Gastroesophageal Motility and Reflux Following Bariatric Surgery for the Treatment of Severe Obesity

by

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Abstract

Obesity is a recognized complex chronic disease that impacts millions of people globally. Bariatric surgery is the only evidence-based method for sustainable weight loss and resolution of obesity associated morbidities. However, complications can occur after surgery, in particular gastroesophageal reflux (GERD) and esophageal motility disorders after laparoscopic sleeve gastrectomy (LSG). Existing literature describes many contradictory causes for symptoms of GERD and investigators remain uncertain whether reflux following LSG is present, and if present, whether it is alkaline/acidic, and what precise pathophysiology leads to these symptoms. In fact, patients are empirically treated with anti-secretory therapy based on heartburn symptoms. In addition, while literature points to higher rates of esophageal motility disorders in the obese and bariatric population, the relationship with body mass index (BMI) is poorly understood.

A case of a patient with severe dysmotility syndrome and reflux symptoms initiated this thesis. The objective of this thesis was to determine the relationships between bariatric surgery and gastroesophageal motility and reflux. The hypothesis was that the anatomical changes after bariatric surgery created disturbances in esophageal and gastric motility causing non-acid gastroesophageal reflux and related symptoms.

This thesis began by exploring this hypothesis by performing a chart review of surgical patients at the Edmonton Adult Bariatric Specialty Clinic to determine the prevalence of postoperatively treated or identified reflux and esophageal motility disorders. One in five LSG patients developed reflux, but there were very few reported cases of esophageal motility disorders before or after surgery. These patients were identified or treated based on symptoms, which prompted the following study, where patients were asked to complete the

Gastrointestinal Symptom Rating Scale questionnaire to observe how symptoms changed before and after surgery and, how complications impact symptoms. There was no decisive pattern in symptoms observed after surgery and fewer than expected complications from which to draw firm conclusions. The symptomatic population was explored further at the Gastrointestinal Motility Laboratory and a prospective chart review of patients undergoing high-resolution esophageal manometry and 24h pH-impedance testing was performed. Body mass index (BMI) was not associated with esophageal motility disorders, nor were esophageal motility disorders more frequent in obese patients. BMI was also not traditionally linked to the DeMeester Score and had a logarithmic rather than linear relationship. Patients that had previous bariatric surgery were sub-grouped. There were no significant differences in esophageal motility abnormalities between symptomatic obese and bariatric patients. The mechanism for these abnormalities were not associated with BMI, but were associated with increased intragastric pressure after LSG, as previously hypothesized. Also, symptoms after bariatric surgery were not associated with esophageal motility disorders or reflux. To study this group of patients before and after bariatric surgery, a prospective cohort study to compare reflux, esophageal motility, and symptoms after LSG and laparoscopic Roux-en-Y gastric bypass (LRYGB) was performed. Although the parietal cell mass was removed, the sleeve remained acidic; however, it was non-acid reflux not acid reflux that was attributed to patients with reflux symptoms. Symptoms of reflux persisted after the number of reflux events reduced, which may indicate an esophageal hypersensitivity.

Anti-secretory therapy, such as a proton-pump inhibitors (PPI), may alleviate symptoms to reduce the total number of reflux events for patients, but ultimately a therapy targeted at non-acid reflux and esophageal hypersensitivity would be more beneficial.

Preface

This thesis is an original work by Caroline Sheppard. The research projects compiled in this thesis received human research ethics approval from the University of Alberta Research Ethics Board, as noted in the following: "Rates of reflux before and after laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass of Weight Wise Clinic patients", No. Pro00037461, March 1, 2013, "Gastroesophageal Motility and Reflux Following Laparoscopic Sleeve Gastrectomy for the Treatment of Obesity", No. Pro00034359, April 1, 2013, "Impact of Body Mass Index on Gastroesophageal Motility and Reflux", No. Pro00051509, October 2, 2014, and "Gastrointestinal Symptom Rating Scale (GSRS) use in the bariatric surgery population", No. Pro00034360, October 27, 2014.

Chapter 2 of this thesis has been published as C.E. Sheppard, D.C. Sadowski, and D.W. Birch, "A Case Study of Severe Esophageal Dysmotility Following Laparoscopic Sleeve Gastrectomy", *Case Reports in Surgery,* 2016. I was responsible for the chart review and manuscript composition. D.C. Sadowski and D.W. Birch flagged the case and assisted with manuscript composition. Chapter 3 of this thesis has been published as C.E. Sheppard, D.C. Sadowski, C.J. de Gara, S. Karmali, and D.W. Birch, "Rates of Reflux Before and After Laparoscopic Sleeve Gastrectomy for Severe Obesity", *Obesity Surgery*, 2015, 25(5):763-8). I was responsible for data collection, data analysis, and manuscript composition. D.C. Sadowski contributed to concept formation for analysis and manuscript composition. C.J. de Gara, S. Karmali, and D.W. Birch contributed to manuscript composition.

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List of Abbreviations

%EWL	Percent Excess Weight Loss
24h	24 Hour
ACh	Acetylcholine
BID	Twice per Day
BMI	Body Mass Index
BPD	Biliopancreatic Diversion
CAMIS	Centre for the Advancement of Minimally Invasive Surgery
CCK	Cholecystokinin
CD	Crural Diaphragm
CI	Confidence Interval
CT	Computerized Tomography
DCI	Distal Contractile Integral
DGER	Duodenal Gastroesophageal Reflux
DS	Duodenal Switch
DVT	Deep Vein Thrombosis
EABSC	Edmonton Adult Bariatric Specialty Clinic
ECL	Enterochromaffin-Like
EGJ	Esophagogastric Junction
EGJ-OO	Esophagogastric Junction – Outlet Obstruction
EM	Esophageal Motility
EMD	Esophageal Motility Disorder
ER	Emergency Room

F	French
GE	Gastroesophageal
GERD	Gastroesophageal Reflux Disease
GI	Gastrointestinal
GLP-1	Glucagon-Like Peptide-1
GRP	Gastrin-Releasing Peptide
GSRS	Gastrointestinal Symptom Rating Scale
H_2	Histamine 2 Receptor
H_2RA	Histamine 2 Receptor Antagonist
HCl	Hydrochloric Acid
$5\text{-}HT_4$	5-hydroxytryptamine
IAP	Intra-abdominal Pressure
IEM	Ineffective Esophageal Motility
IEP	Intra-esophageal Pressure
IGP	Intra-gastric Pressure
IF	Intrinsic Factor
IWQOL	Impact of Weight on Quality of Life-Lite
LABA-2	Long-Acting ß2-Adrenoceptor Agonist
LAGB	Laparoscopic Adjustable Gastric Band
LES	Lower Esophageal Sphincter
LRYGB	Laparoscopic Roux-en-Y Gastric Bypass
LSG	Laparoscopic Sleeve Gastrectomy
M_2	Muscarinic Acetylcholine 2 Receptor

MMC	Migrating Motor Complex
NERD	Non-Erosive Reflux Disease
NHMRC	National Health and Medical Research Council
NICE	United Kingdom National Institute for Clinical Excellence
NIH	United States National Institute of Health
NMDA	N-methyl-D-aspartate
OR	Odds Ratio
PE	Pulmonary Embolism
pH	Potential of Hydrogen
PPI	Proton-Pump Inhibitors
PPGAP	Postprandial Proximal Gastric Acid Pocket
QD	Once Per Day
QOL	Quality of Life
Reg. Coef	Regression Coefficient
ROC	Receiver Operating Characteristic
SAP	Symptom Association Probability
SI	Symptom Index
SSI	Symptom Sensitivity Index
TLESRs	Transient Lower Esophageal Sphincter Relaxations
TRPV1	Transient Receptor Potential Vanilloid 1
UES	Upper Esophageal Sphincter
VBG	Vertical Banded Gastroplasty
WHO	World Health Organization

Introduction

Obesity is a disease that impacts millions globally. Bariatric surgery is the only evidence-based method for treating obesity and its associated comorbidities. Laparoscopic sleeve gastrectomy (LSG) and laparoscopic Roux-en-Y gastric bypass (LRYGB) are two common bariatric procedures. While LRYGB has been performed for decades, LSG is a relatively new procedure.

LSG is becoming a more popularly used stand-alone bariatric procedure. Due to LSG's recent application in bariatric surgery, very little literature exists on the physiology of the sleeve and its impact on patients long-term. A dilemma after bariatric surgery is attributing gastrointestinal (GI) symptoms to physiological or anatomical abnormalities. Since there is no standardized technique in LSG, identifying the anatomical or physiological cause of reflux after surgery is difficult. The hypothesis was that the anatomical changes after bariatric surgery created disturbances in esophageal and gastric motility, causing troublesome symptoms related to non-acid gastroesophageal reflux. The objective of this thesis was to determine the relationships between bariatric surgery and gastroesophageal motility and reflux.

Chapter 1 - Background

1.1 Obesity

1.1.1 Definition of Obesity

As defined by the World Health Organization (WHO), obesity is abnormal or excessive fat accumulation that may impair health (1). Obesity is determined using the body mass index (BMI) by weight in kg divided by height in m^2. Individuals need to have a BMI equal to or greater than $30kg/m^2$ to be classified as obese (Refer to **Table 1-1**) (2). Obesity is considered a global epidemic and a complex chronic disease. Each year 2.8 million adults die prematurely because of either being overweight or obese (1). As of 2014, over 600 million adults globally are obese (1). According to Statistics Canada, in 2014 approximately 54.0% of Canadians were either overweight or obese (20.2% obese), and 55.0% of Albertans were either overweight or obese (21.5% obese) (3). Consequently, weight management strategies and bariatric surgery have increased in necessity. While most provincial healthcare systems in Canada have a funded bariatric surgery program, the procedures available and number of procedures that can be funded vary between provinces.

Table 1-1: Classification of body mass index and associated risk for comorbidities by the World Health Organization (2).

Classification	Body Mass Index (kg/m^2)	Risk of Comorbidities
Underweight	<18.5	Low
Normal	18.5-24.9	Average
Overweight	25.0-29.9	Increased
Obese Class I	30.0-34.9	Moderate
Obese Class II	35.0-39.9	Severe
Obese Class III	>40	Very severe

1.1.2 Potential Causes of Obesity

Simply understood, weight gain occurs from an imbalance of energy in and energy out. Excess energy is stored in adipose tissue. However, the causes of obesity are multifactorial

and complex. There is also a great deal of stigma surrounding obesity. A stereotype is that obesity results from laziness and lack of self-care. This presumption is false. While obesity ultimately results from poor diet and sedentary lifestyle, the catalyst contributing to this lifestyle may be caused by socioeconomic conditions. As society becomes more industrialized, it also becomes characterized as obesogenic through the overconsumption of high calorie-low nutrition foods and an inactive lifestyle (4). **Table 1-2** lists the types of potential causes of obesity and their impact they have on the individual and society.

Table 1-2: Types and sub-types of potential causes of obesity and their impact at the individual and societal level.

Type	Sub-type	Impact
Physiological	*Energy balance*: Energy absorption, microbiome, neuropeptides, cyclical "yo-yo", pregnancy weight gain	*Gastrointestinal*: non-alcoholic fatty liver disease, gastroesophageal reflux, irritable bowel disease, pancreatitis, and gallstone disease
	Genetics: (Rare endocrinological disease, gene methylation, childhood predisposition	*Cardiovascular*: coronary heart disease, stroke, hypertension, and dyslipidemia
	Medical Conditions: Physical disability, hypothyroidism, medications, insomnia	*Hormonal:* insulin resistance and type II diabetes mellitus
		Orthopedic: muscle/joint pain, Blount's disease, and degenerative osteoarthritis
		Other: cancer, polycystic ovarian syndrome, and sleep apnea (5)
Social	*Environment*: industrialization, high calorie-low nutrition food, industry marketing, food deserts, limited healthcare resources, biased food guidelines (6)	Stigma
		Social injustice (unfair employment, public shaming, discrimination)
	Socioeconomic Status: lack of resources for food and exercise	Healthcare burden
Psychological	*Behavioural Disorders*: emotional eating, smoking	Decreased quality of life and self-esteem
	Attention Deficit/ Hyperactivity Disorder: highly linked to obesity (7, 8)	Depression
	Addiction: food addiction to hyper-palatable foods (9)	Worsening of existing psychiatric issues

The physiological, psychological, and social aspects of obesity are intertwined. The combinations of these aspects are unique for every individual and therefore make the design of preventive strategies and management of obesity complex.

1.1.3 Considerations for Bariatric Surgery Versus Medical Weight Loss

Medical weight loss involves lifestyle changes such as improved nutrition, increased exercise, and in certain cases medication to lose weight. These medications include orlistat (lipase inhibitor), sibutramine (appetite suppressant), phenteramine (amphetamine), and liraglutide (glucagon-like peptide-1 receptor agonist). These medications have resulted in modest weight loss for patients when combined with healthcare provider monitored lifestyle improvements.

Many individuals with obesity are recommended by their primary care physician to begin with medical weight loss. Yet, approximately 95% of the individuals with obesity that endeavor to lose weight without surgery are not able to sustain their weight loss, and may end up gaining more than their initial weight (10). Several institutions such as the National Health and Medical Research Council (NHMRC), the UK National Institute for Clinical Excellence (NICE) and the US National Institutes of Health (NIH) agree that bariatric surgery is the only method for maintainable weight loss and comorbidity resolution (11-13). These institutions are unanimous that bariatric surgery should be made available to all individuals with obesity (10, 14). In addition to comorbidity resolution, an increase in quality of life (QOL) and decreased mental health concerns are observed. Medical weight loss cannot improve comorbidities as thoroughly as surgery (15).

Bariatric surgery is not a stand-alone procedure used to obtain and sustain weight loss. Even within the health care profession, there is stigma that surgery is a quick fix. Surgery is

a process, which involves a bariatric intervention team before and after surgery, and a life-long effort on the part of the patient to adhere to postoperative lifestyle changes. The bariatric intervention team consists of nurses, dieticians, psychologists, psychiatrists, general practitioners, and exercise specialists.

1.2 Bariatric Surgery

1.2.1 Candidacy and Bariatric Team

There are several criteria that make an individual eligible for bariatric surgery. The patient's BMI is required to be a minimum of 35kg/m^2 with noticeable comorbidities or have a minimum BMI of 40kg/m^2 with or without comorbidities (11). Comorbidities include life-threatening cardiovascular diseases, severe sleep apnea, and type II diabetes mellitus (Refer to **Table 1-3** for criteria).

Table 1-3: United States National Institutes of Health criteria for bariatric surgery (16).

US National Institutes of Health Guidelines for Bariatric Surgery Patient Selection
≥100 lb. excess weight
BMI ≥40kg/m^2 without obesity-associated comorbidities (e.g. diabetes, cardiovascular disease, arthritis, obstructive sleep apnea)
BMI 35.0-39.9kg/m^2 with 1 or more associated medical problem
Previous failed weight-loss attempts (e.g. nonsurgical interventions: diet control, behavioural modification, exercise)

BMI: Body mass index, US: United States.

Bariatric surgery is performed predominantly in the adult population for ages 18 to 65 (15). Additional criteria include medical history. Based on their history, patients may be most suitable for a specific procedure. LSG can be an optimal choice over LRYGB for patients with chronic anemia, continual oral immunosuppressive medication, chronic inflammatory bowel disease, Crohn's disease, previous colorectal surgery, and/or aspirin use (17-20). **Table 1-4** lists the contraindications for bariatric surgery.

Table 1-4: Contraindications for bariatric surgery (21, 22).

Absolute Contraindications
Severe mental illness (Psychiatrist recommendations, i.e. suicidal)
Severe medical illness (Internist recommendations, i.e. cardiorespiratory, renal, thromboembolic)
Age >65 yrs (At booking)
Active cancer diagnosis, work-up or treatment
Active Smoking (Consider blood nicotine levels)
Prader Willi syndrome
Cirrhosis (Non-alcoholic steatohepatitis)
Weight gain > 10% baseline
Pregnancy
Relative Contraindications
Age 60-65 yrs
Extensive abdominal surgery
Crohn's or Ulcerative colitis
Non-compliance with clinic recommendations
History of fundoplication, paraesophageal hernia repair, or gastrectomy
Human immunodeficiency virus, Hepatitis C
Severe esophageal dysmotility

LSG is not recommended by *Snyder-Marlow et. al.* for patients with severe gastroesophageal reflux disease (GERD), inflammation of the esophagus or stomach, or ulcers in the lesser curvature of the stomach (23).

Patients are asked to begin a weight loss regimen with the bariatric intervention team. Patients are expected to demonstrate a willingness to lose weight, change their lifestyle, and adhere to preoperative and postoperative lifestyle changes. Patients must be emotionally and mentally prepared for the changes that follow significant weight loss following surgery. These changes include proper nutrition, physical activity, and no smoking (24).

A weight loss between 5-30% is preferable before surgery (10). This reduction decreases the fatty tissue from the liver, and allows the procedure to be technically less challenging with a shorter operative time (25). The importance of decreasing the liver size is for visualization of the gastrointestinal system.

1.2.2 Surgical Procedures

There are two kinds of bariatric surgeries: malabsorptive and restrictive. Malabsorptive procedures reduce the number of calories and fats that are absorbed by the intestinal tract. Restrictive procedures decrease the volume of food that can be consumed.

Bariatric procedures are performed laparoscopically. The rational for laparoscopic surgery, as compared to open surgery, is reduced postoperative pain, earlier ambulation, and decreased incidence of pulmonary embolism (PE), infection and hernia (a major source of postoperative morbidity), all of which contribute to the patient's accelerated recovery (26).

Laparoscopic Sleeve Gastrectomy

Brief History

LSG for severe obesity has become globally more popular over the past decade (12). LSG was originally used for resection of gastric neoplasms, and has since been adapted to bariatric surgery after weight loss was observed (20). LSG is considered a restrictive procedure, because of its reduction in size of the stomach, thereby increasing satiation. However, LSG also influences gastrointestinal hormones, such as ghrelin (13).

In 1993, *Marceau et. al.* suggested LSG as an alternative procedure with a duodenal switch (DS) to the biliopancreatic diversion (BPD) (18). To further increase the safety of patients, these two procedures were divided into sequential procedures. When the weight loss from LSG has plateaued, DS is performed (12). There was significant weight loss with only LSG, which was suggested by *Gagner et. al.* to be used as a solo procedure in 2001 (27). At present, the NIH 1991 Consensus Development Conference Statement on Gastrointestinal Surgery for Severe Obesity have approved LSG as a stand-alone procedure, as well as part of a staged procedure (28).

General Surgical Technique

The patient is placed in reverse-trendelenberg. A pneumoperitoneum is created through carbon dioxide insufflation of the abdominal cavity using a veress needle (29). Surgeons perform this surgery laparoscopically using either 5 or 6 trocars spread across the abdomen (30). A ruler is used to measure an appropriate distance (about 6cm) from the pylorus, and the position is marked with a suture. This distance allows for the preservation of the antral pump. The lesser sac is accessed by entering through the greater omentum (31).

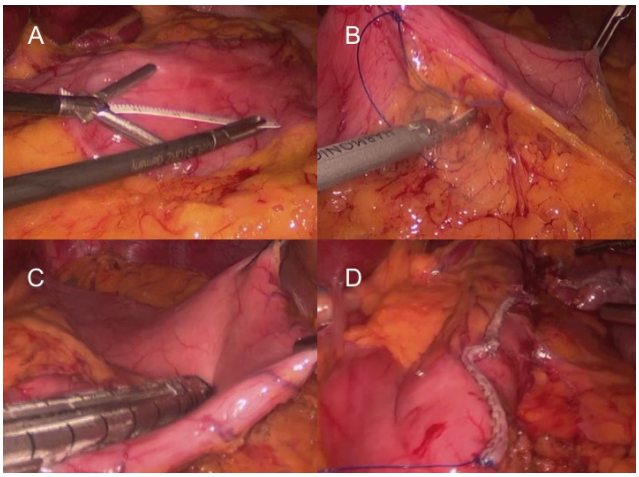
Mobilization of the stomach begins by resecting the blood vessels supplying the greater curvature of the stomach, as well as the gastrophrenic ligament (30). Division begins using an ultrasonic dissector or a bipolar electrosurgical device (32). Surgeons devascularize and mobilize the gastric greater curve (31). The posterior wall of the stomach is freed from any attachments (30). Once the left crus is visible, the stomach has been completely mobilized.

The bougie is inserted by the anesthesiologist through the mouth into the stomach ending at the pylorus. A stapler is used to divide the stomach along the lesser curvature, beginning at the marked antrum. Two sequential firings occur at the antrum to compensate for the thick nature of the tissue (30). A linear stapling device provides three rows of parallel staples on either side of the dissected tissue. The stapler continues along the lesser curvature tight against the bougie and ends at the angle of His about 1cm from the esophagus (15). The bougie is then removed (refer to **Figure 1-1**).

The resected free portion of the stomach is removed through the 15mm upper right quadrant incision. Saline is added to the field, as well as an endoscope through the mouth for adding compressed air (31). If there are no bubbles in the saline, then the sleeve is

intact. Methylene blue is also introduced into the sleeve to check for staple line leaks (29). The trocar incision sites are sutured closed.

Figure 1-1: Main points of laparoscopic sleeve gastrectomy: A) Measurement for placement of marker suture near pylorus, B) Resection of blood vessels supplying the greater curvature using an ultrasonic dissector, C) Resection of greater curvature around bougie using a surgical stapler, and D) Final product of gastric sleeve. Figure adapted from Centre for the Advancement of Minimally Invasive Surgery (CAMIS) surgical video, Royal Alexandra Hospital (29).



This procedure generally requires 1.5 hours to complete. Patients remain in hospital for 1-2 days.

Laparoscopic Roux-en-Y Gastric Bypass

Brief History

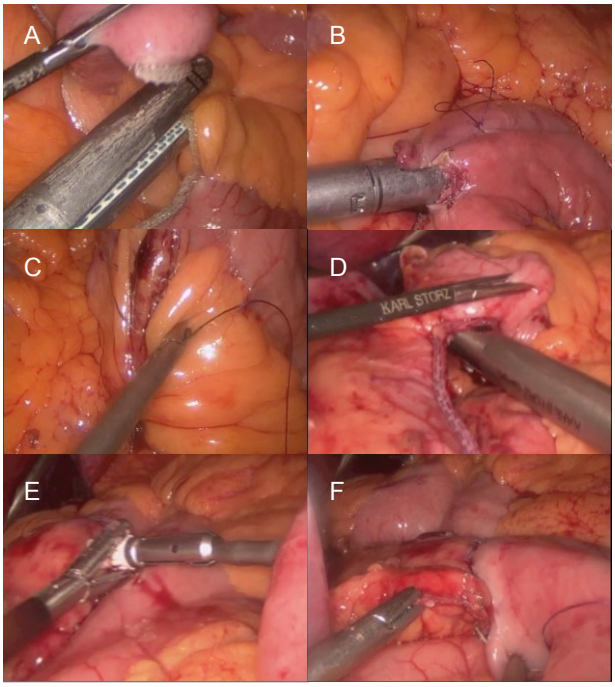
The LRYGB is the most commonly performed bariatric procedure. The first procedure was performed in 1966 by Dr. Edward Mason (22). The procedure was modified in 1977 by Dr. Griffen to include a Roux limb to create a malabsorptive component (33). The Roux limb is attributed to reducing both gastroesophageal and bile reflux after surgery. Although, recent evidence from *Vizhul et. al.* demonstrated that a lack of fat malabsorption from LRYGB

could warrant a reclassification of this bariatric procedure (34). A final modification by Dr. Torres allowed for a better blood supply by creating an anastomosis at the gastric lesser curvature (33).

General Surgical Technique

Refer to **Figure 1-2** for main LRYGB steps.

Figure 1-2: Main points of laparoscopic Roux-en-Y gastric bypass: A) Division of the small bowel to create the biliopancreatic limb, B) Stapler creating the side-to-side jejunojejunal anastomosis, C) Closure of the mesentery defect with a continuous stitch, D) Staple lines of the newly formed gastric pouch and gastric remnant, E) Spike entering anvil of circular stapler to create the gastrojejunostomy, and F) Anti-tension stitches placed distal to the gastrojejunostomy. Figure adapted from CAMIS surgical video (29).



The abdomen is prepared for surgery in a similar fashion to the LSG patients by placing the patient in reverse trendelenberg position, creating a pneumoperitoneum using a veress needle, and placing 5 to 6 trocars in the abdomen.

The biliopancreatic limb is created by identifying the ligament of Treitz and the small bowel is stapled 40cm distal to the ligament. The small bowel mesentery is mobilized by dividing the mesentery, further using the same surgical stapler (29). The jejunojejunal anastomosis is created by first measuring 100cm to 110cm distal to the Roux limb. Two enterotomies are created at this junction using an ultrasonic dissector to create an opening for the surgical stapler. The stapler is fired to create a side-to-side anastomosis (35).

The mesentery defect created when making the jejunojejunostomy is closed by using a continuous running stitch. The omentum is divided using an ultrasonic dissector to allow the Roux limb to pass antecolic (29).

The gastric pouch is created by first identifying the fat pad near the angle of His and then the fundus of the stomach is mobilized using a blunt dissector. Below the left gastric vein, a surgical stapler is used to divide the mesentery (29). The remainder of the pouch is created by stapling along a bougie entered through the mouth. The size of the pouch is dictated by the size of the bougie, and ultimately is most correlated with complications rather than weight loss (35). The gastric pouch is completely separated from the gastric remnant.

The gastrojejunostomy is created by first using cautery to open the gastric pouch at the anvil. The Roux limb is brought up to the gastric pouch antecolic. An ultrasonic dissector is used to create an enterotomy at the staple line of the Roux limb. The circular stapler is passed through the 15mm port site and the spike of the circular stapler enters the enterotomy of the Roux limb to connect to the anvil. The circular stapler is fired. The enterotomy of the Roux limb “blind limb” is closed using a surgical stapler and excess tissue is removed through a surgical port (29).

The same leak check used for LSG is performed. This procedure generally requires 2 hours to complete. Patients remain in hospital for 2-3 days.

1.2.3 Surgical Complications

A meta-analysis of literature from 2003-2012 by *Chang et al.* found that the overall complication rate of 161,756 patients after LSG was 13% and LRYGB was 21% (36). In general, LRYGB has higher complication rates than LSG attributed to the technical difficulty of LRYGB and the multiple anastomoses. Mortality rates after bariatric surgery are <1% of which a PE is the most common cause (37).

Staple Line/Anastomotic Leaks

Staple line and anastomotic leaks occur when the stapled tissues dehisce. Staple line leaks comprise 1-3% of complications after LSG (24, 38). The location of leaks along the staple line usually occurs near the angle of His under the gastroesophageal junction near the left crus of the diaphragm (20, 39, 40). Anastomotic leaks after LRYGB can vary from <1% at our institution to 2.1-3.2% in the literature (41, 42). The majority is at the gastrojejunal anastomosis (42). It is imperative to screen for and identify leaks early for medical treatment as this can be a potentially fatal complication (32, 43, 44).

Ulcer and Stricture

Ulcers occur when the tissue lining erodes creating a sore. Ulcers usually only occur after LRYGB at the gastrojejunal anastomosis with an incidence of 4.6% (45). Ulcers can cause pain, nausea, vomiting, and can be potentially severe if the ulcer should perforate or bleed. The formation of ulcers has been attributed to a low pH in the gastric pouch and treatment using proton-pump inhibitors (PPI) have been shown to prevent ulcer formation. Nonsteroidal anti-inflammatory drugs (NSAIDs), smoking, and *Helicobacter pylori* have

also been attributed to ulcer formation. However, the evidence does not describe a solid positive effect, since NSAIDs and smoking effects are difficult to quantify, while conflicting literature exists for *H. pylori* (45).

Strictures are a narrowing of the tissue, which can occur either at an anastomotic site or most commonly at the incisura angularis of the gastric sleeve (46). Symptoms include dysphagia, nausea, or vomiting. Ulcers can cause strictures by the scar tissue encapsulating the ulcer (47). Regardless, strictures are also able to form independently. Strictures can be caused by a defect in the sleeve, hematoma and edema (39). Strictures are dilated using a balloon catheter during endoscopy.

Gastroesophageal Motility and Reflux

Gastroesophageal motility and reflux disease after bariatric surgery will be discussed in 1.3.5 and 1.3.6.

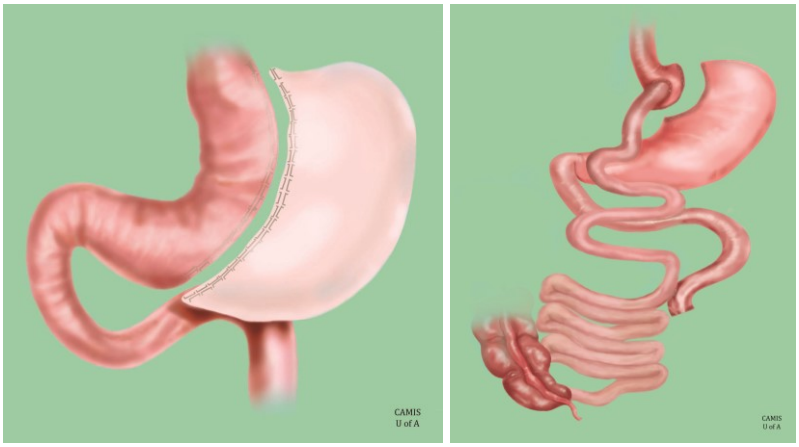
Other Complications

Other complications associated with bariatric surgery include intraabdominal or gastric hemorrhage, PE, deep vein thrombosis (DVT), surgical site infections, abscess, and incisional, ventral or internal hernias (44, 48). Gallstone formation has also been found to increase after bariatric surgery, possibly from excess cholesterol being mobilized and introduced into bile during weight loss (49).

1.2.4 Comparison of Bariatric Surgical Procedures

The most commonly performed procedure is LRYGB (11). However, because of the many advantages of LSG, it is becoming a more frequently chosen procedure. **Figure 1-3** illustrates LSG and LRYGB anatomy.

Figure 1-3: Laparoscopic sleeve gastrectomy (left) and laparoscopic Roux-en-Y gastric bypass (right). Figure adapted from CAMIS, Royal Alexandra Hospital.



Surgical Complications

LSG has reduced complication rates compared to LRYGB, which can exceed 20% in patients and produces a higher mortality rate (50). LSG does not require a gastrointestinal anastomosis, such as in LRYGB, making the procedure technically straightforward (12, 13). Therefore, there is no risk for anastomotic ulcers, intestinal obstructions, or internal hernia for the patient (12).

In short-term studies, LSG has been found to have much lower rates of malnutrition and vitamin deficiency (10, 51), but long-term studies are still needed to confirm these findings (27, 52). Long-term follow-up is necessary with malabsorptive procedures. Therefore, LSG may be favorable for patients who are unable to comply with many post-operative visits because of SES or geographical factors (53).

Excess Weight Loss and Long-Term Results

Excess weight loss (EWL) is defined by the following equation: Percentage of Excess Weight Loss (%EWL) = [(Preoperative Weight - Follow-up Weight) / (Preoperative Excess

Weight – Ideal Body Weight)] x 100 (54). Ideal Body Weight is the patient's weight when their BMI is 25kg/m^2 (55).

The %EWL after LRYGB ranges from 41% after 3 months, 57% after 6 months, 66-78% after 1-2 years, and 61-73% after 3-5 years (56-61). LRYGB at 10 years is 57% (62).

The %EWL after LSG ranges from 18-30% after 1 month, 37-41% after 3 months, 54-61% after 6 months, and 50-78% after 1-3 years, alongside either a large reduction or complete resolution of comorbidities (23, 63-65). The literature reported similar %EWL after LSG of approximately 55-57% after 5-6 years (53, 66, 67). Some researchers reported weight gain after surgery, with *Bohdjalian et. al.* reporting almost 20% of patients regaining weight after 5 years (66).

Weight Recidivism

Insufficient weight loss is characterized as a %EWL less than 25-50% (17, 68). The rate of weight recidivism ranges from 10-20% depending on the bariatric procedure (69). Long-term, that is, two to five years after surgery, is usually the most difficult period to maintain weight loss (10). These results can be affected by age, preoperative BMI, pouch or sleeve dilation, excess gastric fundus, and maladaptive lifestyle recidivism (39, 53, 70).

For a representation of procedure advantages and disadvantages, refer to **Table 1-5**.

Table 1-5: Comparison of advantages and disadvantages of laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass.

	Laparoscopic Sleeve Gastrectomy	**Laparoscopic Roux-en-Y Gastric Bypass**
Safety	Moderate	Moderate
Complexity	Moderate	High
Nutritional Impact	Low	High
Restricted Medication	Moderate	High
Long term data	Low	High
Weight Loss	Moderate (60-80lbs)	High (100lbs)
Weight Recidivism	Moderate (15-20%)	Low (10%)

1.3 The Gastrointestinal System & Gastroesophageal Reflux Disease

1.3.1 Anatomy and Physiology of the Gastrointestinal System

The GI system is composed of a tubular network starting at the mouth and ending at the anus, and includes the pancreas, liver, and gallbladder (71). The esophagus is a tube composed of striated (upper third) and smooth muscle (lower two thirds) with a transition zone separating the muscle layers (72). A longitudinal muscle layer, muscularis mucosa, runs along the inner layer of the mucosa between the basement membrane and submucosa. The outer layer of the mucosa, muscularis propria, contains a layer of circular and longitudinal muscles involved in food propagation. The myenteric plexus controls this layer (73). The esophagus is responsible for conveying food from the mouth into the stomach through coordinated muscle contractions called peristalsis (72). The lower esophageal sphincter (LES) separates the esophagus and stomach at the level of the diaphragm. The LES remains closed and contracted (myogenic tone) by the esophagus joining the stomach at an angle and the pressure difference at the diaphragm. For the contraction to be continuous, the LES is innervated by the vagus nerve. The myenteric nerve plexus and submucosal plexus, within the intrinsic nerves, regulate LES resting tone (71, 74).

The stomach is a reservoir for food. Its primary role is to digest food for absorption in the intestines. The stomach can be identified by the lesser and greater curvature, with several functional components and regions. The regions of the stomach are the cardia, fundus and body, and antrum and pylorus (72). To be able to store food, the stomach distends at the greater curvature of the stomach, the fundus, and causes intragastric pressure (IGP) to remain stable while the volume of food increases. The fundus contains two thin layers of

muscle that facilitate its expansion. The expansion sends satiety signals to the hypothalamus (75). For this reason, the fundus is a target for restrictive bariatric surgery to reduce stomach volume and decrease time to satiation. Two valves allow for the passage of food either from the esophagus or into the intestinal tract. These valves are the LES and the pylorus. The pylorus is located below the fundus in the antral region (76).

1.3.2 Gastroesophageal Motility

Esophageal Motility

Normal Esophageal Motility

Esophageal motility (EM) involves peristalsis, coordinated contractions of the circular muscle of the muscularis propria, to move a bolus from the upper esophageal sphincter (UES) to the LES. Primary peristalsis is initiated by a voluntary swallow. Secondary peristalsis in involuntary and occurs from either a portion of a bolus remaining in the esophagus or the clearing of refluxed stomach contents (73). A swallow is propagated by the following aspects: 1) A bolus is created through chewing and mixing with saliva and propelled by the tongue to the posterior pharynx, 2) The soft palate elevates to close the nasopharynx and pharyngeal constrictor muscles contract to push the bolus and fold the epiglottis over the glottis, 3) The UES (pharyngeal and cricopharyngeal muscles) relaxes and the suprahyoid muscles contract, 4) Peristalsis (muscle relaxation and contraction), and 5) The LES relaxes once the bolus has entered the esophagus and closes after the bolus has passed into the stomach (77).

Normal motility has been classified using several manometric parameters. The original Chicago Classification of esophageal motility disorders (EMD) outlined these parameters. Refer to **Table 1-6** for the normal manometric parameters.

Table 1-6: Normal range of manometric parameters for esophageal motility.

Manometric Parameter	Normal Range
Number of Peristaltic Swallows (%)	>70%
Double-Peaked Waves (%)	<15%
Mean Wave Amplitude (mmHg)	30-180
Mean Wave Duration (s)	2.7-5.4
Distal Contractile Integral (mmHg/cm/s)	500-5000
Lower Esophageal Sphincter Pressure (mmHg)	13-43
Lower Esophageal Sphincter Residual Pressure (mmHg)	<15
Upper Esophageal Sphincter Pressure (mmHg)	34-104
Upper Esophageal Sphincter Residual Pressure (mmHg)	<12

Abnormal Esophageal Motility

There are several types of abnormal motility disorders, divided into neuromuscular (achalasia I-III, ineffective esophageal motility, hypercontractile esophagus, scleroderma, esophagogastric junction outlet obstruction (EGJ-OO), and esophageal spasm) and mechanical (cricopharyngeal bar, foreign body, and esophageal cancer) (78). The most common is ineffective esophageal motility (IEM). Depending on the type of abnormality, several causes for EM are possible (**Table 1-7**). However, many motility disorders are idiopathic. Symptoms can vary from dysphagia (difficulty swallowing), non-cardiac chest pain, globus, and odynophagia (painful swallowing).

Obese individuals are naturally predisposed to abnormal EM (39). Impedance studies performed by *Quiroga et. al.* confirmed that patients with GERD have abnormalities in esophageal clearance, particularly with defective bolus transit. Motor functions were significantly inferior in obese patients compared to normal controls. How obesity causes dysmotility remains unknown (79).

Table 1-7: Types, causes, detection, and treatment of esophageal motility disorders.

Disorder	**Cause**	**Manometric Detection** (80)	**Treatment**
Achalasia I-III	Immune infection and genetic susceptibility Myenteric plexus inflammation causing distal esophagus and lower esophageal sphincter inhibitory postganglionic neuron dysfunction (81)	Elevated lower esophageal sphincter residual pressure 100% failed peristalsis Panesophageal pressurization Spastic contractions	Calcium channel blockers Nitrates Botulinum toxin Lower esophageal sphincter dilation Heller-myotomy (81)
Ineffective Esophageal Motility	Unknown Initial gastroesophageal reflux (82).	Decreased response time of peristaltic movement Decreased peristaltic events Low-amplitude or simultaneous contractions	Reflux management with acid suppressant or prokinetic therapies (83)
Hypercontractile Esophagus (Jackhammer)	Unknown trigger Excessive excitatory response from increased number of choline acetyltransferase-positive neurons (84)	Swallows with elevated distal contractile integral	Calcium channel blockers Nitrates
Esophageal Spasm	Unknown	Normal lower esophageal sphincter residual pressure Premature contractions Normal distal contractile integral	Botulinum toxin Anti-Depressants (84)
Esophagogastric Junction Outlet Obstruction	Unknown trigger Evolving achalasia Mechanical obstruction (85) Impaired lower esophageal sphincter relaxation (86)	Elevated lower esophageal sphincter residual pressure Peristalsis present	Botulinum toxin Lower esophageal sphincter dilation Heller-myotomy (81)
Scleroderma	Unknown trigger Autoimmune disease causing atrophy and fibrosis of smooth muscle	No peristalsis No lower esophageal pressure Esophageal shortening	Reflux management with acid suppressant or prokinetic therapies Stricture dilation (87)
Cricopharyngeal Bar	Unknown trigger Fibrosis of cricopharyngeal muscle (88)	Continuous and elevated pressure near the upper esophageal sphincter	Cricopharyngeal dilation or myotomy

Gastric Motility

Normal Gastric Motility

The antrum is responsible for the churning and pumping mechanism of the stomach (76). Oblique, longitudinal, and circular muscles coordinate to break down food into a semi-liquid, chyme, and move it towards the pylorus. Enteric and autonomic nerves control these muscles. The fundus and antrum continue to relax and pylorus activity is stimulated (71). A feedback system created by intestinal nutrient intake affects the constant emptying rate. Neural control through pacemaker cells, found in the interstitial cells of Cajal in the greater curvature, control the contractions of the pylorus (89). The interdigestive migrating motor complex (MMC) is activated between meals, and causes the contraction of the stomach to move remaining food particles towards the pylorus (90). These contractions create a pressure gradient between the stomach and duodenum to facilitate emptying (74). Normal gastric emptying of a standardized meal consists of 70% retained after 30 minutes, 30-90% retained at 60 minutes, 30-60% retained at 120 minutes, and <10% retained at 240 minutes (91).

Abnormal Gastric Motility

Gastroparesis, functional dyspepsia, dumping syndrome, and cyclic vomiting syndrome are all abnormalities of gastric motility. Gastroparesis occurs when there is delayed gastric emptying with no associated mechanical obstruction resulting in either smooth muscle fibrosis, low density nerve fibres, interruption of interstitial cells of Cajal, or neurotransmitter changes (92). Causes of delayed gastric emptying can be diabetes, scleroderma, and neural disorders. In addition, cases can be idiopathic (92). Symptoms include nausea, vomiting, epigastric pain, and early satiety.

Delayed gastric emptying is generally accepted to contribute to GERD by extending the retention of acidic gastric contents within the stomach and increasing their availability to be refluxed. *Buckles et. al.* found that approximately 33% of patients suffering from GERD had decreased gastric motility at 120min postprandial, and 26% at 240min postprandial. In addition, slower gastric emptying resulted in longer distention of the stomach, which increases the rate of transient lower esophageal sphincter relaxations (TLESRs) causing reflux (93). Delayed gastric motility has also been suspected of causing a postprandial proximal gastric acid pocket (PPGAP), which has been involved in severe GERD. PPGAP is an unbuffered layer of acid capable of being refluxed and located below the EGJ in the proximal stomach (94). However, individuals with obesity are not pre-disposed to delayed gastric emptying (95). Treatment includes prokinetic therapies, anti-emetics, gastroesophageal reflux management with anti-secretory therapies, and more invasive therapies such as botulinum toxin or pyloromyotomy (92).

