

Metabolic Surgery for Type 2 Diabetes Mellitus

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ABSTRACT

Background: Metabolic surgery for morbid obesity induces significant weight loss and resolution of many obesity-related comorbidities, the most notable of which is remission of type 2 diabetes mellitus (DM). Such changes seem to precede significant weight loss in this population shortly after undergoing diversionary procedures.

Objective: This article explores the evidence for salutary metabolic benefits of bariatric surgery, with special emphasis on glycemic control and remission of type 2 DM.

Methods: We conducted a query of the PubMed database for articles published in English within the past 15 years using the search terms *bariatric surgery*, *obesity*, *type 2 diabetes*, *gastric bypass*, *gastric banding*, *incretins*, *enteroinsular axis*, *GLP-1* (glucagon-like peptide-1), and *GIP* (glucose-dependent insulinotropic polypeptide). We targeted review articles as well as those discussing the effects of bariatric surgery on the enteroinsular axis and the respective effects on glycemic control.

Results: Most of the clinical reports indicated a high remission rate ($\geq 85\%$) for type 2 DM, and relatively higher rates in patients who underwent diversionary procedures. Studies with small cohorts and laboratory data suggested a role for gastrointestinal hormones in the regulation of glucose homeostasis after bariatric surgery.

Conclusions: Gastrointestinal surgery for severe obesity, through restrictive and/or neurohormonal effects, is an effective treatment for type 2 DM. Surgically induced weight loss was found to be sustainable, durable, and associated with remission of type 2 DM, a reduction in mortality, and improvement in quality of life. (*Insulin*. 2009;4:136–143)
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Key words: bariatric surgery, obesity, type 2 diabetes, gastric bypass, gastric banding, incretins, enteroinsular axis, GLP-1, GIP.

CASE HISTORY

A 43-year-old female customer service representative with World Health Organization (WHO) class III obesity¹ (body mass index [BMI], 53 kg/m²), type 2 diabetes mellitus (DM), obstructive sleep apnea, hyperlipidemia, hypothyroidism, and bilateral lower-extremity edema was referred for evaluation and treatment of clinically significant obesity. The patient's diabetes was diagnosed 3 years earlier, and she began taking glyburide. One year later, regular insulin (20 units twice daily) was added to her regimen to augment glycemic control. Despite persistent attempts to diet and exercise, she progressively gained weight and could not adequately manage her diabetes. Her serum glucose level was 373 mg/dL, and her glycosylated hemoglobin (A1C) level was 14.8% despite taking 4 antihyperglycemic medications (insulin glargine 100 units, exenatide 5 mg, and glyburide/metformin 5 mg/500 mg, all twice daily).

The patient underwent a comprehensive evaluation by an interdisciplinary team, including a bariatrician, psychologist, nutritionist, and bariatric surgeon,² in accordance with the National Institutes of Health (NIH) guidelines,³ and subsequently underwent a laparoscopic Roux-en-Y gastric

bypass (RYGB). Postoperatively, her serum glucose levels were monitored regularly and controlled using a regular insulin sliding scale. Her blood glucose level during the first 3 postoperative days (PODs) ranged from 115 to 456 mg/dL. On POD 4, her finger-stick blood glucose level ranged from 45 to 75 mg/dL. She was discharged home 5 days after surgery on 40 units of insulin glargine 3 times daily and a low-calorie, low-carbohydrate, liquid diet. By POD 15, she was off insulin glargine and her finger-stick blood glucose level ranged from 140 to 160 mg/dL. Six weeks after surgery, her A1C level had dropped to 8.8%. By 8 weeks, she had lost 28 lb and her BMI was 45 kg/m². By 3 months, her A1C level had decreased to 6.7%. At the 6-month postoperative visit, her BMI was 41 kg/m² and she remained off all antihyperglycemic medications; her blood glucose level ranged from 100 to 120 mg/dL. At her annual follow-up visit, she had lost 80 lb, her BMI was 39 kg/m², and her finger-stick blood glucose level was within normal range.

