

In Brief

Obesity and diabetes are two often interrelated and escalating health problems. For patients with clinically severe obesity and diabetes, surgery provides the best option for the cure of both disease processes. The resolution of diabetes may not result from weight loss alone, but instead may be caused by (surgical) alteration of the enteroinsular axis.

The Impact of Bariatric Surgery on Severely Obese Patients With Diabetes

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The prevalence of diabetes is estimated at more than 20 million in the United States and more than 135 million worldwide.^{1,2} These numbers are expected to increase in the coming decades, translating to an economic burden of > \$100 billion in direct and indirect health care costs in the United States alone. The worldwide prevalence of diabetes is expected to increase to 300 million by the year 2025.^{3,4}

About 90% of all individuals with diabetes have type 2 diabetes,⁵ and a direct relationship between obesity and type 2 diabetes has been established.⁶ Obesity, as defined by a BMI > 30 kg/m², affects more than 250

million individuals worldwide and 34 million individuals in the United States alone.⁷ Obesity can be subcategorized into three classes (Table 1).

In addition to diabetes, morbidities attributable to obesity may involve any organ system, including the cardiovascular, renal, pulmonary, venous, gastrointestinal, and musculoskeletal (Table 2). The risk of developing a comorbidity secondary to obesity is directly related to the severity of the obesity.^{8,9} Clinically severe obesity, previously termed “morbid obesity,” a somewhat redundant term, may be defined as a BMI > 40 kg/m² or a BMI > 35 kg/m² with the presence of a clinically serious condition, e.g., obesity

Table 1. Classification of Obesity

	Class	BMI (kg/m ²)
Normal		18.5–24.9
Overweight		25–29.9
Obesity	I	30.0–34.9
	II	35.0–39.9
Clinically severe obesity	III	> 40.0

hypoventilation, sleep apnea, diabetes, hypertension, cardiomyopathy, or musculoskeletal dysfunction. A BMI > 40 kg/m² roughly corresponds to 100 lb. above ideal body weight or > 200% of ideal body weight.¹⁰

The health consequences of obesity have been well documented. For individuals with a BMI > 35 kg/m², mortality is 12 times higher in men aged 25–34 years and 6 times higher in men aged 35–44 years compared to age-matched nonobese control subjects.¹¹ Furthermore, evidence suggests that not only the absolute percentage of body fat, but also the distribution of body fat, influences the development of comorbidities. Central obesity, with a large amount of visceral fat, carries a greater risk of morbidity and mortality than does peripheral obesity.^{12–14}

Obesity and Diabetes

More than 80% of individuals with type 2 diabetes are obese, and obesity is considered one of the most important risk factors for developing type 2 diabetes.^{15,16} In both children and adults, obesity is associated with peripheral insulin resistance,^{14,17,18} with the prevalence of insulin resistance directly related to BMI.¹⁹

Moreover, the probability of developing diabetes doubles for every 20% increase above ideal body weight, establishing a direct link between the two conditions. Patients with clinically severe obesity have a 10–28% incidence of type 2 diabetes, with an additional 10–31% incidence of impaired glucose tolerance (IGT).⁷

The precise molecular link between obesity and insulin resistance in type 2 diabetes has yet to be elucidated. A leading theory suggests that free fatty acids from adipocytes exert a direct effect on the liver, leading to decreased hepatic insulin extraction and to decreased hepatic responsiveness to insulin secretion.^{20,21} Adipocyte secretion of free fatty acids is also implicated in insulin resistance in peripheral tissues.²² Additional studies have implicated proinflammatory cytokines released by adipose tissue as mediators of peripheral insulin resistance. Specifically, increased expression of tumor necrosis factor- α (TNF- α) mRNA in adipose tissue closely correlates with elevated plasma insulin levels in otherwise healthy obese females.²³ In addition, TNF- α secretion by skeletal muscle is significantly elevated in insulin-resistant and type

2 diabetic patients, possibly leading to a change in glucose transporter GLUT1 expression.^{24,25} Further animal studies identified an adipocyte-specific protein, resistin, that impairs glucose tolerance.²⁶ In murine models, resistin levels were increased in both genetic and diet-induced obese subjects. Administration of anti-resistin antibodies lowered blood glucose levels and improved glycemic control. These findings provide some molecular clues towards the understanding of the clinical link between obesity and type 2 diabetes.

