REVIEW

Impact of obesity treatment on gastroesophageal reflux disease

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Abstract

Gastroesophageal reflux disease (GERD) is a frequently encountered disorder. Obesity is an important risk factor for GERD, and there are several pathophysiologic mechanisms linking the two conditions. For obese patients with GERD, much of the treatment effort is focused on weight loss and its consistent benefit to symptoms, while there is a relative lack of evidence regarding outcomes after novel or even standard medical therapy is offered to this population. Physicians are hesitant to recommend operative anti-reflux therapy to obese patients due to the potentially higher risks and decreased efficacy, and these patients instead are often considered for bariatric surgery. Bariatric surgical approaches are broadening, and each technique has emerging evidence regarding its effect on both the risk and outcome of GERD. Furthermore, combined anti-reflux and bariatric options are now being offered to obese patients with GERD. However, currently Roux-en-Y gastric bypass remains the most effective surgical treatment option in this population, due to its consistent benefits in both weight loss and GERD itself. This article aims to review the impact of both conservative and aggressive approaches of obesity treatment on GERD.

Key words: Obesity; Gastroesophageal reflux disease; Fundoplication; Sleeve gastrectomy; Gastric banding; Gastric bypass

Core tip: Obesity and gastroesophageal reflux disease (GERD) have a well-defined relationship, and both the medical and surgical treatment options for both conditions are advancing. However, there is shortage of literature consolidating the effect of obesity treatment on the outcome of GERD. This article aims to detail the evidence behind both standard and novel obesity treatments on the risk and outcome of GERD.

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common condition characterized by the presenting symptoms of heartburn and/or regurgitation. The prevalence of GERD is estimated to be between 10%-20% in the Western world, with a lower frequency in Asia[1].

An important risk factor for GERD is obesity, which has been increasing in prevalence and is strongly associated with adverse metabolic, cardiovascular, chronic inflammatory and malignant health outcomes. Notably, the treatment of obesity remains at the forefront of preventative healthcare.

A variety of non-surgical and surgical obesity treatments can impact the severity and natural history of its associated diseases. This article aims to review the evidence surrounding the epidemiology, pathophysiology and potential impact of obesity treatment on GERD.

PATHOPHYSIOLOGY

Although it has limitations the degree of adiposity in adults can be categorized by the body mass index (BMI) calculation (weight in kilograms divided by height in meters squared). Both overweight (BMI 25-29.9) and obese (BMI $\geqslant$ 30) patients have been shown to be at higher risk for GERD[2,3]. The Nurses' Health Study data demonstrated that incremental weight gain among patients with a normal BMI (18-24.9) is associated with a proportional increased risk for reflux symptoms, whereas weight loss was associated with decreased reflux symptoms. Specifically, the risk of reflux symptoms was linked to the parameter waist-to-hip ratio in a dose-responsive fashion, though BMI itself appeared to be even more closely associated with symptoms than this ratio[3].

Several mechanisms have been postulated to link obesity and the development of GERD. One area of investigation has focused on the anatomic displacement of the esophagus into the chest cavity.

Obese patients are over three times as likely to have hiatal hernias compared to non-obese individuals[4]. Furthermore, after controlling for hiatal hernias, the relationship between BMI and esophagitis was non-significant in one study, suggesting that hiatal hernias mediate the link between obesity and GERD. Hiatal hernias have been linked to obesity-associated reflux symptoms due to the increased intragastric pressure and gastro-esophageal pressure gradients during inspiration, as well as increased axial separation between the extrinsic crural diaphragm and the lower esophageal sphincter (LES) in the setting of an elevated BMI[5,6].

Extrinsic gastric compression from increased visceral adiposity in overweight and obese patients may also lead to increased intragastric pressure and thus a favorable pressure gradient for reflux to occur[6]. Obese patients have been reported to have higher rates of esophageal motility disorders and bolus transit impairments compared to normal BMI patients with GERD[6,7].

Mechanisms leading to an increased prevalence of GERD in obese patients may also differ according to gender. Although questionnaire-based studies have reported similar GERD symptoms between men and women, one study using pH monitoring reported that women secrete less gastric acid and tend to have less physiologic reflux compared to men[8,9].

