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Remnant Gastropathy due to Bile Reflux after Roux-en-Y Gastric Bypass: A Unique Cause of Abdominal Pain and Successful Treatment with Ursodiol

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Abstract

Background—Chronic abdominal pain can occur after Roux-en-Y gastric bypass (RYGB), and can remain unexplained despite extensive investigation. Bile can pool in the gastric remnant and create a bile reflux gastropathy. The aim of this study was to assess gastric remnant findings in patients with RYGB and chronic abdominal pain of unclear etiology, and to determine the effectiveness of ursodiol therapy for patients with confirmed remnant gastropathy.

Methods—All consecutive patients with RYGB and a diagnosis of chronic abdominal pain, and a negative diagnostic workup (including physical examination, routine laboratory work, cross sectional imaging, and standard upper endoscopy), who underwent device-assisted enteroscopy for evaluation of the gastric remnant were included. Pathology reports, treatments, and clinical follow-up were recorded.

Results—28 post-RYGB patients (all female) with chronic abdominal pain and negative evaluation were included. Pooling of bile with gastric erythema was noted in 22/28 patients. All 22 patients with endoscopic erythema had pathology consistent with bile reflux chemical gastropathy. Of these patients, 12 were started on a proton pump inhibitor (PPI) alone, and 10 were started on ursodiol. Of the ursodiol group, 8/10 (80%) patients reported substantial improvement or resolution of abdominal pain at clinical follow-up. All 3 ursodiol patients with repeat endoscopic examination of the gastric remnant had endoscopic and histologic resolution of gastropathy. Of the PPI patients, 1/12 reported improvement in abdominal pain at clinical follow-up ($p=0.002$), and both patients with repeat endoscopic examination of the gastric remnant had persistent remnant gastropathy.

Conclusions—RYGB patients with unexplained chronic pain, and biopsy-confirmed chemical gastropathy, had a significantly higher rate of abdominal pain resolution with ursodiol treatment compared to PPI. Remnant gastropathy due to bile reflux is a treatable cause of chronic abdominal pain in RYGB patients, and ursodiol should be considered for empiric treatment in Roux-en-Y patients with unexplained chronic abdominal pain.

Keywords

Roux en Y gastric bypass; abdominal pain; ursodiol; bile; remnant gastropathy

Background

Chronic abdominal pain in patients who have had Roux-en-Y gastric bypass (RYGB) is a common issue. Possible etiologies include ulceration of the gastric pouch or gastrojejunal anastomosis, cholecystitis, stenosis, bowel obstruction, internal hernia, and abdominal wall syndromes ¹. These patients are typically subjected to expensive and often invasive testing, including abdominal exploration. Nevertheless, despite aggressive evaluations an etiology is still not identified in over 15% of patients ².

RYGB anatomy creates a biliopancreatic limb that no longer directly participates in the digestion and absorption of nutrients. This altered anatomy, in which food no longer passes through the remnant stomach, duodenum, or proximal jejunum, causes decreased nutrient delivery to the excluded segment, can directly impair mucosal function, and can lead to alteration in the gut microbiome ^{3,4,5,6}. Additionally, this alteration in anatomy and exclusion of nutrient flow can affect motility and may predispose to the pooling of bile in the gastric remnant. Bile is known to be toxic to gastric mucosa, and it is possible that the pooling of bile in the remnant stomach may contribute to bile reflux gastropathy and chronic abdominal pain in this patient population.

The aim of this study was to assess gastric remnant findings in patients with RYGB and chronic abdominal pain of unclear etiology, and to determine the effectiveness of ursodiol therapy for patients with confirmed remnant gastropathy.

Methods

This study was a retrospective review of a prospectively collected database, under Partners HealthCare Institutional Review Board study 2003P001597. All consecutive patients with RYGB and a diagnosis of chronic abdominal pain, and a negative diagnostic workup (including physical examination, routine laboratory work, cross sectional imaging, and standard upper endoscopy), who underwent device-assisted enteroscopy for evaluation of the gastric remnant were included. Pathology reports, treatments, and clinical follow-up were recorded.

Means were compared with Student's *t*-test and proportional comparison between groups was performed with Fisher's Exact test. All statistics are reported as mean $\pm$ SEM.

Results

28 patients (all female) were included. All patients described having abdominal pain for several years' duration, and a negative evaluation was documented in all cases. Other than chronic abdominal pain, symptoms were not specific. Location of pain was typically in the mid-abdomen or left upper quadrant. The quality of pain varied, and included burning,

gnawing, dull and sharp descriptions. Pain was occasionally and inconsistently worse with meals, and was accompanied by intermittent nausea in many cases. Endoscopic examination of the remnant and biopsies had been performed in all patients. On endoscopic evaluation, pooling of bile with gastric erythema was noted in 22 of the 28 patients. Of these 22 patients, pathology was consistent with bile reflux chemical gastropathy. Common findings included epithelial regenerative changes, foveolar hyperplasia and edema, tortuosity of the surface and foveolar epithelium, thinning of the foveolar epithelium, loss of the columnar shape in epithelial cells, smooth muscle hyperplasia, increased mitosis and nuclear hyperchromasia, and the presence of acute and chronic inflammatory cells. *Helicobacter pylori* was not reported in any cases.