Weight Loss and Diabetes

Just as obesity and physical inactivity have been strongly linked to diabetes,^{27–29} weight loss or other lifestyle interventions may significantly reduce the risk for developing type 2 diabetes.^{30–32} Moreover, fasting blood glucose, hemoglobin A_{1c} (A1C), and diabetes-related mortality can be reduced with intentional weight loss.^{33–35} In patients with clinically severe obesity, a weight loss of ~50% of excess body weight results in a 30-fold risk reduction in the subsequent development of type 2 diabetes.³⁶

The mechanisms responsible for improved glycemic control are suggested by rodent models of visceral fat excision. In obese Sprague-Dawley rats, the surgical removal of visceral fat (perinephric and epididymal fat pads) improved hepatic insulin sensitivity and altered the expression of TNF- α and leptin genes in subcutaneous fat cells.³⁷ This study suggests that the loss of visceral fat mass may

Table 2. Medical Comorbidities of Obesity

Cardiovascular <ul style="list-style-type: none"> • Coronary artery disease • Congestive heart failure 	Endocrine <ul style="list-style-type: none"> • Diabetes
Respiratory <ul style="list-style-type: none"> • Sleep apnea • Obesity hypoventilation syndrome 	Increased intra-abdominal pressure <ul style="list-style-type: none"> • ERD • Stress urinary incontinence • Venous disease (DVT, edema) • Hernias (inguinal, incisional)
Musculoskeletal <ul style="list-style-type: none"> • Arthritis 	Cancer risk <ul style="list-style-type: none"> • Uterus • Colon • Cervical • Kidney • Prostate
Sex hormone dysfunction <ul style="list-style-type: none"> • Amenorrhea • Hirsutism • Stein-Leventhal syndrome (Polycystic Ovary Syndrome) • Infertility 	

be causative in improving serum glucose control in diabetic patients.

Surgical Treatment of Diabetes in Severe Obesity

The indications for surgery in severely obese patients include a BMI > 40 kg/m² or a BMI > 35 kg/m² if associated with comorbidities.^{10,38} Weight control alone, however, is not usually the primary goal of bariatric surgery; rather, most patients are referred for treatment of comorbidities associated with clinically severe obesity (Table 2).³⁹

The mainstay for treatment of type 2 diabetes centers on aggressive control of blood glucose levels. Unfortunately, attaining euglycemia is frequently impossible in patients with clinically severe obesity, particularly those with insulin resistance. The traditional approach to patients with type 2 diabetes employs a stepwise strategy of diet and exercise, then oral hypoglycemic agents, combination therapy, and finally insulin therapy.⁴⁰ Long-term weight loss is rarely achieved through low-fat diets, anti-obesity drugs, or exercise.⁴¹ While these measures are adequate for patients with mild or moderate obesity, for most patients with clinically severe obesity, any weight loss that does occur is eventually regained. In patients with clinically severe obesity whose weight loss has been refractory to the aforementioned interventions, the recommendation for surgery as the treatment of choice is espoused by the National Institutes of Health.³⁸

Approximately 40,000 bariatric operations are performed in the United States annually; the four main procedures done are the vertical band gastroplasty, Roux-Y gastric bypass, biliopancreatic diversion, and adjustable silicone gastric banding.^{7,42} In 1966, Mason and Ito performed the first gastric bypass procedure for the treatment of severe, refractory obesity. They later presented their data to the American College of Surgeons in 1969, in which they showed an excess weight loss of 44% 1 year after gastric bypass.⁴³ Although the initial results with gastric bypass were modest, the chief advantage of the Roux-Y gastric bypass was the lack of diarrhea, malabsorption, and metabolic sequelae as seen with jejunioileal bypass, a procedure introduced in the 1950s and popularized in the 1960s and 1970s, which also effectively produced significant weight loss.⁴⁴⁻⁴⁶

Since its introduction, Roux-Y gastric bypass has undergone multiple modifications and has emerged as the dominant operation for the treatment of severe obesity. Today, most surgeons create a 20–30 cc gastric pouch and a 60–150 cm Roux limb (Figure 1). The gastric pouch-jejunal anastomosis, as well as the jejunum-jejunum anastomosis, may be constructed using a stapled or hand-sewn technique. The gastric bypass produces weight loss by restricting caloric intake (accomplished by decreasing gastric capacity) and inducing anorexia and/or early satiety.⁵⁰ The gastric bypass is considered by most to be the gold standard bariatric procedure, with excess weight loss \geq 50% and maintained in ~85% of patients at 2 years and 60% at 5 years.⁴⁷⁻⁵⁰ Pories et al.⁵¹ demonstrated a maintained 42% excess weight loss at 11 years postoperatively.

Prevention, improvement, or even cure of type 2 diabetes is seen in patients treated with a variety of bariatric procedures, including jejunioileal bypass (now abandoned), gastric bypass, biliopancreatic diversion, vertical band gastroplasty, and adjustable silicone gastric banding.⁷ One of the first studies to demonstrate this came from Herbst et al.⁵² in 1984. They examined 23 severely obese patients with insulin-requiring type 2 diabetes who underwent either Roux-Y gastric bypass or vertical-banded gastroplasty. Fourteen patients (60%) were able to discontinue insulin postoperatively, and seven patients (an additional 30%) decreased their insulin requirements.