The effect of estrogen on GERD has been examined, as estrogen increases the synthesis of nitric oxide, a vasodilator leading to smooth muscle relaxation that can include the LES[10]. The effect of hormone replacement therapy (HRT) on GERD has been analyzed in several studies, specifically estrogen versus combined estrogen and progesterone. Historically, progesterone treatment was linked to GERD, but recently it was demonstrated that estrogen only HRT was more strongly associated with GERD symptoms than was combined estrogen and progesterone treatment[10,11]. However, when analyzing the impact of naturally occurring sex hormones on GERD among individuals not on HRT, it was found that sex hormone levels in both pre- and post-menopausal women and excess acid exposure were not associated once age and BMI were taken into account[12]. The authors in this study concluded that another mechanism, such as increased intragastric pressure associated with a higher BMI, better explains the sex hormone-BMI-GERD dynamic. The authors further concluded that the increased rates of GERD in pregnant patients may in fact not be due to increased sex hormone levels but rather the increased transmitted gastric pressure from the enlarged uterus[12].

While fewer studies have looked at differences among ethnicities, Corley and authors found that the correlation between BMI and reflux symptoms was highest in whites and lower in blacks or Asians. The authors suggested that differential patterns of visceral adiposity among ethnicities along with differences in *Helicobacter pylori* prevalence could also explain the findings[13].

Adipokines have also been an important area for research on GERD and obesity, with increasing interest in ghrelin and leptin. Ghrelin, an orexigenic hormone, acts in the arcuate nucleus of the hypothalamus by activating neuropeptide Y (NPY) and agouti-related peptide (AgRP) neurons, leading to increased food intake[14]. The adipose tissue-derived hormone leptin is produced in proportion to fat stores. Circulating leptin serves to communicate the state of body energy repletion to the central nervous system in order to suppress food intake and permit energy

expenditure[15].

In a study comparing rats with surgically-induced GERD to those with sham operations, the rats with GERD had significantly decreased food intake and body weight, despite having significantly increased levels of ghrelin[16]. Even with repeated administration of acyl ghrelin, GERD rats had no improvement in food intake or body weight, suggesting that GERD rats may need a higher level of exogenous ghrelin for its predicted effect. The authors concluded that aberrantly increased secretion of peripheral ghrelin and decreased ghrelin responsiveness may occur in GERD rats. When analyzing the various steps in the orexigenic signaling pathway, the authors also found that while NPY and AgRP mRNA expression in GERD rats was increased, the GERD rats appeared to have dysfunction further along in the orexigenic signaling pathway, potentially leading to suppression of ghrelin signaling. In humans ghrelin has been reported to be positively associated with Barrett's esophagus but inversely associated with GERD symptoms[17].

Leptin has also been implicated in the relationship between obesity and GERD symptoms. In a study on Egyptian patients with GERD, leptin was found to be significantly positively correlated with symptom score severity, weight, BMI, waist circumference, waist-to-height ratio, total abdominal fat, subcutaneous abdominal adipose tissue, and intra-abdominal adipose tissue; yet it was negatively correlated with waist-to-hip ratio[18].

The adipokine adiponectin has been investigated in GERD, because it is secreted from visceral fat and can suppress tissue inflammation. Adiponectin has been shown to be inversely correlated to BMI, and in a study on male patients with and without erosive esophagitis, serum adiponectin levels were found to be lower in patients with erosive disease. The authors concluded that low adiponectin levels may be associated with an increased risk for erosive esophagitis in men[19].

A recent study has also shown a link between nonalcoholic fatty liver disease (NAFLD) and GERD. While NAFLD has a known association with obesity, in this study of 206 outpatients with NAFLD in a single center the prevalence of typical GERD symptoms was higher in these patients compared with controls and independent of BMI[20]. The authors postulated that higher serum levels of certain cytokines found in patients with NAFLD, which can be independent of obesity and also overexpressed in the esophageal mucosa of GERD patients, may help explain the findings. As NAFLD has been proposed as a potential new criterion to define metabolic syndrome and is associated with many of the outcomes of obesity[21], further study on the specific role in NAFLD leading to GERD is warranted.

Overall, while there are several pathophysiologic mechanisms that may explain the risk of GERD in the obese population, both the predisposition for hiatal hernias and direct impact of visceral adiposity remain the most substantiated. Further studies are needed to decipher the influence of adipokines on the development of GERD in this population, as well as the potential differences in the incidence of GERD by gender and ethnicity.

