TITLE: Bariatric Surgery For The Treatment Of Type 2 Diabetes Mellitus

AUTHOR: Jeffrey A. Tice, MD
Assistant Professor of Medicine
Division of General Internal Medicine
Department of Medicine
University of California San Francisco

PUBLISHER: California Technology Assessment Forum

DATE OF PUBLICATION: June 20, 2012

PLACE OF PUBLICATION: San Francisco, CA
INTRODUCTION

The California Technology Assessment Forum (CTAF) was asked to assess the evidence for the use of bariatric surgery in the treatment of type 2 diabetes mellitus (T2DM). CTAF considers laparoscopic Roux-en-Y gastric bypass (RYGB) to be the gold standard for bariatric surgery and on 10/28/2009, laparoscopic adjustable gastric banding met CTAF criteria. Bariatric surgery is indicated for patients with a body mass index (BMI) > 40 kg/m² and for patients with a BMI > 35 kg/m² who suffer from at least one obesity-associated comorbidity, such as T2DM. The most important unanswered question is whether the evidence supports extending the use of bariatric surgery in patients with T2DM and a BMI < 35 kg/m².

BACKGROUND

Twin epidemics of obesity and type 2 diabetes mellitus

Obesity is a chronic disease that has increased rapidly in the United States. The degree of obesity is usually described using body mass index (BMI). It is calculated
as weight (in kilograms) divided by height (in meters) squared. Class 1 obesity is defined as a BMI $\geq 30$ kg/m$^2$, class 2 obesity as BMI $>35$ kg/m$^2$, and class 3 (severe, previously termed morbid) obesity as a BMI $\geq 40$ kg/m$^2$ or $\geq 35$ kg/m$^2$ and at least one serious obesity-associated comorbidity. Patients with a BMI $> 50$ kg/m$^2$ are sometimes classified as super-obese. The percentage of obese men in the US nearly doubled between 1991 and 1998, and the percentage of obese women has increased by 50 percent.$^{1-4}$ The prevalence of obesity among U.S. adults in 2010 was approximately 35.5% in men and 35.8% in women.$^1$

In 2008 the worldwide prevalence of diabetes in adults was 9.8% in men and 9.2% in women.$^5$ This represents an increase in the number of adults with diabetes from 153 million in 1980 to 347 million in 2008.$^5$ In 2010 in the US, there were an estimated 25.8 million people with diabetes representing 11.3% of the adult population.$^6$ Much of the increase in diabetes prevalence is thought to be due to the increasing obesity of the world’s population. For example, among 52,000 male health professionals, those with a BMI $\geq 35$ kg/m$^2$ had more than a 40-fold increased risk for the development of diabetes compared to those with a BMI $< 23$ kg/m$^2$. Similarly, among 115,000 nurses without diabetes, those with a BMI $\geq 29$ kg/m$^2$ who gained at least five kilograms from age 18 years had 50 times the incidence of diabetes compared to nurses with a BMI $< 22$ kg/m$^2$ who maintained a stable weight.$^7$ The complications of diabetes are usually classified as macrovascular (heart attacks, strokes, peripheral vascular disease) or microvascular (vision loss from retinopathy, peripheral neuropathy, and kidney disease leading to renal failure). People with type 2 diabetes have two to six times increased risk of death from cardiovascular disease. This epidemic of obesity and diabetes is a major public
health issue commanding the attention of policy-makers worldwide.\textsuperscript{5,9,10}

**Obesity, weight loss, and health outcomes**

Obesity is associated with premature death as well as an increased risk for diabetes, hypertension, hypercholesterolemia, heart disease, osteoarthritis, sleep apnea and gall bladder disease. Studies have demonstrated that weight loss is associated with a decreased risk for development of these diseases. The Nurses’ Health Study, a cohort study of over 100,000 women aged 30 to 55 years, found that weight loss above five kilograms was associated with a graded decrease in the risk of diabetes mellitus.\textsuperscript{11} A second cohort study of 28,388 overweight women aged 40 to 64 years found that intentional weight loss of more than 9.1 kg was associated with a 25% decrease in all-cause, cardiovascular and cancer mortality.\textsuperscript{12} In addition, any amount of intentional weight loss was associated with a 10% reduction in cardiovascular disease, a 20% reduction in all-cause mortality, a 30 to 40% reduction in mortality from diabetes, and a 40 to 50% reduction in mortality from cancers related to obesity. Finally, the social stigma associated with obesity leads to decreased quality of life. Weight loss has been shown to improve both social functioning and quality of life.\textsuperscript{13,14}

**Treating obesity**

Behavior modification, diet, and exercise are the primary treatments for obesity. Pharmacologic therapy (orlistat, sibutramine) may be indicated for patients who have medical complications of obesity, but drug therapy is limited by side effects and modest efficacy. Regaining lost weight is a common problem. Among subjects
who lose weight during any treatment program, most do not maintain the weight loss. Characteristics of patients who maintain weight loss include a weight loss of more than two kilograms in four weeks, frequent and regular attendance at a weight loss program, and the subject's belief that his or her weight can be controlled. Systematic reviews of behavioral and drug therapy report average long-term weight loss of between four and seven kilograms. A Cochrane review of lifestyle and behavioral interventions for adults with T2DM is particularly relevant for this assessment. They summarized 22 randomized trials that included 4,659 participants followed for at least one year. The pooled weight loss compared to usual care was 1.7 to 3.9 kg or 1.6 to 3.6% of their initial body weight depending on the type and intensity of the intervention. There were no significant differences between groups in measures of glycemic control.

**Gastrointestinal surgery for obesity**

Surgical procedures of the upper gastrointestinal tract that are designed to induce weight loss are collectively referred to as bariatric surgery. Bariatric surgery is either restrictive, malabsorptive, or a combination of both. Restrictive procedures reduce the size of the stomach leading to early satiety and decreased total caloric intake. Malabsorptive procedures create separate intestinal pathways (limbs) for food and biliary/pancreatic secretions. They eventually connect, but the length of small intestine that is common to both food and the secretions is short leading to decreased absorption of both calories and nutrients.

Purely restrictive procedures reduce food intake, but do not disrupt normal digestion. Usually a small pouch is made in the stomach that holds only about one
ounce of food and has a small outlet. Thus, patients are unable to eat large amounts of food at one sitting without significant discomfort and nausea. This requires significant changes in the patients eating habits. The two procedures in common use today that are primarily restrictive are laparoscopic adjustable gastric banding and laparoscopic sleeve gastrectomy.

The laparoscopic adjustable gastric band (LAGB) is designed to induce weight loss by limiting food consumption. An inflatable band is placed around the upper stomach, allowing the formation of a small gastric pouch and stoma. There is no resection or stapling of the stomach itself, and no gastric or intestinal bypass. Postoperatively, the surgeon may adjust the stoma size percutaneously by injecting or aspirating saline from the access port with a needle.\textsuperscript{22}

Sleeve gastrectomy (SG) is performed laparoscopically. The surgeon removes the greater curvature of the stomach leaving a tubular stomach approximately 25\% of the size of the original stomach. The pyloric valve and the normal digestive pathway are left intact. This partial gastrectomy removes the cells producing ghrelin, a gut hormone involved in food intake regulation. This may contribute to the effectiveness of this procedure.

The RYGB is the most common form of bariatric surgery in the US.\textsuperscript{23,24} A recent meta-analysis estimated that patients lose between 62\% and 70\% of excess body weight following the procedure with frequent resolution of obesity-associated comorbidities.\textsuperscript{25} For example, diabetes resolved in approximately 77\% of patients. Clinical trials suggest that performing RYGB laparoscopically reduces hospital length of stay and complications.\textsuperscript{26-29} The majority of RYGB procedures in the United States
are now performed laparoscopically.\textsuperscript{30,31}

The RYGB is primarily a restrictive procedure with a variable amount of malabsorption. First a small stomach pouch (about 20 cc to 30 cc) is made to restrict food intake. Then a portion of the jejunum is attached to the pouch to allow food to bypass the distal stomach, duodenum, and proximal jejunum. The length of the Roux limb (portion of the jejunum from the new stomach pouch to the anastamosis with the segment connecting with the gallbladder and pancreas) is usually between 50 cm and 150 cm. Absorption of nutrients primarily occurs in the common channel, which is the portion of the small intestine containing both the biliopancreatic enzymes and the food.

The biliopancreatic diversion (BPD) is primarily a malabsorptive procedure. The surgeon performs a sleeve gastrectomy and creates a long Roux limb with a short common channel. More dramatic weight loss usually occurs with this procedure, but lifelong malabsorption affects quality of life due to ongoing steatorrhea and significant risks for micronutrient as well as protein-calorie malnutrition. For example, patients may suffer from hypoalbuminemia, vitamin D deficiency, and calcium deficiency despite protein, vitamin, and mineral supplementation.

