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Original Article

Bile Reflux Gastropathy and Functional Dyspepsia

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Background/Aims
The pathoetiology of functional dyspepsia remains unclear; one mechanism could be chemical gastropathy from chronic bile reflux. We aim to examine the association of bile reflux gastropathy with functional dyspepsia and identify predisposing factors.

Methods
In a retrospective study, patients with functional dyspepsia (Rome III) who completed symptom assessment, esophagogastroduodenoscopy, and biopsies were categorized into 3 groups; bile gastropathy (BG), non-bile gastropathy (NBG), and no gastropathy (NG). Demographics, symptoms, endoscopy, and motility data were compared between groups. Multivariate analysis identified clinical factors associated with BG.

Results
Of 262 patients (77.5% female), 90 had BG, 121 had NBG, and 51 had NG. Baseline demographics were similar, however, patients with BG reported significantly more severe abdominal pain than NBG or NG groups ($P = 0.018$). Gastric erythema was significantly more common in BG vs NBG groups ($P < 0.001$). Cholecystectomy was significantly associated (OR, 6.6; $P = 0.003$) with the presence of gastropathy in BG compared to NBG or NG group. Patients with cholecystectomy had significantly more severe abdominal pain ($P < 0.05$), gastric erythema ($P < 0.03$), and gastritis ($P < 0.05$), and were more likely to be prescribed narcotic medications ($P < 0.004$) than patients without cholecystectomy.

Conclusions
Bile reflux gastropathy is associated with functional dyspepsia and causes more severe symptoms. Cholecystectomy predisposes to BG and abnormal pain, and could contribute to the pathogenesis of functional dyspepsia.
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Key Words
Bile reflux; Cholecystectomy; Dyspepsia; Gastritis

Introduction

Dyspepsia, defined as discomfort or pain arising from the central, upper, or gastroduodenal region is a common condition affecting 25.0% of the United States population.[1] In the absence of known organic etiologies such as peptic ulcer disease or *Helicobacter pylori* infection, many patients with such symptoms are labeled as suffering with functional dyspepsia. Functional dyspepsia is a heterogeneous disorder with a number of proposed pathophysi-

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ological mechanisms including impaired gastric accommodation, altered gastric emptying, gastric hypersensitivity to balloon distension, dysregulated acid production, and more recently duodenal eosinophilia.[2,3]

Gastric luminal irritants include the reflux of duodenal contents into the stomach such as bile salts, alkaline pancreatic, and duodenal secretions, lysolecithin, or ingestion of non-steroidal anti-inflammatory drugs (NSAIDs). All of these agents can cause chemical injury to the mucosa leading to a reactive or chemical gastropathy.[4] Such a gastropathy has long been recognized as a post-gastric surgery problem, and has been reported following Billroth II gastrectomy.[5] However, whether bile reflux causes dyspeptic symptoms in a normal, non-operated stomach is unclear, and there are conflicting reports in the literature.[6,7] Furthermore, the exact cause(s) of duodenogastric reflux and its association with symptoms is incompletely understood.[6,8,9]

Cholecystectomy may serve as a risk factor for bile reflux into the stomach.[6] Following gallbladder removal, there may be unregulated and increased delivery of bile into the duodenum. This excessive amount of bile could impair duodenal motility,[10-12] leading to bile retention and proximal spillage from duodenogastric reflux.

The aim of our study is to evaluate whether bile reflux into the stomach could contribute to the development of functional dyspepsia symptoms, by assessing the demographic, clinical, endoscopic, and gastrointestinal motility characteristics in a cohort of patients with bile gastropathy (BG) and comparing this with patients categorized as non-bile gastropathy (NBG) or no gastropathy (NG).