NON-SURGICAL MANAGEMENT OF GERD IN OBESE PATIENTS

Lifestyle modifications have long been paramount to the management of GERD, and while most behavioral factors have not been extensively studied in the obese population, many of the interventions have proven to be effective in both normal weight and obese individuals.

Weight gain and weight loss are associated with an increase and decrease in reflux symptoms, respectively, in both normal and overweight individuals[3,22,23]. One study specifically demonstrated that weight loss *via* dietary advice can improve reflux symptoms in overweight individuals[24].

While not specific to obese individuals, elevation of the head of the bed, left lateral decubitus position, and deep breathing exercises (inducing a change from thoracic to abdominal breathing) are associated with improvement of GERD symptoms[25]. Furthermore, both fruit and fiber consumption in the overall population have been found to be protective against GERD symptoms, yet whether this effect is independent of a patient's BMI has not been evaluated[26,27].

Coffee and caffeine have also been examined for their effects on GERD symptoms. One study has shown that coffee, independent of caffeine, itself may be responsible for the reflux symptoms[28]. Further complicating the potential relationship between coffee, caffeine and a predilection for GERD are two discordant studies showing that coffee either can lower the LES pressure (LESP) or increase it[29,30]. The recommendation to avoid caffeinated beverages is still used routinely in patients with GERD, but whether coffee or caffeine itself is a major factor in the pathophysiology of GERD, particularly in the obese population, remains to be elucidated.

The effect of protein and fat has been studied in both the general and obese population. Protein and dietary fat have been found to have opposite effects on the LES; ingestion of protein increased LESP whereas ingestion of fat decreased LESP[27,31]. Ingestion of total fat, saturated fat, and cholesterol were found to be higher in patients with GERD symptoms than those without symptoms in one study. However, only in patients with a BMI > 25 were high saturated fat, cholesterol, and fat servings associated with GERD symptoms[27]. Dietary fat may have an independent role in the pathophysiology of GERD, particularly in obese people.

In addition to lifestyle changes, a variety of medications are used in the management of GERD. Particularly, antacids, H2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs) are often

necessary to provide as acid inhibition. McDougall *et al*[32] found an association between higher BMI and the requirement of longer-term H2RA or antacid therapy, suggesting that obese patients are not as responsive to these medical treatments. The efficacy of PPIs in obese patients with GERD was not affected by BMI in one study[33], however, another report noted that doubling the dosage of pantoprazole in obese or overweight patients provided better specific control of symptoms, and other studies have corroborated these findings[34-36]. Novel treatments, including CCK inhibitors, GABA agonists, and TCAs are currently being studied for their effects on GERD symptoms, but there is a lack of data on their precise roles in the obese population.

SURGICAL MANAGEMENT

A variety of surgical approaches have been offered in patients with both GERD and obesity, and this section will detail the effects of both sets of approaches in the obese population with GERD.

Fundoplication

Since its advent in 1955, Nissen fundoplication has been used as a surgical approach for GERD. Although there are different variations, the concept of the surgical approach is to emphasize return of the esophagogastric junction into the abdominal cavity by transhiatal mobilization of the esophagus *via* division of the short gastric vessels, achieve complete mobilization of the gastric fundus, and ultimately recreate a high pressure zone at the lower esophageal sphincter. The enveloped portion of the distal esophagus then is compressed as intragastric pressure and volume increase, thereby preventing reflux[37].

Nissen fundoplication is associated with acceptable outcomes in non-obese patients, with good symptom control on medical therapy as well as those with only partial response to PPIs. There have been consistent data showing less esophageal acid exposure and significantly increased LES pressure after surgery, and a trend towards superiority in other measures of outcome, such as quality of life, when compared to medical therapy[38-40]. Fundoplication is considered a long-term treatment option on par with medical therapy in patients with typical symptoms of GERD. However, it is generally not recommended in patients who are PPI non-responders as the long-term benefits are not expected to outweigh risks and side effects in this group[1].

While a higher complication or failure rate after fundoplication is expected in obese patients due to higher abdominal pressure and the influence of other comorbid conditions, the preponderance of evidence has not clearly shown this to be true. Notably, there is a relatively small body of evidence suggesting a greater proportion of obese and overweight patients have recurrent reflux after Nissen fundoplication

compared to normal weight patients[41,42].

