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Cholecystectomy and Clinical Presentations of Gastroparesis

The NIDDK Gastroparesis Clinical Research Consortium (GpCRC)*

Abstract

Background—Many patients with gastroparesis have had their gallbladder removed.

Aim—To determine if clinical presentations of patients with gastroparesis differ in those with prior cholecystectomy compared to patients who have not had their gallbladder removed.

Methods—Gastroparetic patients were prospectively enrolled into the NIDDK Gastroparesis Registry. Detailed history and physical examinations were performed; patients filled out questionnaires including Patient Assessment of GI Symptoms (PAGI-SYM).

Results—Of 391 subjects with diabetic (DG) or idiopathic gastroparesis (IG), 142 (36%) had a prior cholecystectomy at the time of enrollment. Patients with prior cholecystectomy were more often female, older, married, and overweight or obese. Cholecystectomy had been performed in 27/59 (46%) of T2DM compared to 19/78 (24%) T1DM and 96/254 IG (38%) (P=0.03). Patients with cholecystectomy had more comorbidities, particularly chronic fatigue syndrome, fibromyalgia, depression, and anxiety. Postcholecystectomy gastroparesis patients had increased health care utilization and had a worse quality of life. Independent characteristics associated with prior cholecystectomy included insidious onset (OR=2.06; p=0.01), more comorbidities (OR=1.26; P<0.001), less severe gastric retention (OR(severe)=0.68; overall P=0.03) and more severe symptoms of retching (OR=1.19; P=0.02) and upper abdominal pain (OR=1.21; P=0.02),

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less severe constipation symptoms (OR=0.84; P=0.02), and not classified as having IBS (OR=0.51; P=0.02). Etiology was not independently associated with a prior cholecystectomy.

Conclusions—Symptom profiles in patients with and without cholecystectomy differ: postcholecystectomy gastroparesis patients had more severe upper abdominal pain and retching and less severe constipation. These data suggest that prior cholecystectomy is associated with selected manifestations of gastroparesis.

Keywords

gastroparesis; cholecystectomy; gallbladder; gastric emptying; diabetes

Introduction

Gastroparesis is associated with a variety of symptoms including early satiety, postprandial fullness, nausea, vomiting, and abdominal pain (1,2). Symptoms of gastroparesis are nonspecific, being seen in peptic ulcer disease, partial gastric or small bowel obstruction, gallbladder disease, and several functional GI disorders. The most common etiologies of gastroparesis are primarily diabetic and idiopathic causes, with both T1DM and T2DM being associated with diabetic gastroparesis.

Symptomatic cholelithiasis is an indication for cholecystectomy (3). For some patients, cholecystectomy is performed for symptoms felt to be consistent with gallbladder dysfunction or for abnormal biliary scintigraphy rather than for definitive evidence of symptomatic gallstone disease (4). Unfortunately for many of these individuals, symptoms persist postoperatively and, upon further evaluation, a diagnosis of gastroparesis is made (5). In other patients, gastroparetic symptoms may occur after removal of their gallbladder for gallstones possibly from surgical disruption of neural pathways to the gastrointestinal tract.

The association between cholecystectomy and the clinical presentation of gastroparesis (symptoms, gastric emptying) is not known. If symptoms differ, knowledge of this may help better understand persistent symptoms in gastroparesis patients who have previously undergone a cholecystectomy. The NIDDK Gastroparesis Registry provides a good opportunity to evaluate the relationship of cholecystectomy and the clinical presentation of gastroparesis. Thus, the aim of this study was to determine if clinical presentations of patients with gastroparesis differ in those having a cholecystectomy prior to study enrollment compared to patients who have not had their gallbladder removed.

Methods

The NIDDK Gastroparesis Clinical Research Consortium (GpCRC) is a cooperative network of seven clinical centers and one Data Coordinating Center (DCC) funded through the NIDDK of the National Institutes of Health (NIH). The ongoing Gastroparesis Registry (ClinicalTrials.gov Identifier: NCT00398801) was implemented as an observational study of patients with gastroparesis enrolled prospectively at seven centers (6,7). Enrolled patients met specific entry criteria being 18 years or older with symptoms of at least 12 weeks duration, delayed gastric emptying scintigraphy (GES) using the 4 hour Eggbeaters protocol (gastric retention > 60% at 2 hours and/or > 10% at 4 hours) within 6 months of enrollment, and no structural abnormality as seen by upper endoscopy within one year of enrollment. Registry data at enrollment were extensive and included detailed medical history and physical examinations, validated symptom questionnaires including Patient Assessment of Upper Gastrointestinal Disorders Symptoms Severity Index (PAGI-SYM), Quality of Life questionnaires, and psychological inventory questionnaires, upper endoscopy results, 4 hour

gastric emptying scintigraphy results, and laboratory tests including hematology and blood chemistries.

During face-to-face interviews with each subject, the study physicians or coordinators at each Clinical Center completed case report forms including data relating to gastroparesis disease onset, symptoms, disease profile, associated medical conditions, including diabetes, and medication and supplemental therapies. Prior surgeries including cholecystectomy, appendectomy, hysterectomy were enquired. The study physicians performed a comprehensive physical examination. Laboratory measures were obtained, including hemoglobin $A1_C$ values.