Materials and Methods

Study Inclusion Criteria

A retrospective cohort analysis was performed of all patients referred to a gastrointestinal clinic in a tertiary care center between January 2012 and September 2015 with dyspeptic symptoms, and those who fulfilled the Rome III criteria for functional dyspepsia.[13] Patients were included in the study if they underwent esophagogastroduodenoscopy (EGD) and gastric biopsies as part of their diagnostic evaluation. Patients were excluded if they had a history of stomach (antrectomy or pyloroplasty) or proximal small bowel resection (ie, Whipple, Billroth I or II), including gastric bypass surgery (ie, sleeve gastrectomy). Patients were further excluded if they had a history of untreated *H. pylori* infection, history of alcohol abuse, were pregnant, or had severe comorbid illnesses such as chronic renal failure, chronic obstructive pulmonary disease and chronic heart failure, or previous strokes as assessed by history, laboratory testing, and/or appropriate consultations. All endoscopies were performed by a single experienced endoscopist (S.S.C.R.) to exclude any inter-rater variability in interpretation, sampling, or documentation. Biopsy specimens were collected from the gastric antrum and body and sent for pathology review with hematoxylin and eosin staining. The histopathologists convened a meeting and agreed on descriptors and criteria for chemical gastropathy in January 2012,[14] in order to minimize any inter-observer disagreement, and *H. pylori* testing was performed according to the Sydney System.[14] The study was approved by our Institutional Review Board (IRB No. 744920-4).

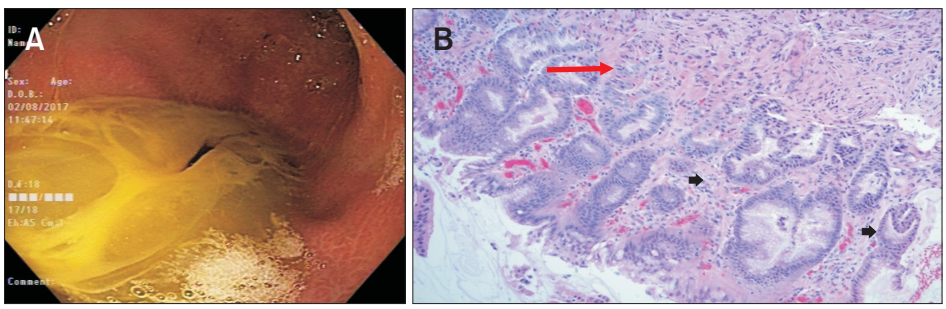

Figure 1. (A) Characteristic endoscopic appearance of bile gastropathy with a large pool of thick yellowish-green bile noted in the antrum, and an underlying erythematous, inflamed gastric mucosa, indicative of bile gastritis/gastropathy after aspiration of bile. (B) Biopsy of gastric mucosa showing cork-screwing of foveolar glands (red arrow) and splaying of smooth muscle into the lamina propria (black arrows), typical of bile-induced chemical gastropathy. No significant inflammation is seen in the lamina propria.

Patient Cohorts

All patients underwent upper endoscopy (EGD) with careful inspection of the gastric lumen for any endoscopic evidence of gastropathy including erythema, edema, erosions, or ulcerations. Specifically, we documented the presence of duodenogastric bile reflux, defined as mucosal erythema with or without gastritis or erosions along with the presence of intragastric bile (Fig. 1A) during endoscopy.[15] EGD findings together with histopathology were used to categorize patients into 1 of 3 cohorts: (1) BG cohort characterized by the presence of sufficient amount of intragastric bile together with histopathologically identified chemical gastropathy (Fig. 1B), (2) NBG cohort characterized by the presence of chemical gastropathy but without intragastric bile, or (3) NG cohort characterized by normal gastric mucosa and histology and without visible bile in the stomach. Endoscopic findings were correlated with pathology reports of biopsy specimens.

Gastrointestinal Symptom Evaluation

Patients' symptoms were assessed using validated bowel symptom questionnaires obtained as part of their routine clinical evaluation.[16] Briefly, participants were asked to rate the frequency, intensity, and duration of 9 common gastrointestinal complaints such as abdominal pain, nausea, and fullness on a 0-3 Likert-type scale. Component scores were summated to obtain a total score with maximum possible range of 0-9. Total scores < 3 points were considered mild, scores 3-6 were considered moderate, and scores ≥ 7 were considered severe.