However, the balance of evidence supports that outcomes do not differ greatly between obese and normal weight individuals. Fraser *et al*[43] reported in a review of 194 patients that postoperative heartburn scores were significantly higher in a normal weight group compared to overweight and obese patients. This subjective finding was supported by objective data collected in several different studies[44-46]. A study conducted in Australia demonstrated no statistically significant difference in gastrointestinal quality of life index and symptom grading, with improvements in typical and atypical reflux symptoms for normal weight and obese individuals. In addition, both groups exhibited increased LES pressures, significantly decreased acid reflux events seen on 24-h ambulatory multichannel intraluminal impedance (MII), and significantly decreased DeMeester scores, one year after surgery, without statistical difference between the two groups. Postoperative complications and the requirement for later surgical revision were not influenced by the preoperative weight[47]. A similar study with a follow up period of average 41.5 mo demonstrated that the above findings may persist long-term[48]. A cohort study of 312 patients further emphasized that there was no difference in outcomes in obese patients undergoing fundoplication, with the exception of poorer outcomes seen in the morbidly obese (BMI > 35)[49].

Although there is limited evidence suggesting that obesity diminishes the efficacy of Nissen fundoplication, several relevant factors have been discussed in the literature that may impede the outcome of the procedure. Firstly, obesity can create several technical difficulties resulting in surgical failure of laparoscopic approaches. For instance, an enlarged left lobe of the liver can interfere with visualization of the hiatus. Fatty deposition at the esophagogastric junction can also impede accurate suture placement. Lastly, a thick abdominal wall may hinder manipulation of laparoscopic instruments.

However, Perez *et al*[41] showed that laparoscopic versus transthoracic approaches did not differ in their failure rates, suggesting that perhaps the root cause of failures lies in the breakdown of a surgical repair rather than a failure to construct a properly functioning anti-reflux barrier at the time of surgery. Other studies suggest that herniation of the fundoplication is the most common mechanism of failure after laparoscopic Nissen fundoplication[50].

In addition, intra- and post-operative complications have been found to be higher in patients with a higher BMI undergoing fundoplication. These complications included hemorrhage, perforation, pneumothorax, fundoplication herniation, infection, and gastric ulcer[51]. This may be a reflection of higher number of comorbid conditions often found in obese patients, and also a result of longer operating times[46].

Ultimately, the results of Nissen fundoplication in

the obese population are not as positive as in normal weight patients. While there are many studies with comparable outcomes in patients of all weight groups, the favored recommendation is that obese patients with GERD should consider other surgical options[1] as will be discussed in the sections to follow. If fundoplication is chosen, the general recommendation is to advise significant weight loss with diet and behavioral modification before fundoplication, in order to minimize adverse outcomes of surgery due to obesity comorbidities.

In the recent years, new data regarding an endoscopic approach to fundoplication has emerged. Transoral incisionless fundoplication (TIF) was developed in an attempt to achieve the benefits of fundoplication without the risks of laparoscopic surgery. A randomized controlled trial comparing TIF and PPI showed promising results in the short term with improved quality of life and pH normalization, but failed to display long-term objective reflux control[52]. Alternatively, Testoni *et al*[53] reported encouraging long-term results following 50 patients prospectively for up to six years after TIF showing lasting symptom relief and decreased reflux on pH-impedance monitoring. More data regarding long term efficacy of this approach is needed, as well as specific data regarding feasibility and efficacy of TIF in obese patients.

Bariatric surgery - sleeve gastrectomy

Sleeve gastrectomy was first developed in 1988 as the restrictive part of the restrictive and malabsorption operation known as biliopancreatic diversion/duodenal switch. Since its development, the sleeve gastrectomy has gained popularity worldwide as a primary bariatric operation, earning official endorsement by the American Society for Metabolic and Bariatric Surgery in 2012 as an effective standalone treatment option for obesity. Its increasing popularity as a single, definitive procedure for weight loss is based on its success, relative ease of operation, and low complication profile. This surgical approach uses a large French nasogastric tube as a guide to staple off and resect a majority of the gastric body which serves as a reservoir, leaving a gastric tube, or sleeve, with a narrow width from the pylorus to the incisura angularis[54]. The potential advantages of sleeve gastrectomy include immediate restriction of caloric intake, the lack of a need for placement of a foreign body or requirement for adjustments post-operatively, and it is generally a simpler procedure than bypass with a shorter operating time[55].

