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Longer-Term Physiological and Metabolic Effects of Gastric Bypass Surgery

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Abstract

Obesity is closely associated with the development of type 2 diabetes. Many strategies have been used in the past to combat these two conditions, but very few provide for stable and durable glycemic control. Bariatric surgery has emerged as a powerful tool for treating obesity and in over 70 % of cases provides a short-term cure for diabetes. While the acute metabolic effects of surgery are striking, it remains important for us to also consider the long-term effects. This review aims to summarize the chronic or long-term metabolic and physiological effects of Roux-en-Y gastric bypass (RYGB) surgery on pancreatic function, skeletal muscle and hepatic insulin sensitivity, and gastrointestinal remodeling. An increased understanding of the current state of research in these areas can provide the basis for stimulating further research that would contribute to new treatment and management strategies for obesity and diabetes.

Keywords

Obesity; Diabetes; Gastric bypass; Insulin resistance; Beta cell function

Introduction

Current societal trends in the USA reflect a hazardous health environment that is promoted by excess caloric intake coupled with a sustained decline in physical activity. These conditions have led to a dramatic increase in the rates of obesity-associated disease conditions, including type 2 diabetes (T2D). As of 2010, it was estimated that 285 million adults had diabetes worldwide with the further prediction that 439 million people would have the disease by 2030 [1]. These numbers are consistent with a 69 % increase in T2D in developing countries and a 20 % increase in developed countries [1]. Obesity and diabetes

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Compliance with Ethical Guidelines

Human and Animal Rights and Informed Consent All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

All procedures performed in studies involving animals were in accordance with the ethical standards of the institution or practice at which the studies were conducted.

Conflict of Interest J. David Mosinski and John P. Kirwan declare that they have no conflict of interest.

are usually treated with intensive medical therapy that includes varying combinations of diet, exercise, and pharmacotherapy. The goals of these treatment regimes are to lower body weight, improve insulin sensitivity, and establish glycemic control. Work from our lab has shown that short-term (7 days) exercise leads to a rapid improvement in insulin sensitivity in older obese adults with T2D [2]. Furthermore, we have seen that longer-term exercise (12 weeks) coupled with a low glycemic index diet reduces insulin resistance in obese pre-diabetic subjects [3]. Other studies have also shown that employing a traditional diet and exercise program leads to significant weight loss and metabolic improvements [4]. These treatment approaches are effective in the short term, but lifestyle change is difficult to sustain and often unrealistic for long-term management of the disease. Recently, surgical interventions that alter the intestinal physiology have emerged as highly effective, and although durability is still unclear, the approach may represent the best chance of long-term success for management of body weight and the chronic diseases that are associated with obesity.

Over the past 20 years, the number of patients with severe obesity has increased dramatically and bariatric surgery is recognized as the treatment of choice for these patients. Currently, two of the more popular surgical operations are Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy [5]. Both of these operations result in significant weight loss and rapid improvement in glycemic control, both in humans [6–11] and animals [12, 13]. Intriguingly, ~70 % of T2D patients undergoing RYGB surgery experience diabetes remission within days after the surgery [8]. This happens before any significant surgically induced weight loss. Furthermore, we and others have shown that gastric bypass surgery coupled with intensive medical therapy is a more effective treatment for T2D than intensive medical therapy alone [6, 11] and the effects of the surgery are more durable over time [8, 14•, 15, 16•, 17–20]. These positive health benefits are consistent with a number of studies that show significant long-term improvements in cardiovascular health [9, 21, 22] and overall mortality [20, 23, 24]. Observations regarding the acute metabolic response to surgery have prompted several mechanistic theories to explain the outcome. They include, an improved incretin response, elevated insulin secretion, beta (β)-cell protection and proliferation, and increased glucose utilization in the gut. While these short-term effects of the surgery are noteworthy and significant, it remains important that we assimilate new research regarding the chronic/long-term metabolic effects and outcomes. Herein, we review the current literature regarding; pancreatic β cell function and adaptation, peripheral insulin sensitivity, gastrointestinal changes, and bile acid metabolism as they pertain to the longer-term metabolic effects of bariatric surgery.