The clinical severity of gastroparesis was graded on a scale originally proposed by Tack et al and reported in the ANMS review on treatment of gastroparesis (8). The severity was graded as grade 1: mild gastroparesis (symptoms relatively easily controlled and able to maintain weight and nutrition on a regular diet); grade 2: compensated gastroparesis (moderate symptoms with only partial control with use of daily medications, able to maintain nutrition with dietary adjustments); grade 3: gastroparesis with gastric failure (refractory symptoms that are not controlled as shown by the patient having ER visits, frequent doctor visits or hospitalizations and/or inability to maintain nutrition via an oral route).

Each patient filled out the 20 item PAGI-SYM questionnaire which assesses symptoms of gastroparesis, dyspepsia, and gastroesophageal reflux disease (9); it includes the nine symptoms of the Gastroparesis Cardinal Symptom Index (GCSI) which asks about nausea, retching, vomiting, stomach fullness, inability to finish meal, excessive fullness, loss of appetite, bloating, and abdominal distension (10). The GCSI equals the mean of the nausea/vomiting subscore, postprandial fullness/early satiety subscore, and bloating subscore where: Nausea/vomiting subscore = mean of the scores for nausea, retching, and vomiting; Postprandial fullness/early satiety sub-score = mean of the scores for stomach fullness, inability to finish meal, excessive fullness, and loss of appetite; and Bloating subscore = mean of the scores for bloating and large stomach. The PAGI-SYM also inquires about symptoms of gastroesophageal reflux including daytime heartburn, heartburn lying down, daytime chest discomfort, nighttime chest discomfort, daytime reflux, nighttime reflux, and bitter taste. In the PAGI-SYM, patients are asked to assess the severity of their symptoms during the previous two weeks using a 0 to 5 scale where no symptoms = 0, very mild = 1, mild = 2, moderate = 3, severe = 4, and very severe = 5.

Disease-specific quality of life was assessed by the Patient Assessment of Upper Gastrointestinal Disorders Quality of Life (PAGI-QOL) survey, which scores 30 factors from 0 (none of the time) to 5 (all of the time) (11). Patients were asked how often gastrointestinal problems they may be experiencing have affected different aspects of their quality of life and well-being in the past two weeks. Overall PAGI-QOL scores were calculated by taking means of all subscores after reversing item scores; thus a mean PAGI-QOL score of 0 represents poor quality of life while 5 reflects the best life quality.

The Medical Outcomes Study 36-Item Short-Form Health Survey version 2 (SF-36v2) was additionally used to assess the patients' views of overall physical and mental health in the past 4 weeks (standard recall form). The 8 subscales were standardized to the 1998 U.S. general population with a mean (±SD) of 50±10. Physical and mental health summary measures were computed. A higher score reflects higher quality of life (12).

Psychological functioning was assessed using the Beck Depression Inventory (BDI) and State-Trait Anxiety Inventory (STAI). BDI is a widely used 21-question multiple-choice self-report inventory that relate to depression, cognition, and physical well-being and is extensively employed to quantify depression in a range of clinical conditions (13,14). Each

answer is scored on a scale of 0 to 3. Higher total scores indicate more severe depressive symptoms with 29–63 indicating severe depression (13). The STAI consists of 20 questions relating to state anxiety (a temporary or emotional state) and 20 questions pertaining to trait anxiety (long standing personality trait anxiety with a general propensity to be anxious) and has been well validated (15). A score of ≥ 50 denotes significant anxiety.

Gastric emptying scintigraphy was performed using a low-fat, egg white meal with imaging at 0, 1, 2, 4 hours after meal ingestion, as described by a published multicenter protocol (16) and endorsed by the Society of Nuclear Medicine and American Neurogastroenterology and Motility Society (17). This protocol ensures standardized information about gastric emptying across sites. The delayed gastric emptying was graded according to the gastric retention at 4 hours: mild (≤20% gastric retention at 4 hours), moderate (>20 to 35%), and severe (>35%) (17,18).

Patients were also categorized into classes of functional gastrointestinal disorders using the Rome III Diagnostic Questionnaire and an analysis program developed by the Rome Foundation (19). The Rome III categories of interest are functional dyspepsia, postprandial distress syndrome (PDS), epigastric pain syndrome (EPS), chronic idiopathic nausea (CIN), functional vomiting, and irritable bowel syndrome (IBS).

This report focuses on patients with either idiopathic or diabetic gastroparesis. The diabetic patients could have either Type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) as defined by the patient and physician. The diagnosis of patients with the idiopathic etiology was based on no previous gastric surgery, no diabetes history (before or after the onset of gastroparesis at enrollment), a normal hemoglobin $A1_C$, and no other known etiologies. Twenty-five patients were diagnosed with other causes of gastroparesis (e.g., post-surgical or ischemic) but were too few in number to be meaningfully included in these analyses.

Identification of the patients who had undergone a cholecystectomy prior to enrollment was determined through detailed information from the Baseline History form that queried if the patient had ever had any abdominal procedure, and specifically if they had undergone a cholecystectomy.

All studies were approved by the Institutional Review Board at each Clinical Center and at the Data Coordinating Center.

