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# Understanding the Effects of Roux-en-Y Gastric Bypass (RYGB) Surgery on *Type 2* Diabetes Mellitus

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## 1. Introduction

Obesity is a grave public health concern in the United States today. From 2007 to 2008, the prevalence of obesity was over one-third of the U.S. adult population [1]. It contributes to significant morbidity and mortality including heart disease, stroke, cancer, arthritis and sleep apnea. *Type 2* diabetes mellitus (T2DM) also has been shown to increase with increasing obesity. Findings from the National Health and Nutrition Examination Survey (NHANES) (1999 – 2006) showed that nearly half of individuals with a body mass index greater than 40 kg/m$^2$ have diabetes [2]. Results from various studies have shown that weight reduction significantly reduces the risk of developing T2DM in obese individuals [3], as well as improving glycemic control in those already with T2DM [4,5].

Long term medical therapy for obesity is often unsuccessful for the majority of patients in clinical practice. Bariatric weight loss surgery has remained the most effective means of achieving and maintaining weight loss. More significantly, it has been shown to decrease mortality [6]. The Roux-en-Y gastric bypass (RYGB) is a type of bariatric surgery that involves the creation of a smaller stomach with a connection to the middle portion of the small intestine, bypassing the duodenum and a portion of the jejunum (see figure 1). Two limbs are created after the surgery. One limb, referred to as the alimentary or *Roux limb*, is where nutrient boluses pass from the stomach pouch. The other limb, which is the bypassed portion of the gastrointestinal tract, is known as the biliopancreatic limb. This limb transports secretions from the pancreas, liver, and gastric remnant. Most remarkably, many obese *diabetic* patients who undergo RYGB are relieved of their anti-diabetic medications in a matter of days. This improvement in glycemic control occurs before any significant weight loss [7].
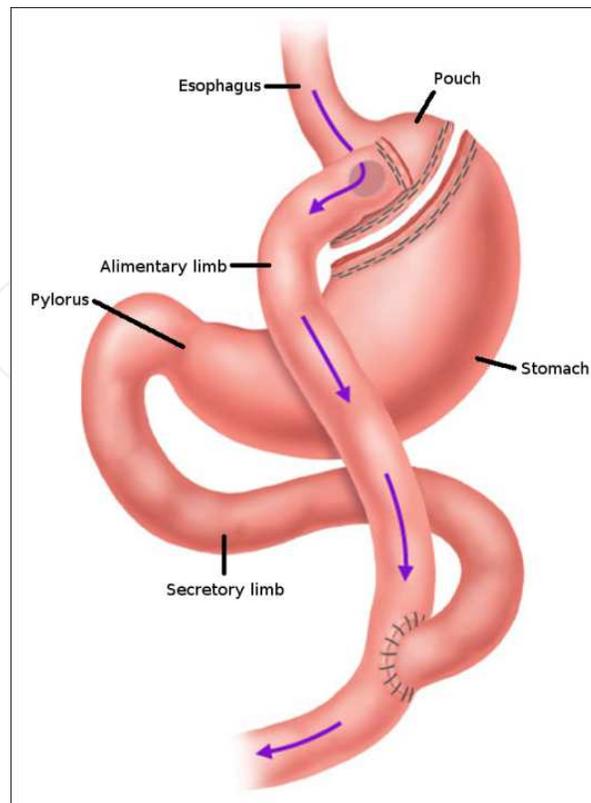
Dirksen C, Jorgensen NB, Bojsen-Moller KN et al. Mechanisms of improved glycemic control after Roux-en-Y Gastric Bypass. *Diabetologia. 2012*;55:1890-1901.

**Figure 1.** Roux-en-Y Gastric Bypass (RYGB)

This dramatic effect of gastric bypass on T2DM is not well understood. Improvement or remission of T2DM was thought to be due to weight loss in obese subjects [3, 5]. This was further supported by studies with gastric banding, a form of enforced caloric restriction [8]. However, clinicians began to observe that glucose levels were significantly lower in RYGB subjects as compared to weight matched controls [7]. Although malabsorption also likely contributes to the improved dysglycemia, there are other hormonal changes that are likely contributing to this effect. The most significant hormone changes occur in the secretion patterns of gut hormones. These are hormones that are secreted by enteroendocrine cells from the stomach, pancreas, and small intestine. A unique but significant post-prandial elevation of gut hormones is observed after RYGB. This is a well accepted phenomenon seen with RYGB subjects, and is believed to contribute significantly to this improvement of hyperglycemia in diabetics.

To better understand how RYGB affects those with *T2DM*, we will review the changes that occur with RYGB in key glucoregulatory organ systems within the body. In the ensuing sections, we will discuss in detail, the changes of *peripheral insulin sensitivity* and *insulin secretion* brought on by gastric bypass, and their effects on hyperglycemia. Identifying these changes will permit us to better understand how RYGB improves diabetes. We will also discuss the role that *caloric restriction* and *gut hormone elevation* may have in this process. Figure 2

demonstrates glucoregulatory variables that RYGB appears to modify. Cumulatively, this will permit the reader to develop an understanding of the relationship of how RYGB affects diabetes. We will begin our discussion describing the clinical potency of RYGB on T2DM.
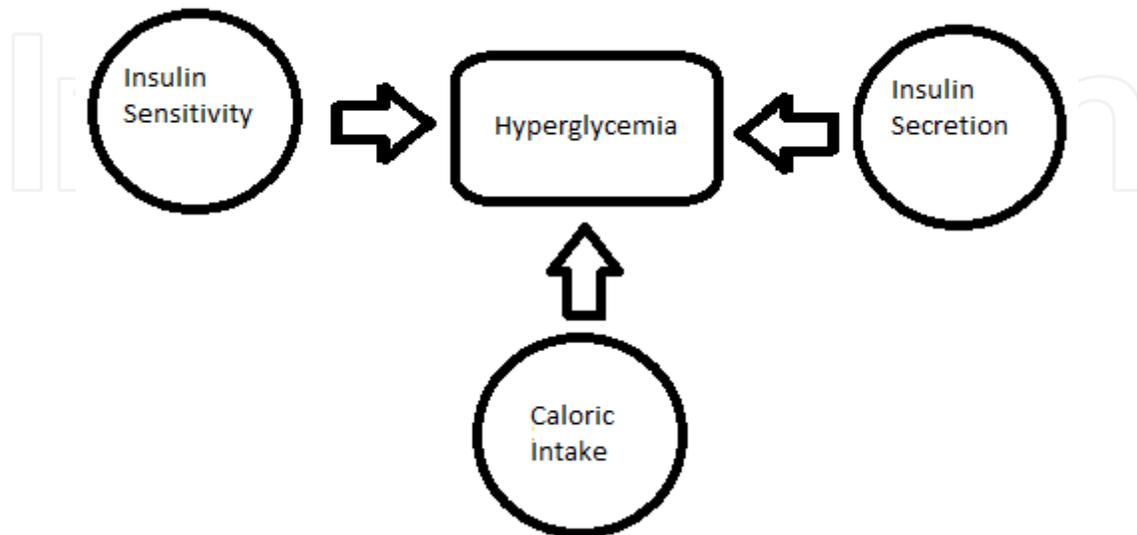


