Bariatric Surgery as a Novel Treatment for Type 2 Diabetes Mellitus

A Systematic Review

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Objective: To systematically review the literature pertaining to the reversal of type 2 diabetes mellitus (DM2) after Roux-en-Y gastric bypass and adjustable gastric banding.

Data Sources: We conducted a review of the literature using PubMed and searched the reference lists of published studies to identify additional studies.

Study Selection: We selected all published articles that were relevant with respect to bariatric surgery and its metabolic effects.

Data Extraction: Only 9 original articles reporting on DM2 reversal rates after bariatric surgery were identified: 1 randomized controlled trial and 8 observational studies. Other referenced articles serve as background literature.

Data Synthesis: Roux-en-Y gastric bypass leads to a reversal rate of DM2 of 83%. Adjustable gastric banding confers a reversal rate of 62%, and this effect is achieved later after surgery.

Conclusions: Bariatric surgery leads to marked and long-lasting weight reduction. A large proportion of patients undergoing bariatric surgery have DM2. In fact, the presence of diabetes mellitus is a compelling argument to perform bariatric surgery in those who are eligible according to international criteria. Glycemic control improves in the months after laparoscopic adjustable gastric banding, but it improves more rapidly and completely after laparoscopic Roux-en-Y gastric bypass surgery. Thus, both types of surgery are capable of improving or even curing DM2, but the mechanisms may differ.

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In 2004, at least 33% of the adult population of the United States had a body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) of more than 30, and more than one-third of this group had a BMI of more than 35. Moreover, the prevalence of obesity is expected to further increase in the coming years.1,2 This epidemic of obesity is accompanied by an increase in obesity-related morbidity, such as type 2 diabetes mellitus (DM2), hypertension, dyslipidemia, obstructive sleep apnea syndrome, and cardiovascular diseases.3,4

Weight loss in obese individuals will likely increase life expectancy and decrease morbidity. However, the results of noninvasive interventions, such as lifestyle changes and pharmacotherapeutic treatments, as well as the more invasive intervention of intragastric balloon placement, have been disappointing.5 Bariatric surgery appears to be the most effective and long-lasting treatment for obesity.6,7 The indication for bariatric surgery has been internationally determined by the International Federation for the Surgery of Obesity and essentially consists of a BMI of greater than 40 or a BMI of greater than 35 with significant obesity-related comorbidity. Worldwide, approximately 344,000 bariatric procedures were performed in 2008, of which 220,000 were performed in the United States and Canada.8

This review focuses on the role of bariatric surgery as a possible treatment option for patients with DM2. The relevance of this topic is supported by the fact that 90% of DM2 is attributable to obesity.9 Conversely, the prevalence of DM2 is 15% in patients with a BMI of 30 to 40 and 26% in patients with a BMI of greater than 40.10 Finally, DM2 qualifies as significant comorbidity in the National Institutes of Health consensus statement on the indications for bariatric surgery.11
In the past, anecdotal evidence of high rates of complete cure of DM2 after bariatric surgery has been published, but reversal rates for DM2 vary among the different types of surgery. Hence, it is timely to systematically review the role of bariatric surgery in the prevention and treatment of DM2.

**METHODS**

**SEARCH STRATEGY**

We performed a PubMed search using the following keywords: type 2 diabetes mellitus, diabetes, reversibility, bariatric surgery, gastrointestinal surgery, adjustable gastric banding, AGB [adjustable gastric band], laparoscopic adjustable gastric banding, LAGB [laparoscopic AGB], Roux-en-Y gastric bypass, and RYGB. Abstracts were assessed for applicability; of the relevant articles, references were checked for articles not found using our search strategy.

**TYPES OF BARIATRIC SURGERY**

Bariatric surgery can be divided into 3 categories: restrictive procedures that reduce the ability to consume large amounts of food, malabsorptive procedures that reduce intestinal uptake of nutrients, and procedures that combine these 2 aspects.\(^1\) The LAGB procedure is a popular restrictive technique performed approximately 145,000 times annually worldwide.\(^8\) With this intervention, a rigid ring with an inflatable inner balloon is placed below the lower esophageal sphincter, thus creating a small-capacity gastric pouch (Figure 1). The balloon can be inflated or deflated to adjust the passage of the gastric pouch.