Statistical Methods

An exploratory analyses was conducted comparing patients with cholecystectomy prior to enrollment to those patients with a gallbladder for a set of pre-specified baseline characteristics including: demographic, anthropometric, gastroparesis specific medical history, psychological and quality of life inventory scores, gastric emptying scintigraphy results, PAGI-SYM symptom severity scores and six ROME III categories. Both univariable and multivariable analyses were performed. Univariable results are expressed as mean ± standard deviation (SD) or by percentages, where appropriate. Differences in baseline clinical characteristics between the two groups were tested using either a chi-square test for non-ordered categories, Fisher's exact test for categories with small expected numbers or a Kruskal-Wallis test for continuous features (20).

An independent set of characteristics associated with having a prior cholecystectomy were determined from fitting the pooled set of characteristics with significance at the 0.05 level from bi-directional stepwise (both forward and backward) multiple binary logistic analyses (21). The candidate set of characteristics analyzed were: gender, age at enrollment (18-34,

35-49, 50+ years), race (white versus non-white), ethnicity, marital status (yes versus no), education (college or more), work status (missed more than 2 weeks in past year), income, BMI category (underweight/normal, overweight, obese), etiology (idiopathic, T1DM, T2DM), duration of symptoms, initial infectious prodrome, predominant symptom prompting evaluation, acute symptom onset (versus insidious), nature of symptoms, gastric failure, any and number of co-morbidities, any and number of hospitalizations in past year, selected co-morbidities (major depression, anxiety, migraines, fibromyalgia), current use of medication classes (proton pump inhibitors, prokinetics, antiemetics, analgesics or NSAI, narcotics, hormones, neuropathic pain modulators, antidepressants, anxiolytics), or gastric electric stimulation, STAI (each score ≥ 50), BDI (> 28), PAGI-QOL total score, SF-36 physical and mental components, gastric retention category (mild, moderate, severe), individual PAGI-SYM scores, ROME III categories (functional dyspepsia, PDS, EPS, IBS). Final models were determined based on the use of the Akaike Information Criteria (AIC) statistic, as well as tests of model fit (22). Our studies comparing gastroparesis features in diabetic compared to idiopathic patients have suggested some differences (23); therefore, multiple regression analyses was also performed separately on patients with each etiology, as well as on all patients combined. Models were forced to include terms for age at enrollment, gender, and race. All final models had respectable goodness of fit using the Hosmer-Lemeshow Goodness of Fit test (21). The odds ratios for each characteristic derived from the multiple logistic regression models shown in Tables 4 through 6 that are greater than 1 indicate a higher odds of having a prior cholecystectomy for those with the characteristic compared to the reference level of the characteristic shown in the table. P values are two-sided, nominal, with a level of 0.05 considered to be statistically significant.

Both SAS statistical software (version 9.3 of the SAS system for Windows, SAS Institute, Cary, NC, 2002-2010) and Stata (release 12, Stata Corp, College Station, TX, 2011) were used for all analyses (23).

Results

General

Of 391 subjects with diabetic (DG) or idiopathic gastroparesis (IG), 142 (36%) had a prior cholecystectomy at the time of enrollment. Patients with prior cholecystectomy were more often female (88 vs 80%; P=0.05), older age (45±14 vs 41±14 years, P=0.007), married (70 vs 51%; P<0.001), and overweight or obese (60 vs 49%; P=0.05). Cholecystectomy had been performed in 27/59 (46%) of T2DM, compared to 19/78 (24%) T1DM and 96/254 IG (38%)(P=0.03) (Table 1).

Symptoms, gastric emptying, treatments

Patients with cholecystectomy more frequently had insidious onset of symptoms (58 vs 43%; P=0.005). At the time of enrollment into the registry, patients with prior cholecystectomy had more severe nausea (3.6±1.3 vs 3.3±1.4; P=0.04), retching (2.5±1.8 vs 1.8±1.7; P <0.001), vomiting (2.5±1.9 vs 2.0±1.8; P=0.02), visible stomach distention (3.1±1.7 vs 2.6±1.7; P=0.01), upper abdominal pain (3.3±1.7 vs 2.9±1.8; P=0.03), GERD symptoms (2.2±±1.5 vs 1.9±1.3; P=0.05), and diarrhea (2.1±1.8 vs 1.7±1.7; P=0.04).

Patients with prior cholecystectomy more frequently used antiemetic agents (70 vs 59%; P=0.03) and narcotic analgesics (52 vs 40%; P=0.02) (Table 1).

Gastric retention at 2 hours tended to be less in patients with prior cholecystectomy (62±18% vs 65±19%; P=0.08), but were not significantly different at 4 hours (32±22% vs 33±23%; P=0.58). More gastroparesis patients with prior cholecystectomy had only mildly

delayed gastric emptying and more patients without cholecystectomy had moderate delay in gastric emptying (overall P=0.05) (Table 1).

