REVIEW

CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will advise patients on bariatric surgery's indications and possible benefits

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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.

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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/m^2 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.[1,2]

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.[3,4] Fat

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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 A_{1c} 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.

Patients tend to gain back the weight they lose by behavioral changes and weight-loss drugs

Furthermore, multiple studies, including a randomized controlled trial[14] (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,[14] 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

Outcomes of different bariatric procedures

	LAPAROSCOPIC ADJUSTABLE GASTRIC BANDING	ROUX-EN-Y GASTRIC BYPASS	BILIO-PANCREATIC DIVERSION
Excess weight loss	46.2%	59.5%	63.3%
Operative mortality	0.1%	0.5%	1.1%
Remission of type 2 diabetes mellitus	56.7%	80.3%	95.1%
Remission of hyperlipidemia	59%	97%	99%
Remission of hypertension	43%	68%	83%

DATA FROM BUCHWALD H, ESTOK R, FAHRBACH K, ET AL. WEIGHT AND TYPE 2 DIABETES AFTER BARIATRIC SURGERY: SYSTEMATIC REVIEW AND META-ANALYSIS. AM J MED 2009; 122:248–256; AND BUCHWALD H, AVIDOR Y, BRAUNWALD E, ET AL. BARIATRIC SURGERY: A SYSTEMATIC REVIEW AND META-ANALYSIS. JAMA 2004; 292:1724–1737.

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Hence, different procedures have different effects on diabetes.[12] 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.[15] This does not happen after gastric restrictive procedures.[12,16]

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[15] 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 A_{1c} levels. Marked improvements in hyperlipidemia, hypertension, fertility, osteoarthritis, and obstructive sleep apnea were also noted.

The effect of Roux-en-Y surgery on diabetes may not be completely attributable to weight loss

Schauer et al[17] 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 A_{1c} 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 ($P < .001$).

The Swedish Obese Subjects (SOS) study[18] 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.[13]

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.[15] In the SOS study,[18] the frequency of diabetes was 30 times lower at 2 years and five times lower at 8 years after surgery.

Studies of biliopancreatic diversion

Data on the effects of biliopancreatic diversion, a primarily malabsorptive procedure, are limited to European studies.

Scopinaro et al[19,20] 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.

Others have noted similar findings.[21,22]

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/m^2, 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

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TABLE 2

Antidiabetic effects of bariatric procedures

	LAPAROSCOPIC ADJUSTABLE GASTRIC BANDING	ROUX-EN-Y GASTRIC BYPASS	BILIOPANCREATIC DIVERSION
Tempo of diabetes remission	Slow	Rapid	Rapid
Insulin sensitivity	Improved	Improved	Supranormal
Insulin secretion	Reduced	Increased	Reduced
Glucagon-like peptide-1 levels	No change	Increased	Increased
Peptide YY levels	No change	Increased	Increased
Glucose-dependent insulinotropic peptide levels	No change	No change or increased	Reduced

ADAPTED FROM MINGRONE G. ROLE OF THE INCRETIN SYSTEM IN THE REMISSION OF TYPE 2 DIABETES FOLLOWING BARIATRIC SURGERY. NUTR METAB CARDIOVASC DIS 2008; 18:574–579, WITH PERMISSION FROM ELSEVIER; HTTP://WWW.SCIENCEDIRECT.COM/SCIENCE/JOURNAL/09394753.

clear how specific bariatric procedures were chosen or what criteria were used for performing bariatric surgery. A lack of complete follow-up data is also a concern.

Needed are large randomized trials evaluating the effects of various bariatric procedures in a less obese cohort with type 2 diabetes, ie, typical patients seen in the community. Moreover, surgery has not been compared directly with more vigorous medical weight-loss strategies, such as those used in the Diabetes Prevention Project[6] and the Look AHEAD trial.[7,8]

A randomized controlled trial of gastric banding

The only randomized controlled trial to date that compared standard medical diabetes therapy with bariatric surgery was conducted by Dixon et al.[14]

Sixty patients with type 2 diabetes (duration < 2 years and mean hemoglobin A_{1c} 7.7%) were randomized either to receive medical management as defined by the American Diabetes Association guidelines or to undergo laparoscopic adjustable gastric banding.