Gastrointestinal Motility Testing

Patients underwent motility testing as indicated by their symptoms, and this included a standard 4-hour gastric emptying scintigraphy study or a wireless motility capsule test (SmartPill; Medtronics, Minneapolis, MN, USA). An abnormal study was defined using standard American Neurogastroenterology and Motility Society consensus criteria.[17,18] Duodenal aspirates were obtained to assess for small intestinal bacterial overgrowth (SIBO) or small intestinal fungal overgrowth (SIFO) as previously described.[19] SIBO was diagnosed using either glucose breath testing and/or quantitative duodenal aspirate cultures ($\geq 10^3$ CFU/mL), with patients adjudged as positive for SIBO if either test was positive.[19,20] SIFO was diagnosed with positive duodenal aspirate for fungal cultures ($\geq 10^3$ fungal CFU/mL).[19,20] Additional medical and surgical history were obtained from the electronic medical record.

Statistical Methods

Curated clinical data were compared between BG, NBG, and NG cohorts to identify variables associated with bile reflux gastropathy. All data were stored in a password-protected Microsoft Office database (Redwood, CA, USA). Categorical data were compared using chi-square test. Continuous data were compared using one-way analysis of variance or Kruskal–Wallis test, as appropriate. Variables significant ($P < 0.05$) on univariate testing were evaluated using multiple logistic regression. Two binary models were created with BG coded as dichotomous dependent variable: BG (coded = 1) vs NBG + NG (both coded = 0), and a second model restricted to BG (coded = 1) vs NBG (coded = 0). The Hosmer-Lemeshow statistic was used to assess model goodness-of-fit. All data were analyzed using SigmaPlot version 10.2 (Systat Software, San Jose, CA, USA). A P-value < 0.05 was considered statistically significant.

Results

Patient Characteristics

A total of 262 patients with functional dyspepsia were included in the study (Fig. 2). Patients were predominantly female (77.5%), middle aged (mean age, 48.9 years), and overweight (mean body mass index, 27.0 kg/m^2). Severe (≥ 7) gastrointestinal symptoms most frequently reported were bloating (64.4%), fullness (56.0%), and abdominal pain (51.0%). Most patients were on proton pump inhibitors (57.0%) or histamine H2 receptor antagonists (6.5%)

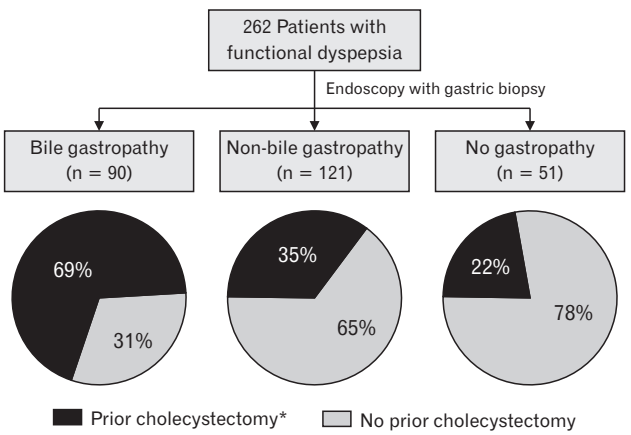

Figure 2. Consort flow diagram of subjects with functional dyspepsia including the proportion of patients with a history of cholecystectomy (*$P < 0.05$).

Table 1. Patient Demographic Features for the Study Cohorts

Demographics	Bile gastropathy (n = 90)	Non-bile gastropathy (n = 121)	No gastropathy (n = 51)	*P*-value
Age (yr)	49.3 ± 16	49.7 ± 16.0	51.0 ± 16.0	0.823
Female	85.6%	71.9%	76.5%	0.062
Body mass index (kg/m^2)	28.2 ± 9.0	26.6 ± 8.0	25.8 ± 5.0	0.145
Diabetes mellitus	16.7%	14.1%	15.7%	0.869
Hemoglobin A1C (%)	8.0 ± 2.0	7.6 ± 1.6	8.2 ± 1.9	0.804
Histamine H2 receptor antagonists use	5.6%	6.6%	7.8%	0.867
Proton pump inhibitors use	58.9%	54.5%	56.9%	0.819
Any anti-acid medication use	64.4%	61.2%	64.7%	0.852
Aspirin use	14.4%	12.4%	13.7%	0.907
NSAID use	13.8%	19.1%	11.1%	0.374
Chronic prescription narcotics	24.4%	20.7%	15.7%	0.468