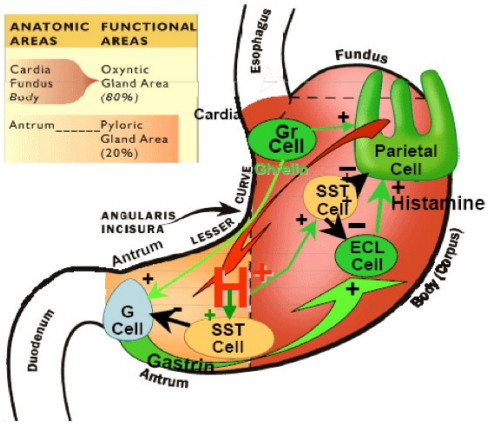
1.3.3 Gastric Acid Secretion

Gastric acid is secreted from the stomach as a component of gastric juice for food digestion. Gastric juice is composed of hydrochloric acid (HCl), intrinsic factor (IF), pepsinogen, and mucus (96) and has a pH between 1 and 3. These components are secreted from different cells in the stomach lining.

The layers of the stomach are made of columnar gastric epithelium cells. These cells have gastric pits, which enter the lamina propria. All the pits are connected by gastric glands through the isthmus. The glands deliver HCl, pepsin, and other constituents for digestion of food. Mucous cells produce an alkaline mucus to protect the epithelium lining of the stomach from acid. Enteroendocrine G cells secrete gastrin to stimulate acid production

and increase gastric motility. **Figure 1-4** illustrates the layers of stomach cells, as well as location of hormone release. Parietal cells found in the gastric glands of the gastric fundus and body produce HCl. Parietal cells are also responsible for the secretion of IF for vitamin B_{12} absorption and gastroferrin for iron absorption (71, 97).

Figure 1-4: Functional aspects of gastric secretion, showing major stimulatory and inhibitory pathways regulating gastric acid secretion (left) (98). Adapted from Konturek et. al., 'Brain-Gut and Appetite Regulating Hormones in the Control of Gastric Secretion and Mucosal Protection' with permission from the *Journal of Physiology and Pharmacology*, 2008, 59(Suppl 2).



Gr: Ghrelin, SST: Somatostatin, ECL: Enterochromaffin-like, +: Increase, -: Decrease.

Acid secretion can be separated into three phases: cephalic, gastric, and intestinal. The cephalic phase occurs before food enters the stomach, and is triggered by smell, taste, sight, and thought of food (99). Through these sensory triggers, the hypothalamus prepares the stomach to receive food by activating saliva and triggering the vagal nerve to release acetylcholine (ACh) and gastrin-releasing peptide (GRP) for gastrin and histamine secretion (99). The gastric phase produces the majority of gastric secretions. Distention of gastric tissues to accommodate a meal activates both short and long reflexes of the neural

pathway through stretch receptors, causing ACh release to stimulate gastrin production. Gastrin in turn stimulates parietal and enterochromaffin-like (ECL) cells to produce gastric juice (99). Acid secretion is initiated by activation of the muscarinic acetylcholine (M_2), cholecystokinin B (CCK2), and histamine (H_2) receptors within parietal cells by ACh, gastrin from the G cells, and histamine from the ECL cells, respectively (71). A positive feedback loop is in place until the potential of hydrogen (pH) changes from alkaline to acidic. Somatostatin inhibits gastric acid secretion by inhibiting the parietal cell from releasing histamine and gastrin (100). Somatostatin is released from D cells and acts on the somatostatin receptor 2 (SSTR2) on the parietal and ECL cells once the pH in the stomach is below 2 (99, 101). In the intestinal phase, the small intestine receives acidic secretions. The duodenum is the source of inhibitory influences on acid secretion. The enterogastric reflex is a neural reflex originating in the intestine and contributes to the reduction of stomach acid secretion (97). Secretin is also released during this phase by the S-cells in the duodenum. Secretin stimulates bicarbonate secretion in the duodenum to neutralize incoming acidic chyme and inhibits gastrin release (102).

1.3.4 Gastroesophageal Reflux Disease

Symptoms of Gastroesophageal Reflux Disease

GERD is made up of a complex series of symptoms. Symptoms include heartburn, regurgitation, vomiting, dysphagia, and odynophagia. Heartburn, a retrosternal burning sensation, is the most common symptom of GERD. On occasion, reflux can be aspirated into the larynx and cause discomfort, chronic cough, and hoarseness. Regurgitation of gastric contents is usually bitter or acidic in taste (30).

Moderate to severe reflux can lead to dysphagia or esophagitis. Lower esophageal nerve endings signal discomfort and pain, which can develop into chronic pain. If reflux is chronic, inflammation of the esophagus can occur, as well as erosion of the non-cornified stratified squamous epithelium lining the esophagus. The lining will be converted into gastric or intestinal simple columnar epithelium, a process called metaplasia, causing Barrett's esophagus, and increases the risk of developing esophageal adenocarcinoma. Interestingly, Barrett's esophagus has been observed to be asymptomatic (71).

Causes of Gastroesophageal Reflux Disease

GERD pathophysiology is comprised of mechanical, chemical, and physiologic factors (refer to **Table 1-8**). Some reflux is acceptable and not harmful when eating, drinking, or swallowing saliva (71).

Transient Lower Esophageal Sphincter Relaxations and Lower Esophageal Sphincter Tone

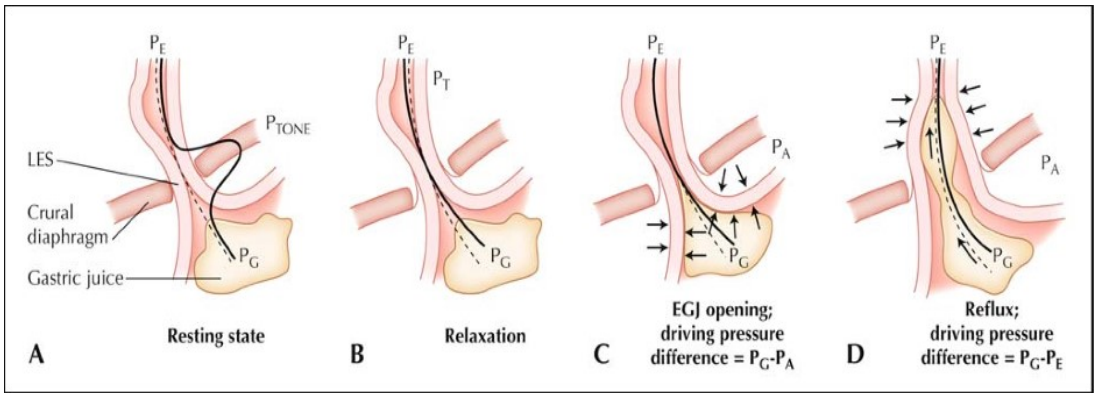
A probable cause is thought to be the neurophysiology of the esophagogastric junction (EGJ) involving TLESRs. The EGJ is comprised of the intrinsic sphincter (LES) and the external crural diaphragm (CD), and provides a high-pressure barrier to block reflux from entering the esophagus (103). A TLESR is vagally mediated, occurs when the LES relaxes spontaneously with no voluntary swallow, and occurs most frequently after meals to allow for gas and air to escape the stomach. TLESRs are frequently observed after meals in order to release excess gas from the stomach (104). An increase in reflux occurs during TLESRs reflexes and patients with GERD have more TLESRs.

As mentioned earlier, the body has a natural antireflux mechanism. The mechanism is made of a group of muscular fibres from both the esophagus and stomach that control the

pressure and tone of the LES, CD, and phrenesophageal and cardiophrenic ligaments. Changes in any of these fibres can result in reflux (105). There are gastric sling/clasp fibres that encircle the EGJ, and proceed into the greater curvature of the cardia. These fibres provide structure for the upper and lower components of the LES. The upper component moves the sling fibres responsible for the crura. The lower LES is regulated by the gastric sling/clasp fibres. These fibres combine to create a complex regulation of sphincter control to prevent gastric contents from refluxing (103).

Anatomical issues with the LES are generally the cause of GERD in average weight individuals (106). In obese individuals, LES pressure is decreased most likely due to increased intra-abdominal pressure (IAP) from excess weight (106). As described by *Ghosh et. al.,* the LES pressure mechanism for reflux can be broken down into four stages (refer to **Figure 1-5**). First, at rest the myogenic tone keeps the sphincter closed. Any dysfunction of the muscle tone allows for the EGJ to be susceptible to pressures from below, allowing the sphincter to open. The sphincter will then begin opening from an imbalance in pressure. The transmural pressure difference of the gastric wall near the sphincter rises, and overtakes the pressure the muscles are exerting to keep the sphincter closed. Finally, once the EGJ has opened, the difference between IGP and intraesophageal pressure (IEP) causes a pressure gradient that forces gastric acidic contents into the distal esophagus. The volume of gastric contents released into the esophagus is proportional to the size of the EGJ opening (103).

Figure 1-5: A schematic of the interaction between physiologic and mechanical changes in the esophagogastric junction (EGJ) associated with opening from below. A, The high-pressure zone of the EGJ in the resting state. B, The relaxation of the EGJ, which results in removal of the high-pressure barrier. C, The dominant forces (in arrows) that drive EGJ opening. D, The trans-sphincteric pressure gradient that drives refluxate flow into the esophagus (103). *Current Gastroenterology Reports*, Biomechanics of the Esophagogastric Junction in Gastroesophageal Reflux Disease, vol.10, 2008, pg.247, Sudip K. Ghosh, (Copyright © 2008 by Current Medicine Group LLC) reproduced with permission of Springer.



Arrows show the passive esophageal forces due to luminal distention. LES—lower esophageal sphincter; PA: Intra-abdominal pressure, PE: Intraesophageal pressure, PG: Intragastric pressure, PT: Intrathoracic pressure, PTONE: LES tonic pressure.

There are two theories for the cause of malfunctioning sphincters: the static approach and dynamic approach. The static approach states that the cause for GERD is from a defect in the sphincter, which will be more difficult to treat than normal sphincters. Normal LES pressure fluctuates throughout the day. Although, only in patients that suffer from reflux does the LES pressure suddenly drop close to zero. These abrupt changes are observed when swallowing, after meals, during distention of the fundus, with increased cholecystokinin (CCK), and when IAP exceeds resting LES pressure. These rapid changes in pressure are caused by TLESRs, and characterize the dynamic approach to GERD. It has

been observed that the diaphragmatic crura is inhibited during TLESRs. Therefore, it has been suggested that both the vagal and phrenic nerves are involved in reflux (107).

An impaired CD function is predictive of GERD. *Ghosh et. al.* found there was a correlation between LES-CD separation and the number of patients suffering from GERD. An increased BMI with abdominal obesity can cause the separation between LES and CD by a hiatus hernia, causing increased trans-sphincteric pressure gradient and increased abdominal pressure (103).

A vicious cycle can form during GERD. Whether reflux of acid across the LES caused by another means causes damage to the LES tissue or whether initial LES dysfunction causes acid reflux and in turn tissue damage remains unknown. However, *Crookes et. al.* suggested that damage to the LES from acid reflux is the primary cause of this cycle. The weakened LES is then the main cause of increased acid reflux into the esophagus, causing esophagitis and Barrett's (107).

Anatomy and Hiatus Hernia

The EGJ can be disrupted for anatomical reasons, such as by a hiatal hernia or muscle wall compliance from changes in LES musculature or strictures. To restore the anatomical function, surgery may be necessary (103). A hiatus hernia affects the angle of His and disrupts the effect of the diaphragm on sphincter pressure. The EGJ is forced in the thorax above the diaphragm, causing the sphincter pressure to drop, IAP to rise, and gastric contents to enter the esophagus (71).

Gastroesophageal Motility

To keep reflux under control, peristalsis is involved in removing acid from the esophagus, as well as neutralizing the pH of the gastric contents through saliva. If the reflux is

adequately cleared, esophageal damage can be minimized (82). In addition, delayed gastric emptying can increase the risk of contents being refluxed into the esophagus.

Intraabdominal Pressure

An individual with obesity may develop gastric reflux due to excess adipose tissue causing an increase in IAP and release of the GE valve (108). IAP can be chronically elevated in patients who are either overweight or obese (71). There is a clear positive association between BMI and reflux episodes, possibly caused by increased IAP from excess weight (109). When IAP rises, the increased pressure opens the LES and forces gastric contents into the esophagus. The length of sphincter affected by IAP has become an important factor in varying IAP. As the abdominal pressure rises from excess mass, the sphincter length becomes shorter. The sphincter length shortens again after consuming a meal from gastric distension and increases the risk of gastric contents refluxing into the esophagus (107). Individuals with abdominal-centred obesity are thought to have an increased IAP, which may explain the association between obesity and GERD. Approximately 45-70% of individuals with obesity have GERD (79, 108).

Diet and Lifestyle

Consumption of certain foods and beverages can aggravate reflux, such as carbonated beverages. These beverages cause gastric distension and exert pressure on the LES. When gastric distension occurs, TLESRs are triggered and facilitate reflux (107). The acidity of tomato juice and citrus juices is known to affect the esophageal mucosa, and may cause symptoms of reflux. Fatty foods, chocolate, alcohol and certain liqueurs can also cause relaxation of the LES and irritate the mucous layer of the stomach (110). Caffeine causes an increase in acid production, and could also precipitate reflux symptoms. Reclining after

consuming a meal can also lead to reflux through loss of gravity on the LES and gastric emptying (30). Obese individuals suffering from GERD are recommended to change their lifestyle, and weight loss becomes a necessary component of treatment (107).

Table 1-8: Summarization of etiology of gastroesophageal reflux disease.

Potential Cause of Reflux	Description
LES Tone and TLESRs	Cause dysfunction of the antireflux mechanism forcing gastric contents to enter the esophagus during mechanical stomach churning
Anatomy and Hiatus Hernia	Cause LES abnormality in turn causing gastric contents to be trapped in the esophagus
Gastroesophageal Motility	Decreases clearance and neutralization of acid contents from the esophagus Postprandial proximal gastric acid pocket traps acidic contents in the esophagus Delayed gastric emptying
Intraabdominal Pressure	Overcomes intraesophageal pressure and forces gastric contents out of the stomach
Diet and Lifestyle	Promotes increase of acidic contents or inhibits LES function

LES: Lower esophageal sphincter, TLESRs: Transient lower esophageal sphincter relaxations.

Duodenal Gastroesophageal Reflux

Duodenal gastroesophageal reflux (DGER) involves the forceful movement of duodenal contents into the esophagus. DGER has been implicated in the pathogenesis of esophagitis and Barrett's esophagus. A limitation to studying DGER is the difficulty to determine the amount of acid and duodenal contents within refluxate. Currently, no clinical investigations exist to identify non-acid reflux (pH>4) or bile reflux (pH 7-8) accurately or efficiently. Finding these amounts is important, because acid and bile may work synergistically in the pathogenesis of esophagitis. Duodenal motility abnormalities may include disordered antroduodenal motility, decreased gastric emptying, and pylorus abnormalities. Bile reflux has been observed commonly after surgical procedures that affect the function of the pylorus (82).

Detection and Treatment of Gastroesophageal Reflux Disease

The management of GERD follows an algorithmic approach with the overall goal of relieving symptoms. The first step is lifestyle and dietary modifications, especially in patients who have not received previous treatment for GERD (111). Numerous modifications have been proposed and evaluated in randomized trials. A systematic review of those trials, however, found that only two modifications had any benefit for patients with GERD. Weight loss was found to significantly improve symptoms if the patient was overweight (112). Additionally, elevation of head of bed when sleeping significantly improved esophageal pH profile (113).

Mild heartburn can also be improved by consuming substances capable of buffering the acidic gastric contents, such as antacids (110). A low dose histamine 2 receptor antagonist (H_2RA) is advocated for patients with mild symptoms in addition to lifestyle modifications or if those modifications initially do not improve symptoms (114). The general approach is for clinicians to reassess symptoms at 2-4 week intervals. Therapy is escalated until symptom relief is achieved. Failure of twice daily H_2RA is followed by the use of a PPI. PPIs are more effective at relieving GERD symptoms when compared to H_2RA (115). Indications for upper endoscopy are controversial for patients with GERD. If only heartburn and/or regurgitation is present, then upper endoscopy is not required (116). Patients with heartburn and alarm symptoms (dysphagia, anemia, weight loss, gastrointestinal bleeding, recurrent vomiting) should undergo upper endoscopy (116). The added advantage of endoscopy is to evaluate for the presence of erosive esophagitis and Barrett's esophagus.

Manometric studies can be used to study the pressure function of the gastroesophageal sphincter. 24hour (24h) pH or 24h pH-impedance studies can be performed using a pH electrode introduced transnasally down the esophagus to 5cm above the LES. These studies can measure the passage of acidic material (71). Impedance studies are used to measure the motility of fluids and gas in the esophagus (103).

If symptoms resolve while on medical treatment for GERD, then a trial off medication is recommended (116). Only patients with severe erosive esophagitis or Barrett's esophagus are the exception to this strategy (116). If symptoms do not improve despite medical therapy, then the next step is surgical management. The type of antireflux surgery depends on numerous patient factors, but in general the Nissen fundoplication is performed (117). The proximal region of the stomach is wrapped around the distal esophagus, recreating the antireflux barrier (118). LRYGB is a preferred surgical procedure for patients who also suffer from obesity, since some research reflects that fundoplication in patients with obesity is more likely to fail (116).

1.3.5 Physiology of the Gastrointestinal System After Laparoscopic Sleeve Gastrectomy

Changes in Gastroesophageal Function

Intragastric and Intraabdominal Pressure

Anatomy and physiology of the intestinal system significantly changes after LSG. The stomach becomes similar to a high-pressure tube (119). LaPlace's law dictates that sleeve luminal tension (T) is equal to internal sleeve pressure (P) on the wall multiplied by sleeve radius (R) (T=PR). As the radius of the sleeve decreases the greater pressure will be exerted on the sleeve wall, as the expandable fundus has been removed, leaving the sleeve

lumen non-compliant. *Yehoshua et. al.* tested the IGP of the sleeve when the sleeve was empty and filled with saline. The IGP was significantly higher in sleeve gastrectomy patients compared to normal gastric anatomy after filling with saline (76). A recent study by *Mion et. al.* observed increased IGP after a sleeve gastrectomy using high-resolution esophageal manometry, and observed that this increased pressure was not linked to reflux symptoms or manometric impedance findings (120). While it has been hypothesized that IAP would decrease with subsequent weight loss and reduce reflux symptoms after LSG, this proposal has not been tested.

Esophageal Motility

Few studies have explored EM after LSG. *del Genio et. al.* described increased ineffective peristalsis and normal LES pressure and relaxation after LSG (121). *Petersen et. al.,* however, described increased LES residual pressure and improvement in EM after LSG (108).

Gastric Motility

Gastric emptying transit has been observed to increase after LSG (122, 123). The exact reason for the increase is still under debate. Possible causes have been suggested to be the amount of the antral pumping mechanism and fundus remaining after surgery, the effect of glucagon-like peptide-1 (GLP-1), changes in compliance and contraction of the sleeve, and resection of pacemaker cells from the body (124, 125). All of these coordinate together to achieve gastric motility, and have a significant effect on the fundus and body relaxation (126). When one of these functions is impeded, the other regions compensate. Therefore, problems arising in gastric motility occur through multiple functions being inhibited, such as after LSG (89).

Bernstine et. al. suggest preserving the antrum to decrease the effect LSG has on gastric emptying transit. Their patients had increased satiety, reduced food intake, and reduced side effects consisting of vomiting and gastroesophageal reflux. The results suggested that by preserving the antrum, the gastric emptying rate will be unchanged after surgery, as well as the IGP. A concern is sleeve dilation at the remaining flexible antrum. Although, the antrum does not significantly change the volume of the sleeve. In addition, *Bernstine et. al.* suggest that keeping the antrum intact is the most likely explanation for the lack of dumping syndrome in patients after LSG (125).

Gastroesophageal Reflux

LSG removes the fundus containing the acid producing cells, and, accompanied with weight loss, should resolve GERD symptoms. Few studies describe factors contributing to gastric acid production after LSG. *Grong et. al.* and *Sillakivi et. al.* described serum gastrin levels when LSG compared to controls after a meal was not significantly different (127, 128).

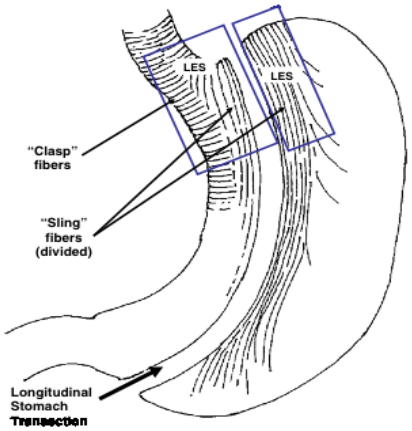
Curiously, even with the acid-producing cells having been removed during surgery, several studies reported an increased incidence of GERD after LSG. GERD symptoms are generally seen immediately postoperative to one year after LSG, with a decrease in symptoms approximately three years later. A range of GERD rates before LSG has been reported 5%-47%, all of which noticed some increase after surgery, and then a later decrease either with time or conversion to LRYGB (12, 17, 105, 129).

Many hypotheses as to the cause of GERD symptoms after LSG exist (see **Figure 1-7**). Some surgeons have observed that LSG improves GERD; however, it could be that these results were taken a few months later, which resulted in sleeve compliance (129). It has

been suggested that the lack of gastric compliance could be the cause of initial reflux, and the decrease in symptoms is the increase in sleeve flexibility (75, 105). No evidence has been found to confirm this improvement, but many factors are thought to contribute to reflux after LSG.

A possible cause of reflux is the blunted angle of His if the surgeon resects too close to the esophagus. The angle of His can also be compromised by the cleavage of sling fibres (**Figure 1-6**).

Figure 1-6: Line of transection of gastric wall during sleeve gastrectomy and division of sling fibres of LES (130). Obesity Surgery, Manometric Changes of the Lower Esophageal Sphincter After Sleeve Gastrectomy in Obese Patients, vol.20, 2009, pg.360, Italo Braghetto, Enrique Lanzarini, Owen Korn, Héctor Valladares, Juan Carlos Molina, and Ana Henriquez, (© Springer Science+Business Media, LLC 2009) reproduced with permission of Springer.



LES: Lower esophageal sphincter.

When the angle of His is blunted, the function of the LES is compromised, leading to the possibility of reflux (122). The decrease in GERD symptoms later could be the angle of His being restored (75, 105).

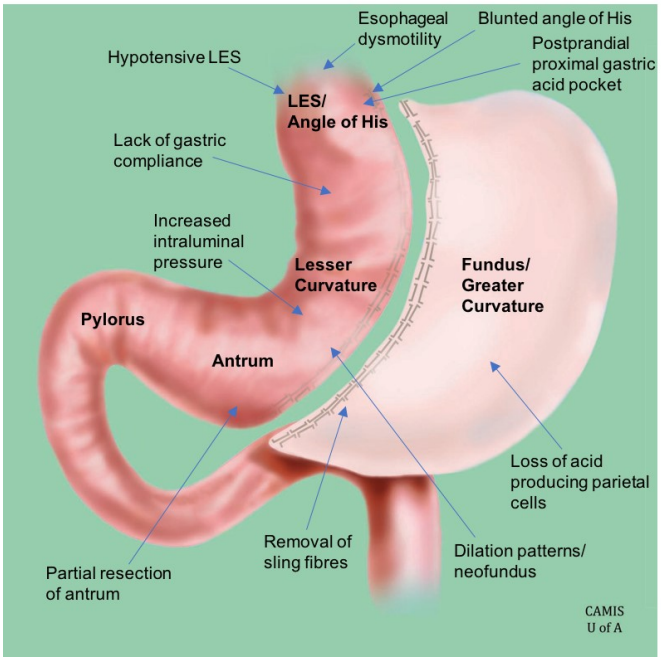
The high intraluminal pressure of the sleeve, together with the reduced effectiveness of the LES, may lead to reflux (106). Two studies found that patients with a normal preoperative LES had a hypotensive LES after surgery (105, 129). Decreased LES tone affects the antireflux mechanism by impairing the integrity of the cardia, and could also lead to reflux of non-acidic content, considering gastric acid production should be reduced (126). The hypotensive LES could be caused by the sling fibres responsible for the integrity of the sphincter pressure being resected during surgery (126). In contrast, *Petersen et. al.* found that LES pressure increased after LSG. They were also able to associate the cause of this increase to the surgery and the bougie size used. A smaller bougie size was correlated with a higher LES pressure (108). While LES pressure is a major determinant, it is not the only factor thought to cause GERD postoperatively (108). An additional possibility of reflux could be from resecting part of the antral pump, causing issues in motility (106).

Dilation of the sleeve can occur and cause morphologic/anatomical patterns in the remnant stomach (53). *Triantafyllidis et. al.* found that to protect the EGJ, a certain amount of the posterior fundus can be preserved and cause superior pouch formation. They found that 54.5% of patients with a superior pouch had symptoms of GERD (44). However, this determination was not conclusive, due to incomplete data collection. *Himpens et al.* also found that dilation with midstomach stenosis could create a neofundus in LSG patients, which could be contributing to the increased symptoms of GERD (105). *Lazoura et. al.* argued that a pouch might help the stomach distend when consuming a meal to increase compliance of the sleeve, and decrease the likelihood of the gastric contents being refluxed (126). *Gagner et. al.* also agreed with keeping a “dog ear” or “triangle” in the sleeve to decrease the IGP to prevent leaks, and could decrease the incidence of reflux (30). *Roslin*

et. al. disagreed stating that the pouch has a limited blood supply, could expand leading to weight gain, and change the pressure of the sleeve leading to reflux (106). Sleeve dilation could also potentially contribute to PPGAP, but this possible cause has not been studied in patients after LSG.

Whether the reflux observed is acidic or bilious is unknown. *del Genio et. al.* are the only researchers to describe 24h pH-impedance results after LSG. They found that after a median follow-up of 13 months, LSG patients had a significant increase in the number of non-acid reflux events (median: 17 versus 36) and no change in the number of acid reflux events (median: 12 versus 16). An increase in non-acid reflux events would confirm the hypothesis that gastric acid should not increase after LSG; however, acid reflux events did not decrease after surgery and esophageal acid exposure was significantly increased (median: 1.47% versus 3.25%) (121).

Figure 1-7: Summary of possible causes of gastroesophageal reflux disease after laparoscopic sleeve gastrectomy. Figure adapted from CAMIS.



LES: Lower esophageal sphincter.

Bohdjalian et. al. found that after treating patients with pantoprazole and omeprazole, their reflux symptoms were resolved. One patient had to be converted to LRYGB due to excessive reflux 15 months after surgery (66). Therefore, it could be possible that the remaining cells from the fundus produce acid, and so it becomes imperative that the entire fundus is removed during surgery (106).

1.3.6 Anatomy and Physiology of the Gastrointestinal System After Laparoscopic Roux-en-Y Gastric Bypass

Changes in Gastroesophageal Function

Intragastric and Intraabdominal Pressure

IGP and IAP are not well defined in the literature after LRYGB.

Esophageal Motility

EM is poorly understood after LRYGB. *Merrouche et. al.* found that before LRYGB, 69% of patients with obesity had a hypotensive LES and 41% had low amplitude esophageal contractions during peristalsis. However, there was no significant linear relationship between LES tone and BMI or waist-hip ratio. Regardless of this high frequency of EM issues preoperatively, they did not find a significantly different frequency of EM issues (LES relaxation, LES tone, contraction amplitude, and dyskinesia) after LRYGB (131). Comparatively, *Korenkov et. al.* described no pre- or postoperative EM abnormalities after LRYGB (132).

Other authors found that the LES tone was significantly altered after LRYGB. *Madalosso et. al.* described a significantly decreased LES pressure after LRYGB, but the average pressure in the population was within the normal range (133). In contrast, *Valezi et. al.* described a significant increase in the frequency of patients with EMDs after LRYGB

(45.6% before to 62.9% after), with hypotensive LES being the primary abnormal finding. However, the only significant difference after LRYGB was an increased contraction amplitude (8.1% before to 19.6% after) (134). *Valezi et. al.* found these differences difficult to interpret, and concluded that until further research was performed, preoperative esophageal manometry is not necessary for patient selection.

Gastric Motility

Very little research exists that specifically examines the gastric motility and emptying after LRYGB. *Dirksen et. al.* found gastric emptying time decreased (135). In light of the reduced size of the pouch and resection of the pylorus, these results are not surprising.

Gastroesophageal Reflux

LRYGB has become an accepted treatment option for persistent reflux after LSG. LRYGB has been shown to significantly decrease the DeMeester Score after surgery from 24.8 to 5.8 (normal <14.7) (131). This decrease is most likely from the decrease in median esophageal acid exposure, described by *Madalosso et. al.*, from 5.1% to 1.1% (133). The gastric pouch of the LRYGB no longer contains the parietal cell mass to produce large quantities of acid, which would explain the reduction in acid reflux. Nevertheless, *Madalosso et. al.* also found that the pouch remains acidic in 86% of patients after LRYGB (133). An acidic pouch could explain how some studies have shown no improvement or continued reflux after LRYGB even though these studies were predominantly based on patient symptom scoring. In terms of gastrin serum levels contributing to gastric acid production, studies show that either the levels reduce or remain the same (127, 128). Since the gastric remnant containing the antrum where gastrin is produced can no longer be stimulated by a meal, a decrease in serum levels is understandable. The most likely

hypothesis for the pouch remaining acidic would be that some parietal cells remain along the staple line of the pouch.

In summary, existing literature describes many contradictory causes for symptoms of GERD following bariatric surgery. Investigators are uncertain whether reflux following LSG is present, if it is alkaline/acidic if present, and what constitutes the precise pathophysiology that leads to these symptoms. While PPI treatment may not be logical considering the resection of the parietal cell mass, conversion to LRYGB does appear to be a solution for reflux after LSG. In general, most surgeons feel that preoperative GERD is a contraindication for LSG (106).

The objective of this thesis was to determine the relationships between obesity, bariatric surgery, gastroesophageal motility, and reflux. The hypothesis was that the anatomical changes after bariatric surgery created disturbances in esophageal and gastric motility, contributing to non-acid gastroesophageal reflux and troublesome symptoms.

One specific patient at our institution launched our interest in understanding the complexity of gastroesophageal motility and reflux following LSG. This case is described in the following chapter.

Chapter 2 – Sleeve Dysmotility Syndrome

Adapted from a publication entitled 'A Case Study of Severe Esophageal Dysmotility Following Laparoscopic Sleeve Gastrectomy' by Sheppard CE, Sadowski DC, Richdeep G, Birch DW (*Case Reports in Surgery*, 2016).

2.1 Introduction

Following bariatric surgery, some patients have been observed to experience reflux, dysphagia, and/or odynophagia. The etiology of this constellation of symptoms has not been systematically studied to date. Often these symptoms are treated empirically with proton-pump inhibitors or dilation of strictures despite the lack of evidence for acid-peptic pathology or mechanical obstruction (136). A case of persistent severe esophageal dysmotility following LSG is presented in this study.

2.2 Case

A 36-year-old female with a BMI of 39.7kg/m^2 underwent an uncomplicated laparoscopic sleeve gastrectomy using a 50 French (F) bougie with dissection 6cm proximal to the pylorus. Her prior medical history consisted of PE, neurocardiogenic syncope, and back pain. She denied any symptoms of dysphagia or gastroesophageal reflux preoperatively. Three months post LSG, she developed recurrent mild retrosternal pain. Her imaging was negative for a PE, and she was treated with proton-pump inhibitors for presumed gastroesophageal reflux. She underwent gastroscopy, computerized tomography (CT), and full cardiac work-up, which were unremarkable. No hiatal hernia, stricture, ulcer, leak, partial dilation of the sleeve, retained fundus, or abnormality in the gastroesophageal junction was observed. However, over the next six months the symptoms worsened, and

she presented to hospital eight times requiring admission for assessment of severe high epigastric pain.

One year post LSG, esophageal manometry and 24h pH studies were performed to investigate a possible esophageal etiology of her pain. The manometry study demonstrated a pattern consistent with hypertensive peristalsis with an average distal contractile interval (DCI) of 5216mmHg/cm/s (normal DCI = 500-5000mmHg/cm/s) with solicited swallows. The 24h esophageal pH study was normal (Jamieson/DeMeester Score of 15.0) with a negative Symptom Index (SI) score (0.0%) between acid reflux episodes and chest pain symptoms. Her symptoms of dysphagia continued, and she steadily declined in weight to a BMI of 27.8. To treat the hypertensive peristalsis, the patient was begun on therapy with diltiazem 30mg once per day (QD).

Due to continuing symptoms while on diltiazem, further investigations were carried out one year later. A second manometry demonstrated weak lower esophageal sphincter pressure, with normalization of manometry parameters while on diltiazem (**Table 2-1**).

Table 2-1: Changes in esophageal motility after 30mg Diltiazem per day therapy.

Esophageal Manometry Measurement	Pre-Diltiazem	Post-Diltiazem	Normal Value
Completed peristalsis (%)	100	100	≥80%
LES pressure (mmHg)	40.5	10.8	13.0-43.0
LES residual pressure (mmHg)	13.4	4.0	<15.0
Contraction amplitude (mmHg)	210.4	76.6	30.0-180.0
High amplitude contraction (%)	100.0	0.0	-
Distal Contractile Integral (mmHg/cm/s)	5216.4	1481.7	500.0-5000.0

LES: Lower esophageal sphincter.

An esophageal 24h pH-impedance study was normal (DeMeester score of 3.2). During the study a high number of nonacid reflux episodes occurred (n=71), but this was not significantly linked to Symptom Association Probability (SAP) (74%). She continued to have severe retrosternal chest pain and episodes of dysphagia with solids, despite evidence that the hypertensive peristalsis appeared to have improved with therapy. Botox injection

of 100 units at the gastroesophageal junction was performed to attempt relieving the esophageal spasms. These appeared to have little effect on the patient's symptoms. Dysphagia symptoms began to worsen to both liquids and solids, and multiple emergency room visits were again observed. After more than three years post LSG, various treatments had been used to treat her esophageal spasms, including calcium channel blockers (Diltiazem), long-acting ß2-adrenoceptor agonists (LABA-2) (Symbicort), vasodilators (Nitrate), anti-spasmodic medication (Lyrica, Gabapentin, Botox), analgesics (Tylenol 4, Tramadol, Butrans, oxyNEO, viscous lidocaine, Hydromorph contin, Fentanyl, Methadone, Dilaudid, Morphine, Clonidine), muscle relaxants (Baclofen, Tizanidine, Zanaflex, Cyclobenzaprine), anti-migraine (Zomig), pro-motility (Domperidone), anti-emetic medication (Zofran), anti-reflux medication (Nexium, Omeprazole, Pantoloc), benzodiazepine (Ativan), non-benzodiazepine hypnotics (Zopiclone), cannabinoid (Cesamet), tricyclic antidepressant (Nortriptyline, Elavil), serotonin norepinephrine reuptake inhibitor (Cymbalta), and selective serotonin reuptake inhibitors (Prozac). Proposed treatment options for this escalating esophageal pain included botox injection to the pylorus, pyloromyotomy, partial esophageal myotomy, or a gastric bypass to try to reduce the hypothesized high-pressure sleeve. As a last resort, some surgeons may also consider a total gastrectomy. After discussion with the patient, a laparoscopic Roux-en-Y gastric bypass was performed, which seemed to relieve the dysphagia and retrosternal pain. A repeat esophageal manometry was performed, which found that

After the gastric bypass, both emergency room (ER) and outpatient visits decreased by two-fold (0.5 vs 0.2 ER visits/month and 0.6 vs 0.3 Outpatient visits/month), attributed to pain relief. Presently five years following LSG, pain symptoms are being managed with

analgesics and neuropathic treatment being considered. This complicated patient has had over 100 visits with specialists over the past 6 years to manage her obesity and chronic dysphagia. Her dysphagia is no longer considered to be associated with a structural cause, but is now attributed to a 'sleeve dysmotility syndrome'.

2.3 Discussion

Esophageal dysmotility occurs when the muscles and sphincters of the esophagus have impaired coordination, altered contraction strength, and/or contractile duration causing impaired esophageal transit. The combination of these abnormalities after LSG has not yet been described.

Symptoms of foregut dysmotility are disconcerting when they arise following LSG. These symptoms are varied and include dysphagia, odynophagia, nausea, vomiting, heartburn and pain.

Carabotti et al found that dysphagia developed in 19.7% of patients after LSG, which manifested in retrosternal or throat discomfort when consuming solids or liquids (137). A significant increase in dyspepsia (59.4%) was also attributed to increased pressure in the sleeve (137). *Kleidi et al* found a combination of reflux and dysphagia significantly increased after LSG (138). Additional reports describe dysmotility after laparoscopic adjustable gastric banding (LAGB) as causing symptoms of dysphasia and reflux (139). These symptoms normally resolve after adjustment or removal of the band. In contrast, dysmotility following LSG may be irreversible.

The case demonstrated manometric evidence for hypertensive peristalsis. It is unclear if this disorder was present before LSG surgery, whether this was a pre-existing condition that was exacerbated by the LSG, or whether the syndrome was created by the LSG.

Despite that, treatment with calcium channel blockers reversed the manometric abnormalities, but failed to resolve symptoms. Sleeve dysmotility syndrome causes persistent dysphagia and reflux-like symptoms, and may respond partially to gastric bypass.

It is difficult to determine whether technique contributes to this sleeve dysmotility syndrome, as many of these esophageal syndromes are idiopathic. Bougie size for LSG and its impact on leak rate and gastroesophageal reflux have been extensively discussed in the literature. *Parikh et al.* described in their meta-analysis using data from nearly 10,000 patients that a bougie size equal or greater to 40F decreased the odds of developing a postoperative leak (140). The literature on technique contributing to gastroesophageal reflux symptoms proposes many theories (i.e., retained fundus, blunted angle of His, bougie size, resection of antrum, high-pressure system, etc). This patient was negative for both a leak and acid reflux, which made it challenging to assess whether technique contributed to the patient's symptoms based on current literature. The patient had manometric abnormalities, and the causal relationship of LSG technique and esophageal dysmotility has yet to be defined.

The LSG has been described as creating a high-pressure system in the sleeve from simultaneous gastric and pyloric contractions (119). When filled with saline, the IGP is increased after LSG (43mmHg) compared to normal gastric anatomy (34mmHg) (76). By reducing the 'high-pressure' system to a 'low-pressure' system, i.e., by LRYGB, the goal was that this strategy would alleviate the hypertensive esophagus and esophageal spasms. The LRYGB has been successful for improving or resolving other gastroesophageal issues

after the LSG, such as uncontrollable gastroesophageal reflux (141), and may be the preferential choice for managing dysmotility.

Preoperative manometry is used to avoid major postoperative issues of dysphagia before anti-reflux surgery. Concurrent 24h pH testing is also used to confirm the presence of reflux. These results can detect upwards of 1 of 14 patients being inappropriate for surgical intervention (142). Consequently, preoperative manometry may be a method to screen patients with dysmotility to select an appropriate bariatric procedure. Screening would avoid significant postoperative complications and the ultimate need for reoperation.

This is a complicated question that has significant impact on the investigation burden placed on the patient. Considering the difficulties with managing sleeve dysmotility syndrome, one must consider the need for preoperative testing. The question is whether motility studies should be required for all patients planning to undergo a LSG. Manometry results would identify patients that may not be able to tolerate a high-pressure sleeve either from esophageal spasms, hypertensive esophagus, achalasia, or scleroderma. Consequently, they may be better candidates for a LRYGB.

This case demonstrates the complexity of EM and reflux symptoms after surgery. To further understand the prevalence of these disorders in this population, in the following chapter the results of a retrospective chart review performed to identify patients with EM or reflux issues and management strategies are described.

Chapter 3 – Rates of Reflux after Bariatric Surgery

Adapted from a publication entitled 'Rates of Reflux Before and After Laparoscopic Sleeve Gastrectomy for Severe Obesity' by Sheppard CE, Sadowski DC, de Gara CJ, Karmali S, and Birch DW (*Obesity Surgery*, 2015 25(5):763-8). Reproduced with permission of Springer.

3.1 Purpose and Rationale

LSG provides substantial weight loss results with fewer complications than LRYGB (23, 63-65). However, observational studies have demonstrated that LSG has a higher incidence of postoperative GERD compared to LRYGB (12, 17, 133, 143-145). Most patients with reflux symptoms following bariatric surgery are treated with anti-secretory drugs, such as H_2 antagonists or PPIs (146), with the presumption that the esophageal refluxate is acid. Yet, since most of the gastric parietal cell mass has been removed during surgery, subsequent acid production should be negligible. Few studies to date have characterized the pathophysiology associated with reflux symptoms after LSG, and consequently current treatment practices may have questionable effectiveness (137). The objective of this study was to determine the incidence of preoperative and postoperative reflux in LSG and LRYGB patients, and characterize reflux treatment type and response. The hypothesis was that reflux would increase after LSG and decrease after LRYGB.

3.2 Study Design

A retrospective chart review was carried out to identify patients who underwent either LSG or LRYGB between January 2010 and December 2012 as part of the EABSC. This program adheres to the NIH criteria for bariatric procedures and performs approximately 300 procedures a year (16). The preoperative protocol requires patients to attend a median

of 9 clinic appointments with a multidisciplinary team to undergo counseling for behaviour modification, lifestyle changes, and surgical preparation (147). Preoperative gastroscopies or barium swallows were performed if the patient had either a history of reflux, esophagitis, gastritis, or hiatal hernia, or based on the individual surgeon's protocol for pre-surgery screening. Patients are selected based on their medical history, weight loss goals, and ability to attend postoperative follow-up. The follow-up protocol required patients to return for assessment at 1, 3, 6, and 12 months post-operatively. In the clinic, usual clinical practice was to prescribe PPI therapy to patients with symptoms of reflux, heartburn, or dyspepsia. If symptoms persisted a gastroscopy was performed for further assessment.