At 2 years, the rate of remission (defined as hemoglobin A_{1c} < 6.2% and a normal fasting glucose level) was 13% in the medical treatment group vs 73% in the surgery group (P < .001). Patients receiving medical treatment had lost a mean of 1.7% of their body weight, vs 20.7% in the surgical patients (P < .001). Weight loss was strongly associated with remission of type 2 diabetes after surgery.

This study was controversial in that the medical intervention in this trial was not as aggressive as in the Diabetes Prevention Project and Look AHEAD trials.

INDICATIONS FOR BARIATRIC SURGERY IN PATIENTS WITH DIABETES

According to guidelines from the National Institutes of Health,[23] the current indications for bariatric surgery include a BMI of 40 kg/m^2 or higher, or a BMI between 35 and 40 kg/m^2 with at least two obesity-related comorbidities. Diabetes is considered a key comorbidity that justifies the risk of surgery. The guidelines suggest that bariatric surgery be discussed with all severely obese patients (BMI > 35 kg/m^2) with type 2 diabetes who have not been able to lose weight with other weight-control approaches.

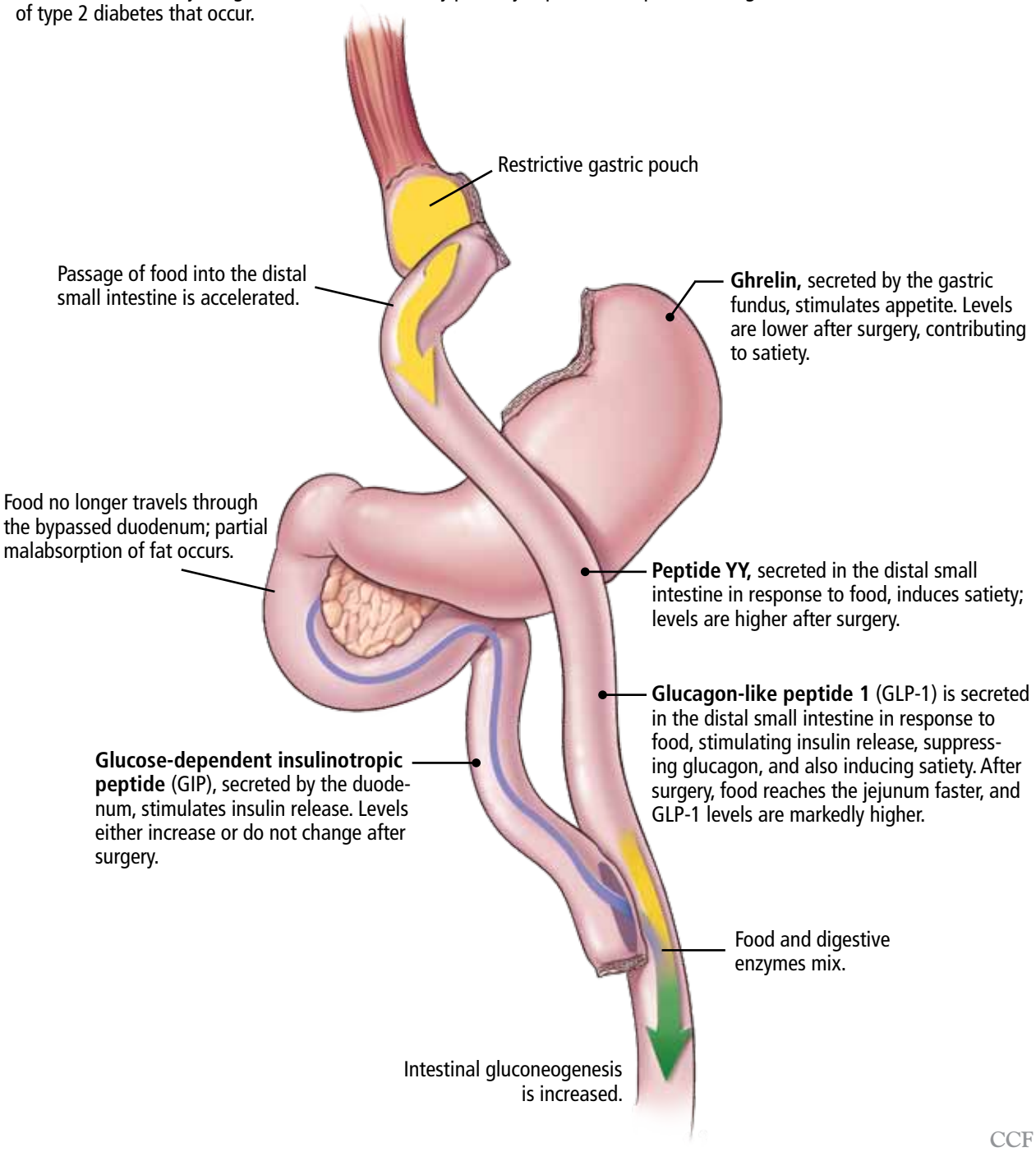
Since type 2 diabetes mellitus is a progressive disease characterized by relentless deterioration of beta-cell function, many endocrinologists favor aggressive weight-loss approaches early in the course of the disease. We believe that bariatric surgery should be considered early, as it may help preserve pancreatic beta-cell function and slow the progression of microvascular and macrovascular complications.