NSAID, non-steroidal anti-inflammatory drug.
Values are presented as mean ± SD.

without group differences. Approximately 1 in 5 (21.0%) patients were prescribed narcotic pain medications.

Patients were stratified into 3 cohorts: BG group (n = 90), NBG group (n = 121), and NG group (n = 51) (Table 1 and Fig. 2). The demographic variables in the 3 cohorts were similar (Table 1). However, patients with BG reported significantly more severe (> 7) abdominal pain than patients with NBG or NG group ($P < 0.05$; Fig. 3). The severity of other bowel symptoms such as bloating, nausea, and fullness was not different between groups. Patients with BG had a significantly higher prevalence of cholecystectomy (68.0%) than patients with NBG (35.0%) or NG (22.0%) groups, respectively (Fig. 2).

Endoscopy Findings

Endoscopic findings for BG and NBG cohorts are summarized in Table 2. BG patients had significantly higher prevalence of gastric erythema than NBG patients (88.9% vs 63.6%; $P < 0.001$). NBG patients had significantly increased prevalence of superficial erosions (22.3% vs 8.9%) and gastric polyps (8.3% vs 0.0%; both $P < 0.05$). The location of gastropathy was not different between groups, occurring predominantly in the gastric antrum and less frequently in the body or fundus. A representative endoscopic image of BG is shown in Figure 1A, showing moderate to severe erythematous gastric mucosa with thick overlying yellowish staining from duodenogastric reflux of bile.

Gastric Pathology

Pathology results were correlated with endoscopic findings, showing as expected, benign mucosa (95.0%) in most patients in NG cohort. Gastropathy was associated with a marked increase in the prevalence of foveolar hyperplasia (BG: 82.2% and NBG: 83.5%) and reactive glandular changes (BG: 84.4% and NBG: 82.6%) (Fig. 1B and Table 2). However, within the gastropathy groups, there was a striking increase in the prevalence of gastritis (37.8% vs 7.4%), edema (30.0% vs 0.8%), and chronic active inflammation (7.8% vs 1.7%) in BG vs NBG groups, suggesting that bile reflux into the stomach is associated with more severe gastric mucosal alterations than NBG.

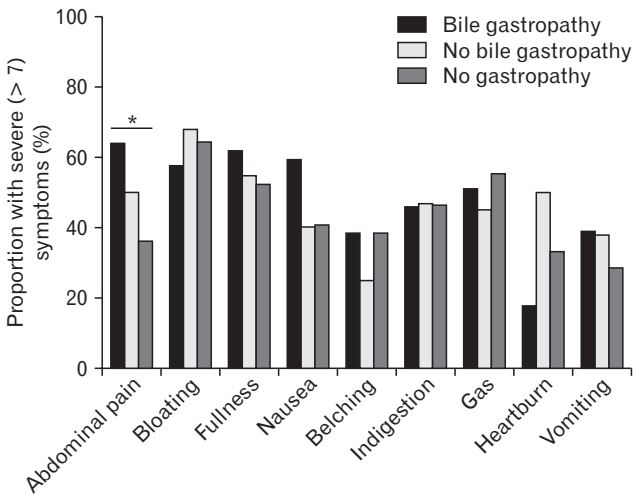

Figure 3. Proportion of patients with severe (score > 7) gastrointestinal symptoms in the 3 cohorts with functional dyspepsia (*$P < 0.05$).