Pancreas/Beta Cell Changes

During the early stages of T2D development, the functional capacity of the pancreatic islets is challenged by gluco- and lipotoxicity that is accompanied by increasing peripheral insulin resistance. This metabolic milieu places high and sustained demand on the β cell so that insulin secretion is sufficient to maintain normoglycemia. The β cells have an intrinsic flexibility that allows them to adapt and compensate for these conditions. Typically, obesity-induced insulin resistance is associated with elevated basal insulin secretion [25] as well as increased glucose stimulated insulin secretion [26, 27]. This metabolic flexibility may be

explained by an expansion and/or maintenance of the overall β cell mass. This view is supported by observations in human cadaver studies [28] as well as animal studies [29, 30]. The maintenance of β cell mass is controlled by a balance of proliferation/neogenesis and apoptosis [31]. During pre-diabetes, there seems to be a shift towards β cell proliferation, but as the disease progresses to T2D, apoptosis begins to dominate. These observations are supported by human cadaver studies that show obese normal glucose tolerant (NGT) individuals have higher β cell mass when compared to lean NGT individuals [28]. Increased β cell mass is also seen in the Zucker Diabetic Fatty (ZDF) rat model. These animals develop insulin resistance between 8 and 10 weeks of age and become overtly diabetic by 12 weeks of age. Islet morphology changes in the ZDF rats with the progression of disease. Pre-diabetic ZDF rats have larger islets with undefined boundaries [32, 33]. Furthermore, there is a strong correlation between islet DNA content and serum insulin levels [33]. This suggests that islet hyperplasia may be playing a role in the adaptation to diabetes.

Insulin resistance and hyperglycemia also elicit adaptations in the β cell that include upregulation of insulin synthesis/secretion pathways. There is evidence that in response to hyperglycemia increased mRNA translation in the β cell provides a larger insulin pool for subsequent secretion upon metabolic stimulation [34]. Furthermore, there is evidence that in the presence of peripheral insulin resistance, the β cell can compensate sufficiently so as to maintain relatively normal glucose metabolism [35–37]. This compensation has been attributed to elevated glucose metabolism in the β cells via up-regulation of glucokinase activity in the presence of both insulin resistance [38] and elevated blood glucose levels [39]. Evidence for this effect is further supported by data from β cell specific glucokinase-deficient mice that are unable to compensate for peripheral insulin resistance [40]. Elevated glucokinase activity is observed in isolated β cells from normoglycemic ZDF and Zucker Fatty (ZF) rats when compared to Zucker Lean (ZL) rats [41]. Also, it has been shown that there is a 1.5–2.0-fold increase in glucose utilization and oxidation in ZF rats when compared to ZL rats [38]. These data suggest that elevated glucose metabolism is essential for the β cell to compensate for peripheral insulin resistance. This concept is further supported by data from ZDF rats showing that genes involved in glucose metabolism are downregulated during the progression of β cell dysfunction and development of T2D [33]. The overall dysfunction and death of the β cells in T2D may be caused by dysfunctional organelles such as the endoplasmic reticulum [42] and the mitochondria [43], because both of these organelles play an integral role in the synthesis and secretion of insulin. The deterioration of β cell mass and function is thought to be a major contributor to the progression to T2D. This highlights the need to fully understand the underlying mechanism. If the β cells can be protected from further loss of mass and function there is the likelihood that it will be possible to reverse and/or prevent T2D from occurring. It is known that RYGB surgery can reverse diabetes and it appears that this may be occurring through a preservation of β cell function and mass. The mechanism driving this response is largely unknown but two emerging hypotheses revolve around altered gut hormone signaling, i.e., the “hindgut hypothesis” and the “foregut hypothesis.”