Laparoscopic adjustable gastric banding is considered the safest bariatric procedure currently performed

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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.



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FIGURE 1

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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/m^2), the patients had insulin sensitivity levels similar to those in a control group of lean people (BMI < 25 kg/m^2).

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 al[24] suggests that accelerated transit of concentrated nutrients (particularly glucose) to the distal intestine results in increased production of insulinotropic and appetite-controlling substances, which account for the reversal of hyperglycemia and obesity.

In contrast, the "foregut hypothesis" raised by Rubino et al[28] 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 insulinotropic 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.

Laferrère et al[31] and others[32,33] 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 al[28,34] 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]

The risks of bariatric surgery must be weighed against the risks of continued obesity and type 2 diabetes

Noninsulinotropic peptides: Ghrelin, peptide YY

Noninsulinotropic gut peptides that are altered after Roux-en-Y surgery include ghrelin and peptide YY.

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TABLE 3

Nutritional deficiencies after gastric bypass surgery

Vitamins A, E, and K
Vitamin B_{12}
Vitamin D (25-hydroxyvitamin D_3)
Zinc
Iron
Ferritin
Selenium
Folate
Thiamine

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 postprandial peptide YY and GLP-1 levels after gastric bypass.[32,33,39–41]

ACUTE EFFECTS OF BARIATRIC SURGERY ON INSULIN SECRETION, SENSITIVITY

Bariatric surgery alters both insulin secretion and insulin sensitivity, thus improving glucose regulation.

The relationship between insulin secretion and sensitivity is a hyperbolic curve, so that any change in insulin sensitivity is balanced by a reciprocal and proportionate change in insulin secretion. The development of type 2 diabetes is characterized by a reduction in insulin secretion (decompensation) relative to the severity of insulin resistance.

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[13] 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_{12}, 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]

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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 B_{12} deficiency),[45,46] 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 B_{12} and D have been reported in one-third to one-half of patients undergoing these procedures, and nutritional supplementation is mandatory.[43] 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.[36,47] 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.

TABLE 4

Nutritional supplementation after bariatric surgery procedures

	ROUX-EN-Y GASTRIC BYPASS	LAPAROSCOPIC ADJUSTABLE GASTRIC BANDING
Calcium and vitamin D	Calcium citrate 1,500 mg per day	Calcium citrate 1,500 mg per day
Vitamin D	Ergocalciferol 50,000 U 3–4 times a week	Ergocalciferol 50,000 U 1–2 times a week if low
Vitamin B_{12}	1,000 µg intramuscularly every month, or 100–300 µg by mouth every day	Not required unless low
Vitamins A, D, E, and K	1 multivitamin tablet per day	1 multivitamin tablet per day
Iron	45–60 mg/day	45-60 mg/day
Vitamin C	500 mg/day	500 mg/day
Zinc	15 mg/day	15 mg/day

ADAPTED FROM TUCKER ON, SZOMSTEIN S, ROSENTHAL RJ. NUTRITIONAL CONSEQUENCES OF WEIGHT-LOSS SURGERY. MED CLIN NORTH AM 2007; 91:499–514, WITH PERMISSION FROM ELSEVIER; HTTP://WWW.SCIENCEDIRECT.COM/SCIENCE/JOURNAL/00257125.

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[48] 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.[49] A decrease in the death rate related to diabetes has played an important role in these results. ■

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