**Figure 2.** Glucoregulatory Variables

## 2. Problem statement: What is the effect of roux-en-Y gastric bypass on type 2 diabetes mellitus?

### 2.1. Roux-en-Y Gastric Bypass (RYGB) and its weight independent effect on T2DM

Since the early portion of the 21$^{st}$ century, there has been a growing interest in bariatric surgeries and their effect on ameliorating the diabetic state. Pories et al was arguably the first to describe remission of diabetes following gastric bypass. He reported gastric bypass not only caused weight loss, it also led to normalization of blood sugars in over 80% of his diabetic patients [9]. Initially, the normalization of blood sugars was thought to be directly caused by the weight loss. However, it has subsequently been noted that blood glucose control improves immediately following the surgery, prior to any significant weight loss. The concept that weight loss alone was not the reason for diabetes improvement after RYGB was a paradigm shift in the world of weight loss surgery, as well as the world of diabetes. This led to an explosion of research that attempts to understand how the surgery works.

There were few to no trials evaluating the efficacy of surgical treatment of obesity until the creation of the Swedish Obesity Study (SOS). The SOS trial is one of the largest prospective data collections to date that studies the clinical effects of various types of bariatric surgery. The SOS data demonstrates durable weight loss by as much 25% reduction at 10 years with various surgery types. The greatest weight loss is observed with RYGB [6] as compared to gastric
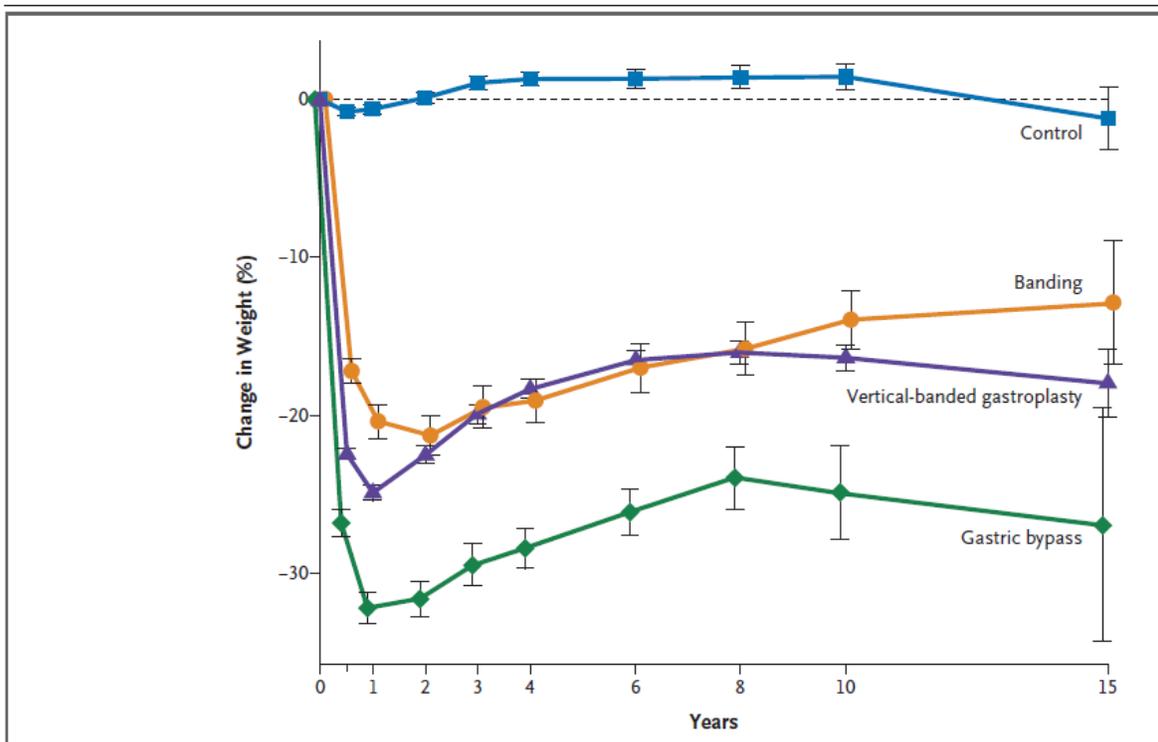
**Figure 3.** Weight loss over 15 years between control groups (blue), gastric banding (orange), vertical banded gastroplasty (purple), and gastric bypass (green).

banding, and a modified restrictive surgery known as vertical banded gastroplasty, (see figure 3). Since SOS, additional studies of obese subjects that have undergone RYGB have verified that weight loss from the surgery is durable and long lasting [10, 11].

While durability of the surgery continues to be validated in ongoing trials, its weight independent effect on diabetes was initially uncertain during the infancy of bariatric surgery. This uncertainty was at least partially due to the absence of appropriate "control groups" in various studies. For instance, the SOS data demonstrated reduced incidence of diabetes in surgically treated groups, but this was compared to non-standardized medically treated groups [12]. Medical weight loss therapy can be difficult to implement effectively, and therefore, comparison to surgical subjects is often imbalanced. This begs the question that if we can implement a medical treatment that *is as effective at achieving weight loss as gastric bypass, would we see similar improvements in diabetes?* Are there available studies that compare effective calorie restriction versus RYGB in terms of diabetes improvement? There are published studies using strict low calorie diets as a comparator group [13-15]. One such study by Plum et al demonstrated greater improvement in diabetes in RYGB subjects when compared to low calorie diets over three months [13]. Both groups had similar amounts of weight loss, suggestive that RYGB has weight independent effects on diabetes.