Effects of bariatric surgery on endocrine control of energy, appetite, body weight, and diabetes

The control of energy balance and its effects on body weight, appetite, and blood sugar is complex and incompletely understood. There have been several
recent detail reviews of the studies of the hormones involved and the impact of different bariatric procedures on these hormones.\textsuperscript{32-38} Bariatric surgery, particularly forms that bypass some portion of the small intestine, has dramatic and almost immediate effects on glycemic control. In particular, investigators have observed that patients with T2DM have normal blood glucose levels without medication within days of RYGB, while it often takes months for patients treated with purely restrictive forms of bariatric surgery to obtain the same benefit. This has been taken as evidence that surgeries bypassing part of the small intestine immediately affect the balance of hormones involved in glucose homeostasis. It is unclear if the primary cause is bypassing the distal stomach and proximal small intestine or the delivery of nutrient rich contents to the distal ileum, or some combination of both. There is ongoing debate about whether the hormones primarily produced by the stomach and duodenum (the foregut hypothesis) or those produced by the distal ileum (hindgut hypothesis) play a more central role in the impact of some bariatric procedures on glycemic control and satiety.

Leptin generated tremendous excitement when it was first discovered, but does not appear to be involved in the specific effects of bariatric surgery on weight, appetite, and glycemic control. It is a circulating hormone whose levels are proportional to fat mass and is thought to act at the level of the hypothalamus to decrease the intake of food and increase energy expenditure.

Ghrelin is a small peptide hormone secreted by the stomach and duodenum. Levels of ghrelin increase prior to each meal and decrease after the meal. It is thought to increase appetite and is inversely proportional to BMI. With weight loss, ghrelin levels increase and presumably hunger increases as well. When given to
humans, it increases food intake and promotes weight gain. Some authors have argued that a decrease in ghrelin levels following RYGB is responsible for the reduction in appetite following surgery and thus some of the difference in weight loss observed between RYGB and other procedures. However, as Ashrafian and le Roux report, among the 42 studies they reviewed, half (21) reported a decrease in ghrelin, eleven reported no change, and ten reported an increase in ghrelin following bypass procedures. Among the 22 studies measuring ghrelin levels following purely restrictive surgeries, only four reported a decrease in ghrelin, seven reported no change, and half (11) reported an increase in ghrelin following bypass procedures. Thus, the data from a large number of studies present an inconsistent picture, but suggest that ghrelin levels may play a role in the effectiveness of bariatric surgery.

Peptide tyrosine tyrosine (PYY) is secreted from enteroendocrine cells in the terminal ileum and colon. It induces a feeling of fullness when it is released after eating, delaying gastric emptying and decreasing acid secretion. It is secreted in two circulating forms: PYY$_{1-36}$ and PYY$_{3-36}$. Injections of PYY$_{3-36}$ have been demonstrated to lower the threshold for satiety in humans and decrease food intake over time. PYY is suppressed during fasting. More than 40 studies demonstrate an increase in PYY levels following bypass procedures. There are only three studies measuring PYY after restrictive procedures: two showed no change and one showed an increase in PYY levels.

Glucose-dependent insulinotropic peptide or gastric inhibitory peptide (GIP) is another peptide hormone released by enteroendocrine cells of the duodenum. Like PYY, it peaks after a meal, but seems to play more of a role in stimulating
pancreatic beta cells to release insulin and to replicate and resist apoptosis, thus increasing the number of functioning insulin-producing cells. Studies of bypass surgery suggest that GIP levels decrease both between and immediately after meals. Purely restrictive procedures seem to have little effect on GIP.

Glucagon-like peptide-1 (GLP-1) is a peptide hormone secreted by the distal ileum. Blood levels increase after a meal, but it has a very short half-life. Like GIP, it potentiates insulin secretion and stimulates the growth of pancreatic beta-cells. Like PYY, it increases the sensation of satiety, reduces hunger, suppresses gastric acid secretion and slows gastric emptying. Injections of GLP-1 in humans induced weight loss within five days. Exenatide (Byetta), a GLP-1 agonist, is FDA approved for the treatment of diabetes. As was the case for PYY, more than 40 studies demonstrate an increase in GLP-1 levels measured post-prandially or between meals following bypass procedures. There are only three studies measuring GLP-1 after restrictive procedures: two showed no change and one showed a decrease in GLP-1 levels.

**Treatment of diabetes**

There is consensus among the American Diabetes Association and The European Association for the Study of Diabetes on how to initiate and adjust therapy for diabetes. All patients should receive lifestyle interventions aimed at increasing physical activity and decreasing weight with a goal to reduce HbA1c to less than 7%. Unfortunately, a systematic review of 22 randomized trials evaluating lifestyle and behavioral interventions in adults with T2DM did not find significant differences in glycemic control. If therapeutic goals are not met, then the first
line medication should be metformin unless the patient has contraindications or is intolerant of metformin. The next step is to add insulin or a sulfonylurea. The subsequent tier of medications includes the thiazolidinediones and the glucagon-like peptide-1 agonists. Other, less well studied alternatives include amylin agonists, alpha-glucosidase inhibitors, the glinides, and dipeptidyl peptidase 4 inhibitors. Most patients require additional medication over time, leading eventually to insulin therapy. The natural history of diabetes is of inexorable progression with increasing weight and insulin resistance leading to intensification of drug therapy.

Surgery is another option for patients at high-risk of complications from obesity. A recent systematic review and meta-analysis concluded that patients achieved effective weight loss with surgery and that most patients had complete resolution or improvement of their diabetes, hypertension, hyperlipidemia, and obstructive sleep apnea. Indeed, surgical interventions for obesity are increasingly popular in the United States. Between 1998 and 2004, the number of bariatric surgeries performed increased from about 13,000 annually to 121,000, a nine-fold increase. Over the same period, inpatient mortality associated with bariatric surgery decreased from 0.89% to 0.19% and the average length of stay decreased from five to 3.1 days. More recently, inpatient mortality has declined to less than 0.1%.

Surgical intervention has the advantage of being a long-term treatment for diabetes. Surgery leads to more substantial weight loss than the lifestyle or medical therapy. However, surgery for diabetes is a major surgery with associated complications and lifelong effects on dietary habits. The National Institutes of Health consensus conference on obesity surgery recommends that surgery be
considered only in the following populations:\textsuperscript{42}:

- Patients with a BMI > 40 kg/m\textsuperscript{2}

- Patients with a BMI > 35 kg/m\textsuperscript{2} who also have serious medical problems, (diabetes, obstructive sleep apnea) that would improve with weight loss.

All patients must have failed sustained weight loss programs, have acceptable operative risk, and be committed to life-long follow-up. These remain the recommendations today, despite significant reductions in surgical complications. There is considerable interest in expanding the indications for surgery to less obese patients, particularly those with diabetes.\textsuperscript{43-47}

TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.

The majority of bariatric operations are considered procedures by the FDA and are not subject to FDA approval. The devices used for laparoscopic adjustable gastric banding (LAGB) are subject to FDA approval.

There are two products approved for LAGB: LAP-BAND by Allergan Inc., and REALIZE Adjustable Gastric Band by Ethicon Endo-Surgery Inc.

1. The LAP-BAND\textsuperscript{®} Adjustable Gastric Banding (LAGB) Systems by Allergan Inc.
received FDA premarket approval (P000008) on June 5, 2001 (BioEnterics Corporation, Carpentaria, CA). This device is indicated “for use in weight reduction for severely obese patients with a Body Mass Index (BMI) of at least 40 kg/m², or a BMI of at least 35 kg/m², with one or more severe comorbid conditions, or those who are 100 lbs. or more over their estimated ideal weight according to the 1983 Metropolitan Life Insurance Table. It is indicated for use only in severely obese adult patients who have failed more conservative reduction alternatives, such as supervised diet, exercise and behavior modification programs.” On February 16, 2011, the FDA approved the expanded use of the LAP-BAND to include obese individuals with a BMI of 30 - 34 kg/m² who also have an existing condition related to their obesity.

2. The REALIZE® Adjustable Gastric Band System by Ethicon Endosurgery received FDA premarket approval (P070009) on September 2007 for “use in weight reduction for morbidly obese patients...with a Body Mass Index (BMI) of at least 40 kg/m²...or at least a BMI of 35 kg/m² with one or more comorbid conditions.”

TA Criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The Medline database, Embase, Cochrane clinical trials database, Cochrane
reviews database and the Database of Abstracts of Reviews of Effects (DARE) were searched using the key words “diabetes” OR “type 2 diabetes mellitus” AND “bariatric” OR “gastric banding” OR “gastric bypass” OR “biliopancreatic diversion.” The search was performed for the period from 1945 through May 2012. The bibliographies of systematic reviews and key articles were manually searched for additional references. References were also solicited from local experts. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full. We included case series in patients with diabetes, comparative studies with medical therapy in patients with diabetes, and randomized trials comparing bariatric surgery to medical therapy in patients with diabetes.