There is significant data in a variety of studies showing the new development of GERD after sleeve gastrectomy in patients without GERD pre-operatively. *De novo* GERD symptoms have been experienced by 8.6%-47% of patients by symptom criteria[56-58]. By endoscopic measures in a study at least one year after surgery, *de novo* erosive esophagitis was found

in 63.6% of 55 patients without such evidence prior to operation[57]. Esophageal acid exposure measured on pH-metry also significantly increased in two studies[59,60].

While the majority of the evidence points toward a higher prevalence of GERD after sleeve gastrectomy, a few studies show some improvement or at least maintenance of the same level of pre-existing GERD. Two small studies by Melissas *et al*[61,62] reported no change or a decrease in GERD after sleeve gastrectomy. A few other studies corroborate these findings, with small potential improvement in GERD[63,64]. In a series of studies, Himpens *et al*[65,66] showed a biphasic pattern of GERD prevalence after sleeve gastrectomy, with 21.8% *de novo* PPI use one year after sleeve gastrectomy, which improves to 3.1% at three years, but increases again to 23% at six year follow up.

There are several pathophysiologic mechanisms of sleeve gastrectomy that can theoretically alter the quantity and severity of gastroesophageal reflux postoperatively. Sleeve gastrectomy can promote less GERD by reversal of the weight and visceral adiposity. There is also the potential for increased gastric emptying, thereby decreasing stomach pressure and reducing GERD[61]. Furthermore, as a large part of the fundus is resected during sleeve gastrectomy, this results in removal of the majority of the parietal cells of the stomach.

However, there are multiple factors that may explain the worsening of GERD after sleeve gastrectomy. First is the alteration of the angle of His, the acute angle between the esophagus and the cardia of the stomach, which normally acts as a valve to prevent reflux of stomach contents into the esophagus. This angle is often blunted during surgery, which can lead to immediate appearance of GERD in previously asymptomatic patients. Himpens *et al*[65,66] showed that after three years, the rate of GERD after sleeve gastroectomy decreased, potentially due to restoration of the angle of His evidenced on barium swallow at follow up.

LES dysfunction can also occur after sleeve gastrectomy. With transection near the angle of His during gastrectomy, the sling fibers at the fundus are divided, which can subsequently decrease LES pressure. Braghetto and Burgerhart have each reported a significant decrease in LES pressure after sleeve gastrectomy[59,67]. By resecting a large portion of the stomach, sleeve gastrectomy results in a narrow sleeve, with significantly decreased gastric compliance[65]. This decreased compliance can lead to relative stasis in the proximal remnant, provoking an increase of transient LES relaxation[68], further allowing reflux to occur.

A further anatomic change observed after sleeve gastrectomy is hiatal herniation. One study showed that the prevalence of hiatal hernias increased significantly (6.1% to 27.3%) following sleeve gastrectomy[57]. Another study reported that a significant number of

patients had migration of the proximal sleeve above the level of the hiatus after sleeve gastrectomy on CT[69]. In both instances the influence of the diaphragm on LES tone is lessened, leading to decreased LES overall pressure[70].

In an effort to avoid fistulas, surgeons can also leave excess fundus at the time of operation, which then results in a sleeve-tube with a conical rather than cylindrical shape. In combination with a relative distal downstream stenosis, a "neofundus" or proximal dilation of the postoperative stomach can form. The formation of a neofundus has been associated with both weight regain and GERD[66] possibly due to the neofundus serving as a reservoir for food, gastric stasis and increased acid production[70]. Keidar *et al*[71] reported a correlation between formation of neofundus, as seen on barium swallow studies, with severe gastroesophageal dysmotility and reflux after sleeve gastrectomy. The development of neofundus later on may explain the second peak of GERD symptoms seen by Himpens *et al*[65,66] at six year follow up after interim improvement of GERD at three years.

In addition to anatomic changes, it is theorized that alteration in gastric motility can influence reflux. As the majority of the fundus is excised in sleeve gastrectomy, there are decreased levels of ghrelin after sleeve gastrectomy[70]. This may explain the slowed gastric emptying seen one year after sleeve gastrectomy[65]. However, Melissas *et al*[61,62] have repeatedly shown acceleration in emptying up to two years after the operation, thought to be due to absence of receptive relaxation of the excised fundus.

Although sleeve gastrectomy is now considered an effective weight loss surgery[72] due to the consistent data regarding development and worsening of GERD in patients with and without pre-existing reflux preoperatively, it generally is not recommended in patients with GERD and obesity as a first-line option[1].

