Bariatric surgery for type 2 diabetes: Weighing the impact for obese patients

ABSTRACT

Obesity is a potent risk factor for the development and progression of type 2 diabetes, and weight loss is a key component of diabetes management. Bariatric surgery results in significant weight loss and remission of diabetes in most patients. After surgery, glycemic control is restored by a combination of enforced caloric restriction, enhanced insulin sensitivity, and increased insulin secretion.

KEY POINTS

After Roux-en-Y gastric bypass and biliopancreatic diversion, normoglycemia is restored within days, even before the patient has lost much weight.

Alterations in postprandial levels of intestine-derived hormones (glucagon-like peptide 1, peptide YY, and ghrelin) contribute to the robust metabolic benefits of intestinal bypass procedures.

Nutritional deficiencies are common after bariatric surgery, and long-term follow-up is mandatory for surveillance of metabolic status.

Although curing diabetes cannot yet be considered a goal of bariatric surgery, it may be a serendipitous benefit.

Evidence is mounting for the use of bariatric surgery to treat type 2 diabetes mellitus in patients whose body mass index (BMI) is 35 kg/m² or higher. In obese patients who also have type 2 diabetes, bariatric surgery sends it into remission (defined as normoglycemic control without the need for diabetic medications) in more than three-fourths of cases, with higher rates with the Roux-en-Y gastric bypass procedure than with the laparoscopic adjustable gastric banding procedure.

However, data on the effects of this surgery on type 2 diabetes come primarily from observational studies that lacked appropriate control groups, and the relative benefit of bariatric surgery vs aggressive medical antidiabetic therapy is not yet known. Needed are randomized trials comparing the two types of therapy (and the various types of bariatric surgery) in diabetic patients with less-severe obesity.

Further, why would bariatric surgery help with diabetes, and why would one procedure do it better than another? To be honest, we are not sure, but evidence points not only to weight loss but also to better insulin sensitivity and to alterations in levels of hormones secreted by the gut that increase insulin secretion.

OBESITY PROMOTES DIABETES; WEIGHT LOSS COUNTERACTS IT

Type 2 diabetes mellitus is a complex metabolic disease characterized by insulin resistance and progressive failure of pancreatic beta cells, resulting in hyperglycemia.¹²

Obesity, a potent risk factor for type 2 diabetes, contributes to its development by inducing insulin resistance and inflammation, which in turn impair glucose regulation.³⁴
deposits in the abdomen, muscles, and liver contribute to elevations of circulating free fatty acids and adipocyte-derived cytokines that mediate insulin resistance and inflammatory pathways.5

In the Diabetes Prevention Program,6 modest weight loss (5% to 10% of body weight) through diet and exercise reduced the incidence of type 2 diabetes, and in the ongoing Action for Health in Diabetes (Look AHEAD) study of the National Institutes of Health, it improved glucose homeostasis.7,8

The current medical approach to type 2 diabetes includes advising the patient to lose weight through lifestyle modification, and prescribing drugs that restore glycemic control by reducing insulin resistance (biguanides, glitazones) and improving insulin secretion (incretin mimetics and analogues and sulfonylureas).9,10

However, several factors make type 2 diabetes challenging to treat in obese people. Patients who lose weight via behavioral changes and weight-loss drugs tend to gain the weight back. Antidiabetic drugs pose the risk of hypoglycemia. Moreover, although many new classes of drugs have been developed to treat type 2 diabetes, most patients fail to achieve the American Diabetes Association goal for glycemic control, ie, a hemoglobin A1c level lower than 7%.11

### BARIATRIC PROCEDURES AND THEIR EFFECT ON DIABETES CONTROL

After bariatric surgery, patients lose more weight than with traditional weight-loss methods—up to 25% of their total body weight. Furthermore, of those with type 2 diabetes, 87% achieve at least better glucose control and need fewer antidiabetic medications,12 and an average of 78% achieve normal glycemic control without taking any antidiabetic medications at all.12,13

But not all bariatric procedures have the same effect on weight and diabetes: certain procedures have a greater effect.

The two major types are classified as gastric restrictive procedures and intestinal bypass procedures. The classification was initially based on the presumed mechanism of weight loss.

**Gastric restrictive procedures** (laparoscopic adjustable gastric banding, sleeve gastrectomy, vertical gastroplasty) limit gastric volume and, hence, restrict the intake of calories by inducing satiety. Afterward, patients lose approximately 10% to 20% of their total body weight.