Co-morbidities

Patients with cholecystectomy had more comorbidities (5.2±3.3 vs 3.3±2.5; P <0.001), particularly chronic fatigue syndrome, fibromyalgia, major depression, and severe anxiety. Fifty-nine percent of those with a cholecystectomy had been hospitalized in the past year (vs 45%; P <0.001) (Table 2). Prior cholecystectomy patients had poorer quality of life based on the PAGI-QOL (2.2±1.1 vs 2.6±1.1; P=0.004) and the SF-36 health survey (physical: 32±10 vs 34±10; P=0.05; mental: 36±13 vs 38±12; P=0.13). Table 3 depicts the Rome III categorization of the patients. There were no significant differences between the cholecystectomy groups for any of the Rome III categories.

Multivariable analyses

Multiple logistic regression analyses compared the postcholecystectomy group to the no cholecystectomy group for the candidate set of characteristics. Characteristics independently associated with a cholecystectomy prior to enrollment are shown in Table 4. Patients who were female (OR=2.71; P=0.007), or married (OR=2.11; P=0.01), had an insidious onset of gastroparesis (OR=2.06; P=0.01), more comorbid conditions (OR=1.26; P<0.001) or any hospitalization in the past year (2.02; P=0.009), more severe retching (1.19; P=0.02) and upper abdominal pain (OR=1.21; P=0.02), and less severe constipation (OR=0.84; P=0.02) have a higher odds of having a prior cholecystectomy than those not having those characteristics. Those patients having a cyclic pattern of gastroparesis symptoms compared to a chronic, stable symptom nature (OR=0.25: P=0.01), those with moderate or severe gastric retention compared to mild (OR=0.42; OR=0.68, overall P=0.03), and those classified with IBS (OR=0.51; P=0.02) have lower odds of having a cholecystectomy than those patients without those characteristics.

Independent characteristics associated with idiopathic patients having a prior cholecystectomy were: married (OR=2.59; P=0.004), more comorbid conditions (OR=1.28; P <0.001), more hospitalizations in the past year (OR=1.23; P=0.001), less migraine headache diagnosis (0.50; P=0.04), more current use of pain relieving analgesics (P=1.93; P=0.04), and more severe stomach distention (OR=1.20, P=0.05) (Table 5).

Regression analyses of all diabetic gastroparesis patients including the type of diabetes as a predictor, resulted in the following independent characteristics being associated with a prior cholecystectomy: having Type 2 diabetes (OR=0.37 of T1DM vs T2DM; P=0.05), being female (OR=3.00; P=0.06), more comorbid conditions (OR=1.24; P=0.01), lower PAGI quality of life (OR=0.56; P=0.02), more severe vomiting (OR=1.41; P=0.02) and not classified as PDS (OR=0.26; P=0.04) or IBS (OR=0.35; P=0.04 (Table 6). Similar analyses were obtained when analyzing the entire group with diabetes without adjustment for type; with the addition of being older (OR=9.84; P=0.001), having an insidious onset (OR=2.96, P=0.03) and less severe lower abdominal pain severity (OR=0.67; P=0.04) (data not shown).

Discussion

This study has examined the association between cholecystectomy and clinical presentations of gastroparesis. In our cohort of patients with gastroparesis, nearly one third of the patients have had their gallbladder removed before enrollment in the Gastroparesis Registry. This study provides information to the clinician on the likely profile of the patient presenting with gastroparesis having had a prior cholecystectomy. Our study shows that prior cholecystectomy in patients with gastroparesis more frequently has occurred in older,

female, and T2DM patients. Importantly, gastroparesis patients with prior cholecystectomy have more severe gastroparesis symptoms (particularly abdominal pain and vomiting/retching), greater comorbidities including borderline increases in psychological dysfunction, more health care utilization, and worse quality of life. These data suggest that there is an association between cholecystectomy and selected manifestations of gastroparesis.

Thirty-six percent of our gastroparesis patients had undergone a prior cholecystectomy. This result is similar to the 39% reported in a smaller study by Deeb et al (5). In Deeb's study, 36% of patients undergoing cholecystectomy had a normal gallbladder. In addition, 72% of their patients did not report clinical improvement after cholecystectomy. Prior studies suggested that 8% of patients with idiopathic gastroparesis had their onset of gastroparesis symptoms immediately after cholecystectomy (2). This study postulated that vagal nerve damage occurred during the abdominal exploration and removal of the gallbladder.

Cholecystectomy is performed primarily for symptomatic cholelithiasis. In addition, cholecystectomy may be performed for functional gallbladder disorders without gallstones such as biliary dyskinesia or gallbladder hypomotility (4). Removal of the gallbladder often results in resolution of symptoms for symptomatic cholelithiasis (3). In a large series of patients undergoing cholecystectomy for gallstones, relief of upper abdominal pain was associated with the pain features and negatively associated with concomitant GERD, IBS, and somatization (3). Preoperative nausea and vomiting, suggesting a global GI motility disorder, have a poorer response to cholecystectomy for biliary dyskinesia (32). This study points that gastroparesis may also be a cause of their symptoms, a finding also suggested by Deeb et al (5). Concomitant gastroparesis and biliary tract disease negatively affect patients with biliary tract disease (33). Psychological factors have been prominent in some patients with persistent GI symptoms after cholecystectomy (34). Our study shows that patients with gastroparesis and prior cholecystectomy have higher amounts of depression and anxiety compared to gastroparetic patients without prior cholecystectomy.