Bariatric surgery - gastric banding

Laparoscopic adjustable gastric banding, introduced officially in 1993, is one of the most frequently performed surgical procedures to treat obesity worldwide. It is relatively simple to perform, minimally invasive, and easily adjustable. A major benefit of this procedure is its low reported complication rate[73], as it does not involve any excision or anastomosis. Using a laparoscopic approach, an inflatable donut shaped band is positioned around the proximal stomach and connected to a port reservoir that is fixed to the sternum. Subsequently, the band is filled with saline, creating a small gastric reservoir above the band, ensuring early satiety and reduced food intake. The volume of the inflation can be adjusted during follow up to balance food intake reduction with adverse effects such as solid food intolerance[74]. The adjustable nature of the band is considered an advantage as it allows physicians to change the gastric volume in response to side effects or degree of weight loss[75].

A review of the current literature on gastric banding shows a pattern of short term improvement of GERD after gastric banding which can reverse course to an eventual worsening of GERD.

The short term data show a decrease in the use of PPI in 83% of patients with pre-existing GERD prior to undergoing gastric banding in one study, albeit only in six patients[65]. This finding is corroborated by other studies that found 76%-80% of patients with preexisting GERD had full resolution of their symptoms beginning as soon as three weeks after surgery, and lasting up to two years[76,77]. Other studies have shown objectively that there is a complete resolution of all esophageal lesions by one year follow up[78], reduction of total number of reflux episodes, total reflux time, and DeMeester score in 19 mo[79], and decrease in pathologic reflux six months after gastric banding[80].

Although there is some symptom data supporting improvement of pre-existing GERD after three years[65,78], a more significant portion of the available literature suggests a relapse in GERD postoperatively after several years. Measured by the regular use of PPIs, Himpens *et al*[65] record 20.5% of *de novo* GERD by three years post-op. In a study by Gutschow with frequent follow up out to 84 mo after gastric banding, one year marked the pivotal point after which the initial improvement of pre-existing heartburn symptoms reversed. At three to four years after gastric banding, pathologic reflux rates became significant on endoscopy and with pH-metry[81].

The anti-reflux effect of the band is thought to be related to augmentation of the LES by creating a longer intraabdominal pressure zone, as well as prevention of hiatal herniation by creating a physical barrier below the diaphragm[80]. However, this is likely ultimately outweighed in the majority of patients by several potential negative effects of the band on esophageal reflux disease.

The incidence of esophageal dilation after gastric banding is significant and can worsen GERD postoperatively. Although one study showed no correlation to percent excess weight loss, the majority of the patients with esophageal dilation after banding were symptomatic with emesis and GERD-like symptoms[82]. It is thought that the inflated band reduces transstomal flow by narrowing the esophageal outlet, leading to reduced esophageal clearance, stasis of ingested food and refluxed material, and exerting physical expansion of the distal esophagus. Another plausible mechanism of esophageal dilation is through incomplete LES relaxation and increased LES pressures, which causes impairment of esophageal body function and esophageal dilation. The finding that deflation or removal of the gastric band reverses the dilation implicates the band as a causative factor in esophageal dilation[83]. Klaus *et al*[84] discovered in a prospective cohort study that those patients who remained symptomatic from GERD after gastric banding had a significantly poorer esophageal body motility preoperatively, suggesting that pre-

operative esophageal dysmotility may aggravate GERD postoperatively. Lastly, cases of complete esophageal aperistalsis, or pseudoachalasia, have been reported in six patients who were referred for dysphagia or heartburn after gastric banding, and were shown to be only potentially reversible with deflation or removal of the band[85]. Overall, esophageal dysmotility, a relatively common postoperative complication from laparoscopic banding, can either worsen GERD or symptoms suggestive of the illness.

Pouch formation after gastric banding has also been found to be a major determinant in pathologic reflux, esophagitis, and use of antireflux medication. Inaccurate placement of the band is thought to be the primary cause of early pouch dilation, *via* tunneling of the band through the omental bursa and subsequent migration[80]. Late pouch dilation, however, is likely the result of inclusion of fundus above the band, and eventual dilation of the proximal pouch. Unlike esophageal dilation, pouch formation is often irreversible with deflation of the band, and can lead to dangerous complications such as infarction of the dilated pouch. The mechanism through which an enlarged proximal pouch causes increased reflux is similar to the mechanism of hiatal hernias, in which a reservoir for holding ingested food is created, causing frequent regurgitation[86]. Due to the tight stenosis created by the band, refluxate can follow the path of least resistance into the esophagus[87].