Roux-en-Y gastric bypass (RYGB) surgery involves significant rerouting of the intestinal tract. The procedure requires the creation of a small gastric pouch (30 ml) that is anastomosed directly to the distal portion of the jejunum. The rest of the stomach, the

duodenum, and the initial portion of the jejunum is excluded from the flow of food and reattached to the ileum to allow digestive juices to mix with food in the distal intestine [44]. When food enters the lower portion of the gut it stimulates the release of incretin hormones, specifically glucagon-like peptide-1 (GLP-1), which acts on the pancreas to amplify glucose induced insulin secretion and the subsequent regulation of blood glucose concentrations. This response forms the central tenet of the “hindgut” hypothesis [45]. Animal data from our lab has shown that RYGB surgery increases plasma GLP-1 levels and also increases glucose stimulated insulin secretion from isolated pancreatic islets [46]. These data are corroborated by observations from the literature that are based on using an ileal transposition model in rodents [47, 48]. In addition to the acute effect of GLP-1 to amplify glucose-stimulated insulin secretion from the β cell, animal studies have shown that GLP-1 also regulates the expression of the glucose transporter, GLUT-2, as well as glucokinase and insulin, suggesting that it plays a wider pleiotropic role in glucose metabolism and insulin secretion [31]. GLP-1 has also been shown to influence β cell mass by stimulating β cell proliferation and islet neogenesis [49] along with having an inhibitory effect on cellular apoptosis [50, 51]. Lindqvist et al. [52] recently reported that RYGB surgery increased β cell mass and islet number in pigs. They went on to show that pancreatic expression of insulin and glucagon were elevated and that there were more GLP-1 receptors in the RYGB group versus control. These data suggest that GLP-1 signaling is driving the improvement in β cell mass and function. Combined, these data paint a picture of GLP-1 as a hormone that acutely regulates insulin secretion, while at the same time sets the stage and lays the molecular foundation for the pancreas to be able to chronically secrete more insulin as needed.

The “foregut” hypothesis represents an alternative mechanism for improved glucose control after bariatric surgery. This hypothesis is built on the premise that exclusion of the upper gut (duodenum) holds the key to understanding normalization of glycemic control [45]. In this case, nutrients entering the duodenum stimulate the release of an unknown hormone that counteracts the action of GLP-1, i.e., an “anti-incretin.” Bypassing this segment of the gut inhibits the release of this anti-incretin thus allowing normal glycemic control. We have shown that the effects of RYGB surgery can be abrogated when Sprague Dawley rats are fed through a gastric tube that is placed directly into the bypassed segment of the gut [53]. We have also reported similar observations in obese patients with T2D [54]. Studies using Goto-Kakizaki rats where the foregut is bypassed without any stomach restriction also support this hypothesis [55, 56]. While it is likely that both hypotheses play a role in the remission of diabetes, further in-depth studies in humans are needed to determine their relative roles.

Insulin Sensitivity and Glycemic Control

It is known that weight loss enhances peripheral insulin signaling, glucose uptake, and glycemic control [3]. Traditionally, these effects are achieved using a combination of diet, exercise, education, and pharmacotherapy. While this approach is effective [3] long-term changes in lifestyle are difficult to maintain and many of the drugs that are used to control blood glucose also lead to weight gain. Consequently, bariatric surgery has become an exciting new treatment for T2D because it can provide immediate positive effects on glycemic control while also providing a weight loss mechanism for the long-term management of blood glucose levels. Knowledge of the mechanism that explains the

remission of T2D following gastric bypass surgery has been under progressively more intense investigation since the early observations by Pories and colleagues who reported that the normalization of glucose metabolism after gastric bypass surgery was not solely dependent on weight loss [57]. In the context of improved glycemic control following surgery we and others have seen an acute improvement in β cell function and survival, thus leading to compensation of insulin resistance via elevated insulin secretion [15, 55, 58–61].