The surgical obesity procedure known as the gastric band may be perceived as a superior "control group" to dietary weight loss. The gastric band is an anatomically enforced form of caloric restriction and can be difficult to "cheat." Diabetes remission in subjects who had the gastric band has been shown to be directly related to weight loss, and was superior to conventional therapy programs [8]. However, prospective longitudinal studies comparing RYGB to gastric banding have demonstrated that RYGB promotes greater insulin sensitivity along with superior weight loss at one year [16]. Additional other types of studies have validated the potency of RYGB on diabetes through the use of other controls. One such study by Adams et al [17] was a large retrospective study of several thousand, comparing RYGB subjects to weight matched controls. This study demonstrated a remarkable 92% reduction in diabetes. Despite the overall lack of prospectively randomized control trials, there has been compelling data to demonstrate RYGB effectively treats hyperglycemia and the diabetic state.

Only in 2012 were the first prospectively, randomized, non blinded controlled studies made available, comparing weight loss surgery to medical weight loss therapy. Schauer et al [18] compared the RYGB and gastric sleeve surgical procedures to medical therapy in the STAMPEDE study (Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently). Mingrone et al [19] compared RYGB and biliopancreatic diversion (BPD) procedures to medical therapy. The two studies had similar findings of greater "normalization" of glucose levels in the surgical patients as compared to medical therapy. However, there was still greater weight loss in the surgical groups, contributing to the greater glycemic improvement. Schauer et al [18] further demonstrated that the post-operative weight loss appeared to have no correlation with glucose control. This further highlights that RYGB has weight-independent effects on glucose control.

Both of the above discussed studies use *diabetes remission* as their endpoint. Before discussing the antidiabetic mechanisms behind RYGB, a further discussion of the meaning of *diabetes remission* will be explored. A seemingly simple concept, we wish to elaborate on the meaning of "diabetes remission," as well as discuss the associated complexities.

## 3. Application area: Can roux-en-Y gastric bypass be used to treat type 2 diabetes mellitus?

### 3.1. Roux-en-Y gastric bypass and remission of type 2 diabetes mellitus

Many subjects who undergo RYGB surgery and have T2DM observe a rapid normalization of their glucose levels, leading them to believe they have been "cured" of their diabetes. While these authors feel the term "cure" is incorrect, we cannot deny, and in fact pleasantly enjoy, watching the marked improvement in hyperglycemia following surgery. We agree that instead, the term *diabetes remission* should be used for these patients. Buse et al had [20] recently defined *prolonged diabetes remission* as hyperglycemia that is below the diagnostic threshold for diabetes for at least five years, while on no active pharmacologic therapy for diabetes. The increasing number of *diabetes remissions* after RYGB surgery has caused practitioners to revisit the definition.

Mingrone and Schauer's studies included similar definitions of *diabetes remission* in their trials, although their studies were less than five years in duration. Using diabetes remission as an endpoint acknowledges the potency of RYGB. But many questions come to mind amongst practitioners who manage diabetes. How does the surgery mediate such a potent effect? Should a reduced hemoglobin A1c be adequate for remission? Are the diabetic microvascular complications also reversed and should practitioners stop following these patients if they do go into remission? If there is complete reversal, why not use the term "cure?" Most important, has the characteristic pancreatic beta cell dysfunction reversed itself? These are questions proposed by these authors, some of which will be addressed in later sections.

Despite these questions, it is very hard to ignore the potent clinical effect the surgery has on diabetes. For those physicians and health care practitioners who struggle with uncontrolled diabetic patients, it is a seemingly effective and attractive solution. The metabolic potency of RYGB has even been addressed by the International Diabetes Federation (IDF) in a statement published in 2011 [21]. They discussed that bariatric surgery should be considered an option in those with a body mass index greater than 35 kg/m$^2$ and have T2DM. While a compelling argument can be made for this, we caution practitioners that not all RYGB subjects experience diabetes remission.

There are a small, but significant number of patients that have T2DM and undergo RYGB, but remain hyperglycemic post-operatively. In a retrospective review by DiGiorgi et al [22], as much as 24% of T2DM who had undergone RYGB had recurrence of their diabetes over a three year period, while a longer five year study demonstrated 31% recurrence [23]. Diabetes recurrence has also been seen as early three months following surgery [24]. These various studies demonstrated a number of factors that may contribute to recurrence. Higher BMI's, age, prior use of antidiabetic medications, and male gender were identified as factors associated with diabetes recurrence [23, 24]. A similar study in Chinese subjects demonstrated that diabetes duration, BMI, and fasting C-peptide were predictors for diabetes remission at one year. Based on this study by Dixon et al [25], suggestions of C-peptide above 2.9 ng/mL was a positive predictor for diabetes remission, which also implies residual good beta cell function within the diabetic group. These investigators were the first to suggest predictors and possible cutoffs in assessing the glycemic responses to RYGB.

Determining how to use RYGB in diabetes management is still in the early stages of development. Traditionally, this surgery was perceived only as a weight loss procedure. However, this has been an evolving paradigm within recent years. BMI alone is no longer the sole criteria for surgery in mildly obese subjects. Since 1991, the National Institutes of Health used both BMI and the presence of obesity-related comorbidities as the criteria for surgical weight loss. Even recent international guidelines still do not stray from these recommendations [26]. In the past, most studies looking at the effects of RYGB on diabetes have primarily focused on significantly obese subjects (BMI >35 kg/m$^2$), although this is now changing. We have already pointed out that post-operative weight loss does not always seem to correlate with glycemic control [18]. A recent study by Cohen et al [27] examined people who had a lower BMI (30-35 kg/m$^2$) and underwent bariatric surgery. They also demonstrated similar diabetes remission rates of 90%. Seeing such high rates of diabetes remission in a lower BMI range reinforces the

concept of weight-independent effects of surgery on diabetes. As most obese individuals fall within this BMI range, clinicians may even consider recommending surgery at an earlier BMI.

Increasing evidence shows that BMI alone is not an adequate measure to predict successful health outcomes after RYGB. This is true for obese diabetics as well. We have mentioned that assessing for adequate beta cell function [25] could be used as criteria for successful diabetes remission. Additional evidence has suggested that those who have most benefited from surgery have elevated insulin levels, or insulin resistance [28, 29]. The simultaneous improved cardiovascular effects observed from the surgery [28] may also highlight the intrinsic relationship between insulin resistance and cardiovascular disease, often referred to as the metabolic syndrome. *As clinicians and scientists, it is critical for us to evaluate the effects of RYGB surgery beyond simple weight loss.* This may begin to help us stratify who best may benefit from the surgery. In the remaining portion of this chapter we will characterize the basic driving forces for T2DM and how the surgery brings about an improved glucose effect. This specifically will include *insulin sensitivity* and *insulin secretion*.