Given the current data on increased adverse outcomes in the long term with laparoscopic adjustable gastric banding, which include GERD, as well as the high rate of reoperation or conversion to a more definitive bariatric surgery, the procedure is expected to be less utilized going forward[86,88] Specifically, obese patients with GERD or esophageal dysmotility should be cautioned on receiving this form of bariatric surgery.

Bariatric surgery - gastric bypass
The gastric bypass, developed many decades ago, originally consisted of a horizontal partitioning of the upper stomach for gastric capacity reduction *via* pouch formation, ultimately in a Roux-en-Y reconstruction. Pouch formation is typically achieved by partial or complete division of the upper stomach at the staple line, and the proximal portion of the stomach is connected to the proximal jejunum as a gastrojejunostomy, allowing ingested nutrients to be transmitted through the tract in the absence of bile and pancreatic juice. This limb is distally anastomosed to the biliopancreatic limb, at which point the nutrient stream, bile, and pancreatic secretions come together[89]. The weight loss effect of gastric bypass surgery is a combination of the restrictive effect of a small gastric pouch and impedance of absorption of nutrients due to the small bowel bypass. Roux-en-Y gastric bypass (RYGB) is still the most utilized form of bariatric surgery despite its complex surgical technique and potential complications, due to its excellent

outcomes in weight loss.

The outcome of GERD in patients who undergo RYGB is generally positive. Symptom resolution or improvement has been reported in the vast majority of patients in several studies[90-93]. One study looking at 55 patients with preoperative GERD showed that no patients had aggravation of their disease, while 96% showed improvement or resolution of symptoms[93]. Esophageal acid exposure, esophagitis, percent time at esophageal pH < 4, number of reflux episodes, number of reflux episodes lasting > five minutes, and DeMeester score have all shown to be significantly better in short and long term studies up to 39 mo[92,94]. Frezza *et al*[95] demonstrated that in addition to typical symptoms, atypical symptoms of GERD, such as wheezing, laryngitis, and aspiration, which are often refractory to conventional medical therapy, were also improved after RYGB, with lasting effects at three year follow up.

The positive effect on GERD after RYGB stems from various factors relating to the new anatomy after surgery. First, a significant elimination of acid production in the gastric pouch is achieved *via* division of the stomach at a very proximal level. The cardia region of the stomach, where the pouch is created, has been shown to relatively lack parietal cells[95]. Smith *et al*[96] have shown a virtually absent basal and stimulated gastric acid secretion in the gastric pouch after bypass, lending credibility to this theory. Additionally, the volume of the gastric pouch created in Roux-en-Y is small, averaging 20-30 cc[89], minimizing any reservoir capacity to promote regurgitation. Importantly, bile reflux is also eliminated due to biliary diversion.

In the advent of less invasive, endoluminal approaches to bariatric procedures without risk of anastomotic leaks and major operative complications, whether RYGB will still outcompete other treatment options remains to be investigated. Notably, the laparoscopic greater curvature plication, although still considered investigational at the present time, is gaining recognition. The benefits of this approach are its technical simplicity and low complication rate, due to the absence of anastomotic lines and risk of leak from staple lines. No worsening of GERD or *de novo* GERD has been reported thus far[97]. The available results on laparoscopic greater curvature plication are similar to those achieved with laparoscopic sleeve gastrectomy[98], and a focused investigation of its effect on GERD is warranted.

A recent variation on the RYGB is the omega-loop gastric bypass, also known as the mini-gastric bypass or one-anastomosis gastric bypass. In this procedure, the surgeon creates a long linear lesser-curvature gastric tube with a terminolateral gastroenterostomy approximately 180-200 cm distal to the ligament of Treitz. There have been concerns about the proximity of the biliary flow to the gastric tube in this procedure compared to RYGB, and the potential for both biliary reflux and esophagitis. However, in a small but rigorous study of 15 patients receiving high-resolution

impedance manometry and 24-h pH-impedance monitoring, both before and one year after the omega-loop gastric bypass, this procedure did not cause *de novo* gastroesophageal reflux or esophagitis[99]. Long-term data on the risk of GERD developing after this particular procedure is needed.