Other important but less often performed restrictive techniques are sleeve gastrectomy and vertical banded gastroplasty.\(^8,13,14\) Purely malabsorptive techniques, such as the duodenal switch and biliopancreatic diversion, are performed in few bariatric procedures worldwide.\(^8,15,16\)

The (laparoscopic) Roux-en-Y gastric bypass (RYGB; Figure 2) is a restrictive and malabsorptive technique. In the United States and Canada, it is the most-performed type of bariatric surgery, with more than 112,000 procedures performed annually. In Europe, this technique is rapidly gaining popularity, with more than 26,000 procedures performed annually.\(^9\) A gastric pouch is created that is completely separated from the gastric remnant and anastomosed to the jejunum. An entero-entero anastomosis is created between the pancreatobiliary limb and alimentary limb 75 to 150 cm distally from the gastrojejunostomy. The gastric pouch restricts food intake, and the bypass of the duodenum and part of the jejunum reduces absorption.\(^17\)

In this review, we focus on the most commonly performed types of surgery (ie, AGB and RYGB) because most data pertaining to the effects of bariatric surgery on DM2 have been published with these modalities. Also, because these types of bariatric surgery are those performed most often, they bear the greatest relevance in practice.

**RESULTS**

**EFFECTS OF BARIATRIC SURGERY ON WEIGHT LOSS**

Bariatric surgery is the most effective way to help people lose excessive weight, with RYGB being more effective
than AGB. After an RYGB, patients with DM2 lose less weight than do patients without DM2. One explanation for this phenomenon is that patients with DM2 use insulin or oral antidiabetic medications, which increase circulating insulin and/or increase insulin sensitivity, thereby stimulating lipogenesis and muscle synthesis.18,19

A large, prospective, nonrandomized intervention trial in Sweden, the Swedish Obese Subjects (SOS) study that examined data from 4047 patients, found, regardless of the type of intervention, a maximum reduction in weight at 1 year after bariatric surgery. In the group treated with AGB, the mean (SD) weight loss after 1 year was 21% (10%), but patients who underwent gastric bypass reported 38% (7%) weight loss at 1 year.7 After 10 years, the reduction in body weight compared with baseline persisted at a level of 3% (13%) in the AGB group and 25% (11%) in the RYGB group.7 Data for DM2 were not reported separately in the SOS study.

Another study,20 which assessed the effects of AGB in 30 patients with DM2, found a weight reduction of 20% (9.4%) after 2 years compared with 1.4% (4.9%) in the control group who underwent conservative treatment, which translated into a loss of excess weight of 62.5% and 4.3%, respectively. This excess weight loss is commonly used to express the amount of weight loss after bariatric surgery and is defined as follows: (weight loss in kilograms/excess weight in kilograms) × 100, where excess weight = total preoperative weight – ideal weight.

A meta-analysis addressing the effects of bariatric surgery in obese patients with DM2 undergoing AGB found a weight loss of 26.0 kg, corresponding to 41% excess weight lost. Patients who underwent RYGB lost 50.5 kg on average, ie, 66% of their excess weight.21

**PREVENTION OF DM2**

Because of the extensive weight loss after bariatric surgery and because even a modest weight loss of 5% to 10% confers metabolic benefits, a preventive effect of bariatric surgery on the development of DM2 would be expected.21 In the aforementioned SOS study, the incidence of new DM2 was 24% in the control group and 7% in the surgery group at a follow-up of 10 years, translating into a relative risk reduction of no less than 71%.7

**REVERSIBILITY OF DM2 AFTER BARIATRIC SURGERY**

The first study23 to describe the effect of bariatric surgery on DM2 reported that, of 23 patients with DM2 using insulin, 14 were able to discontinue its use and in 7 others, the amount of insulin needed was substantially reduced. In the following years, many subsequent studies appeared, which are summarized in the Table. Most of the studies are observational. A single randomized controlled trial was performed, randomizing 30 patients to AGB or conservative treatment. Taken together, AGB was performed in 211 and RYGB in 424 patients with DM2. (The series by Sjöström et al22 and Herbst et al23 are not included because of ambiguity regarding the exact number of the different procedures performed in patients with DM2.)