The search identified 2,187 potentially relevant studies (Figure 1). After elimination of duplicate and non-relevant references the search identified three systematic reviews and meta-analyses describing over 100 studies and an additional 26 additional case series, six comparative observational studies, and four randomized trials not fully described in the meta-analyses. One systematic review of 29 studies, five case-series not included in the systematic review, and two of the observational studies with controls focused on patients with a BMI < 35 kg/m². Two of the randomized trials with a medical therapy included patients with BMIs both above and below 35 kg/m² and one additional randomized trial compared two bariatric procedures in patients with a BMI between 25 and 35 kg/m².
Level of Evidence: 1 through 5.

TA Criterion 2 is met.

TA Criterion 3: The technology must improve net health outcomes.

Bariatric surgery has many effects on health, but among patients with diabetes, the most important outcomes include long-term remission of diabetes, reduction in
the complications of diabetes including cardiovascular disease events, renal failure, blindness, and quality of life. Quality of life is important to assess, because bariatric surgery permanently alters eating habits and can be associated with lifelong adverse effects that may impact a person’s quality of life. Until recently, there has been no standard definition for remission of diabetes. All of the definitions require patients to be off of medications, but the HbA1c cut off points vary from 6% to 7% and some also require fasting glucose levels to be normal. A recent consensus group proposed the following definitions. They defined partial remission of diabetes as Hba1c < 6.5%, fasting glucose < 126 mg/dL, and no medications for diabetes for at least one year. They defined complete remission of diabetes as a normal HbA1c, fasting glucose < 100 mg/dL, and no medications for diabetes for at least one year. Finally, they defined prolonged remission of diabetes as a normal Hba1c, fasting glucose < 100 mg/dL, and no medications for diabetes for at least five years.

The Swedish Obese Subjects Study

The Swedish Obese Subjects (SOS) study is the largest prospective study on the effects of operative treatment for obesity. A total of 2,010 patients were allocated to one of the three surgical procedures (gastric banding, vertical banded gastroplasty, or gastric bypass). For comparison, the study enrolled 2,037 contemporary controls matched to the surgical patients on 18 variables including age, sex, BMI, clinical site, and co-morbidities such as diabetes, blood pressure, cholesterol, smoking, menopausal status, and psychosocial parameters. The average BMI in both groups was 41 kg/m² and 11% had diabetes at baseline. To date, the study subjects have
been followed for fifteen to twenty years with 99% complete follow-up in both groups.\textsuperscript{62-69} Preliminary analyses at two years found that surgical patients had lost 28 kg and controls had lost 0.5 kg. The patients treated with gastric bypass lost significantly more weight (44 kg) than those who had either of the other two procedures (31 kg VBG; 26 kg gastric banding)\textsuperscript{62}. Weight loss was greatest one to two years following surgery, but remained stable at the 10, 15, and 20-year follow-up visits.\textsuperscript{69} Overall, the surgical group maintained approximately 17% weight loss at 10, 15, and 20-year follow-up while the control group lost approximately 1% of their initial weight.\textsuperscript{69} At 10, 15, and 20-year follow-up, weight loss was significantly greater for gastric bypass (25%) compared with vertical banded gastroplasty (20%), and gastric banding (15%).\textsuperscript{69} Patients in the surgical group had greater improvements in quality of life measures compared to the medically treated patients within one year.\textsuperscript{70} At ten years they scored significantly better on the health related quality of life questionnaire in the domains of current health perceptions, social interaction, psychosocial function, and depression.\textsuperscript{70}

After two and ten years of follow-up, the majority of cardiovascular risk factors were significantly better in the bariatric surgery groups compared with the control group: in addition to diabetes, this included triglyceride levels, HDL-cholesterol, hypertension, and hyperuricemia.\textsuperscript{67} More importantly, there were fewer cardiovascular deaths and major cardiovascular events in the surgical group.\textsuperscript{69} In addition, after a median follow-up of 11 years with 99.9% complete follow-up, there was a statistically significant 29% reduction in all cause mortality for the patients in the surgical group compared with the control group.\textsuperscript{68} Other large observational studies have reported even greater reductions in total mortality (40% to 89%),
although these studies were not as carefully designed as the SOS study.\textsuperscript{71-74}

Compared to the carefully matched control group of patients of similar weight at baseline, the two-year incidence rates of diabetes mellitus and hypertension were lower in the surgically treated patients, and they had less hyperinsulinemia and hypertriglyceridemia and higher serum high-density-lipoprotein (HDL) cholesterol concentrations.\textsuperscript{62} Among patients with diabetes at the start of the study, 72\% of the patients in the surgical group had remission of their diabetes compared with 21\% of controls (p<0.001). However, their diabetes tended to recur over time. At ten years, only 36\% of the surgical patients with diabetes at enrollment were in remission compared with 13\% of controls (p=0.001).\textsuperscript{67} Diabetes remission was not reported separately by bariatric procedure. Because cardiovascular disease is the primary cause of death in patients with diabetes, bariatric surgery might be particularly effective at reducing cardiovascular events in this subgroup of obese patients. There was a statistically significant 37\% reduction in cardiovascular events in patients with diabetes prior to surgery (95\% CI 10\% to 55\%, p=0.01).\textsuperscript{69} This was greater than the 16\% reduction observed in patients without diabetes, although the test for effect modification did not reach statistical significance (p=0.20).\textsuperscript{69}

This study is the only well controlled study of bariatric surgery comprehensively reporting outcomes through 20 years of follow-up. The surgical techniques used in the study have now primarily been replaced by laparoscopic RYGB and LAGB, but the long-term results are informative. There is a long-term reduction in risk factors for cardiovascular disease, cardiovascular death, and all cause mortality. Weight loss and diabetes remission peak between one and two years of follow-up, but remain clinically and statistically significant at 10 years. More than one third of patients with
diabetes were in remission ten years after bariatric surgery. Between 10 and 20 years of follow-up, weight did not change significantly and the patients with the greatest weight loss were those who were received RYGB. The data on diabetes remission beyond 10 years have not been reported, but the reduction in cardiovascular events following bariatric surgery was particularly high among patients with diabetes through a median follow-up of 14.7 years.

Case series and meta-analyses of bariatric surgery in patients with T2DM and BMI > 35 kg/m²

Buchwald and colleagues⁴⁸ systematically reviewed the literature on bariatric surgery and diabetes. Among 621 studies, irrespective of study design, they identified 8,088 patients with T2DM. They found that 78% of patients had remission of their diabetes. Remission was greatest for patients treated with BPD (95%), followed by RYGB (80%) and gastroplasty (80%), and then gastric banding including LAGB (57%). Sleeve gastrectomy was relatively uncommon at the time of the review and results from that procedure were not reported separately.

Meijer and colleagues published a second systematic review of bariatric surgery and diabetes in 2011. They focused specifically on RYGB and LAGB because these are the two most commonly performed bariatric surgeries. Their search identified nine primary articles. They found that RYGB led to T2DM remission in 83% of treated patients compared to 62% for LAGB. These results are comparable to those described by Buchwald et al.⁴⁸
Since 2009, there have been a number of additional case series of patients with diabetes or insulin resistance treated with bariatric surgery.\textsuperscript{75-88} Most of the studies were small, single site case series with similar findings to those described in the two meta-analyses. Only two of the studies reported outcomes on more than 100 subjects with diabetes.\textsuperscript{83,86} In 2010, Kim et al reported on 219 subjects treated with RYGB and followed for up to four years. Their HgbA1c decreased from 7.6% to 6.1% and was stable for four years. The percentage of patients in remission was likewise stable for four years (73% at year one, 72% at year two, 74% at year three, and 78% at year four). In 2012, Pournaras et al\textsuperscript{86} compared the rates of remission using a new, stricter definition of remission\textsuperscript{61} among 209 subjects with diabetes treated with RYGB, SG, or LAGB. Using the earlier definition that required subjects to reach a HbA1c < 6% or a normal fasting glucose off of diabetes medication, 49% of all subjects achieved remission. The new consensus definition for remission requires a HbA1c < 6%, a fasting glucose < 100 mg/dL, and no medications for diabetes for at least one year. Using this definition, only 34% of subjects achieved remission including 41% of patients treated with RYGB, 26% of patients treated with SG, and 7% of patients treated with LAGB (p<0.001 for between group differences). These are lower remission rates than those reported in the meta-analyses and highlight the need for general agreement in the definition of study outcomes in the treatment of diabetes.

