

# Gastric Bypass

## Why Roux-en-Y? A Review of Experimental Data

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**Objective:** To highlight the clinical and experimental rationales that support why the Roux-en-Y limb is an important surgical principle for bariatric gastric bypass.

**Data Sources:** We reviewed PubMed citations for open Roux-en-Y gastric bypass (RYGBP), laparoscopic RYGBP, loop gastric bypass, chronic alkaline reflux gastritis, and duodenoesophageal reflux.

**Study Selection:** We reviewed clinical and experimental articles. Clinical articles included prospective, retrospective, and case series of patients undergoing RYGBP, laparoscopic RYGBP, or loop gastric bypass. Experimental articles that were reviewed included in vivo and in vitro models of chronic duodenoesophageal reflux and its effect on carcinogenesis.

**Data Extraction and Synthesis:** No formal data extraction was performed. We reviewed published opera-

tive times, lengths of stay, and anastomotic leak rates for laparoscopic RYGBP and loop gastric bypass. For in vivo and in vitro experimental models of duodenoesophageal reflux, we reviewed the kinetics and potential molecular mechanisms of carcinogenesis.

**Conclusions:** Recent data suggest that laparoscopic loop gastric bypass, performed without the creation of a Roux-en-Y gastroenterostomy, is a faster surgical technique that confers similarly robust weight loss compared with RYGBP or laparoscopic RYGBP. In the absence of a Roux limb, the long-term effects of chronic alkaline reflux are unknown. Animal models and in vitro analyses of chronic alkaline reflux suggest a carcinogenic effect.

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**T**HE OBESITY EPIDEMIC IN THE United States has brought about much interest in bariatric surgery. Data from the National Health and Nutrition Examination Survey (NHANES) suggest that 32% of adults in the United States are obese, with obesity defined as a body mass index (calculated as weight in kilograms divided by height in meters squared) of 30 or greater.<sup>1</sup> Most concerning is the observation that the number of overweight children in the United States has significantly increased in the past 6 years, from a prevalence of 14% (1999-2000 NHANES data) to 18% (2003-2004 NHANES data).<sup>1</sup> The number of bariatric surgical procedures has dramatically increased during a similar time frame, from 13 000 in 1998 to 103 000 in 2003.<sup>2</sup>

### See Invited Critique at end of article

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Surgical procedures for the treatment of morbid obesity have undergone several iterations since loop gastroenteros-

tomy was introduced by Mason and Ito in 1967.<sup>3</sup> Prospective studies have demonstrated that Roux-en-Y gastric bypass (RYGBP), performed by either open or laparoscopic means, is an effective therapy for morbid obesity. Conventional RYGBP can be performed with minimal morbidity, allows for weight loss of approximately 60% of calculated excess body weight at 5 years, and can alleviate comorbid conditions such as diabetes mellitus, hyperlipidemia, hypertension, and obstructive sleep apnea.<sup>4,5</sup>

### LOOP GASTRIC BYPASS

In the original laparoscopic loop gastric bypass only 1 anastomosis was performed, leading to a faster and perhaps safer procedure than the RYGBP. As shown in **Figure 1**, a laparoscopic loop gastric bypass involves the creation of a gastric pouch in the shape of a tube by dividing the stomach at the junction of the body and the antrum, parallel to the lesser curve.<sup>7</sup> A loop of jejunum is then anastomosed to the gastric pouch. Rutledge and