## 4. Observations and research: How does roux-en-Y gastric bypass improve Type 2 diabetes mellitus?

### 4.1. Effects of gastric bypass surgery on insulin resistance

Insulin action has a key role in regulating glucose homeostasis, facilitating glucose uptake in various tissue types. Its inability to cause glucose uptake is believed to be a key step in the pathogenesis of T2DM. This phenomenon is defined as insulin resistance. What mediates insulin resistance continues to be an active area of research. Glucose transport is maintained primarily through insulin-regulated glucose transporters, such as GLUT4. Commonly proposed theories that may mediate insulin resistance include impaired insulin signaling defects, GLUT transporter dysfunction, as well as increased availability of circulating free fatty acids. Both environmental and molecular factors may contribute to the development of insulin resistance. Obesity, as an environmental source, is believed to be a very common contributor.

Insulin resistance has been significantly observed at the level of the liver, skeletal muscle, adipose tissue, and pancreas. But it is skeletal muscle and adipose tissue that account for over 80% of total body glucose uptake. Because the reversal of diabetes immediately following gastric bypass is so profound, an alteration of peripheral tissue insulin sensitivity was thought to be the mechanism for achieving normoglycemia. With RYGB having superior weight loss, it has been well accepted that improved insulin sensitivity in surgical patients is also superior. However, the timing of when peripheral insulin sensitivity improves has been an area of uncertainty. Answering when peripheral insulin sensitivity begins after RYGB will also help to elucidate if it is a weight independent event.

The most frequently used measure of insulin resistance is the Homeostasis Model Assessment Insulin-Resistance (HOMA-IR). The ease of obtaining measurable glucose parameters have made this a popular method for quantifying insulin sensitivity. Several sources cite RYGB

improves HOMA-IR from four days to two weeks following surgery in diabetic and non-diabetic subjects [30-31]. This is often before marked weight loss has taken place. In a non-weight controlled study, HOMA-IR was also decreased at three days following surgery [32]. However, these same sources demonstrate that HOMA-IR in RYGB subjects has comparable improvement to that of diet controlled subjects at similar time intervals while on calorie restriction [30-31]. Interestingly, there was minimal weight loss between the two study groups. *These findings are suggestive that immediate changes in HOMA-IR following RYGB are possibly related to caloric restriction alone.*

Besides HOMA-IR, there are other standard techniques for measuring insulin sensitivity. The gold standard remains the hyperinsulinemic euglycemic clamp. While most accurate in assessment of glucose uptake of *in vivo* systems, it requires experienced and skilled personnel often not readily available. The small body of literature that uses clamp data in gastric bypass subjects supports that insulin sensitivity in the post-operative period correlates with weight loss [31, 33], and therefore, is not a weight independent event in both diabetics and non-diabetics. Only Kashyap et al [34] demonstrated a slight increase of insulin sensitivity using clamp studies at one week following surgery for subjects that underwent gastric bypass as compared to gastric banding. However, as with all control groups, it is unclear if the oral intake of gastric band subjects was equivalent to the RYGB study group. Further molecular studies in rodent models that have undergone RYGB support the notion that insulin sensitivity is weight dependent. GLUT4 mRNA expression in skeletal muscle and adipose tissue of rodents that have undergone RYGB, does not increase until 28 days after surgery [35]. Therefore, the presence of adiposity reinforces the presence of insulin resistance. Because insulin clamp studies are the gold standard in assessment of peripheral insulin sensitivity, the *rapid glycemic improvement seen immediately following surgery appears not due to increased peripheral glucose uptake.*

Why there is this discordant finding between HOMA-IR measures and insulin clamp studies is unclear. Although HOMA-IR is an index of insulin sensitivity, it may also be used as a surrogate for hepatic insulin sensitivity. Therefore, one may observe there are more rapid improvements of hepatic insulin sensitivity than that seen with peripheral insulin sensitivity. However, there are only very few studies that intimately compare the two indices. HOMA-IR and peripheral insulin sensitivity were assessed through clamp studies, with individuals undergoing RYGB one month following surgery by Lima et al [36]. They demonstrated that there was no improvement of peripheral insulin resistance despite weight loss, although HOMA-IR did improve. Dunn et al used more dynamic and definitive methods for assessing hepatic insulin resistance using hyperinsulinemic euglycemic clamp studies with isotropic tracers, while also collecting data to asses for peripheral insulin resistance. They also demonstrated that there was also improvement in hepatic insulin sensitivity as compared to no improvement of peripheral insulin sensitivity at one month [37]. The reason for this requires further research.

Although RYGB and insulin secretion will be discussed in a later section, there are few studies that have measured hepatic glucose output in subjects that have undergone RYGB. Dunn et al [37] demonstrated decreased hepatic glucose production using clamp studies as described earlier. However, there was no appropriate dietary control group in this study. Contrary to

these findings, Camastra et al [33] showed no improvement of endogenous glucose production one week following surgery against BMI matched controls. Because of these discrepant findings, the precise characterization of how RYGB affects hepatic glucose output also requires additional studies.

The clinical observation amongst practitioners in bariatric surgery is that in the immediate post-operative period after gastric bypass there is a rapid decrease of fasting glucose levels. However, dietary caloric restriction alone has been shown to decrease hepatic glucose output without affecting whole body glucose disposal [38-39]. People who undergo RYGB often have a post-operative decrease in appetite, anatomically imposed caloric restriction, and healing gastrointestinal anastomoses that require smaller nutrient boluses to allow for healing. In caloric restriction, the improvement of the endogenous glucose production (EGP) appears to be due to reduced glycogenolysis [40]. This finding is consistent with a study by Isbell et al [30] demonstrating comparable liver improvements (HOMA-IR) between RYGB subjects and calorie restricted subjects. Therefore, the rapid *alterations in hepatic metabolism seen immediately following gastric bypass may be from calorie reduction alone and not alterations brought on by the surgery itself.*

Further molecular studies have supported the notion that RYGB does not induce a weight independent effect on peripheral insulin sensitivity. Time-dependent GLUT4 expression in skeletal and adipose cells in rodents after RYGB and weight loss was discussed earlier [35]. Intramuscular lipid content has also been noted to decrease one year following surgery by as much as 44%, which also contributes to enhanced insulin action [41]. These observations alone suggest why peripheral insulin sensitivity is delayed and appears to be affected only by the presence of adiposity. Alteration in gut hormone levels have been strongly implicated as a cause for the metabolic improvement seen in RYGB subjects, but has not clearly been associated with the changes in altered insulin sensitivity. Glucagon-like peptide-1 (GLP-1) has been the most well studied of these gut hormones. The effect of GLP-1 on peripheral tissue has demonstrated some effect on glucose uptake in adipocytes and skeletal muscle cells [42-43]. However, the authors feel the effect of GLP-1 has more clinically significant effects on pancreatic function. The role of GLP-1 is discussed further in the section "*Identifying anti-diabetic factors of gastric bypass.*"