Time trends in BMI, serum glucose levels, and A1C levels for this patient are depicted in **Figure 1**. These are critically important in framing the indications for and outcomes of bariatric surgery.

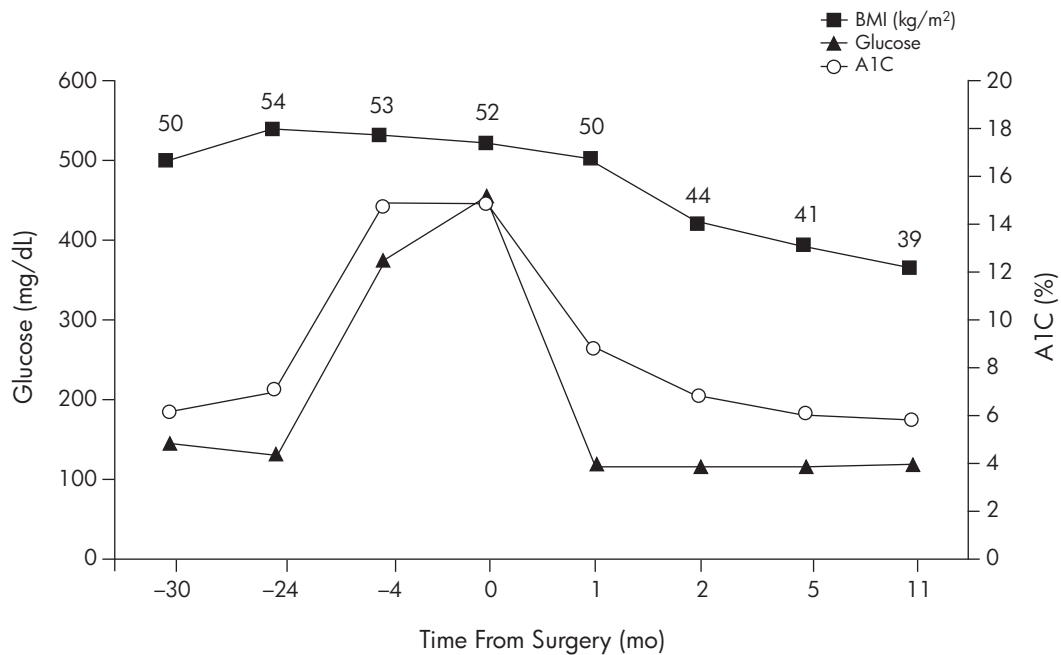


Figure 1. Time trends in body mass index (BMI), serum glucose, and glycosylated hemoglobin (A1C) in a patient who underwent Roux-en-Y gastric bypass.

- Weight gain is associated with poor glycemic control and a progressive need for multiple antihyperglycemic medications.
- Modest weight loss (decrease in BMI of 1–2 kg/m²) can be achieved by interdisciplinary weight management; our patient's BMI dropped from 53 to 52 kg/m² during the 4 months of evaluation and follow-up with our team in preparation for surgery; however, her serum glucose and A1C levels did not change during the same period.
- Significant correction of A1C levels and normalization of serum glucose levels are achieved within 1 month of bariatric surgery and are disproportionately better than weight loss.
- Although most patients have normal serum glucose levels by the time they are discharged from the hospital after bariatric surgery, some patients with severe visceral obesity, like our patient, require intensive monitoring of glucose while medications are being reduced in the immediate postoperative period.

INTRODUCTION

At present, DM affects 240 million people worldwide.⁴ Despite advances in behavioral, medical, and pharmacologic therapy, <50% of patients with DM achieve adequate glycemic control.⁵ Recent evidence strongly suggests that surgically induced weight loss induces remission of obesity-related comorbidities. This review explores the evidence for salutary metabolic benefits of bariatric surgery, with special emphasis on glycemic control and remission of type 2 DM.

METHODS

We conducted a query of the PubMed database for articles published in English within the past 15 years using the search terms *bariatric surgery*, *obesity*, *type 2 diabetes*, *gastric bypass*, *gastric banding*, *incretins*, *enteroinsular axis*, *GLP-1* (glucagon-like peptide-1), and *GIP* (gastric inhibitory polypeptide). We targeted review articles as well as those discussing the effects of bariatric surgery on the enteroinsular axis and the respective effects on glycemic control.