Several of the larger case series evaluated patient characteristics to predict diabetes remission. Schauer et al\textsuperscript{89} found that subjects with a longer history of diabetes and those requiring insulin were less likely to go into remission following RYGB. Among patients with diabetes for less than or equal to five years, 95%
achieved remission compared to 75% of those with diabetes for six to ten years and 54% of those with diabetes for more than ten years. Only 62% of subjects using insulin achieved remission. Similarly, Casella et al\textsuperscript{79} found that the duration of diabetes and the intensity of therapy were independent predictors of a lower response rate to SG. In addition, they found that the pre-operative c-peptide level, a marker of pancreatic function, was inversely associated with response to surgery. Other investigators have reported similar findings.\textsuperscript{60,83} The studies agree that younger age, shorter duration of diabetes, higher c-peptide levels, and lower intensity of diabetes medical treatment all are associated with a higher likelihood of remission of diabetes following bariatric surgery. It is important to measure and control for these potential confounders in studies of bariatric surgery for the treatment of diabetes.

Case series and meta-analyses of bariatric surgery in patients with T2DM and BMI < 35 kg/m\textsuperscript{2}

One systematic review published in 2012 by Reis and colleagues summarized the data from 29 small studies including 675 patients with T2DM and a pre-operative BMI < 35 kg/m\textsuperscript{2}.\textsuperscript{50} The majority of the studies reported outcomes at one year or shorter follow-up. The average BMI of the study subjects dropped from 29.9 to 24.8 kg/m\textsuperscript{2} over a variable length of follow-up, their fasting glucose decreased from 208 to 114 mg/dL and their HbA1c decreased from 8.9 to 6.4%. Eighty four percent of the subjects were able to stop medications after surgery and maintain a HgbA1c < 7% (87% BPD, 90% RYGB, 47% SG, 70% LAGB). With a stricter definition
of diabetes remission (fasting glucose < 100 mg/dL or HgbA1c < 6% on no medication) the remission rate was 54% (48% BPD, 70% RYGB, 13% SG, 70% LAGB). The relative efficacy of the various bariatric procedures differed from that observed in the reviews of Buchwald and Meijer.\textsuperscript{48,49} This may represent differential benefits by BMI category, but more likely represents the very small numbers in the surgical subgroups (52 BPD, 115 RYGB, 30 SG, 27 LAGB) and heterogeneity in their patient populations, the definitions used for remission, and the length of follow-up.

Our search identified an additional five publications\textsuperscript{51-55} not among the 29 studies included by Reis et al that described outcomes in patients with diabetes and a BMI < 35 kg/m\textsuperscript{2} who were treated with bariatric surgery. Three studies describing a total of 40 subjects treated with RYGB, BPD, or gastrectomy will not be described further because of their small numbers.\textsuperscript{51,52} The two other studies\textsuperscript{53,55} appear to include overlapping patient populations, so only the larger, more recent publication\textsuperscript{55} will be described.

Lee and colleagues\textsuperscript{55} treated 200 patients from Asian centers with T2DM and BMI < 35 kg/m\textsuperscript{2} with RYGB (n=172), SG (n=24), or LAGB (n=4). The average BMI decreased from 28.5 kg/m\textsuperscript{2} at baseline to 23.4 kg/m\textsuperscript{2} at one year. Remission from T2DM was more common among patients treated with RYGB (79%) than those treated with SG (55%) or LAGB (50%). Remission rates were higher among patients with greater initial BMIs (79% for BMI 30-35 kg/m\textsuperscript{2}; 68% for BMI 25-30 kg/m\textsuperscript{2}; 55% for BMI < 25 kg/m\textsuperscript{2}; p=0.027). As in the meta-analysis, RYGB was the most effective bariatric surgery. The lower remission rate in the thinnest patients suggests that the balance of risks and benefits may not favor surgery in thinner patients, though this was a small, uncontrolled study. Either randomized trials or skillfully designed and
analyzed comparative studies are needed to answer this question.

**Comparative studies of bariatric surgery with medical therapy: BMI ≥ 35 kg/m²**

Four observational studies⁹⁰-⁹³ compared bariatric surgery to medical therapy for the treatment of diabetes in patients with a BMI greater than or equal to 35 kg/m². The first study was published by Inge and colleagues in 2009.⁹² They compared the results of 11 adolescents treated with RYGB to 97 unmatched controls. At one year, remission was achieved in 91% of the RYGB group compared to 0% of the medical therapy group although HbA1c data were only available for 45% of the surgical group at one year. The one patient in the RYGB group not in remission required 238 units of insulin daily prior to the surgery. The only adverse event in the surgical group was a hospital admission to treat dehydration in one patient. The control group was poorly matched to the RYGB group making between group comparisons problematic. For example the two groups differed in age (RYGB 18; control 15 years, p NR), BMI (RYGB 50; control 35 kg/m², p < 0.001), and baseline HbA1c (RYGB 7.3%; control 7.8%, p = 0.005).

Hofso and colleagues compared outcomes in 146 patients treated with RYGB or an intensive lifestyle intervention. The study included 38 patients with T2DM (20 RYGB; 18 lifestyle). Remission of diabetes was defined as a fasting glucose < 125 mg/dL and a HbA1c < 6.2% off of medication. The criteria for remission was met by 70% of patients in the RYGB group and 30% of patients in the lifestyle group. Weight changes and surgical complications were not presented separately for the patients with diabetes. Among the 76 patients in the surgical group, there were four
perioperative complications and 13 late complications. The authors did not report the baseline characteristics of the patients with diabetes separately, so it is not possible to evaluate the similarities and differences of the two groups. In the larger cohort, the RYGB group was significantly younger (p=0.023) and had a higher BMI at baseline (p<0.001).

Dorman and colleagues published a matched cohort study of diabetic patients in 2012. They compared 27 patients treated with duodenal switch (DS), 30 patients treated with LAGB, and 29 patients treated medically with 86 patients treated with RYGB matching on age, sex, HbA1c, and BMI, though not on duration of diabetes or c-peptide level. RYGB was associated with greater weight loss and normalization of HbA1c than medical management or LAGB. DS was associated with similar weight loss, but greater normalization of HbA1c than RYGB. Diabetes remission occurred in 3.4% of medically treated patients, 20% of patients treated with LAGB, 81% of patients treated with DS, and 58% of patients treated with RYGB. Over one year of follow-up readmission rates were lowest in the LAGB group (6.7% LAGB, 11.6% RYGB, 14.8% DS) and overall complications were highest in the DS group (10% LAGB, 15.1% RYGB, 40.7% DS). This study is somewhat larger and better controlled than the prior studies, but it still suffers from short follow-up and a lack of power for cardiovascular outcomes.

The final study compared results in 152 patients with T2DM treated with RYGB who had complete data through two years of follow-up to an unmatched cohort of 115 patients with T2DM and a BMI>35 kg/m². There were large baseline differences between the groups that were not adjusted for in the analyses. These include sex (73% RYGB versus 50% medical, p=0.0002) and BMI (47.4 kg/m² RYGB versus 40.7
kg/m\(^2\) medical, p<0.0001). As expected, BMI, HbA1c, LDL-cholesterol, and SBP significantly improved in the RYGB group, but not in the medically managed group. This study was particularly interested in evaluating the proportion of patients meeting the triad of goals recommended by the American Diabetes Association: HbA1c<7.0%, LDL-cholesterol < 100 mg/dL, and systolic blood pressure < 130 mm Hg. At two years, 38.2% of patients in the RYGB group met all three goal compared to 17.4% of the medically managed group (p<0.01). The authors did not report on diabetes remission or on the incidence of cardiovascular events. Patients in the RYGB group had 82 hospital readmissions and 36 emergency room visits in the 90 days following surgery. Significant adverse events in the RYGB group included five intra-abdominal bleeds requiring surgery, two incarcerated ventral hernias requiring emergency surgery, four bowel obstructions, two gastric outlet obstructions, four pulmonary emboli and three deep venous thrombosis.

Overall, these four comparative studies were methodologically weak, even for comparative observational studies, and they were too small and too short to adequately assess the balance of risks and benefits of bariatric surgery in patients with T2DM with a BM \(\geq 35\) kg/m\(^2\).