Furthermore, multiple studies, including a randomized controlled trial14 (more about this below), have shown remission of type 2 diabetes with laparoscopic adjustable gastric banding but not with conventional medical therapy. The effect is primarily mediated by weight loss and improved insulin sensitivity, both of which occur several months following surgery. Of note, however: in this trial, all the patients had diabetes of short duration, less than 2 years.

Furthermore, multiple studies, including a randomized controlled trial14 (more about this below), have shown remission of type 2 diabetes with laparoscopic adjustable gastric banding but not with conventional medical therapy. The effect is primarily mediated by weight loss and improved insulin sensitivity, both of which occur several months following surgery. Of note, however: in this trial, all the patients had diabetes of short duration, less than 2 years.

**Intestinal bypass procedures** (Roux-en-Y gastric bypass, biliopancreatic diversion) also restrict caloric intake, the way gastric banding and vertical gastroplasty do. But because the small intestine is shortened, they have an added component of malabsorption of fat and nutrients. Afterward, more patients experience remission of type 2 diabetes (82%–99%) than after gastric restrictive operations, even patients with longer duration of disease, including those treated with insulin (TABLE 1).12,13

### TABLE 1

<table>
<thead>
<tr>
<th>Outcomes of different bariatric procedures</th>
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<tbody>
<tr>
<td><strong>LAPAROSCOPIC ADJUSTABLE GASTRIC BANDING</strong></td>
</tr>
<tr>
<td>Excess weight loss</td>
</tr>
<tr>
<td>Operative mortality</td>
</tr>
<tr>
<td>Remission of type 2 diabetes mellitus</td>
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<tr>
<td>Remission of hyperlipidemia</td>
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<td>Remission of hypertension</td>
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Patients tend to gain back the weight they lose by behavioral changes and weight-loss drugs.
BARIATRIC SURGERY FOR TYPE 2 DIABETES

Hence, different procedures have different effects on diabetes. The speed at which type 2 diabetes goes into remission differs with restrictive vs malabsorptive procedures. After Roux-en-Y gastric bypass and biliopancreatic diversion, diabetes remits within days, even before the patient has lost much weight. This does not happen after gastric restrictive procedures.

Observational studies of the effect of Roux-en-Y surgery on diabetes

Several observational studies have evaluated the benefit of Roux-en-Y surgery for patients with type 2 diabetes mellitus. Pories et al followed 608 severely obese patients, of whom 165 (27%) had type 2 diabetes or impaired glucose tolerance. At a mean follow-up of 7.6 years after surgery, 83% of the diabetic patients were off their antidiabetic drugs, and 99% of those with impaired glucose tolerance were normoglycemic, with normal fasting glucose and hemoglobin A1c levels. Marked improvements in hyperlipidemia, hypertension, fertility, osteoarthritis, and obstructive sleep apnea were also noted.

Schauer et al observed similar results in 1,160 morbidly obese patients, of whom 240 (21%) had type 2 diabetes or impaired fasting glucose. After laparoscopic Roux-en-Y gastric bypass surgery, fasting glucose and hemoglobin A1c levels returned to normal levels in 83% of cases and were markedly improved in the remaining 17%. Significantly (80%) fewer patients needed oral antidiabetic agents or insulin (79% fewer). Patients most likely to achieve complete remission of diabetes were those with the shortest duration of diabetes (< 5 years), the mildest severity of diabetes (diet-controlled), and the greatest weight loss after surgery. The rate of diabetes remission in patients who had been diabetic for 5 years or less was 95%, compared with 75% in those who had been diabetic for 6 to 10 years and 54% in those who had been diabetic for more than 10 years (P < .001).

Scopinaro et al reported long-term follow-up data on 312 patients with type 2 diabetes who underwent biliopancreatic diversion; 310 patients (99%) achieved normal fasting glucose values by 1 year after surgery. At 10 years after surgery, 98% of the patients were still in complete remission of diabetes, defined as normal glucose values without the use of antidiabetic medications.

The Swedish Obese Subjects (SOS) study prospectively followed 1,703 patients, of whom 118 had type 2 diabetes, for 10 years after various bariatric surgery procedures (primarily vertical gastroplasty). In a control group that received medical therapy, 77 patients had type 2 diabetes. Medical therapy was ill-defined with respect to aggressiveness and adherence to intervention with lifestyle and pharmacotherapy.

At 2 years, the surgical group had lost a mean of 28 kg, glycemic control had improved in the diabetic patients, and many of them had been able to stop taking oral hypoglycemic drugs or insulin. In contrast, the need for these agents increased in the medically treated patients. The proportion treated by diet alone rose from 59% to 73% in the surgical group, but declined from 55% to 34% in the nonsurgical group.