In 1987, a 7-year study was conducted on 141 severely obese patients, 88 with type 2 diabetes and 53 with IGT, who underwent the gastric bypass.⁵³ All but two of the patients (98%) became euglycemic within 4 months after surgery without diabetes medications or special diets. The study was expanded in 1992 and again in 1995 to include a total of 146 individuals with type 2 diabetes and 152 individuals with glucose impairment, followed over a period of up to 14 years postoperatively.^{51,54} At the time of follow-up, 83% of patients with type 2 diabetes and 99% of patients with glucose impairment maintained normal plasma glucose, A1C, and insulin levels. Mortality in this patient population was reduced by gastric bypass from 4.5 to 1% per year.

In a prospective, randomized trial examining a variety of gastric restrictive procedures, researchers found that 75% of subjects with type 2 diabetes were euglycemic off of all diabetes medications 3 years after surgery.⁴⁷ Smith et al.⁵⁵ reported the results of an 8-year trial of 205 morbidly obese diabetic patients treated with a Roux-Y gastric bypass. Postoperatively, 76% of insulin-requiring patients were off insulin, and 82% of those remaining on insulin required lower doses. Of the patients on oral hypoglycemic agents preoperatively, 94% were able to stop them completely after gastric bypass. A small prospective study of 11 severely obese women, 9 of whom were diabetic and 8 with IGT, showed an increase in peripheral insulin sensitivity, a decrease in fasting plasma

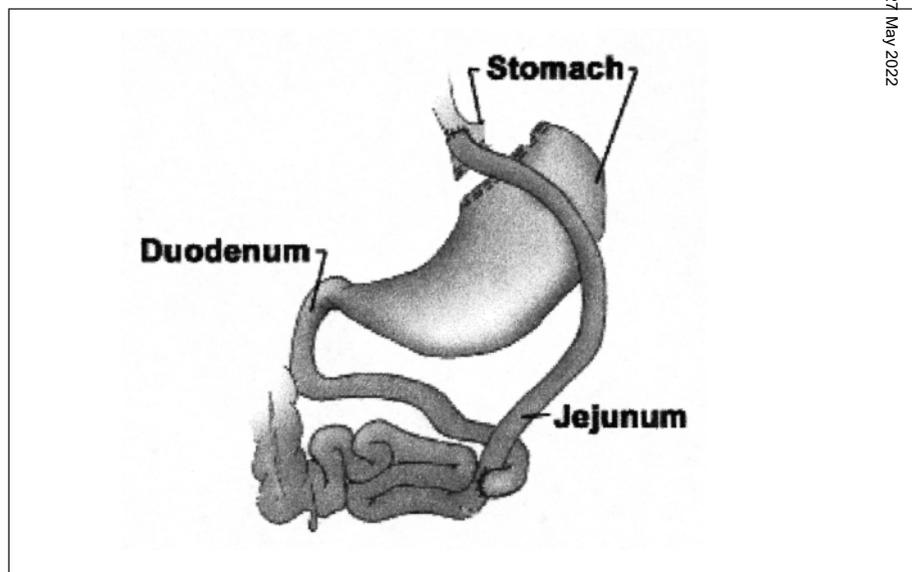


Figure 1. Roux-Y gastric bypass

glucose, and a decrease in A1C. This effect was most pronounced in patients with type 2 diabetes.⁵⁶ This dramatic effect of glycemic control in severely obese individuals is also seen in adolescents treated with gastric bypass.⁵⁷

Obesity surgery not only is an effective treatment of type 2 diabetes in the severely obese, but also may prevent the progression of IGT to diabetes in the same patient population. In a prospective, nonrandomized control study, 136 individuals with clinically severe obesity and IGT were followed for an average of 5.8 years following either gastric bypass surgery or no surgery in the control group.³⁶ The surgically treated group experienced an excess weight loss of ~50% and had a more than 30-fold reduction in the progression of IGT to diabetes. In the control group, 22% of patients developed frank diabetes over the same time period.