Cholecystectomy and Functional Dyspepsia

To examine if cholecystectomy is a risk factor for BG and func-

Table 2. The Prevalence of Endoscopic and Histologic Features in Patients With Bile Gastropathy, Non-bile Gastropathy and No Gastropathy Cohorts

Endoscopy features	Bile gastropathy (n = 90)	Non-bile gastropathy (n = 121)	No gastropathy (n = 51)	*P*-value
Erythema	88.9%	63.6%	0.0%	< 0.001
Erosions	8.9%	22.3%	0.0%	0.016
Ulcers	1.1%	6.6%	0.0%	0.107
Polyps	0.0%	8.3%	0.0%	0.046
Atrophy	1.1%	1.7%	0.0%	0.796
Gastropathy involvement				0.148
Antrum	66.3%	65.0%	0.0%	
Body	32.6%	28.2%	0.0%	
Fundus	1.2%	6.8%	0.0%	
Pathology description	**Bile gastropathy (n = 90)**	**Non-bile gastropathy (n = 121)**	**No gastropathy (n = 51)**	
Normal mucosa	0.0%	0.0%	95.0%	
Foveolar hyperplasia	82.2%	83.5%	0.0%	
Reactive glandular changes	84.4%	82.6%	0.0%	
Gastritis (any)	37.8%	7.4%	0.0%	
Minimal gastritis	35.6%	3.3%	0.0%	
Mild gastritis	2.2%	3.3%	0.0%	
Moderate gastritis	0.0%	0.8%	0.0%	
Edema	30.0%	0.8%	5.0%	
Chronic inactive inflammation	5.6%	6.6%	0.0%	
Chronic active inflammation	7.8%	1.7%	0.0%	
Intestinal metaplasia	2.2%	1.7%	0.0%	

P-value < 0.05 was considered statistically significant (bile gastropathy vs non-bile gastropathy).

Table 3. Multivariate Logistic Regression Evaluating Bile Gastropathy (n = 90) Group vs Non-bile Gastropathy or No Gastropathy (n = 172) Group

Demographic variable	Model A			Model B		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age[a]	-	-	-	1.48	0.91-2.39	0.115
Female gender	-	-	-	8.74	0.81-93.7	0.073
BMI[b]	-	-	-	1.55	0.92-2.58	0.095
GERD	0.53	0.11-2.56	0.433	0.54	0.10-2.80	0.465
Appendectomy	1.79	0.39-8.26	0.451	1.69	0.32-8.66	0.531
Delayed colon transit	0.50	0.16-1.63	0.255	0.46	0.12-1.66	0.238
Cholecystectomy	6.60	1.87-23.30	0.003	6.44	1.51-27.44	0.012

[a]Age coded as increasing deciles.
[b]Body mass index (BMI) coded as < 20.0, 20.0-24.9, 25.0-29.9, 30.0-34.9, ≥ 35 kg/m^2.

tional dyspepsia, we performed multivariate regression modeling comparing BG group (n = 90) vs NBG + NG group (n = 172). This revealed that cholecystectomy (OR, 6.60; 95% CI, 1.87-23.30; $P = 0.003$; Model A) (Table 3) was significantly associated with BG. Other clinical factors such as GERD or appendectomy were not significantly associated with BG ($P > 0.05$). A second regression (Model B) was constructed where additional baseline demographic factors such as age, female gender, and body mass index were included as covariates in the model. This model again revealed that cholecystectomy (OR, 6.44; 95% CI, 1.51-27.44; $P = 0.012$)

was significantly associated with BG (Table 3).

Patients with cholecystectomy (n = 114) also reported significantly more severe (> 7) abdominal pain, fullness, and nausea than patients without prior cholecystectomy (n = 148) (Supplementary Figure). Erythema was significantly more common in patients with cholecystectomy than those without cholecystectomy (81.6% vs 67.6%; $P = 0.030$). Similarly, gastritis (30.0% vs 6.0%), edema (25.0% vs 0.0%), and chronic active inflammation (6.0% vs 1.0%) were more frequently reported in gastric biopsies of patients with cholecystectomy. Patients with cholecystectomy were also significantly more likely to be prescribed chronic prescription narcotics than those without cholecystectomy (30.0% vs 14.0%; $P = 0.003$). Stratifying the entire cohort into patients with (≥ 7) and without (< 7) severe abdominal pain, our analysis revealed that cholecystectomy ($P = 0.037$) as the only variable was also significantly associated with severe pain (Supplementary Table 1). Regression analysis also found that cholecystectomy was significantly associated with severe abdominal pain (OR, 2.05; 95% CI, 1.09-3.86; $P = 0.026$).

