

**THE ROLE OF THE PROXIMAL SMALL INTESTINE IN IMPROVEMENTS IN  
DIABETES RESOLUTION AND INSULIN SENSITIVITY FOLLOWING BARIATRIC  
SURGERY IN TYPE 2 DIABETES.**

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Bariatric surgery is an effective, rapid, and durable treatment for obesity and type 2 diabetes mellitus (T2DM). Roux-en Y Gastric Bypass (RYGB) resolves T2DM in 80% of cases, while gastric banding (LAGB) resolves T2DM in only 45%. One significant difference between RYGB and LAGB is the bypassing of the proximal small intestine in RYGB. Inadequate insulin secretion and insulin resistance are well known contributors to T2DM and both improve following RYGB. To determine if RYGB produces greater improvements in insulin secretion and insulin sensitivity than LAGB in T2DM, we studied obese, T2DM, Caucasian women who underwent RYGB (N=9) or LAGB (N=3). Insulin secretion (AIRg) and insulin sensitivity (Si) were measured pre- and 1-wk post-surgery by Minimal Model analysis following an insulin modified intravenous glucose tolerance test (IVGTT). Post-surgery analysis at 1-wk eliminates the potential contribution of differences in weight loss or food consumption as these are rigorously controlled for 1 wk following these surgical procedures. There was a trend ( $p = 0.053$ ) for an increase in Si from pre-surgery to 1-wk post-surgery, but there was no difference in Si between surgical groups (RYGB, Pre:  $0.85 \pm 0.15$  and 1-wk:  $2.30 \pm 0.43$ ) and (LAGB, Pre:  $1.32 \pm 0.26$  and 1-wk:  $1.67 \pm 0.60$ ). There was a trend for an Interaction ( $p = 0.056$ ) in AIRg with an increase in RYGB (Pre:  $42.0 \pm 23.3$  and 1-wk:  $94.7 \pm 52.6$ ), but decrease among LAGB (Pre:

519.7 ± 392.9 and 1-wk: 391.8 ± 291.6) with surgery. There was also a trend ( $p = 0.067$ ) for a greater AIRg in LAGB compared to RYGB regardless of surgery status. These results in obese, T2DM, Caucasian women suggest that insulin sensitivity may be increased similarly in RYGB and LAGB questioning the role of the proximal small intestine bypass in the reversal of insulin sensitivity following bariatric surgery. In contrast, improvements in insulin secretion may be greater in RYGB than LAGB. Additional gastric banding patients are required to provide adequate power for statistical analysis.



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## CHAPTER 1: INTRODUCTION

As obesity increases at an epidemic rate worldwide society is faced with a surge in obesity-related health comorbidities. It is estimated that over 400,000 people each year in the U.S. die of causes directly attributable to obesity (Obesity Resource Center). An individual is classified as obese if they have a body mass index (BMI) greater than or equal to  $30 \text{ kg/m}^2$ . Characteristics of obesity are not limited to excess body weight; it is a physical health condition that is closely associated with several other ailments, including hypertension, type 2 diabetes mellitus (T2DM), dyslipidemia, heart disease, osteoarthritis, sleep apnea, hepatobiliary disease, and certain types of cancers (Kissebah et al. 1989). Obesity is a major independent risk factor for the development of T2DM (Dixon et al., 2002). According to the American Diabetes Association, 80% of type two diabetics are obese, demonstrating that these health conditions go hand in hand (Bloomgarden Z., 2000).

Individuals suffering from T2DM possess disturbances in glucose homeostasis characterized by impaired insulin secretion and decreased ability of insulin to perform its physiological function (insulin resistance) in muscle, adipose and liver (DeFronzo et al., 2004). While there are several disease management options for T2DM, none to date have proven more successful than bariatric surgery (Buchwald et al., 2004). Bariatric surgery was once thought to only serve as a treatment for morbidly obese individuals in need of drastic and rapid weight loss; however, in recent years this same surgical procedure has proven to be immensely effective in the reversal of T2DM.

Bariatric surgery is an operation of the upper gastrointestinal tract designed to induce weight loss (American Society for Bariatric and Metabolic Surgery). Bariatric surgery methods involve restriction, malabsorption, or both (Cannon & Kumar, 2009). Among the bariatric

surgical procedures, the two most commonly performed procedures are Roux-en Y gastric bypass (RYGB) and laparoscopic adjustable gastric banding (LAGB) (Cannon & Kumar, 2009). Both have proven highly successful in facilitating weight loss for obese individuals and are successful in the reversal of T2DM (Pories et al., 1995). Weight loss following RYGB is very rapid when compared to the LAGB. Patients who undergo the bypass procedure will lose 60-70% of their excess weight within 1-2 years (Buchwald et al., 2004). LAGB patients on the other hand will lose 50-60% over a 3-year period (Buchwald et al., 2004). In terms of diabetes treatment, 86.0% patients who have undergone any form of bariatric surgery have improved or reversed their conditions significantly within the first year post operation.

The mechanisms by which these bariatric procedures reverse T2DM are highly debated and no consensus currently exists. Both RYGB and LAGB have demonstrated success in diabetes reversal; however, RYGB has proven to be more successful due to the fact it induces not only restriction, but malabsorption as well by bypassing a portion of the small intestine (American Society for Bariatric and Metabolic Surgery). It is known that the RYGB and LAGB procedures are effective for weight loss due to the creation of a smaller stomach that allows the individual to feel satisfied faster with smaller amounts of food. It is still unknown however, how this same procedure rapidly reverses T2DM. Furthermore, it is unclear how RYGB and LAGB differ in their ability to reverse T2DM immediately following the surgical procedure. T2DM reversal has proven successful for both procedures over one to three years when excess weight loss is achieved (Cannon & Kumar, 2009 and Buchwald et al., 2004). However, RYGB patients resolve their T2DM before significant weight loss has occurred (Pories et al., 1995). This factor suggests that weight loss alone does not solely contribute to the reversal of T2DM but rather some other mechanism associated with the gastric bypass procedure plays an important role.

Insulin resistance is the inability of insulin to perform its physiological function in the body. It is the failure of target tissues to increase whole-body glucose disposal in response to insulin (Abdul Ghani et al., 2006). Insulin resistance is one of the primary disease characteristics of type 2 diabetics. It relates to the peripheral tissue's ability to utilize insulin for glucose uptake and metabolism, and refers primarily to the skeletal muscle (DeFronzo et al., 2004, Muoio et al., 2008). Using the IVGTT minimal model, one can assess insulin sensitivity and more specifically the muscle insulin sensitivity because approximately 80% of insulin-induced glucose disposal (uptake) occurs in skeletal muscle (DeFronzo et al., 1981). Thus, the IVGTT minimal model will provide a strong indication of the relationship between improvements in insulin sensitivity in T2DM between RYGB and LAGB.