For the purposes of analysis, GERD was defined as the presence of heartburn symptoms of sufficient severity to require pharmacological intervention with antacids, H_2 antagonists, or PPIs. The primary study outcome was the proportion of patients at each observation point with GERD. Patients were excluded from the analysis if they had previous bariatric or gastric surgery, perioperative complications, or if they required surgery for an immediate complication. Statistical analysis for PPI usage was performed using McNemar's test (148). Categorical data variables (prescription type, dosage, and response, endoscopic findings, and patient demographics) were represented as a percentage (number). Continuous data variables (BMI and age) were presented as average ± standard deviation, and analyzed for statistical significance using a paired t-test. Graphs were created using GraphPad Prism 5.0 software.

LSG surgery: Under general anesthesia, a Veress needle was inserted and the abdomen was insufflated. The angle of His was dissected from the left crus. The Harmonic™ scalpel (Ethicon Johnson & Johnson) was used to divide the vessels of the greater curvature

starting from a point 6cm proximal to the pylorus. The sleeve staple line was made using two black loads for the antrum and four purple loads for the stomach body using a Covidien Endo GIA™ 60mm staples with Tri-Staple™ technology (Covidien, Minneapolis, MN) along a 50F bougie following the lesser curvature. The greater curvature was resected to 1cm from the esophagogastric junction. The resected free portion of the stomach was removed. Gastroscopy was performed after hemostasis to check the staple line. An air test and methylene blue test were used to identify leaks.

LRYGB surgery: Under general anesthetic, the ligament of Treitz was identified; 30cm distal to this, the small bowel and its mesentery were divided using an Echelon™ 60mm stapler (Endosurgery, Ethicon Johnson & Johnson). A Roux limb of 100cm was created and a stapled side-to-side jejunojejunostomy was completed. Anti-obstruction sutures were placed and the small bowel mesenteric defect was closed. The omentum was divided for an ante-colic Roux limb placement. A Storz dissector was used to dissect the angle of His and enter the lesser sac. The neuro-vascular bundle at the lesser curve was divided using a gray load Endo GIA™ stapler (Ethicon Johnson & Johnson), approximately 7cm below the EGJ. A 50F bougie was inserted and blue loads were used to create a 50cc gastric pouch. The gastrojejunostomy was completed using 25mm circular EEA stapler (Covidien OrVil™, Covidien, Minneapolis, MN). A gastroscopy and leak test were performed similarly to the LSG.

For both procedures, any significant hiatal hernia was repaired at the time of surgery by re-approximating crural edges with interrupted sutures.

3.3 Results

3.3.1 Patient Demographics

From January 2010 to December 2012, a total of 412 LSG or LRYGB surgeries were performed by two surgeons (SK, DWB) at our institution. Of these cases, 34 were excluded because patients were either out-of-province with incomplete follow-up (n=18), had previous gastric surgery (n=6), or charts could not be located (n=10). A total of 378 cases were included in the review. Demographic data for included cases is outlined in **Table 3-1**.

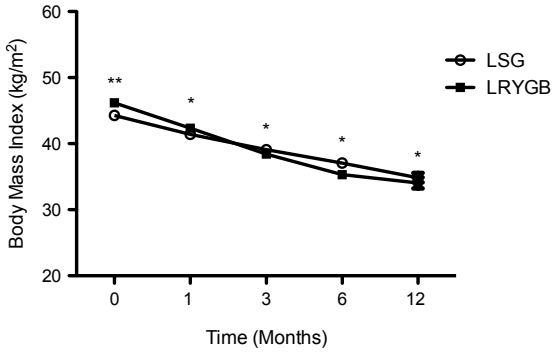
Table 3-1. Patient preoperative demographics.

	Laparoscopic Sleeve Gastrectomy (n=205)	**Laparoscopic Roux-en-Y Gastric Bypass (n=173)**
Age (Years)	43.8±9.5	43.6±8.6
Gender (% Female)	82.0	81.5
Smoking (% Yes)	6.8	6.6
Initial BMI (kg/m^2)	48.5±9.7	49.3±8.4
Hiatus Hernia (%)	29.3	19.0
Proton-Pump Inhibitor Use (%)	28.4	31.7
Upper Gastrointestinal Studies (%)	(n=137)	(n=99)
Normal	63.5	79.8
Gastritis/Esophagitis	7.3	11.1
Gastroesophageal reflux	25.5	3.0
Barrett's	0.7	2.0
Helicobacter pylori	0.0	3.0
Ulcers	0.7	1.0
Other	2.2	0.0

BMI: Body mass index.

The only significant difference between surgical groups was a larger preoperative BMI in LRYGB patients ($p<0.05$). Both surgical groups had a significant decline in postoperative BMI ($p<0.001$). The magnitude of weight loss was similar for both LSG and LRYGB groups (**Figure 3-1**).

Figure 3-1. Average body mass index with standard error over time for laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass groups.



Significance: *p<0.001 before and after surgery. **p<0.05 between LSG and LRYGB.
LSG: Laparoscopic sleeve gastrectomy, LRYGB: Laparoscopic Roux-en-Y gastric bypass.

In total, 58 (15%) patients required postoperative gastroscopy for upper abdominal pain, obstructive symptoms, or persistent reflux. Nine percent of these patients had documented pre-existing reflux issues. The gastroscopy findings were 17% esophagitis/gastritis, 3% *H. pylori*, 22% ulcers, 14% strictures, 7% other findings, and 36% were normal.

A total of 15% of documented or confirmed hiatus hernias required surgery in the LSG group. There was no significant difference in reflux rates between patients with a hiatus hernia versus those without. Nor was there a difference between patients that had their hiatus hernia fixed during surgery versus those that did not, at any follow-up time. No LSG patients were converted to LRYGB for refractory reflux symptoms at the time of this study.

3.3.2 Esophageal Motility Disorders after Surgery

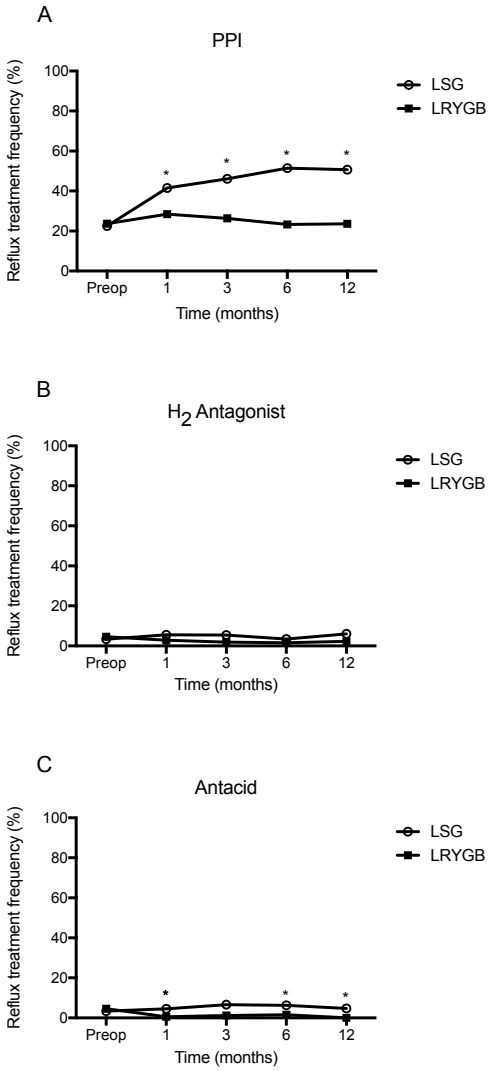
A single LSG patient had documented 'positional dysmotility' before surgery, but did not have any symptoms of dysphagia or reflux after surgery. One LRYGB at 3 months after surgery had distal esophageal dysmotility with mild spasm and GE reflux confirmed by 24h pH and high-resolution esophageal manometry. One LSG at 12 months after surgery

had mild spastic contractions of the distal esophagus on high-resolution esophageal manometry.

3.3.3 Frequency and Type of Reflux Treatment

Figure 3-2 demonstrates reflux treatment therapy frequency up to 12 months after surgery.

Figure 3-2. Anti-reflux treatment frequencies of proton-pump inhibitor (A), H_2 antagonist (B), or antacids (C) as pharmacological treatment for heartburn symptoms in laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass patients over time.



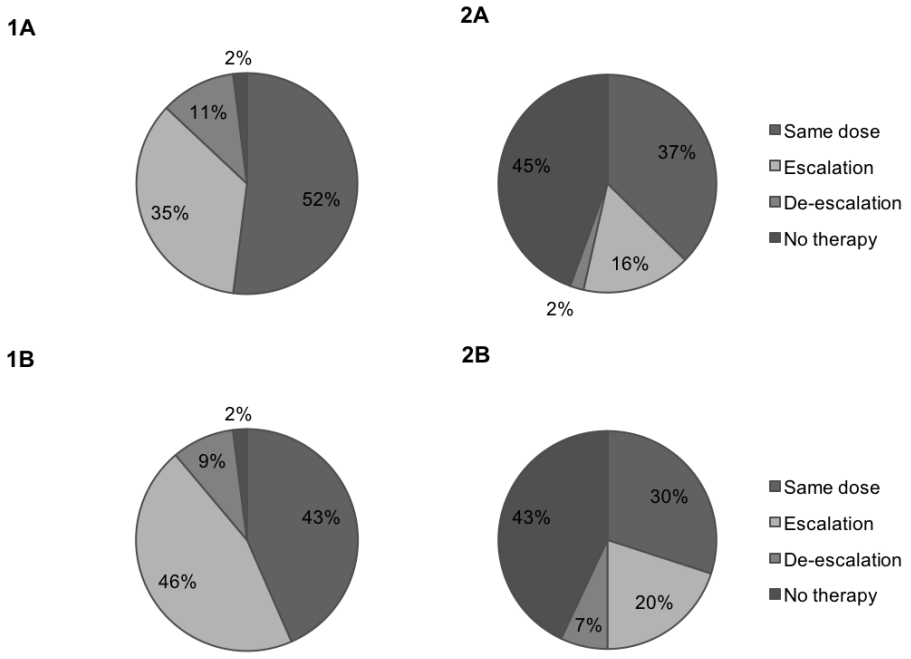
Significance: *p<0.001.
LSG: Laparoscopic sleeve gastrectomy, LRYGB: Laparoscopic Roux-en-Y gastric bypass, Preop: Preoperative, PPI: Proton-pump inhibitor.

Both LSG and LRYGB groups had similar preoperative rates of total reflux treatment (28 vs. 32%, respectively, p=n.s.). A significant difference in PPI use between surgical groups was seen at 1 month ($p<0.05$) to 1-2 years ($p<0.001$). There was no significant difference in PPI use in the LRYGB group from 1 month to 1-2 years. At 1 month, LSG patient PPI use increased from 28% to 50%, and peaked at 6 months (61%).

3.3.4 Dosage of Reflux Treatment

Figure 3-3 demonstrates the postoperative changes in PPI dosage for both groups undergoing preoperative treatment for reflux.

Figure 3-3. Changes in anti-secretory therapy dosages in patients with pre-existing reflux after laparoscopic sleeve gastrectomy (1) and laparoscopic Roux-en-Y gastric bypass (2) patients at 6 months (A) and 12 months (B) follow-up.



LSG: Laparoscopic sleeve gastrectomy, LRYGB: Laparoscopic Roux-en-Y gastric bypass.
1A: n=54. 2A: n=43. 1B: n=44. 2B: n=30.

In an equivalent timeframe, 102 (85%) patients from both groups with continual PPI treatment noted reflux symptom relief. A greater rate of reported symptom relief was observed in the LRYGB group at 1 month ($p<0.01$), while at 6 and 12 months LSG patients began to report greater rates of relief ($p<0.05$). In addition, only 6 (5%) patients found their reflux treatment was ineffective. In the LSG and LRYGB groups, 3 (2%) and 13 (43%) patients, respectively, could stop reflux medications 12 months after surgery and remain symptom free. In total, 10 (22%) patients noticed the discontinuation of PPI caused a rebound in reflux symptoms (p=n.s.).

3.4 Discussion

Obese individuals are at an increased risk of GERD, esophagitis, and esophageal adenocarcinoma (130). These risks may be primarily caused by central adiposity (149). 30% of patients before surgery had reflux symptoms severe enough to require daily therapy with PPIs. This rate of severity is consistent with other observations of the pre-bariatric surgery population (105, 150). According to the American College of Gastroenterology GERD management guidelines, LRYGB is the preferred method of surgically managing reflux in the obese population (151). Despite an average weight loss of 20kg in the LSG group by 6 months after surgery, a paradoxical increase in PPI usage for GERD symptoms (29% of patients) was observed. As well, 35% of LSG patients on pharmaceutical intervention for reflux before surgery required an escalation in their daily dose. Several previous studies have identified GERD as a complication of LSG with rates ranging from 10-35% after surgery (12, 17, 143, 144). Proposed mechanisms for the increase in GERD after LSG include increases in IGP, alterations in gastric emptying, and reduction in LES effectiveness due to blunting of the angle of His, and resection of the gastric sling fibres

(44, 75, 94, 106, 122). Yet, no single study has been able to pinpoint the pathophysiologic cause of reflux (152). Variations in postoperative reflux rates could be accounted for by differences in surgical technique. For example, a smaller sleeve size could result in reductions in pouch compliance and pouch outlet obstruction both predisposing patients to GERD. Bougie sizes ranging from 46-50F have been found to decrease or resolve reflux symptoms, while more restrictive sleeves tended to be associated with increased rates of postoperative reflux (153, 154). A recent systematic review by *Parikh et. al.* described no significant impact on 36-month weight loss based on bougie size for LSG (140), while an international expert panel led by *Rosenthal et. al.* came to a consensus (87%) that the ideal bougie size is between 32-36F, and that using a bougie outside of this range may lead to increased complication rates and dilation of the sleeve (155). However, no consensus exists on the relationship between bougie size and reflux. Variations in technique also exist for repairing hiatal hernias. Repairs during bariatric surgery require re-approximating the crural edges or placing a single suture depending on the size of the hernia (156). Some research has shown that while variation does exist, hiatal hernia repairs are ultimately beneficial for reflux rates. But, no statistical difference in reflux rates was found for patients that had their hernia repaired in this patient group. Despite parietal cell mass removal with the gastric remnant, PPI treatment has been found to be successful in treating patient symptoms (66). However, a placebo effect (19%) has been demonstrated to play a role in PPI reflux therapy (157).

Some investigators have observed that the prevalence of reflux is considerably reduced after LSG (153, 154) or diminishes over time after an initial increase (75, 143). Physiologically, reductions in acid reflux events should be expected after LSG due to

gastric parietal cell mass resection, reduction of BMI, and decreased IAP; even so, reflux symptoms did not lessen regardless of a significant decrease in BMI.

Disturbances in esophageal and LES motility have also been proposed as playing a pivotal role in postoperative GERD. Another possible explanation for the increase in reflux symptoms in the LSG group could be bile reflux. Active bile can be refluxed from the duodenum into the pouch and subsequently into the esophagus causing mucosal damage. While it is possible to measure non-acid reflux events using Bilitec technology, these studies have yet to be performed in the obese or bariatric population, nor are they generally performed in Canada. In examining the motility profile of the foregut, *del Genio et. al.* found that LES pressures did not change postoperatively, but peristalsis and complete bolus movements were reduced from 90% to 50%. There was also evidence of a significant increase in non-acid reflux events (121). Few patients were identified to have EM issues after surgery. However, patients have been observed to be asymptomatic to these disorders and without active screening, the number of patients with EM issues may be higher (158).

LRYGB appears to be the only current surgical option not associated with postoperative acid reflux (60, 130). *Madalosso et. al.* found that LRYGB decreases reflux symptoms, esophageal acid exposure, and PPI usage, despite the observation that the gastric pouch remained acidic by 24h pH monitoring (133). The same conclusion was not drawn from the LRYGB reflux data in this population, which demonstrated no significant decrease in PPI use. Some bariatric centres mandate that preoperative reflux is a contraindication to LSG and LRYGB should be offered as an alternative (30, 107).

Dosage of PPI in both LSG and LRYGB groups decreased only by 2-7%, indicating that reflux was being controlled by PPI, by which the majority of patients expressed symptom

relief to clinic staff. Over time LRYGB patients were more likely to be able to stop taking PPIs (2% versus 43%). Currently, patients' symptoms are treated with PPI and surgically managed with LRYGB should reflux persist.

PPI does have its limitations such as rebound symptoms, and more data is needed to determine the cause of reflux to elucidate an effective treatment strategy. Gastrin serum levels are an indication of the level of acid production within the pouch. While these gastrin serum levels have been shown to decrease after LRYGB, no change has been observed after LSG (128, 159).

The limitations of this study were the amount of information available in the charts, patients not attending follow-up appointments, and the clinic's variable follow-up time from 12 to 24 months. In addition, patients with pre-existing reflux remained on their acid-suppressant therapy after surgery, and may not have stopped this medication because of continuing symptom management. Reflux symptoms and PPI prescription type and dosage were noted in the prescription list, nursing notes, and surgeon letters. A potential explanation for the lack of reduction in reflux symptoms after LRYGB could be that physicians are less vigilant to remove patients from anti-secretory therapies than other therapies for diabetes, hypertension, or dyslipidemia. In addition, 17 LRYGB patients were placed on PPI for anastomotic ulcer treatment, which could mask a decrease in PPI usage. Perhaps with a longer consistent prospective follow-up of patients a decreasing trend for both LSG and LRYGB reflux symptoms at 2-3 years after surgery could be observed. Several mechanisms are speculated to cause a decrease in reflux symptoms years after LSG, including increased compliance of the sleeve, sleeve shape, and return of the angle of His (160).

Endoscopy results were a secondary outcome, because of the discrepancies between surgeons for preoperative gastroscopy screening. Only 25% of patients that had a preoperative gastroscopy underwent one postoperatively, leading to a 'de novo' esophagitis rate of 4%. A controlled study of patients undergoing both pre- and postoperative gastroscopy would be needed to clarify an accurate rate of 'de novo' esophagitis after LSG. In conclusion, reflux symptoms are significantly increased after LSG. LSG patients more frequently required initiation of reflux treatment after surgery than LRYGB patients. Furthermore, reflux treatment with acid-suppressant therapies has been reported by patients to relieve reflux symptoms after surgery. Nevertheless, the removal of the parietal cell mass calls into question the pH of the refluxate and appropriate management of reflux symptoms.

It is well known that symptoms do not always correlate with an identifiable disorder. In order to investigate the relationship between GI symptoms and postoperative complications, including reflux, patients were asked to complete a GI questionnaire before and after surgery while following them 6-12 months after surgery.

Chapter 4 – Gastrointestinal Symptom Reporting After Bariatric Surgery

4.1 Purpose and Rationale

Bariatric surgery has been known to cause changes, resolution, or onset of gastrointestinal symptoms. Patients may present with symptoms of persistent nausea, constipation, and abdominal pain after bariatric surgery (161, 162). Invasive clinical investigations have not been able to determine the etiology of these complaints.

Assessment of gastrointestinal symptoms is often performed by administering questionnaires. One such questionnaire is the Gastrointestinal Symptom Rating Scale (GSRS). This interview-based rating scale was developed in Sweden and published in 1988 (163). The GSRS was found to be reliable and have good construct validity (164). Results from the GSRS have been primarily reported after LRYGB in the bariatric population and shown that GI symptoms improve after surgery (165, 166).

GI quality of life (QOL) has also been explored after bariatric surgery and was found to improve 24 months after surgery (167). Similarly, obesity contributes to QOL. The Impact of Weight on Quality of Life-Lite© questionnaire was developed to assess this relationship. This questionnaire has also been used to assess QOL after bariatric surgery. After LRYGB and BPD-DS, results from the IWQOL demonstrated a marked increase in QOL (168-170).

The purpose of this project was to identify the chief gastrointestinal complaints of postoperative patients, identify emerging QOL trends after surgery, and determine whether specific patterns in GSRS symptom reporting were linked to postoperative complications or QOL. The hypothesis was that patients with surgical complications after bariatric surgery would experience a flare in specific symptoms, while patients without complications would experience less severe GI symptoms than before surgery.

4.2 Study Design

Consecutive patients from the EABSC were asked to complete the GSRS and IWQOL questionnaires by study staff before and 6-12 months after LRYGB or LSG. Patients that underwent an LAGB or did not proceed with surgery were excluded. Patients also gave written consent for study staff to access their EABSC medical chart for medical history and surgical follow-up.

4.2.2 Questionnaires

Gastrointestinal Symptom Rating Scale

The GSRS questionnaire was developed in Sweden by *Svedlund et al.* to assess gastrointestinal symptoms in patients with irritable bowel disease and peptic ulcer disease (163). The GSRS questionnaire consisted of 15 questions regarding gastrointestinal symptoms ranging from reflux symptoms to urgency of bowel movements in five categories (reflux syndrome, indigestion syndrome, constipation syndrome, diarrhea syndrome, and abdominal pain syndrome). Answers were on a Likert 7-point scale ranging from 1 'No discomfort at all' to 7 'Very severe discomfort'. Patients were required to recall their symptoms occurring over the past week.

The GSRS questionnaire content was previously validated and tested for reliability with gastroesophageal reflux disease, among other GI disorders, including dyspepsia and inflammatory bowel disease (164, 171, 172).

The GSRS Likert scale was represented as mild (average score of 1-2), moderate (average score of 3-5), and severe (average score of 6-7) symptoms to more easily convey the results graphically. A dashed line was used to represent the transition in syndrome severity. A line was drawn on the GSRS result graphs to represent the average score of 2126 individuals

from the general population (Abdominal Pain: 1.56, Reflux: 1.39, Indigestion: 1.78, Diarrhea: 1.38, Constipation: 1.55) (173).

Impact of Weight on Quality of Life

The IWQOL-Lite© questionnaire is a short-form questionnaire with 31 questions across five quality of life domains (physical function, public distress, self-esteem, sexual life, and work) (Unable to reproduce due to copyright) (174). The questionnaire was first developed at the Duke University Diet and Fitness Center to assess patients' concerns and dissatisfactions with their obesity. Each question began with "Because of my weight…" and answers were on a Likert scale ranging from 1 'Never true' to 5 'Always true'. Patients were asked to complete all questions they felt comfortable completing, as some questions were sensitive in nature.

This questionnaire was previously validated in the obese population (175) and tested in the bariatric surgery population (168-170).

The total scores for each domain were transformed into a percentage of the total possible score (i.e. [maximum domain score-raw domain score]/domain score range*100) according to the IWQOL questionnaire manual. Patient results were compared to a community sample (176).

4.2.3 Design

Both questionnaires were administered 1-2 weeks before bariatric surgery and repeated 6-12 months after surgery. Surgical technique was as described in Chapter 3. The follow-up timeframe was chosen based on clinical experience, as most symptoms of reflux and ulcer development have been observed to peak at this time. Follow-up time was dependent on when the patient returned to the clinic, as one third of the patient population resides outside

of Edmonton.

Questionnaire results were separated by LSG and LRYGB to compare scores between procedures, and compare the change before and after each surgery. Patients that experienced a confirmed intermediate (>3 months to <6 months after surgery) complication were asked to answer their follow-up questionnaire while keeping their complication symptoms in mind. If the patient experienced adverse GI symptoms without a defined complication, they were monitored for another 6 months to see if they develop a confirmed late complication (>6 months to <12 months after surgery).

Patients taking a PPI were considered to have reflux. Patients that experienced persistent abdominal pain for >3 months with no anatomical or physiological cause after investigation were considered to have chronic abdominal pain.

4.2.4 Primary Outcome

The primary outcome was to observe changes in GI symptoms before and after bariatric surgery and explore whether specific GI symptom changes were associated with complications of the GI tract.

4.2.5 Secondary Outcome

The secondary outcome was to observe changes in QOL before and after bariatric surgery and its relationship to BMI and GI symptoms.

4.2.6 Sample Size

A sample size of 100 was chosen based on evidence that 50 patients within each arm of the cohort was an ideal balance between significant power (80%) and over-stretched resources (177). This sample size seemed appropriate considering the complication rates previously investigated in a retrospective chart review of 512 patients at the EABSC (unpublished

data). 16% of LRYGB and 1% of LSG were expected to have an ulcer or stricture. 28% of LRYGB and 10% of LSG were expected to have chronic abdominal pain. Reflux was expected to resolve in 24% of LRYGB and worsen in 20% of LSG patients. LRYGB hernia prevalence was expected to be 5%.

4.2.7 Data Analysis

A Wilcoxon test was used to compare GSRS and IWQOL-Lite scores within a surgical group, and a Mann-Whitney U test was used to compare between surgical groups (LSG and LRYGB) to assess statistical differences in symptom reporting. A Mann-Whitney U test was used to compare GI symptom scores between patients with and without complications. A Kruskall-Wallis test was used to assess significant differences between BMI and QOL domains before and after bariatric surgery. Significance was $p<0.05$. Non-parametric measures were selected in order to account for deviations from normality. Data was presented as average±standard deviation or median (range).

4.3 Results

4.3.1 Patient Demographics

In total, 100 patients were asked to complete the GSRS before surgery (40 LSG, 60 LRYGB). The questionnaire response rate was 92%. Patients did not complete follow-up, because 1 died in a MVC, 5 patients did not return to clinic after surgery, and 1 patient did not complete the questionnaire at follow-up. 60 of the patients that completed the GSRS were also asked to complete the IWQOL-Lite© before surgery (25 LSG, 36 LRYGB). The questionnaire response rate was 90%. LSG patients were 90% female and on average were 45.3±10.2 years old. LRYGB patients were 82% female and on average were 43.7±10.5

years old. Refer to **Table 4-1** for patient comorbidities. Only 1 LSG and 2 LRYGB had no comorbidities.

Table 4-1: Patient preoperative comorbidities by procedure.

Comorbidities (%)	Laparoscopic Sleeve Gastrectomy (n=40)	Laparoscopic Roux-en-Y Gastric Bypass (n=60)	Total (n=100)
Hormonal Comorbidities			
Diabetes/Impaired Glucose Tolerance[1]	13	28	20
Hypothyroidism	13	17	15
Polycystic Ovarian Syndrome	10	7	8
Cardiovascular Comorbidities			
Hypertension	50	33	40
Hyperlipidemia	28	20	23
Stroke	0	2	1
Anemia	5	0	2
Gastrointestinal Comorbidities			
Gastroesophageal Reflux	30	25	27
Gastrointestinal Inflammatory Disorders	8	8	8
Fatty Liver Disease	23	8	14
Respiratory Comorbidities			
Obstructive Sleep Apnea	50	42	45
Asthma/Chronic Obstructive Pulmonary Disease[2]	18	12	14
Psychological Comorbidities			
Depression/Anxiety Disorders[3]	48	45	46
Attention Deficit-Hyperactivity Disorder	3	2	2
Orthopedic Comorbidities			
Osteoarthritis/Rheumatoid Arthritis[4]	43	35	38
Chronic Pain	13	5	8
Multiple Sclerosis/ Fibromyalgia[5]	3	3	3

[1] 1 LSG and 1 LRYGB had impaired glucose tolerance
[2] No LSG and 1 LRYGB had chronic obstructive pulmonary disease and obesity hypoventilation syndrome
[3] 4 LSG and 2 LRYGB had an anxiety disorder
[4] 1 LSG had rheumatoid arthritis
[5] No LSG and 2 LRYGB had multiple sclerosis
LSG: Laparoscopic sleeve gastrectomy, LRYGB: Laparoscopic Roux-en-Y gastric bypass.

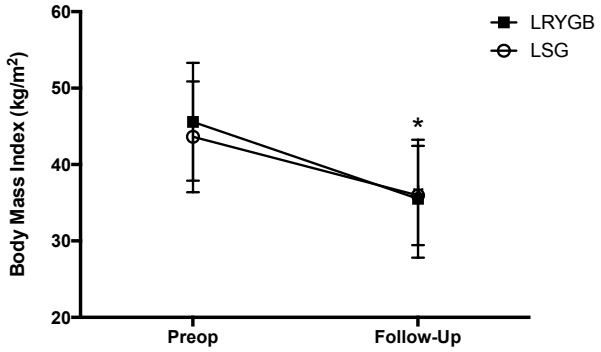
5% of LSG and 15% of LRYGB had a previous cholecystectomy. Preoperatively, 21% of LRYGB and 20% of LSG patients were taking a PPI. No patients were taking other medications for their GI system.

4.3.2 Postoperative Weight Loss

Patients had an average BMI of 47.4±9.7kg/m^2 (LSG) and 48.8±9.5kg/m^2 (LRYGB) at initial presentation to clinic. Patients' BMI reduced to an average BMI of 43.6±7.3kg/m^2

(LSG) and 45.6±7.7kg/m^2 (LRYGB) before surgery. Average postoperative follow-up was 7.1±1.9months (LSG) and 6.7±1.7months (LRYGB). BMI at follow-up was reduced to 36.0±6.5kg/m^2 (LSG) and 35.5±7.7kg/m^2 (LRYGB) (**Figure 4-1**). This reduction in weight was equivalent to a %EWL of 45.7% (LSG) and 53.7% (LRYGB). There was no statistical difference between LSG and LRYGB weight loss (p=0.067).

Figure 4-1: Reduction in body mass index after laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass.



Significance: *p<0.001 preop-follow-up.
LSG: Laparoscopic sleeve gastrectomy, LRYGB: Laparoscopic Roux-en-Y gastric bypass, Preop: Preoperative.

4.3.3 Postoperative Complications

At follow-up, 10.3% LSG and 27.3% LRYGB had a surgical complication (i.e., late bleed, ulcer, wound infection, PE, hernia). Additionally, 41.0% of LSG and 34.6% of LRYGB had symptoms related to GI complications (chronic abdominal pain, reflux, marginal ulcer, *H. pylori,* intraabdominal bleed, ventral hernia) (**Table 4-2**). The single hernia was repaired by laparoscopic component separation. No deaths occurred related to surgical complications.

Table 4-2: Percentage of patients with perioperative complications and follow-up complications after laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass.

Complications	Laparoscopic Sleeve Gastrectomy (n=40)	Laparoscopic Roux-en-Y Gastric Bypass (n=60)
Perioperative Complications (%)		
Anastomotic or Staple Line Leak	0.0	0.0
Pulmonary Embolism	2.6	0.0
Intraabdominal Bleed[1]	0.0	7.3
Surgical Site Infection or Abscess	5.1	10.9
Complications at Follow-Up (%)		
Gastro-Gastric Fistula	-	0.0
Ulcer or Stricture	0.0	7.3
Ventral or Incisional Hernia	0.0	1.8
Internal Hernia	-	0.0
Gastroesophageal Reflux[2]	30.8	9.1
Chronic Abdominal Pain	15.4	18.2

[1] 1 LRYGB had recurrent intraabdominal bleeding at follow-up
[2] 1 LRYGB and 1 LSG were positive for *H. pylori* at follow-up
LSG: Laparoscopic sleeve gastrectomy, LRYGB: Laparoscopic Roux-en-Y gastric bypass.

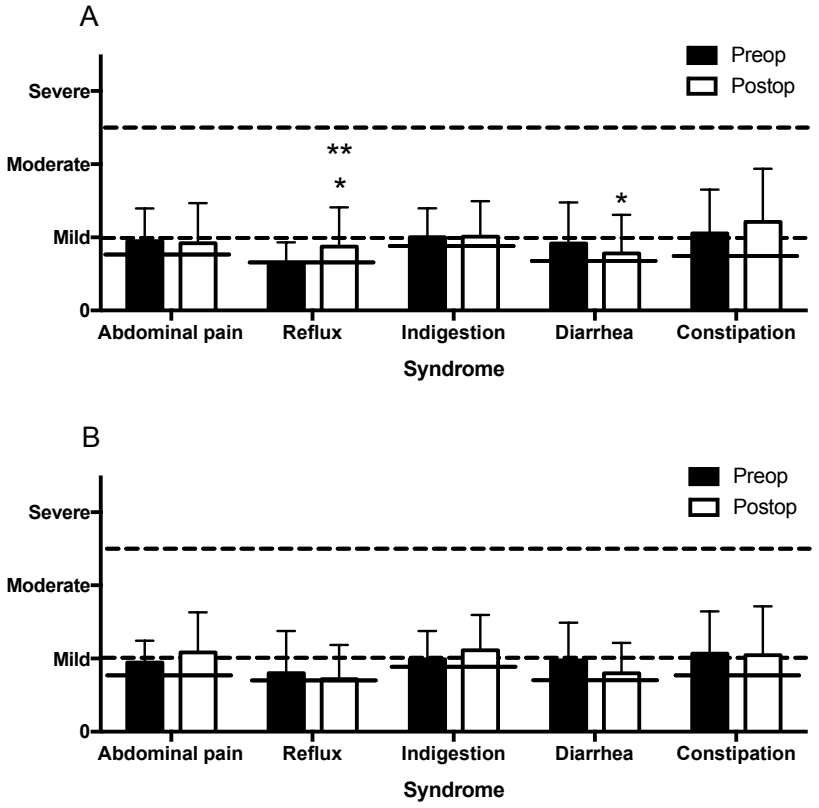
Several investigations were required to assess complications or complaints after LSG, including 2 ultrasounds, 2 CTs, 4 gastroscopies, and 1 esophageal manometry (67% normal). LRYGB patients required many more investigations, including 1 barium swallow, 2 ultrasounds, 2 CTs, 6 gastroscopies, 1 diagnostic laparoscopy, and 3 readmissions. Many of these investigations were overwhelmingly normal (92%) for patients with a complaint (i.e., chronic abdominal pain).

Postoperatively, 30.8% of LSG and 23.6% of LRYGB were taking a PPI. This result excludes LRYGB patients taking a PPI for mucosal protection. The incidence of GERD treated by PPI increased by 22.6% after LSG, and 62.5% of patients taking a PPI preoperatively continued therapy after LSG. 66.7% of patients taking a PPI before surgery were able to discontinue therapy after LRYGB. Additionally, 7.7% of LSG and 10.9% of LRYGB required a GI medication, such as sucralfate, Zantac, or Zofran. At the time of this study only 3 LRYGB patients were on a PPI for gastric protection.

4.3.4 Gastrointestinal Symptoms

The average scores for each gastrointestinal syndrome were mild at pre-op (1.6-2.1) and remained mild after LSG (1.6-2.4) and LRYGB (1.6-2.2) (**Figure 4-2**).

Figure 4-2: Gastrointestinal Symptoms Rating Scale results pre- and post- laparoscopic sleeve gastrectomy (A) and laparoscopic Roux-en-Y gastric bypass (B).

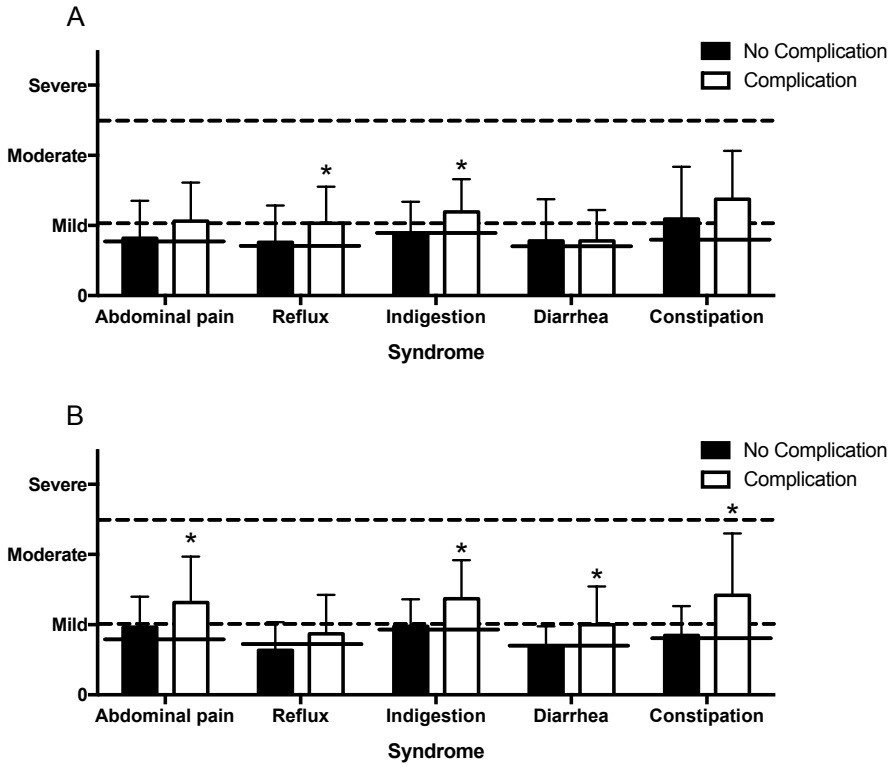


Significance: *p<0.05 pre-postop, **p<0.05 LSG-LRYGB.
— General population values. --- Separation of syndrome severity.
LSG: Laparoscopic sleeve gastrectomy, LRYGB: Laparoscopic Roux-en-Y gastric bypass, Preop: Preoperative, Postop: Postoperative.

Some syndromes were statistically different from the general population scores before (LSG: reflux p=0.017, constipation p=0.0051 and LRYGB: abdominal pain p=0.0004, diarrhea p=0.0028, constipation p=0.043) and after (LSG: abdominal pain p=0.0017, constipation p=0.003 and LRYGB: reflux p=0.028, indigestion p=0.023) surgery.

Only LSG patients had significantly different GSRS scores before and after surgery: an average 0.5 increase in reflux syndrome score (p=0.01) and an average 0.3 decrease in diarrhea syndrome score (p=0.046). All scores, with the exception of preoperative reflux syndrome score before LSG, were higher than the average score of healthy controls. GSRS scores were significantly increased in patients with postoperative abdominal complications (**Figure 4-3**).

Figure 4-3: Gastrointestinal Symptoms Rating Scale results for patients with and without postoperative abdominal complications after laparoscopic sleeve gastrectomy (A) and laparoscopic Roux-en-Y gastric bypass (B).



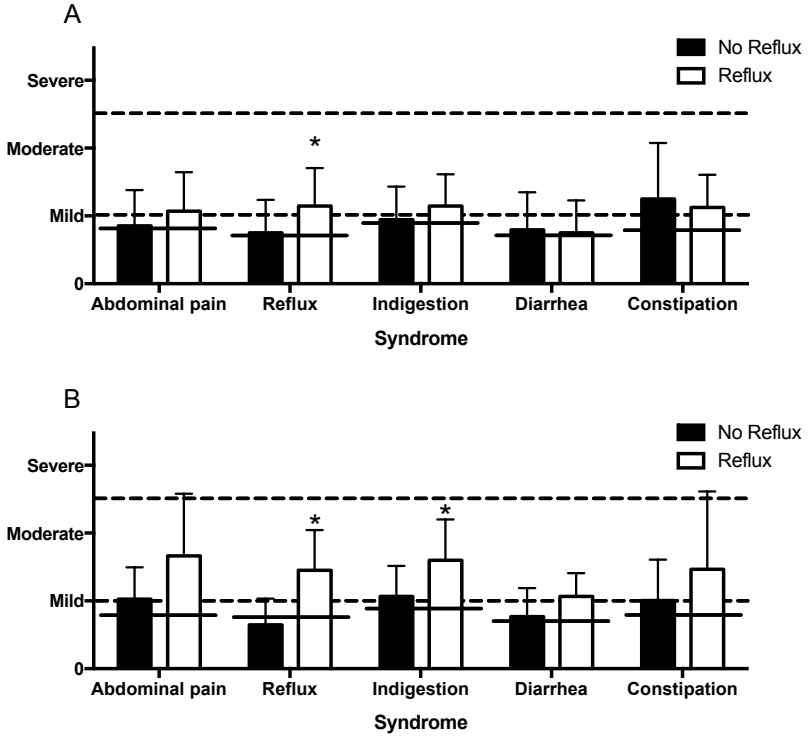
Significance: *p<0.05 between no complication and complication.
— General population values. --- Separation of syndrome severity.

Indigestion syndrome score was significantly increased in patients with complications after LSG by an average of 0.6 (1.8 to 2.4, p=0.02). Reflux syndrome score was also

significantly increased by an average of 0.5 (1.6 to 2.1, p=0.014). LRYGB patients with a postoperative abdominal complication had increased average scores for abdominal pain syndrome (0.7 increase, p=0.05), indigestion syndrome (0.8 increase, p=0.009), and constipation syndrome (1.1 increase, p=0.022). However, these average scores were still mild to moderate symptoms overall.

Patients that complained of heartburn or reflux had significantly higher reflux syndrome scores after both LSG (1.5 vs 2.3, p=0.006) and LRYGB (1.3 vs 2.9, p=0.0001) compared to patients without symptoms (**Figure 4-4**). LRYGB patients also had a significantly increased indigestion syndrome score (2.1 to 3.2, p=0.044).