Apparent from our study is that the postcholecystectomy gastroparesis group has more pain, both abdominal pain and other types of pain disorders such as fibromyalgia. Our data also show that patients who had undergone prior cholecystectomy have more severe symptoms and comorbidities. This chronic pain and more severe symptomatology could have prompted the cholecystectomy. Other chronic conditions, such as IBS and fibromyalgia, are associated with increased rates of various surgeries – cholecystectomy, appendectomy, and hysterectomy (35,36,37). These associations between chronic disorders and surgery are important from a health care utilization perspective.

Since there is innervation between the gallbladder and the upper gastrointestinal tract via vagal and sympathetic pathways (25), cholecystectomy might interrupt neural pathways and interfere with gastric function. However, we observed gastric retention rates that were not greater in those gastroparetics who had undergone prior cholecystectomy suggesting that surgery itself may not have disrupted nerve pathways regulating gastric emptying. Other studies on the effect of cholecystectomy on gastric motility have been conflicting. In early studies, persistent dyspepsia after cholecystectomy was associated with delay in gastric emptying (26). Some studies suggest that gastric emptying time is related to symptoms after a variety of upper gastrointestinal and biliary operations (27). Others have suggested that cholecystectomy results in a faster gastric emptying time with normalization of gastric myoelectric activity (28). Studies suggest that there is disturbed proximal gastric function in symptomatic gallstone patients with dyspepsia which improves after cholecystectomy (29). More recent studies have suggested that laparoscopic cholecystectomy improves dyspeptic symptoms of abdominal pain, early satiety, nausea, and vomiting but does not alter gastric

emptying (30). In patients with diabetic gastroparesis, gallbladder emptying was slowest in diabetics with autonomic neuropathy (31).

Our NIDDK registry has data on a large number of patients with gastroparesis. Our data collection did not address several surgical and clinical issues that, in retrospect, might be of interest to the practitioner. The information collected at the time of enrollment in the Gastroparesis Registry did not provide details pertaining to (i) the reasons patients underwent cholecystectomy, (ii) the symptomatic response to cholecystectomy, and (iii) the relationship of the cholecystectomy and the development of gastroparesis symptoms. We also do not have data from any comparable cohort for whom the operation provided symptom relief to determine what features were specific for persistent symptomatology in the post-cholecystectomy patients who were ultimately found to have gastroparesis. Our data do not provide sufficient evidence to suggest that cholecystectomy predisposes to gastroparesis development or to determine if biliary dyskinesia occurs more frequently in patients with gastroparesis. It is likely that symptoms of abdominal pain and retching were initially attributed to gallbladder disease or dysfunction in many patients, which could have delayed diagnosis of gastroparesis. One can speculate that gastroparesis only was considered when symptoms did not resolve postoperatively. Prospective investigations might provide insight to address these questions.

Since we do not have the data from patients with or without gastroparesis that did well after cholecystectomy we can only speculate on how to treat these patients. In a patient with upper abdominal symptoms and gallstones on ultrasound, if abdominal pain is located in the right upper quadrant, then the gallbladder is often removed to reduce the abdominal pain; having a diagnosis of gastroparesis would not change that decision. A gastric emptying test is occasionally obtained in a patient with abdominal pain if there is also prominent nausea and vomiting. If the gastric emptying study is delayed and the gallbladder evaluation shows a positive HIDA scan but negative ultrasound for stones, then the gallbladder might be removed trying to reduce pain. However, cholecystectomy in the absence of gallstones is controversial (4) and the gastroparesis related symptoms of postprandial nausea and vomiting may continue. It may be appropriate to have this type of patient evaluated by a specialist in GI motility and functional GI disorders to determine if medical options might be more appropriate than surgery. Our study showed that gastroparesis patients with prior cholecystectomy and those with intact gallbladders had similar usage of prokinetic agents and proton pump inhibitors. However, gastroparesis patients with prior cholecystectomy were treated more frequently with antiemetic agents and narcotic analgesics.

In summary, this study shows that a substantial portion (36%) of patients with gastroparesis have had their gallbladder removed. Prior cholecystectomy in patients with gastroparesis more frequently had occurred in older, female, T2DM patients, and often with more comorbidities, both functional and psychological. Symptom profiles in patients with and without cholecystectomy differ: patients with prior cholecystectomy have higher severity of upper abdominal pain and retching but less severe constipation. Postcholecystectomy gastroparesis patients have increased health care utilization and worse quality of life. These data suggest that prior cholecystectomy is associated with selected manifestations of gastroparesis.

