERCP. The prevalence of bile reflux gastritis was (71.43 %) post-ERCP. Previous studies have shown that the prevalence of bile reflux after therapeutic biliary procedures was 60% (19).

Our study showed that there were statistically significant positive correlations between obesity, increased gastric aspirate pH, increased gastric bilirubin, RBS, and bile reflux gastritis occurrence in the studied groups. Such findings went with that of the former studies. Obesity was a risk factor for bile reflux gastritis (20). Deenadayalu et al (21). demonstrated a significantly higher rate of post-ERCP complications in obese patients (BMI≥30 kg/m2) in comparison to overweight (BMI 25-30 kg/m2), normal-weight (BMI 18.5-25 kg/m2), and underweight (BMI<18.5 kg/m2) patients (22). Shenouda et al (13). declared that increased gastric aspirate bilirubin level and pH are confirmatory tools to diagnose biliary gastritis with a significant relationship between the level of gastric bilirubin and the degree of inflammation (14). The gastric bilirubin level above 20 mg/dL could indicate severe esophagitis, erosive gastritis, or gastroesophageal metaplastic changes. In fact, more severe biliary gastritis was associated with higher bilirubin levels in the gastric aspirates (22).

Diabetes mellitus was considered a risk factor for bile gastritis (2). Barakat et al (5). reported that diabetes mellitus might be considered a risk factor for primary biliary gastritis (5). Prevalence of type II diabetes mellitus was associated with gastroduodenal dysmotility (23). Diabetes gastroparesis

was a condition where persistent hyperglycemia, in either type 1 or type 2 diabetes, could cause Vagus nerve damage, which was responsible for proper gastric movement resulting in delayed gastric emptying without mechanical obstruction (24). Severe bile reflux gastritis was a consequence of diabetes gastroparesis (25,26).

Our study showed that there were no correlations between age, sex, epigastric pain, heartburn, vomiting, and the presence of bile reflux gastritis. A few previous research had looked into the relationship between age and biliary gastritis. Byrne et al. stated that there was no evidence of a connection between age and bile reflux gastritis (27). Bollschweiler et al.also could not prove any significant difference between the patient's age and occurrence of bile reflux gastritis (28).

In our study, histopathological examination of gastric mucosa revealed chronic atrophic gastritis showing per glandular fibrosis, chronic inflammatory infiltrate, and mild dysplasia (Figure 2a), chronic gastritis showing per glandular fibrosis and mild chronic inflammatory infiltrate (Figure 2b), chronic gastritis showing focal bile stasis (figure 2c), and chronic gastritis showing diffuse intestinal metaplasia and interstitial inflammation (figure 2d). The former studies reported histopathological alterations because of bile gastritis similar to our findings in form of chronic gastric mucosa inflammation, lamina propria edema, foveolar hyperplasia, antral atrophy, and intestinal metaplasia (29). Vere et al. observed chronic gastritis, foveolar hyperplasia, intestinal metaplasia, gastric dysplasia, acute inflammation, chronic atrophic gastritis, polyps, benign ulcers, and edema (2). The histologic alterations owing to bile reflux gastritis in 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. The limitations of our study are that the patients total number was low because of the restrict exclusion criteria.

The prevalence of bile reflux gastritis was (20%) in CG, while it was (71.43 %) in PEG. Diabetes, obesity, increased gastric bilirubin, and increased gastric pH were risk factors for bile reflux gastritis in both groups. However, there were no correlations between age, sex, epigastric pain, heartburn, vomiting, and the presence of bile reflux gastritis in both groups.

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