In these studies, surgery also reduced the risk of progressing from impaired glucose tolerance to type 2 diabetes; the risk was 30 times lower in the study by Pories et al. In the SOS study, the frequency of diabetes was 30 times lower at 2 years and five times lower at 8 years after surgery.

Limitations of the studies

Although these data seem encouraging, these studies had major limitations. The patients were mostly white women with severe obesity, ie, a BMI greater than 40 kg/m², which is not representative of patients with type 2 diabetes in the community. Only about 20% had glucose intolerance or overt type 2 diabetes mellitus. Would other groups benefit, particularly men and those with less-severe obesity?

Moreover, these studies were observational, with no randomized control groups. Many reports consisted of large case series. It is not clear that the findings can be extrapolated to the general population.
清楚如何具体采用的减重手术及选择减重手术的指导原则。缺乏完整的长期随访数据也是一个问题。

需要的是大型的随机对照试验，评估各种减重手术在较不肥胖的2型糖尿病患者中（即一般社区常见者）的效果。此外，手术尚未与更积极的医学减肥策略直接比较，如糖尿病预防项目（Diabetes Prevention Project）和Look AHEAD试验。

一项随机对照试验
胃旁路手术
到目前为止，唯一的一项随机对照试验是Dixon等14年进行的，该试验将60名2型糖尿病患者（病程<2年，平均血红蛋白A1c 7.7%）随机分配至标准医学治疗组或胃旁路手术组。

<table>
<thead>
<tr>
<th>指标</th>
<th>结果</th>
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<tbody>
<tr>
<td>糖尿病缓解速率</td>
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</tr>
<tr>
<td>胰岛素敏感性</td>
<td>改善</td>
</tr>
<tr>
<td>胰岛素分泌增加</td>
<td>增加</td>
</tr>
<tr>
<td>胰高血糖素-1水平变化</td>
<td>无变化</td>
</tr>
<tr>
<td>肽YY水平变化</td>
<td>增加</td>
</tr>
<tr>
<td>葡萄糖依赖的胰岛素分泌水平</td>
<td>无变化（或增加）</td>
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14年，将60名2型糖尿病患者（病程<2年和平均血红蛋白A1c 7.7%）随机分配至标准医学治疗组或胃旁路手术组。医学治疗组的平均体重减轻率为1.7%，而手术组为20.7%（P < .001）。体重减轻与2型糖尿病的缓解率显著相关。

研究具有争议性，因为它认为医学干预比糖尿病预防项目和Look AHEAD试验更不积极。

糖尿病代谢并发症

类型2糖尿病通常视作一项进展性疾病，其特点是β细胞功能的持续恶化。许多内分泌学家支持在疾病早期采用激进的减肥策略。我们认为，应早期考虑减重手术，因为它可能有助于保留胰岛β细胞功能并延缓微血管和大血管并发症的进步。

减重手术在有糖尿病患者的使用

根据国家卫生院的指南，这种类型的减重手术包括BMI为40 kg/m²或更高，或BMI介于35和40 kg/m²之间，同时至少有二个与肥胖相关的合并症。糖尿病被认为是关键合并症，它能够评估手术的风险。这些指南建议必须讨论减重手术，特别是对于那些未能通过其他减肥方法减重的严重肥胖的2型糖尿病患者。

根据疾病的发展阶段，许多内分泌学家认为在早期使用激进的减肥策略是合理的。我们相信，与激进的减肥策略相比，早期使用减重手术可能有助于保留胰岛β细胞功能并延缓微血管和大血管并发症的进步。

Laparoscopic adjustable gastric banding is considered the safest bariatric procedure currently performed.
How gut hormones may contribute to regression of diabetes after Roux-en-Y surgery

After Roux-en-Y surgery, the anatomy of the gastrointestinal tract is altered, and so are the levels of various hormones secreted by the gut. These alterations may partially explain the impressive weight loss and reversal of type 2 diabetes that occur.

**Restrictive gastric pouch**

- **Ghrelin**, secreted by the gastric fundus, stimulates appetite. Levels are lower after surgery, contributing to satiety.
- **Glucagon-like peptide 1** (GLP-1) is secreted in the distal small intestine in response to food, stimulating insulin release, suppressing glucagon, and also inducing satiety. After surgery, food reaches the jejunum faster, and GLP-1 levels are markedly higher.
- **Peptide YY**, secreted in the distal small intestine in response to food, induces satiety; levels are higher after surgery.
- **Glucose-dependent insulinotropic peptide** (GIP), secreted by the duodenum, stimulates insulin release. Levels either increase or do not change after surgery.