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Table 1

Baseline demographics and symptom characteristics of patients by cholecystectomy prior to enrollment

	Prior Cholecystectomy				
	No (N=249)		Yes (N=142)		
Characteristic	**No.**	**Mean or %†**	**No.**	**Mean or %†**	***P*‡**
Demographic, lifestyle, anthropomorphic:					
Gender (females)	200	80.3%	125	88.0%	**0.05**
Age at enrollment	249	40.9 ± 13.5	142	45.0 ± 14.2	**0.007**
Ethnicity (any Hispanic)	9	3.6%	10	7.0%	0.13
White (yes vs. no)	210	84.3%	124	87.3%	0.42
Marital status (yes vs no)	128	51.4%	100	70.4%	**<0. 001**
College degree or higher (yes vs no)	73	29.3%	38	26.8%	0.59
Body mass index (kg/m^2)	249	26.2 ± 7.3	142	28.1 ± 7.2	**0.006**
BMI category*:					**0.05**
Underweight/normal	126	50.6%	57	40.1%	
Overweight/obese	123	49.4%	85	59.9%	
Etiology:					
Etiology:					**0.03**
Idiopathic	158	63.5%	96	67.6%	
DM Type 1	59	23.7%	19	13.4%	
DM Type 2	32	12.9%	27	19.0%	
Medical history:					
Age gastroparesis symptoms started (years)	249	36.2 ± 13.9	142	39.6 ± 14.8	**0.03**
Duration (years) of symptoms from enrollment:	249	4.8 ± 5.7	142	5.5 ± 6.8	0.06
Initial infectious prodrome (yes vs no)	50	20.1%	16	11.3%	**0.02**
Predominant symptom prompting evaluation:					0.73
Nausea	86	34.5%	51	35.9%	
Vomiting	56	22.5%	36	25.4%	
Abdominal pain	46	18.5%	27	19.0%	
Other	61	24.5%	28	19.7%	
Type of symptom onset (insidious vs acute)	107	43.0%	82	57.8%	**0.005**

	Prior Cholecystectomy				
	No (N=249)		Yes (N=142)		
Characteristic	**No.**	**Mean or %†**	**No.**	**Mean or %†**	***P*‡**
Nature of gastroparesis symptoms:					**0.02**
Chronic, but stable	58	23.5%	26	18.3%	
Chronic, but progressive worsening	73	29.6%	58	40.9%	
Chronic with periodic exacerbations	83	33.6%	50	35.2%	
Cyclic pattern	33	13.4%	8	5.6%	
Gastroparesis severity:					0.26
Mild (grade 1)	34	13.8%	15	10.6%	
Compensated (grade 2)	135	54.7%	71	50.0%	
Gastric failure (grade 3)	78	31.6%	56	39.4%	
Gastric electric stimulator (current use)	16	6.4%	13	9.2%	0.32
Medications (current use):					
Proton pump inhibitor or other GI medication	192	77.1%	112	78.9%	0.69
Prokinetic	140	56.2%	77	54.2%	0.70
Antiemetic	148	59.4%	100	70.4%	**0.03**
Pain relieving analgesic, NSAI, or aspirin in past 6 months	144	57.8%	91	64.1%	0.22
Narcotic	99	39.8%	74	52.1%	**0.02**
Any hormones (HRT, estrogen, progestin) in past 6 months	53	21.3%	31	21.8%	0.90
Any pain modulators	47	18.9%	33	23.2%	0.30
Any antidepressants	78	31.3%	55	38.7%	0.14
Anxiolytics	37	14.9%	20	14.1%	0.83
Gastric emptying (scintigraphy):					
Percent gastric retention at 2 hours	249	65.3 ± 18.6	142	62.3 ± 18.1	0.08
Percent gastric retention at 4 hours	249	33.1 ± 22.7	141	32.1 ± 22.4	0.58
Severity of delayed gastric emptying at 4 hr:					**0.05**
Mild (≤ 20%)	88	35.3%	61	43.3%	
Moderate (21% - 35%)	78	31.3%	28	19.9%	
Severe (≥ 35%)	83	33.3%	52	36.9%	
PAGI-SYM severities:					
Nausea severity	249	3.3 ± 1.4	142	3.6 ± 1.3	**0.04**

	Prior Cholecystectomy				
	No (N=249)		Yes (N=142)		
Characteristic	**No.**	**Mean or %†**	**No.**	**Mean or %†**	***P*‡**
Retching severity	249	1.8 ± 1.7	142	2.5 ± 1.8	**<0.001**
Vomiting severity	249	2.0 ± 1.8	142	2.5 ± 1.9	**0.02**
Stomach fullness severity	249	3.5 ± 1.4	142	3.7 ± 1.2	0.19
Inability to finish a meal severity	249	3.4 ± 1.4	142	3.5 ± 1.4	0.62
Feeling excessively full after meals	249	3.6 ± 1.4	142	3.6 ± 1.3	0.76
Appetite loss severity	249	2.9 ± 1.5	142	3.1 ± 1.4	0.36
Bloating severity	249	3.1 ± 1.6	142	3.4 ± 1.4	0.08
Stomach visibly larger severity	249	2.6 ± 1.8	142	3.1 ± 1.7	**0.01**
Cardinal symptom index (GCSI)¶	249	2.9 ± 1.0	142	3.2 ± 0.9	**0.002**
Upper abdominal pain severity	249	2.9 ± 1.8	142	3.3 ± 1.7	**0.03**
Upper abdominal discomfort severity	249	3.1 ± 1.6	142	3.4 ± 1.5	0.17
Lower abdominal pain severity	249	2.1 ± 1.6	142	2.2 ± 1.7	0.43
Lower abdominal discomfort severity	249	2.2 ± 1.6	142	2.3 ± 1.7	0.80
Gastrointestinal reflux (GERD) sub-scale¶	248	1.9 ± 1.3	142	2.2 ± 1.5	**0.05**
Constipation severity	249	2.4 ± 1.7	142	2.4 ± 1.9	0.69
Diarrhea severity	249	1.7 ± 1.7	142	2.1 ± 1.8	**0.04**

*Body mass index (BMI) in kg/m^2: Normal/underweight (<25), Overweight/obese (≥25).