The purpose of this study was to perform a comparative analysis in the ability of RYGB and LAGB to increase insulin sensitivity in T2DM patients. It was hypothesized that T2DM patients undergoing RYGB would see greater improvements in their insulin sensitivity one-week post surgery than T2DM patients who undergo LAGB. T2DM patients were studied at one-week post-op because at this time weight loss is minimal and likely similar between RYGB and LAGB due to strict and regimented post-op diet and medical treatment for one week. Thus, differences in insulin sensitivity would be due to proximal small intestine bypass and not differences in weight loss or food restriction.

### Statement of the Problem:

The mechanism for improvements in insulin sensitivity following bariatric surgery in type two diabetes following gastric banding and gastric bypass surgery are not clear.

### Hypothesis:

Improvements in insulin sensitivity index will be greater following RYGB than LAGB in T2DM patients.

### Definitions:

Body Mass Index (BMI): a comparison of weight relative to height expressed in  $\text{kg}/\text{m}^2$

### Delimitations:

1. Subjects are restricted to Caucasian women
2. Subjects are from the age 18-60 years
3. Subjects must have a BMI 35-65  $\text{kg}/\text{m}^2$
4. Subjects are not pregnant.
5. Subjects have scheduled a bariatric surgery

### Limitations:

1. The study is limited to only one part of the population, Caucasian women.
2. Group have different insulin sensitivity status pre-surgery.
3. Small sample size (N=12)

## CHAPTER 2: REVIEW OF LITERATURE

### *Prevalence of Obesity in the United States*

Obesity is defined as a body mass index (BMI) greater than or equal to 30 kg/m<sup>2</sup>, and according to the National Health and Nutrition Examination Survey (2001-2004), 66% of American adults aged 20 years and older are overweight or obese (BMI  $\geq$  25 kg/m<sup>2</sup>) (Ogden et al., 2007). The prevalence of obesity is growing at a rapid pace in the United States, and this is due to the combination of several factors including high fat diets, over consumption of energy dense foods, and a lack of regular physical activity (Cannon and Kumar, 2009). Obesity is associated with several major health consequences and comorbidities that include hypertension, type two diabetes mellitus, dyslipidemia, heart disease, osteoarthritis, sleep apnea, hepatobiliary disease, and certain types of cancers (Kissebah et al. 1989). It is clear that obesity directly impacts one's quality of life in a negative way, and with 133.6 million United States adults suffering from this physical condition; it is imperative to find a resolution.

### *Obesity Management*

Current treatment options for morbidly obese individuals include pharmacological agents, low-calorie diets, behavioral modification, regular exercise, and surgical procedures. The treatment strategies that require long-term lifestyle modifications by changing one's diet to be healthier and increasing physical activity and exercise levels, have been insufficient in many circumstances, so more drastic courses of action may need to be taken (Tice et al, 2008). Drug therapy is one method of treatment, however, adequate data on long-term safety is lacking and only modest weight loss has been observed (Cannon & Kumar 2009, Tice et al. 2008). In the case of obese and morbidly obese individuals (BMI  $\geq$ 30 or  $\geq$ 40) suffering from obesity related

comorbidities there is a need for rapid and drastic weight loss to decrease risk of fatality. To date, the most effective treatment option for these individuals is bariatric surgery (Cannon & Kumar 2009, Tice et al, 2008). Bariatric surgery is an option for those obese individuals who have a BMI  $\geq 40$  kg/m<sup>2</sup> or a BMI  $\geq 35$  kg/m<sup>2</sup> with one or more of the following obesity-related comorbidities: hypertension, type two diabetes mellitus, heart disease, gallstones, gout, stroke, osteoarthritis, sleep apnea, and some forms of cancer (American Society for Metabolic and Bariatric Surgery).

### *Bariatric Surgery Methods*

Bariatric surgery is a surgical procedure of the upper gastrointestinal tract designed to induce weight loss (Tice et al. 2008). Bariatric surgery methods involve inducing restriction, malabsorption, or both (Cannon & Kumar, 2009). According to one systematic review, patients achieved an average weight loss of approximately 40 kg after bariatric surgery and most had complete resolution or improvement of their diabetes, hypertension, hyperlipidemia, and obstructive sleep apnea (Buchwald et al., 2004). Between 1998 and 2004, the number of bariatric surgeries performed in the United States increased from approximately 13,000 annually to 121,000 (Zhao et al., 2007) and in 2008 alone it is estimated 220,000 bariatric surgeries were performed (Garb et al., 2009). As obesity rates have rose in the United States, so have the rates of bariatric surgeries, and among those procedures the two most commonly performed bariatric surgeries are Roux-en Y gastric bypass (RYGB), and laparoscopic adjustable gastric banding (LAGB) (Tice et al., 2008). Both procedures are characterized as restrictive procedures; however, LAGB is marked as a less invasive, potentially reversible alternative to RYGB, because the procedure does not require gastrointestinal bypass and reanastomosis.

LAGB functions by limiting food intake after the placement of an inflatable tube around the stomach just below the gastroesophageal junction (Pories et al., 1995). The placement of a saline-filled silicone band around the upper part of the stomach allows for adjustment of the size of the subcutaneous port (Pories et al., 1995). This procedure is characterized as a restrictive only procedure that reduces the size of the stomach, and thus, causes patients to experience satiety more rapidly (Cannon & Kumar, 2009). In a follow-up study looking at patients who underwent the LAGB procedure, the percent of excess-weight loss was 61% among patients, five years post surgery (Christou & Efthimiou, 2009).

RYGB, the most common bariatric surgical procedure in the United States, also creates a small stomach pouch to restrict food intake, but a portion of the jejunum is attached to the pouch to allow food to bypass the distal stomach, duodenum, and proximal jejunum (American Society for Metabolic and Bariatric Surgery). This procedure involves both restriction and malabsorption methods. The bypass methodology of this procedure is what induces the malabsorptive state (Pories et al. 1995). The creation of a bypass that shortens the length of the small intestine reduces digestion and absorption time. The restrictive aspect of this procedure is the reduction in the size of the stomach, which in turn reduces the stomach's storage capacity (American Society for Metabolic and Bariatric Surgeries).

Bariatric surgery has proven to be very successful in aiding weight loss for morbidly obese patients (Buchwald et al., 2004, Cannon & Kumar, 2009). In a systematic review by Buchwald et al., 136 studies were extracted and reviewed, revealing that the percentage of excess weight loss for all patients undergoing some form of bariatric surgery was 61.2%. For RYGB alone, the average weight loss of these surgical patients is approximately 39.7 kg and an excess weight loss percent of 68.2% (Buchwald et al., 2004). Additionally, bariatric surgery has proven



to be 76.8% successful in treatment for those individuals suffering from T2DM; RYGB having an 83.7% success rate versus LAGB, which has a 47.9% success rate (Ferchak & Meneghini, 2004, Buchwald et al., 2004). Obesity is a major independent risk factor for the development of T2DM (Dixon et al., 2002). Approximately 80% of type 2 diabetics are obese, demonstrating that these health conditions go hand in hand (Bloomgarden Z., 2000).