**Intestinal gluconeogenesis is increased.**

**Food and digestive enzymes mix.**

**Passage of food into the distal small intestine is accelerated.**

**Food no longer travels through the bypassed duodenum; partial malabsorption of fat occurs.**
HOW DOES BARIATRIC SURGERY IMPROVE TYPE 2 DIABETES?

Three major mechanisms have been proposed to explain how bariatric surgery reverses diabetes.24,25 Table 2 summarizes the effects of the different procedures on factors involved.

Hypothesis 1: Weight loss increases insulin sensitivity
The enforced caloric restriction, negative energy balance, and weight loss after bariatric surgery reduce insulin resistance. Consequently, the beta cells can rest because they don’t need to produce as much insulin. These effects have been observed after both gastric restrictive procedures and gastric bypass procedures.

Hypothesis 2: Less lipotoxicity, inflammation
Another theory is that bariatric surgery lessens insulin resistance by reducing “lipotoxicity,” a condition related to dysregulated fatty acid flux, lipid metabolites in tissues, and direct and indirect effects of hormones secreted by adipocytes.

The strongest evidence for this theory comes from Bikman et al,26 who found that insulin sensitivity increased after Roux-en-Y surgery more than expected from weight loss alone. One year after surgery, even though they remained anthropometrically obese (BMI > 30 kg/m²), the patients had insulin sensitivity levels similar to those in a control group of lean people (BMI < 25 kg/m²).

Insulin sensitivity begins to improve within 1 week of intestinal bypass procedures,15,27 suggesting that these procedures are doing something more than simply forcing weight loss via caloric restriction, as gastric restrictive procedures do.

Hypothesis 3: An effect on gut hormones
The third theory is likely the most relevant and relates to various hormones secreted by the gut in response to food (Figure 1). Surgical exclusion of the duodenum in the Roux-en-Y procedure and exclusion of the duodenum and jejunum in biliopancreatic diversion result in altered sites—or at least altered relative distribution—of carbohydrate and fat absorption.

The “hindgut hypothesis” raised by Cummings et al24 suggests that accelerated transit of concentrated nutrients (particularly glucose) to the distal intestine results in increased production of insulinoactive and appetite-controlling substances, which account for the reversal of hyperglycemia and obesity.

In contrast, the “foregut hypothesis” raised by Rubino et al28 suggests that nutrient interactions in the duodenum are diabetogenic and, hence, bypassing the duodenum would reverse this defect. Their conclusions come from experiments in rodents that underwent jejunoileal bypass and subsequent refeeding through the bypassed intestine.

GUT HORMONES AND OTHER PEPTIDES ALTERED BY BARIATRIC SURGERY

Incretin hormones: GLP-1, GIP
Gastrointestinal hormones that increase insulin release after a meal are known as incretins. Of interest, they have this effect only when glucose is ingested orally—not when it is infused intravenously.29,30

Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinoactive peptide (GIP) account for 50% to 60% of nutrient-related insulin secretion. In addition to stimulating insulin, GLP-1 suppresses glucagon and slows gastric emptying, which delays digestion and reduces postprandial glycemia. GLP-1 also acts on the hypothalamus to induce satiety.

Laferrière et al31 and others32,33 documented robust increases in postprandial levels of GLP-1 within 4 weeks after Roux-en-Y surgery. GLP-1 levels did not increase with comparable weight loss induced by diet.

Rubino et al28,34 documented similar findings that occurred prior to marked weight loss, suggesting that the benefit of Roux-en-Y surgery on remission of diabetes may not be completely attributable to reduced caloric intake and weight loss. Insulin secretion is generally reduced after gastric restrictive procedures (eg, laparoscopic adjustable gastric banding) and biliopancreatic diversion,35 and is increased after Roux-en-Y gastric bypass.32,33,36

Noninsulinoactive peptides: Ghrelin, peptide YY
Noninsulinoactive gut peptides that are altered after Roux-en-Y surgery include ghrelin and peptide YY.
BARIATRIC SURGERY FOR TYPE 2 DIABETES

Ghrelin, a hormone derived from the gastric fundus, stimulates appetite. Ghrelin concentrations are lower after Roux-en-Y surgery, indicating that suppression of hunger signals helps sustain weight loss. In contrast, ghrelin levels increase with diet-induced weight loss.37 However, the data on ghrelin levels at various times after bariatric surgical procedures are not consistent.33,38

Peptide YY, like GLP-1, is secreted by L cells of the distal small intestine and is responsible for increasing satiety and delaying gastric emptying after meals. Numerous studies have consistently documented increases in post-prandial peptide YY and GLP-1 levels after gastric bypass.32,33,39–41