RESULTS

Diabetes and Obesity: The Epidemic

In western countries, 90% of the cases of type 2 DM are attributable to weight gain. The prevalence of obesity exceeds 30% among men and women.⁶ Sixteen percent of children and adolescents aged 2 to 18 years are obese, scoring at or above the 95th percentile of the 2000 BMI-for-age growth charts.⁷ Obesity is precipitating premature type 2 DM in children and adolescents, a condition that is particularly difficult to manage once established.^{8,9}

The economic burden of diabetes exceeded \$174 billion (USD) in 2007. Medical expenditures were estimated to be \$116 billion, and disease-related loss of productivity was estimated to be \$58 billion.¹⁰

Diabetes and Obesity: The Link

Type 2 DM accounts for 90% to 95% of all newly diagnosed cases of diabetes and is characterized by a progressive decline in glycemic control, end-organ damage, and worsening quality of life.¹¹ Among patients with type 2 DM, 85% are overweight (BMI >25 kg/m²) and 55% are obese (WHO class 1 obesity; BMI >30 kg/m²).¹² Clinical reports and regional studies have suggested that type 2 DM in children and adolescents is being diagnosed more frequently.¹³

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The Link Between Obesity, Diabetes, and Inflammation

Obesity and type 2 DM are causally linked. Excess adiposity induces insulin resistance through several mechanisms. Obesity is associated with low-grade, chronic inflammation and adipocyte dysfunction. Abnormal adipokine production and the activation of proinflammatory signaling pathways result in increased insulin resistance, impaired glucose tolerance, and the development of diabetes. Notably, increased levels of C-reactive protein, tumor necrosis factor- α (TNF- α), and interleukin-6 have been implicated in the pathogenesis of type 2 DM.¹⁴ Insulin resistance places a greater demand on pancreatic β -cell capacity to produce insulin, which also declines with age, leading to the development of diabetes. Physical inactivity—a cause and a consequence of weight gain—also contributes to insulin resistance. Nonetheless, data from our laboratory studies in obese rats and mice suggested that inflammation is not limited to adipose tissue; we found greater increases in oxidative stress and inflammatory cytokines within the liver parenchyma in obese rats and mice than in nonobese animals.¹⁵

Increased levels of C-reactive protein, TNF- α , and interleukin-6 have been implicated in the pathogenesis of type 2 DM.

Reducing Obesity and the Development of Type 2 DM

Among adults, weight loss of 5% to 7% achieved through caloric restriction and increased physical activity will reduce the development of type 2 DM. Nevertheless, the lifestyles and behaviors that are associated with obesity and type 2 DM are often deeply ingrained and resistant to current medical treatments.¹⁶ Many patients who respond initially

to weight management eventually relapse because of poor long-term adherence to hypocaloric diet and lifestyle modification.¹⁷ Diabetes therapy has been associated with progressive weight gain,¹⁸ and <50% of patients with diabetes achieve A1C levels <7.0% despite use of numerous therapeutic strategies.⁴

The recent American Diabetes Association (ADA) guidelines¹⁹ state that “bariatric surgery should be considered for adults with BMI >35 kg/m² and type 2 DM, especially if the diabetes is difficult to control with lifestyle and pharmacologic therapy.” Surgically induced weight loss is an order of magnitude greater than that of nonoperative therapy for the treatment of severe obesity (BMI >40 kg/m²).²⁰ Operative treatment results in weight loss of 20 to 30 kg that is maintained for up to 10 years or longer and is accompanied by significant improvements in multiple comorbid conditions, including diabetes and the metabolic syndrome.²¹ Similarly, bariatric surgery for patients with a BMI of 34 to 39 kg/m² is highly effective.²²

Bariatric Procedures

The NIH Consensus Development Conference Statement on gastrointestinal surgery for severe obesity³ as well as the recent ADA guidelines¹⁹ sanctioned operative intervention for obesity in patients who are well informed and motivated, have failed previous nonsurgical weight loss management plans, and are at acceptable risk for surgery. The BMI cutoff of 40 kg/m² (or 35 kg/m² in conjunction with serious obesity-related comorbidities such as type 2 DM, sleep apnea, cardiomyopathy, or severe joint disease) continues to be challenged by emerging studies of the efficacy of bariatric surgery in patients whose BMI is \leq 35 kg/m².