### *Type 2 Diabetes Mellitus*

Type 2 Diabetes Mellitus is characterized by a loss in metabolic fuel homeostasis and is associated with a failure of target tissues to increase whole body glucose disposal in response to insulin (DeFronzo et al., 2004). Chronic over nutrition, or metabolic overload, combined with genetic factors are thought to induce a state of impaired insulin signaling that leads to defective insulin secretion as well as defective insulin stimulated glucose uptake (insulin resistance). The risk of developing T2DM increases with the degree of obesity, duration of obesity, central fat distribution, and weight gain during adulthood (Chan J. et al., 1994).

Glucose is the principal fuel used by humans and is derived from the carbohydrates consumed in foodstuff (DeFronzo, 2004). It is the sole source of energy for the brain. Homeostasis of this vital energy substrate is tightly monitored and controlled by several physiological and metabolic mechanisms (DeFronzo, 2004). A primary mechanism for glucose homeostasis is the hormone insulin. Insulin is secreted by the beta-cells of the pancreas and it controls fuel homeostasis through the stimulation of glucose uptake into peripheral tissues and by suppressing the release of stored lipids from adipose tissue (Jitrapakdee et al., 2010).

### *Glucose Homeostasis: Normoglycemia*

Under normal, non-diabetic conditions, the maintenance of glucose homeostasis is dependent on whole body glucose disposal in insulin-independent and insulin-dependent tissues (Jitrapakdee et al., 2010). Following the ingestion of a typical mixed meal (postabsorptive state) a majority of total body glucose disposal takes place in insulin-independent pathways, which include the brain, and splanchnic area (liver plus gastrointestinal tissues). The brain and splanchnic areas account for approximately 75% of all glucose disposal, and the remaining 25% is used by the insulin-dependent tissues, primarily muscle and to a lesser extent adipose (DeFronzo et al., 2004).

Following carbohydrate ingestion, the increase in plasma glucose concentration stimulates insulin release, and the combination of hyperinsulinemia and hyperglycemia leads to stimulation of glucose uptake by splanchnic and peripheral (muscle) tissues and suppression of endogenous glucose production by the liver (DeFronzo, 2004). While a majority of glucose uptake by the peripheral tissues occurs in the muscle, a small and very significant amount occurs in the adipose tissue, and it plays an important role in total body glucose homeostasis by regulating the release of free fatty acids (FFA) from stored triglycerides and through the production of adipocytokines that influence insulin sensitivity in muscle and liver (DeFronzo et al., 2004 and Muoio et al., 2008). Elevated plasma insulin inhibits lipolysis, leading to a decline in the plasma level of FFA. As a result, muscle glucose uptake is enhanced, and hepatic glucose production is inhibited, thus playing an important role in the maintenance of normoglycemia (Muoio et al., 2008).

### *Impaired Glucose Homeostasis and Type 2 Diabetes Development*

Chronic disturbances in the homeostasis of glucose control can have several detrimental effects, including the development of T2DM. T2DM is the result of impaired insulin secretion and action, leading to several metabolic abnormalities and high-risk health conditions.

Comorbidities associated with T2DM include; heart disease, hypertension, stroke, metabolic syndrome, high blood pressure, dyslipidemia, nervous system disorders, dental disease and complications with pregnancy (American Diabetes Association, 2002).

The onset of T2DM is progressive and includes multiple intermediate states that are clear signs of future risk for T2DM development. Obesity is a key feature of T2DM such that greater than 80% of all T2DM patients are or have been obese (Felber & Golay, 2002, Bloomgarden Z., 2000), which demonstrates that there exists a relationship between the progression from obesity to T2DM. The relationship between obesity and T2DM is dependent upon the individual's insulin resistance and insulin secretion (Tice et al, 2008). Signs of insulin resistance are common in non-diabetic, obese individuals (Felber & Golay, 2002). Chronic hyperglycemia (glucotoxicity phenomenon) impairs insulin sensitivity, while sustained hyperinsulinemia inhibits both insulin secretion and insulin action (Tice et al., 2008).

Furthermore, a physiological factor that dominates in obesity is the permanent elevation of plasma free fatty acids, both in the basal state and following glucose load (Felber & Golay, 2002). Similarly, elevated plasma FFA levels represent a major factor in insulin resistant individuals as well (Baldeweg et al. 2000). The progression from an obese insulin resistant individual to a diagnosed T2DM patient is related to the progression of the disease and the exact mechanism for this occurrence is of great interest and debate among the science field to date. An individual progressing to diagnosed T2DM may experience impaired glucose metabolism in the

form of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). Insulin resistance and impaired insulin secretion due to beta cell dysfunction are the primary defects of T2DM and both can be detected along with IFG and IGT (Abdul-Ghani et al., 2006).

### *Insulin Resistance*

Insulin resistance is the inability of insulin to perform its physiological function in the body. It is the failure of target tissues to increase whole-body glucose disposal in response to insulin (Abdul Ghani et al., 2006). Insulin resistance is one of the primary disease characteristics of T2DM patients, and relates to the peripheral tissues ability to utilize insulin for glucose uptake and metabolism, primarily in skeletal muscle (DeFronzo et al., 2004, Muoio et al., 2008). Insulin resistance in the skeletal muscle is of particular importance due to the role of skeletal muscle in insulin-stimulated glucose disposal. Skeletal muscle is responsible for greater than 80% of insulin stimulated whole-body glucose disposal, thus, it plays an important role in the pathogenesis of the disease (DeFronzo et al., 2004). Among the research to date, there has been a great deal of investigation on the role of skeletal muscle insulin resistance and the pathogenesis of T2DM. It is widely established that insulin resistance is associated with several diseases such as T2DM, hypertension, obesity and cardiovascular disease. In an analysis of 211 apparently healthy obese adults, subjects with the highest degree of insulin resistance had higher blood pressure, higher fasting and postprandial glucose and plasma triglyceride levels, and lower high density lipoproteins levels than obese subjects with the highest degree of insulin sensitivity (McLaughlin et al., 2007).

Numerous studies have observed an association between insulin resistance and obesity (Peiffer, 2000, Koves et al., 2008, Felber and Golay, 2002, Hulver, 2003), leading researchers to

consider that chronic over nutrition associated with weight gain and the accumulation of lipid-derived metabolites in the cell, causes impaired insulin action in the body (Peiffer, 2000).

Intramuscular levels of lipid signaling molecules, such as long chain fatty acyl CoAs (LC-CoAs), diacylglycerol (DAG), and ceramides, positively correlate with triglyceride concentrations and negatively correlate with insulin sensitivity (Hulver et al., 2003). RYGB has proven successful in increasing skeletal muscle insulin sensitivity by 300% and thus reversing the detrimental effects of insulin resistance in the muscle (Friedman et al., 1992).

### *Mechanisms of Bariatric Surgery Responsible for Type 2 Diabetes Reversal*

The two most common bariatric procedures, LAGB and RYGB, both facilitate weight loss by limiting food intake and enhancing a feeling of fullness by effectively reducing stomach size. These bariatric procedures are therefore known as "restrictive" procedures (Cannon & Kumar 2009). The resultant smaller stomach size is what contributes to the significant weight loss seen over time among patients who underwent either surgery (Buchwald et al., 2004). In addition to a restrictive component, RYGB also promotes weight loss via introducing an element of malabsorption (Cannon & Kumar 2009). RYGB involves re-directing or re-routing of ingested food away from the main body of the stomach and first part of the small intestine. This effectively reduces contact with digestive enzymes, which enter the bowel at this point.