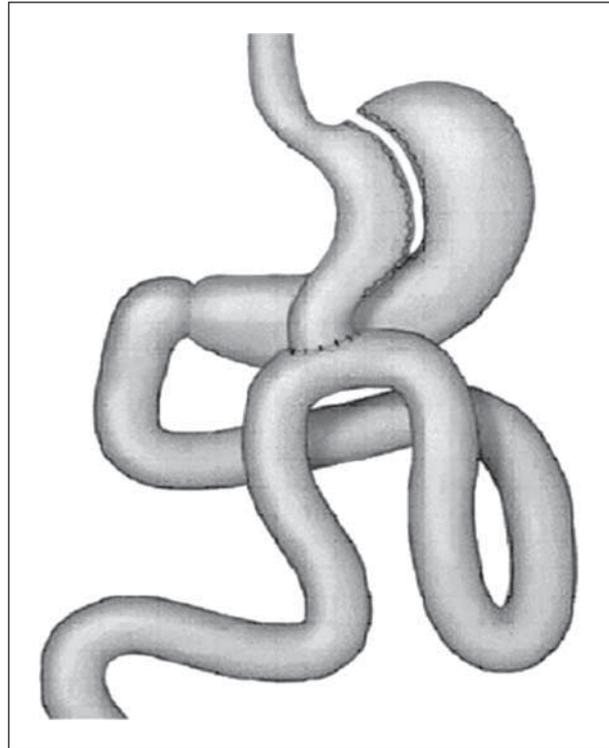
Walsh<sup>6</sup> provide a 6-year follow-up of 2410 patients who underwent loop gastric bypass. These researchers report a mean preoperative body mass index of 46, a mean operative time of 37.5 minutes, and conversion to open mini-gastric bypass in 0.17% of cases. Their average length of stay was 1.4 days, and their anastomotic leak rate was 1.08%. The authors note that these data are comparable with those reported by other high-volume centers that perform laparoscopic RYGBP. For example, Higa et al<sup>4</sup> provide data from their series of 1500 consecutive laparoscopic RYGbps, reporting an average operating time of 60 minutes, a length of stay of 1.4 days, and no cases of anastomotic leak.

### THE LOOP GASTRIC BYPASS CONTROVERSY

Critics of loop gastric bypass call into question the effect of chronic alkaline reflux gastritis and cite previous complications associated with other loop gastrojejunostomies, such as Mason loop gastric bypass.<sup>8</sup> Mason loop gastric bypass involves a pouch that is horizontal and contains a considerable amount of fundus. Proponents of loop gastric bypass defend the approach by citing data from Deitel et al,<sup>9</sup> who examined the effect of vertical banded gastroplasty on lower esophageal sphincter tone. These authors found that vertical banded gastroplasty improved the resting pressure of the lower esophageal sphincter when patients were studied 13 weeks after surgery. Rutledge and Walsh<sup>6</sup> drew a similar conclusion for their vertical gastric tube, although no data are provided that lower esophageal sphincter pressures have ever been seen in patients undergoing laparoscopic loop gastric bypass. Because patients with vertical banded gastroplasty typically develop gastroesophageal reflux months to years after their procedure, the durability of this effect on lower esophageal sphincter tone is questionable. Some patients who undergo loop gastric bypass develop symptomatic bile reflux gastritis and esophagitis, necessitating conversion to RYGBP.<sup>10</sup> In addition, historical cohorts demonstrate an increased incidence of gastric cancer in patients with gastric and duodenal ulcers undergoing partial gastrectomy and loop gastrojejunostomy.<sup>11</sup>