It is of interest that RYGB and other weight loss surgeries have differential effects on insulin sensitivity and insulin secretion. The biliopancreatic diversion (BPD), a more malabsorptive surgery with a more extensive bypass, is often reserved for the super-obese population. However, this surgery been suggested to improve glycemia through normalization of insulin sensitivity [44]. This contrasts to RYGB, which we have discussed here, in that it does not appear to rely on insulin sensitivity for rapid improvement of hyperglycemia. We have demonstrated here that peripheral insulin sensitivity improves as a function of weight loss, independent of RYGB, whereas hepatic insulin sensitivity improves as a function of caloric restriction. Neural based mechanisms have also been implied as contributors to the glycemic improvement, although much is still not understood. This will be further discussed later in "*Other contributing factors to the anti-diabetic effect of RYGB.*" We now will discuss how RYGB may affect pancreatic beta cell function, an essential hormonal regulator of glucose control.

### 4.2. Effects of gastric bypass surgery on pancreatic function

T2DM is characterized by both peripheral insulin resistance, as well as pancreatic beta cell dysfunction. For this reason, understanding how RYGB affects the pancreas may allow us to better understand why diabetes improves after the surgery. The majority of available studies involve dynamic biochemical measurements involving nutrient challenges. The impetus for study of these nutrient challenges, such as mixed meal testing, is based on the link between RYGB and postprandial gut hormone hypersecretion [45]. Exaggerated gut hormone secretion appears to occur because of the altered transit of nutrient boluses caused by the gastric bypass, and is a well accepted phenomenon. Several gut hormones have been suggested to also alter insulin secretion, and are termed "incretins." The *incretin* effect relates to the ability of an oral glucose load to result in an enhanced insulin response as compared to a similar intraveous glucose load. The distal gut hormone GLP-1 has been shown to be primarily responsible for mediating this effect, although other possible contributing anti-diabetic factors have yet to be characterized. There have been surprisingly few studies that have addressed the impact of RYGB on the release of insulin secretion and its relation to other gut hormones. We will first characterize the pancreatic secretory alterations brought on by the surgery, and then further explain associated hormonal and pancreatic cellular changes.
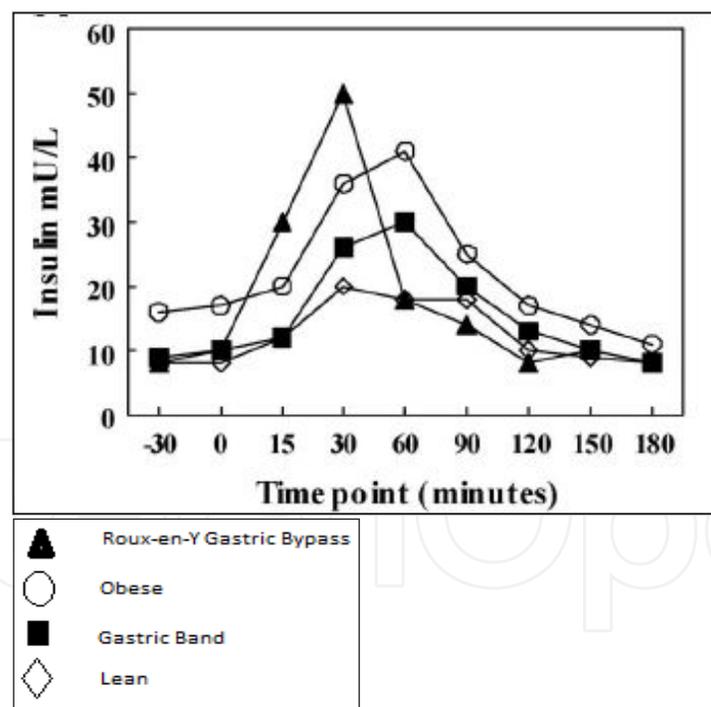


Le Roux CW, Aylwin SJ, Batterham RL et al. Gut Hormone Profiles following bariatric surgery favor an anorectic state, facilitate weight loss, and improve metabolic parameters. *Ann Surg.* 2006;243(1):108-14.

**Figure 4.** Roux-en-Y Gastric Bypass Insulin levels in Response to a Test Meal Le Roux C et al

Review of the descriptive studies of insulin secretion following RYGB suggest that fasting insulin levels appear to decrease within one week following RYGB in both diabetics and non-

diabetics [32-34], which may be more of a function of improved hepatic insulin sensitivity. The majority of studies also demonstrate *a postprandial rise of insulin concentration that has a higher and earlier peak than seen pre-operatively* [32-34, 46-48]. While this suggests a possible restoration of the first phase of insulin secretion, this remains unclear. It also does not explain the exaggerated postprandial peak of insulin. The insulin peak also does not appear to be as marked as the postprandial GLP-1 elevations. The insulin peak is typically followed by a rapid decrease of insulin and glucose levels following the peak. This rapid decrease in levels is also not well explained. However, the insulin area under the curve (AUC), based on these prior studies, is either unchanged or decreased as compared to pre-operative measurements. Figure 4 demonstrates an example of post-prandial insulin levels in subjects that underwent gastric band and RYGB, as compared to control obese and lean subjects. The control obese subjects were matched to the pre-operative BMI of the surgical patients, and the subjects that underwent either operation had an equivalent post-operative BMI. Here, RYGB subjects exhibit the largest post-prandial insulin peak as compared to the gastric band and the remaining non-surgical subjects. Obese subjects likely have elevated insulin levels due to insulin resistance.

Decreased insulin levels following RYGB was generally believed to be the case with the perceived notion that insulin sensitivity was improved. However, as mounting evidence shows that peripheral insulin sensitivity is not immediately improved, these alterations in insulin secretion may hold more significance. Potential changes in alpha cell secretion of glucagon was then investigated to see if that had a possible role in these glycemic changes, namely if levels were decreased. However, they also had unexpected post-prandial elevations [48]. Why hyperglucagonemia would be present during the glycemic improvement seen after RYGB is unclear, and needs further studies to validate these findings.