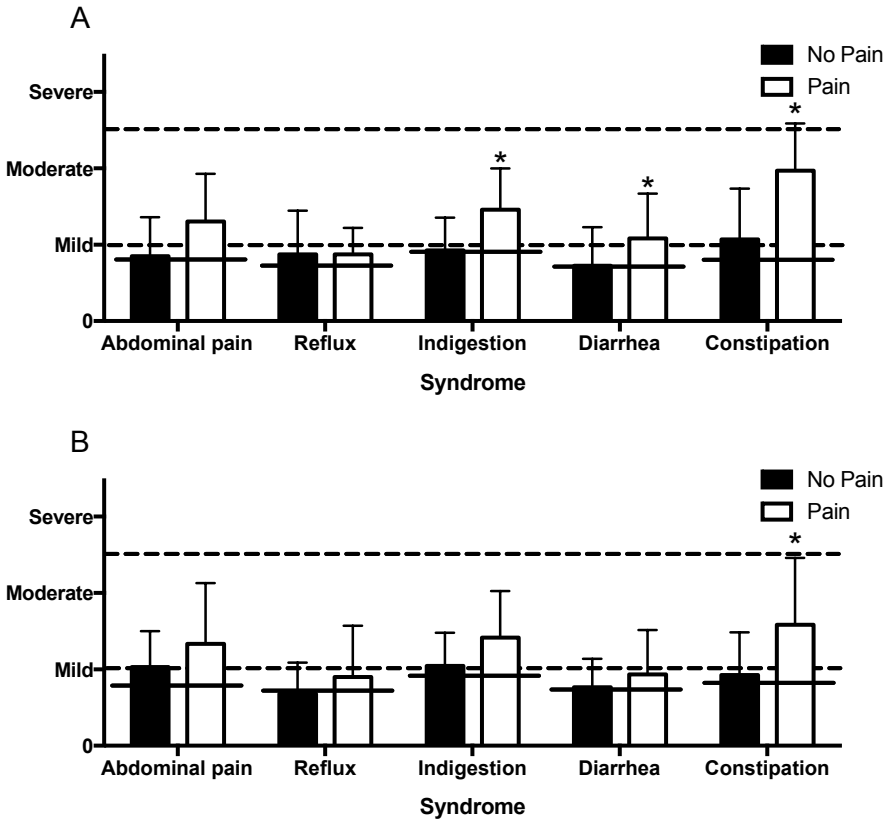
Figure 4-4: Gastrointestinal Symptoms Rating Scale results for patients with and without heartburn or reflux complaints after laparoscopic sleeve gastrectomy (A) and laparoscopic Roux-en-Y gastric bypass (B).



Significance: *p<0.05 between reflux and no reflux.
— General population values. --- Separation of syndrome severity.

Chronic abdominal pain was a complication that was highly investigated in patients and the majority of these investigations were normal. It appears that the symptoms that were most associated with chronic abdominal pain were not abdominal pain syndrome, but constipation syndrome (**Figure 4-5**).

Figure 4-5: Gastrointestinal Symptoms Rating Scale results for patients with and without chronic abdominal pain after laparoscopic sleeve gastrectomy (A) and laparoscopic Roux-en-Y gastric bypass (B).



Significance: *p<0.05 between pain and no pain.
— General population values. --- Separation of syndrome severity.

Patients with chronic abdominal pain had an average constipation score 1.8 higher in LSG patients (p=0.0075) and 1.3 higher in LRYGB patients (p=0.022). Unlike LRYGB patients, which only had significantly higher constipation syndrome scores, LSG also had

significantly higher indigestion (1.1, p=0.017) and diarrhea (0.7, p=0.0074) scores associated with chronic abdominal pain. Compared to the results for overall abdominal complications, reported symptoms were moderate discomfort (3.2-3.9) for constipation syndrome.

There were no ulcers or strictures in the LSG group that could contribute to chronic abdominal pain, nor did the LRYGB with ulcers or strictures have chronic abdominal pain or have significantly different GSRS scores compared to patients without an ulcer or stricture.

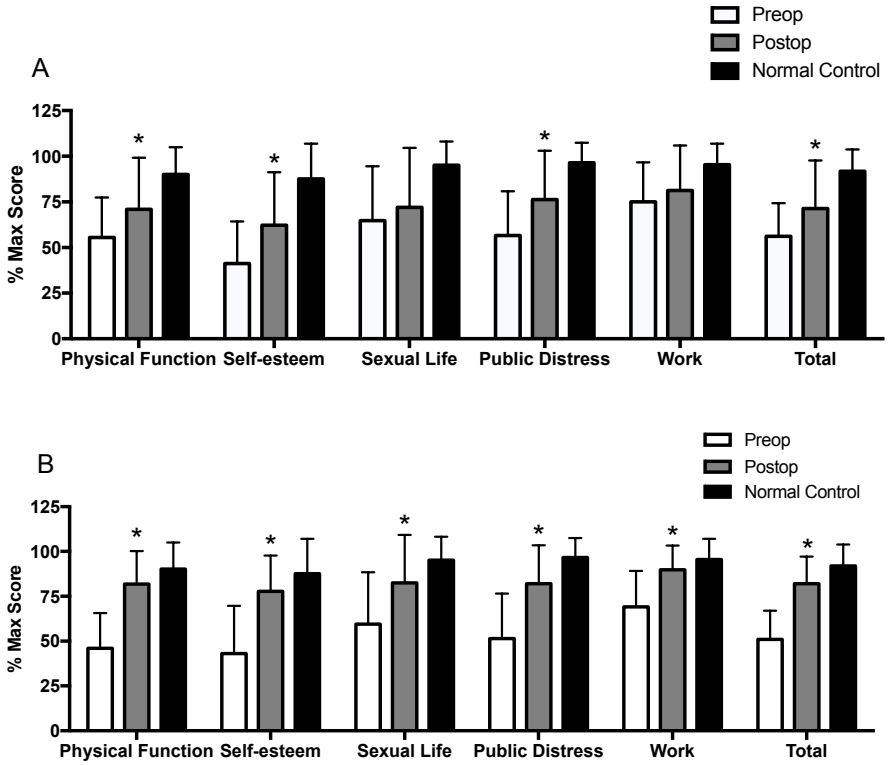
Some GI manifestations have been linked to psychological disorders in the literature, such as irritable bowel syndrome (178). However, there were no significant differences in postoperative symptom scores or in patients with complications that were noted to have depression or anxiety at their preoperative assessment.

4.3.5 Quality of Life

Patient QOL measured at follow-up significantly increased after both bariatric procedures (**Figure 4-6**). Only work and sexual life did not increase significantly after LSG. There were no significant differences in pre- or postoperative QOL measures between LSG and LRYGB. Only LRYGB achieved a non-significant difference with the normal controls (Physical Function: p=0.1, Sexual Life: p=0.15, and Work p=0.14).

There were no significant differences in QOL before or after bariatric surgery in patients with or without a psychiatric disorder. A decrease in BMI was significantly related to an increase in postoperative QOL assessed by the Kruskall-Wallis test. There were no significant associations between total GSRS score and QOL before or after surgery.

Figure 4-6: Impact of Weight on Quality of Life-Lite results before and after laparoscopic sleeve gastrectomy (A) and laparoscopic Roux-en-Y gastric bypass (B).



Significance: *p<0.05 between preop and postop.
Preop: Preoperative, Postop: Postoperative.

4.4 Discussion

Bariatric surgery is known to cause disturbances or resolution of gastrointestinal symptoms. Some symptoms seem to be idiopathic and not have any conclusive associated functional abnormalities. The objective of this project was to observe changes in gastrointestinal symptoms after bariatric surgery and any emerging patterns in gastrointestinal symptoms related to confirmed complications.

4.4.1 Patient Population

The study had a very good response rate for both questionnaires (90-92%). The study population had similar demographics, use of PPIs, and weight loss (**Figure 4-1**) compared to the population in the retrospective chart review performed in Chapter 3.

The study population had very few complications compared to a retrospective chart review performed in 2013 (unpublished data). The complication rates of ulcers and strictures were 15.7% in the LRYGB group compared to the study population of 7.3%. The complication rates were comparable to those in the literature (36).

4.4.2 Gastrointestinal Symptom Rating Scale

The primary finding from the GSRS questionnaire was an increase in reflux symptoms after LSG. Increased reflux requiring PPI was also found in Chapter 3. There were no significant changes after LRYGB, and while there was no reduction in heartburn symptoms after LRYGB, PPI use decreased significantly.

Resolution of GERD symptoms post-bariatric surgery has been explored in recent literature. A large retrospective review of the Bariatric Outcomes Longitudinal Database (BOLD) reported on the resolution rates of GERD. GERD resolved in 62% of patients after RYGB (145). This effect was shown to be long lasting in a recent study, following patients three years post-surgery (179). In fact, RYGB has gained significant support in the literature as the operation of choice for patients with obesity and comorbid GERD (180). In contrast, only 15.9% of LSG patients were found to have resolution of their GERD symptoms (145). Additional studies have supported this modest improvement (53, 181). However, there remains controversy in the literature. A recent study reported 63% of patients developed new erosive esophagitis, diagnostic for GERD, one year after a LSG

(182). Further studies argue that the LSG actually promotes the development of GERD (129, 145).

No literature exists on the use of the GSRS after LSG. GSRS has been used after LRYGB. GI symptoms after LRYGB were noted to improve significantly (165, 166). No significant improvement or change in GI symptoms after LRYGB was observed in this study. *Petereit et. al.* found that indigestion, constipation, abdominal pain, and reflux syndrome symptoms all decreased significantly after RYGB. They found that increased diarrhea syndrome scores were a significant predictor of pathological endoscopic findings. These findings included gastritis, esophagitis, hiatal hernia, and *H. pylori* infection (165). However, the relationship between diarrhea syndrome and these findings were not explored. Their preoperative GSRS scores were similar to this population as they did not exceed 2.3. BMI was also not significantly related to GSRS scores. *Søvik et. al.* observed abdominal pain syndrome increased and reflux syndrome decreased one and two years after RYGB (166). This study also had similar baseline preoperative measures to their study.

Boerlage et. al. found that GSRS scores were significantly increased after RYGB compared to non-surgical obese patients (median score 2.2 compared to 1.7) with the most notable increase in indigestion syndrome (183). They attributed these symptoms to an increase in food intolerance. Interestingly, this study did find a relationship between weight loss and abdominal pain syndrome.

4.4.3 Gastrointestinal Symptom Rating Scale and Surgical Complications

There is very limited literature focusing on GI symptom patterns associated with postoperative complications. Looking at overall abdominal complications, LSG only had increased indigestion and reflux symptoms. As for the LRYGB group, overall abdominal

complications were associated with a significant increase in abdominal pain, reflux, indigestion, and constipation syndromes. The most prevalent abdominal complications, chronic abdominal pain and reflux, were further explored. For patients that complained of reflux symptoms and required a PPI, both LSG and LRYGB groups had significantly increased reflux syndrome scores. This finding was expected of the GSRS questionnaire as it has been validated in the GERD population (164). While the GSRS is not a screening tool (184), the reflux syndrome score most indicative of patients requiring a PPI to treat their symptoms, the average score of 2.5 was observed to have the best specificity and sensitivity by non-parametric receiver operating characteristic (ROC) analysis (90.8% specificity and 47.1% sensitivity, 82.8% correctly classified, ROC: 0.84). This was lower than scores reported in the literature of 3.09 for patients with GERD (164).

Interestingly, patients with reflux symptoms after LSG that were treated with a PPI did not have a significantly decreased reflux syndrome score. This higher score could indicate that PPI treatment may not be the appropriate approach to relieve reflux symptoms, and as discussed previously, these reflux symptoms may be attributed to non-acid reflux.

Chronic abdominal pain was also observed after both LSG and LRYGB. Patients were considered to have chronic abdominal pain when patients had ongoing abdominal pain with no discernable cause. LRYGB patients with chronic abdominal pain had significantly increased constipation syndrome. An average constipation syndrome score of 3.33 had a 91.1% specificity, 50.0% sensitivity, and classified patients with chronic abdominal pain correctly 83.6% of the time (ROC: 0.73). The high classification of chronic abdominal pain could be an indication that constipation symptoms may be the cause of abdominal pain manifestations in this patient group, and a targeted approach to manage constipation before

pursuing invasive investigations may be a preferable option. LSG patients with chronic abdominal pain had significantly increased indigestion, diarrhea, and constipation syndromes. Constipation was the most significant syndrome associated with abdominal pain. The exact mechanism that could lead to chronic abdomen pain after sleeve gastrectomy is difficult to ascertain with the given results. A total GSRS score of 37 had an 81.3% specificity, 83.3% sensitivity, and classified patients with chronic abdominal pain correctly 81.6% of the time (ROC: 0.85). Interestingly, chronic abdominal pain or recurrent epigastric pain, as seen in the case study in Chapter 2, was also not related to reflux in this study.

The 2013 retrospective chart review also found that 28.3% of LRYGB and 10.4% of LSG patients complained of chronic abdominal pain with no discernable cause. Similarly, to the study population, patients underwent many investigations to explore the ongoing abdominal pain, including contrast studies (LSG: 5.9%, LRYGB: 9.8%), CT imaging (LSG: 5.2%, LRYGB: 13.2%), endoscopy (LSG: 5.9%, LRYGB: 21.7%), and diagnostic laparoscopy (LSG: 3.7%, LRYGB: 12.3%). Concerns for chronic abdominal pain include ulceration, internal hernia, strictures, etc. However, the burden to the patient, especially undergoing reoperation, is great and can be frustrating when no cause for the abdominal pain is found.

Høgestøl et. al. described chronic abdominal pain 5 years after RYGB (185). They found that 32.8% of their patients with chronic abdominal pain had an abdominal pain syndrome score of 3 or greater. These patients had episodes of abdominal pain once to several times per week and their quality of life was impacted by these symptoms. They found that gender (female patients), BMI, average bodily pain, and total pain catastrophizing scale score were

significantly related to chronic abdominal pain. Compared to the results, depression and anxiety were not significantly related to postoperative abdominal pain.

Greenstein et. al. described that upwards of half of postoperative complaints and emergency room visits were on account of abdominal pain after RYGB. They attribute these symptoms to a broad range of causes: behavioural and dietary disorders, GI functional disorders (i.e., constipation, irritable bowel syndrome, motility disorders), biliary disorders, pouch or remnant stomach disorders, small bowel disorders, and miscellaneous issues. The results most likely fit into the GI functional disorder category. *Greenstein et. al.* conveyed the importance of a detailed patient history and exam to guide diagnostic testing after RYGB, which may include reoperation to rule out disorder with the biliary tree or remnant stomach (186). This patient population needs an experienced bariatric surgical team to make these decisions and emphasize continued patient follow-up.

4.4.4 Impact of Weight on Quality of Life after Bariatric Surgery

According to *Nickel et. al.*, gastrointestinal quality of life index (GIQLI) scores improved after SG and RYGB, with SG showing significantly more improvement than RYGB (167). Yet, when looking at IWQOL scores, one observes that RYGB has a greater improvement in QOL than LSG, regardless of similar weight loss between the two procedures.

Several studies found that all 5 domains were improved significantly after RYGB (169, 170, 187). The results also demonstrated a significant improvement in QOL after LRYGB in all five domains. However, LSG did not show significant improvement in sexual life and work domains. *Amichaud et. al.* found that at both 6 and 12 months after LSG, all domains of IWQOL were improved (188).

On average, the preoperative total IWQOL score after LSG and LRYGB was considered to be a severe impairment in QOL (LSG: 56% and LRYGB: 51%). At follow-up, total IWQOL score improved on average to moderate impairment after LSG (71%) and mild impairment (82%) after LRYGB. *Crosby et. al.* described that based on the baseline severity of the IWQOL score, clinical improvements with weight loss varied from 7.7-12.0 points in the total IWQOL score (189). At the time of follow-up, 61% of LSG and 84% of LRYGB patients achieved a clinically significant change in QOL. *Reynolds et. al.* found that a %EWL of 40% or greater led to a clinically significant change in QOL 4-5 years after LAGB and LSG (190). The results found that for every 1% increase in %EWL, the odds of achieving a clinically significant change in QOL increased by 4% (OR: 1.04, 95% CI 1.00-1.07, p=0.05). The %EWL threshold for achieving a statistically significant clinical change in QOL for the study was also 40% or greater (p=0.014) at 6-12 months after bariatric surgery.

4.4.5 Limitations

A limitation of this study was that there were significantly fewer complications than anticipated to explore GSRS patterns in GI complications and as a result some of the analysis may be underpowered. There was no statistical difference in GSRS scores in patients with an ulcer or stricture, which is most likely attributed to the low number of patients with these complications.

4.4.6 Conclusion

This study demonstrates the difficulty assessing and diagnosing patients with complications based on patient symptoms. Regardless that patients have confirmed abdominal complications, these appear to only be associated with a small increase in gastrointestinal

symptom scores and could be attributed to functional disorders, such as constipation. This diagnostic difficulty emphasizes the importance of a bariatric clinic follow-up with extensive experience to limit unnecessary clinical interventions.

One clinical intervention, 24h pH-impedance, is capable of linking patient symptoms to pathological GERD. While esophageal manometry does not assess symptoms, it evaluates the esophagus for any functional disorders. To further explore the relationship between reflux symptoms, obesity, EM, and GERD findings, a review of patients referred to the Gastrointestinal Motility Laboratory was undertaken.

Chapter 5 – Impact of Body Mass Index on Esophageal Motility and Reflux

5.1 Purpose and Rationale

Some degree of gastroesophageal reflux is physiologic, but becomes pathologic either from the presence of symptoms or mucosal injury on endoscopy (191). The Montreal Classification is commonly used to define GERD: reflux is a condition where reflux of gastric contents causes symptoms or complications (192). Epidemiological data is complicated by the fact that studies do not always use a strict definition for GERD. The literature is mired with survey type sampling and poor correlation of symptoms with clinical GERD. Despite that, a large systematic review that included studies with strict GERD criteria found the North American prevalence to be 10-20% (193).

Classic symptoms of GERD include regurgitation, heartburn (pyrosis), and dysphagia (192). These symptoms are crucial for the clinical diagnosis of GERD. However, there are additional symptoms that represent extra-esophageal manifestations of GERD, including chronic cough, chest pain, water brash, globus sensation, odynophagia, and nausea.

The cause of gastroesophageal reflux has been attributed to disturbances in the antireflux mechanisms, higher than normal TLESRs, inhibited esophageal clearance, delayed gastric emptying, esophageal hypersensitivity, or external causes, such as mucosal injury (194). Complications from GERD can result from direct damage of the refluxate on tissue or result from the healing process that ensues. Complications include erosive esophagitis, damage to the esophageal mucosa resulting in erosions and ulceration, esophageal strictures, Barrett's esophagus, and increased risk of esophageal adenocarcinoma (82, 195).

Obesity is a risk factor for GERD (149, 196). Specifically, abdominal obesity has been associated with an increase in reflux symptoms (197). Unfortunately, the mechanism to

explain this association is not well understood. Studies have found a correlation between BMI and waist circumference with gastroesophageal pressure gradient, intragastric pressure, and resulting EGJ disruption (198). Additionally, LES dysfunction appears to play an important role in obesity-related reflux (199).

EMDs are also a known risk factor for reflux (79, 118, 200). EMDs can generally be classified as primary (isolated to the esophagus) or secondary (associated with other diseases). Primary disorders have been classified according to the Chicago Classification (201). A combination of manometry and topography were used to divide motility disorders according to the relaxation of the LES and function of esophageal peristalsis. Achalasia is the prototypical motility disorder due to its significant clinical symptoms for the patient. Other disorders include diffuse esophageal spasm, hypertensive peristalsis, hypertensive LES, IEM, and hypotensive LES. The impact that obesity has on these EMDs is not clear and has mostly been explored in the selective pre-bariatric surgery population (132, 158, 202-206).

The objective of this study was to quantify the relationship between obesity, gastroesophageal reflux, and EM in a population requiring investigations for esophageal symptoms. The hypothesis was that both reflux and EMD would be positively associated with BMI.

5.2 Study Design

A review of patient medical records from the Gastrointestinal Motility Laboratory, University of Alberta Hospital, Edmonton, Alberta, was performed for patients that underwent ambulatory 24h pH-impedance testing and/or high resolution esophageal manometry. Patients were referred to the GI Motility Lab by their primary care physician

to assess both characteristic and uncharacteristic symptoms of GERD for acid reflux or EM disturbances. Patient data were prospectively collected over a 22-month period. Test results were first interpreted by the nursing staff and subsequently reviewed and approved by Royal College certified gastroenterologists with a specialization in EM at the University of Alberta Hospital. Test results were scanned and uploaded to an electronic medical record database, called 'eClinician'. Patient medical history was also entered into eClinician. Data were extracted from eClinician reports.

5.2.1 Inclusion and Exclusion Criteria

Adult patients that tolerated and completed either high-resolution esophageal manometry, 24h pH, or 24h pH and impedance testing were included.

Patients were excluded if they were pediatric patients (<17 years old), underwent anorectal manometry or colonic transit, underwent testing for preoperative assessment with no presenting symptoms, or underwent testing in the endoscopy suite. Patients were also excluded if they were not ambulatory to measure their BMI. Patients with previous gastric surgery, including Nissen fundoplication, Heller myotomy, or any bariatric surgery were excluded. Postoperative lung transplant patients were also excluded.

5.2.2 Esophageal Manometry

High resolution esophageal manometry was used to measure the motility of the esophagus. The esophageal manometry probe contained 36 pressure channels spaced circumferentially 1cm apart. The solid-state strain gauge transducer sensed intraluminal pressures of the esophagus and relayed this information to a recording device (207).

Patients were asked to fast at least 6h prior to their appointment. Patients were not required to stop any medications. The manometry probe (ManoScan EAN3137, Medtronic,

Minneapolis, MN) was passed transnasally while the patient was under topical anesthesia (lidocaine gel) by asking the patient to swallow small increments of water. Appropriate placement was confirmed once the probe had passed the LES. A 30 second basal measurement was taken during which the patient was asked not to swallow. EM was assessed by analyzing ten 5cc sips of water followed by a swallow stress test, which was inputted into the system (ManoScan 360™, Given Imaging, Duluth, GA). A topographic display was created by the system and results were analyzed by Manoview 3.0 (Given Imaging, Duluth, GA) analysis software. EMDs were identified using the Chicago 3.0 classification scheme.

5.2.3 24h pH and 24h pH-Impedance

Ambulatory 24h pH and 24h pH-impedance studies determined gastroesophageal content transport and assessed temporal association of the symptoms with acid and non-acid reflux episodes. 24h pH consisted of a thin flexible catheter with an internal antimony pH-electrode at the end of the catheter. The pH probe was calibrated in two buffer solutions at pH 4.0 and 7.0. The 24h pH-multichannel intraluminal impedance monitoring included a measure of alternate current resistance in the esophageal lumen along the catheter (3, 5, 7, 9, 15, and 17cm above the LES) to measure reflux events (i.e., drop in resistance) up to the proximal esophagus (208).

The normal pH of the esophagus should be approximately 7.0. Acid reflux events and percent clearance time or percent time were measured when the pH probe measured a pH of 4.0 or less in the esophagus. Non-acid reflux was considered a reflux event measured by impedance above a pH of 4.0. Weakly acid reflux events were not measured. 24h pH without impedance could not measure non-acid reflux. Reflux events were also recorded by

body position as upright or recumbent. Symptoms related to reflux events were also measured by three measures: symptom index (SI), symptom sensitivity index (SSI), and symptom association probability. Symptoms were considered positive for acid reflux if the SI was above 50%, SSI was above 10%, and SAP was above 95%.

The DeMeester score is an objective measure of clinically significant reflux calculated from ambulatory 24h pH testing. It was first introduced in 1976, when Johnson and DeMeester published their study on 24h pH monitoring in the *American Journal of Gastroenterology* (209). The score is a composite of multiple measured values: percent total time pH <4, percent upright time pH <4, percent supine time pH<4, number of reflux episodes, number of reflux episodes ≥ 5 min, and longest reflux episode in minutes. A score greater than 14.7 indicated significant acid reflux. The Jamieson/DeMeester score cut-off was 16.0.

Patients were asked to fast at least 6h prior to their appointment time. Depending on the primary care physician referral, patients may have been asked to stop taking their PPI 5 days prior to their appointment (210). An ambulatory 24h pH or 24h pH-impedance probe (ComforTec® Z/pH ZAN-130-44, Sandhill Scientific, Highlands Ranch, CO) was inserted transnasally into the esophagus and stopped 5cm above the LES. The distance to the LES was either previously known from high-resolution esophageal manometry or a LES-locator was used (a single solid-state pressure transducer) (211). A portable computer (Zephr Sleuth, Sandhill Scientific, Highlands Ranch, CO) recorded reflux activity. Patients were asked to perform their usual daily routines, including eating and drinking habits. Patients were also given a diary to record any episodes external to those programmed on the

portable computer. The probe was removed after 20 to 24 hours. Sandhill Scientific Zephr Sleuth© 2011 software analyzed the dual 24h pH and impedance studies.

5.2.4 Design

BMI was measured at the time of testing by measuring height and weight on a scale in the procedure room. Patients were stratified based on the 6 WHO BMI categories: underweight (<18.5kg/m^2), normal (18.5-24.9kg/m^2), overweight (25.0-29.9kg/m^2), obesity class I (30.0-34.9kg/m^2), obesity class II (35.0-39.9kg/m^2), and obesity class III (>40.0kg/m^2). Both manometry and 24h pH and impedance studies were reviewed. The data collected from the manometry studies were presence of hiatal hernia and size, LES pressure and residual pressure, esophageal body peristalsis, UES pressure and residual pressure, mean wave amplitude and duration, DCI, percentage of swallows with double peaked waves, and Chicago classification diagnosis. LES pressure was measured automatically from the Manoview software during the 30 second baseline period. Atmospheric pressure was used as a reference pressure for the LES measurement (207). IGP was measured 5cm below the LES margin. IGP was used to approximate IAP (198, 212).

Total LES length, intra-abdominal length, EGJ type, LES-PI, EGJ-CI, and total EGJ-CI were all measured according to the methods outlined in *Jasper et. al.* using the esophageal manometry SmartMouse tool in the Manoview software (213). Total LES length was measured from the upper to lower margin of the LES. Intra-abdominal length was measured from the lower margin of the LES to the pressure inversion point. EGJ type was defined by *Pandolfino et. al.* as 4 subtypes of CD/LES morphology: Type I – no separation, Type II – separation 1-2cm, Type IIIa – >2cm separation with pressure inversion point proximal to CD, and Type IIIb – >2cm separation with pressure inversion point proximal to

LES (214). LES-PI defined by *Hoshino et. al.* measured the average baseline LES pressure over ten seconds (215). EGJ-CI defined by *Nicodème et. al.* measured the average baseline LES pressure over three respiratory cycles (216). Total EGJ-CI measured average LES pressure from the first to last swallow between the upper margin of the LES to 2mmHg above the gastric pressure.

Data collected from 24h pH and impedance studies included the DeMeester score, number of acid and non-acid reflux episodes in the proximal and distal esophagus, percent time clearance of pH<4 from the esophagus, and symptom association with reflux episodes.

5.2.5 Primary Outcome

The primary outcome was to explore the relationship between BMI, EM, and gastroesophageal reflux.

5.2.6 Secondary Outcome

The secondary outcome was to explore the relationship of EGJ-CI with BMI, EM, and gastroesophageal reflux.

5.2.7 Sample Size

A range of 100-150 patients has been used to establish normal motility values in a healthy population and a range of 60-72 patients has been used to establish normal gastroesophageal reflux (80, 217, 218). A total of 285 patients have been used to detect a relationship between intragastric pressure and BMI (198). A total of 100-250 charts per BMI category were reviewed. It was not possible to obtain 100 or more patients in certain BMI categories, such as BMI of <18.5kg/m^2 or >40kg/m^2; this is an acknowledged limitation.

5.2.8 Data Analysis

Relationships between BMI categories, reflux, and motility parameters were explored by a Kruskall-Wallis test. The relationship of each reflux and motility parameter to BMI was assessed graphically with a line of best fit and regression coefficient (adjusted-R^2). The relationship of each EGJ parameter was also explored in relation to each other and the DeMeester Score to observe collinearity. A parameter was chosen based on its fit with the model (adj-R^2). A logistic multivariate regression was used to identify predictors of abnormal EM. A linear multivariate regression model was used to explore the DeMeester score. A logistic multivariate regression was also used to identify predictors of abnormal reflux (DeMeester>14.7) or (Jamieson/DeMeester>16.0). A negative binomial distribution was used to identify significant relationships with the number of non-acid reflux events. A non-parametric receiver operating characteristic analysis was used to compare EGJ parameter results to those reported by *Jasper et. al.* (213). Significance was considered $p<0.05$.

5.3 Results

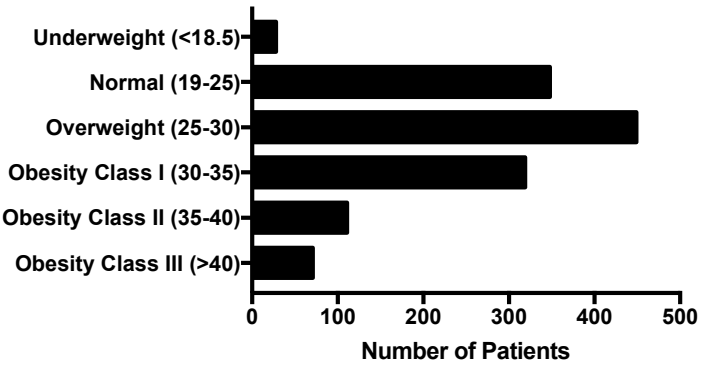
Patient data were collected from 1614 patients with 124 patients excluded because of previous esophageal or gastric surgery (49 bariatric surgeries, 65 fundoplications, 8 myotomies, 2 esophageal lump removals, and 2 vagotomy and pyloroplasty).

5.3.1 Esophageal Motility

Patient Demographics

A total of 1326 patients underwent esophageal manometry. The average age was 54.2±14.9 (2-90) years and 63% were female. The average BMI was 28.9±6.2 (14.4-67.5) kg/m^2 (Refer to **Figure 5-1** for BMI categories).

Figure 5-1: Body mass index separated by the six World Health Organization body mass index categories in patients that underwent esophageal manometry testing.



Patient surgical and medical histories included 55 cholecystectomies, 7 hiatal hernia repairs, 13 esophageal dilatations, 6 with a history of Barrett's esophagus, 8 with a history of Schatzki's ring, 3 with a partial gastrectomy, 3 with a history of scleroderma, 1 esophageal tear repair, and 1 with Chiari syndrome.

Symptoms

Patients presented with a range of symptoms, including heartburn (55.8%), dysphagia (49.5%), epigastric pain or chest pain (20.2%), regurgitation (21.9%), chronic cough (8.0%), burping (4.1%), odynophagia (2.3%), and other (27.9%). Other symptoms included nausea, globus, vomiting, gagging, and bloating.

Relationship of Esophageal Motility and Body Mass Index

Specific relationships were explored based on significant overall differences between BMI categories using the Kruskal-Wallis test (Refer to **Appendix Table A-1**). Hiatal hernia (Regression Coefficient (Reg. Coef): 1.58, 95% Confidence Interval (CI) 0.78-2.38, $p<0.001$), intragastric pressure (Reg. Coef: 0.38, 95% CI 0.32-0.43, $p<0.001$), LES residual pressure (Reg. Coef: -0.07, 95% CI -0.11- -0.03, $p=0.001$), UES pressure (Reg. Coef: -0.01, 95% CI -0.02- -0.01, $p<0.001$), and failed peristalsis (Reg. Coef: -0.02, 95% CI -0.03

- -0.01, p=0.001) were all significantly associated with BMI overall (**Figure 5-2 – 5-6**). LES pressure was significantly lower in overweight (p<0.001), obesity class I (p<0.001), and obesity class II (p=0.025) compared to normal weight (**Figure 5-7**), but not when BMI was a continuous variable.

Figure 5-2: Distribution of body mass index by presence of hiatal hernia.

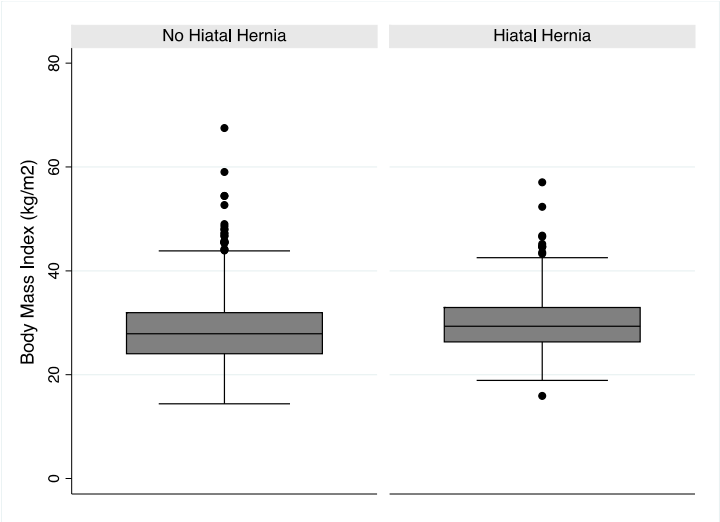


Figure 5-3: Relationship between body mass index and average intragastric pressure.

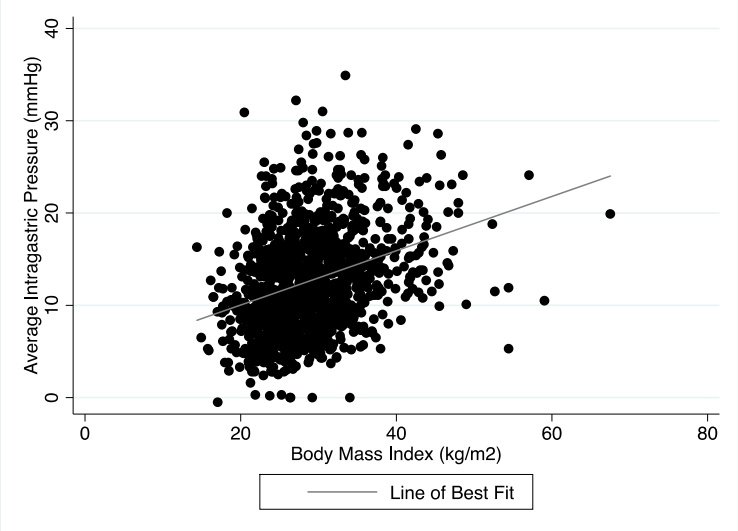


Figure 5-4: Relationship between body mass index and lower esophageal sphincter residual pressure.

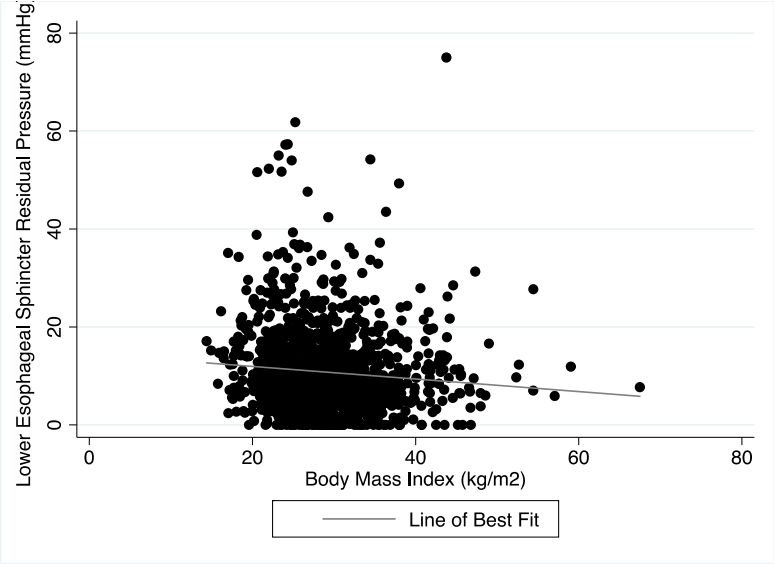


Figure 5-5: Relationship between body mass index and upper esophageal sphincter pressure.

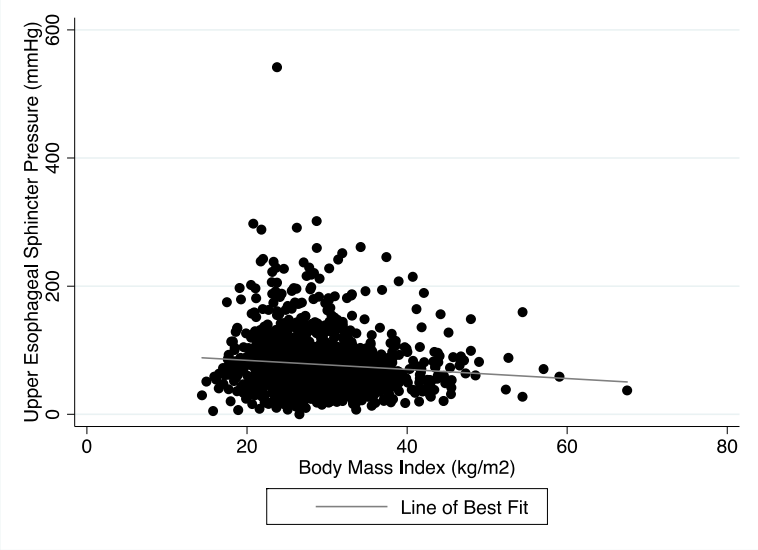


Figure 5-6: Relationship between body mass index and percentage of failed elicited swallows (peristalsis).

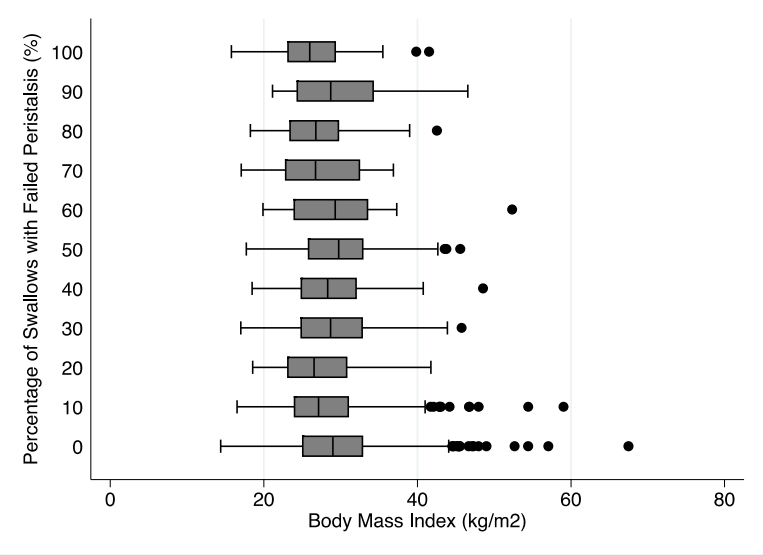
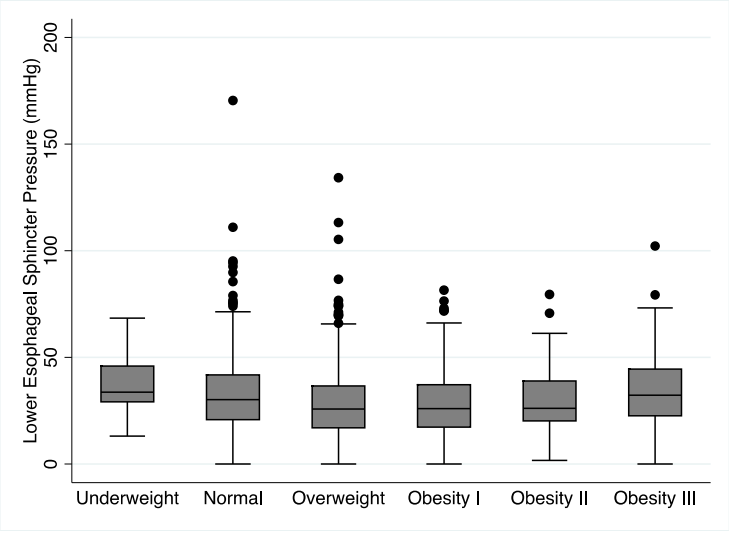


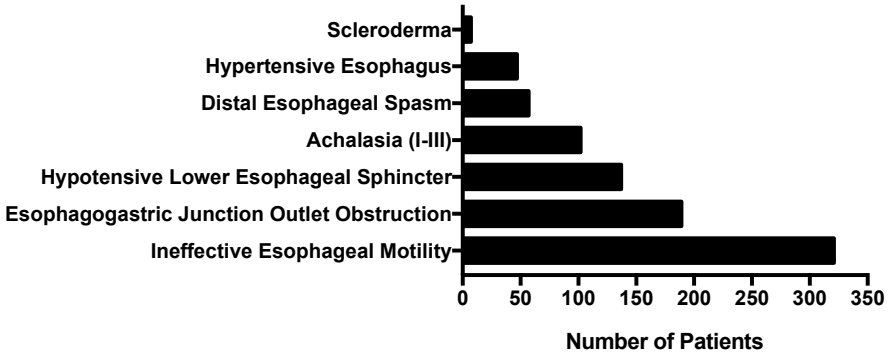
Figure 5-7: Lower esophageal sphincter pressure at baseline by body mass index category.



Predictors of Esophageal Motility Disorders

57% (n=750) of patients had abnormal manometry results, most frequently IEM (24%, n=321) and EGJ outflow obstruction (14%, n=189) (**Figure 5-8**). The parameters of the high-resolution esophageal manometry were stratified between normal and abnormal results and assessed for significant differences (Refer to **Appendix 1 Tables A2-4**).

Figure 5-8: Types of esophageal motility disorders observed during high-resolution esophageal manometry.



Patient demographics, BMI, symptoms, presence of hiatal hernia, and average intragastric pressure were tested as predictors for all EMD. Significant predictors for EMDs from the univariate logistic regression are listed in **Table 5-1**.

Table 5-1: Odds ratio and 95% confidence interval of variables after univariate logistic regression to predict esophageal motility disorders.