Some of the first studies to examine the mechanism of the long-term effects of bariatric surgery on insulin sensitivity and ultimately the reversal of T2D following gastric bypass surgery were performed by Friedman and the East Carolina group [62] in the early 1990s. Since then, there has been an ongoing search for the specific details of the mechanism that underlies this effect. Recent data from our lab and others have shown that bariatric surgery is more effective and durable than intensive medical therapy (IMT) alone in the reversal of diabetes [6, 11, 63, 64]. Specifically, the STAMPEDE trial was one of the first randomized control trials to show that at 12 months post-surgery a substantially greater percentage of obese diabetic patients achieve an $\text{HbA}_{1\text{C}}$ $\leq 6.0\%$ after IMT and bariatric surgery compared to IMT alone [11]. These strong metabolic effects appear to be somewhat durable. At 24 months post-surgery, the percentage of patients with an $\text{HbA}_{1\text{C}}$ $\leq 6\%$ went from 27 to 11% in the sleeve gastrectomy group, while in the gastric bypass group, it remained slightly higher at 33% [15]. The more persistent response in the RYGB group may be due to both a decreased accumulation of truncal fat and an elevation in β cell function seen in these patients [15]. Three-year follow-up data from STAMPEDE revealed that glycemic control was sustained in both the RYGB group and the sleeve gastrectomy groups with 35 and 20% of patients achieving a $\text{HbA}_{1\text{C}}$ $\leq 6.0\%$, respectively [14•]. There are several recent studies that support and are consistent with these long-term metabolic effects [6, 16•, 63, 65•]. Furthermore, it should be noted that adjustable gastric banding (AGB) is also more effective than IMT to induce diabetes remission. Dixon et al. [66] has shown that 22 out of 33 patients who underwent AGB achieved an $\text{HbA}_{1\text{C}}$ $\leq 6\%$ at the end of a 2-year follow-up. Alternatively, recent data from Ding et al. shows that AGB has similar metabolic improvement to IMT and weight loss at 1 year of follow-up [67]. However, the durability of AGB is dependent on frequent band adjustment and this somewhat limits its appeal as a therapeutic option.

Indeed, many of the long-term metabolic improvements seen following bariatric surgery may be explained via the maintenance of significant weight loss. Many studies report weight loss after bariatric surgery in terms of excess weight loss, i.e., the number of pounds lost relative to the patient's ideal body weight [68]. Buchwald et al. [8] report 61% excess weight loss for all bariatric procedures combined, and this result remains remarkably consistent 2 years past the date of surgery. There is variability in weight loss with RYGB operations producing greater excess weight loss (up to 68%) than AGB (62%). Weight loss in the metabolic literature is generally reported in terms of pounds lost relative to baseline weight. Using this outcome measure bariatric surgery produces a weight loss in the range of 15–30% of initial body weight. Three-year follow-up data in the STAMPEDE trial demonstrated that patients who had the RYGB procedure maintained 24.5% weight loss from baseline, while the sleeve gastrectomy group maintained 21.1% weight loss from baseline [14•]. Taken as a whole, these data provide evidence that bariatric surgery is an effective

method for attaining and maintaining significant excess weight-loss and glycemic control, although robust data on insulin sensitivity using definitive procedures such as glucose clamps are still not widely available.

There is general agreement that gastric bypass surgery exerts a profound metabolic effect specifically at the site of the liver, adipose tissue, and skeletal muscle. There is good evidence that abundance and activity of proteins in the insulin-signaling pathway in skeletal muscle remain unchanged during the early period following surgery. In contrast, there are significant increases in protein expression and sensitivity in the long term. The latter effects are largely attributed to the significant weight loss that occurs after surgery. The exact mechanism responsible for the change in insulin sensitivity and signaling remains unclear. Recent data from Bojsen-Moller et al. [69] characterized peripheral (hyperinsulinemic-euglycemic clamp) and hepatic (hepatic insulin sensitivity index) insulin sensitivity at 1 week, 3 months, and 12 months following RYGB surgery. The improvement in peripheral insulin sensitivity was greatest 12 months post-surgery, i.e., after major weight loss. On the other hand, hepatic insulin sensitivity improved within 1 week after surgery and continued to improve throughout the duration of follow-up. These data support the view that in the immediate post-operative period, caloric intake is reduced and a state of negative energy balance leads to reduced gluconeogenesis and hepatic glucose production [70, 71]. Further, the negative energy balance and hepatic insulin resistance arising from the stress of surgery would be expected to contribute to a reduction in liver glycogen content and decreased glycogenolysis, thus adding another element to the decrement in fasting plasma glucose concentration. These data provide a plausible answer for how immediate glycemic control may be achieved through metabolic regulation in the liver, while longer-term control may occur primarily through enhanced insulin sensitivity and greater glucose uptake into skeletal muscle. Recent data from our lab supports the important role of the liver in both short- and long-term glycemic control following RYGB surgery [72•]. Despite eating a high fat diet for 90 days post-surgery, rats that received RYGB surgery lost over 20 % of their body weight and improved insulin sensitivity compared to a Sham control group. Hepatic steatosis and gene expression in the endoplasmic reticulum (ER) stress pathway were normalized in the RYGB group compared to both Sham and lean controls. Significant TUNEL staining in liver sections from the obese Sham group, indicative of accelerated cell death, was absent in the RYGB and lean control groups. These data suggest that in obese rats, RYGB surgery protects the liver by attenuating ER stress and excess apoptosis.