The 2 most commonly undertaken bariatric procedures are laparoscopic adjustable gastric banding (LAGB) and RYGB.²³ LAGB involves placing an inflatable silastic ring around the proximal stomach to make a 15- to 30-mL pouch (**Figure 2**). The band is connected to a subcutaneous reservoir that can be accessed percutaneously. Saline is injected into the reservoir, thereby increasing the degree of restriction to oral intake.

RYGB involves dividing the proximal stomach to make a 15- to 30-mL pouch (**Figure 3**). The proximal jejunum (Roux limb) is anastomosed to the pouch; the biliopancreatic limb delivers gastric, pancreatic, and biliary secretions to the Roux limb 100 to 150 cm distal to the gastrojejunostomy. The common channel is where most digestion and absorption of nutrients occur.

Sleeve gastrectomy (a restrictive procedure) and biliopancreatic diversion (BPD) with duodenal switch (Roux anatomy and malabsorption) are being undertaken more frequently.²³ Although long-term data are still emerging with regard to remission of type 2 DM, evidence suggests that sleeve gastrectomy shares a common tolerability profile with LAGB, whereas BPD is similar to RYGB.²⁴

The tolerability of bariatric surgery has become well established. The 30-day morbidity in contemporary cohorts

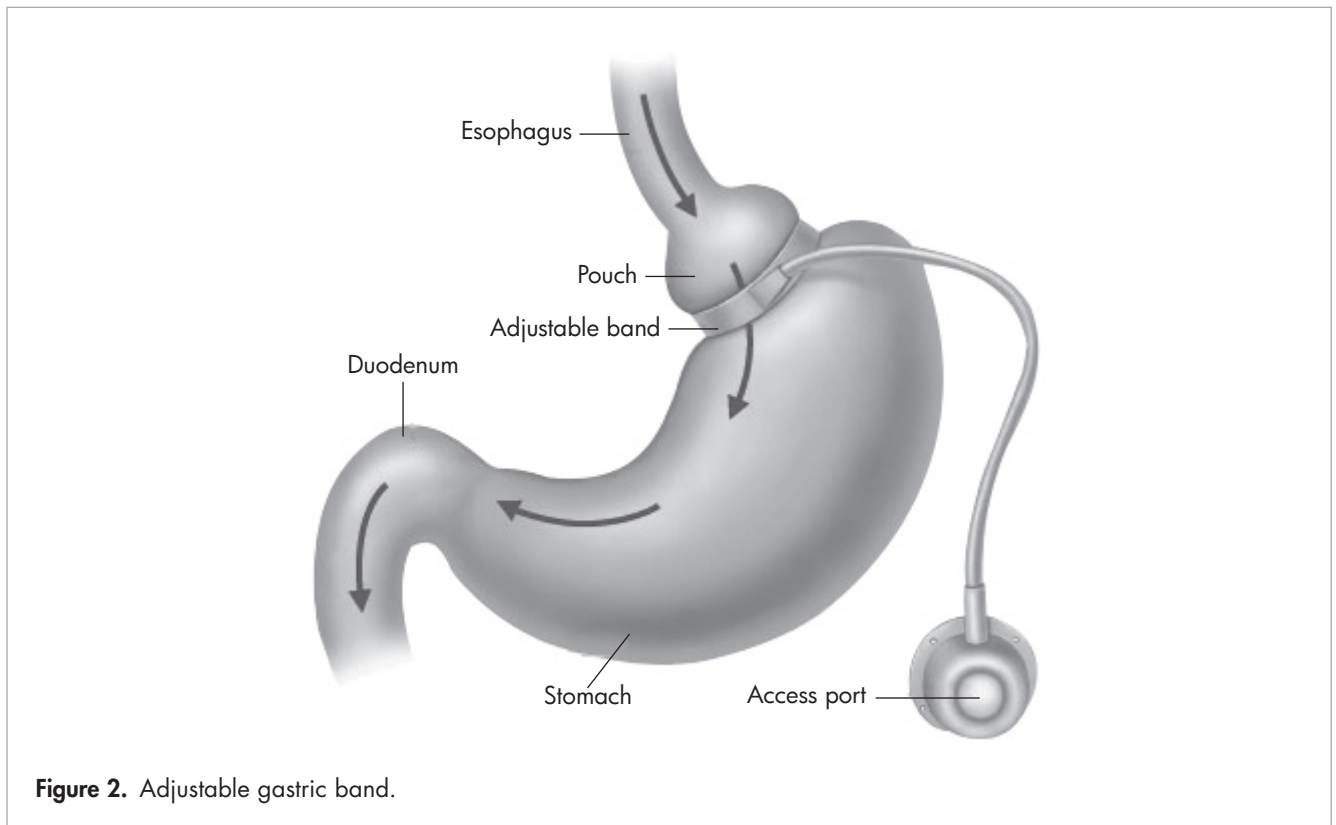


Figure 2. Adjustable gastric band.

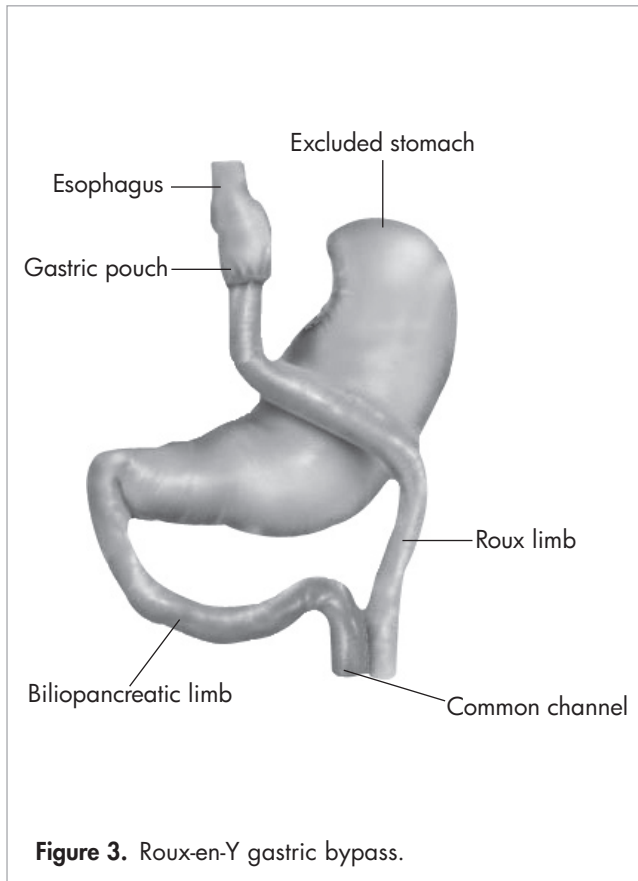


Figure 3. Roux-en-Y gastric bypass.

is $\leq 0.3\%$,^{23,25-27} which is comparable to the mortality rate for laparoscopic cholecystectomy ($\leq 0.1\%$) and has an inverse relationship to provider volume (ie, experience in performing the procedure).²⁸

Efficacy of Bariatric Surgery in the Treatment of Type 2 DM

Marked improvements in insulin sensitivity have been observed in bariatric patients within the first few days after RYGB and before any measurable weight loss has occurred. Significant improvement in insulin resistance within 6 days of RYGB was sustained at 12 months postoperatively in a cohort of 31 diabetic patients.²⁹ In this series, only 3 patients continued to use antihyperglycemic medication after being discharged from the hospital.²⁹

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The Swedish Obese Subjects (SOS) Intervention study²⁰ compared 1703 patients who underwent bariatric surgery with matched controls who opted for nonoperative therapy.