Comparative studies of bariatric surgery with medical therapy: BMI < 35 kg/m\(^2\)

Two observational studies compared bariatric surgery to medical therapy for the treatment of diabetes in patients with a BMI less than 35 kg/m\(^2\).\(^{56,57}\) Serrot and colleagues\(^{57}\) retrospectively compared the outcomes in 17 patients with T2DM and class I obesity (BMI 30-34.9 kg/m\(^2\)) to controls matched on BMI. At baseline the
RYGB group was younger (56 versus 62 year, p=0.05) and had a higher proportion of females (76% versus 35%, p=0.04). In addition, the RYGB group had a higher initial HbA1c (8.2 versus 7.0, p=0.04). The duration of diabetes was not reported. All of the surgical cases initially had a BMI >35 kg/m², but lost weight prior to surgery, suggesting that they might be among the more motivated patients and might be expected to do better. They do not represent typical patients with T2DM and a BMI < 35 kg/m² who might be considering bariatric surgery. Their average BMI was 34.6 kg/m², so the results may not apply to patients with a BMI of 30 to 32 kg/m². The average BMI of the RYGB group dropped to 25.8 kg/m² at one year with the thinnest patient still in the normal BMI range. In the RYGB group, the HbA1c decreased from 8.2% to 6.1% at one year while that of the control group did not change (7.0 to 7.1%). Diabetes remission rates were not reported. Eighteen percent of the RYGB group was readmitted. Two patients had incisional hernias requiring repair and two developed marginal ulcers that were treated medically. There were no deaths in either group. This was a small, retrospective study with poorly matched controls that did not attempt any adjustment for the large baseline differences. The results are less useful than the larger case series that described patients with a larger range of BMI’s less than 35 kg/m².

The second comparative study of patients with T2DM and a BMI < 35 kg/m², compared one year results in nine patients treated with SG to those of 9 controls matched on BMI, HbA1c, c-peptide levels, medication use, a duration of diabetes. Patients in the SG group were significantly younger (45 versus 56 years, p=0.003). The SG group also had somewhat higher HbA1c levels (8.1 versus 7.5%, p NS) and slightly short duration of diabetes (7.1 versus 8.6 years, p NS). The average BMI in
the SG group decreased from 32.7 to 21.1 kg/m\(^2\) at one year while that of the control group remained stable (31.9 to 31.7 kg/m\(^2\)). The average HbA1c in the SG group decreased steadily from 8.1 to 5.9% at one year while that of the control group dropped initially, but rebounded (7.5 to 6.9% at 6 months and 8.2% at 12 months). The rate of diabetes remission at one year was 89% in the SG group. The definition of remission was a fasting glucose < 126 mg/dL and Hba1c < 6.5% off of diabetes medications. The one patient in the SG group without remission carried a diagnosis of diabetes for 20 years, was using 87 units of insulin daily, and had a low preoperative c-peptide level (1.5 ng/mL). There were no major surgical complications. Again this study was small, with significant baseline differences between the surgical and medical groups, and a short follow-up. However, the controls were more closely matched to the surgical group than in the prior study. Thus, the results are preliminary, but suggest good results with SG in this population. The low BMI in the surgical group at one year raises concerns about excessive weight loss in some patients. Longer follow-up is needed to evaluate the long-term consequences of SG in this lower weight population.

As with the studies in more obese patients, these two comparative studies were methodologically weak, small and had short follow-up. Larger, well designed studies are needed adequately address the important question about the balance of risks and benefits of bariatric surgery in patients with T2DM with a BM < 35 kg/m\(^2\).
Randomized clinical trials of bariatric surgery versus medical therapy in patients with type 2 diabetes

1. LAGB versus medical therapy

Dixon et al. published the first randomized trial comparing bariatric surgery to medical therapy for T2DM in 2008. It was a single center study in Australia. The investigators randomized 60 patients with T2DM diagnosed in the past two years and a BMI between 30 and 40 kg/m$^2$ to either LAGB or medical therapy focused on weight loss by lifestyle changes. The primary outcome was remission of diabetes defined as a fasting glucose less than 126 mg/dL and HbA1c less than 6.2% without the use of medication therapy for diabetes. The study randomized 30 patients to each group. One patient in the surgical group withdrew prior to surgery and four patients in the medical therapy group withdrew in the first 4 months following randomization. All 60 patients were included in the primary analysis. The two year assessment was completed by 97% in the surgical group and 87% in the medical group.

There were no significant differences between the two groups at baseline. The mean age was 47 years and 53% were female. Their average HbA1c level was 7.7% and their average BMI was 37 kg/m$^2$. Thirteen patients had a baseline BMI less than 36 kg/m$^2$: six were randomized to surgery and seven to medical therapy. Interventions in the medical group included a very low calorie diet (n=11) and sibutramine (n=7).

A higher proportion of patients in the surgical group had remission of their diabetes (73% versus 13%, p<0.001). If the one patient who withdrew from the
surgical group is assumed to not be in remission and the four patients who withdrew from the medical group are assumed to be in remission, the difference would still be statistically significant (73% versus 27%, p<0.001). Patients in the surgical group lost a greater percentage of their excess weight (62.5% versus 4.3%, p<0.001) and weight loss was highly correlated with diabetes remission ($R^2=0.46$). The patients’ age, sex, baseline BMI, c-peptide level, physical activity, and randomization group were not associated with diabetes remission after controlling for weight loss. Compared to medical therapy, the surgical intervention was strongly associated (p≤0.002) with favorable changes in weight, waist circumference, HbA1c, plasma glucose, plasma insulin, HOMA IR, and HDL cholesterol. Unfortunately, none of the results were reported for the subgroup of patients with a baseline BMI < 35 kg/m$^2$.

Adverse events in the surgical group included one superficial wound infection, one post-operative fever, and one patient who had his band removed at 15 days due to persistent regurgitation, even with no saline in the band. In addition, at ten months, two patients developed gastric pouch enlargement that required removal and replacement of the band. In the medical therapy group, two patients were intolerant of the very low-calorie meal replacement, one had a vasculitic rash on rosiglitazone, and three patients had GI symptoms related to metformin.

There are several concerns about the study that limit its generalizability. Results for the subgroup of patients with a BMI < 35 kg/m$^2$ were not reported even though this is the patient population of greatest interest. Bariatric surgery is already considered a therapeutic option for patients with diabetes and a BMI ≥ 35 kg/m$^2$. In addition, the study was performed in patients with a recent diagnosis of diabetes.
As discussed above in the section describing observational studies, it has been demonstrated that the longer patients have diabetes, the less likely they are to go into remission with bariatric surgery. Thus, the study population in this trial was enriched for patients with a high likelihood of response to surgery. The study was not blinded, but it would be very difficult to perform an appropriate sham surgery that would truly blind patients to the intervention. The sample size was too small and the follow-up too short to evaluate the effect of the surgery on the more important macrovascular and microvascular complications of diabetes. Finally, no quality of life outcomes were reported. Patients with diabetes who underwent LAGB unequivocally had higher rates of remission compared with controls, but it is difficult to assess the balance of risks and benefits in patients with a BMI < 35 kg/m² from this study.

2. Roux-en-Y gastric bypass or biliopancreatic diversion versus medical therapy

Mingrone et al. published a similar randomized trial comparing bariatric surgery to medical therapy for T2DM in 2012.\(^94\) It was a single center study in Italy. These investigators randomized 60 patients with T2DM diagnosed more than five years prior to enrollment and a BMI of at least 35 kg/m² to Roux-en-Y gastric bypass, biliopancreatic diversion, or medical therapy. The primary outcome was remission of diabetes defined as a fasting glucose less than 100 mg/dL and HbA1c less than 6.5% without the use of medication therapy for at least one year. The study randomized 20 patients to each group. One patient in each surgical group withdrew during the first year due to surgical complications (incisional hernia; intestinal occlusion) and two patients in the medical therapy group withdrew in the first three months following randomization. All 60 patients were included in the
There were significant differences in cholesterol levels between the two groups at baseline (p=0.01). For example, the total cholesterol and LDL levels were higher in the medical therapy group than in the RYGB group (237 mg/DL versus 182 mg/dL; 154 mg/DL versus 109 mg/DL). This was due to a higher proportion of patients in the RYGB group receiving lipid-lowering therapy than in the other two study groups. The investigators did not describe their methods for allocation concealment, so there may have been some inadvertent selection bias. The mean age of the study subjects was 43 years and 53% were female. Their average HbA1c level was 8.7%, their average BMI was 45 kg/m², and their average duration of diabetes was six years.

At two years, a higher proportion of patients in the surgical groups had remission of their diabetes (95% BPD; 75% RYGB, versus 0% medical, p<0.001). If the one patient who withdrew from each surgical group is assumed to not be in remission and the two patients who withdrew from the medical group are assumed to be in remission, the differences would still be statistically significant (p<0.001). All patients in the surgical groups discontinued medication for diabetes within 15 days of surgery. The time to normalization of HbA1c and blood glucose was significantly shorter in the BPD group (4 months versus 10 months, p=0.01). Patients in the surgical groups lost a greater percentage of their weight (33.8% BPD; 33.3% RYGB; 4.7% medical therapy, p<0.001) and of their excess weight (69.4% BPD; 68.13% RYGB; 9.3% medical therapy, p<0.001). Of note, patients in the medical therapy group lost a remarkable amount of weight at two years (6.5 kg). Contrary to the prior study, weight loss did not correlate with normalization of blood glucose.
suggesting that other factors play a role. Compared to medical therapy, the surgical intervention was strongly associated ($p \leq 0.001$) with favorable changes in weight, waist circumference, HbA1c, plasma glucose, total cholesterol, LDL cholesterol, and HDL cholesterol. Unfortunately, none of the results were reported for the subgroup of patients with a baseline BMI < 35 kg/m$^2$.