Although the popularity of RYGB has decreased somewhat in the recent years, it still remains the most commonly employed bariatric surgery, due to its benefit in GERD as well as long-term weight loss. With the development of a laparoscopic approach, certain complication rates have improved while others remain comparable to that of the open surgery[93]. Currently, RYGB is the preferred bariatric surgery for GERD patients[1].

Future exploration - surgery
Of the current surgical options described, the Nissen fundoplication has produced satisfactory results in controlling GERD in a specific subset of patients, but exerts no effect on weight. Alternatively, options such as the sleeve or gastric plication have good weight loss results without clear significant benefit to GERD. There are a few small studies evaluating the feasibility and outcome of combination surgeries, which aim to complement the shortcomings of two different surgical approaches.

A small study of three patients underwent a Nissen fundoplication and sleeve gastrectomy, all with good weight loss at five to seven months and no evidence of erosive esophagitis on follow up EGD[100]. In addition, a study of 25 patients after laparoscopic Nissen fundoplication with gastric plication showed a significant decrease in erosive esophagitis on follow up EGD (80% *vs* 17%) with a steady increase in mean weight loss last up to 12 mo[101]. A similar study of 16 patients further support the findings of Lee *et al*[102] at 12 mo, with GERD symptoms and esophagitis, which were present in all patients, completely resolving. More studies are needed to identify if this combination approach is an appropriate option in patients with obesity and GERD.

Further exploration - endoscopic bariatric approaches
Recently there has been increased interest in the development of endoscopic approaches to bariatric procedures, as alternatives for patients at high operative risk. The following approaches are recent inventions, and further research on the efficacy, feasibility, complication risk, effect on comorbid conditions, and sustainability will be needed before these procedures can be incorporated into standard of care[103]. Furthermore, since there is little data on the effect of these approaches on the outcome of GERD they present opportunities for further investigation.

Transoral gastroplasty is an endoluminal approach to reduction in gastric capacity. A few studies with small sample sizes have shown technical feasibility

with a wide range of weight loss ranging from 16% to 58% excess weight loss over one to 24 mo[104-111]. A nonrandomized trial comparing transoral gastroplasty with sleeve gastrectomy showed comparable weight loss lasting two years[112]. One patient, who underwent this procedure for treatment of GERD, showed resolution of reflux-related symptoms with significant improvement in his quality of life assessment and DeMeester score two years postoperatively off PPI[106].

StomaphyX was approved by the FDA in 2007 as a rescue procedure in patients with weight regain or inadequate loss after bariatric surgery, and there are small data evaluating its role as a revisional procedure after failed bariatric surgery. However there is no available data on its implication in obese patients with GERD.

Several different forms of intra-gastric balloons have been studied, and are designed as a temporary aid in weight loss by decreasing the gastric reservoir with the placement of a space-occupying device[103]. The saline filled devices have been associated with gastric distention and side effects including increased GERD[113] and erosive esophagitis[114] potentially due to increased transient LES relaxations[115].

Gastric botulinum toxin injection has been shown to be an option for weight loss, particularly with wide area injection including the fundus or body in addition to the antrum[116]. Although no significant side effects have been reported in the setting of increased gastric emptying time[117], given the risk of smaller gastric capacity and slower gastric motility, it can be cautiously concluded that this procedure may increase the incidence of GERD.

Finally, the bypass sleeve is a flexible, nutrient impermeable endoluminal barrier, designed as a temporary weight loss procedure that reduces jejunal absorption of nutrients. It is anchored in the duodenal bulb and extends into the proximal jejunum, fixed in place with a self-deploying stent. It has been shown to have low complication rates and good weight loss[118], but there is currently no reported data regarding its effect on GERD.

CONCLUSION
Obesity and GERD have a well-defined association due to several anatomic and hormonal pathophysiologic mechanisms. Ultimately, while the medical and surgical treatment of GERD is advancing, there is a relative lack of specific studies looking at novel GERD treatments in the obese population. The primary focus in these patients still remains the reversal of the excess weight, either with lifestyle modification or consideration of bariatric surgery.

While each form of bariatric surgery poses certain challenges in the obese patient with GERD, RYGB remains the procedure of choice for this set of patients, due to both its predicted level of sustained

weight loss as well as benefit on GERD itself. With the advent of more bariatric and GERD endoscopic and surgical options, as well as the possibility of combining two techniques for the same patient, more studies are needed to decipher the optimal procedural approach when treating obese patients with GERD.

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