Surgically induced weight loss reduced the incidence of diabetes and hypertriglyceridemia and lowered high-density lipoprotein cholesterol levels compared with controls at 2 and 10 years after intervention.^{20,21} In addition, the adequately powered SOS study reported the survival advantage of bariatric surgery: the adjusted hazard ratio for overall mortality 11 years after surgery was reduced by 29% in the operative treatment group.³⁰

Similarly, in a retrospective cohort study of 7925 patients who had undergone gastric bypass surgery,²⁸ the adjusted overall long-term mortality rate decreased by 40% compared with matched controls. Deaths from coronary artery disease were reduced by 56% ($P = 0.006$), and cancer-related deaths decreased by 60% ($P < 0.001$); furthermore, disease-specific mortality from diabetes decreased by 92% ($P = 0.005$).

In another study,³¹ patients who were randomized to LAGB lost 21% of excess weight after LAGB compared with 4% for those who received nonoperative treatment consisting of a very low-cholesterol diet, pharmacologic therapy, and lifestyle changes. Furthermore, remission of type 2 DM was reported in 73% of the 30 patients who underwent LAGB. The mean weight loss and remission of type 2 DM in the group that received conventional therapy were 9% and 13%, respectively. As expected after restrictive procedures (LAGB), remission of type 2 DM was related to weight loss and lower baseline A1C levels.³¹ Similarly, resolution or improvement of type 2 DM was $\geq 60\%$ in 129 studies (28,980 patients) that specifically focused on LAGB.³²

Among 240 patients with impaired glucose tolerance or type 2 DM who had undergone RYGB, fasting plasma glucose and A1C levels normalized in 83% of patients and improved in the remaining 17%.³³ Furthermore, a meta-analysis of 136 studies involving 22,094 patients who had undergone RYGB reported resolution of diabetes in 84% of patients.²² Similarly, several large studies of patients undergoing RYGB reported that 82% to 98% of patients with diabetes achieved complete disease remission, as indicated by a reduction in the use of antihyperglycemic medications.^{23,34-36} Results of these studies suggested that younger age and shorter duration of diabetes were associated with higher rates of remission. Furthermore, bariatric surgery (LAGB or RYGB) was cost-effective in terms of quality-adjusted life years (QALY) ($< \$25,000/\text{QALY}$) compared with treatment of lifelong obesity and its related comorbidities.³⁷

Figure 4 depicts the relative risk for surgery (30-day mortality), remission of type 2 DM, and excess weight loss.^{22,23} Restrictive procedures are associated with lower mortality and a variable degree of weight loss, and, hence, variable remission of diabetes. Diversionary procedures, however, are associated with higher operative risk; the degrees of weight loss and remission of diabetes are higher, with less variability.^{22,23}

As discussed in a recent meta-analysis of 621 studies (135,246 patients),³⁸ limitations exist in the collection of data, including, but not limited to, a high attrition rate of patients for follow-up, diversity of diabetes outcomes data collection, and lack of information on specific subpopulations such as

ethnicity. However, the consistency of outcomes across all studies allowed for the strong inference that bariatric surgery is a powerful and effective treatment of type 2 DM in morbidly obese patients.³⁸

Role of Incretins: Enteroinsular Axis

Although drastic reduction in caloric intake following bariatric surgery may explain some of the acute improvement in glycemic control, the incretin effect of gut hormones such as GLP-1 and GIP continues to be intensively investigated.⁴