There were no operative deaths. Adverse events in the BPD group included one incisional hernia, two cases of iron deficiency anemia, two cases of hypoalbuminemia, one case of osteopenia, and one case of osteoporosis. Adverse events in the RYGB group included one intestinal occlusion and two cases of iron deficiency anemia. The only adverse events in the medical therapy group were two cases of diarrhea associated with metformin that resolved when the medication was discontinued.

As with the prior study, there are several concerns that limit its generalizability. No patients in this study had a BMI < 35 kg/m$^2$, so it is unclear if the results extend to that population. The study was not blinded, though again, it would be very difficult to perform an appropriate sham surgery that would truly blind patients to the intervention. The sample size was too small and the follow-up too short to evaluate the effect of the surgery on the more important macrovascular and microvascular complications of diabetes. The study was also underpowered to detect differences in long-term harms between the two surgical procedures. Finally, no quality of life outcomes were reported. This study was done in a population of patients living with diabetes for at least five years, which makes the high remission rate particularly striking in comparison with the prior study. Patients with diabetes who underwent BPD or RYGB unequivocally had higher rates of remission.
compared with controls, but it is difficult to assess the balance of risks and benefits in patients with a BMI < 35 kg/m² from this study. A higher proportion of patients with diabetes were in remission at two years following BPD than RYGB despite similar weight loss.

3. The Surgical Therapy and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) Trial: Roux-en-Y gastric bypass or sleeve gastrectomy versus medical therapy

The third randomized trial comparing bariatric surgery to medical therapy for T2DM was published by Schauer et al. in the same issue of the New England Journal of Medicine as the prior study. It was a single center study at the Cleveland Clinic in the United States. These investigators randomized 150 patients with T2DM and a BMI between 27 and 43 kg/m² to Roux-en-Y gastric bypass, sleeve gastrectomy, or intensive medical therapy. The primary outcome was remission of diabetes defined as a HbA1c less than or equal to 6.0% without the use of medication therapy at one, two, and five years of follow-up. This publication reports the one year outcomes. The study randomized 50 patients to each group. One patient in the sleeve gastrectomy group did not undergo sleeve gastrectomy and nine patients in the medical therapy group did not complete follow-up (seven with no follow-up visits, two missing the 9 and 12 month visits). These ten patients were not included in the outcomes analyses.

There were no significant differences between the three groups at baseline, although there were trends towards more women, fewer smokers and a lower body weight in the sleeve gastrectomy group. For example, 22% of patients in the sleeve gastrectomy group were smokers compared to 36% in the medical therapy group.
and 40% in the gastric bypass group. The mean age of the study subjects was 49 years and 66% were female. Their average BMI was 36 kg/m² and 51/150 (34%) had a BMI of less than 35 kg/m². The average duration of diabetes was 8.5 years and 44% of the subjects in each group were using insulin. Their HbA1c at baseline was 9.3%.

At one year, the proportion of patients with a HbA1c ≤ 6% was 42% in the RYGB group, 37% in the SG group, and 12% in the medical therapy group (p<0.01 for each surgical therapy versus medical, p=0.59 for the difference between surgical groups). A higher proportion of patients in the surgical groups had HbA1c ≤ 6% with no use of diabetes medication (42% RYGB; 27% SG, versus 0% medical, p<0.001). If all nine patients who were lost to follow-up in the medical group are assumed to have a HbA1c ≤ 6%, then 28% would have met the criteria for primary outcome (analysis not presented by the investigators). The average number of medication(s) per patient decreased from 2.6 to 0.3 in the RYGB group, from 2.4 to 0.9 in the SG group, and increased from 2.6 to 3.0 in the intensive medical therapy group (p<0.001). Despite fewer medications, the average glycemic control improved more in the surgical groups (9.3% to 6.4% RYGB; 9.5% to 6.6% SG, versus 8.9% to 7.5% medical, p<0.001).

As expected, patients in the surgical groups lost a greater percentage of their weight (28% RYGB; 25% SG; 5.2% medical therapy, p<0.001). Of note, in spite of an increase in their medication use, patients in the medical therapy group lost a remarkable amount of weight at one year (5.4 kg). Contrary to the prior study, weight loss did not correlate with normalization of blood glucose suggesting that other factors play a role. Compared to medical therapy, the surgical intervention
was strongly associated (p≤0.001) with favorable changes in weight, waist circumference, HbA1c, plasma glucose, insulin, LDL cholesterol, HDL cholesterol, and c-reactive protein. Changes in weight and BMI were greater in the RYGB group than in the SG group (p<0.04). Unfortunately, none of the results were reported for the subgroup of patients with a baseline BMI < 35 kg/m².

There were no operative deaths. In the first year of the study, 22% of the RGBY patients, eight percent of the SG patients, and nine percent of the medical therapy group required hospitalization for serious adverse events. Adverse events in the RYGB group included four patients for intravenous hydration, three patients for reoperation, two patients with pneumonia, and one each for a significant drop in hemoglobin, transfusion, renal insufficiency, cholelithiasis, wound infection, and a hernia. Adverse events in the SG group included two patients for intravenous hydration, one patient for reoperation, one patient for transfusion, one for a gastrointestinal leak, one for arrhythmia, and one for a pleural effusion. The adverse events in the medical therapy group were two arrhythmias, one cellulitis, and one kidney stone. Less serious adverse events of note included 8% of patients in the RYGB group with ulcers at the anastomosis. Hypoglycemic episodes were common in all three groups (56% RYGB; 80% SG; 81% medical).

This study has several limitations. It was a single center, unblinded study. Even though 51 subjects in this study had a BMI < 35 kg/m², no results were presented for this important subgroup. The sample size was larger than the prior two studies combined, but still too small and the follow-up too short to evaluate the effect of the surgery on the more important macrovascular and microvascular complications of diabetes. The study is designed to follow these patients for a total of five years,
so additional important information should be published in the future. Finally, no quality of life outcomes were reported. At one year, patients with diabetes who underwent RYGB or SG had higher rates of ideal glycemic control and remission compared with intensive medical therapy, but they had more serious adverse effects including the need for additional surgical procedures. The long-term balance of risks and benefits in patients with a BMI < 35 kg/m² remain unclear.

Randomized trials in patients with a BMI < 35 kg/m²

There are several randomized trials comparing different bariatric procedures in patients with a BMI > 35 kg/m² that report changes in measures of glucose metabolism and resolution of diabetes, usually in a small subset of the patients who were randomized. There was only one study that randomized patients who had T2DM and a BMI < 35 kg/m², but the study did not have a medical therapy only group. Lee and colleagues randomized 60 patients with T2DM, HbA1c > 7.5%, c-peptide ≥ 1.0, and a BMI > 25 and < 35 kg/m² to either gastric bypass (n=30) or sleeve gastrectomy (n=30). Remarkably, both patients and the outcome assessors were blinded to the surgical procedure performed for the first year following surgery. This was possible as both procedures were performed laparoscopically. Moreover, randomization was performed in the operating room after pneumoperitoneum was completed. Their primary outcome was remission of diabetes defined as HbA1c < 6.5% and fasting glucose < 126 mg/dL on no diabetes medications at the one-year follow-up. Follow-up was 100% in both groups at one year.
The study participants had an average age of 45 years, an average BMI of 30 kg/m\(^2\) (range 25 to 34), and an average HbA1c of 10.0%. The authors state that there were no significant differences between the two surgical groups at baseline. They did not report the sex distribution, the c-peptide levels, the duration of the participants’ diabetes, nor the type or intensity of diabetes therapy. There were no deaths, no major complications, and no conversions to open procedures in either group. There were no differences in the surgical time or hospital length of stay between the two groups and minor complications were identical in the two groups (10%).

The diabetes remission rate was higher in the RYGB group (93% versus 47%, \(p=0.02\)). The average reduction in HbA1c at one year was also higher in the RYGB group (4.2% versus 3.0%, \(p<0.001\)). At the one year follow-up, the average HbA1c was lower in the RYGB group (5.7% versus 7.2%, \(p<0.001\)), as was the average fasting glucose level (99 versus 140, \(p<0.001\)), the LDL-cholesterol (97 versus 137, \(p<0.001\)), and BMI (22.8 versus 24.4, \(p=0.009\)). The authors concluded that both procedures were safe and effective in patients with T2DM and BMI < 35 kg/m\(^2\), but that RYGB was more effective than SG. As with the prior randomized trials, the study was underpowered and too short to investigate the more important microvascular and macrovascular complications of diabetes. In addition, quality of life outcomes were not reported.