Based on the postprandial insulin concentration profile demonstrated in figure 4, the glycemic effects do not clearly show why there would be an improvement of hyperglycemia. Available studies do not demonstrate consistently how postprandial glucose levels behave in response to these insulin secretory changes. Some have demonstrated significantly elevated postprandial glucose levels with a subsequent decrease [32], while others mostly show the postprandial decrease [8]. Inconsistency may have to do with varying nutritional content of test meals and timing after the surgery. Using other methods in assessment of glycemic changes with RYGB, continuous glucose monitoring (CGM) has revealed unusual patterns. In a group of RYGB subjects, CGM revealed increased glycemic variability using a calculation parameter known as "mean amplitude of glycemic excursions" (MAGE) [49]. The *increased glucose variability* may reflect an *altered postprandial insulin profile* that has been observed following RYGB, although this variability has only been identified in those afflicted with the condition known as *post-gastric bypass hypoglycemia* (*see Anti-diabetic effect gone too far? Postgastric bypass hypoglycemia* for further discussion). Studies into those RYGB patients without symptoms or documented hypoglycemia are ongoing. It is possible glycemic variability is a precursor to the metabolic complication *post-gastric bypass hypoglycemia*. Our laboratory is involved in trials studying this effect.

There are a greater number of studies examining the changes of insulin resistance in those that undergo RYGB and caloric restriction. There are far fewer studies comparing these two groups

and assessing for differences in beta cell function. One study by Hofso D et al [50] compared RYGB to "intensive lifestyle intervention" as the nearest appropriate control. However, as expected, RYGB achieved superior weight loss, with significantly improved beta cell function. There are no available or appropriate weight matched trials to compare diet to RYGB on beta cell function.

The anatomic and histologic changes brought on by RYGB on the pancreas are also not well studied, due to the inability to easily access pancreatic tissue. The body of literature of known histologic or molecular changes within the pancreas that have been observed are restricted to rodent models, or those afflicted with post-gastric bypass hypoglycemia. One may expect hyperinsulinemia, especially in the setting of a marked peak in the postprandial insulin level. However, if the AUC of postprandial insulin levels are unchanged from prior to surgery, it is difficult to assess what cellular changes would occur if the same quantity of insulin was made by the beta cell. In rodents that have undergone RYGB, there has been a demonstrated increase in pancreatic beta cell area [51], less beta cell apoptosis [52], and increased beta cell proliferation [53]. This suggests that RYGB surgery enhances insulin secretion and insulin activity. However, as with all studies, appropriate controls are needed.

Much may also be learned of how RYGB affects the pancreas by the associated complication known as post-gastric bypass hypoglycemia (*reviewed further in"Antidiabetic effect gone too far? Post gastric bypass hypoglycemia*). Meier et al [54] demonstrated in human subjects who are afflicted with hyperinsulinemic post-gastric bypass hypoglycemia, the pancreatic beta cell area was not increased as compared to obese or even lean control subjects. They did demonstrate increased beta cell nuclear diameter in those afflicted with post-gastric bypass hypoglycemia compared to BMI-matched controls, suggestive of altered insulin production and secretion. One may therefore hypothesize that the decreased weight in response to the elevated insulin levels in RYGB subjects may be the responsible factor that improves glycemic control.

Despite these studies, further characterization is needed to understand how the pancreas responds to RYGB in T2DM independent of weight loss. Beta cell dysfunction is considered a hallmark of T2DM, often with hyperinsulinemia and gradual insulinopenia. This prompts the question of whether RYGB induces a reversal of these states. The altered post-prandial insulin profile seen after RYGB suggests beta cell function has only been altered, and not necessarily restored to appropriate physiologic function.

### 4.3. Identifying anti-diabetic factors of gastric bypass

Alterations of insulin secretion itself is a contributing factor that ameliorates the diabetic state in RYGB. Other contributing anti-diabetic factors brought on by RYGB are still being identified. Several investigators have proposed various intestinal mediators that may induce euglycemia, none of which have fully explained the clinical potency of RYGB.

Earlier studies suggested that exclusion of the proximal gut was responsible for the improvement of hyperglycemia, implying a potential "diabetogenic factor." Rubino et al [55] was the first to support this concept, by performing a duodenal-jejunal exclusion in diabetic rodents

known as Goto-Kakizaki rodents. This was a surgery that led to preservation of gastric volume, with a pure exclusion of proximal intestinal absorptive surfaces. The initial excitement of his findings surrounded the premise that there was greater glycemic control as compared to calorie restricted rodents, simply by removing a portion of the intestine without creating caloric restriction. Born from this procedure was the concept of the "*foregut theory*." From this, it was perceived that there was a "diabetogenic factor" in this region of the intestine. However, this concept was later challenged by the "*hindgut theory*."

The "*hindgut theory*," perhaps more popular, operated on the premise that there were factors in the distal intestine that became elevated and had potent anti-diabetogenic effects. It is the author's opinion that this is the more likely theory. Further support for this are studies performed with feeding tubes placed in the gastric remnant of the intestine following RYGB. Hansen et al [56] demonstrated that using gastric feeding tubes led to increased gut hormones, as well as via oral (jejunal) routes. The similar alterations in insulin sensitivity between the two nutrient routes suggest the exclusion of nutrients from the foregut is not significant. Instead, distal gut factors such as GLP-1 may more likely be the cause.

GLP-1 physiology will not be covered here in depth. Its anti-diabetic effect in gastric bypass has been demonstrated in rodent models that underwent RYGB [57]. Research into GLP-1 led to drug development of GLP-1 receptor agonists. These agents are now in clinical use for the treatment of hyperglycemia. Its usage operates on the premise of augmenting beta cell function. Use of GLP-1 agonists or GLP-1 continuous infusions increased basal insulin secretion, often leading to an improved second phase of insulin secretion [58, 59]. Because fasting GLP-1 levels do not increase following surgery, many questions remain regarding its postprandial effects. Perhaps the most important evidence that there are other factors besides GLP-1 in RYGB that contribute to the anti-diabetic effect, is that the pharmacologic use of GLP-1 agonists have not led to the equivalent potency of RYGB surgery alone. This suggests there continues to be factors of the surgery that have still yet to be identified.

## 4.4. Other contributing factors to the anti-diabetic effect of RYGB

### 4.4.1. Roux-en-Y gastric bypass, satiety, and the central nervous system

The importance in assessment of decreased caloric intake with diabetes remission has already been discussed, in particular those that undergo gastric banding [8]. Similarly, the RYGB involves creation of a small stomach size, causing similar restriction. It is remarkable that subjects that undergo RYGB actually appear to have a markedly decreased appetite as compared to their gastric band counterparts. Because postprandial elevation of gut hormones is a distinguishing factor of RYGB from gastric banding, investigation of their orexogenic and anorexogenic tendencies have recently begun to be characterized. Earlier prospective studies generally demonstrated RYGB induced altered satiety [45, 60-62], although the field appears to be lacking trials that are appropriately controlled.