†Data are means ± standard deviations or percents. Percents are noted as (%).

‡The significance of difference in categorical variables between groups was tested with either a chi-square test for non-ordered categories or Fisher's exact test. All *P* values are two-sided.

¶Definitions:
Cardinal symptom index = (nausea sub-score + postprandial fullness sub-score + bloating sub-score)/3 where:
GERD sub-scale = (daytime heartburn + heartburn lying down + daytime chest discomfort + chest discomfort at night + daytime reflux + reflux lying down + bitter taste in mouth)/7

Table 2

Comorbidities, psychological function inventories and quality of life assessment in gastroparesis patients by prior cholecystectomy

	Prior Cholecystectomy				
	No (N=249)		Yes (N=142)		
Characteristic	**No.**	**Mean or %†**	**No.**	**Mean or %†**	***P*‡**
Comorbidities & hospitalizations:					
Number of comorbid conditions	249	3.3 ± 2.5	142	5.2 ± 3.3	**<0.001**
Any comorbidities	228	91.6%	140	98.6%	**0.005**
Comorbidities (ever diagnosed):					
Migraine	87	34.9%	57	40.1%	0.31
Chronic fatigue syndrome	12	4.8%	18	12.7%	**0.009**
History of CVD	15	6.0%	11	7.8%	0.51
Fibromyalgia	20	8.0%	24	16.9%	**0.008**
Eating disorder	9	3.6%	3	2.1%	0.55
Major depression	48	19.3%	47	33.1%	**0.002**
Severe anxiety	22	8.8%	22	15.5%	**0.05**
Number of hospitalizations in the past year	249	2.1 ± 4.6	142	3.3 ± 4.7	**<0.001**
Any hospitalization in the past year	112	45.0%	84	59.2%	**0.007**
State-Trait inventory (STAI):					
State anxiety score	249	44.5 ± 13.0	142	47.6 ± 14.1	**0.05**
Trait anxiety score	249	43.5 ± 11.7	142	46.3 ± 13.4	0.07
Beck Depression Inventory (BDI):					
BDI Inventory score:	249	18.5 ± 11.1	142	20.6 ± 11.4	0.06
BDI > 28 (severe depression)	45	18.1%	32	22.5%	0.29
Quality of life (PAGI- QOL) (past 2 weeks):					
Activity sub-score	249	2.4 ± 1.2	142	2.0 ± 1.2	**0.002**
Clothing sub-score	249	3.1 ± 1.7	142	2.6 ± 1.7	**0.002**
Diet sub-score	249	1.6 ± 1.2	142	1.4 ± 1.2	0.09
Relationship sub-score	249	3.1 ± 1.5	142	2.7 ± 1.6	**0.01**
Psychological sub-score	249	2.7 ± 1.4	142	2.5 ± 1.4	0.16
Total score	249	2.6 ± 1.1	142	2.2 ± 1.1	**0.004**

	Prior Cholecystectomy				
	No (N=249)		Yes (N=142)		
Characteristic	**No.**	**Mean or %†**	**No.**	**Mean or %†**	***P*‡**
SF-36v2 Health Survey (past 4 weeks):					
Physical health component sub-score	248	33.8 ± 10.1	141	31.8 ± 10.1	**0.05**
Mental health component sub-score	248	37.7 ± 12.4	141	35.6 ± 12.9	0.13

†Data are means ± standard deviations or %

‡The significance of difference in categorical variables between groups was tested with either a chi-square test for non-ordered categories or Fisher's exact test. All *P* values are two-sided.

Table 3

Rome III classification for gastroparesis patients by prior cholecystectomy

	Prior Cholecystectomy				
	No (N=249)		Yes (N=142)		
Rome III categories*	**No.**	**Percent**	**No.**	**Percent**	***P*‡**
Functional dyspepsia:					0.95
Yes	211	84.7%	120	84.5%	
No	38	15.3%	22	15.5%	
Functional dyspepsia, *Postprandial Distress Syndrome or PDS:*					0.59
Yes	222	89.2%	124	87.3%	
No	27	10.8%	18	12.7%	
Functional dyspepsia, *Epigastric Pain Syndrome or EPS:*					0.71
Yes	4	1.6%	3	2.1%	
No	245	98.4%	139	97.9%	
Chronic idiopathic nausea or CIN:					0.12
Yes	74	29.7%	32	22.5%	
No	175	70.3%	110	77.5%	
Functional vomiting:					0.46
Yes	101	40.6%	63	44.4%	
No	148	59.4%	79	55.6%	
Irritable bowel syndrome or IBS:					0.32
Yes	170	68.3%	90	63.4%	
No	79	31.7%	52	36.6%	

* Rome III diagnoses determined from the Rome III Diagnostic Questionnaire analyzed using an analysis program developed by the Rome Foundation (http://www.romecriteria.org/rome_iii_sas/, accessed 03 February 2010).