**Ongoing randomized trials**

In ClinicalTrials.gov, there are dozens of ongoing randomized trials evaluating
bariatric surgery for the treatment of diabetes including at least five studies exclusively enrolling subjects with a BMI < 35 kg/m\(^2\). The majority of the studies are too small and planned follow-up too short to provide definitive answers to the comparative effectiveness of medical versus surgical therapy in less obese patients. One of the studies has called for a consortium to standardize the measurements and outcomes so that study results can be combined to have sufficient power to examine long-term effects on cardiovascular outcomes in addition to shorter term outcomes.\(^{101}\)

**Summary**

The Swedish Obese Subjects study demonstrated that bariatric surgery in patients with a BMI ≥ 35 kg/m\(^2\) reduced cardiovascular risk factors for more than a decade after surgery and this translated into a reduction in both cardiovascular mortality and total mortality compared to carefully matched controls. Weight loss was greatest one year after surgery, but remained stable and significant between ten and twenty years of follow-up. At ten years, diabetes remained in remission for 36% of the patients with diabetes who underwent surgery. Among those with diabetes, there was a statistically significant 37% reduction in cardiovascular endpoints.

Subsequent observational studies in patients with a BMI ≥ 35 kg/m\(^2\) confirmed the durable weight loss, markedly greater remission of diabetes, a reduction in other cardiovascular risk factors, and a reduction in medication use for patients treated with bariatric surgery using current surgical techniques (laparoscopic BPD,
laparoscopic RYGB, LAGB, and laparoscopic SG) compared to those treated with medical therapy. The observational data, including studies comparing the procedures to each other suggest that the rate of diabetes remission is greatest with BPD, followed by RYGB and SG. The remission rate was lowest with LAGB. However, the definition for diabetes remission varied widely across studies, so cross-study comparisons may not be valid. Major complication rates requiring rehospitalization and reoperation were highest with BPD followed by RYGB, with SG and LAGB having the lowest complication rates. In the Bariatric Outcomes Longitudinal database, the one-year significant complication rate was 26% for BPD, 15% for RYGB, 11% for SG, and 5% for LAGB. The 30-day mortality followed the same pattern: 1.1% for BPD, 0.5% for RYGB, and 0.1% for LAGB. The three randomized trials also demonstrated markedly higher rates of diabetes remission in patients randomized to bariatric surgery (BPD, RYGB, SG, or LAGB) compared to medical therapy. None of the recent studies have reported data on the microvascular and macrovascular complications of diabetes, but for patients with a BMI $\geq 35$ kg/m$^2$, the Swedish Obese Subjects study offers compelling evidence supporting long-term benefits. Patients with a BMI $\geq 35$ kg/m$^2$ and diabetes already meet guidelines for bariatric surgery and the evidence supports long term benefits in terms of cardiovascular disease and all cause mortality in this population.

The evidence base for patients with diabetes and a BMI < 35 kg/m$^2$ is much less robust. In the case series and comparative studies, bariatric surgery did improve glycemic control and diabetes remission rates more than would be expected with medical therapy. However, there are fewer studies, shorter follow-up and no randomized trials comparing bariatric surgery to medical therapy. There is no
equivalent to the Swedish Obese Subjects study in patients with a BMI < 35 kg/m². There is a complete lack of data on outcomes other than glycemic control and other cardiovascular risk factors. Two of the randomized trials with a medical therapy control group did include some participants with BMI < 35 kg/m² but the outcomes were not reported separately for this subgroup.

Patients with a lower BMI may have less to gain from bariatric surgery and may be at higher risk for excessive weight loss and malnutrition, particularly with BPD. If these relatively thinner patients lose the five to seven kilograms of excess weight that was achieved in the medical therapy arms of the randomized trials, they may achieve more significant benefits than those seen for more obese patients. In addition, the biology of T2DM may be different in less obese patients. It is notable that the relative efficacy of the bariatric procedures may be different in thinner patients with diabetes. In the meta-analysis and comparative studies, the remission rate was highest for RYGB followed by BPD and then LAGB. SG seemed to be the least effective procedure for less obese patients with T2DM, although the numbers studied were low and most of the comparisons were not randomized.

TA Criterion 3 is met for patients with a BMI \( \geq 35 \) kg/m²

TA Criterion 3 is not met for patients with a BMI < 35 kg/m²
TA Criterion 4: The technology must be as beneficial as any established alternatives.

The established therapy for T2DM is intensive lifestyle modification focusing on improving diet, weight loss, and increasing daily exercise. If adequate control is not achieved, there are many classes of effective oral and parenteral medications that can be used.

Three randomized trials described above compared bariatric surgery to the combination of lifestyle and medical therapy. Patients in the medical therapy groups did remarkably well as they lost between five and seven kilograms of weight through one to two years of follow-up and achieved an average HbA1c of approximately 7.5%. Up to 95% of patients treated surgically had their diabetes go into remission. The number of patients needed to treat with bariatric surgery to have one patient go into remission varied from two to four patients across the studies. This varied by the surgical technique used, the definition of remission, and the characteristics of the patient population studied. However the longest of these three trials reported two year follow-up. From the SOS study, we know that many patients treated with bariatric surgery initially have remission from diabetes, but relapse over time. In that study, 72% of patients with diabetes were in remission at the two year follow-up, but only 36% were in remission at ten years.

There are significant harms associated with bariatric surgery. The initial surgical procedure requires hospitalization and a prolonged recovery. Surgery is associated with a small, but real risk for peri-operative heart attacks, arrhythmias, pulmonary emboli, infections, and death. Patients are frequently rehospitalized for
complications due to their surgery and may require reoperation for bleeding, hernias, bowel obstruction, and intestinal leakage. There are also long-term effects on eating habits and possible nutrient deficiencies. In order to balance the significant harms associated with surgery, the trials need to demonstrate a reduction in cardiovascular endpoints including heart attacks, strokes, and death from cardiovascular disease. The randomized trials were too small and too short to have significant numbers of cardiovascular endpoints. For patients with a BMI ≥ 35 kg/m², the high quality SOS study provides strong observational evidence that bariatric surgery reduces cardiovascular endpoints and total mortality compared to medical therapy, and the benefits appear to be greatest in patients with diabetes.

Comparable evidence is lacking for patients with a BMI < 35 kg/m². Two of the three randomized trials included patients with a BMI < 35, but the results were not presented separately for those subgroups. There is one randomized trial in this patient population, but the study compared RYGB to SG and did not have a medical therapy group for comparison. The observational studies demonstrated high rates of diabetes remission, but presented no data on cardiovascular outcomes. Less obese patients may derive less overall benefit from bariatric surgery, yet be at risk for all of the complications and be at higher risk for excessive weight loss. Although promising, the evidence is not yet sufficient to demonstrate that the benefits of bariatric surgery in patients with diabetes and a BMI < 35 kg/m² outweigh the harms.

TA Criterion 4 is met for patients with a BMI ≥ 35 kg/m²

TA Criterion 4 is not met for patients with a BMI < 35 kg/m²
TA Criterion 5: The improvement must be attainable outside of the investigational setting.

The number of bariatric procedures performed annually has increased dramatically over the past two decades. At the same time, operative mortality has decreased significantly. Given the complexities of pre-operative evaluation to select appropriate candidates for surgery and the need for long-term follow-up by a multidisciplinary team, bariatric surgery is performed at recognized centers of excellence. For patients with a BMI ≥ 40 kg/m² or a BMI ≥ 35 kg/m² with T2DM, TA criterion 5 is met when performed at one of the centers of excellence. However, among patients with a BMI < 35 kg/m², TA criterion 5 has not been met because improvements in long-term outcomes have yet to be demonstrated in the investigational setting.

TA Criterion 5 is met for patients with a BMI ≥ 35 kg/m²

TA Criterion 5 is not met for patients with a BMI < 35 kg/m²
CONCLUSION

More than one in three adults in the United States is obese and the prevalence has doubled in the past twenty years. Obesity is the strongest risk factor for T2DM, so that in 2010, one in nine adults has diabetes. Lifestyle interventions focusing on diet, exercise, and weight loss can prevent diabetes in those at risk and can be used to treat diabetes, but the vast majority of patients with diabetes fail to maintain lifestyle changes sufficient for long-term remission of diabetes.

Bariatric surgery has been proposed as a treatment for diabetes in obese patients. Bariatric surgery decreases daily caloric intake and is associated with dramatic weight loss in most patients, both of which help ameliorate diabetes. There is also strong evidence that bariatric surgery directly impacts the secretion of enteric hormones associated with both satiety and glucose metabolism. It is clear from the evidence that all forms of bariatric surgery dramatically reduce fasting glucose levels and HbA1c while reducing the need for diabetes medication. The reported rates of remission from diabetes range from approximately 60% for LAGB to 95% for BPD. Three randomized trials confirmed that the remission rates are much higher with bariatric surgery than with intensive lifestyle and medical therapy. The randomized trials also documented greater reductions in other risk factors for cardiovascular disease, but they were not powered to assess cardiovascular event rates. Unfortunately, none of them reported comparative data on quality of life either.