Variable	Odds Ratio ± Standard Error (95% Confidence Interval)	Significance (p-value)
Age (years)	1.02±0.00 (1.01-1.02)	<0.001*
Gender (Female to Male)	0.70±0.08 (0.56-0.88)	0.002*
Body Mass Index (kg/m^2)	0.98±0.01 (0.96-0.99)	0.008*
Underweight to Normal	1.00±0.40 (0.46-2.21)	0.993
Overweight to Normal	0.92±0.13 (0.69-1.22)	0.557
Obesity Class I to Normal	0.71±0.11 (0.52-0.97)	0.031
Obesity Class II to Normal	0.62±0.13 (0.40-0.95)	0.027
Obesity Class III to Normal	0.75±0.20 (0.45-1.25)	0.267
Heartburn Symptoms	0.65±0.07 (0.52-0.81)	<0.001*
Dysphagia Symptoms	1.64±0.18 (1.32-2.05)	<0.001*
Epigastric/Chest Pain Symptoms	0.82±0.11 (0.63-1.07)	0.145*
Regurgitation Symptoms	1.00±0.13 (0.77-1.30)	0.997
Chronic Cough Symptoms	1.09±0.22 (0.73-1.63)	0.676
Burping Symptoms	0.96±0.27 (0.55-1.66)	0.879
Odynophagia Symptoms	1.22±0.45 (0.59-2.53)	0.596
Other Symptoms	0.87±0.11 (0.68-1.10)	0.242
Hiatal Hernia	1.12±0.15 (0.86-1.46)	0.391
Hiatal Hernia Size (cm)	0.98±0.06 (0.87-1.10)	0.702
Average Intragastric Pressure at Baseline (mmHg)	0.99±0.01 (0.97-1.01)	0.61

Significance: *p-value≤0.2.

Age, gender, BMI, heartburn, dysphagia, and epigastric/chest pain symptoms were included in a multivariate logistic regression (**Table 5-2**).

Table 5-2: Odds ratio and 95% confidence interval of variables after multivariate logistic regression to predict esophageal motility disorders.

Variable	Odds Ratio ± Standard Error (95% Confidence Interval)	Significance (p-value)
Age (years)	1.01±0.00 (1.01-1.02)	<0.001*
Gender (Female to Male)	0.71±0.08 (0.57-0.90)	0.005*
Body Mass Index (kg/m^2)	0.98±0.01 (0.96-0.99)	0.022*
Underweight to Normal	1.08±0.45 (0.48-2.43)	0.853
Overweight to Normal	0.88±0.13 (0.65-1.18)	0.385
Obesity Class I to Normal	0.73±0.12 (0.53-1.01)	0.054
Obesity Class II to Normal	0.65±0.15 (0.41-1.00)	0.053
Obesity Class III to Normal	0.80±0.21 (0.47-1.36)	0.410
Heartburn Symptoms	0.78±0.09 (0.61-0.98)	0.036*
Dysphagia Symptoms	1.43±0.17 (1.13-1.81)	0.003*
Epigastric/Chest Pain Symptoms	0.91±0.13 (0.69-1.20)	0.501

Significance: *p-value≤0.05.

Significant predictors of EMDs included age, gender, BMI, and heartburn and dysphagia symptoms. Epigastric or chest pain symptoms were not a confounding variable and were removed from the model. There was a significant interaction between age and heartburn symptoms (p=0.045) that was included in the model. Age and BMI both meet the linear assumption. The model was a good fit, p=0.44.

The odds of having an EMD was 43% higher in patients with dysphagia symptoms compared to patients without dysphagia symptoms (OR: 1.43, 95% CI 1.13-1.81). The odds of having an EMD was 66% lower in patients with heartburn symptoms compared to patients without heartburn symptoms after adjusting for age (OR: 0.34, 95% CI 0.14-0.79, p=0.039). In patients with heartburn symptoms, for every 10 year increase in age, the odds of having an EMD increased by 25% (OR: 1.25, 95% CI 1.12-1.38, p<0.0001). Female patients were 31% less likely than men to have an EMD (OR: 0.69, 95% CI 0.55-0.87, p=0.002).

Surprisingly, for every 1 unit increase in BMI, the odds of having an EMD decreased by 2% (OR: 0.98, 95% CI 0.96-0.99, p=0.027). Although, pairwise comparisons between WHO BMI categories were not statistically significant. When re-categorized to 4 categories with obesity class I-III as a single category, patients that were in obesity class I-III were 27% less likely to have an EMD compared to normal weight patients (OR: 0.73, 95% CI 0.55-0.97, p=0.033). Achalasia (OR: 0.93, 95% CI 0.90-0.97, p<0.001), EGJ-OO (OR: 0.98, 95% CI 0.95-1.00, p=0.062), hypertensive esophagus (OR: 0.97, 95% CI 0.92-1.02, p=0.2), and hypotensive LES (OR: 1.03, 95% CI 1.00-1.05, p=0.064) were the disorders significantly associated with BMI from univariate logistic regression. However, after multivariate analysis none of the above disorders was significantly associated with BMI. Contrary to commonly held views, BMI did not appear to play a significant role in EMDs.

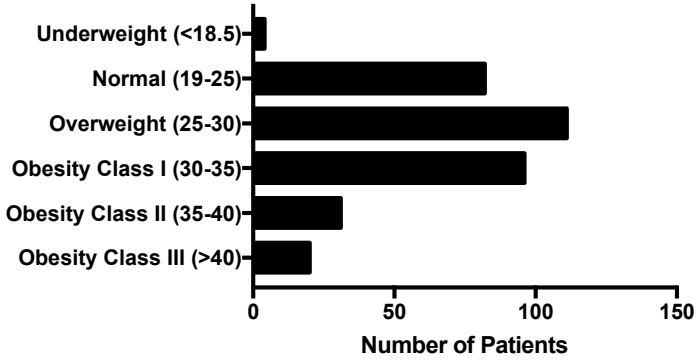
5.3.2 Gastroesophageal Reflux

Demographics

A total of 589 patients underwent both esophageal manometry and 24h pH-impedance testing. 344 of those patients remained off anti-secretory therapy (PPI) for the procedure. The most common dosage was 40mg QD, 40mg twice daily (BID), or 60mg QD. Only 7.5%, 11.5%, and 5.0% of patients were taking an H_2 blocker, antacid, or pro-motility agent, respectively. Patients using antacids were not excluded.

Patients were an average age of 51.1±14.1 years and 62% were female. Average BMI was 29.5±6.2 (15.9-59.0) kg/m^2 (**Figure 5-9**). Patient medical history included 18 cholecystectomies, 2 esophageal dilations, 2 with a history of Barrett's, and 1 partial gastrectomy.

Figure 5-9: Body mass index separated by the six World Health Organization body mass index categories in patients that underwent esophageal manometry and 24h pH-impedance testing.



Symptoms

Patients presented to clinic primarily for heartburn (77.3%), nausea, vomiting, globus, and gagging (34.3%), regurgitation (27.9%), dysphagia (26.5%), and epigastric or chest pain (21.8%), and less frequently for chronic cough (12.8%), burping (4.1%), and odynophagia (1.8%).

Patients that were using an anti-secretory therapy for treatment of GERD, but were not taking the medication during the test, reported that they did receive some relief from their medication (59.7%). The majority was taking only a single medication (61.1%), but others required 2-4 simultaneous medications (13.1%, 2.3%, 0.3%, respectively) which did not necessarily relieve symptoms more frequently compared to those taking a single medication.

Relationship Between Patient Symptoms and Reflux

45% of patients had pathological reflux (DeMeester Score >14.7 or Jamieson/DeMeester Score >16.0). The median DeMeester Score was 12.4 (0.8-133.9). Refer to **Appendix Table A5** for number of reflux events and esophageal acid exposure.

Symptoms were measured by SI, SSI, and SAP during 24h pH-impedance and SI during 24h pH. Refer to **Appendix Table A6** for frequency of positive symptom association with acid, non-acid, and total reflux events, as well as the frequency of positive symptoms with positive reflux findings and presenting symptoms.

The presenting symptoms of the patient were not generally related to reflux events, apart from burping (92.9%), with the remaining symptoms being associated with reflux less than 60%. Burping and regurgitation were also the only presenting symptom that was 50% or more associated with positive reflux findings (DeMeester Score >14.7). However, when looking at patients that had both a positive symptom and reflux finding, all presenting symptoms were similarly linked (53.9%-70.7%). Most positive reflux symptoms, according to SI, were reported when the patient was upright (57.7%), while only 26.9% were recumbent reflux.

BMI does not appear to play a significant role in symptom presentation or symptom association with reflux, with the following two exceptions. Patients presenting with chronic cough were on average 2.2 BMI units heavier than patients without chronic cough symptoms (95% CI 0.3-4.1, p=0.027) and patients presenting with odynophagia were on average 6.8 BMI units lighter than patients without odynophagia (95% CI -11.7 - -1.8, p=0.007).

Relationship Between Esophagogastric Junction and Acid Reflux

Several parameters were used to describe the EGJ. The EGJ parameters in patients with and without reflux are described in **Table 5-3**.

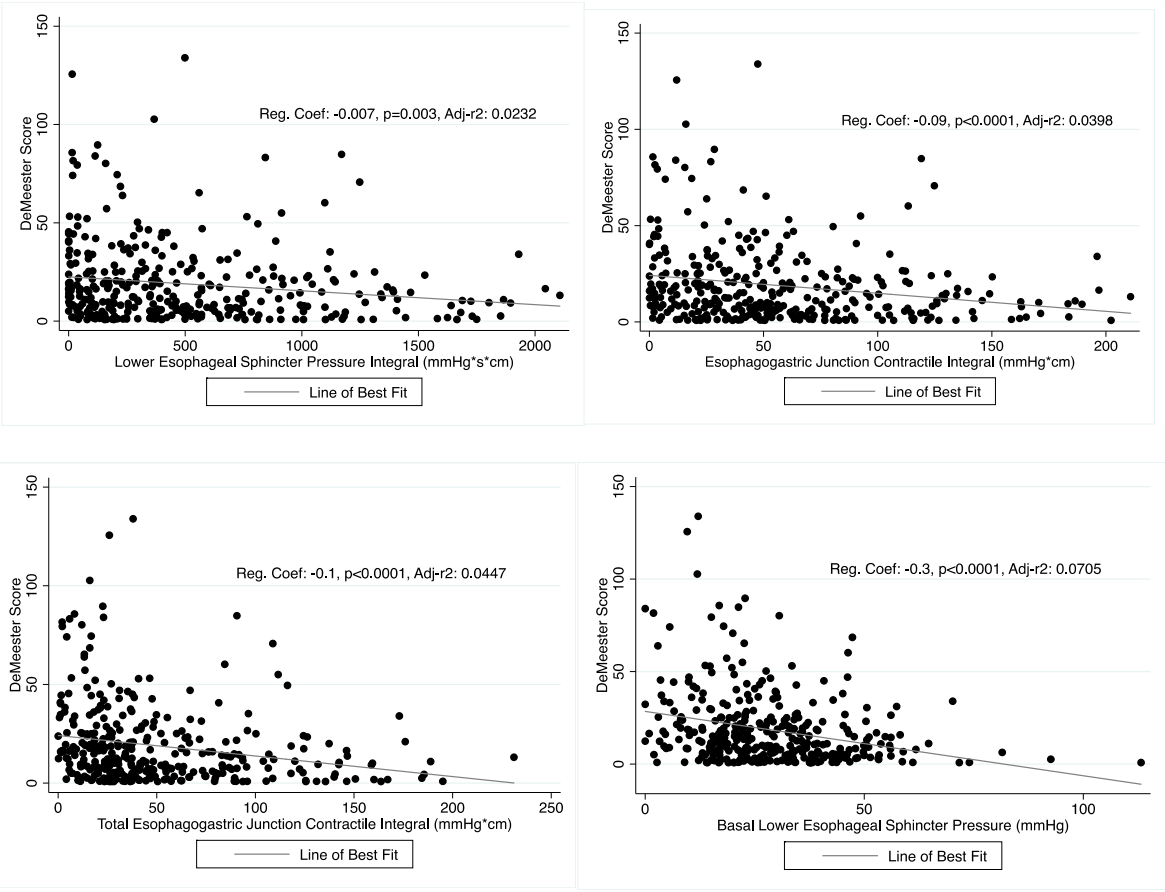
Table 5-3: Esophagogastric junction parameters in patients with and without reflux and the significant difference in measurements between these groups.

	No Reflux (n=189)	**Reflux (n=153)**	**Significance (p-value)**
LES Length (cm)	4.4±1.1	4.3±1.7	0.0931
Intraabdominal Length (cm)	2.2±1.2	1.9±1.6	0.0106
EGJ Type (%)			<0.001
Type I	78.8	51.6	
Type II	15.3	30.7	
Type IIIA	1.6	10.5	
Type IIIB	4.2	7.2	
Hiatal Hernia (%)	17.8	43.1	<0.001
Basal LES Pressure (mmHg)	31.5±16.5	24.2±13.9	<0.001
LES Residual Pressure (mmHg)	10.7±7.2	7.5±5.3	<0.001
LES Pressure Integral (mmHg·s·cm)	603.5±622.2 (460.4, 0-5764.3)	419.2±424.2 (289.1, 0-2044.1)	0.0007
EGJ Contractile Integral (mmHg·cm)	71.3±108.8 (52.5, 0-1408.9)	46.4±40.6 (38.4, 0-196.9)	0.0002
Total EGJ Contractile Integral (mmHg·cm)	64.5±88.1 (44.5, 0.2-1091.2)	38.3±35.9 (26.2, 0.05-176.0)	<0.001

LES: Lower esophageal sphincter, EGJ: Esophagogastric junction.

LES-PI, EGJ-CI, and total EGJ-CI were highly correlated to each other ($0.73 \leq r \leq 0.85$, $p<0.001$). Basal LES pressure was also highly correlated to LES-PI (0.62, $p<0.001$) and EGJ-CI (0.61, $p<0.001$). While all other continuous variables listed above were significantly correlated with each other, except for total LES length and LES residual pressure, these correlations were below 0.48. The LES-PI, EGJ-CI, LES pressure, and total EGJ-CI correlations were explored to determine which of these variables best explained the relationship with acid reflux (**Figure 5-10**).

Figure 5-10: Linear relationships between esophagogastric junction parameters and acid reflux DeMeester Score.

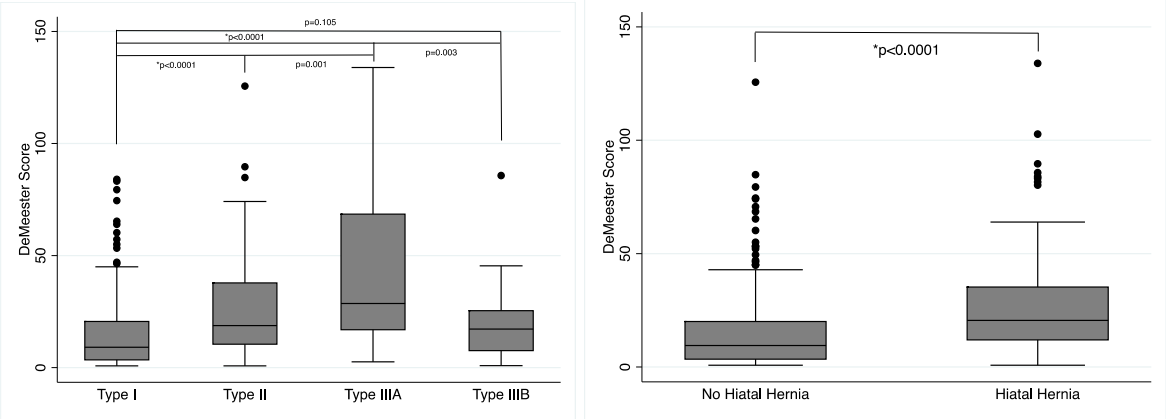


Basal LES pressure was the superior measurement to address the relationship between the EGJ and acid reflux, because the adjusted R^2 explained the greatest amount of variability in the model. Regardless of transforming LES-PI, EGJ-CI, and total EGJ-CI to their square root to reduce variability in the model, the adjusted R^2 did not exceed that of the basal LES pressure. The small adjusted R^2 indicated that other factors needed to be included to explain the relationships with reflux.

EGJ type included hiatal hernia, and the two variables were investigated to observe which was best associated with the acid reflux DeMeester Score (**Figure 5-11**). The adjusted R^2 was 0.061 for hiatal hernia (Reg. Coef: 11.4). The adjusted R^2 was 0.11 for EGJ type (Reg.

Coef compared to Type I: 10.4, 26.7, 7.5). EGJ type was the superior choice to explain the variation in the relationship with acid reflux.

Figure 5-11: Relationship of esophagogastric junction type (left) and presence of hiatal hernia (right) with DeMeester Score.

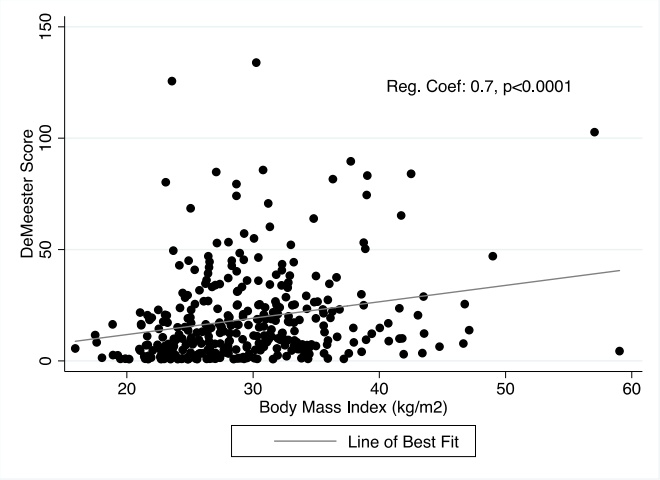


Relationship Between Body Mass Index, Acid Reflux, and Esophageal Motility

The relationship between the BMI, EM, and EGJ parameters and the DeMeester Score was investigated to determine which variables should be included in the multivariate linear regression.

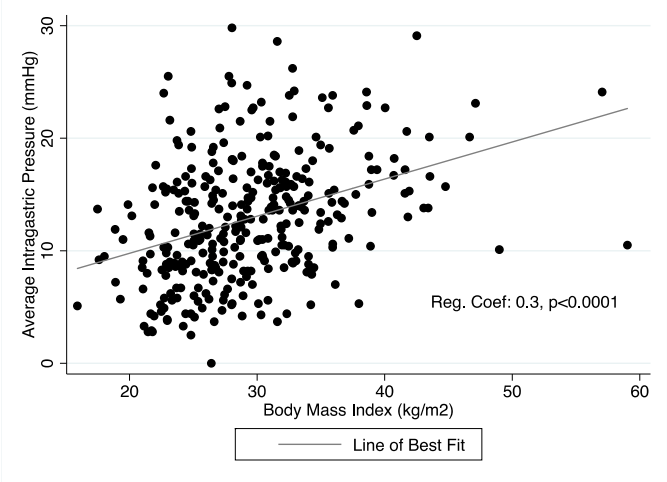
The hypothesis was that acid reflux is impacted by BMI through its interaction with IGP and LES pressure, as well as reduced EM. A positive association was observed between BMI and DeMeester Score: on average for every 1 unit increase in BMI, the DeMeester Score increased by 0.7 units ($p<0.0001$) (**Figure 5-12**). The relationship with the DeMeester composite score factors was between BMI and the percent time clearance ($p<0.0001$), total number of acid reflux events ($p<0.004$), and total number of reflux events ($p<0.0001$).

Figure 5-12: Relationship between DeMeester Score and body mass index.



A positive association was also observed between BMI and IGP: on average for every 1 unit increase in BMI, the average IGP increased by 0.3mmHg (p<0.0001) (**Figure 5-13**).

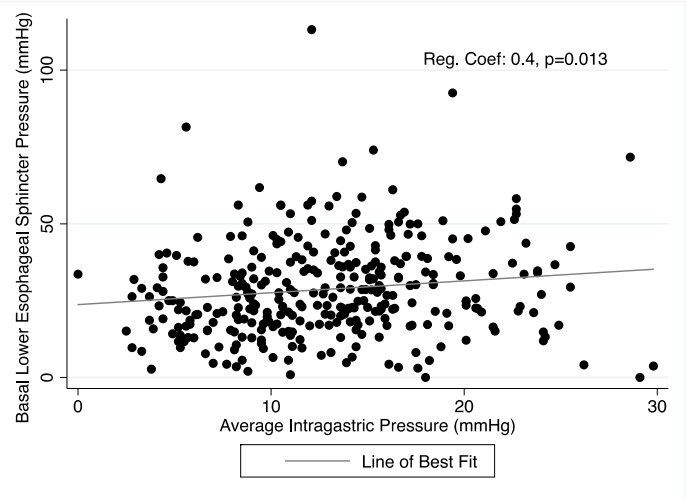
Figure 5-13: Relationship between body mass index and average intragastric pressure.



Surprisingly, a positive association was observed between IGP and LES pressure, rather than a negative association: on average for every 1mmHg increase in IGP, LES pressure increased by 0.4mmHg (p=0.013) (**Figure 5-14**). To further explore this relationship, the DeMeester Score was stratified into normal (<14.7) and abnormal (>14.7). Patients with acid reflux did not have a significant relationship between LES pressure and IGP. Only

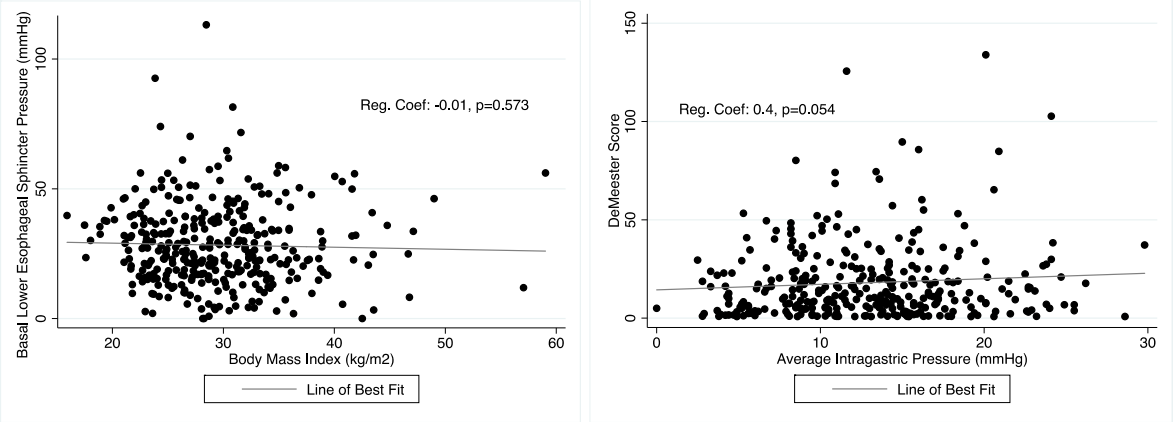
patients with no acid reflux had a positive relationship between IGP and LES pressure (0.6, p=0.014).

Figure 5-14: Relationship between average intragastric pressure and basal lower esophageal sphincter pressure.



This positive relationship was also observed between LES-PI and IGP ($p<0.0001$) in patients with a normal DeMeester Score and EGJ-CI and IGP ($p=0.02$) in patients with an abnormal DeMeester Score. There was no significant association between total EGJ-CI and IGP ($p=0.57$). As mentioned earlier, a negative association exists between LES pressure and the DeMeester Score (Reg. Coef: -0.3, $p<0.0001$) by reducing esophageal acid exposure ($p=0.004$) and total number of acid and non-acid reflux events ($p<0.0001$). LES length and BMI were positively associated (Reg. Coef: 0.54, $p=0.026$). LES pressure and BMI did not have a statistically significant association ($p=0.57$) nor did DeMeester Score and IGP, therefore, these relationships could not explain the lack of association between IGP and LES pressure (**Figure 5-15**).

Figure 5-15: Relationship between body mass index and basal lower esophageal sphincter pressure (left) and between average intragastric pressure and DeMeester Score (right).



However, EGJ type was associated with LES pressure and DeMeester Score. Yet EGJ type was not significantly related to IGP or BMI (**Table 5-4**).

Table 5-4: Relationship between DeMeester Score, lower esophageal sphincter pressure, distal contractile integral, average intragastric pressure, body mass index and esophagogastric junction types compared to Type I.

Compared to Type I	Type II	Type IIIA	Type IIIB
DeMeester Score	+ 10.4 (p<0.0001)	+ 26.7 (p<0.0001)	+ 7.5 (p=0.11)
LES Pressure (mmHg)	- 8.2 (p<0.0001)	- 11.3 (p=0.002)	- 18.1 (p<0.0001)
DCI (mmHg/cm/s)	- 579.6 (p=0.002)	- 301.4 (p=0.362)	- 679.3 (p=0.04)
Average Intragastric Pressure (mmHg)	- 0.5 (p=0.46)	- 1.4 (p=0.3)	+ 1.7 (p=0.23)
Body Mass Index (kg/m^2)	+ 1.0 (p=0.21)	+ 2.3 (p=0.12)	+ 2.4 (p=0.099)

LES: Lower esophageal sphincter, DCI: Distal contractile integral.

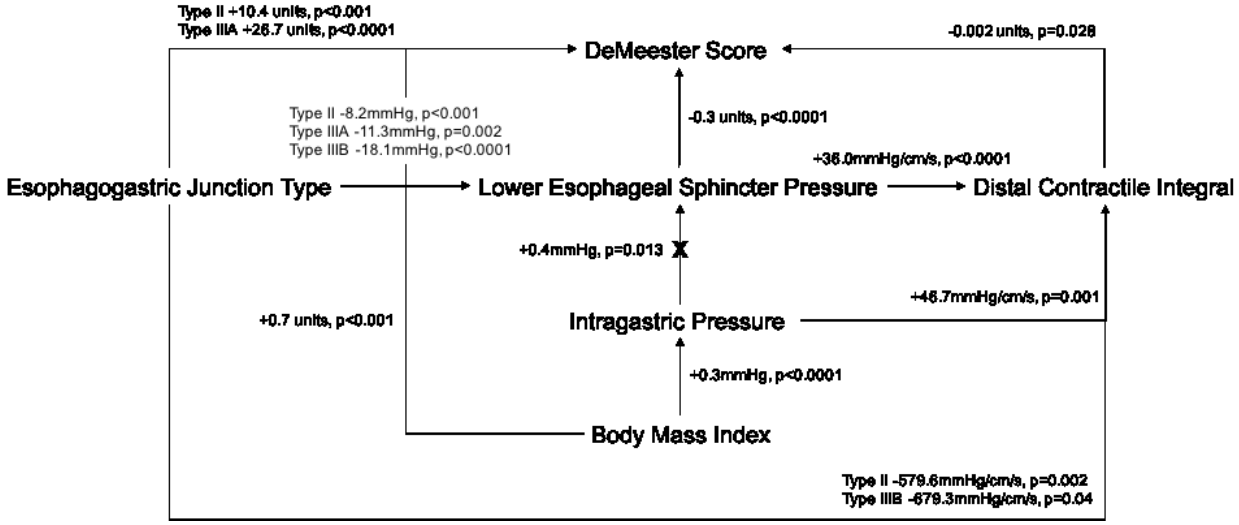
Interestingly, a significant relationship existed between BMI and presence of hiatal hernia (Reg coef: 1.8, p=0.013), but was also not related to IGP p=0.473.

Few EM parameters were associated with the DeMeester Score. EGJ-OO and achalasia were negatively associated with the DeMeester Score, as expected considering the elevated LES pressure characteristic of both disorders. Yet, IEM was positively associated with the DeMeester Score (Reg. Coef: 7.4, p=0.003). Percentage of swallows displaying peristalsis was not associated with the DeMeester Score (p=0.701). Characteristic of weak peristalsis

of IEM, on average for every 1 unit increase in the DeMeester Score, DCI decreased by 8mmHg/cm/s (p=0.028). The exact mechanism for this relationship could not be determined as both mean wave amplitude and mean wave duration had no significant relationship with DeMeester Score (p=0.09 and p=0.792, respectively), but an increase in DCI was associated with a decrease in non-acid (p<0.001) and total number of reflux events (p=0.001). BMI was not associated with DCI (p=0.659), but IGP was positively associated with DCI (Reg. Coef: 46.7, p=0.001).

A summary of significant associations is illustrated in **Figure 5-16**.

Figure 5-16: Summary of significant direct and indirect associations with DeMeester Score.



Predictors of Acid Reflux

Patient demographics, BMI, symptoms, and LES and EM parameters were tested for a linear association with the DeMeester Score. Significant associations for acid reflux from the univariate linear regression are listed in **Table 5-5**.

Table 5-5: Variables tested in a univariate linear regression with DeMeester Score and natural logarithm of DeMeester Score.

Variable	DeMeester Score Significance (p-value)	Log DeMeester Score Significance (p-value)
Age (years)	0.681	0.471
Gender (Female to Male)	0.191*	0.969
Body Mass Index (kg/m^2)	<0.001*	<0.001*
Underweight to Normal	0.586	0.834
Overweight to Normal	0.021*	0.001*
Obesity Class I to Normal	0.008*	<0.001*
Obesity Class II to Normal	0.001*	<0.001*
Obesity Class III to Normal	0.009*	0.001*
Heartburn Symptoms	0.002*	<0.001*
Epigastric/Chest Pain Symptoms	0.098*	0.285
Regurgitation Symptoms	0.001*	<0.001*
Chronic Cough Symptoms	0.738	0.367
Burping Symptoms	0.038*	0.133*
Other Symptoms	<0.001*	<0.001*
Average Intragastric Pressure at Baseline	0.054*	0.225
Lower Esophageal Sphincter Pressure	<0.001*	<0.001*
Distal Contractile Integral	0.028*	<0.001*
Esophagogastric Junction Type		
Type II to Type I	<0.001*	<0.001*
Type IIIA to Type I	<0.001*	<0.001*
Type IIIB to Type I	0.105*	0.038*

Significance: *p<0.2 included in multivariate analysis.

None of the continuous variables that entered the multivariate analysis displayed collinearity and all had a tolerance above 0.1. Significant associations for acid reflux from the multivariate linear regression are listed in **Table 5-6**.

Table 5-6: Variables tested in a multivariate linear regression with DeMeester Score and natural logarithm of DeMeester Score.

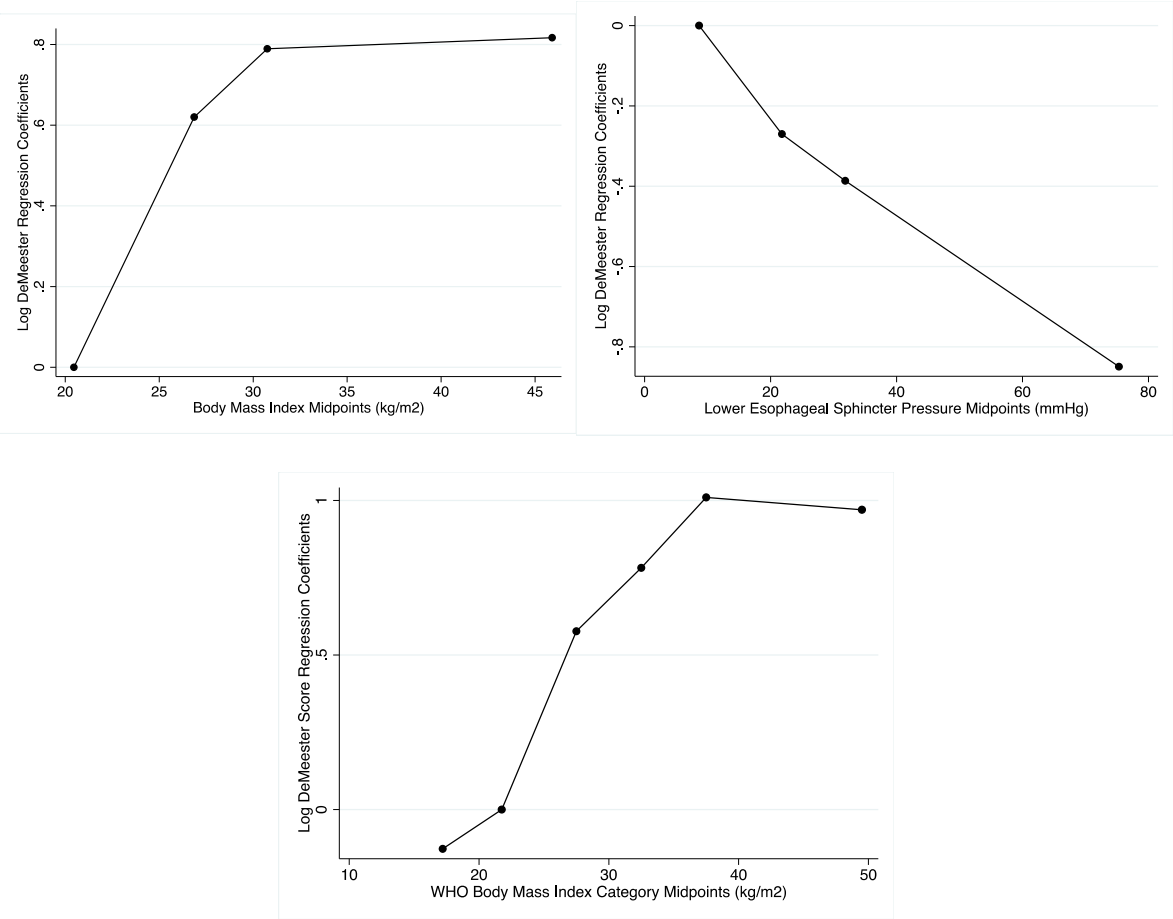
Variable	DeMeester Score Significance (p-value)	Log DeMeester Score Significance (p-value)
Gender (Female to Male)	0.031*	-
Body Mass Index (kg/m^2)	0.005*	<0.001*
Underweight to Normal	0.737	0.637
Overweight to Normal	0.500	0.016*
Obesity Class I to Normal	0.077	<0.001*
Obesity Class II to Normal	0.115	0.001*
Obesity Class III to Normal	0.039*	0.002*
Heartburn Symptoms	0.001*	<0.001*
Epigastric/Chest Pain Symptoms	0.173	-
Regurgitation Symptoms	0.001*	0.001*
Burping Symptoms	0.052	0.304
Other Symptoms	0.035*	0.005*
Average Intragastric Pressure at Baseline	0.063	-
Lower Esophageal Sphincter Pressure	0.007*	0.004*
Distal Contractile Integral	0.944	0.137
Esophagogastric Junction Type		
Type II to Type I	0.002*	0.018*
Type IIIA to Type I	<0.001*	0.002*
Type IIIB to Type I	0.934	0.617

Significance: *p<0.05 included in final model.

The model did not meet the assumption of normal distribution with the DeMeester Score in its natural form and was logarithmically transformed to perform the linear regression again (**Table 5-5 & 5-6**). Burping symptoms and DCI were not confounding variables. Clinically plausible interactions, such as BMI and EGJ type, BMI and LES pressure, were tested and were not significant. The final model contained BMI, heartburn, regurgitation and other symptoms, LES pressure, and EGJ Type II and IIIA compared to EGJ Type I. The adjusted R^2 was 0.25. Homoscedasticity, independence, and normality (after taking the natural logarithm of the DeMeester Score) assumptions were met. Some influential data were detected as 20 outliers. These outliers were excluded as they substantially altered the regression coefficients. The adjusted R^2 was 0.32 after removing outliers. The linearity assumption was not met: while LES pressure displayed a linear relationship with the

DeMeester Score, BMI did not (**Figure 5-17**). BMI was re-entered into the model as the 6 WHO categories to satisfy the assumption, which increased the adjusted R^2 to 0.33.

Figure 5-17: Linear and non-linear relationships of body mass index (upper left), lower esophageal sphincter pressure (upper right), and World Health Organization body mass index categories (bottom) with DeMeester Score regression coefficients.



WHO: World Health Organization.

For every 1mmHg increase in LES pressure, the DeMeester Score decreased by 4% ($p<0.0001$) when all other variables were fixed. Patients with other symptoms (nausea and vomiting) also had a lower DeMeester Score by 30% than patients without symptoms. Patients with regurgitation and heartburn symptoms had a higher DeMeester Score by 63% and 56% than patients without symptoms ($p<0.0001$ and $p=0.001$, respectively). Patients

with a Type II EGJ and Type IIIA EGJ had a higher DeMeester Score by 69% and 108% than Type I EGJ patients ($p<0.001$ and $p=0.002$, respectively). The DeMeester Score was higher in overweight, obesity class I, obesity class II, and obesity class III patients by 51%, 100% 138%, and 114% ($p=0.004$, $p<0.0001$, $p<0.0001$, and $p=0.002$, respectively). Predictors of acid reflux (DeMeester Score>14.7) were also tested by logistic regression, whose results can be found in **Appendix Tables A7-A9**. The final logistic model contained the same variables as the linear regression model, except DCI was a significant predictor of acid reflux (OR: 0.99, 95% CI 0.99-0.99, $p=0.041$) and only obesity class I was a significant predictor of acid reflux from the 6 WHO BMI categories (OR: 1.75, 95% CI 1.01-3.03, $p=0.045$). This model was a good fit, $p=0.12$.

Non-Acid Reflux and Body Mass Index

The definition of non-acid reflux varies in the literature; however, the general consensus is that the DeMeester Score should be <14.7 to qualify for non-acid reflux (219, 220). Patients with a DeMeester Score <14.7 were separated by whether they were taking a PPI during the 24h pH-impedance test or not (**Table 5-7**).

Table 5-7: Number of non-acid reflux events, frequency of positive symptom association probability for non-acid reflux by symptom, and frequency of positive symptom association probability for non-acid reflux associated with the patient's presenting symptoms in patients with a DeMeester Score <14.7 by patients on and off a proton-pump inhibitor.

	Off (n=167)	**On (n=224)**	**Significance (p-value)**	**Total (n=391)**
Number of Non-Acid Reflux Events				
Distal Upright	30.7±20.6 (26, 2-96)	42.0±30.2 (34, 4-182)	0.0001*	37.2±27.1 (30, 2-182)
Distal Recumbent	4.4±7.7 (2, 0-50)	6.2±10.9 (3, 0-112)	0.0106*	5.4±9.7 (2, 0-112)
Distal Total	35.2±23.9 (27, 2-120)	48.0±34.7 (38, 5-220)	0.0001*	42.5±31.2 (33, 2-220)
Proximal Upright	15.3±13.8 (11, 0-67)	23.0±22.1 (16, 0-141)	0.0001*	19.7±19.4 (14, 0-141)
Proximal Recumbent	1.8±4.5 (0, 0-42)	2.9±7.0 (1, 0-84)	0.0218*	2.4±6.1 (1, 0-84)
Proximal Total	17.1±15.4 (12, 1-81)	25.8±25.0 (17, 1-157)	<0.001*	22.1±21.8 (15, 1-157)
Percent Symptom Association	56.3	69.2	0.009*	63.7
Probability of Non-Acid Reflux (%)				
Heartburn	5.0	6.1	0.673	5.6
Regurgitation	21.4	23.8	0.869	22.9
Epigastric or Chest Pain	3.3	0.0	0.484	1.6
Coughing	11.6	20.9	0.019*	16.9
Burping	51.5	61.7	0.049*	57.4
Percent Symptom Association	10.2	14.3	0.280	12.5
Probability of Non-Acid Reflux with Presenting Symptoms (%)				
Heartburn	5.4	7.1	0.626	6.4
Regurgitation	50.0	40.0	0.733	42.9
Epigastric or Chest Pain	25.0	0.0	0.285	12.5
Coughing	18.2	25.0	0.558	21.5
Burping	62.5	100.0	0.069	83.3

A significant difference existed between patients on and off PPI for the number of non-acid reflux events at the distal and proximal pH lead. SAP with non-acid reflux for burping and coughing symptoms were also significantly increased in patients taking a PPI during the test. Since non-acid reflux is a mechanistic not a secretory issue, LES pressure and DCI

were explored, but were not significantly different between patients on or off PPI. A conservative approach of using patients off PPI was taken to assess non-acid reflux. Definitions of non-acid reflux in the literature include positive SAP for non-acid reflux and may vary depending on the presenting symptom of interest (219, 221). 56.3% of patients off PPI with a DeMeester Score <14.7 had a positive SAP for non-acid reflux. Burping symptoms are well known to be positively associated with non-acid reflux in the healthy population (222, 223), and after excluding patients that had a positive SAP for burping with non-acid reflux and without burping as a presenting symptom, only 18.0% had a positive SAP for non-acid reflux off PPI and with a DeMeester Score <14.7.

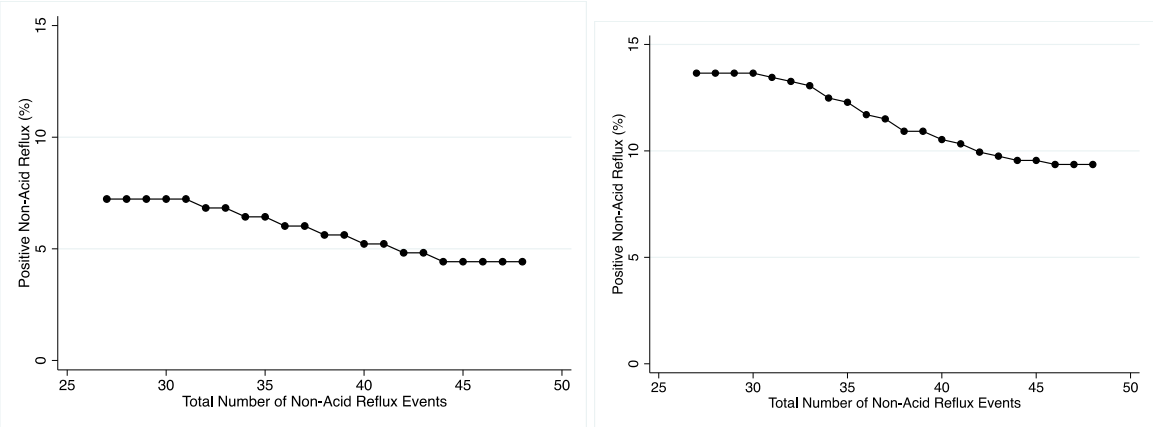
The final component of non-acid reflux was the number of non-acid reflux events patients experienced. **Table 5-8** describes the number of non-acid reflux events by definition of non-acid reflux.