Table summarizes the reported DM2 reversal rates associated with both procedures in the cumulative observational studies and the randomized controlled trial. The DM2 reversal rates of conservative treatment have been described from the studies that included a conservative treatment group.7,20

As shown in the Table, RYGB generally creates a stronger antidiabetic effect than AGB. On average and through different time frames, RYGB achieves a reversal rate of approximately 83%, but AGB achieves an average reversal rate of 62%.

To date, only 1 randomized controlled trial has been published examining the effects of bariatric surgery on DM remission in patients with DM2 who have a BMI greater than 30.20 In that study, 60 obese patients with recently diagnosed DM (maximum duration, <2 years)
underwent intensive conventional treatment focused on weight loss or AGB in combination with intensive conventional treatment. In the surgically treated group, 22 of 30 (73%) achieved favorable glycemic control without the use of glucose-lowering agents compared with the conventionally treated group, in which 4 of 30 (13%) achieved favorable glycemic control without further treatment. This relative risk reduction of 70% is comparable to that found in more morbidly obese individuals, suggesting that bariatric surgery is also a viable option for obese patients with DM2 who have more moderate degrees of obesity.

In patients undergoing RYGB, remission may be achieved within the first days after surgery, but the effect takes longer for AGB. A longer-term temporal relationship in the reversal of DM2 is suggested because 66% of patients can stop taking their hypoglycemic medications at the 1-year time point and 80% had stopped taking their medication at 2 years. However, the beneficial effect may weaken after several years. After 10 years, only 36% of patients who previously had diabetes still had favorable glycemic control. The weakening of the antidiabetic effect is presumably attributable to weight gain but also may be due to other underlying mechanisms.

**PREDICTORS OF REVERSIBILITY**

For both types of bariatric surgery, the extent of weight loss is the most important predictor of DM2 remission. Diet-controlled DM2 before surgery is a favorable prognostic factor. In contrast, insulin use and a high hemoglobin A1c level are negative predictors. Furthermore, patients with a history of DM2 of less than 5 years have a greater chance of reversal of their DM after AGB than patients with a history of longer than 5 years (83% vs 33%). Conceivably, the lower reversal rate in patients with long-standing DM2 is due to progressive deterioration of β-cell reserve and function during the disease. Consequently, it is important to perform surgery for severe obesity early in DM2.

**HOW BARIATRIC SURGERY MIGHT LEAD TO A RESOLUTION OF DM**

The underlying mechanisms leading to improved glycemic control after bariatric surgery only have been partly elucidated. Figure 4 gives a short overview of the mechanisms responsible for the resolution of DM after bariatric surgery.

Any short-term reduction in energy intake leads to a rapid improvement in plasma glucose levels. Within a few days after caloric restriction, a rapid reduction of liver fat occurs. Liver fat is important in the pathogenesis of insulin resistance and DM2. Notably, all types of bariatric surgery cause a reduction in caloric intake, but purely restrictive procedures require a much longer period to achieve DM reversal (ie, months) than malabsorpitive and combined procedures (ie, weeks); sometimes DM reversal occurs even before significant weight loss has occurred.

Furthermore, in patients undergoing AGB, the effect of bariatric surgery on resolution of DM2 is correlated mainly with the degree of weight loss, but the same correlation is much weaker in patients undergoing RYGB. In a modified RYGB procedure, performed in nonobese rodents, a positive effect on DM2 is observed despite similar caloric intake and weight gain as those of the control group, providing additional support for specific antidiabetic effects of RYGB other than weight loss.