Albers et al. [73•] published a detailed description of the time course of the specific adaptations in skeletal muscle and adipose tissue that may contribute longer-term glycemic control after RYGB surgery. Insulin signaling proteins, GLUT-4 protein expression, and insulin-stimulated phosphorylation of Akt and glycogen synthase in skeletal muscle and adipose tissue were all increased 12 months after the surgery. In adipose tissue, phosphorylation of AMP-activated protein kinase and acetyl-CoA carboxylase was also noted. In addition, Chen et al. [74] provide confirmatory data on increased Akt activity 4 months after surgery, although it is interesting to note that they did not see a corresponding increase in insulin sensitivity at this time point. Bonhomme and colleagues [75] provide additional support for enhanced insulin signaling following RYGB using an animal model of T2D. RYGB surgery was performed on diet induced obese Sprague Dawley rats and key

steps in the insulin signaling pathway in skeletal muscle, liver and adipose tissue were assessed at 14 and 28 days post-surgery. Insulin receptor protein expression in skeletal muscle and liver was increased at day 28 post-surgery. Furthermore, expression of phosphorylated insulin receptor and insulin receptor substrates 1 and 2 was increased in skeletal muscle and liver at day 28, while GLUT-4 protein expression was increased in both skeletal muscle and adipose tissue at day 28. It should be noted that the reported changes in insulin signaling are occurring after the animals have lost a significant amount of their baseline weight. The elevated expression of GLUT-4 in the skeletal muscle after surgery is supported by data from Lesari et al. who found that increases in GLUT-4 mRNA expression was initiated within 24 hours after surgery in obese humans [76]. Together, these findings provide insight into some of the molecular adaptations that may contribute to a more insulin sensitive phenotype after bariatric surgery, and strongly suggest that longer-term glycemic control is mostly dependent upon weight-loss from the surgery.

Gastric Remodeling and Glucose Utilization

Several studies report long-term remodeling of the gastrointestinal mucosa following gastric bypass surgery [77–81]. One of the first observed structural changes to the gastrointestinal mucosa came from Evrard et al. [81] who found an elevation in intestinal mass following gastric bypass surgery. This trophic effect was attributed to expedited food delivery to the small intestine. A subsequent study by Nadreau et al. [77] found an increased thickness in the intestinal walls and thus a greater surface area following gastric bypass surgery. The increased surface area could act as a mechanism to improve nutrient absorption following surgery although there was no change in fecal energy content. Studies from Le Roux et al. [78] and Mumphrey et al. [79] suggest that the hypertrophic effect of surgery on the intestinal mucosa may be helping to improve the secretion of incretins following surgery, thus improving glycemic control. Others have suggested that gastric remodeling requires an elevated energy supply and this would imply that more glucose absorption is necessary. Saeidi et al. [80] discovered that resting energy expenditure was elevated after gastric bypass surgery although overall nutrient absorption appeared to be decreased. In a separate study, this same group also showed that glucose absorption and utilization was elevated in the hypertrophic portions of the intestine [82]. This suggests that while overall nutrient absorption may be decreased, glucose absorption and utilization may be elevated to allow intestinal hypertrophy to occur. A study from Cavin et al. [83] lends additional support to the view that gastric bypass causes intestinal hypertrophy and shows that glucose absorption is elevated and glucose becomes trapped within the intestinal epithelial cells. Finally a study from Nguyen et al. [84] reports elevated GLUT-1 and 2 expression in the intestine following surgery. This increased expression could facilitate increased glucose absorption following surgery, and thus prevent carbohydrate malabsorption. Together these data suggest that gastric bypass surgery may improve glycemic control by stimulating intestinal hypertrophy and glucose utilization. Further long-term studies are necessary to determine if these effects are durable.