Mechanism of Action of Gastric Bypass in Diabetes

As noted previously, it is widely accepted that weight reduction has a beneficial effect on patients with type 2 diabetes or glucose intolerance. In fact, improvements in insulin sensitivity and β -cell function are seen after severely obese individuals sufficiently lose weight.⁵⁹ Several observations suggest that, in surgically treated individuals, factors other than weight loss are likely involved. This is especially evident in gastric bypass operations that exclude the hormonally active foregut. Multiple studies have demonstrated either euglycemia or a dramatic improvement in diabetes control that was achieved long before the patients lost a significant amount of weight.^{39,54,57} Moreover, the remission of diabetes was far more complete than the improvement observed with weight loss through diet alone.⁵⁸

In a study comparing two matched cohorts of obese women, one group underwent bypass surgery, while the control group was treated without surgery. Despite the fact that both groups were matched for weight throughout the study—thus excluding weight loss as a variable—the surgical group nonetheless had a lower fasting plasma insulin, fasting plasma glucose, and higher insulin sensitivity.³⁹ Improvement in insulin resistance in nondiabetic severely obese patients, uniformly seen in patients after gastric bypass, also occurred sooner than

could be accounted for by weight loss alone.⁶⁰

These studies support the notion that postoperative decreased food intake and exclusion of the foregut play a major role in diabetes control following bypass surgery. The observation that vertical band gastroplasty, which does not bypass the stomach or duodenum, produces inferior control of glucose and insulin levels as compared with gastric bypass, despite significantly lowering food intake. This suggests that exclusion of the foregut is a dominant factor.

Bypassing the stomach, duodenum, and the first portion of the jejunum excludes the foregut from the enteroinsular axis and delivers partially digested food to the mid-small bowel. Pories et al. have suggested that the exclusion of food from the stomach and duodenum results in a secondary alteration in hormone signals from the enteroinsular axis. In normal individuals, insulinotropic factors (incretins) are released from cells of the foregut in response to a meal stimulus. The two best studied incretins are gastric inhibitory polypeptide (GIP) and glucagon-like polypeptide-1 (GLP-1), implicated as central to the enteroinsular axis in type 2 diabetes.^{58,61}

It is possible that an abnormal incretin signal from the gut seen in type 2 diabetic patients leads to a cycle of hyperinsulinemia and worsening insulin resistance; GLP-1 infusion has been shown to affect fasting hyperglycemia in patients with type 2 diabetes.⁶² It is proposed that this cycle is subsequently broken by foregut exclusion.⁵⁸ Alternatively, Rubino and Gagner¹⁰ have proposed that stimulation of the foregut in diabetic patients may induce the overproduction of an unknown factor that antagonizes incretin function, leading to dysregulated insulin production and glucose intolerance. Gastric bypass therefore eliminates this anti-incretin phenomenon. Simultaneously, early presentation of food to the more distal gut may induce the production of pro-insular hormones (such as GLP-1). This latter effect is also seen following jejunoileal bypass, where elevated levels of GIP and GLP-1 are noted 20 years postoperatively.⁶³

Thus, it is clear that the physical bypass of the foregut in gastric bypass surgery is central to the long-term normalization of glucose metabolism in obese patients with type 2 diabetes. Although alterations in production of

known gut hormones have been implicated in this function, their precise role is still unclear. In addition, it is possible that as yet unidentified mediators play a role in postoperative maintenance of glucose homeostasis. Clinical experiments remain to be carried out to better define the function of the incretins in normal and diabetic patients, identify other gastrointestinal hormones involved in the process of glucose metabolism, and study the long-term effects of surgical foregut exclusion on these processes and their relevance to the treatment of diabetes.

Conclusion

Obesity and type 2 diabetes are significant health problems worldwide that often coexist in the same individuals. Most people who have type 2 diabetes are obese, and obesity is one of the most important risk factors for developing type 2 diabetes.^{15,16} Weight loss is at the cornerstone of medical treatment programs for diabetes, but long-term results are often disappointing, especially in the severely obese population.⁷

Bariatric surgical procedures provide consistent, long-term weight-loss in severely obese patients. In addition, such procedures, especially bypass operations, provide a high rate of cure from type 2 diabetes and prevent the progression to diabetes in high-risk populations.

Recently, gastric bypass surgery has been performed using a minimally invasive approach. The procedure is performed utilizing four 5-mm incisions and two 12-mm incisions (total of six small incisions). Through these small incisions, the stomach is transected and a Roux limb of small intestine is created just as one would for the open procedure, which requires a 20–30 cm incision. When this procedure is performed laparoscopically, patients experience less postoperative pain, shorter lengths of stay, and fewer wound complications.^{64,65} Equally important, the correction of medical comorbidities after laparoscopic Roux-Y gastric bypass is comparable to the success of the open procedure.⁶⁶

Curiously, the resolution of diabetes after bariatric surgical procedures is independent of weight loss alone, and exclusion of the foregut appears to play a necessary role. More studies are needed to fully elucidate this mechanism, which may also help in our understanding of the patho-

physiology of type 2 diabetes in general. Clearly, surgery for clinically severe obesity provides a potential for cure in patients with type 2 diabetes and should be considered in all severely obese, individuals with diabetes.

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