The explanation for the additional antidiabetic effects of RYGB is incompletely understood. An increasing body of evidence, however, suggests a role for gut-derived hormones and adipokines.

**Gut-Derived Hormones**

Incretins are gut-derived hormones that stimulate insulin production and are responsible for the greater insulin response after an oral glucose load than after an equivalent intravenous glucose load. Glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide (GIP) are the most important and most studied incretins.

The distal ileum produces GLP-1 in response to nutrient exerts antiapoptotic properties on the β cell and sending a satiety signal to the brain. Concentrations of GLP-1 increase after RYGB, but restrictive procedures do not affect GLP-1 concentrations. An increased GLP-1 concentration after RYGB may be caused by an increased delivery of nutrients to the distal ileum, as stated by the hindgut hypothesis. This hypothesis contradicts the foregut hypothesis, which proposes that an unidentified anti-incretin or putative signal is produced in the proximal gut, causing insulin resistance and DM2. Bypassing the proximal gut would prevent the production of this anti-incretin.

Another incretin, GIP, augments glucose-stimulated insulin release. In DM2, a decrease in sensitivity to the incretin-releasing function of GIP has been observed. In 2 studies, GIP did not increase after AGB but it did so in the RYGB control group in 1 of these studies. Changes in incretin concentrations occur not only in pa-
Patients with obesity and DM but also in patients with obesity who do not have DM by favorably altering insulin secretion and preserving \( \beta \) cells. Changes in incretin concentrations may play a role in the prevention of DM in this latter group.

Another gut-derived hormone without effects on insulin secretion is ghrelin. Ghrelin is produced in the stomach and duodenum; it stimulates appetite. Ghrelin levels decrease substantially after RYGB, conceivably due to decreased food passage along its production sites.\(^3\) The reported effects of AGB on ghrelin are inconsistent. In some studies, ghrelin levels increase after AGB, creating a slight counterproductive effect; in others, ghrelin levels remain unaffected.\(^4\),\(^5\),\(^6\),\(^7\)

Hence, divergent effects of AGB vs RYGB on GLP-1, GIP, and ghrelin are compatible with the observed superiority of RYGB for resolution of DM2. The field of incretin physiology, however, is relatively new, and more studies are clearly needed to delineate their precise role in different types of bariatric surgery.

**Adipokines**

Adipokines are adipocyte-derived hormones that affect several biological processes in the body, such as metabolism, hemostasis, and inflammation. Members include, among others, tumor necrosis factor (TNF), leptin, and adiponectin. When the total mass of adipose cells increases, TNF and leptin are produced in higher quantities, but the production of adiponectin decreases.\(^8\),\(^9\),\(^10\)

Increased levels of inflammatory adipokines affect the insulin signaling cascade and thus attenuate insulin sensitivity.\(^8\),\(^9\) Likewise, leptin is associated with peripheral insulin resistance, but higher adiponectin levels are associated with improved insulin sensitivity.\(^11\)

Leptin concentrations had decreased significantly at 24 months and correlated with weight loss and insulin sensitivity in a group undergoing RYGB in the study by Trakhtenbroit et al.\(^12\) Conversely, in the same study, in the group who underwent AGB, leptin decreased only moderately after 9 months; thereafter, it increased to levels higher than baseline despite ongoing weight loss.\(^12\) The reason for this rebound increase in leptin is unknown, but the increase may be responsible for the attenuated antidiabetic effect of AGB.

In that study, adiponectin concentrations inversely correlated with fat mass in the RYGB-treated patients. Adiponectin increased in both groups but correlated with insulin sensitivity only in the RYGB group.\(^12\) Increasing insulin sensitivity also is beneficial for individuals without DM because low insulin sensitivity confers an important risk factor for cardiovascular risk and the development of DM.\(^13\),\(^14\)

Finally, TNF and high-sensitivity C-reactive protein (CRP) levels decreased in the treatment arms over time, with a more marked reduction in CRP levels in the RYGB group.\(^15\) Another study\(^16\) confirmed the reduction in pro-inflammatory adipokines (TNF and interleukin 6) and CRP level 1 year after RYGB.