Motility Testing

Wireless motility capsule testing (n = 137) revealed that the prevalence of delayed colonic transit was significantly increased in NBG group vs other groups ($P = 0.045$; Supplementary Table 2). Other upper gastrointestinal tract conditions such as gastric emptying or small bowel transit disorders were not significantly different between groups. Similarly, duodenal aspirate and breath testing studies (n =241) revealed that the prevalence of SIBO and SIFO were not different between groups (Supplementary Table 2).

Discussion

Functional dyspepsia is a heterogeneous, polysymptomatic disorder of unclear etiology. Furthermore, there is no effective or Food and Drug Administration-approved therapy, and empirical trials have only helped a minority of patients.[21] Our objective was to ascertain whether duodenogastric reflux of bile plays a role in the pathogenesis of symptoms in patients with functional dyspepsia, and if so, to examine the influence of phenotypic, environmental and clinical factors.

In a well characterized population, we found that duodenogastric bile reflux significantly contributed to the pathogenesis of symptoms in over one third of patients with chronic functional dyspepsia. Moreover, we found that cholecystectomy was a significant predisposing risk factor for the development of bile reflux, and was associated with more severe gastrointestinal symptoms, and use of narcotic pain medications. These findings not only confirm but extend previous case reports and indicate that cholecystectomy significantly increases the risk of duodenogastric bile reflux and causes more severe symptoms of functional dyspepsia, necessitating a need for stronger analgesia in many patients.[11,22] However, whether opioid use predates cholecystectomy cannot be excluded from our observations.

We found that the prevalence of specific symptoms such as abdominal pain, fullness, and nausea not only increased following cholecystectomy but were also more severe in intensity. This observation is particularly alarming given the increasing number of cholecystectomies that are being performed,[23] and often for less defined indications, such as biliary dyskinesia, or unexplained right upper quadrant pain with or without low ejection fraction on a hepatobiliary iminodiacetic acid scan with an otherwise normal gallbladder.[23] As observed in this study, the dyspeptic symptoms were likely exacerbated rather than relieved by cholecystectomy.

Several factors such as pyloroplasty may increase the reflux of duodenal contents into the stomach and cause chemical gastropathy.[10] In a previous study, we showed that the duodenum serves as both a capacitative resistor and a resistive resistor,[12] both of which could impair duodenal motility leading to retention of duodenal contents, and possible bile reflux into the stomach. Furthermore, infusion of bile into the duodenum decreased duodenal motility in healthy subjects causing stasis of duodenal contents.[12]

Irrespective of the predisposing factors, prolonged and excessive bile reflux into the stomach can cause direct chemical injury to the mucosa resulting in mucin depletion and hydrogen ion influx into the enterocytes and decreased transepithelial resistance.[24] This likely begins a cascade of events leading to mast cell degranulation, edema, vascular congestion, and foveolar hyperplasia, alongside other characteristic histopathological changes.[6] The degree and duration of bile exposure that is needed to develop gastropathy is not fully understood, but once developed it manifests as gastric mucosal edema and hyperemia along with symptoms of functional dyspepsia. Endoscopically, this could appear as erythematous mucosa initially, progressing to moderately severe gastritis, and in more advanced cases superficial erosions may be seen.[24-26] Although, these features are likely bile-induced, most patients are treated with acid suppression.[27] We found that approximately 60.0% of our patients were on acid suppresant therapy, but mostly without relief.