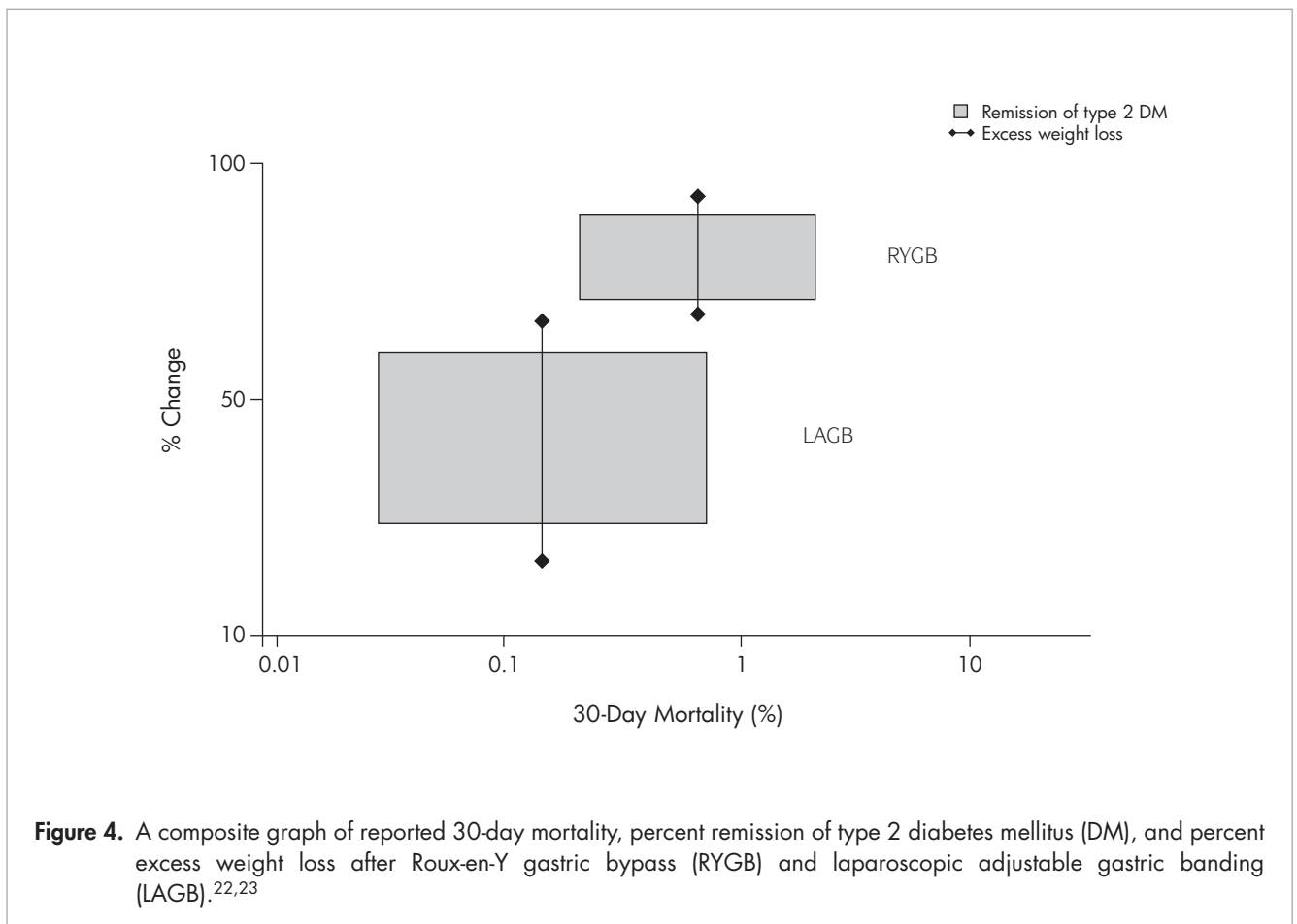
The main function of incretins is to stimulate postprandial glucose-dependent insulin secretion. Patients with type 2 DM exhibit a diminished incretin effect despite normal levels of GIP and respond to exogenous GLP-1. Incretins play a role in the maintenance of body weight through their influence on β -cell mass, insulin biosynthesis, and inhibition of glucagon secretion, as well as slowing of gastric emptying.³⁹