**TABLE 3**

**Nutritional deficiencies after gastric bypass surgery**

Vitamins A, E, and K
Vitamin B<sub>12</sub>
Vitamin D (25-hydroxyvitamin D<sub>3</sub>)
Zinc
Iron
Ferritin
Selenium
Folate
Thiamine

In the first 6 weeks after Roux-en-Y gastric bypass or biliopancreatic diversion, insulin sensitivity improves while insulin secretion increases disproportionately, associated with a robust increase in GLP-1, and resulting in normal glucose homeostasis.16,31,42

In contrast, patients who lose weight by dieting or undergoing gastric restrictive procedures show a modest increase in insulin sensitivity and a compensatory reduction in insulin secretion, termed “beta-cell rest.”16,31,42

**RISKS OF BARIATRIC SURGERY**

**Short-term risks**

An important concern about using bariatric surgery to treat type 2 diabetes is the risk of morbidity and death associated with these procedures. Buchwald et al performed a meta-analysis of 136 bariatric studies that included 22,094 patients. The 30-day operative death rates were 1.1% with biliopancreatic diversion, 0.5% with Roux-en-Y surgery, and 0.1% with restrictive procedures.

Laparoscopic adjustable gastric banding is considered the safest of the current bariatric procedures. It does not involve bowel anastomosis, and the risks of major hemorrhage, gastric perforation, and pulmonary embolism are less than 1%. Late complications requiring reoperation include band slippage or prolapse (5%–10%) and band erosion (1%–3%). The entire intestinal tract is left intact, so subsequent nutritional deficiencies are rare.43

Roux-en-Y gastric bypass carries an overall risk of major complications of 10% to 15%. Anastomotic leak (1%–5%), pulmonary embolism (< 1%), and hemorrhage (1%–4%) can be life-threatening but are rare if the staff are experienced. Late complications such as ulcer or stricture formation at the gastrojejunostomy site occur in 5% to 10% of cases and are managed nonoperatively.

**Nutritional deficiencies**

Nutritional deficiencies, including protein-calorie malnutrition and deficiencies of iron, other minerals, and vitamins A, E, D, and B<sub>12</sub>, occur in 30% to 70% of patients (TABLE 3). Patients at high risk of developing severe nutritional deficiencies include those who have lost more than 10% of their body weight by 1 month, those with anastomotic stenosis, those undergoing surgical revision, and those with persistent vomiting.44
Protein-calorie malnutrition is recognized by signs such as edema, hypoalbuminemia, anemia, and hair loss. To minimize this problem after Roux-en-Y surgery, we suggest that patients take in 60 to 80 g of protein and 700 to 800 kcal a day.

Vitamin deficiencies can lead to Wernicke encephalopathy (due to thiamine deficiency), peripheral neuropathy (due to vitamin B₁₂ deficiency), and metabolic bone disease (due to long-term deficiencies of vitamin D and calcium). Often, vitamin deficiencies are present before surgery and require prompt supplementation to avoid exacerbation of these deficiencies afterward.

Biliopancreatic diversion procedures are performed at relatively few centers worldwide, largely because of the massive amounts of protein, fat, and carbohydrate malabsorption they cause. Long-term deficiencies of fat-soluble vitamins, iron, calcium, and vitamins B₁₂ and D have been reported in one-third to one-half of patients undergoing these procedures, and nutritional supplementation is mandatory. Protein-calorie malnutrition occurs in 7% of cases, and 2% of patients require operative revision to lengthen the common channel.

Monitoring of nutrient and vitamin levels after bariatric surgery is recommended at least every 6 months. TABLE 3 summarizes the nutrient deficiencies to expect after Roux-en-Y surgery; TABLE 4 lists replacement strategies.

In rare cases, severe hypoglycemia has been noted after Roux-en-Y surgery and is associated with prandial hyperinsulinemia related to elevated GLP-1 levels. Neuroglycopenia and seizures have been reported in severe cases. Initial treatment of hypoglycemia involves dietary modification targeting carbohydrate restriction, the use of alpha glucosidase inhibitors such as acarbose (Precose), and referral to an endocrinologist for further management.

Long-term death rates
Death rates after bariatric surgery must be weighed against the long-term cardiovascular risks of continued obesity and type 2 diabetes.

Strong evidence now exists that bariatric surgery increases life expectancy and that this is largely attributable to reduction in cardiovascular risk factors such as diabetes and cancer. Recent studies have found that the long-term death rate is 32% to 73% lower for patients undergoing bariatric surgery than in matched controls who do not undergo surgery. A decrease in the death rate related to diabetes has played an important role in these results.

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