The evidence continues to mount for this gut brain communication effect, with several biochemical mechanisms that affect neural signaling of hunger and satiety being discovered.

Therefore, RYGB has effects on satiety that are *independent* of the physical limitations imposed by the formation of the gastric pouch. The effect gut hormones have on the neural circuitry are most studied specifically within the hypothalamus [63], with the balance of orexogenic and anorexogenic hormones. Prime hormonal candidates for these changes include insulin, leptin, GLP-1, peptide YY (PYY), and ghrelin [61-62, 64-65]. While findings with ghrelin have been mixed, there is growing evidence that the other aforementioned hormones may play a significant role. PYY [66-67] and GLP-1 [68-69] are currently being studied in great detail. Origins of these mediators come from multiple different organ systems, which subsequently affect neurons within the arcuate nucleus and other hypothalamic regions. These lead to alterations in food intake and body fat mass. Research into these anti-obesity mechanisms for pharmacologic uses are still being investigated.

### 4.4.2. Roux-en-Y gastric bypass, type 2 diabetes mellitus, and the central nervous system

Autonomic nerve regulation has often been the target for pharmacologic weight loss therapy. Therefore, there has been renewed interest in the role of the vagus nerve within bariatric surgical procedures to determine its role in weight loss. Preservation of the vagus nerve is a common practice by many bariatric surgeons. An intact vagus nerve with RYGB appears to have a significant and improved effect on food intake and weight loss [70]. However, the beneficial effect appears to carry over to improved glucose metabolism that also appears to be weight independent.

Obese and diabetic rodent models studies have demonstrated that hepatic vagotomy will worsen glucose metabolism [71-72]. This further highlights the necessary role of the vagus for helping attain euglycemia via hepatic-mediated mechanisms. This is not without some conflicting studies such as by Shin et al [73], although their focus was on food intake, body weight, and energy expenditure. Vagal signaling to the liver is mediated predominantly by parasympathetic fibers. These parasympathetic fibers are derived from the medio-basal hypothalamus. The source of this neuroendocrine regulation may suggest that hepatic glucose metabolism is uniquely regulated by a hypothalamic source.

Pocai A et al [74] demonstrated that activation of potassium-ATP channels within the hypothalamus appears to lower blood glucose through hepatic gluconeogenesis. This was a significant advance in better understanding the mechanisms that may mediate hepatic gluconeogenesis. Similarly, insulin presence near the hypothalamus has also been demonstrated to suppress lipolysis [75], which directly affects insulin resistance and T2DM. Additional characterization of the hypothalamic and vagal mediated effects may also help us to better understand the role of the nervous system in glucose and lipid regulation. Besides insulin, other hormonal candidates that were discussed earlier (e.g. PYY) may not only have anorexogenic effects that modify caloric intake, but they may also directly mediate glucose regulation via central nervous system mechanisms. Further identification of where gut hormone receptors exist are needed to better understand this potentially significant glucose-governing mechanism.

### 4.5. Anti-diabetic effect gone too far? Postgastric bypass hypoglycemia

Perhaps best described by the title of the article by Patti ME et al "*Hypoglycemia following gastric bypass surgery-diabetes remission in the extreme*?"[76] the condition of post-gastric bypass hypoglycemia has been an increasingly observed phenomenon. Contrasting mechanisms of how this occurs have been proposed, with the initial reports suggesting islet cell hyperplasia [77]. However, follow up studies suggested there was no change in beta cell mass, although there was an increase in beta cell nuclear diameter [54]. The increase in beta cell diameter may be more of a function of increased nuclear transcriptional activity of insulin production. This would coincide with those afflicted with this condition may have hypersecretion of insulin.

Hypersecretion of insulin at disproportionate levels to the decreased BMI following surgery may potentially lead to clinically significant hypoglycemia. This has been demonstrated in weight matched individuals by Goldfine AB et al [78]. If we recall the changes in peak of insulin secretion discussed earlier brought on by RYGB [32-34, 46-48], a comparison to BMI-matched subjects afflicted with hypoglycemia demonstrated a greater post prandial peak of insulin secretion [78]. This may lead to increased glycemic variability, which has been demonstrated in subjects who are afflicted with post-gastric bypass hypoglycemia [40].

While this is suggestive that RYGB may induce hypoglycemia via pancreatic mediated mechanisms, the question of the contribution of peripheral insulin sensitivity to hypoglycemia was answered by Kim et al [79]. Using intravenous glucose infusions in BMI matched controls, Kim et al [80] showed that those who are afflicted with hypoglycemia demonstrated appropriate insulin secretion rates in response to intravenous glucose challenges. Therefore, it appears the hypoglycemia is only brought on by ingestion of nutrient boluses which elicits an abnormal insulin response. While the response may be effective in mediating improved glucose control, it is unclear why some subjects develop hypoglycemia and others do not. Possible causes may have to do with prior history of diabetes and residual insulin resistance.

Because of the increasing number of bariatric surgeries being performed, this is an area that is in urgent need of further study. Understanding how this condition develops will also likely shed light on how the surgery helps improve hyperglycemia. Currently, our laboratory is involved with ongoing clinical trials to better understand the mechanisms behind this clinically significant phenomena.

## 5. Further Research: Can other weight loss surgeries help type 2 diabetes mellitus?

### 5.1. Sleeve gastrectomy: The future?

The growing popularity of the bariatric weight loss surgery known as the sleeve gastrectomy is worthy of discussion. The procedure involves the removal of the antrum of the stomach, with a creation of a sleeve-like structure. The potency of the sleeve gastrectomy on diabetes has been demonstrated by Schauer et al [18]. While the improvement of hemoglobin A1c

reduction was greater in those that underwent RYGB, the sleeve gastrectomy had a similar reduction of almost 3% at one year following surgery. There was also a comparable reduction in BMI between the two surgeries. The question remains if there is a weight-independent effect of diabetes improvement with this surgery?