Gastric bypass is associated with a more rapid weight loss among patients when compared to gastric banding (Buchwald et al., 2004). Within the first 1-2 years post-surgery RYGB patients can expect to lose 60-70% of their excess weight (Buchwald et al., 2004, Pories et al., 1995). It is believed that this drastic and rapid weight loss is due to the bypassing of the small intestine, which induces the state of malabsorption. However, when examining patients

over a longer time period, the weight loss results appear equal between RYGB and LAGB (O'Brien et al., 2006).

According to a systemic review of over 136 fully extracted studies on Bariatric Surgery, diabetes was completely resolved in 76.8% of patients and resolved or improved in 86% (Buchwald et al., 2004). When examining the various forms of bariatric surgery in this systematic review, gastric bypass proved successful in T2DM reversal of 83.7%, while 47.9% was successful for gastric banding (Buchwald et al., 2004). Initially researchers attributed the anti-diabetic effects of bariatric surgery to caloric restriction and subsequent weight loss associated with the caloric deficit. When comparing the bariatric procedure results, RYGB appears to be the superior procedure for T2DM reversal due to its more rapid effects (Buchwald et al., 2004). Several researches attribute this due to the fact that the banding procedure is purely restrictive and involves no changing of bowel anatomy to re-route of food and no stomach stapling surgery.

Pories et al., (1995) hypothesized that RYGB improved T2DM conditions through mechanisms associated with the proximal small intestine after surgery, and not solely from the resultant weight loss seen with bariatric surgery. Pories' "foregut hypothesis" suggests that an unknown mechanism associated with the proximal small intestine results in the reversal of T2DM following gastric bypass (1995). Support of this theory is demonstrated in Buchwald et al.'s systematic review in that a greater success rate of T2DM reversal is seen with patients receiving the bypass procedure over the banding procedure (Buchwald et al., 2004). Furthermore, patients receiving another form of bariatric surgery called Biliopancreatic Diversion Procedure (BPD) saw even greater success rates than those who received the RYGB procedure. The BPD procedure also bypasses the small intestine, however, it bypasses a greater

portion than that of the RYGB procedure (Buchwald et al., 2004).

Dramatic remission of T2DM and normalization in glucose metabolism occurs within 1-2 weeks of RYGB (Pories et al., 1995). These immediate metabolic benefits of gastric bypass surgery occur much before significant weight reduction, which takes place over several months following the procedure. The mechanism by which this occurs is under great debate and no known mechanism has been accepted to date. Our question was whether T2DM resolution and improvements in insulin sensitivity with bariatric surgery are exclusively due to reduced caloric intake and subsequent weight loss or does the bypassing of the proximal small intestine contribute to resolution? Are T2DM resolution and insulin sensitivity improved similarly between gastric bypass and gastric banding? It was hypothesized that patients undergoing RYGB would see greater improvements in their blood glucose levels and insulin sensitivity, one-week post surgery, than would those patients undergoing LAGB. Patients were studied at one-week post-operations because at that time weight loss was minimal and likely similar between RYGB and LAGB due to strict and regimented post-op diet and medical treatment for one week post surgery. Thus, differences in T2DM resolution and insulin sensitivity would be attributed to proximal small intestine bypass and not differences in weight loss or caloric restriction.

## CHAPTER 3: METHODS

### *Subjects*

Nine, Caucasian, type two diabetic females between the ages of 18 and 60 were recruited to participate in the study. The diagnosis of diabetes was confirmed in accordance with the criteria of the NIH Consortium for the Longitudinal Assessment of Bariatric Surgery (LABS). The participants must have been previously scheduled to have laproscopic adjustable gastric banding surgery (LAGB) performed. They must also have been capable of understanding the requirements and consequences of surgery and the study and were willing to comply with the study requirements and the follow up that is involved. The women must also have had a negative pregnancy test. Any patients who were having a repeat gastric bypass procedure, taking thiazolidinediones, or who were unable to hold their insulin coverage for 48 hours prior to research visits were excluded from the study.

The LAGB procedure was used in order to investigate the effect of the meal challenges without rerouting of the food flow, as is done with gastric bypass procedures. Recruiting gastric banding patients to participate in the study allowed for comparison of the glucose and insulin responses to compare with a recently completed study employing Roux-en Y Gastric Bypass (RYGB). RYGB patients were recruited and analyzed prior to my enrollment at East Carolina University, and these data were used for comparison with LAGB patients we recruited analysis.

The participants were recruited through Pitt County Memorial Hospital and the Outpatient Clinics of the Brody School of Medicine. All of the participants were approached for participation in the study after they had scheduled a gastric banding procedure. It is important to note that the participants were voluntarily having gastric banding surgery and were not influenced to do so by the researchers.



## *Procedure*

Before agreeing to participate in the study, the patients were given an informed consent document and verbal explanation informing them of the exact procedures and purpose of the study as well as what the expected requirements of the participants were. Diabetic patients were studied preoperatively and one week after the LAGB surgery in order to compare LAGB with the gastric bypass data that has been previously collected.

The participants were given specific guidelines that would instruct them on how they should prepare for each research visit. The participants were asked to hold their anti-diabetic medication for 48 hours prior to each research visit in order to accurately measure and analyze the glucose and insulin responses to the intravenous glucose challenge. They were fasted for at least 12 hours prior to their visit and they were restricted to a 350-calorie liquid mixed meal (Ensure) the evenings prior to the research visits. Each research visit included an IV glucose tolerance test with minimal model analysis for insulin sensitivity (Si), the acute insulin response to glucose (AIRg), and the disposition index (DI) (Bergman et al., 1985). The sample collection began within 15 hours from when the patient began their fast.

### *IVGTT:*

Patients were weighed after voiding at the start of each visit and a fasting bedside glucose was drawn and analyzed. The weight recorded was used to determine the amount of glucose and insulin to be administered during the IVGTT, as calculated with the following

equations:

$$\text{GLUCOSE: mls of 50\% solution of glucose} = \text{body mass (kg)} * 0.3\text{g} * 2 \quad (\text{Eq. 1})$$

$$\text{INSULIN: body mass (kg)} * 0.025 \text{ U} \quad (\text{Eq. 2})$$

A catheter was inserted into the brachiocephalic vein of each arm. This allowed one arm to be used for drug administration and one arm to be used for sample draws. If a catheter could not be inserted in both arms, a one-arm approach was used. A saline lock was attached to the IV catheter to facilitate the blood draw at each specific time point. Prior to the glucose administration, 40 cc of blood was drawn in order to establish a baseline for the lab assays. The amount of the 50% glucose solution that was calculated was then administered over 1 minute. After glucose administration blood was drawn at minutes 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, and 19. At minute 20 the calculated dose of insulin was administered over one minute. The blood draws continued at minutes 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, and 180.