**EXERCISE**

Although one would expect that physical exercise would be easier after bariatric surgery and subsequent weight loss, the compliance rate has been observed to decrease from 51% before surgery to 39% after surgery.\(^17\) Patients who adhered to the exercise program had greater weight loss than those who did not, but these observations were subject to confounding in this study. The effect of compliance with an exercise program on the remission of DM2

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**Figure 4.** Mechanisms of bariatric surgery on glucose metabolism. FFA indicates free fatty acids; GLP-1, glucagon-like peptide 1; IL-6, interleukin 6; LAGB, laparoscopic adjustable gastric banding; RYGB, Roux-en-Y gastric bypass; and TNF, tumor necrosis factor.\(^3\),\(^4\),\(^5\),\(^6\)
has not been studied. However, exercise has beneficial effects on glucose metabolism, independent of the extra weight loss achieved.

**EFFECTS OF BARIATRIC SURGERY ON CLINICAL END POINTS**

Perioperative Morbidity and Mortality

No strong data regarding perioperative outcomes in patients with DM2 exist. It is known, however, that RYGB is accompanied by a higher complication rate than AGB.\(^{62}\) Not only is the complication rate lower but the length of stay and readmission rate also favor AGB.\(^{62}\)

In a large study\(^{63}\) addressing perioperative outcomes after bariatric surgery, no patients in the AGB group, 0.2% of the patients who underwent laparoscopic RYGB, and 2.1% of patients who had undergone open RYGB had died within 30 days. Also, the subsequent operation rate was higher in the RYGB group. In this study, DM did not enhance perioperative risk.\(^{63}\)

Long-term Morbidity and Mortality

In a retrospective cohort study\(^{64}\) in 9949 patients undergoing gastric bypass surgery who were followed up for a mean of 7.1 years, mortality was reduced by 40%. After a mean follow-up period of 10.9 years, 5% in the surgically treated group had died vs 6.3% in the conservatively treated group (\(P = .04\)).\(^{65}\) In particular, deaths related to DM2, cardiovascular disease, and cancer decreased, with DM-related mortality decreasing by a stunning 92%.\(^{66}\)

Undergoing any type of bariatric surgery seemed to be a better predictor of survival than the extent of weight loss or the type of bariatric surgery performed. There was, however, insufficient power to prove this.\(^{65}\)

Besides the effects on DM2, improvements in other important risk factors explain the reduced mortality rates after bariatric surgery. These improvements are outside the scope of this review. Briefly, hypertension improves in approximately 80% of patients. Hypercholesterolemia, hypertriglyceridemia, and cardiac function improve and obstructive sleep apnea lessens after bariatric surgery.\(^{21,27,66,67}\)

In conclusion, bariatric surgery, especially RYGB, leads to a reversal of or improvement in DM2. Bariatric surgery must be considered in patients with poorly controlled DM2 and a BMI greater than 35. In fact, this approach may be cost-effective.\(^{68,69}\) However, the decision to perform surgery should not be delayed for long because the success rate depends partially on the duration of DM2. Although excellent results are reported, bariatric surgery in patients with DM2 and a BMI less than 35 is controversial and requires further study.

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**REFERENCES**

What’s in a Name?

The numbers are staggering. According to the Centers for Disease Control and Prevention, 23.5 million US adults (10.7% of people aged 20 years or older) have DM, more than 90% of which is DM2. In 2007 alone, 1.6 million new cases were diagnosed. Diabetes mellitus can result in heart disease, stroke, blindness, kidney disease, and amputations. Overall, the risk of death in individuals with DM is approximately twice that of individuals without DM of similar age. In 2007, estimated total direct and indirect costs related to DM in the United States were $174 billion. After adjusting for population age and sex differences, average medical costs for disease and bariatric surgery: a review. Am J Clin Nutr. 2007;91(3):393-414.