### ANIMAL MODELS OF ESOPHAGEAL CANCER

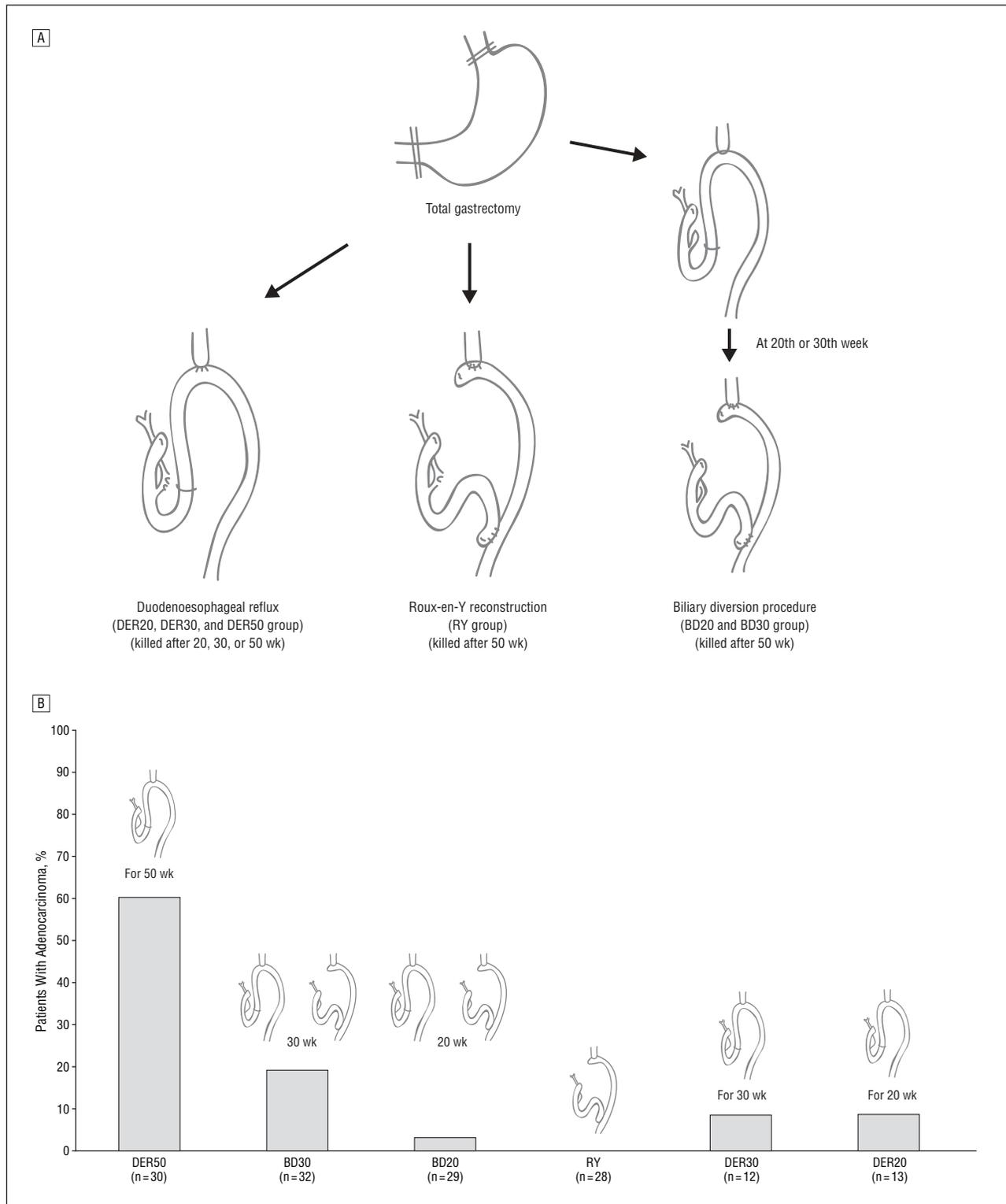
Although loop gastric bypass seems to possess the attractive qualities of a successful weight loss operation, it is worrisome that the anatomical configuration of the bypass is similar to that in animal models of esophageal cancer. Much of our understanding of the pathogenesis of esophageal intestinal metaplasia and the subsequent development of adenocarcinoma is derived from rat models of surgically induced duodenoesophageal reflux. Attwood et al<sup>12</sup> demonstrated that surgically induced duodenoesophageal reflux plus the ingestion of the carcinogen 2,6-dimethylnitrosomorpholine or methyl-N-amylnitrosamine in rats produced distal esophageal adenocarcinomas. Because the ingestion of these carcinogens in rats had previously been known to cause esophageal squamous carcinomas, the shift to adenocarcinomas in



**Figure 1.** Mini-gastric bypass. The stomach is divided vertically along the lesser curvature, against a 28F bougie. Loop gastrojejunostomy is then performed approximately 180 cm from the ligament of Treitz. Reprinted with permission from *Obesity Surgery*.<sup>6</sup>

the presence of duodenal contents suggested an interesting role for bile in the pathogenesis of esophageal adenocarcinoma. Several research groups<sup>13,14</sup> have subsequently demonstrated that esophageal reflux of duodenal contents alone, without any adjuvant carcinogens, is sufficient for the development of esophageal cancers. Miwa et al<sup>13</sup> established duodenoesophageal reflux by means of an anastomosis between the duodenum and the fore-stomach, yielding distal esophageal cancers in 36% of animals after 50 weeks of observation. Fein et al<sup>14</sup> similarly noted esophageal adenocarcinomas in 48% of rats 16 weeks after esophagojejunal anastomosis. Nishijima et al<sup>15</sup> expanded on these observations by examining the protective effects of a Roux-en-Y esophagojejunal anastomosis in the pathogenesis of the progression of Barrett esophagus to invasive adenocarcinoma. As shown in **Figure 2**, biliary diversion with a Roux-en-Y anastomosis significantly prevents the development of esophageal adenocarcinoma in rats that had previously undergone esophagojejunostomy either 20 or 30 weeks earlier. In this study, none of the rats that underwent Roux-en-Y esophagojejunal anastomosis developed Barrett metaplasia or carcinoma.