#### *Sample Analysis and Preservation*

All of the samples collected during each of the research visits were centrifuged and the plasma stored in a -80°C freezer until the samples were ready to be analyzed. Glucose and insulin analysis of the blood samples was done using a Beckman Coulter UniCel DxC 600i (Beckman Coulter, Synchron Access Clinical Systems, Brea, California USA).

#### *Statistical Analysis*

Student's t-test was used to analyze differences in age and HbA1c between groups. A two-way mixed-plot factorial analysis of variance (surgical procedure × time) was used for all other variables. Following a significant *F* ratio, a Bonferroni post-hoc analysis was used. Significance was established at  $P < 0.05$  for all statistical data and sets were reported as Mean ± SE.

## CHAPTER 4: RESULTS

### *Subject Characteristics:*

The study was limited to Caucasian women to exclude the influences of race and gender. All subjects were sedentary, with a BMI > 40 kg/m<sup>2</sup>. Subject characteristics for RYGB and LAGB patients Pre-surgery and 1-wk post-surgery are in Figure 1: Pre-surgery Age (A), Pre-surgery HbA1c (B), Weight (C), and BMI (D). Nine (N=9) RYGB patients and three (N=3) LAGB patients completed the pre- and post-op testing. There was no difference in age between RYGB and LAGB. RYGB had significantly higher HbA1c compared to LAGB indicating a more severe state of T2DM. Bariatric surgery decreased weight and BMI similarly in both groups one-week post surgery.

### *Fasting Glucose and Insulin:*

Fasting glucose (A), fasting insulin (B), and HOMA-IR (C) Pre-surgery and 1-wk post-surgery in diabetic RYGB and LAGB patients are in Figure 2. Bariatric surgery tended to improve fasting glucose (p=0.090), fasting insulin (p=0.068), and HOMA-IR (p=0.057) at 1-wk post-surgery similarly in both groups (Main effect of Time). Fasting glucose was higher in RYGB compared to LAGB (Main effect of Surgical procedure group), consistent with higher pre-surgery HbA1c in RYGB. There was no difference in fasting insulin or HOMA-IR between groups.

### *Insulin Sensitivity*

There was a trend towards improved insulin sensitivity one week post-surgery for all patients' under-going bariatric surgery (p=0.053). RYGB increased insulin sensitivity by 3.3-

fold post-surgery (Pre:  $0.85 \pm 0.15$  AU and 1-wk:  $2.30 \pm 0.43$  AU) and LAGB increased insulin sensitivity 2.4-fold (Pre:  $1.32 \pm 0.26$  and 1-wk:  $1.67 \pm 0.60$ ).

### *Insulin Secretion*

There was a trend for an Interaction ( $p = 0.056$ ) in AIRg with an increase in RYGB (Pre:  $42.0 \pm 23.3$  and 1-wk:  $94.7 \pm 52.6$ ), but a decrease in LAGB (Pre:  $519.7 \pm 392.9$  and 1-wk:  $391.8 \pm 291.6$ ) with surgery. There was also a trend ( $p = 0.067$ ) for a greater AIRg in LAGB compared to RYGB regardless of surgery status. The disposition index (DI) tended ( $p=0.086$ ) to be increased by surgery. Disposition index is a value representing how well the body can dispose of glucose from the blood, based on Si and AIRg.

**FIGURE 1**

Subject characteristics in RYGB and LAGB patients pre-surgery and one-week post surgery.

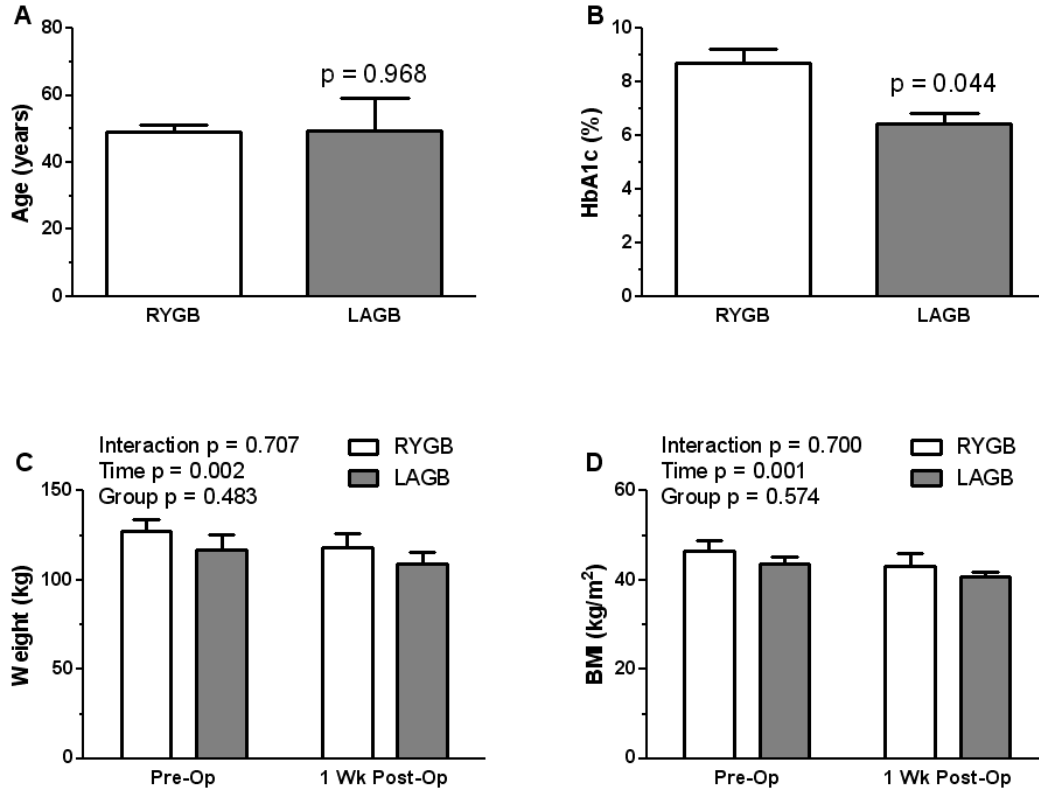


Figure 1: Pre-surgery Age (A), Pre- surgery HbA1c (B), Weight (C), and BMI (D). RYGB had significantly higher HbA1c compared to LAGB indicating a more severe state of T2DM.

Bariatric surgery decreased weight and BMI.

**FIGURE 2**

Fasting glucose, fasting insulin, and HOMA-IR pre-surgery and one-week post-surgery in diabetic RYGB and LAGB patients.