All patients had attempted a proton pump inhibitor. Twelve of the patients with remnant gastropathy were managed on a proton pump inhibitor alone, but it was given as omeprazole capsules opened into a spoon of applesauce to optimize absorption. Subsequently, the next ten remnant gastropathy patients were started on ursodiol 500mg po BID after histology results returned. Of the ursodiol group, 8/10 (80%) patients reported substantial improvement or resolution of abdominal pain at clinical follow-up, between 3 and 6 months after starting ursodiol. Of the three ursodiol group patients who had subsequent examination of the gastric remnant, all had endoscopic and histologic resolution of gastropathy. Of the patients with remnant gastropathy who received proton pump inhibitor alone, 1/12 (8.3%) reported improvement in abdominal pain at clinical follow-up at 3–9 months ($p=0.002$). Of these patients, two had repeat examination of the gastric remnant, and both had persistent remnant gastropathy. None of the 6 patients without remnant gastropathy on initial evaluation experienced resolution of symptoms on clinical follow-up. No adverse events or intolerances were reported, and no patients discontinued therapy.

Discussion

The diagnosis of chronic abdominal pain in Roux-en-Y patients can be challenging. A variety of tools with various degrees of invasiveness are available to help determine the correct etiology. Cross-sectional imaging can be useful to rule out internal hernia or mesenteric defects. Upper endoscopy can rule out causes for pain in the esophagus and gastric pouch, such as marginal ulceration. These tests should be performed; if they are unremarkable, however, the workup of persistent pain can lead to increasingly invasive testing including abdominal exploration with or without lysis of adhesions.

In these cases, device-assisted enteroscopy may be considered for examination of the gastric remnant. This is particularly important in the setting of heme positive stools, or iron deficient anemia, without a clear etiology. However, device-assisted enteroscopy is challenging, time-consuming, and associated with adverse events such as perforation and pancreatitis. Additionally, specialized equipment and expertise are required. Empiric treatment for bile reflux chemical gastropathy offers patients the potential to avoid invasive testing. However, in patients with concerning findings in addition to chronic abdominal pain, such as anemia thought to be due to a gastrointestinal source, weight loss, or family history of gastric cancer, device-assisted enteroscopy remains an important diagnostic tool. Additionally, *Helicobacter pylori* should be eradicated if present. Testing for this organism

in patients with gastric bypass is best performed using either stool antigen, off PPI for two weeks duration, or serologic antibody testing.

Although the histologic findings were reported as bile gastropathy or chemical gastropathy in this series, these entities are identical, and distinguished primarily by history. Anatomic changes that result from RYGB surgery can lead to the pooling of bile in the gastric remnant. Bile acids have a surfactant effect in order to enable lipid absorption, however, they may have a cytotoxic effect at high concentrations^{7,8}. The hydrophobicity of bile acids correlates with their cytotoxicity⁹. Although bile is one of several components of biliopancreatic secretions that reflux into the gastric remnant, studies have shown that bile is most significant for damaging the gastric mucosa and disrupting the gastric mucosal barrier¹⁰. Nevertheless, presence of pancreatic enzymes, pH, bile salt concentration, and type of bile salts are also thought to effect the toxicity of the fluid. The blind gastric remnant in RYGB patients allows stasis of bile for long periods, resulting in protracted contact. Additionally, stasis at a higher pH allows bacteria to convert bile salts to unconjugated bile acids, which are more injurious to the gastric mucosa⁶.

Ursodiol, or ursodeoxycholic acid, is a secondary bile acid that competitively displaces more irritating bile acids. It does not prevent the pooling of bile in the gastric remnant; however, it changes the relative concentrations of caustic bile acids, and with time promotes mucosal healing. Ursodiol has been used for treatment of bile acid gastropathy, often in patients with a Billroth II reconstruction. Ursodiol has proven safe in long-term use, and is generally well-tolerated¹¹. As the medication changes the character of bile, allowing gastritis to heal, the efficacy will not be immediate. In this study, the majority of patients had resolution of abdominal pain after 3 months. Ursodiol is likely more effective than agents that rely on mucosal coating as part of their mechanism of action, as the remnant stomach in RYGB patients is no longer in direct contact with food or ingested medications.

RYGB patients with chronic pain of unclear etiology, in this series, were likely to have remnant gastropathy. Of those patients with biopsy-confirmed chemical gastropathy, there was a significantly higher rate of abdominal pain resolution with ursodiol treatment compared to PPI alone. Additionally, there was endoscopic, and histologic improvement in most patients treated with ursodiol who received repeat endoscopic evaluation. It is possible that pooled bile is a contributory factor, amongst other inciting factors. However, the exact pathophysiology in the development of remnant gastropathy is unclear, and this may be important as discontinuation of therapy is being considered. We have recently started to wean patients from ursodiol when they reach one symptom-free year.

This study reports remnant gastropathy due to bile reflux as a treatable cause of chronic abdominal pain in RYGB patients. This was confirmed on pathology and reversed with ursodiol treatment, with resolution of symptoms. These findings suggest that ursodiol should be considered for empiric treatment in Roux-en-Y patients with chronic abdominal pain not explained by standard evaluation.

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Figure 1.
Endoscopic view of remnant gastropathy due to bile reflux

Figure 2.
Histologic view of gastric remnant biopsy consistent with bile gastropathy