Table 5-8: Total number of distal non-acid reflux events by percentile for patients with a DeMeester Score<14.7 and a positive symptom association probability for non-acid reflux.

Total Number of Distal Non-Acid Reflux Events by Percentile	**DeMeester Score <14.7 (n=167)**	**DeMeester Score <14.7 & Symptom Association Probability with Non-Acid Reflux (including burping) (n=94)**	**DeMeester Score <14.7 & Symptom Association Probability with Non-Acid Reflux (limited burping) (n=30)**
50th Percentile	27	32	37
75th Percentile	47	52	59
90th Percentile	67	67	89
95th Percentile	88	89	90
99th Percentile	113	120	120

The threshold for the number of non-acid reflux in healthy controls was reported to be 27-48 events (217, 218). The percentage of patients that had positive non-acid reflux (DeMeester Score<14.7 and a positive SAP with non-acid reflux) was plotted against the reported range of non-acid reflux events threshold (27-48) **Figure 5-18**.

Figure 5-18: The percentage of patients positive for non-acid reflux based on a DeMeester Score<14.7 and positive symptom association probability for non-acid reflux over the total number of normal non-acid reflux events for patients off a proton-pump inhibitor (left) and patients on and off medication (right).

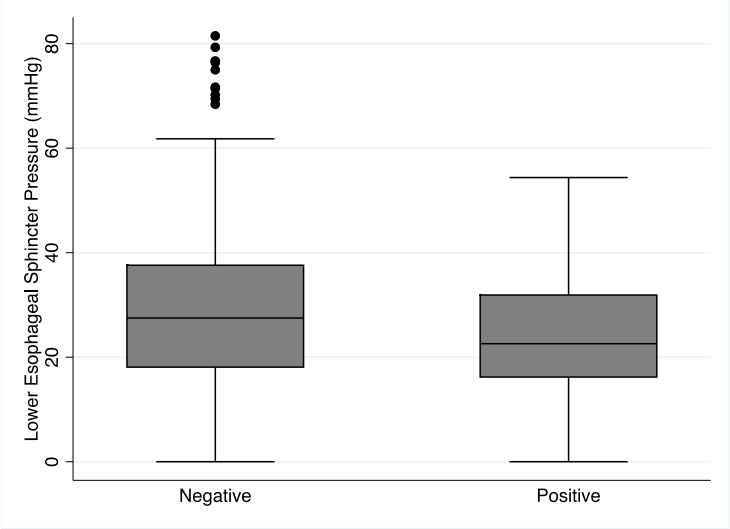


There was no significant difference in the frequency of positive non-acid reflux patients identified using 27 or 48 non-acid reflux events tested by Chi^2 (p=0.25). The midpoint, that is, 37 non-acid reflux events, was used for the definition of positive non-acid reflux. 6.0% of patients off PPI, 16.7% on PPI, and 11.5% total were positive for non-acid reflux.

A negative binomial distribution regression was fitted for total number of non-acid distal reflux events as the Poisson model did not meet the assumptions. An increase in age (p<0.001), increased percentage of swallows with peristalsis (p<0.001), and increased LES pressure (p<0.001) were all significantly associated with a reduction in total number of non-acid reflux events. An increase in BMI (p=0.044), patients on proton-pump inhibitor for study (p<0.001), and presence of a hiatal hernia (p=0.004) were all significantly associated with an increase in total non-acid reflux events. No presenting symptoms were predictive of non-acid reflux, apart from burping (p=0.008). Although, only LES pressure

was associated with non-acid reflux based on the above definition using logistic regression (OR: 0.97, 95% CI 0.95-0.99, p=0.043) (**Figure 5-19**).

Figure 5-19: Lower esophageal sphincter pressure in patients negative or positive for non-acid reflux. Positive: DeMeester Score<14.7, positive symptom association for non-acid reflux, and >37 total non-acid reflux events.



Data Summary

- BMI was significantly associated with hiatal hernia, IGP, LES pressure, LES residual pressure, UES pressure, and failed peristalsis
- Significant predictors of abnormal EM were increased age, male gender, lower BMI, no heartburn symptoms, and dysphagia symptoms
- Patients referred for burping and regurgitation had the greatest likelihood of positive reflux findings
- LES pressure was a superior measurement of the EGJ region compared to LES-PI, EGJ-CI, or total EGJ-CI

- The interactions involved in the mechanism between BMI and reflux were not present as LES pressure and IGP were positively associated and no other interactions were found to support the hypothesis that BMI disrupts the EGJ region
- Reduced DCI was the only EM parameter predictive of an increased DeMeester Score
- Significant predictors of reflux were reduced LES pressure, no 'other' symptoms, regurgitation and heartburn symptoms, EGJ type II and IIIA, overweight BMI, obesity class I and II, and DCI
- BMI had a logarithmic relationship with the DeMeester Score, instead of linear
- Non-acid reflux was found in 11.5% of patients overall and was predicted only by reduced LES pressure

5.4 Discussion

The purpose of this study was to explore the relationship between obesity, gastroesophageal reflux, and EM in a population requiring investigations for esophageal symptoms. This was an interesting group of patients, as most were referred for dysphagia and intractable heartburn or non-classic presentation of reflux symptoms. The expected outcome was that both the probability of reflux and EMDs would be associated with an increase in BMI.

5.4.1 Esophageal Motility

To date, this study is the largest evaluation of esophageal manometry (n=1326) in the literature. Unexpectedly, this population was the average BMI of the average Canadian population (overweight). The expectation was that patients with EMDs and difficult swallowing would be either underweight or normal weight, since some EMDs are associated with weight loss. While patients with EMDs had a significantly lower BMI than

those without (28.5kg/m^2 versus 29.4kg/m^2, p=0.0091), this difference is arguably not clinically significant as both groups are overweight.

The mechanism of BMI and EMDs is not well described in the literature. The results were that BMI was significantly linearly associated with hiatal hernia, IGP, UES pressure, and failed peristalsis. According to the literature, hiatal hernias were commonly found in obese patients (202, 206). IGP was also significantly positively associated with BMI (198). No literature has documented the increased relationship of UES pressure and obesity. Obesity was also related to non-propagated swallows in 13% of patients with hypomotility (204). Of these factors, only IGP was explored linearly in the literature. LESP was not linearly associated to BMI, but was significantly different between the BMI categories. Several publications have described this relationship with obesity compared to normal weight patients, but none has explored the linear relationship with BMI (202, 206, 224).

The most common EMDs in this group were IEM and EGJ outflow obstruction. In the literature, 20% of patients that underwent esophageal manometry had IEM (83), 8% had EGJ outflow obstruction (225), and 10% had a hypotensive LES (226).

There was a significant difference in age, gender, BMI, LES and UES residual pressure, and all EM parameters, except for percentage of swallows with double peaked waves, between patients with and without EMDs. These parameters have been investigated in the literature and had similar relationships to the findings in this study, including increased age (227), male gender (228), increased BMI (202, 206), and different sphincter-motility parameters, as reported in the Chicago Classification (80).

Heartburn symptoms were not significantly associated with EM. In light of the plethora of literature describing the link between EM and gastroesophageal reflux (82), especially in

the obese population (79, 203, 205), it was surprising that patients without heartburn symptoms were more likely to have an EMD.

BMI was linearly related to EMDs. Extensive literature describes an association between obesity and EMDs, although most studies are in the selective pre-bariatric surgery population. *Koppman et. al.* found that 41% of patients with obesity had some form of EMD, with non-specific EMD being the most common (23%) (229). *Küper et. al.* found that patients with obesity had a reduced LES pressure, increased contraction frequency, and decreased contraction amplitude (206). *Hong et. al.* found that 54% of their patients screened before bariatric surgery had an EMD. However, their most common motility disorder was hypotensive and hypertensive LES with few esophageal body motility issues (205). Another study by *Suter et. al.* found that 74% of patients with obesity had normal EM and only 18% of patients had reduced LES pressure (203). A linear relationship with BMI has yet to be described in the literature.

Achalasia was the most significantly associated disorder with BMI. This reduction in BMI was expected, as achalasia is known to cause weight loss (230). Nevertheless, BMI does not appear to play a role in specific disorders after adjusting for other variables.

5.4.2 Gastroesophageal Reflux

Obesity is an important risk factor for the development of GERD (231). An increase in BMI significantly increases the risk of GERD symptoms being present in a population. This relationship makes GERD a common comorbidity present in the bariatric surgery population. 32 – 50% of preoperative patients presenting for bariatric surgery were found to have GERD (145, 232). The results show that patients who had a significantly higher

average BMI also had an abnormal DeMeester Score compared to patients with a normal score (30.4 versus 28.1, $p<0.001$).

Burping symptoms were highly associated with symptoms of reflux. As described earlier, burping is commonly associated with reflux symptoms, because of the mechanical disruption of the EGJ during burping. Burping, regurgitation, and heartburn were the constellation of symptoms most related to reflux events, abnormal DeMeester score, and presenting symptoms. These are expected symptoms, as they are highly associated with acid reflux in the literature and asked in GERD symptom questionnaires such as the GSRS. All EGJ parameters were significantly related to reflux, except LES length. These parameters were first explored together by *Jasper et. al.* (213). *Hoshino et. al.* also found that LES length was not significantly related to acid reflux (215). LES pressure appeared to be the best approach to explain the variability in the association with DeMeester Score. This finding was contrary to the original literature regarding LES-PI, EGJ-CI, and total EGJ-CI (213, 215, 216). However, EGJ-CI was the only EGJ parameter linked to patients with an abnormal DeMeester Score, similar to the results reported by *Nicodème et. al.* (216). Yet, *Jasper et. al.* found that only total EGJ-CI was significantly related to patients with positive reflux (213). Regardless of assessing the ROC, total EGJ-CI area under the curve was 0.342 compared to 0.746 in their study. LES pressure area under the curve was similar at 0.364. In addition, EGJ type better approximated the variability in the DeMeester Score than hiatal hernia. EGJ type is classified by the size of separation of the LES and crural diaphragm, which would include hiatal hernia.

The mechanism behind the association of BMI and DeMeester Score was unclear. The hypothesis was that BMI causes increased IGP, which causes a disruption of the EGJ and

LES tone, increasing the risk of reflux (233). BMI was associated with both acid exposure and acid reflux events. BMI was also associated with IGP. However, IGP was not associated with LES pressure in patients with reflux. Only in patients that had no reflux was there a significant positive relationship between IGP and LES pressure, the opposite of the hypothesis. Interestingly, the links between BMI and reflux have not been tested together in the literature. Primary literature describing LES increasing as IGP increases has not been mentioned in subsequent literature exploring the BMI-reflux relationship. Two studies looked at IAP and LES pressure. *Mittal et. al.* found that LES pressure increased as IAP increased in healthy subjects (234). Whereas *Dodds et. al.* found that LES pressure in healthy controls either remained the same or increased with IAP, in patients with esophagitis a small decrease in LES pressure was noted with 100mmHg of abdominal compression, but this was not significantly different from the healthy control group and was not considered to be clinically significant (235).

Only EGJ-CI in patients with reflux had a significant relationship with IGP, but this was again a positive relationship. Interactions were explored, such as LES pressure and BMI and DeMeester Score and IGP, to explain the disconnect in the BMI-acid reflux mechanism; however, none of these interactions proved significant. The lack of a relationship between LES pressure and BMI is contrary to the results seen in patients with or without 24h pH monitoring. In fact, EGJ type was not significantly related to BMI. Although, there was a significant relationship to patients with BMI and hiatal hernia. This finding is contrary to the literature, which showed that EGJ disruption in patients with obesity was highly related to GERD (198, 236).

The multivariate model included EGJ type, LES pressure, symptoms, and BMI. BMI did not meet the linear assumption and instead appeared to have a logarithmic relationship with the DeMeester Score, instead of the classic linear relationship described in the literature. It could be that once a certain BMI threshold is reached, BMI no longer substantially contributes to reflux pathology. A large study of 1,659 patients by *Ayazi et. al.* found that BMI was significantly related to the DeMeester Score: for every 1 unit increase in BMI, the DeMeester Score increased by 1.46 (224). Whether their model met the assumptions of a multivariate regression was unclear. However, after adjusting for other factors, such as age and gender, only 13% of the variance in the DeMeester Score was explained by their model compared to this model which accounted for 33%. Roughly, the larger the adjusted-R^2 the greater the explanation of the variability in DeMeester score and the more suitable the model. *El-Serag et. al.* found that BMI was significantly related to the DeMeester Score, but had a better association once BMI was adjusted by waist-circumference (237). The results did not find that intragastric pressure contributed to the relationship with BMI and DeMeester Score.

As explored earlier, BMI was related to EMDs through an unknown mechanism, and, as the literature states, EMDs are related to reflux. In the literature, IEM is associated with GERD and acid reflux and has been studied as a mechanism in reflux development. Disruptions in EM also did not explain the relationship in linear regression. Patients with an EMD were not more likely to have abnormal DeMeester Score either. Despite that, logistic regression found that patients with weak peristalsis (low DCI) from ineffective esophageal peristalsis was significant. Reduced DCI was only related to recumbent acid exposure ($p=0.02$), number of non-acid reflux events ($p<0.0001$), and total number of

reflux events (p=0.001). Reduced DCI was found in patients with erosive reflux, which continued to decrease the more severe the reflux was (82, 238). However, as IGP increased, DCI also significantly increased, and BMI was not significantly related to DCI. *Küper et. al.* found that contraction amplitude was decreased in obese patients (206).

23% of patients had both gastroesophageal reflux and an EMD. The same logistic regression was performed to assess the predictors of this group. Increased LESP decreased the odds by 6% (p<0.0001), heartburn symptoms increased the odds by 216% (p=0.004), other symptoms decreased the odds by 51% (p=0.028), and EGJ type II compared to type I increased the odds by 84% (p=0.048). The model was a good fit (p=0.07). There appear to be some factors missing to evaluate this population, as BMI was no longer significantly associated with this group.

Non-acid reflux occurs when reflux episodes with a pH greater than 4 are attributed to the patient symptoms and is generally seen in patients with reflux symptoms refractory to PPI treatment (221). The diagnosis of non-acid reflux is difficult and controversial, as many techniques such as esophageal bilirubin reflux measurements are limited and not performed in Canada because of its low cost-efficiency (239). Non-acid reflux is not a secretory mechanism, but instead is attributed to mechanical disruptions of the anti-reflux barrier. However, the results of this study found that patients on a PPI had a significantly higher number of non-acid reflux issues than those off PPI. Generally, patients that are treated with a PPI are being treated for acid reflux and are likely to have a LES mechanistic issue. Yet, with the reduction in acid secretion, the proportion of non-acid reflux events was hypothesized to be higher than patients not taking a PPI. This might also be a referral bias,

as patients that are on a PPI during the test may have different reflux presentation or disease than patients able to come off their PPI.

Using the available literature, a definition of non-acid reflux was created, and 6.0% of patients off PPI were considered to have non-acid reflux. The percentage of patients with non-acid reflux was significantly less than the number of patients with acid reflux (45%) ($p<0.0001$). The prevalence of patients with non-acid reflux is largely undescribed in the literature. LES pressure was the only factor that was predictive of non-acid reflux, which supports the hypothesis that non-acid reflux is a mechanistic reflux. In addition, BMI did not play a role in predicting non-acid reflux, nor was it related to LES pressure in this population.

5.4.3 Limitations

One of the limitations of this study was the limited number of patients in the underweight and obesity class III for evaluating reflux. The limitation of 24h pH-impedance is that these procedures do not measure the volume of the refluxate (208). The limitation of esophageal manometry is that this test is not designed to capture TLESRs, an increasingly recognized factor in GERD. In order to evaluate TLESRs, patients would need to either have an ambulatory esophageal manometry or a prolonged esophageal manometry (i.e., 120mins (104)). Another limitation for non-acid reflux is that non-acid bolus exposure was not extracted. Gastroscopy results were incomplete and not included in this study either, which limited the ability to discuss mucosal damage as a factor in EM and GERD.

5.4.4 Conclusions

As a stand-alone factor, a relationship between BMI and reflux does exist. Nevertheless, from this study, the relationship does not appear to be the linear relationship other studies

have reported. The obesity-reflux relationship still remains unclear based on traditional teachings. BMI was also not related to non-acid reflux. However, BMI appears to be linearly related to the odds of having an EMD and may be an important factor to consider when referring patients for esophageal manometry.

This chapter described the impact of increasing BMI and obesity in the non-surgical population on EM and gastroesophageal reflux. These relationships in the bariatric population were explored further. Patients that had undergone bariatric surgery were analyzed separately to determine if this population would be more likely to have disruptions in EM compared to the non-surgical population.

Chapter 6 – Esophageal Motility and Reflux in Non-Surgical Obese and Bariatric Surgery Patients

6.1 Purpose and Rationale

A significant number of patients with obesity appear to have a primary EMD, an under-recognized problem in this population. Common symptoms include dysphagia, heartburn, regurgitation, and dyspepsia. While commonly associated with GERD, esophageal dysmotility also contributes to this symptom cluster. The literature describes a high frequency of patients with obesity having an EMD (79, 206). One study by *Côté-Daigneault et. al.* in 2014 found that 51% of a random selection of patients with obesity had esophageal dysmotility, with esophageal hypomotility as the most common disorder (204).

The assumption that EM is unchanged by bariatric surgery is being challenged in the literature. A recent study by *Mion et. al.* in 2016 found that LSG significantly altered EM (120). New onset of postoperative gastroesophageal reflux symptoms was correlated to IEM. Additionally, LSG was found to decrease LES pressure postoperatively (130). Similarly, the RYGB was also found to decrease LES tone and increase UES tone (134, 240). However, the evidence is largely from small retrospective studies. There is a significant paucity of research into this area of bariatric surgery.

The objective of this study was to determine the frequency and types of EM abnormalities in postoperative bariatric patients referred for troublesome gastroesophageal symptoms. The hypothesis was that bariatric surgery patients would be more likely to have an EMD than non-surgical patients with obesity.

6.2 Study Design

A subset of patient data was extracted from Chapter 5 results. These patients included patients with obesity class I-III and no previous gastric surgery and patients who underwent bariatric surgery. The outcomes were to explore the relationship between bariatric surgery EM and gastroesophageal reflux. Refer to Chapter 5 methods for the full study design. The relationships between patients with obesity and bariatric surgery types with reflux and motility parameters were explored by a Kruskall-Wallis test. Non-parametric testing was used to address normality, as fewer than 30 bariatric patients were expected. Chi^2 Fisher's exact test was used to test significance of categorical variables between bariatric surgery types. Data were presented as mean±standard deviation or median (range). Significance was considered $p<0.05$.

6.3 Results

6.3.1 Patient Demographics and Symptoms

In the study group, 557 patients met the definition for obesity (BMI greater than $30kg/m^2$) and had no previous gastric surgery. A total of 49 patients had undergone previous bariatric surgery, including 14 SG, 13 RYGB, 9 AGB, and 13 vertical banded gastroplasty (VBG). Four AGB patients had a band removal prior to visiting the GI motility lab. Refer to **Table 6-1** for patient demographics and presenting symptoms.

Table 6-1. Patient demographics and presenting symptoms.

	Obese (n=557)	SG (n=14)	RYGB (n=13)	AGB (n=5)	VBG (n=13)	Significance (p-value)
Average age (years)	53.7±13.7	49.4±13.1	49.2±11.5	55.4±8.6	54.9±9.6	0.24
Gender (% Female)	68*	100	92	100	100	<0.001
Average BMI (kg/m^2)	35.1±5.1	35.5±4.5	32.9±7.9	36.3±9.1**	38.9±9.0**	0.0039
Time to Study (years)	-	3.0±2.2	10.2±13.1	11.3±9.3	17.7±6.1	0.0008
	-	3	3	7*	16*	
	-	(0.5-7)	(1-37)	(5-22)	(11-30)	
Presenting Symptoms (%)						
Heartburn	60	79	23**	80	54	0.024
Dysphagia	40	29	38	60	46	0.78
Epigastric or Chest Pain	19	21	54***	40	8	0.046
Regurgitation	24	29	23	20	23	1.0
Chronic Cough	10	14	0	0	8	0.83
Burping	5	0	0	0	8	1.0
Odynophagia	2	0	0	0	8	1.0
Other	28	21	31	20	31	0.94

* Significantly different from bariatric surgery groups
** Significantly different from obese, sleeve gastrectomy, and Roux-en-Y gastric bypass groups
*** Significantly different from obese and vertical banded gastroplasty groups
SG: Sleeve gastrectomy, RYGB: Roux-en-Y gastric bypass, AGB: Adjustable gastric band, VBG: Vertical banded gastroplasty, BMI: Body mass index.

BMI was significantly higher in AGB and VBG patients. AGB and VBG patients presented to clinic later than SG and RYGB patients after surgery. The median time to study after surgery was 5 years (0.5-37years). A greater frequency of female patients was seen in the bariatric surgery groups. RYGB patients were significantly less likely to present to clinic with heartburn symptoms and more likely to present to clinic with epigastric pain symptoms.

6.3.2 Esophageal Motility after Bariatric Surgery

The only significantly different esophageal manometry parameter overall was percentage of swallows with peristalsis (**Table 6-2**). AGB patients had significantly higher UES residual pressure than all other patients (Obese: $p<0.0001$, SG: $p=0.001$, RYGB: $p=0.001$, and VBG: $p=0.002$), but the median UES residual pressure was clinically normal. LES pressure was significantly lower in SG patients than obese patients ($p=0.02$), but the average LES pressure was clinically normal.

Table 6-2. Average esophageal motility parameters for patients with obesity and after bariatric surgery.

	Obese (n=501)	**SG (n=11)**	**RYGB (n=13)**	**AGB (n=4)**	**VBG (n=13)**	**Significance (p-value)**
Hiatal Hernia (%)	27	27	23	50	15	0.52
Hiatal Hernia Size (cm)	3.5±2.0	2.2±0.8	3.2±1.0	5.5±1.8**	4.7±2.3**	0.11
LES Pressure (mmHg)	29.4±15.7	19.5±10.6*	32.0±20.2**	30.8±9.8	30.8±18.0	0.32
LESR Pressure (mmHg)	10.0±8.1 8.4 (0-75)	5.4±5.1* 5.9 (0-11.4)	7.8±5.3 6.6 (0.1-17.3)	3.7±4.7* 2.5 (0-9.9)	8.0±4.3 7.8 (0-15.6)	0.26
Average IGP (mmHg)	14.4±5.3 13.9 (0-34.9)	16.5±3.8 16.5 (10.2-21.4)	19.6±15.2 13.1 (8.9-63.2)	14.7±3.3 14.7 (10.8-18.5)	15.2±4.5 12.7 (11.6-24.9)	0.82
UES Pressure (mmHg)	71.9±39.0	87.1±48.2	82.6±42.5	83.5±23.4	90.0±41.1*	0.93
UESR Pressure (mmHg)	4.2±4.9 2.8 0-32.4	3.5±3.6 2.8 0-11.6	3.8±6.0* 0.2 0-17.7	13.5±13.4*** 9.4 0-32.8	4.5±4.8 4.5 0-13.5	0.23
Percentage of Swallows with Peristalsis (%)	74.1±30.9	88.2±17.8*	80.8±26.0	37.5±29.9***	80.8±23.3	0.047
Mean Wave Amplitude (mmHg)	80.1±47.1 71.7 (0-269)	73.2±32.6 72.2 (21.8-118.3)	93.1±46.8 83.8 (20.4-160.4)	53.6±58.5 42.7 (0-129.1)	76.6±35.3 63.6 (36.7-131.6)	0.47
Mean Wave Duration (s)	3.6±1.6	3.4±0.8	3.6±0.8	2.2±1.8	3.7±1.0	0.50
DCI (mmHg/cm/s)	1582.6± 1373.9 1088.5 (0-6994.7)	1103.8± 534.5 917.5 (322.2-2019.4)	1829.3± 1125.2 2265.3 (127.8-3390.1)	1434.1± 1671.5 1139.8 (0-3457.0)	1533.7± 1225.4 965.3 (263-4187.1)	0.52

* Significantly different from obese group
** Significantly different from sleeve gastrectomy group
*** Significantly different from all groups
SG: Sleeve gastrectomy, RYGB: Roux-en-Y gastric bypass, AGB: Adjustable gastric band, VBG: Vertical banded gastroplasty, LES: Lower esophageal sphincter, LESR: Lower esophageal sphincter residual IGP: Intragastric pressure, UES: Upper esophageal sphincter, UESR: Upper esophageal sphincter residual, DCI: Distal contractile integral.

Overall, abnormal manometric results were found in 47% of bariatric patients compared to 52% in the obese group. No bariatric procedure in particular was more likely to have an EM abnormality. Types of esophageal abnormalities are described in **Table 6-3**.

Table 6-3. Esophageal motility abnormalities in patients with obesity and patients after bariatric surgery.

Abnormality (%)	Obese (n=501)	SG (n=11)	RYGB (n=13)	AGB (n=4)	VBG (n=13)	Significance (p-value)
All Abnormalities	52	45	38	75	46	0.85
Ineffective Esophageal Motility	23	27	15	75	31	0.20
Esophagogastric Junction Outflow Obstruction	12	0	0	0	8	0.18
Hypotensive Lower Esophageal Sphincter	12	27	15	0	8	0.60
Esophageal Spasm	5	0	8	0	8	0.68
Achalasia I-III	5	0	0	0	0	1.00
Hypercontractile Peristalsis	2	0	0	0	0	1.00
Scleroderma	<1	0	0	0	0	1.00

SG: Sleeve gastrectomy, RYGB: Roux-en-Y gastric bypass, AGB: Adjustable gastric band, VBG: Vertical banded gastroplasty.

Ineffective esophageal motility was the most common EMD, followed by hypotensive LES. 50% of AGB patients that had their gastric band removed prior to their esophageal manometry test had EGJ-OO.

No presenting symptoms after bariatric surgery or in patients with obesity were significantly predictive of abnormal EM, including heartburn, dysphagia, or epigastric pain. SG patients with EM abnormalities had a significantly higher average IGP than those with normal EM (14.2mmHg versus 19.2mmHg, $p=0.028$). LSG patients with EM abnormalities had borderline significantly lower average LES pressure (24.5mmHg versus 13.6mmHg, $p=0.053$). The median LES pressure (9.7mmHg, 0-33.1) was hypotensive. Obese ($p<0.0001$), RYGB ($p=0.0040$), and AGB ($p=0.046$) patients with EM abnormalities had significantly fewer solicited swallows with peristalsis (all ≤70%). Only obese patients with EM abnormalities also had significantly reduced DCI ($p<0.0001$). Refer to **Appendix Table A-10** for a complete list of EM parameters by bariatric surgery and abnormal motility disorder.

6.3.3 Gastroesophageal Reflux after Bariatric Surgery

A proportion of patients also underwent 24h pH or 24h pH-impedance off anti-secretory therapy (**Table 6-4**).

Table 6-4: Number of patients that completed 24h pH or 24h pH-impedance and esophageal manometry testing off a proton-pump inhibitor.

Number of Patients by Test	Obese	SG	RYGB	AGB	VBG
24h pH	94	8	2	0	2
24h pH off PPI	70	4	2	0	2
24h pH-impedance	200	1	1	1	2
24h pH-impedance off PPI	98	0	1	1	1
Esophageal Manometry and 24h pH or 24h pH-impedance off PPI	147	4	3	0	3

SG: Sleeve gastrectomy, RYGB: Roux-en-Y gastric bypass, AGB: Adjustable gastric band, VBG: Vertical banded gastroplasty.

75% SG (n=3), 33% RYGB (n=1), 100% AGB (n=1), 33% VBG (n=1), and 48% of obese patients (n=81) had a positive DeMeester score for gastroesophageal reflux off PPI. 100% of SG (n=2), 50% of RYGB (n=1), 0% AGB, 0% VBG, and 58% of obese patients (n=33) had both reflux and an EMD. No AGB and 3 VBG patients underwent esophageal manometry and 24h pH testing off PPI and were not examined further. **Table 6-5** outlines the 24h pH testing results in obese, sleeve gastrectomy and Roux-en-Y gastric bypass patients on and off anti-secretory therapy.

Table 6-5: Median and range 24h pH and 24h pH-impedance results for patients after bariatric surgery compared to non-surgical patients with obesity.

	Obese		SG		RYGB	
	Off PPI	On PPI	Off PPI	On PPI	Off PPI	On PPI
Total Percent Time in Reflux (%)	4.4 (0-20.2)	0.5 (0-12.6)	10.8 (1.9-32.1)	2.0 (0-4.6)	6.7 (1.6-11.7)	-
Total Percent Clearance Time (%)	3.4 (0-35.3)	1.1 (0-15.5)	-	0.3	0.7	-
DeMeester Score	13.6 (0.8-133.9)	3.9 (0.8-94.7)	39.0 (13.6-123.2)	5.3 (0.9-19.9)	9.5 (3.6-48.9)	-
Total Acid Reflux Events	52 (0-690)	15 (0-230)	165 (57-299)	35 (1-66)	39 (7-127)	-
Total Non-Acid Reflux Events	27 (2-213)	46 (8-220)	-	26	98	-
Total Reflux Events	64 (16-412)	65 (8-315)	-	32	105	-
Positive Symptom Association with Presenting Symptoms (%)	49	32	25	20	0	-
Positive Symptom Index with Acid Reflux (%)						
Heartburn	41	11	25	50	0	-
Regurgitation	71	24	-	-	0	-
Epigastric or Chest Pain	47	9	0	0	-	-
Chronic Cough	11	4	0	0	0	-
Burping	38	6	25	0	0	-
Positive Symptom Association Probability with Acid Reflux (%)						
Heartburn	34	22	-	-	0	-
Regurgitation	43	43	-	-	0	-
Epigastric or Chest Pain	0	33	-	-	-	-
Chronic Cough	9	8	-	0	0	-
Burping	64	42	-	0	100	-

SG: Sleeve gastrectomy, RYGB: Roux-en-Y gastric bypass.

Only 25% of LSG had a positive symptom association with their presenting symptoms, which was comparative to the non-surgical obese group (p=0.65). Reduced LES pressure was significantly related to reflux in the non-surgical obese group (p=0.021). Yet, the median LES pressure in SG patients with reflux was 19.1mmHg (6.1-33.8mmHg), which is normal. There was also no significant difference in the average IGP after SG in patients with or without reflux (p=0.65).

6.4 Discussion

The objective of this study was to investigate the frequency and types of motility disorders after bariatric surgery. The hypothesis was that bariatric surgery was more likely to have EM issues when compared to obese controls. The populations in this study were comparable. Demographics and symptoms were not significantly different when comparing the bariatric surgery group with the obese controls. The AGB and VBG groups were significantly heavier when compared to the SG and RYGB groups. This difference is consistent with the literature, which has found better weight loss after SG and RYGB (36). Additionally, significantly more patients were women in the bariatric surgery group. For years, the literature has shown that women are far more likely to undergo bariatric surgery, which explains the discrepancy between these populations (36).

With respect to EM parameters, percentage of swallows with peristalsis was the only parameter that had overall significance between the obese and bariatric surgery groups. Esophageal peristalsis is an important aspect of swallowing and its dysfunction can result in dysphagia symptoms for the patient. This study found that peristalsis of the esophagus increased after LSG when compared to obese controls. SG had similar prevalence of IEM as obese controls, and this may be an indication that obese controls have more severe IEM. In contrast, peristalsis decreased in the AGB group when compared to all other groups. AGB patients had a high frequency of ineffective esophageal motility, which is not surprising considering the placement of the gastric band. In comparison, half of AGB patients had their gastric band removed had EGJ-OO, which could have been either a pre-existing condition to surgery or the development of scar tissue interfering with the EGJ.

EM parameters that were significantly different upon pairwise comparison included UES pressure, UES residual pressure, and LES pressure. A major function of the UES is to prevent esophageal contents from refluxing into the pharynx and to guard against airway aspiration (241). None of the bariatric surgeries impacted the coordination of the esophageal-UES contraction complex, as median UES residual pressure was normal. Therefore, the increase in UES residual pressure after the AGB does not appear to be clinically relevant, except in select cases. UES tone was increased in VBG patients. UES tone has been noted to increase in patients experiencing anxiety or stress during the test (242). The exact mechanism by which the tone increases is currently unknown and has not been explored in the literature.

Furthermore, LES pressure was significantly lower in the SG group; however, the average LES pressure remained clinically normal. The median LES pressure was hypotensive. According to the classic mechanism of GERD, esophageal peristalsis is crucial for clearing refluxate and a competent LES is needed to prevent excessive reflux episodes (243). Several studies found that LES pressure after SG was significantly reduced and the average LES pressure was hypotensive (130, 244). There is conflicting literature, as *Kleidi et. al.* found a non-significant increase in LES pressure after SG (138). This study found that patients with a hypotensive LES were not more likely to have reflux than those with normal LES pressure. However, very few patients underwent 24h pH testing off anti-secretory therapy to draw definitive conclusions.

Overall there was no significant difference between the frequency and types of esophageal disorders between the bariatric surgery and obese control groups. *Merrouche et. al.* found

that after RYGB and AGB, EMD frequency increased, while *Korenkov et. al.* found no significant differences after bariatric surgery (132).

Patients after SG had increased IGP with abnormal motility. This finding is consistent with *Mion et. al.,* who found that increased IGP occurred in 77% of SG patients, but they found this increase was not associated with GI symptoms, abnormal EM, or reflux (120). Their findings were contrary to the hypothesis that the SG is a high-pressure system, when compared to the LRYGB, which could contribute to increased rates of reflux after SG (76, 119, 121). There was insufficient data to analyze the relationship between IGP and LES pressure in SG patients with reflux.

The literature surrounding RYGB and EM is controversial. One of the first studies in the literature found the frequency of EMDs after RYGB to be as high as 60% (158). RYGB patients were found to have decreased peristalsis and more likely to have IEM, similar to the findings in this study. Some studies support hypo-peristalsis (131, 245). Although, other studies found either hypercontractile esophageal peristalsis (134) or normal esophageal peristalsis (132, 246). Hypotonic LES was also observed in the literature (134, 240). Interestingly, though, clinical symptoms do not appear to be related to dysmotility after RYGB.

This study also found that symptoms were not predictive of a corresponding motility disorder, which is supported by the literature (158, 240). The increased awareness of esophageal dysmotility has prompted an important new question in the bariatric literature: how does pre-existing esophageal dysmotility impact post-bariatric surgery outcomes? The under-recognized presence of esophageal dysmotility in the obese patient has many surgeons wondering if routine screening is necessary before bariatric surgery. Some

literature has suggested that routine preoperative manometry is not necessary, because postoperative feeding adaptation was the same for patients regardless of the presence of preoperative dysmotility (134). Consequently, GI symptoms after bariatric surgery were found to be similar regardless of pre-existing dysmotility. Although, controversy exists, as other studies argue that preoperative manometric studies are needed to accurately assess GERD and LES pressure for procedure selection (247).

This study included a small number of patients with 24h pH-impedance measurements as part of their postoperative investigations. SG and RYGB patients were compared to obese controls off PPI. The DeMeester score in SG patients was significantly higher when compared to the obese control group ($p=0.01$), but not RYGB ($p=0.068$). Reflux events after SG appeared to be dominated by acidic refluxate. This finding feeds into the controversy of whether SG causes acid reflux versus non-acid reflux. *del Genio et. al.* found that the non-acid reflux was the predominant pH of refluxate, and esophageal acid exposure was increased in the recumbent position resulting in a significantly increased DeMeester Score after SG (121). This study did not have any patients with 24h pH-impedance monitoring to describe non-acid reflux after SG. While *Thereaux et. al.* did not describe the number of reflux episodes, they did find a significant increase in esophageal acid exposure after LSG in patients with no pre-existing reflux (248).

There were several limitations to this study. The primary limitation was the small sample of patients presenting for 24h pH monitoring after bariatric surgery. The other limitation is the unknown surgical technique of each bariatric procedure, as these patients were not all referred from the EABSC. A variability in the technique could impact the interpretation of the results.

In summary, there were no significant differences in EM abnormalities between symptomatic obese and bariatric surgery patients. The mechanism for these abnormalities does not appear to be associated with BMI, but may involve IGP after SG. Symptoms after bariatric surgery also do not appear to be associated with EMDs or reflux.

The results from this study were not able to speak to whether bariatric surgery could cause EMDs. These patients were also referred to the GI motility lab for symptoms and may not be the best population upon which to conclude whether acid reflux occurs or is caused by SG. A cohort study was performed to explore the gastroesophageal motility and reflux after bariatric surgery.

Chapter 7 – Gastroesophageal Motility and Reflux Following Bariatric Surgery

7.1 Purpose and Rationale

LSG has become a surgical option as a bariatric procedure to treat severe obesity. Symptoms of reflux can be a source of patient morbidity following LSG, despite removing the parietal cell mass. A literature review by *Chiu et. al.* found an increasing pattern of reflux symptoms ranging in 10-35% of patients after LSG (152), while patients after LRYGB have decreased rates of reflux after surgery (12).

While LRYGB bypasses the gastric parietal cell mass, LSG involves resecting the majority of the fundus and gastric body. Similarly to LRYGB, gastric acid production after LSG should be limited. The gastrointestinal alterations after LSG may place patients at risk for reflux of gastric contents. Alkaline and acid reflux may lead to significant disturbances in quality of life, reduced nutritional intake, mucosal injury of the esophagus, esophagitis, strictures, Barrett's esophagus, and risk for esophageal carcinoma (239).

del Genio et. al. observed a significant increase in non-acid reflux events after LSG (121). The pH of the refluxate is mostly unknown; therefore, treating such patients with acid reducing therapies, most commonly PPI, would be ineffective if the reflux is in fact non-acid in nature. Even though acid-producing cells have been reduced, PPI treatment has been found to be successful in treating patient symptoms after LSG (66). At our institution, an increase in reflux symptoms in some patients after LSG was identified (249).

The hypothesis is that following LSG, the pH of gastric refluxate is alkaline and motility disturbances of the esophagus and stomach contribute to reflux. The objectives of this project were to characterize the pH of the reflux and describe the gastroesophageal motility

after LSG. Data on the physiological alterations of the stomach after LSG would be collected, and compare these results to the data collected from the standardized procedure LRYGB. These data may help guide treatment for reflux after LSG.

7.2 Study Design

A prospective cohort study design was used to study reflux and gastroesophageal reflux after LSG and LRYGB. Consecutive patients were recruited while attempting to match for BMI. Written patient consent was obtained to participate in the study.

7.2.1 Inclusion and Exclusion Criteria

Patients were of both sexes between the ages of 18-65 years old. Patients were required to be approved for surgery by the multidisciplinary team. Patients were included in the study if they had a minimum body mass index (BMI) of 35kg/m^2 with comorbidities or a BMI within 40kg/m^2 to 60kg/m^2. A maximum BMI of 60kg/m^2 was selected to avoid patients that were most likely to be staged to LRYGB.

Patients were excluded from the study if they had previous gastric surgery, significant gastrointestinal disorders (Barrett's, Crohn's, cancer), large hiatus hernia or documented evidence of esophageal dysmotility. Patients with significant comorbidities such as Type II diabetes, cirrhosis, or alcoholism were also excluded.

7.2.2 Design

Two groups of 8 patients with obesity who were planned for either LSG or LRYGB were assessed by several gastrointestinal studies (listed below) prior to, as well as 3 and 9 months following their bariatric procedure. By comparing preoperative parameters with the early and late postoperative, we may be able to detect if the changes in the reflux are due to the anatomical modifications alone, altered gastroesophageal motility, or significant weight

loss 9 months following surgery. LSG and LRYGB patient results were also compared to each other for physiological changes.

7.2.3 Manometry and 24h pH and impedance

Patients were asked to discontinue PPIs and H_2-receptor antagonists one week prior to the pH study, and to fast overnight (239). The esophageal manometry and 24h pH-impedance testing was performed as outlined in Chapter 5. An ambulatory dual 24h pH-impedance probe (ComforTec® Z/pH ZAN-130-44, Sandhill Scientific, Highlands Ranch, CO) was used rather than a single probe.

7.2.4 Serum Analysis

A fasting blood sample was collected to analyze gastrin serum levels using a double antibody competitive radioimmunoassay kit (#06B255017, MP Biomedicals, Santa Ana, CA). The analysis was performed at the local laboratory according to local standards (ab133033). Serum gastrin is clinically performed to detect a gastrinoma and requires a wash out period of 2 weeks according to Alberta Health Services (250).

7.2.5 Gastric Emptying Scintigraphy

Participants were asked to fast overnight. Participants underwent gastric emptying scintigraphy using 37MBq (1mCi) Tc 99m sulphur colloid within a standardized meal. The meal was consumed within 10 minutes. One-minute images were taken immediately, 1h, 2h, and 4h after meal consumption in anterior and posterior projections using a gamma camera (Philips Brightview, Best, the Netherlands). Regions of interest around the stomach were drawn for each image and gastric retention at each time point was calculated using the geometric mean (Oasis software, Segami Corporation, Columbia, MD). The protocol and study analysis were previously described by *Abell et. al. (91)* and *Donohoe et. al.* (251).