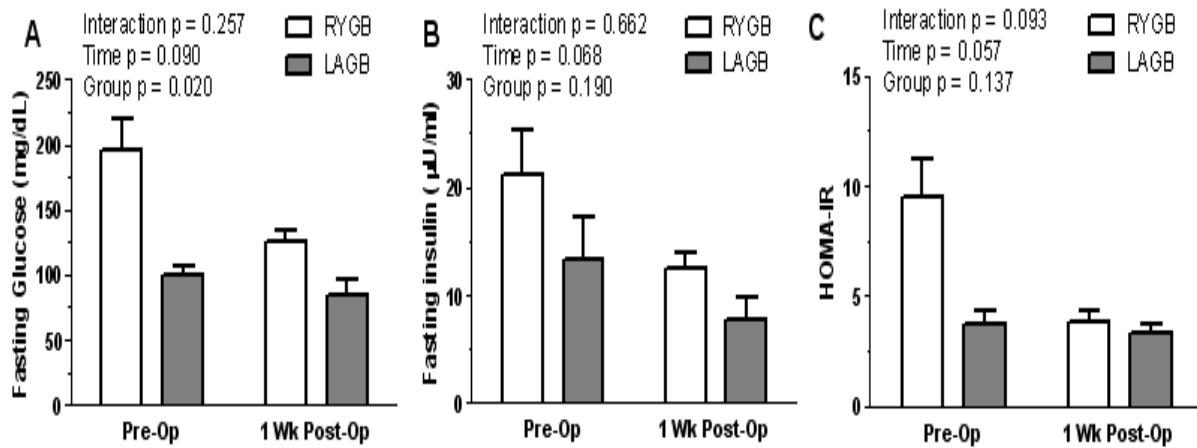


Figure 2: Fasting glucose (A), fasting insulin (B), and HOMA-IR (C) Pre-surgery and 1-wk post-surgery in diabetic RYGB and LAGB patients. Bariatric surgery tended to lower fasting glucose, fasting insulin, and HOMA-IR at 1-wk post-surgery. RYGB had higher fasting glucose than LAGB patients indicating a more severe state of T2DM.

**FIGURE 3**

Insulin sensitivity, acute insulin response to glucose, and disposition index in diabetic RYGB and LAGB patients pre-surgery and one-week post surgery.

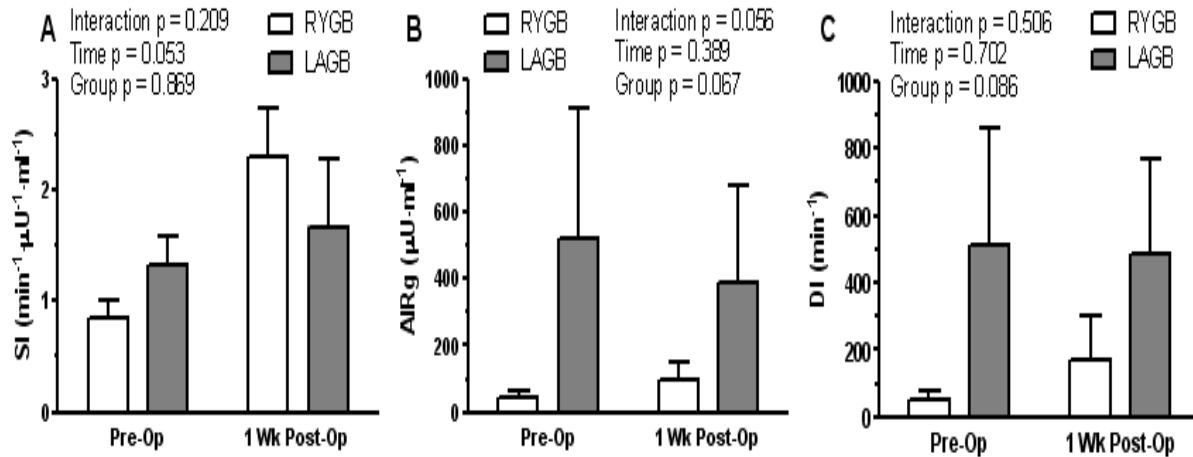


Figure 3: Insulin sensitivity (SI)(A), acute insulin response to glucose (AIRg)(B), and disposition index (DI) (C) in diabetic RYGB and LAGB patients Pre-surgery and 1-week post surgery.

Bariatric surgery tended to increase SI, while AIRg and DI tended to be greater in LAGB than RYGB patients.

## CHAPTER 5: DISCUSSION

The results of this study suggest a trend for an increase in Si from pre-surgery to 1-wk post-surgery, but there was no significant difference in Si between RYGB and LAGB surgical groups. These results suggest that obese, T2DM, Caucasian women undergoing RYGB and LAGB procedures may similarly increase insulin sensitivity 1 wk post-surgery. Additionally, a trend for an Interaction in AIRg appeared with an increase in RYGB surgical patients but not LAGB. There was also a trend for a greater AIRg in LAGB compared to RYGB regardless of surgery status. Thus, improvements in insulin secretion may be greater in RYGB than LAGB. While no significant interaction occurred with this study, the aforementioned trends regarding insulin sensitivity and insulin secretion add to the current body of knowledge and may aid in the development of future research comparing forms of bariatric surgery and clarify the exact role of the proximal small intestines in T2DM resolution.

Bariatric surgery has proven to be the most successful intervention for weight loss in overweight and obese individuals (Buchwald et al., 2004). What was once thought to only serve as a means of causing rapid and significant weight loss has proven to be equally effective in resolving several obesity related comorbidities, including hypertension, dyslipidemia, sleep apnea, heart disease, and T2DM (Pories et al., 1995, Buchwald et al., 2004). There exist a very obvious relationship because obesity and metabolic impairments demonstrated by the fact that approximately 80% of all type 2 diabetics are obese. The percentage of excess weight loss for all patients undergoing some form of bariatric surgery is 61.2% (Buchwald et al., 2004). For RYGB alone, the average weight loss of these surgical patients is approximately 39.7 kg and an excess weight loss percent of 68.2% (Buchwald et al., 2004). Additionally, bariatric surgery has proven to be 76.8% successful in treatment for those individuals suffering from T2DM; RYGB having



an 83.7% success rate versus LAGB, which has a 47.9% success rate (Ferchak & Meneghini, 2004, Buchwald et al., 2004). The more rapid and drastic results associated with the bypass procedures have lead doctors and researchers to believe there is a mechanism associated with the gut that is playing a key role in the pathogenesis of T2DM, and this associated relationship and mechanism are presently unclear. In order to bring about more information on the relationship of the small intestine in T2DM pathogenesis we sought out to investigate the two most common forms on bariatric surgery, the RYGB, which entails bypassing of the small intestine and induces a state of both restriction and malabsorption versus the purely restrictive procedure of the LAGB.

It was hypothesized that T2DM patients undergoing RYGB would see greater improvements in insulin sensitivity one-week post surgery than T2DM patients undergoing LAGB. T2DM patients were studied at one-week post surgery because at this time weight loss is minimal and likely similar between RYGB and LAGB due to strict and regimented post-op diet and medical treatment for one week. Thus, differences in insulin sensitivity would be due to proximal small intestine bypass and not differences in weight loss or food restriction. If other mechanisms, not associated with the proximal small intestine were playing a dominant role in metabolic improvements post surgery we would expect to observe equally effective improvements in glucose tolerance in the banding patients that involves no bypass of the proximal small intestine.

