# Gastroesophageal Mucosal Injury after Cholecystectomy: An Indication for Surveillance?

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**BACKGROUND:** Cholecystectomy alters bile release dynamics from pulsatile meal-stimulated to continuous, and results in retrograde duodeno-gastric bile reflux (DGR). Bile is implicated in mucosal injury after gastric surgery, but whether cholecystectomy causes esophagogastric mucosal inflammation, therefore increasing the risk of metaplasia, is unclear.

**STUDY DESIGN:** This study examined whether cholecystectomy-induced DGR promotes chronic inflammatory mucosal changes of the stomach and/or the esophagogastric junction (EGJ). Four groups of patients were studied and compared with controls. A group of patients was studied before and 1 year after cholecystectomy; 2 further groups were studied long-term post-cholecystectomy (LTPC) at 5 to 10 years and 10 to 20 years. All underwent abdominal ultrasound and upper gastrointestinal endoscopy with gastric antral and EGJ biopsies, noting the presence of gastric bile pooling. Biopsy specimens were stained for Ki67 and p53 overexpression, and the bile reflux index (BRI) was calculated.

**RESULTS:** At endoscopy, bile pooling was observed in 9 of 26 (34.6%) controls, in 8 of 25 (32%) patients pre-cholecystectomy, in 15 of 25 (60%) 1 year post-cholecystectomy patients ($p = 0.047$), and 23 of 29 (79.3%) LTPC patients ($p = 0.001$). Bile reflux index positivity at the EGJ increased from 19% of controls through 41% of LTPC patients ($p = 0.032$). Ki67 was overexpressed at the EGJ in 19% of controls, but in 62% of LTPC patients ($p = 0.044$); p53 was overexpressed at the EGJ in 19% of controls compared with 66% of LTPC patients ($p = 0.001$).

**CONCLUSIONS:** Duodeno-gastric bile reflux was more common in patients with gallstones than in controls, and its incidence doubled after cholecystectomy. This was associated with inflammatory changes in the gastric antrum and the EGJ, evident in most LTPC patients. Ki67 and p53 overexpression at the EGJ suggests cellular damage attributable to chronic bile exposure post-cholecystectomy, increasing the likelihood of dysplasia. Further studies are required to determine whether DGR-mediated esophageal mucosal injury is reversible or avoidable, and whether surveillance endoscopy is indicated after cholecystectomy. (J Am Coll Surg 2017;224:319–326. © 2016 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

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Cholecystectomy—the standard of care for symptomatic cholelithiasis—alters the dynamics of bile storage and release.[1] Bile is normally stored in the gallbladder in the fasting inter-digestive period and is propelled into the duodenum in response to meals under the influence of cholecystokinin (CCK)-mediated gallbladder contraction.[1-3] After cholecystectomy, the facility for bile storage is lost, and bile is continuously released into the duodenum, even during fasting.[1]

There appears to be a clear causal link between cholecystectomy and duodeno-gastric bile reflux (DGR).[2-4]





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**Abbreviations and Acronyms**
BRI = bile reflux index
CCK = cholecystokinin
DGR = duodeno-gastric bile reflux
EGJ = esophagogastric junction
LTPC = long-term post-cholecystectomy

The continuous presence of bile in the duodenum permits its overflow across the pylorus and into the stomach. A significantly greater concentration of bile acids has been confirmed in nasogastric aspirates from patients with gallstones compared with those without, and this increases further after cholecystectomy.[1]

Cholecystectomy also results in elevated serum levels of CCK.[3] Cholecystokinin is an enteric hormone that is normally inhibited by the negative feedback of the CCK-mediated bile bolus in the duodenum,[5] but after cholecystectomy, this switch-off mechanism is lost, resulting in persistent elevation of CCK levels.[3] Exposure of the gastric mucosa to bile has been shown to cause erythema, inflammation, or ulceration of the gastric mucosa.[6,7] Gastric ulceration and gastritis have been shown to attenuate CCK-mediated increases in pyloric muscle tone,[8] which may explain the observation of a bilious refluxate through an open pylorus on gastroscopy of patients with gastritis.[9] The increase in circulating CCK results in reduction of lower esophageal sphincter pressure[10] and increases the frequency of transient lower esophageal sphincter relaxation episodes, potentially further exposing the lower esophageal mucosa to refluxed bile.[11] Increased DGR, in turn, predisposes to increased gastroesophageal reflux injury.

Although we know that these injuries occur, their precise molecular mechanism at the cellular level has yet to be elucidated. We hypothesized that cholecystectomy should be considered a model of iatrogenically induced mucosal injury of the upper gastrointestinal tract, resulting in bile-induced chronic cellular injury to the mucosa of the intact stomach and esophagogastric junction (EGJ). This should be quantifiable as an increase in bile reflux index (BRI) positivity and as an increase in cellular Ki67 and p53 expression of the mucosa of the gastric antrum and gastroesophageal junction.

## METHODS

### Patient cohorts/study groups

In order to determine whether mucosal injury is truly attributable to cholecystectomy, a paired cohort of patients was studied before and after cholecystectomy, and compared with long-standing post-cholecystectomy patients and further with controls. Eighty patients, divided into 5 study groups, were prospectively enrolled into this observational case-control study, in accordance with institutional ethics committee approval.

Group 1 (n = 26) was composed of individuals investigated for dyspepsia, but without evidence of gallbladder disease and who were not on NSAIDs or proton pump inhibitors (PPIs); these acted as the nongallstone control group of patients. Group 2 (n = 25) comprised patients with an ultrasound-confirmed diagnosis of symptomatic cholelithiasis, and were scheduled for cholecystectomy. Because of their symptoms of dyspepsia, they also underwent upper gastrointestinal endoscopy. Group 3 (n = 25) contained the group 2 patient cohort just described, who underwent repeat upper gastrointestinal endoscopy 1 year post-cholecystectomy. Groups 4 and 5 included 29 patients who presented with dyspepsia, but who had previously undergone cholecystectomy; specifically, group 4 patients (n = 10) had undergone cholecystectomy 5 to 10 years previously, and group 5 patients (n = 19) had their cholecystectomy between 10 to 20 years previously. Although recruitment of an additional cohort of patients 5 to 10 years post-cholecystectomy, who were asymptomatic (and therefore not complaining of dyspepsia), could address a potential confounding variable, strengthening our hypothesis-testing and the conclusions that may be drawn from the observed results, prospectively enrolling an adequately powered cohort of well asymptomatic patients for an invasive procedure such as gastroscopy would have posed both ethical and logistic challenges.

### Upper gastrointestinal endoscopy and collection of biopsy samples

Upper gastrointestinal endoscopy was performed on all patients by a single endoscopist (TNW), who recorded common macroscopic findings using standardized consensus criteria for inflammation. The presence or absence of macroscopic bile pooling was noted on endoscopic intubation of the stomach in each patient and photographed for subsequent verification. A minimum of 4 biopsies per site were taken from the gastric antrum and the EGJ. The biopsy specimens were oriented on filter paper and immediately fixed in formalin.

### Bile reflux index

Histologic features of bile reflux in the gastric antrum and EGJ were recorded using the BRI devised by Sobala and colleagues.[12] This was determined by histologic examination of 4 × 1 mm specimen sections, after hematoxylin and eosin staining, by an expert histopathologist (IT), blinded to the clinical details of the patients and to the