The clinical presentation of our patients with BG was similar to that of other patients with functional dyspepsia and the NBG cohort. Hence, symptoms alone may not help to differentiate or identify this problem. An important step in the diagnosis of this

problem is awareness and recognition of the endoscopic features that may include the presence of bile (Fig. 1A), as well as the increased prevalence of erythematous mucosa and gastritis involving either the antrum or the body of the stomach without erosions or ulcerations, especially after aspirating the bile.[6] Confirmation of bile-induced chemical gastropathy with histopathological examination is important, not only to rule out other causes of gastritis, but also to identify conditions such as *H. pylori* infection, and physiologic bile reflux that may occur from retching during upper endoscopy.

The findings of erythematous mucosa on endoscopy together with chemical gastropathy on biopsy is not uncommon, and has been reported in 15.0% of routine screening endoscopy procedures.[28] In most cases, this gastropathy may be secondary to *H. pylori* infection or NSAID. NSAID-induced chemical gastropathy is however indistinguishable from BG histologically, and is clearly one limitation that may contribute to the under recognition of BG.[29] Another limitation is that most endoscopists may not recognize or document duodenogastric bile reflux. We used the presence of bile in the stomach as an endoscopic marker for duodenogastric reflux, as it can be easily identified during endoscopy. Usually, there is little or no bile in the stomach, given the prolonged fasting, and the nature of physiologic bile secretion that usually occurs, post-prandially, often after fatty meals.[24] However, prior studies have suggested that endoscopy has decreased accuracy and a lower positive predictive value when compared to other methods, such as hepatobiliary scintigraphy, further contributing to the missed diagnosis.[6,29-31]

The prevalence of motility disorders was similar to those seen in previous studies of functional dyspepsia, with approximately one third of patients showing delayed gastric emptying.[2,32] The lack of significant delay in gastric emptying, especially in the BG group suggests that a primary gastric emptying/motility problem is unlikely to be an important mechanism and that excess duodenogastric bile reflux is the key driver for this problem. Additionally, we found an increased incidence of delayed colonic transit in the NBG group with about 50.0% of patients showing an abnormal colonic delay suggesting slow transit constipation when compared to a prevalence of 25.0% in the other groups. This suggests an association of constipation with dyspeptic symptoms.[33]

The limitations of our study include the unequal distribution of subjects across the 3 groups, possibly due to the retrospective nature of our study. Although this is the largest controlled study to date that examined BG, our study was performed in a tertiary care center with possible referral bias and in patients with refractory dyspeptic symptoms. Hence, a community-based, prospective, multicenter study is needed to confirm the relationship between bile, chemical gastropathy, and cholecystectomy. Another limitation is the lack of information on the clinical outcome, as most of these patients were not followed-up at our tertiary care center. However, treatment of BG may be useful in the management of these patients, but requires rigorous controlled trials.[6]

In conclusion, duodenogastric bile reflux appears to be common in patients with symptoms of functional dyspepsia, especially in those with a previous history of cholecystectomy. Cholecystectomy appears to be a significant risk factor for the development of BG. The presence of bile gastritis during an upper endoscopy together with chemical gastropathy identified by histology is essential for a diagnosis. Given the rising incidence of cholecystectomy for unexplained abdominal pain,[23] especially in the absence of pathologic gallbladder disease, we recommend caution and awareness of the association of BG and functional dyspepsia.

Supplementary Materials

Note: To access the supplementary tables and figure mentioned in this article, visit the online version of *Journal of Neurogastroenterology and Motility* at http://www.jnmjournal.org/, and at https://doi.org/10.5056/jnm20102.

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Author contributions: Satish S C Rao: study concept and design, performing endoscopy, motility test interpretations, data acquisition, data analysis and interpretation, manuscript preparation, critical revision, preparation of important intellectual content, final approval, and guarantor of the article; Andrew Lake: chart review, data collection and analysis, and manuscript preparation; Sebastian Larion: data analysis, statistics, and manuscript preparation; Helena Spartz: pathology interpretation and manuscript preparation; and Sravan Kavuri: pathology slides, interpretation, and manuscript preparation. All authors have approved the final draft that was submitted.

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