Our group faced several limitations throughout the duration of this clinical study. Among the limitations, the greatest impacting factor was our patient recruitment for the LAGB procedure and thus limited sample size (N=3) compared to the RYGB group (N=9). Interpreting the data comes with caution due to the uneven groups and the particularly small banding patient population. If we revert back to the purpose of this study it was to perform a comparative

analysis in the ability of RYGB and LAGB to increase insulin sensitivity in T2DM patients, however our limited sample size restricts us from making a conclusive and definitive comparison. On the other hand, the data that was collected has proven very promising and confirms the immediate benefits of bariatric surgery on metabolic homeostasis and it can be tied into many recent publications examining this area of research. Among all patients, regardless of surgical procedure, there were non-significant improvements in fasting glucose, fasting insulin, and HOMA-IR one-week post surgery. Furthermore, with insulin sensitivity and insulin secretion there were non-significant improvements among all patients, demonstrating that bariatric surgery is an effective intervention strategy for obese, T2DM Caucasian females. While our hypothesized results were not observed regarding the superiority of the bypass procedure to the banding procedure, this may be due to the limitations experienced by our group. It is important to discuss the limitations of this study, which correspond to the difficulty of running a clinical trial and thus influenced our interpretation of these data.

Subjects were not randomized to the surgical procedures; thus, subjects were not well matched for baseline clinical measures. Physicians need to recommend the most advantageous surgery for their patients based on their diabetic state, and level of obesity. Given the severely obese and diabetic individuals in eastern North Carolina and the greater diabetes resolution with RYGB, RYGB was recommended of potential patients. With that said, the RYGB group demonstrated greater fasting hyperglycemia and higher HbA1c at pre-surgery compared to the LAGB group. Also, patients in the LAGB group appear to have better preservation of AIRg compared to RYGB. These data indicate a more severe state of disease in the RYGB patients and a factor that may influence the post-operation response. In an ideal experimental model we

would have randomly assigned patients to a surgery, however this is not a realistic methodology for a clinical trial.

Due to the complexity associated with a clinical trial involving human subject most of the current research investigating the role of the proximal small intestine in diabetes pathogenesis has employed animal models. For example, Rubino and colleagues (2006) have published several studies over the years using rat models to investigate the pathogenesis of T2DM. Their most recent study attempted to further examine the role of bariatric surgery in diabetes resolution and the popular “foregut hypothesis” which our group was also attempting to elucidate with a comparative analysis. Using the Goto-Kakizaki (GK) type two diabetic rats, Rubino et al., performed on rats either a duodenal-jejunal bypass (DJB), a stomach-preserving RYGB that excludes the proximal intestine, or a gastrojejunostomy (GJ), which creates a shortcut for ingested nutrients without bypassing any intestine. The results reported no difference in food intake, body weight, or nutrient absorption among surgical groups. DJB rats had markedly better oral glucose tolerance tests (OGTT) compared with all control groups, indicating improvements in T2DM directly related to bypassing of the proximal intestine alone. To further confirm the function of proximal small intestine exclusion, rats that had initially undergone the GJ procedure were re-operated on to exclude the proximal intestine; and conversely duodenal passage was restored in rats that had initially undergone DJB. OGTT, food intake, body weight, and intestinal nutrient absorption were measured once again. The rats that had undergone the GJ procedure did not have any changes in glucose homeostasis, but when re-operated on to exclude the duodenal nutrient passage these rats showed significant improvements in glucose tolerance. Conversely, the restoration of the duodenal passage in DJB rats reestablished their impaired glucose tolerance and subsequent diabetic state. This study directly demonstrated the

relationship between bypassing of the proximal small intestine and glycemic control, independent of food intake, body weight, malabsorption, or nutrient delivery to the hindgut (Rubino et al., 2006). In contrast, recent data from our laboratory did not demonstrate an improvement in glycemic control by DJB in GK rats, questioning the effectiveness of duodenal bypass, the GK animal model, or both (Gavin et al. 2010). In the 2010 report from Gavin et al., DJB was performed to reproduce Rubino et al.'s findings in GK rats and then explicitly to investigate the source of improved insulin sensitivity by DJB. In contrast to the results of the study of Rubino et al. (2006), improvement in glucose control, insulin signaling, or muscle glucose disposal following DJB was not observed. Furthermore, human studies employing the DJB surgical procedure observed only modest improvements in glycemic control (Ferzli et al., 2009 and Geloneze et al., 2009), as demonstrated by non-significant improvements in fasting glucose and HbA1c. Thus, while DJB appears to provide some improvements in T2DM, it does not provide the robust improvements in T2DM as RYGB questioning in part the role of the foregut.

More recently, Kashyap and colleagues (2010) at the Cleveland Clinic Foundation in Cleveland, Ohio, published a study investigating the acute effects of RYGB versus gastric restrictive (GR) surgery on glucose metabolism and beta-cell function in obese type two diabetic humans. This study is one of the first published to rigorously evaluate the effects of RYGB on glucose regulation and beta cell function within the first few weeks post surgery. Furthermore, it is one of the first published human studies comparing the acute anti-diabetic effects of RYGB versus a GR procedure and therefore ties strongly into our research. Using the hyperglycemic clamp glucose, insulin secretion and insulin sensitivity were taken pre-, one-week post, and four-weeks post bariatric surgery to examine the relationship between the bypassing of the duodenum

and jejunum in diabetes resolution. In contrast to our study methods with use of the IVGTT minimal model to assess insulin sensitivity, Kashyap et al. (2010) employed the hyperglycemic clamp in which the plasma glucose concentration is acutely raised to 125 mg/dl above basal levels by a continuous infusion of glucose. This hyperglycemic plateau is maintained by adjustment of a variable glucose infusion, based on the rate of insulin secretion and glucose metabolism. Because the plasma glucose concentration is held constant, the glucose infusion rate is used as an index of insulin secretion and glucose metabolism and thus, is often used to assess insulin secretion capacity. In accordance with our results Kashyap et al. (2010) reported that at one-week post surgery both groups experienced similar weight loss and a reduction in their fasting glucose ( $P < 0.01$ ). The RYGB group however showed significant improvements in fasting insulin levels compared to the GR group. The combined decrease in fasting glucose and insulin levels following the RYGB is suggestive of improved insulin sensitivity as demonstrated by the improved HOMA-IR in our study. Kashyap et al. more specifically measured the peripheral uptake and insulin sensitivity via the  $M/I$  ratio, which is a calculation for insulin sensitivity that divides the average glucose infusion ( $M$  value) during the last 40 minutes of the clamp procedure by the average plasma insulin concentration during that same interval ( $M/I$ ). It is a measure of tissue insulin sensitivity to endogenous insulin. Our data demonstrated a trend towards improved insulin sensitivity among all groups as indicated by the minimal model  $S_i$  index value. The  $S_i$  measure (derived from IVGTT data) is a strong indication of peripheral glucose uptake specifically in the skeletal muscle. The minimal model assessment performed by our group is a calculation of glucose concentration under insulin control over the time course and accounting for the effect of insulin and of glucose on glucose disappearance yielding the  $S_i$  parameter ( $\text{min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}$ ). Both measure are an indication of peripheral glucose

disappearance and subsequent insulin sensitivity, however they are determined through different methods. Unlike our group, Kashyap's group saw slight increases in insulin sensitivity (*M/I*) 1-wk post RYGB but not GR. Our group saw a trend towards improvements in insulin sensitivity (*Si*) post bariatric surgery but no significant between group differences were observed. Kashyap et al. (2010) performed a second post-surgical measure at 4 wks post and reported marked differences between groups, with significantly improved insulin sensitivity (*M/I*) in the RYGB group compared to the GR.