7.2.6 Questionnaires

Participants completed two questionnaires between scans: IWQOL-Lite© and GSRS (164). Permission to use the IWQOL questionnaire was obtained from Duke University. GSRS syndrome scores were graphically presented as mild, moderate, and severe as in Chapter 4.

7.2.7 Surgery and Endoscopy

Endoscopy was performed preoperatively. If the patient was not able to attend a preoperative endoscopy, an endoscopy was performed while the patient was under general anesthesia intraoperatively (one LRYGB and one LSG). Several biopsies of the body and antrum of the stomach, and distal esophagus were taken to determine normal histopathology.

LSG and LRYGB was performed for each participant by three bariatric surgeons (DB, SK, AK). The surgical technique was the same as described in Chapter 3.

7.2.8 Primary Outcome

The primary outcome was to analyze acid and non-acid gastroesophageal reflux events through 24hr pH and impedance studies pre- and postoperatively for patients undergoing LSG or LRYGB.

7.2.9 Secondary Outcome

The secondary outcome was to analyze the gastroesophageal motility, gastrin levels, and weight loss and to compare LSG and LRYGB physiology. By comparing preoperative parameters with the early and late postoperative, we may be able to detect if the changes in the reflux are due to the anatomical modifications alone, altered gastroesophageal motility, or significant weight loss 9 months following surgery.

7.2.10 Sample Size

A single study was found to have completed the pH measurement and subsequent DeMeester score for patients after LSG, and power was calculated based on these findings (121, 252). The sample size was 25 LSG patients to find a significance of $p<0.0001$ for non-acid reflux. With these values, the effect size was calculated to be 2.78. A minimum sample size of 3 patients in LSG and LRYGB group was needed to maintain 80% power and a significance of $p<0.05$. Therefore, 8 patients were recruited for each group for a total of 16 patients in the study to accommodate a 20% dropout rate and follow minimum requirements for small studies (252-254).

7.2.11 Data Analysis

The research hypothesis was tested using a Wilcoxon sign rank test between preoperative, 3- and 9-month postoperative reflux activity (acid and non-acid reflux events) for both LSG and LRYGB groups separately. Manometry, gastrin serum levels, gastric emptying scintigraphy, and questionnaire results were analyzed using a Wilcoxon sign rank test between preoperative, 3- and 9-month postoperative results. A Mann-Whitney U test was used to analyze significance between LRYGB and LSG groups at each time point separately. Non-parametric testing was used as fewer than 30 patients would be recruited for the study and results would unlikely be normally distributed. Values were described as average ± standard deviation or median (range).

7.3 Results

7.3.1 Recruitment

A total of 45 patients was approached regarding participation in the study, of which 22 patients were consented. The reason for patients' unwillingness to participate was due to

time constraints with employment. Preoperative measures were taken in 18 patients. Five patients were no longer eligible for the study either because of hospital logistics or development of diabetes while on the wait list. Four patients withdrew from the study after surgery. Thirteen patients completed the study (six LRYGB and seven LSG).

7.3.2 Demographics

The average age in the LRYGB group and LSG were similar (47.2±5.5years and 45.9±10.5years respectively, p=0.57). LRYGB and LSG groups were 83% and 86% female, respectively. At time of entry to the clinic, patients had an initial BMI of 51.5±5.1kg/m^2 (LRYGB) and 46.1±3.7kg/m^2 (LSG), p=0.063. Patients in the LRYGB and LSG groups had similar wait times to surgery (1.7±0.7years and 1.6±0.5years, p=0.89). Preoperative BMI was 46.4±4.9kg/m^2 (LRYGB) and 43.5±5.2kg/m^2 (LSG), p=0.28. One LRYGB and no LSG were taking a PPI before surgery.

7.3.3 Endoscopy and Surgery

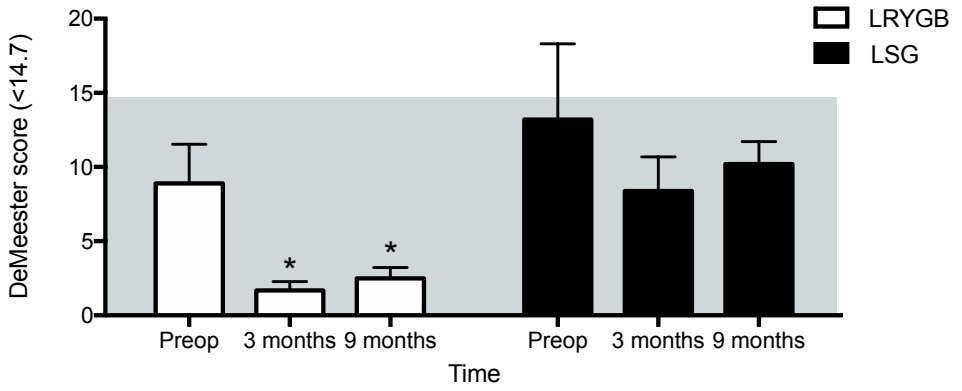
One LRYGB and two LSG had mild esophagitis. Four LSG had chronic inactive gastritis. All patients were negative for *Helicobacter pylori* and hiatal hernia. Complications included one LRYGB and LSG early bleed, as well as one pulmonary embolism after LRYGB. Intraabdominal bleeding was managed by exploratory laparoscopy to identify the source of bleeding. The patient with pulmonary embolism was treated with an antigoagulant (i.e. warfarin) for 3 months.

7.3.4 Primary Outcome

The median DeMeester Score was not significantly different between LRYGB and LSG groups preoperatively (7.1 [3.7-20.8] and 8.4 [0.8-35], respectively, p=0.90) (**Figure 7-1**). There was a significant difference between preoperative and 3 months or 9 months

DeMeester Scores in LRYGB (1 [0.8-4.6] and 2.2 [0.8-5.2], p=0.046, respectively). However, no difference was seen for LSG at 3 months or 9 months (8.6 [0.8-19.1] and 8.5 [6-17.1], p=0.31, p=0.90, respectively).

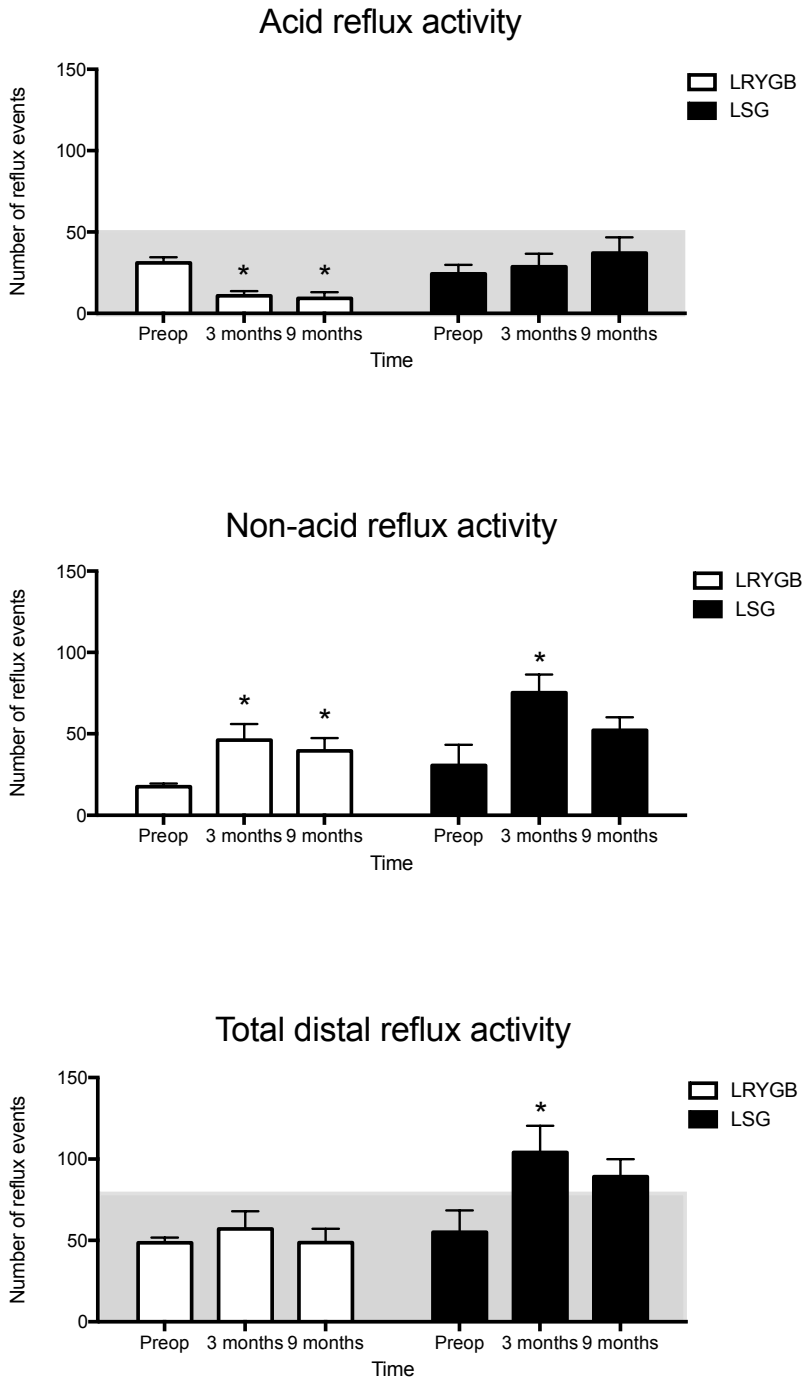
Figure 7-1: DeMeester score before and after laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass.



Significance: *p<0.05 before and after surgery.
Grey: Normal Range <14.7.
LSG: Laparoscopic sleeve gastrectomy, LRYGB: Laparoscopic Roux-en-Y gastric bypass.

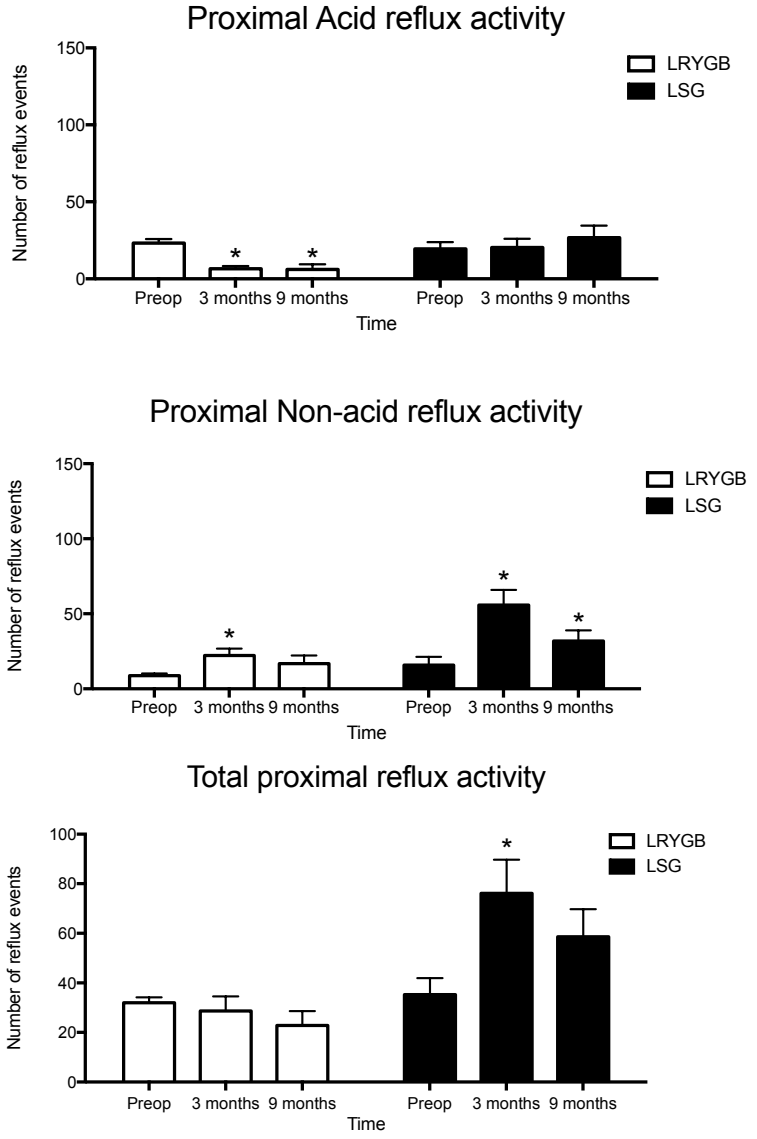
A significant increase in non-acid reflux events was seen in the LSG group at 3 months (p=0.028), and LRYGB at 3 months and 9 months (p=0.027). This increase was also observed at the proximal sensor for LRYGB at 3 months (p=0.028) and LSG at 3 months (p=0.018). Only LRYGB patients had a significant decrease in acid reflux events at 3 months (p=0.028) and 9 months (p=0.028). All patients had significantly more upright than recumbent reflux events (p<0.05). Refer to **Figure 7-2** and **Figure 7-3** for both LRYGB and LSG number of distal and proximal reflux events before, 3 months, and 9 months after surgery, respectively.

Figure 7-2. Distal and total evaluation of reflux activity before and after laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass.



Significance: *p<0.05 before and after surgery.
Grey: Normal Ranges <48 acid events and <74 total events.
LSG: Laparoscopic sleeve gastrectomy, LRYGB: Laparoscopic Roux-en-Y gastric bypass.

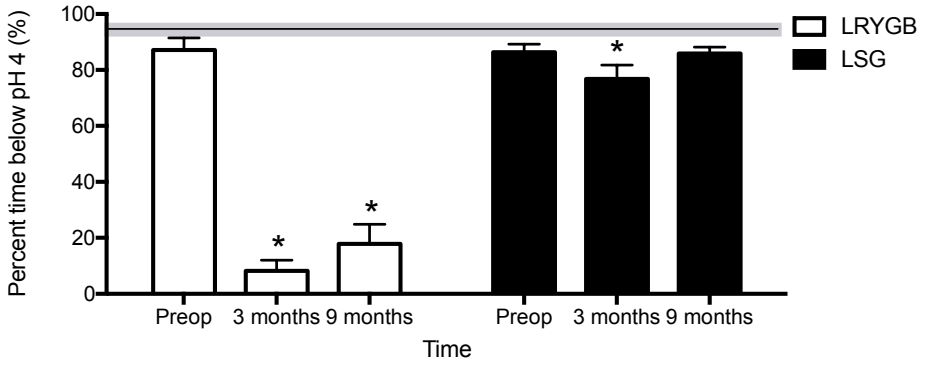
Figure 7-3. Proximal and total evaluation of reflux activity before and after laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass.



Significance: *p<0.05 before and after surgery.
LSG: Laparoscopic sleeve gastrectomy, LRYGB: Laparoscopic Roux-en-Y gastric bypass.

Gastric pH was significantly decreased after LRYGB at both time points (p=0.028), and LSG at 3 months (p=0.018) (**Figure 7-4**).

Figure 7-4. Gastric pH measurements by dual 24h pH and impedance before and after laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass.



Significance: *p<0.05 before and after surgery.
Grey: Normal Range 94.1-97.1% (255).
LSG: Laparoscopic sleeve gastrectomy, LRYGB: Laparoscopic Roux-en-Y gastric bypass.

LRYGB acid exposure significantly decreased at 3 months and 9 months (p=0.046 and p=0.028) and acid bolus exposure significantly decreased at 3 months (p=0.028), while non-acid bolus exposure significantly increased at 3 months and 9 months (p=0.028 and p=0.043). LSG non-acid bolus exposure also significantly increased at 3 months and 9 months (p=0.018). There was no significant change at either follow-up visits in acid exposure (p=0.50, p=0.87) or acid bolus exposure (p=0.18, p=0.063) after LSG.

Four LSG patients began to take a PPI at 3 months and another one at 9 months. One LSG patient stopped PPI at 9 months. The LSG patient with a positive SAP (SAP>95%) for non-acid reflux at 3 months after surgery was placed on PPI (**Table 7-1**). The LSG patient with a positive SAP for acid reflux at 9 months after surgery was already taking a PPI by 3 months after surgery.

Table 7-1: Symptom Association Probability and proton-pump inhibitor usage before and after laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass.

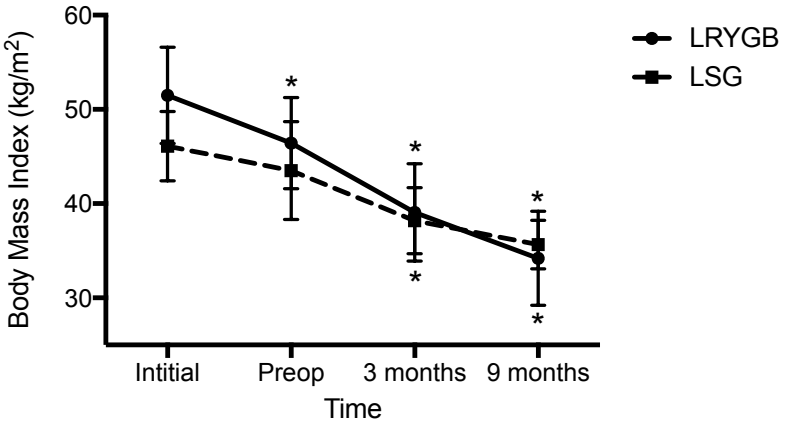
	Laparoscopic Sleeve Gastrectomy						**Laparoscopic Roux-en-Y Gastric Bypass**					
	Preop		3 months		9 months		Preop		3 months		9 months	
	Acid	Non-Acid	Acid	Non-Acid	Acid	Non-Acid	Acid	Non-Acid	Acid	Non-Acid	Acid	Non-Acid
Heartburn	1	0	0	1	1	0	1	0	0	0	1	0
Cough	0	2	0	0	0	0	0	0	0	4	1	1
Burp	5	5	2	5	3	4	4	2	2	2	3	5
PPI	0		4		4		1		1		0	

Preop: Preoperative. PPI: Proton-pump inhibitor.

7.3.5 Secondary Outcome

%EWL at 3 months and 9 months was 27.9%±8.3% and 40.9%±13.0% (p=0.018 from preoperative) for SG and 36.0%±10.7% and 59.1%±15.9% (p=0.028 from preoperative) for LRYGB, respectively. Refer to **Figure 7-5** for change in BMI. There was no significant difference in weight loss between LRYGB and SG groups at 3 months or 9 months (p=0.57 and p=0.72, respectively).

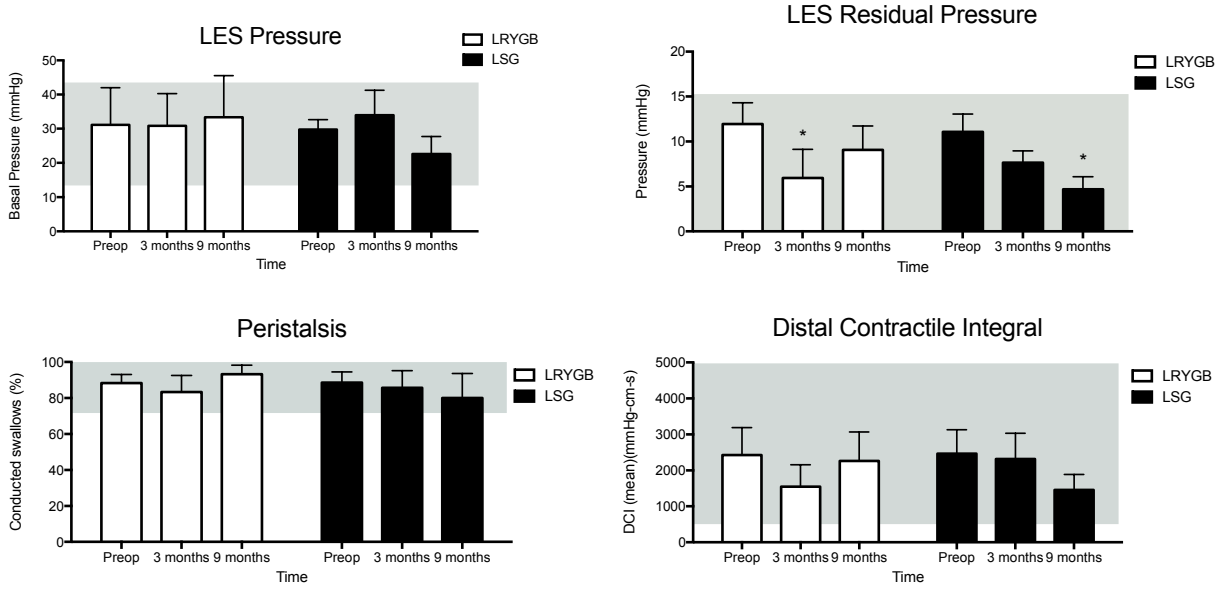
Figure 7-5: Body mass index from initial enrollment in the bariatric surgery program to 9 months postoperative visit for laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass.



Significance: *p<0.05 before and after surgery.
LSG: Laparoscopic sleeve gastrectomy, LRYGB: Laparoscopic Roux-en-Y gastric bypass.

LRYGB had a significantly decreased LES residual pressure at 3 months (p=0.046) and LSG had a significantly decreased LES residual pressure at 9 months (p=0.018). Yet, both were within the normal clinical range for LES residual pressure. Refer to **Figure 7-6** for manometry results.

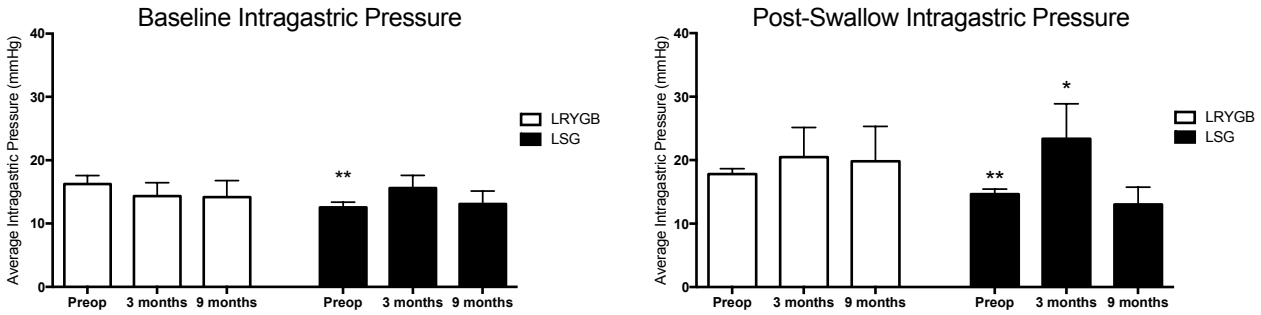
Figure 7-6: Manometric measurements of lower esophageal sphincter pressure, lower esophageal sphincter residual pressure, percent of swallows eliciting peristalsis, and distal contractile integral before and after laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass.



Significance: *p<0.05 before and after surgery.
Grey: Normal Ranges 13-43mmHg LES pressure, <15mmHg LES residual pressure, >70% peristalsis, and 500-5000mmHg/cm/s distal contractile integral.
LSG: Laparoscopic sleeve gastrectomy, LRYGB: Laparoscopic Roux-en-Y gastric bypass, LES: Lower esophageal sphincter, DCI: Distal contractile integral.

However, average intragastric pressure post-swallow was significantly increased at 3 months after LSG (p=0.01) (**Figure 7-7**). This was not significantly associated with non-acid or total reflux events (p=0.53).

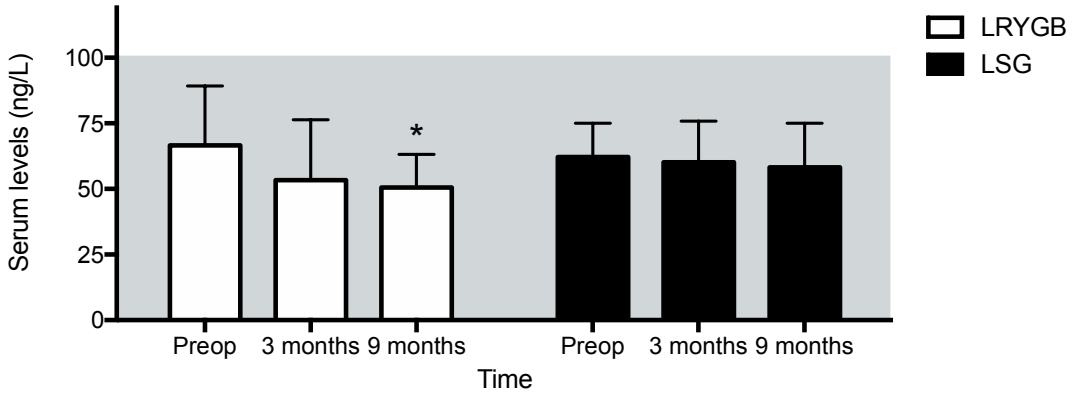
Figure 7-7. Manometric measurement of average intragastric pressure at baseline and after swallowing after laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass.



Significance: *p<0.05 before and after surgery. **p<0.05 between LSG and LRYGB.
LSG: Laparoscopic sleeve gastrectomy, LRYGB: Laparoscopic Roux-en-Y gastric bypass.

Gastrin serum levels were not changed before and 3 months or 9 months after LSG (p=0.74 and p=0.45) (**Figure 7-8**). Gastrin serum levels for LRYGB were unchanged at 3 months (p=0.09), but significantly decreased at 9 months (p=0.035).

Figure 7-8: Gastrin serum levels before and after laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass.

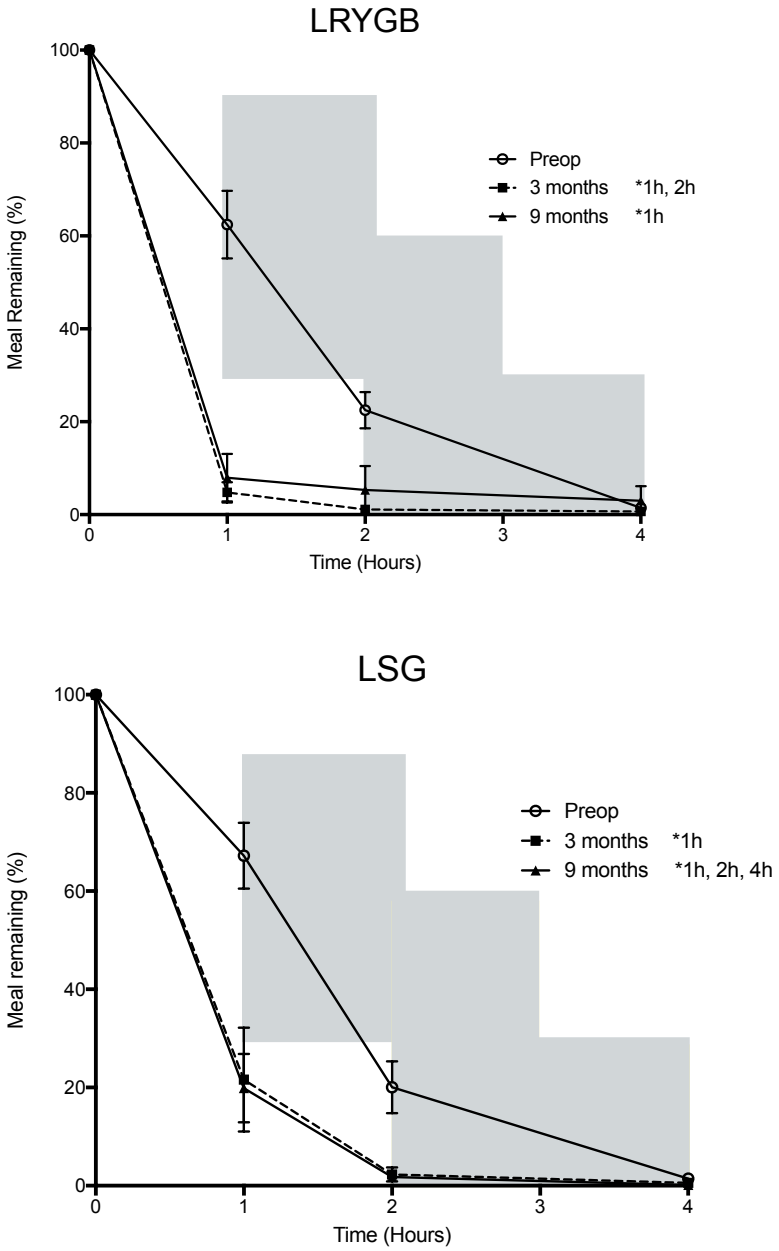


Significance: *p<0.05 before and after surgery.
Grey: Normal Range <100ng/L.
LSG: Laparoscopic sleeve gastrectomy, LRYGB: Laparoscopic Roux-en-Y gastric bypass.

Gastric retention was significantly decreased from preoperative measures in both LSG and LRYGB at 3 months (p=0.018. and p=0.028) and 9 months (p=0.018. and p=0.028) for 1h

measures, respectively, 2h at 3 months in LRYGB (p=0.028), and 2h and 4h at 9 months in SG (p=0.028) (**Figure 7-9**).

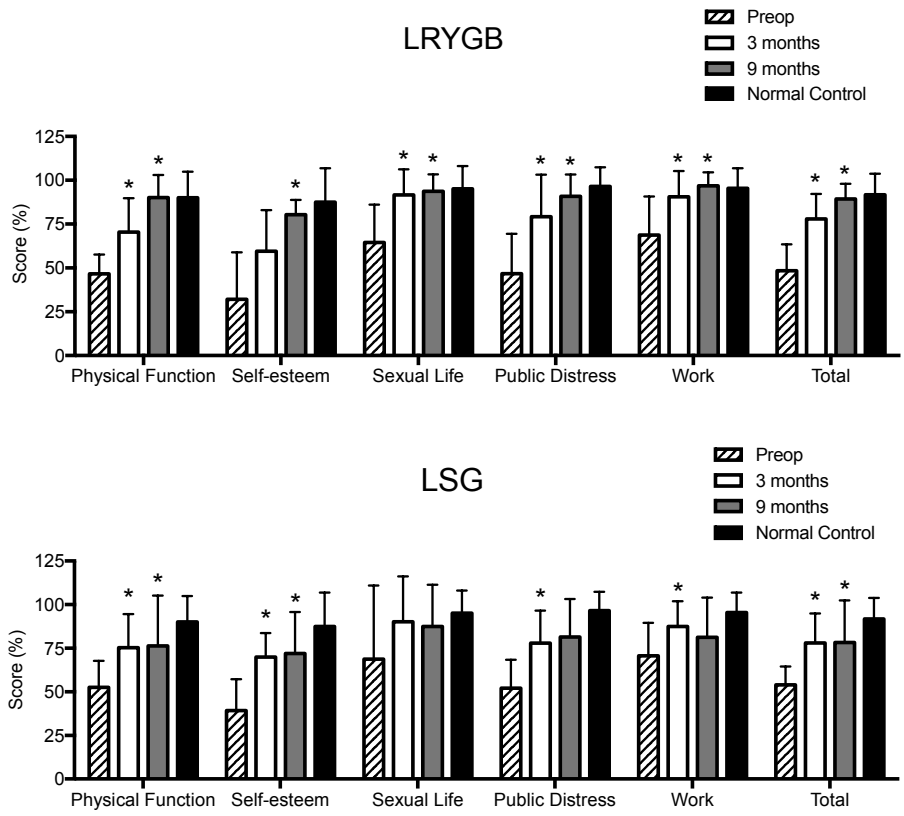
Figure 7-9: Gastric emptying scintigraphy results before and after laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass.



Significance: *p<0.05 before and after surgery.
Grey: Normal Range 1h: 30-90%, 2h: 0-60%, 4h: 0-30%.
LSG: Laparoscopic sleeve gastrectomy, LRYGB: Laparoscopic Roux-en-Y gastric bypass.

IWQOL results in both LRYGB and LSG groups varied by parameter (**Figure 7-10**). By 9 months, all parameters scores were significantly increased in the LRYGB group ($p<0.05$).

Figure 7-10: Impact of Weight on Quality of Life-Lite represented as percent of maximum score after laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass.

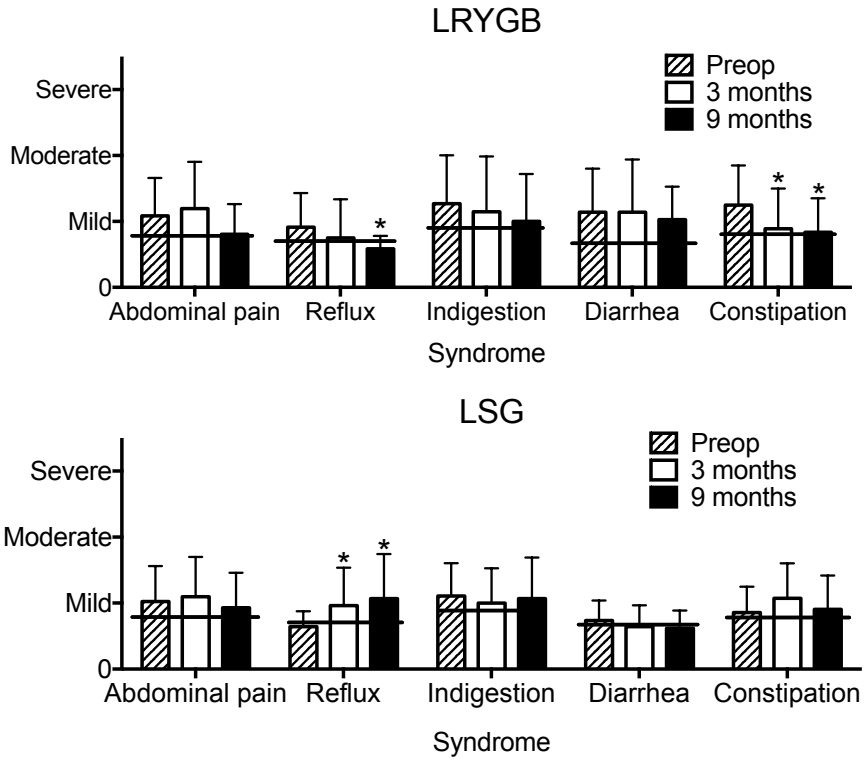


Significance: *$p<0.05$ before and after surgery.
Black: normal control (176).
LSG: Laparoscopic sleeve gastrectomy, LRYGB: Laparoscopic Roux-en-Y gastric bypass.

GSRS scores decreased significantly in the LRYGB group for reflux syndrome at 9 months ($p=0.03$) and constipation syndrome at 3 months ($p=0.02$) and 9 months ($p=0.05$), while reflux syndrome was increased at 3 months ($p=0.03$) and 9 months ($p=0.05$) in the LSG group (**Figure 7-11**). LRYGB patients had a significantly higher diarrhea syndrome score than LSG patients at 3 months and 9 months ($p=0.01$ and $p=0.004$). LSG patients had a significantly higher reflux syndrome score than LRYGB patients at 9 months ($p=0.04$).

LRYGB patients had a significantly higher constipation syndrome score than LSG patients before surgery (p=0.03).

Figure 7-11: Gastrointestinal Symptom Rating Scale scores before and after laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass.



Significance: *p<0.05 before and after surgery.
— General population values (173).
LSG: Laparoscopic sleeve gastrectomy, LRYGB: Laparoscopic Roux-en-Y gastric bypass.

7.4 Discussion

Reflux symptoms have been described after LSG. Varying explanations have been proposed including increased intragastric and intraabdominal pressure, delayed gastric emptying and abnormal esophageal motility, disrupted LES function, blunting the angle of His, removal of sling fibers, affecting postprandial gastric acid pocket, lack of gastric compliance, partial resection of the antrum, and sleeve dilation (44, 94, 106, 122, 256). The

purpose of this study was to characterize the refluxate and gastroesophageal motility of LSG and LRYGB patients.

This study suggests that total reflux events were increased after LSG, with the majority being non-acid. While the DeMeester Score is not significantly different, the number of non-acid reflux events is significantly increased at both 3 and 9 months after LSG. *del Genio et al* described a similar phenomenon with non-acid reflux events increasing 12 months after LSG. A majority of these events was post-prandial. The study found almost twice as many non-acid reflux events. Although, two studies have described increased acid exposure time and DeMeester scores, while the number of reflux events were not significantly increased (130, 244). An important point to consider is that regardless of the parietal cell mass being removed, LSG gastric pH remains acidic, while the LRYGB group had fewer acid reflux events at 3 months and 9 months, as substantiated by a significant drop in gastric pH.

Interestingly, LRYGB patients were also found to have a significant increase in non-acid reflux at both 3 and 9 months. LRYGB had fewer postoperative non-acid reflux events than the LSG group, which was only significant at 3 months ($p=0.05$). Clinically, LSG patients had significant total number of reflux events, compared to LRYGB which remained within the normal range. LSG patients had significantly increased reporting of reflux symptoms at 3 months, while LRYGB patients had significantly decreased reflux symptoms at 9 months. However, the difference in reflux symptom reporting score was not significantly different between groups, except at 9 months. There was a significant difference in the total number of reflux episodes between LSG and LRYGB at 3 months ($p=0.04$) and 9 months ($p=0.02$). It may be possible that the increased combination of reflux events after LSG could be

contributing to a hypersensitivity of the esophagus leading to the increase in reported reflux symptoms. Additionally, only 1 LSG patient had non-acid reflux according to the definition in Chapter 5.

In contrast to Chapter 6, IGP was increased 3 months after LSG, but did not correspond to esophageal motility disorders. Similarly, reflux was not significantly associated with this increase in IGP. This calls into question the 'high pressure sleeve' hypothesis, and what could be contributing to the increase in non-acid reflux if not IGP.

There was no difference in EM after LSG or LRYGB, an important finding considering that a hypotensive LES can facilitate reflux. Other studies have described a hypotensive LES, decreased effective motility, and decreased bolus transit (131, 244, 257, 258). An increased pressurized zone can be seen at the EGJ, explained in the literature as a re-bounded bolus (121). Despite that, no refractory pressure from the bolus above the EGJ was observed. A possible explanation for the normal EM could be the maintenance of the integrity of the sling fibres, as well as the vagal nerve branches controlling the esophagus.

Gastric retention was decreased after both LSG and LRYGB, suggesting more rapid gastric emptying compared to the preoperative state. Several studies have substantiated that this finding occurs (258, 259), while others have found no change (125). One study found that dissection at 7cm increased gastric emptying, while dissection at 4cm delayed gastric emptying (260). The technique involves dissection 6cm from the pylorus to preserve the antrum and maintain the migrating motor complex function for appropriate gastric emptying. Therefore, without delayed gastric emptying, opportunities for reflux to enter the esophagus are reduced.

Neither increased gastrin serum levels nor lack of BMI reduction was observed in this study, which both would contribute to the increased number of reflux events.

LSG and LRYGB were both successful to varying degrees in increasing QOL after surgery. Successful increases in physical function, sexual life, and public distress has also been seen in another publication by *Strain et. al.* (261). The only significant difference between LSG and LRYGB was in the work category at 9 months ($p<0.05$). This finding could be a secondary finding to more patients in the LRYGB group being employed. While quality of life increased, measures of gastrointestinal symptoms decreased in the LRYGB group. However, the LRYGB group had a significantly higher diarrhea symptom rating than the LSG group ($p<0.05$), a possible result from the pylorus and 1m of bowel being excluded, thereby carrying food and liquids to the intestinal tract quickly and presenting as loose stool. Yet, overall symptoms were mild to moderate in most patients.

The increased combination of non-acid and acid reflux causes a hypersensitive esophagus syndrome, which patients describe in the early stages after surgery. This non-acid reflux may be bile or pancreatic juices that are refluxed into the esophagus by the highly pressurized sleeve (119). Whereas LRYGB allows for gastric contents to empty quickly, acid reflux events are reduced, patients are asymptomatic, and bile would need to travel 1m upwards in order to cause non-acid reflux. Therefore, the increased reflux after LRYGB is likely increased mucous production. Future studies are currently being directed at evaluating the biochemical composition of the non-acidic refluxate and the impact on esophageal tissue inflammation.

7.4.1 Limitations

A difficulty in determining the cause of reflux after LSG could be the global unstandardized technique. LSG is a relatively new surgery, and technique is based on the discretion and experience of the surgeon. The variations in LSG centre on dissection length from the pylorus and size of bougie. It is difficult to ascertain whether issues with the technique of LSG or the altered physiology/anatomy causes reflux, thereby reducing the generalizability of these results.

7.4.2 Conclusions

Non-acid reflux is increased after both LSG and LRYGB. LSG patients complain of significantly more reflux symptoms after surgery with a greater number of total reflux episodes. Gastroesophageal motility does not seem to play a role in inducing reflux after LSG or LRYGB. Therefore, treatment strategies that focus on acid suppressant therapies may need to be rethought.

Chapter 8 – Discussion

8.1 Overview

Reflux following bariatric surgery has yet to be fully characterized. As a relatively frequent postoperative complaint, reflux has important implications for patients. These symptoms impact quality of life and typically lead to a series of investigations. They require treatment, and place patients at risk for chronic injury and potentially metaplastic change to the esophageal mucosa.

Existing literature describes many contradictory causes for symptoms of reflux following bariatric surgery. Investigators were unable to come to a consensus as to whether reflux following LSG was present, if present whether it was alkaline/acidic, and the precise pathophysiology that led to these symptoms. EM is also poorly understood after bariatric surgery and small studies have pointed to an assortment of disorders. The mechanism by which bariatric surgery caused these disorders was not investigated in depth, understandably considering the complexity of EM and its interaction with GERD.