Bile Acids and Glycemic Control

Bariatric surgery alters nutrient exposure to bile acids. Bile acids are increasingly recognized as signaling molecules that play a crucial role in lipid and glucose homeostasis [85–88, 89•, 90–95]. Bile acids appear to control hepatic glucose production via interaction with the Farnesoid X Receptor (FXR)-Fibroblast Growth Factor (FGF)-19 pathways in the liver. FXR is a known nuclear target of bile acids and it is highly expressed in the liver, intestine, adipose tissue, and pancreas [96]. FGF-19 has been shown to regulate glycogen synthesis and gluconeogenesis in the liver and its expression is controlled by FXR [97]. When bile acids interact with FXR, this in turn upregulates FGF19 expression and serves to control hepatic glucose output. This regulatory mechanism for glycemic control was characterized by Gerhard et al. where they showed significant elevations in circulating bile acids and FGF-19 expression in diabetic patients at 1 year post-surgery [92]. A connection has also been made between bile acids and GLP-1 secretion following gastric bypass surgery. Pournaras et al. have shown that bile acids correlate well with GLP-1 secretion when the bile acids are delivered directly to the terminal ileum, thus bypassing the duodenum [98]. These data were confirmed by Patti et al. who showed that total bile acids in the plasma correlate with peak GLP-1 levels and are inversely correlated with 2-h post-meal glucose levels [90]. The correlation between bile acids and plasma GLP-1 appears to persist for as long as 2 years following surgery [99]. Importantly, recent evidence supports a regulatory role for bile acid signaling in insulin secretion [100], and data in mice demonstrates that bile acids and FXR signaling are important in determining weight loss after vertical sleeve gastrectomy [101]. Interestingly, the sub-fractions of bile acids seem to respond to gastric bypass differently. Specifically, conjugated bile acids have been shown to increase, while unconjugated bile acids are less affected following RYGB surgery [102]. Our own data in humans suggests that tauroursodeoxycholic acid (TUDCA) may play an important role in the metabolic response to bypass surgery [103]. TUDCA tracks insulin secretion in our human studies, and is reported to reduce ER stress and increase insulin secretion in hIAPP-expressing cells [104], INS-1 cells [105], and in mouse models of type 1 diabetes [106]. Taken together, these data provide some interesting mechanisms through which bile acids may contribute to improved glycemic control following gastric bypass surgery both acutely and long-term.

Conclusion

There is increasing recognition that gastric bypass surgery is a safe and effective treatment for T2D. Literature on the metabolic effects of gastric bypass surgery continues to grow at a rapid rate, and new discoveries are providing important insights into potential targets and mechanisms for diabetes remission. The studies that are summarized herein have advanced our knowledge with regards to the mechanisms that support long-term improvement in glycemic control after gastric bypass surgery and include increased peripheral insulin sensitivity, enhanced pancreatic β cell function, changes in gastrointestinal structure and function, and a direct role for bile acids in maintaining glucose homeostasis. It is well known and widely accepted that childhood obesity and diabetes are rising at an alarming rate. Logically, this suggests that more and more of our younger population are likely to need some form of bariatric surgery intervention. Therefore, it is imperative that we increase

our understanding of the long-term effects of the surgery so that we can safely treat those individuals who will live with the surgery for many years. Furthermore, a greater understanding of current research on these topics may stimulate the research that will lead to novel treatments and management strategies for obesity and diabetes with specific emphasis on long-term improvements that support the remission of chronic metabolic diseases.

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