Table 4

Association of baseline characteristics with prior cholecystectomy in gastroparesis patients

Characteristics	Odds Ratio	95% Confidence Intervals	P*
Demographics, lifestyle, anthropometric:			
Gender (female vs male)	2.71	1.31-5.61	**0.007**
Age at enrollment (years)			0.16
18 - 34			
35 - 49	0.79	0.42-1.49	0.47
50 or older	1.44	0.70-2.97	0.33
Race (white vs non-white)	1.45	0.67-3.13	0.34
Married (vs other)	2.11	1.21-3.66	**0.01**
Medical history:			
Insidious vs acute onset	2.06	1.25-3.39	**0.01**
Nature of gastroparesis symptoms:			**0.04**
Chronic, but stable	1.00		
Chronic, but worsening	1.03	0.51-2.08	0.93
Chronic, periodic exacerbations	0.94	0.47-1.90	0.87
Cyclic pattern	0.25	0.09-0.73	0.01
Number of comorbid conditions	1.26	1.15-1.38	**<0.001**
Any hospitalization in past year	2.02	1.19-3.41	**0.009**
Gastric emptying scintigraphy:			
Severity of delayed emptying:			**0.03**
Mild (≤ 20%)	1.00		
Moderate (21% - 34%)	0.42	0.22-0.79	0.008
Severe (≥ 35%)	0.68	0.38-1.20	0.18
PAGI-SYM symptom severity:			
Retching severity	1.19	1.03-1.38	**0.02**
Upper abdominal severity	1.21	1.03-1.42	**0.02**
Constipation severity	0.84	0.72-0.97	**0.02**
Rome III classification:			
Irritable Bowel Syndrome (IBS)	0.51	0.30-0.88	**0.02**

*Number analyzed: 386

Odds Ratios, 95 % confidence limits, P values determined from logistic regression of cholecystectomy on the full set of baseline characteristics, forcing age, gender, and race into the model. The candidate set is described in Statistical Methods.

Hosmer-Lemeshow goodness of fit: $\chi^2_8 = 1.78$, p=0.9871

Table 5

Associations of baseline predictors on prior cholecystectomy in patients with idiopathic gastroparesis

Characteristics	Odds Ratio	95% Confidence Intervals	P*
Demographics, lifestyle:			
Gender (female vs male)	1.65	0.63 - 4.37	0.31
Age at enrollment (years):			0.68
18 - 34			
35 - 49	0.78	0.37 - 1.64	0.51
50 or older	1.07	0.48 - 2.38	0.88
Race (white vs non-white)	2.06	0.61 - 6.95	0.24
Married (vs other)	2.59	1.34 - 4.97	**0.004**
Medical history:			
Number of comorbid conditions	1.28	1.13 - 1.45	**<0.001**
Diagnosed with migraines	0.50	0.26 - 0.95	**0.04**
No. of hospitalizations in past year	1.23	1.09 - 1.38	**0.001**
Current use of pain relieving analgesics, NSAI, or aspirin (past 6 mo)	1.93	1.04 - 3.57	**0.04**
PAGI-SYM symptom severity:			
Stomach visibly larger severity	1.20	1.00 - 1.43	**0.05**

* Number analyzed: 254

Odds Ratios, 95 % confidence limits, P values determined from logistic regression of prior cholecystectomy on the full set of baseline characteristics, forcing age, gender, and race into the model. The candidate set is described in the Statistical Methods section.

Hosmer-Lemeshow goodness of fit: $\chi^2_8 = 8.81$, p=0.3588

Table 6

Associations of baseline predictors with prior cholecystectomy in patients with diabetic gastroparesis including type of diabetes

Characteristics	Odds Ratio	95% Confidence Intervals	P*
Demographics, lifestyle:			
Gender (female vs male)	3.00	0.95 - 9.48	0.06
Age (50 + vs <50 yrs):	2.03	0.71 - 5.77	0.19
Medical history:			
Diabetes type (1 vs 2)	0.37	0.14 - 0.99	**0.05**
Number of comorbid conditions	1.24	1.07 - 1.44	**0.01**
Psychological inventories & quality of life			
PAGI-QOL total score (past 2 wks)	0.56	0.35 - 0.90	**0.02**
PAGI-SYM symptom severity:			
Vomiting severity	1.41	1.05 - 1.89	**0.02**
Rome III classification:			
Irritable Bowel Syndrome (IBS)	0.35	0.13 - 0.97	**0.04**
Postprandial distress syndrome (PDS)	0.26	0.07 - 0.96	**0.04**

*Number analyzed: 137

Odds Ratios, 95 % confidence limits, P values determined from logistic regression of prior cholecystectomy on the full set of baseline characteristics, forcing age, gender, and diabetes type into the model. The candidate set is described in the Statistical Methods section. Due to estimability issues with the model, white, on ges, any comorbidities, predominant symptom presented, nature of symptoms, current use of hormones or anxiolytics, fibromyalgia, EPS were excluded; age, severity of gastric retention, BMI category and duration of symptoms were regrouped to 2 categories.

Hosmer-Lemeshow goodness of fit: $\chi^2_8 = 8.09$, p=0.4250