The objective of this thesis was to determine the relationships between bariatric surgery and gastroesophageal motility and reflux. The hypothesis was that the anatomical changes after bariatric surgery disrupted esophageal and gastric motility causing non-acid gastroesophageal reflux and related symptoms.

This thesis began by describing “sleeve dysmotility syndrome”, an EMD that developed after surgery, could not be managed by the usual GI treatments, caused significant burden to the patient, and only partially resolved after conversion to LRYGB.

Physiologically divergent reflux syndromes following LSG and LRYGB were characterized. In this patient population, reflux symptoms were significantly increased after

LSG, while symptoms consistent with sleeve dysmotility syndrome or other EMDs were scarcely reported after LSG or LRYGB. LSG patients more frequently required initiation of anti-secretory therapies than LRYGB patients. A large number of patients also reported symptom relief while on anti-secretory therapy.

Exploring symptoms after LSG and LRYGB led us to conclude that patient symptoms were infrequently related to confirmed abdominal complications. In fact, patient symptoms were altered only slightly after surgery and many were not significantly different from before surgery. Reflux symptoms were associated with patients on PPI experiencing symptom relief from anti-secretory therapy.

While no significant differences in GI symptoms were observed between patients before and after bariatric surgery, the literature alludes to a link between obesity, GI symptoms, EM, and reflux. As a stand-alone factor, a relationship between BMI and reflux does exist. However, the relationship does not appear to be the linear relationship that other studies have reported. Patients with a higher BMI were not more likely to present with reflux symptoms and positive reflux findings than patients with a lower BMI. BMI was also not related to non-acid reflux. Although, a lower BMI appears to be linearly related to the odds of having an EMD and may be an important factor to consider when referring patients for esophageal manometry.

When targeting the bariatric population, there were no significant differences in EM abnormalities between symptomatic obese and bariatric surgery patients. The mechanism for these abnormalities does not appear to be associated with BMI, but may involve IGP after LSG. Presenting symptoms after bariatric surgery also do not appear to be associated with EMDs or reflux.

These observations were limited by the small number of bariatric surgery patients in the study and lack of preoperative EM and reflux measures. The final study had patients undergo both esophageal manometry and 24h pH-impedance, among other tests, before and after LSG and LRYGB. This study found that non-acid reflux was increased after both LSG and LRYGB. After surgery, LSG patients complained of significantly more reflux symptoms with a greater number of total reflux episodes. Gastroesophageal motility did not seem to play a role in inducing reflux after LSG or LRYGB.

8.2 Significance

The hypothesis was partially rejected. Almost half of bariatric surgery patients referred to the GI motility lab had an EMD; however, EMDs did not appear to be connected to either patients with obesity, bariatric surgery, or gastroesophageal reflux disease. Part of the hypothesis was not rejected, as it appears that in the bariatric population non-acid reflux significantly increased after LSG and is attributed to symptoms after surgery. While symptoms persist nearly one year after surgery, the number of non-acid reflux events is reduced and the number of acid reflux events begins to increase (although not significantly). This eventual increase in acid reflux events could explain the significant acid reflux after LSG in patients that were referred to the GI motility lab. These findings were significant considering that they drastically change the management and treatment of gastroesophageal reflux and associated symptoms by identifying that anti-secretory therapies are not appropriate treatment for non-acid reflux and symptoms are not a good indicator for referral to the GI motility lab, rather management of esophageal hypersensitivity may be more beneficial.

8.3 Esophageal Motility Disorders

8.3.1 Mechanism

EMDs appear to be rare after bariatric surgery in this study population. Patient symptoms after bariatric surgery do not seem to be related to an EMD. Patients that were screened before and after bariatric surgery and did develop an EMD were asymptomatic. These presentations of EM make determining symptom management difficult, and challenge whether motility disorders require intervention in asymptomatic patients.

No studies have been able to conclude a mechanism by which obesity or bariatric surgery causes EMDs. The findings in this thesis shed no light on this issue. Patients after bariatric surgery and the non-surgical obese group had comparable frequencies of EMDs. Results showed that a lower BMI (i.e., normal weight) was significantly predictive of EMDs. Also, in the cohort study, the EM measurements before and after bariatric surgery were not significantly different. The literature reports a variable prevalence of EMDs after bariatric surgery, but that may be a result of either different surgical techniques and their impact on neural control of EM, or the poor understanding of the cause of EMDs in general.

Contrary to the original hypothesis, EMDs did not play a role in GE reflux, either in patients with obesity or after bariatric surgery. The reason that patients with reduced DCI are more likely to have reflux than patients with EMDs is unclear.

8.3.2 Treatment and Management

Case reports are the only studies in the literature that address whether EMDs are a contraindication for bariatric surgery. The hypothesis is that pre-existing EMDs may be worsened by the anatomical changes from bariatric surgery. However, for understandable

ethical concerns, this hypothesis has not been tested. Whether preoperative manometry screening is necessary to identify patients with motility disorders is unstandardized. This is a complicated issue that has a significant impact on the investigation burden placed on the patient. Given the difficulties with managing sleeve dysmotility syndrome, it is reasonable to consider the need for preoperative testing. However, the question remains whether motility studies should be required for all patients planning to undergo a LSG. Only *Valezi et. al.* addressed the use of esophageal manometry to screen for EMDs. They found that while there was an association between RYGB and EMD, peristalsis was not affected after surgery and patients vomiting after surgery did not have significantly different EM parameters. They concluded that preoperative esophageal manometry was not necessary (134). While the risks associated with esophageal manometry are low (i.e., headache, sore throat, and nose bleed), the test is substantially uncomfortable and 9.8% of patients referred to the GI motility lab are not able to tolerate the procedure. Another question would be whether not tolerating the procedure would be an exclusion criteria for patients undergoing bariatric surgery. Manometry results would identify patients that may not be able to tolerate a high-pressure sleeve due to esophageal spasms, hypertensive esophagus, achalasia, or scleroderma. Nonetheless, studies show that the increased IGP was related to EMDs rather, in select cases of reduced LES pressure, it was related to reflux.

Some EMDs, for example achalasia, have been described in several case reports as being possible to surgically treat during bariatric surgery with a concurrent or postoperative Heller myotomy depending on when the achalasia is detected, which is a safe solution to managing these patients (262). Although depending on which bariatric procedure is to be

performed, extensive thought needs to be put into whether it would be feasible anatomically to manage the achalasia and restrict the gastric volume (263). Other EMD management strategies after bariatric surgery are not mentioned in the literature, apart from strategies for LAGB patients.

Regardless, patients with EMDs may be better candidates for a LRYGB to avoid significant postoperative complications and, ultimately, reoperation. The case study suggests that when other management strategies fail, LRYGB may be the preferential treatment for patients that do develop esophageal dysmotility after LSG.

8.4 Gastroesophageal Reflux

8.4.1 Mechanism

The literature has identified LSG patients with postoperative acid reflux (257). The exact mechanism for how some patients after LSG develop acid reflux versus non-acid reflux is unclear. We now know that GE reflux is a much more complex issue, the refluxate is in fact non-acid, and some patients with de novo non-acid reflux after bariatric surgery are asymptomatic. We are continuing to learn that LSG and LRYGB are very complex surgeries with respect to their anatomical change and physiologic impact on the esophagogastric region. These procedures are performed in very complex patients. We now know that the physiology of reflux disease is more complex than has been documented in the literature. We also know that assumed relationships and dogma may not be valid, and the likelihood of disturbances in EM are misunderstood in the obese and bariatric populations.

There are several possible theories for the reflux mechanism. One theory may have to do with surgical technique and a redundant fundus containing parietal cells combined with a

reduced volume, which contributes to increased acid reflux. Another is that an inflammatory response stimulates histamine, which contributes to acid secretion; however, this latter theory has not been researched.

In terms of mechanical contributors to reflux, increased IGP was related to reduced LES in abnormal DeMeester Score patients after LSG. However, in the cohort study, only LSG patients had an increased IGP at 3 months, but this was not associated with increased non-acid reflux. There was also no relationship between LES pressure and IGP in this patient population. Patients in the cohort study did not have an increase in DeMeester Score after LSG. The mechanism behind the increased non-acid reflux is still unclear as gastroesophageal motility, LES pressure, IGP, and serum gastrin do not seem to play a role after either LRYGB or LSG. As well, while the LRYGB gastric pouch had significantly reduced acid secretion and increased non-acid reflux, LSG patients continued to have an acidic sleeve with predominantly non-acid reflux. It is unclear whether this discrepancy is a limitation of the placement of the 24h pH sensor in the gastric anatomy or the lack of information on reflux volume. LSG patients could have an acidic sleeve, but non-acid reflux volume could be much greater, contributing to the increased number of non-acid reflux events when compared to LRYGB. However, why the volume of non-acid reflux should be increased after either procedure is unknown, considering the lack of a relationship with IGP (i.e., 'high-pressure sleeve').

8.4.2 Treatment and Management

Gastroesophageal reflux was a complex issue before and after bariatric surgery. In this study, heartburn was a conflicting symptom as it was a significant predictor of reflux in patients with obesity and patients treated successfully with anti-secretory therapy after

LSG. However, in another study only 40-50% of patients after LSG had heartburn related to confirmed acid reflux from 24h pH testing, and the cohort study showed no association between heartburn and acid reflux, although there was a connection with non-acid reflux. These conflicting associations make it difficult to decide which treatment strategy is most appropriate.

The first step to managing GERD is anti-secretory therapy to empirically treat symptoms. Subsequent investigative steps are taken if this treatment fails to bring any symptom relief to the patient. At the time of this thesis, anti-secretory therapies were being used, which is consistent with practice in the literature (146, 264). This study found that after LSG, patients were more likely to report reflux symptoms and more than half of patients treated with anti-secretory therapy felt relief. Symptom relief could be from the fact that the sleeve is not devoid of acid and in fact predominantly remains acidic compared to the LRYGB. As well, anti-secretory therapies have a high placebo effect of 19% (157). Regardless, half of patients on pre-existing treatment for reflux required an escalation in their dosage. Symptom relief may not be achieved, because within the first 9 months after surgery, reflux is dominated by non-acid reflux. Therefore, the use of anti-secretory therapy may need to be rethought.

In addition, some medications depend on the stomach pH to dissolve and be absorbed into the GI system. Gastric emptying also affects the duration of drug absorption. A drug's duration in the stomach after LSG can be shorter due to an observed increase in gastric emptying (10). However, some experts disagree that medication absorption is altered after LSG (19, 265). In fact, very little consideration has been given to the pharmacokinetics of anti-secretory therapy have been discussed after bariatric surgery. The results of this study

show that the sleeve remains acidic. Theoretically, anti-secretory therapies could be activated to reduce acid reflux events and ultimately the total number of reflux events contributing to postoperative symptom relief. The LRYGB had next to no acid in the gastric pouch, yet anti-secretory therapies and gastroduodenal cytoprotective agents (i.e., sucralfate) that are activated by a pH below 3.5 (266) are both used prophylactically (267) or postoperatively to prevent and treat marginal ulcers and associated abdominal pain. These treatments appear to be successful, but the exact mechanism for how marginal ulcers occur or are treated is not clearly understood. The volume of gastric acid required to activate these therapies is not described in the literature. Perhaps only a small amount of gastric acid is required to activate these therapies and reduce the gastric acid content to eliminate any acid contact with the jejunum. LRYGB patients also had an increase in postoperative non-acid reflux, but did not have any reflux symptoms associated with this increase in events.

While arguably the reflux symptoms are attributed to non-acid reflux after LSG, determining a treatment option is not a simple task. Non-acid reflux simply means that the refluxate had a pH above 4.0. A distinction can be made between non-acid "weakly acidic" (pH 4-7) and non-acid "weakly alkaline" (pH >7) reflux events using 24h pH-impedance, but the accuracy to detect these differences in events using current calibration standards has not been explored. These distinctions may be able to provide some insight into the composition of the non-acid refluxate, but these distinctions do not identify whether these secretions are duodenal refluxate composed of bile, pancreatic enzymes, or simply mucous. Until the composition of this refluxate can be determined, non-acid reflux will be

considered to be caused by a defect in the anti-reflux barrier, and other therapies such as pro-motility agents could be beneficial.

Other suggested therapies could be H_2 antagonists for acid secretion or more experimentally glutamate receptor ligands (268) and cannabinoid receptor agonists to inhibit TLESRs (269). Clinically, H_2 antagonists are not used as much as PPIs, because of their short half-life and high placebo effect. Histamine is involved in inflammatory processes in GERD. Yet, H_2 antagonists have not been tested in the bariatric population. Another issue is whether these anti-secretory therapies would need to be continued long-term; such use needs to be weighed carefully, given the unreliable symptom reporting by patients and the risks associated with the long-term use of these therapies.

The continual inconsistencies in both this thesis and the literature suggest that perhaps in this select population, patients with reflux symptoms should first be assessed by 24h pH-impedance to determine an appropriate treatment course. The data suggest that preoperative screening for GERD is not required as patients with pre-existing reflux did not have worsening acid reflux after LSG. However, *Moon et. al.* concluded that esophageal manometry is essential to accurately assess the LES tone before surgery to rule out LSG in case of postoperative GERD development (247). *Klaus et. al.* agree with this conclusion based on their literature review, which shows that hypotonic LES pressure before LSG may be a determining factor for GERD development later.

Regardless of whether the refluxate is acid or non-acid, conversion of LSG to LRYGB appears to be both a safe and effective method for relieving intractable reflux symptoms (141). Our clinic has a LSG to LRYGB conversion rate of 6.6% primarily for inadequate weight loss and reflux symptoms (270). Revision surgery does carry its risks, may not be

ideal for every patient, and may not be suitable for patients with persistent heartburn with normal gastroesophageal reflux.

8.5 Gastroesophageal Symptoms

8.5.1 Mechanism

This thesis has highlighted that a large portion of patients may have persistent heartburn and other reflux-associated symptoms, but also have normal gastroesophageal reflux, as assessed by 24h pH testing. This could be functional heartburn, in which patients have symptoms characteristic of gastroesophageal reflux, with no associated motility disorder or elevated DeMeester Score (82). Functional heartburn is a poorly understood syndrome that has been attributed to esophageal hypersensitivity (271). In brief, esophageal hypersensitivity is a visceral response to chemical or mechanical stimuli that can produce heartburn or chest pain because of a reduced threshold for pain perception (272). Esophageal hypersensitivity is also a component of non-erosive reflux disease (NERD) pathogenesis (273). Esophageal hypersensitivity or peripheral hypersensitivity is mediated by serotonin and CCK. Inflammatory mediators transfer information to the sympathetic nervous system. Noxious stimuli, such as acid reflux, are sensed by the sympathetic (dorsal root ganglion) and vagal (nodose ganglion to nucleus tractus solitary) pathways by nociceptive receptors on the esophageal nerves. Noxious stimuli in the esophagus are thought to be mainly sensed by the sympathetic nervous system. The primary nociceptive receptor in acid reflux sensation is thought to be transient receptor potential vanilloid 1 (TRPV1) (273). TRPV1 is important in peripheral hypersensitivity. Patients with NERD and functional heartburn have been found to have increased expressions of TRPV1. Central hypersensitivity can also occur from increased excitability of spinal neurons, which leads

to N-methyl-D-aspartate (NMDA) receptor phosphorylation and increased responsiveness to glutamate (273). Psychosocial factors, such as stress or psychological disorders, mediate both peripheral and central hypersensitivity (273). In fact, stress has been shown to increase mucosal permeability in the esophagus, which is important in sensation and mucosal inflammation.

An inflammatory response caused by the increased number of reflux events is another theory behind persistent reflux symptoms. Inflammation occurs when acid or bile interact with the esophageal mucosa causing damage to the tight junctions between cells (274). This type of inflammation appears to be mediated by inflammatory cytokines, such as interleukin-8, histamine release from neutrophils (275), and oxidative stress (276), which contribute to vascular permeability in the esophageal tissues. H_2 receptors were the most commonly expressed receptor in eosinophilic esophagitis (277). This inflammation of the esophageal tissue allows the surrounding nociceptive receptors to spread the sensation of pain.

These inflammatory responses can eventually contribute to Barrett's esophagus, the metaplasia of esophageal squamous to columnar epithelium (274). Barrett's esophagus is associated with an increased risk of developing esophageal adenocarcinoma. Patients with Barrett's esophagus can also be asymptomatic and the sensory component is not well understood.

8.5.2 Treatment and Management

Management strategies for hypersensitive esophagus are targeted to pain modulation instead of anti-secretory therapies. Considering that nearly 50% of bariatric surgery patients are treated for a psychological condition, functional heartburn may be an

explanation for these symptoms in this population. Common modulation of pain perception is through tricyclic antidepressants or selective serotonin reuptake inhibitors. Pain modulation has been proven to be more effective than anti-secretory therapy in this population (278). Other therapies include 5-hydroxytryptamine $(5\text{-HT})_3$ antagonists and 5-HT_4 agonists (271).

Pain modulation may be the preferred treatment option for patients experiencing significant heartburn or retrosternal chest pain with no associated gastroesophageal reflux. However, this is a complex and poorly understood issue after bariatric surgery. This syndrome emphasizes the importance of follow-up at a bariatric clinic with extensive experience and both general surgeon and gastroenterologist support to limit unnecessary clinical interventions or reoperations.

Depending on the type of esophageal inflammation, several treatment modalities can be considered. These include acid reflux management through long-term PPI use, lifestyle changes, or surgery; inflammatory management through PPI use or oral steroids; or mechanical management through esophageal dilation. Additional treatment methods that are being investigated include TRPV1 antagonists to treat inflammatory pain sensation (279) and H_2 antagonists to reduce the pro-inflammatory response. Considering the use of H_2 antagonists to reduce both gastric acid secretion, inflammatory pain sensation, and esophageal inflammation, H_2 antagonists may be a superior choice to PPIs in the bariatric population.

The next issue to consider is regardless of the composition of the refluxate, should LSG continue to be performed considering the abnormal number of postoperative reflux events and unknown impact on esophageal inflammation and Barrett's esophagus development?

Current contraindications are that patients with reflux should not undergo LSG (30), but this thesis demonstrated that irrespective of preoperative reflux, LSG did not necessarily worsen pre-existing reflux, but rather created de novo refluxers.

8.6 Limitations

LSG is a relatively new surgery (approximately eight years); thus far there is no standardization of the technique (13). Therefore, it is left to the discretion and experience of the surgeon to decide what techniques to use. Variations in technique include resection distance from the pylorus, ranging from 2cm to 10cm (20, 24, 126, 136); and bougie size. Variations in technique can reduce the generalizability of these results. Longer division from the pylorus can preserve the vagal nerve, which is important for the integrity and function of the sleeve, but may contribute to postoperative gastroesophageal reflux after surgery (106, 136, 280, 281). This is controversial per another study that found that resecting from 10cm away from the pylorus leads to lower rates of reflux symptoms (144). Bougie size can also contribute to reducing the generalizability of these results. Some investigators argue that a smaller bougie size reduces the compliance of the sleeve and predisposes patients to gastroesophageal reflux. The tension of the stomach tissue around the bougie can also affect the size of the sleeve. This limitation in technique may explain why most of the patients in Chapter 6 predominantly had acid reflux while the patients in Chapter 7 had non-acid reflux. Patients with a redundant fundus will have more proton-pumps to secrete acid.

As stated earlier, another limitation was the methodology to measure reflux. Refluxate volume could not be measured using 24h pH-impedance. As well, the methodology used

for esophageal manometry testing did not allow for TLESR measurement. This limits the understanding of the complete reflux mechanism.

8.7 Future Directions

Future research is currently directed at identifying the composition of the non-acid refluxate through non-invasive saliva analysis with gastric aspiration validation. Saliva methods rather than gastric aspiration studies would maximize the benefit:risk ratio for patients. Given the high number of proximal non-acid reflux events, the contents of the non-acid reflux should be detectable in saliva. Saliva contents will be analyzed for pH, bilirubin, pepsin, pepsinogen, and types of bile. A methodology has already been established after major gastric surgery (282). Validation studies would need to be performed with gastric aspiration in order to determine whether the contents in the saliva are those found in the stomach and distal esophagus. Based on these findings, an appropriate management strategy for non-acid reflux can be determined.

Other research will also focus on the inflammatory impact of the non-acid reflux. Patients will undergo gastroscopy before and after surgery. Patients will be divided into postoperative reflux and no reflux symptoms. Biopsies will be taken and histopathology assessed in order to identify any inflammatory or metaplastic changes in the esophagus.

Conclusions

This study was an extensive look at gastroesophageal motility and reflux in the obese and bariatric populations. Contrary to the hypothesis, abnormal gastroesophageal motility was not associated with an increase in reflux after LSG. However, LSG patients had increased reflux symptoms attributed to significant increases in non-acid reflux. Anti-secretory therapy may alleviate patient symptoms by reducing the total number of reflux events in the acidic sleeve, but ultimately a therapy targeted at non-acid reflux and esophageal hypersensitivity would likely be more beneficial.

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Appendix

Table A-1: Differences in esophageal motility and esophagogastric junction tone between the six World Health Organization body mass index categories.

Mean Wave Amplitude (mmHg)	Mean Wave Duration (mmHg)	DCI (mmHg/cm/s)	Double Peaked Waves (%)	UES Pressure (mmHg)	UES Residual Pressure (mmHg)	LES Pressure (mmHg)	LES Residual Pressure (mmHg)	IGP (mmHg)	Hiatal Hernia (%)	Average Hiatal Hernia Size (cm)
73.3±52.4 p=0.4295	3.4±1.7 p=0.2789	1638.7±1866.3 (1030.6, 0-8668.6) p=0.4585	12.3±19.7 (0, 0-67) p=0.0701	70.4±33.4 p=0.1057	3.6±4.7 (0.2, 0-13.9) p=0.3231	36.5±14.2 p=0.0588	13.3±7.9 p=0.1924	9.3±4.8 p=0.1854	3.6 p=0.232	1.7 p=0.2412
77.6±53.6	3.4±1.5	1745.6±2122.4 (1176.4, 0-19812.4)	8.5±17.5 (0, 0-100)	85.6±52.7	4.0±5.4 (1.6, 0-37)	33.3±19.0	12.7±9.5	10.5±4.9	13.5	2.5±1.3
78.5±50.5 p=0.2909	3.5±1.3 p=0.0941	1611.7±1660.1 (1120.6, 0-10529.0) p=0.4826	6.4±14.0 (0, 0-90) p=0.07	79.0±43.6 p=0.0608	3.8±5.1 (1.9, 0-29.6) p=0.4095	28.5±17.0* p<0.001	10.1±8.2* p<0.001	12.5±5.4* p<0.0001	25.4* p<0.001	3.2±2.0* p=0.0371
77.4±44.5 p=0.2789	3.6±1.8 p=0.0841	1438.9±1235.2 (999.7, 0-6358.6) p=0.3035	6.2±14.7 (0, 0-100)* p=0.0453	72.8±39.9* p=0.0001	4.0±5.1 (2.0, 0-32.4) p=0.2613	28.4±15.1* p=0.0006	9.6±7.3* p<0.001	13.6±5.1* p<0.0001	27.0* p<0.001	3.4±1.9* p=0.0106
84.7±51.2 p=0.0685	3.6±1.3 p=0.0744	1754.4±1535.6 (1260.4, 0-6994.7) p=0.0986	5.9±12.4 (0, 0-56) p=0.1275	68.2±36.4* p=0.0003	4.0±4.1 (3.1, 0-19.6) p=0.0768	29.1±14.8* p=0.0323	9.8±8.5* p=0.0001	15.2±5.3* p<0.0001	27.0* p=0.002	4.1±2.3* p=0.0008
85.3±51.2 p=0.09	3.6±1.1* 0.0446	1959.7±1600.3 (1464.8, 0-5319.1)* p=0.0352	4.5±10.1 (0, 0-60)* p=0.0472	73.3±39.0* p=0.1056	5.2±5.0 (3.7, 0-18.2)* p=0.0036	34.2±19.0 p=0.2466	11.7±10.6 p=0.1378	16.9±5.2 p<0.0001	25.4* p=0.018	3.3±1.9 p=0.0771
p=0.6070	p=0.4643	p=0.2672	p=0.3655	p=0.0006	p=0.0695	p<0.001	p=0.0001	p=0.0001	p<0.001	p=0.035

	Functional Peristalsis (%)	Simultaneous Peristalsis (%)	Failed Peristalsis (%)
Underweight	62.5±39.1 p=0.2318	13.6±28.4 (0, 0-100) p=0.3598	23.9±34.4 (10, 0-100) p=0.4437
Normal Weight	67.1±36.5	11.0±23.1 (0, 0-100)	22.1±31.1 (10, 0-100)
Overweight	71.2±33.5 p=0.0914	10.2±20.7 (0, 0-100) p=0.4107	18.3±28.5 (0, 0-100)* p=0.0299
Obesity Class I	73.8±30.6* p=0.0321	10.1±20.0 (0, 0-100) p=0.2563	16.1±25.7 (0, 0-100)* p=0.0014
Obesity Class II	76.0±31.5* p=0.0153	9.4±20.6 (0, 0-100) p=0.3748	14.6±27.1 (0, 0-100)* p=0.0011
Obesity Class III	72.5±31.6 p=0.1738	13.0±21.9 (0, 0-100)* p=0.0383	14.2±22.8 (0, 0-100)* p=0.0405
Overall Significance	p=0.1949	p=0.7839	p=0.0253

Significance: *p-value≤0.05 compared to normal weight group.
DCI: Distal contractile integral, UES: Upper esophageal sphincter, LES: Lower esophageal sphincter, IGP: Intragastric pressure.

Table A-2: Differences between normal and abnormal esophageal motility patient demographics.

Demographic	Normal	Abnormal	Significance (p-value)
Age (years)	52.2±15.1	55.7±14.6	<0.0001
Gender (% Female)	67.4	59.2	0.002
Body Mass Index (kg/m^2)	29.4±6.5	28.5±5.9	0.0091
Underweight (%)	1.9	2.3	0.704
Normal Weight (%)	23.8	28.1	0.078
Overweight (%)	32.3	35.1	0.293
Obesity Class I (%)	26.4	22.3	0.092
Obesity Class II (%)	9.9	7.2	0.089
Obesity Class III (%)	5.7	5.1	0.624

Table A-3: Differences between normal and abnormal esophageal motility at the upper and lower esophageal sphincters.

Measurement	Normal	Abnormal	Significance (p-value)
Hiatal Hernia (%)	21.2	23.2	0.39
Average Hiatal Hernia Size (cm)	3.3±1.9	3.2±1.9	0.8556
Intragastric Pressure (mmHg)	12.8±5.2	12.6±5.7	0.4195
Lower Esophageal Sphincter Pressure (mmHg)	29.7±11.4	30.8±20.5	0.2595
Lower Esophageal Sphincter Residual Pressure (mmHg)	8.4±3.9	12.7±10.5	<0.0001
Upper Esophageal Sphincter Pressure (mmHg)	78.2±41.1	77.6±47.3	0.2022
Upper Esophageal Sphincter Residual Pressure (mmHg)	3.3±4.5 (1.3, 0-32.4)	4.5±5.4 (2.7, 0-37)	0.0001

Table A-4: Differences between normal and abnormal esophageal motility in the esophageal body.

Measurement	Normal	Abnormal	Significance (p-value)
Functional Peristalsis (%)	92.3±9.5	54.8±36.3	<0.001
Simultaneous Peristalsis (%)	3.8±7.0 (0, 0-50)	15.8±26.7 (0, 0-100)	<0.001
Failed Peristalsis (%)	3.9±7.0 (0, 0-40)	29.3±33.2 (20, 0-100)	<0.001
Mean Wave Amplitude (mmHg)	89.5±33.6	70.5±58.4	<0.001
Mean Wave Duration (mmHg)	3.7±0.8	3.3±1.9	<0.001
Distal Contractile Integral (mmHg/cm/s)	1674.7±1003.2 (1408.2, 202.2-6409.3)	1607.0±2086.7 (767.4, 0-19812.4)	<0.001
Double Peaked Waves (%)	5.3±11.2 (0, 0-80)	8.1±17.3 (0, 0-100)	0.4147

Table A5: Average, median, and range of esophageal acid exposure and reflux events in the upright and recumbent position during 24h pH testing by normal and abnormal DeMeester Score.

	DeMeester Score <14.7			**DeMeester Score >14.7**		
	Upright	Recumbent	Total	Upright	Recumbent	Total
Percent Time in Reflux (%)	2.0±1.6 (1.7, 0-5.2)	0.4±0.8 (0, 0-3.6)	1.4±1.1 (1.3, 0-3.9)	8.6±6.9* (7.4, 0.1-51)	8.4±9.5* (4.2, 0-45.3)	8.9±6.8* (6.5, 2.7-51)
Percent Time Esophagus Clearance (%)	2.2±2.1 (1.6, 0-9.9)	0.5±1.0 (0, 0-5.6)	1.5±1.3 (1.4, 0-5.2)	9.6±7.8* (8.5, 0.7-41)	7.9±7.6* (6.1, 0-41.5)	9.2±5.1* (7.7, 3.4-35.3)
Number of Distal Acid Reflux Events	24.0±19.4 (20, 0-81)	3.5±6.9 (1, 0-55)	27.2±21.6 (21, 0-90)	73.4±57.5* (65, 7-454)	28.5±49.4* (12, 0-433)	102.0±87.4* (78, 12-690)
Number of Distal Non-Acid Reflux Events	31.5±20.7 (27, 4-94)	4.6±8.3 (2, 0-50)	36.1±24.7 (30, 4-120)	33.6±29.0 (26, 2-183)	8.1±10.6** (4, 0-50)	41.8±36.3 (34, 2-213)
Total Number of Distal Acid Reflux Events	49.5±25.3 (43, 12-121)	7.0±10.1 (3, 0-65)	56.5±29.9 (49, 14-172)	80.6±52.6* (65, 20-300)	22±25.3* (13, 0-112)	102.6±66.9* (81, 21-412)
Number of Proximal Acid Reflux Events	11.8±9.9 (9, 0-43)	1.5±2.7 (0, 0-17)	13.3±10.7 (10, 0-52)	31.1±26.1* (24, 1-149)	8.8±13.2* (4, 0-71)	39.9±33.5* (32, 4-220)
Number of Proximal Non-Acid Reflux Events	15.0±12.7 (12, 0-64)	2.0±5.0 (0, 0-42)	16.9±14.8 (13, 1-81)	15.5±17.9 (12, 1-111)	3.2±5.7*** (1, 0-32)	18.7±22.2 (14, 1-134)
Total Number of Proximal Acid Reflux Events	26.8±17.7 (25, 2-90)	3.5±6.4 (1, 0-52)	30.3±20.3 (27, 2-133)	46.6±36.4* (36, 4-184)	12.0±17.5* (7, 0-86)	58.6±48.4* (47, 7-258)

Significance: *p<0.0001, **p=0.0014, ***p=0.0093.

Table A-6: Symptom measurement during 24h pH-impedance and the association to positive reflux symptoms and findings.

Symptom Sensitivity Index			Symptom Association Probability						Positive Reflux Symptoms with Presenting Symptoms	Positive Reflux Findings with Presenting Symptoms	Positive Reflux Findings and Symptoms with Presenting Symptoms
Abnormal			Normal			Abnormal					
Acid	Non-Acid	Total	Acid	Non-Acid	Total	Acid	Non-Acid	Total			
41.4* (29) p=0.001	18.6* (13) p=0.05	30.0* (21) p=0.0048	18.3 (21)	7.0 (8)	21.7 (25)	60.9* (42) p<0.0001	2.9 (2)	55.1* (38) p<0.0001	51.1 (136)	50.4 (134)	70.6 (96)
8.3* (1) p=0.021	8.3 (1)	8.3 (1)	66.7 (6)	22.2 (2)	44.4 (4)	33.3 (4)	25.0 (3)	33.3 (4)	60.4 (58)	57.3 (55)	70.7 (41)
0.0 (0)	0.0 (0)	0.0 (0)	4.8 (1)	4.8 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	38.7 (29)	38.7 (29)	65.5 (19)
69.9 (51)	63.0 (46)	69.9 (51)	53.3 (64)	50.8 (61)	66.7 (80)	73.6* (53) p=0.0054	51.4 (37)	80.6* (58) p=0.039	92.9 (13)	64.3 (9)	69.2 (9)
18.1 (13)	29.2 (21)	18.1 (13)	10.1 (12)	11.8 (14)	17.7 (21)	15.5 (11)	16.9 (12)	23.9 (17)	59.1 (26)	36.4 (16)	53.9 (14)

Symptom	Symptom Index								
	Normal			Abnormal			Normal		
	Acid	Non-Acid	Total	Acid	Non-Acid	Total	Acid	Non-Acid	Total
Heartburn	16.0 (28)	5.2 (6)	27.8 (32)	62.9* (95) p<0.0001	2.9 (2)	64.3* (45) p<0.0001	19.1 (22)	8.7 (10)	13.0 (15)
Regurgitation	53.9 (7)	33.3 (3)	77.8 (7)	73.9 (17)	15.4 (2)	100 (13)	55.6 (5)	22.2 (2)	33.3 (3)
Abdominal/ Chest Pain	12.5 (3)	9.5 (2)	19.1 (4)	33.3 (5)	10.0 (1)	30.0 (3)	4.8 (1)	4.8 (1)	0.0 (0)
Burp	15.8 (29)	8.3 (10)	43.3 (52)	50.3* (79) p<0.0001	6.9 (5)	67.1* (49) p=0.0014	58.3 (70)	57.5 (69)	60.0 (72)
Cough	5.0 (9)	5.9 (7)	19.3 (23)	16.2* (25) p=0.0006	8.3 (6)	33.3 (24) p=0.03	26.1 (31)	25.2 (30)	24.4 (29)

Table A-7: Univariate logistic regression of acid reflux.

Variable	Odds Ratio (95% Confidence Interval)	Significance (p-value)
Age	1.00 (0.99-1.02)	0.794
Gender (Female to Male)	0.90 (0.58-1.39)	0.622
Body Mass Index	1.05 (1.02-1.09)	0.005*
Underweight to Normal	1	-
Overweight to Normal	2.16 (1.19-3.93)	0.012*
Obesity Class I to Normal	2.38 (1.28-4.41)	0.006*
Obesity Class II to Normal	3.61 (1.52-8.55)	0.004*
Obesity Class III to Normal	2.28 (0.84-6.16)	0.104*
Heartburn Symptoms	3.08 (1.76-5.40)	<0.001*
Epigastric/Chest Pain Symptoms	0.75 (0.44-1.25)	0.268
Regurgitation Symptoms	2.04 (1.26-3.29)	0.004*
Chronic Cough Symptoms	0.64 (0.33-1.24)	0.188*
Burping Symptoms	2.21 (0.73-6.75)	0.162*
Other Symptoms	0.48 (0.30-0.76)	0.002*
Average Intragastric Pressure at Baseline	1.02 (0.98-1.06)	0.444
Lower Esophageal Sphincter Pressure	0.97 (0.95-0.98)	<0.001*
Lower Esophageal Sphincter Pressure Integral	0.99 (0.99-0.99)	0.032*
Esophagogastric Junction – Contractile Integral	0.99 (0.99-0.99)	<0.001*
Total Esophagogastric Junction – Contractile Integral	0.99 (0.98-0.99)	<0.001*
Peristalsis	1.00 (0.99-1.01)	0.718
Distal Contractile Integral	0.99 (0.99-0.99)	<0.001*
Hiatal Hernia	3.26 (2.00-5.32)	<0.001*
Esophagogastric Junction Type		
Type II to Type I	3.05 (1.78-5.23)	<0.001*
Type IIIA to Type I	9.50 (2.69-33.56)	<0.001*
Type IIIB to Type I	2.45 (0.95-6.33)	0.065*

Significance: *p<0.2 included in multivariate model.

Table A-8: Multivariate logistic regression of acid reflux.

Variable	Odds Ratio (95% Confidence Interval)	Significance (p-value)
Body Mass Index	1.05 (1.02-1.10)	0.011*
Underweight to Normal	1	-
Overweight to Normal	1.85 (0.94-3.64)	0.076
Obesity Class I to Normal	2.42 (1.21-4.84)	0.012*
Obesity Class II to Normal	3.12 (1.17-8.30)	0.023*
Obesity Class III to Normal	2.08 (0.67-6.42)	0.203
Heartburn Symptoms	3.15 (1.65-6.00)	0.001*
Regurgitation Symptoms	1.75 (1.01-3.00)	0.044*
Chronic Cough Symptoms	0.79 (0.36-1.75)	0.561
Burping Symptoms	1.59 (0.49-5.22)	0.441
Other Symptoms	0.52 (0.31-0.88)	0.014*
Lower Esophageal Sphincter Pressure	0.98 (0.96-0.99)	0.043*
Lower Esophageal Sphincter Pressure Integral**	-	-
Esophagogastric Junction – Contractile Integral**	-	-
Total Esophagogastric Junction – Contractile Integral**	-	-
Distal Contractile Integral	0.99 (0.99-0.99)	0.038*
Hiatal Hernia**	-	-
Esophagogastric Junction Type		
Type II to Type I	2.27 (1.25-4.11)	0.007*
Type IIIA to Type I	5.89 (1.56-22.14)	0.009*
Type IIIB to Type I	1.34 (0.45-4.00)	0.598

Significance: *$p<0.05$ included in final model. **Not included in model because of collinearity.

Table A9: Final logistic regression model for acid reflux.

Variable	Odds Ratio (95% Confidence Interval)	Significance (p-value)
Body Mass Index		
Obesity Class I to Normal	1.75 (1.01-3.03)	0.045*
Obesity Class II to Normal	2.15 (0.89-5.20)	0.090
Heartburn Symptoms	3.25 (1.74-6.08)	<0.001*
Regurgitation Symptoms	1.84 (1.08-3.16)	0.026*
Other Symptoms	0.49 (0.29-0.83)	0.008*
Lower Esophageal Sphincter Pressure	0.98 (0.96-0.99)	0.018*
Distal Contractile Integral	0.99 (0.99-0.99)	0.041*
Esophagogastric Junction Type		
Type II to Type I	2.24 (1.25-4.00)	0.007*
Type IIIA to Type I	5.98 (1.61-22.22)	0.008*

Significance: *p<0.05.

Table A10: Results of esophageal motility parameters stratified by normal and abnormal esophageal manometry results in obese and bariatric surgery patients.

LESR Pressure (mmHg)	Average IGP (mmHg)	UES Pressure (mmHg)	UESR Pressure (mmHg)	Percentage of Swallows with Peristalsis (%)	Mean Wave Amplitude (mmHg)	Mean Wave Duration (s)	DCI (mmHg/cm/s)
8.3±3.8	14.2±4.9	69.6±36.2	3.6±4.6 (2.4, 0-32.4)	92.4±9.7	90.0±35.9	3.8±0.7	1717.7±1062.3
11.5±10.4	14.6±5.7	74.0±41.4	4.7±5.1 (3.4, 0-28.5)* p=0.014	57.1±34.1* p<0.0001	70.9±54.0* p<0.0001	3.4±2.1* p=0.0001	1456.4±1603.4 (757.7, 0-6994.7)* p<0.0001
6.1±4.8	14.2±3.1	104.2±57.7	2.1±1.8 (2.4, 0-4.3)	96.7±5.2	85.2±23.2	3.6±0.8	1315.3±556.0
4.5±5.9 (0.6, 0-11.4)	19.2±2.8* p=0.028	66.6±25.9	5.1±4.8 (4.7, 0-11.6)	78.0±22.8	58.9±39.0	3.2±0.7	849.9±424.4
9.6±5.1	22.7±18.0	98.9±47.0	3.7±6.3 (0.1, 0-17.7)	95.0±7.6	113.0±40.9	3.8±0.8	2177.2±862.0
4.9±4.7	13.5±4.0	56.5±12.6	3.9±6.3 (2.2, 0-15)	58.0±29.5* p=0.0040	61.2±39.7* p=0.040	3.2±0.9	1272.6±1366.8 (464.8, 127.8-2941.3)
9.9	18.5	93.0	7.8	80	69.6	3.9	2154.5
1.6±2.8 (0, 0-4.9)	13.4±2.7	80.4±27.5	15.3±15.7 (10.9, 2.3-32.8)	23.3±11.5	48.3±70.4 (15.7, 0-129.1)	1.6±1.7 (1.6, 0-3.3)	1194.0±1960.8 (125.0, 0-3457.0)
9.4±3.0	16.4±5.0	113.4±42.5	3.5±5.1 (0, 0-13.5)	92.9±9.5	84.0±36.9	4.2±1.0	1832.0±1314.8
6.4±5.3	12.4±0.4	62.7±15.5* p=0.022	5.6±4.6 (5.3, 0-11.6)	66.7±27.3* p=0.046	68.0±34.5	3.2±0.7	1185.6±1122.2

	Motility	Hiatal Hernia (%)	LES Pressure (mmHg)
Obese	Normal (n=241)	26	29.7±10.9
	Abnormal (n=258)	27	29.2±19.2
SG	Normal (n=6)	17	24.5±5.2
	Abnormal (n=5)	40	13.6±12.9 (9.7, 0-33.1)* p=0.05
RYGB	Normal (n=8)	25	35.5±21.4
	Abnormal (n=5)	20	26.5±19.1
AGB	Normal (n=1)	0	27.4
	Abnormal (n=3)	67	31.9±11.7
VBG	Normal (n=7)	14	35.3±16.2
	Abnormal (n=6)	17	25.5±20.2

LES: Lower esophageal sphincter, LESR: Lower esophageal sphincter residual, IGP: Intragastric pressure, UES: Upper esophageal sphincter, UESR: Upper esophageal sphincter residual, DCI: Distal contractile integral.