GIP is released from K cells in the duodenum and proximal jejunum, and is secreted in response to the ingestion of glucose or fat.³⁹ GIP stimulates insulin secretion from pancreatic β -cells. GLP-1 is secreted from L cells in the distal ileum and colon.³⁹ GLP-1 stimulates insulin secretion, increases glycogenesis, inhibits glucagon secretion, and delays gastric emptying.⁴⁰ In vitro and animal studies have found that GLP-1 increases β -cell mass by 2 mechanisms: stimulating neogenesis and inhibiting apoptosis of islet cells. The improvement of β -cell function can be indirectly observed from the increased insulin secretory capacity of humans receiving GLP-1 or incretin mimetics.⁴¹

Bariatric Surgery and Incretins

The concept that glycemic control is influenced by food-gut-pancreas interaction has been explored for many years, especially in the case of RYGB, which diverts nutrients from the duodenum and the proximal jejunum, and delivers undigested or partially digested carbohydrates, proteins, and fats directly to the distal jejunum and ileum. The impact of diverting nutrients from the proximal gut was investigated in Goto-Kakizaki rats (a spontaneous nonobese model of type 2 DM) that underwent gastrojejunal bypass; the experimental group had significantly improved fasting glucose ($P = 0.02$), glucose tolerance ($P < 0.001$), and insulin sensitivity ($P < 0.05$) compared with sham-operated, food-restricted, or pharmacologically treated rats. The fact that these findings occurred in the absence of significant weight loss strongly suggests that improved glycemic control is secondary to duodenojejunal exclusion rather than weight loss.⁴²

The effect of premature delivery of nutrients to the hindgut was tested in Goto-Kakizaki rats, where a segment of ileum was transposed into the proximal jejunum. Ileal transposition improved glucose tolerance and insulin sensitivity, and induced a more sustained GLP-1 response to oral glucose compared with control rats.⁴⁰ Similarly, ileal interposition in conjunction with sleeve gastrectomy in 58 human subjects with BMIs of 20 to 34 kg/m² showed increases in GLP-1 and GIP and led to significant improvement in glycemic control (91%).⁴³



Such an incretin-like effect appears to be one advantage of diversionary procedures that utilize a Roux anatomy (RYGB and duodenal switch) over purely restrictive procedures (LAGB and sleeve gastrectomy). The incretin-like effects of the Roux anatomy are immediate after surgery, whereas glycemic control in restrictive procedures is entirely dependent on weight loss.

We investigated the role of the liver in glycemic control in rats that were rendered obese by a high-fat diet and subsequently underwent RYGB. RYGB lowered nonfasting serum glucose levels, decreased hepatic TNF- α levels, and reduced oxidative stress in the liver. Moreover, RYGB increased insulin receptors (IRS2/PI3 kinase complex) and downregulated key lipogenic enzymes and genes. These findings were accompanied by resolution of histologic features of steatosis.¹⁵

Evidence from multiple small-cohort clinical studies suggests that the postprandial response of GLP-1 is enhanced after diversionary procedures,⁴⁴⁻⁴⁶ whereas there is no consensus about fasting levels of GLP-1. On the other hand, the data on GIP are less consistent; some studies indicate that GIP is decreased,^{47,48} whereas other studies report no change in GIP after bariatric surgery.^{45,49} Similarly, data to support changes in incretin levels after purely restrictive procedures are scant but showed no change in incretin levels.^{50,51}

CONCLUSIONS AND FUTURE DIRECTIONS

Gastrointestinal surgery for severe obesity (BMI ≥ 40 kg/m²) in carefully selected, moderately obese patients (BMI 35–39 kg/m²) is an effective treatment of type 2 DM and the metabolic syndrome. Surgically induced weight loss was found to be sustainable, durable, and associated with remission of type 2 DM, a reduction in mortality, and improvement in quality of life. These findings have become critically important as health care providers awaken to the diabetes-obesity epidemic. The efficacy of bariatric surgery overshadows other recent advancements in metabolic health.

A unique window of opportunity is upon us; the metabolic changes that accompany weight loss should be viewed with critical questions in mind and used to further the treatment and prevention of diabetes. Our vision of remission of diabetes pivots on collaboration among endocrinologists, surgeons, and basic scientists to facilitate greater understanding of the pathophysiology of metabolic regulation in patients undergoing bariatric surgery.

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