Remission from diabetes alone is not sufficient to counterbalance the significant risks associated with bariatric surgery. These include significant peri-
operative risks as well as long-term complications. Furthermore, diabetes remission is not necessarily durable. The Swedish Obese Subjects study found that about half of patients with diabetes in remission following bariatric surgery relapsed during 10 years of follow-up. However, there was still a significant reduction in cardiovascular events and total mortality in obese patients treated surgically compared to carefully matched controls who were treated with medical therapy. Patients with diabetes prior to surgery appeared to have greater reductions in cardiovascular events than patients without diabetes. Thus, the benefits appear to outweigh the harms, particularly for obese patients with diabetes. The SOS study was not a randomized trial, but it was a large prospective study that carefully matched participants treated with bariatric surgery to medically treated participants using 18 matching variables and followed them up to 20 years. It is important to remember that the results of the SOS study only apply to patients with a BMI $\geq 35$ kg/m$^2$.

It remains unclear whether the benefits of bariatric surgery for individuals with diabetes outweigh the harms for less obese patients. There are no long-term studies documenting a reduction in cardiovascular outcomes in patients with a BMI < 35 kg/m$^2$. Observational studies and one randomized trial without a medical therapy control arm have documented significant improvements in glycemic control and high rates of diabetes remission in this population. But less obese individuals might have less overall benefits from weight loss surgery and may be at higher risk for complications due to excessive weight loss. High quality comparative studies are needed to adequately assess the net benefits of surgery. There are at least five ongoing trials randomizing patients with diabetes and a BMI < 35 kg/m$^2$ to bariatric
surgery or intensive medical therapy. There is also an initiative to standardize the outcomes in the trials so that they can be pooled in a meta-analysis in order to have sufficient statistical power to meaningfully assess the net benefits and harms in this patient population. Patient with diabetes who have a BMI < 35 kg/m$^2$ should only undergo bariatric surgery in the context of clinical trials. A recent expert panel specifically convened to examine the role of bariatric surgery in the treatment of T2DM concluded that additional clinical trials were needed for patients with class I obesity (BMI 30-35 kg/m$^2$).
RECOMMENDATION(S)

Recommendation #1:

It is recommended that use of bariatric surgery meets CTAF TA Criterion 1 through 5 for safety, effectiveness and improvement in net health outcomes when used for the treatment of type 2 diabetes mellitus in obese patients with a BMI $\geq 35$ kg/m$^2$ who are not adequately controlled by lifestyle and medical therapy alone.

_The California Technology Assessment Forum Panel voted unanimously in favor of Recommendation #1 as written._

Recommendation #2:

It is recommended that use of bariatric surgery does not meet CTAF TA Criterion 3 through 5 for safety, effectiveness and improvement in net health outcomes when used for the treatment of type 2 diabetes mellitus in patients with a BMI < 35 kg/m$^2$.

_The California Technology Assessment Forum Panel voted unanimously in favor of Recommendation #2 as written._

June 20, 2012

This is the first review of this technology by the California Technology Assessment Forum.
RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

The BCBSA Technology Evaluation Center (TEC) is currently performing two technology evaluations: 1) Bariatric Surgery for lower BMI thresholds; and 2) Bariatric Surgery for Diabetes Mellitus. Completion dates for these two topics are unknown.

In September 2003, BCBSA TEC published a special report: The Relationship between Weight Loss and Changes in Morbidity Following Bariatric Surgery for Morbid Obesity – which stated that "....compelling evidence for an improvement in comorbid conditions exists for diabetes....a large reduction in diabetes over a 5.5 year mean follow-up for the surgery group...."

Canadian Agency for Drugs and Technologies in Health (CADTH)

In July 2010, CADTH published a Rapid Response Report: Change in Disease Status Following Bariatric Surgery: Clinical Evidence which stated "The two most commonly reported outcomes (of bariatric surgery) were improvement or resolution of type 2 diabetes."

National Institute for Health and Clinical Excellence (NICE)

NICE published the guideline: Obesity – guidance on prevention, identification, assessment and management of overweight and obesity in adults and children in December 2006. Recommendation 1.2.6.1 notes one of five criteria for bariatric surgery is “...a BMI of 40 kg/m2 or more, or between 35 kgm2 and 40 kg/m2 and
other significant disease (for example, type 2 diabetes....) that could be improved if (patients) lost weight.”

Centers for Medicare and Medicaid Services (CMS)

CMS National Coverage Decision (NCD) for Bariatric Surgery for Treatment of Morbid Obesity (100.1) effective February 2009 notes the following procedures are covered for Medicare beneficiaries with body mass index > 35, have at least one comorbidity related to their obesity, and have been previously unsuccessful with medical treatment of their obesity: open and laparoscopic Roux-en-Y gastric bypass (RYGBP), open and laparoscopic Biliopancreatic Diversion with Duodenal Switch (BPD/DS), and laparoscopic adjustable gastric banding (LAGB). These procedures are only covered if they are performed at facilities that are certified by the American College of Surgeons as a Level 1 Bariatric Surgery Center, or certified by the American Society for Bariatric Surgery as a Bariatric Surgery Center of Excellence.

Agency for Healthcare Research and Quality (AHRQ)

A search of AHRQ’s National Guideline Clearinghouse found the 2008 guideline entitled American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery medical guidelines for clinical practice for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient can be found at:
http://www.guideline.gov/content.aspx?id=13022&search=bariatric+surgery#Section420

Stated objectives of the guideline include:

• An overview of the important principles of bariatric surgery as context for interpretation of subsequent evidence-based recommendations
• An evidence-based resource for the perioperative nonsurgical management, especially nutritional and metabolic support, of the bariatric surgery patient
• Specific recommendations regarding the selection of appropriate patients for bariatric surgery
• Specific recommendations regarding the preoperative evaluation for the bariatric surgical patient
• Specific recommendations regarding postoperative nonsurgical management of the bariatric surgery patient
• Specific recommendations regarding the recognition and management of postoperative complications
• Specific recommendations regarding selection of patients for a second (staged) bariatric surgical procedure or a revision or reversal of a previous bariatric surgical procedure
American College of Surgeons (ACS)

ACS did not provide an opinion but did not send a representative to the meeting.

American Gastrological Association (AGA)

AGA did not send an opinion nor send a representative to the meeting.

American Society for Metabolic and Bariatric Surgery (ASMBS)

ASBMS did not provide an opinion but did send a representative to the meeting.

See AHRQ above for description of the jointly developed clinical guideline between AACE, TOS, and ASMBS.

American College of Gastroenterology (ACG)

ACG did not send an opinion nor send a representative to the meeting.

Society of Gastrointestinal and Endoscopic Surgeons (SAGES), CA Chapter AACE

SAGES did not send an opinion nor send a representative to the meeting.

In March 2008, SAGES published a clinical guideline which was also endorsed by ASMBS entitled SAGES guideline for clinical application of laparoscopic bariatric surgery. http://www.sages.org/publication/id/30/
The American Association of Clinical Endocrinologists (AACE), Southern California Chapter

The AACE/So. CA Chapter did not send an opinion nor send a representative to the meeting.

See AHRQ above for description of the jointly developed clinical guideline between AACE, TOS, and ASMBS.

The Endocrine Society

The Endocrine Society did not send an opinion nor send a representative to the meeting.

The Obesity Society (TOS)

TOS did not send an opinion nor send a representative to the meeting.

See AHRQ above for description of the jointly developed clinical guideline between AACE, TOS, and ASMBS.
ABBREVIATIONS

CTAF: California Technology Assessment Forum
T2DM: Type 2 Diabetes Mellitus
RYGB: Roux-en Y Gastric Bypass
DARE: Database of Abstracts of Reviews of Effects
FDA: US Food and Drug Administration
BMI: Body Mass Index
RCT: Randomized Controlled Trial
LAGB: Laparoscopic Adjustable Gastric Banding
SG: Sleeve Gastrectomy
BPD: Bilipancreatic Diversion
PYY: Peptide Tyrosine Tyrosine
GIP: Glucose-dependent Insulinotropic Peptide or Gastric Peptide Inhibitor
GLP-1: Glucagon-like Peptide-1
SOS: Swedish Obese Subjects
VBG: Vertical Banded Gastroplasty
HDL: High Density Lipoprotein
DS: Duodenal Switch
LDL: Low Density Lipoprotein
HOMA IR: Homeostasis Model of Assessment - Insulin Resistance
NS: Not significant
REFERENCES