These well-described rat models of esophageal cancer demonstrate that reflux of duodenal contents is sufficient for producing esophageal cancer in rats. The exact pathogenesis is unclear, although it seems that the reflux of soluble bile acids in a neutral milieu results in severe esophagitis. Inflammation, ulceration, and hyperproliferative changes to the squamous epithelium of the esophagus precede the development of carcinoma.<sup>16</sup> These



**Figure 2.** Biliary diversion (BD) with a Roux-en-Y esophagojejunal anastomosis (RY) prevents adenocarcinoma in a rat model of duodenoesophageal reflux. A, Animals underwent total gastrectomy, followed by either duodenoesophageal anastomosis (DER) or RY. Subsets of animals in the DER group were converted to RY at 20 and 30 weeks. B, Sixty percent of animals (18 of 30) exposed to duodenoesophageal reflux for 50 weeks developed esophageal adenocarcinomas, whereas no cancers were observed in animals protected with an RY (0 of 28). Reprinted with permission from *Annals of Surgery*.<sup>15</sup>

cancers in the rat model were also shown to be phenotypically similar to human esophageal cancer at the histologic and molecular levels.<sup>17</sup> Animal models of esophagojejunal reflux demonstrate up-regulation of the caudal-

related homeobox gene *Cdx2* in Barrett epithelium, a transcription factor that regulates intestine-specific protein expression.<sup>18</sup> In vitro studies also demonstrate that the bile acids cholic and deoxycholic acid dose-

dependently increase *Cdx2* promoter activity and protein production in cultured rat esophageal keratinocytes. Forced expression in *Cdx2* in this same cell line also drove the production of *MUC2*, an intestinal-type mucin. These data suggest an important role for bile acids in the pathogenesis of esophageal intestinal metaplasia. Experimental data also suggest a mitogenic role for bile salts in esophageal neoplasia. Numerous studies<sup>19-21</sup> demonstrate that bile salts activate proliferative and anti-apoptotic pathways in benign native esophageal epithelial explants, Barrett epithelial cell lines, and esophageal adenocarcinoma cell lines.

None of the published studies on rat models of esophageal cancer are identical to the anatomical configuration of loop gastric bypass. The various rat models of esophageal carcinoma described herein suggest that the presence of soluble bile acids in the esophageal refluxate is required for tumor formation. Although no data are available after loop gastric bypass, it is well described that bile acid content and the incidence of gastritis are much greater after loop gastroenterostomy for the management of morbid obesity. McCarthy et al<sup>22</sup> performed endoscopy in 28 patients who had undergone loop gastroenterostomy, loop gastroenterostomy plus diverting enteroenterostomy between the afferent and efferent loops, or Roux-en-Y gastroenterostomy. Total bile acid levels in the gastric pouch were 2080.1 µg/mL (to convert to micromoles per liter, multiply by 2.448) in patients who had undergone loop gastroenterostomy alone compared with 165.0 µg/mL in patients who had undergone Roux-en-Y anastomosis. Moreover, the incidence of gastritis by endoscopy was only 13% in the Roux-en-Y group compared with 71% in the loop gastroenterostomy group. Whether this translates into a greater incidence of reflux esophagitis is unknown. Moreover, the chronic effects of esophageal bile reflux in this subset of patients are unknown because long-term follow-up data are not available.

## SUMMARY

The purpose of this review was to present the experimental data that support the importance of performing a biliary diversion procedure, such as Roux-en-Y, for a proximal gastroesophageal anastomosis. Just as the Food and Drug Administration would call into question any novel therapy that caused cancer in a preclinical animal model, we should proceed with the same degree of caution for any operation. Laparoscopic loop gastric bypass is technically easier than RYGBP because it requires only 1 anastomosis. However, there is a real risk of bile reflux due to the loop configuration that may have long-term damaging effects to the gastric pouch and possibly the distal esophagus. It may take years before clinically significant complications of bile reflux become apparent to the patient or the physician.

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