Earlier prospective studies of the sleeve gastrectomy, as compared to the RYGB, demonstrated that weight loss and glucose homeostasis was also similarly improved between the two [80-81]. However, they also demonstrated increased postprandial elevation of GLP-1, PYY, and insulin levels, although generally slightly less than RYGB. Short term (6 weeks) and long term (1 year) follow up demonstrated comparable GLP-1 responses to mixed meal challenges [82-83]. The alterations of GLP-1 and PYY secretion is confusing and remains not well explained within the literature. RYGB has been associated with earlier transit of nutrients to the distal intestine, stimulating an elevation of the "hindgut hormones." These elevations may potentially explain the glycemic improvement. However, these observations do not explain why the postprandial hormone elevation with the sleeve gastrectomy occurs. The literature still lacks a satisfactory mechanism of the stimulating mechanism for these elevations.
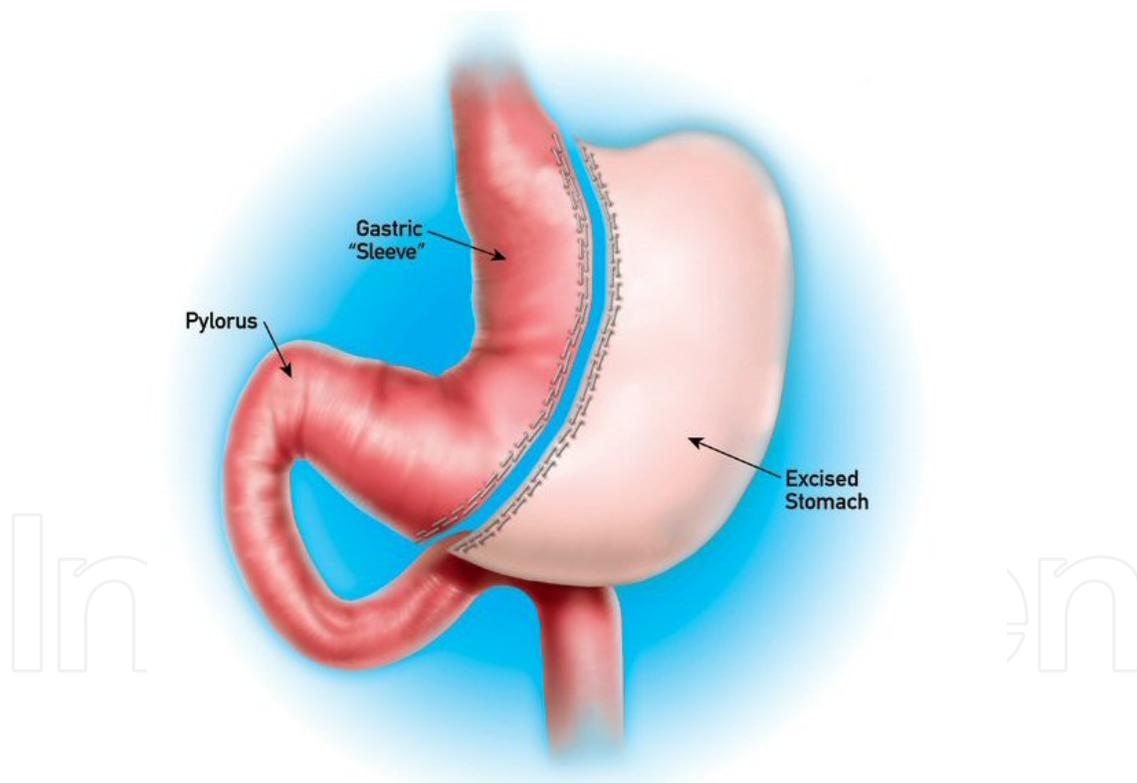


http://www.google.com/imgres?um=1&hl=en&client=tablet-android-asus-nexus&sa=N&rlz=1Y3NDUG_enUS499&biw=1280&bih=699&tbm=isch&tbnid=MwIS5kgaHvl2BM:&imgrefurl=http://www.ct-obesitysurgery.com/index.cfm/PageID/6424&docid=uP3rjSe-Kv1fMM&imgurl=http://ct-obesitysur-gery.com//images_content/sleeve%252520gastrectomy.jpg&w=628&h=568&ei=DOyNUMC2NOPs0QHIzI-CABQ&zoom=1&iact=hc&vpx=184&vpy=183&dur=122&hovh=213&hovw=236&tx=127&ty=142&sig=110329031745694344091&page=1&tbnh=148&tbnw=164&start=0&ndsp=20&ved=1t:429,r:0,s:0,i:112

**Figure 5.** Sleeve Gastrectomy

It should be noted that most of these studies had small samples sizes and lacked appropriate controls. However, the clinical effects of the sleeve gastrectomy on diabetes remains difficult to ignore. The mechanism remains elusive, and many questions remain about the effects of the sleeve gastrectomy. Why do the post-prandial gut hormone elevations occur? What is the biologic mechanism? Is the surgery susceptible to the same post-surgery hypoglycemia seen with the RYGB? The increasing popularity of the procedure is for various reasons. The intact nature of the pylorus prevents the dumping phenomenon. The lack of an intestinal bypass prevents associated malabsorption and the plethora of micronutrient deficiencies. Lastly, the hypoglycemia phenomenon has not yet been reported with this procedure.

Despite these appealing features, we would advise practitioners to evaluate their patients carefully when considering a bariatric surgical method for weight loss. Little to no long-term studies are currently available on their clinical potency, and the lack of understanding how the surgery affects diabetes should give practitioners pause. However, the surgery is still very promising with apparently little metabolic complications. The authors are excited about the growing role of the sleeve gastrectomy in weight loss procedures.

## 6. Conclusion

RYGB unquestionably ameliorates the hyperglycemic state in many of those with T2DM. Many who undergo the surgery gain significant health benefits, and achieve remission of their diabetes. Investigators are attempting to understand the clinical impact of diabetes remission on RYGB patients, as well as the mechanism of how this is achieved. The improvement of peripheral insulin sensitivity appears to be weight dependent, while hepatic insulin sensitivity seems to be a function of caloric restriction. However, alterations in pancreatic function are reflected in the robust postprandial insulin secretion profile, and appear to be a direct result of RYGB. Understanding the condition of the pancreas' endogenous insulin producing ability and the whole body insulin resistance may allow us to predict who will achieve diabetic remission.

The increasing clinical phenomenon of post-gastric bypass hypoglycemia may be a result of an undesired overenhancement of the alterations brought on by surgery. This condition needs further study to better aide those afflicted with this potentially debilitating condition. As a possible alternative, the sleeve gastrectomy may potentially be an alternative weight loss surgery that appears to have lesser metabolic complications than are associated with RYGB. However, understanding of how it mediates its effect on diabetes is still not understood, and also is in great need of additional research.

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