Other results from Kashyap et al. contrasting to our data were in regard to insulin secretion, in particularly the AIRg. There was a modest increase in AIRg after GR surgery even with unchanged insulin sensitivity. Our LAGB (restrictive only procedure) group saw slight decreases in AIRg and a trend towards improved insulin sensitivity. On the other hand, our results present slight increases in AIRg for the RYGB patients, while Kashyap et al. reported slight reductions. Kashyap et al. attributed this change along with the reduced fasting insulin levels to the rapid restoration of beta cell function and the increase in insulin sensitivity. Our study assessed insulin secretion through the acute insulin response to glucose and saw a promising trend for greater improvements in insulin secretion, however Kashyap directly measured the beta cell function and saw marked improvements in insulin secretion in RYGB compared to GR. Both our study and Kashyap et al. (2010) reported similar weight loss after the restrictive surgical procedures (LAGB and GR) however, they did not result in this same outcome, which again makes one question the role of the bypassing of the small intestine.

Further investigation comparing these surgical procedures with similar methodologies is warranted due to the conflicting results discussed above. According to the study, these researchers considered the 4 wk time point to still be an acute measurement point, where we only

examined at 1 wk post surgery. It is also important to mention that similar to our subject population, there was distinct differences in disease severity between groups, with the RYGB group being more insulin resistant state pre-surgery. This study further supports our research purpose to investigate the role of the proximal small intestine in diabetes resolution and demonstrates the acute effects of bariatric surgery on insulin sensitivity without significant weight loss effects or prolonged caloric restriction. A significant between groups difference was not observed until 4 wk post-surgery, which one could argue that post-op care is less controlled for. These results lead us to question if a larger sample size and potentially longer trial (more measurement time points) our trends may have evolved to an interaction, but again, this is difficult to determine with the limitations faced by our group. Replication of this study would be a potential future project.

### *Future Research*

Initially researchers attributed the anti-diabetic effects of bariatric surgery to caloric restriction and subsequent weight loss associated with the caloric deficit; however, the acute and rapid improvements in metabolic homeostasis occur within one week of surgery before substantial excess weight loss has occurred (Buchwald et al. 2004, Rubino et al., 2006, Kashyap et al. 2010). Furthermore, if caloric restriction plays a major role in mediating changes in glucose homeostasis postoperatively then a universal rate of T2DM remission would be expected across all types of bariatric surgery. The rapid and durable success rate of the RYGB over the restrictive only procedures (Buchwald et al., 2004, Rubino et al., 2006, Kashyap et al., 2010) indicate that there is something unique happening in accordance with the bypassing of the proximal small intestine. Some of the most current theoretical mechanisms attribute these acute

and chronically sustained changes to the circulating gut hormone concentrations provoked by surgery (Karra et al., 2010). Future research is needed to distinguish the exact mechanism associated with the benefits of bariatric surgery and more specifically the role of the proximal small intestine. While our study was simply a comparative one, it did not examine the mechanism component; however it would be of great value to investigate the incretin activities in response to various bariatric surgical procedures in hopes of discovering new non-surgical treatment strategies for obesity and T2DM.

### *Conclusion*

Even though the sample size was small for the LAGB group, and thus a major limiting factor in the interpretation of our results and their context, the current data supports the clinical importance of bariatric surgery to patients suffering from obesity, T2DM and the closely associated state of insulin resistance. All patients who received bariatric surgery experienced non-significant improvements in their insulin sensitivity, and a trend suggestive of greater improvements in insulin secretion post RYGB was observed. From a clinical perspective this is valuable in the treatment and remission of the disease for patients. T2DM is a disabling and deleterious disease that progressively worsens with time and bariatric surgery has proven to be the only intervention to incur rapid and drastic improvements in one's metabolic state (Pories et al., 1995, Buchwald et al., 2004, Rubino et al., 2006). Our data further supports the use of bariatric surgery as an intervention for T2DM, and furthermore demonstrate the rapid and acute improvements associated with bariatric surgery. Recruitment and analysis of a complete sample of LAGB patients may bring about a more definitive conclusion on the role of the proximal small intestine in diabetes resolution.



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APPENDIX: INSTITUTIONAL REVIEW BOARD APPROVAL DOCUMENT



EAST CAROLINA UNIVERSITY

University & Medical Center Institutional Review Board Office  
1L-09 Brody Medical Sciences Building • 600 Moye Boulevard • Greenville, NC 27834  
Office 252-744-2914 • Fax 252-744-2284 • www.ecu.edu/irb

TO: Walter Pories, MD, ECU, BSOM, Department of Surgery, PCMH TA-240, Mailstop 639  
FROM: UMCIRB *KWB*  
DATE: April 26, 2011  
RE: Full Committee Approval for Continuing Review of a Research Study Requiring Modifications  
TITLE: Metabolics of RYGB (Roux-en-Y-Gastric Bypass) with Gastrostomy

**UMCIRB #09-0002**

The above referenced research study was initially reviewed by the convened University and Medical Center Institutional Review Board (UMCIRB) on **03/25/2009**. The research study underwent a subsequent continuing review for approval on **03/09/2011** and **04/13/2011** by the convened UMCIRB. Requested modifications were prescribed and received final approval on **04/25/2011** by expedited review. The UMCIRB deemed this **Ethicon Endo-Surgery** sponsored study **more than minimal risk** requiring a continuing review in **12 months**. Changes to this approved research may not be initiated without UMCIRB review except when necessary to eliminate an apparent immediate hazard to the participant. All unanticipated problems involving risks to participants and others must be promptly reported to the UMCIRB. The investigator must submit a continuing review/closure application to the UMCIRB prior to the date of study expiration. The investigator must adhere to all reporting requirements for this study.

The above referenced research study has been given approval for the period of **04/13/2011** to **04/12/2012**. The approval includes the following items:

- Continuing Review Processing Form – revised (dated 04/20/2011)
- Protocol – revised (dated 04/20/2011)
- Informed consent – revised (version 9 dated 04/20/2011)

**\*Reminder: The committee unanimously voted to require re-consent of all participants.**

The following UMCIRB members were recused for reasons of potential for Conflict of Interest on this research study:  
**None**

NOTE: The following UMCIRB members with a potential Conflict of Interest did not attend this IRB meeting:  
**None**

**The UMCIRB applies 45 CFR 46, Subparts A-D, to all research reviewed by the UMCIRB regardless of the funding source. 21 CFR 50 and 21 CFR 56 are applied to all research studies under the Food and Drug Administration regulation. The UMCIRB follows applicable International Conference on Harmonisation Good Clinical Practice guidelines.**



