Surgical Approaches to the Treatment of Obesity: Bariatric Surgery

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• Bariatric surgery • Metabolic surgery • Obesity
• Metabolic syndrome • Diabetes resolution

As bariatric surgery for the treatment of morbid obesity enters its sixth decade, much has been and continues to be learned from the results of several key bariatric operations, particularly the Roux-en-Y gastric bypass. Because of the epidemic of obesity and development of the laparoscopic approach, bariatric procedures have increased exponentially in the past decade and are now among the more commonly performed gastrointestinal operations. In the United States, the laparoscopic adjustable gastric banding procedure was introduced in 2001 and has steadily gained popularity. With the introduction of the laparoscopic approach, the public now views bariatric surgery as a less-invasive procedure for treating a chronic disease that can threaten one's health and longevity. Along with the laparoscopic revolution, immense efforts were initiated to develop a new standard for safety, with a focus on improving outcomes. The concept of *centers of excellence* was developed, whereby centers performing bariatric surgery must adhere to a high standard with regard to the volume of surgery, the availability of a complete bariatric program, and maintenance of acceptable surgical outcomes. Emerging data support the role of bariatric surgery as an effective treatment for improvement or remission of type 2 diabetes, hypertension, dyslipidemia, and multiple other comorbid conditions that accompany obesity. The mechanisms involved in the remission of these conditions, however, remain poorly understood and constitute an exciting area of research. This article delineates the current types of bariatric surgery, their respective outcomes, and their impact on obesity-related medical comorbidities.

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BARIATRIC SURGERY AS TREATMENT FOR SEVERE OBESITY

Obesity is a chronic disease that has become a major nutritional health problem in most industrialized countries, and its prevalence is increasing in the United States. A recent study involving data from the National Health and Nutrition Examination Survey (NHANES) from 2003 to 2004 indicates that obesity was present in 28.5% of adults aged 20 to 39 years, 36.8% aged 40 to 59 years, and 31.0% aged 60 years or older, with obesity defined as a body mass index (BMI) of 30.0 or higher.[1] The number of overweight children and adolescents in the United States is also increasing. According to the NHANES report, the prevalence of overweight individuals aged 12 to 19 years increased from 10.5% in 1988 to 1994 to 15.5% in 1999 to 2000.[2]

The health implications of obesity include increased risk for coronary artery disease, hypertension, hyperlipidemia, type 2 diabetes mellitus, sleep apnea, stroke, arthritis of the weight-bearing joints, and increased prevalence of selected types of cancer. Obesity contributes to approximately 300,000 premature deaths each year as a result of health-related complications.[3] The risk for developing these medical comorbidities is directly proportional to the degree of obesity.[4] Additionally, the relative risk for death increases substantially with increasing BMI, particularly for individuals who have BMI of 35 kg/m^2 or more.[5] Thus, severe obesity is somewhat arbitrarily defined as a BMI of 35 kg/m^2 or more, and morbid obesity is defined as a BMI of 40 kg/m^2 or more with coexistence of significant comorbidity.

The prevalence of severe obesity seems to be increasing at an even higher rate than moderate degrees of obesity.[1] Bariatric surgery, also known as *weight-loss surgery* or *obesity surgery*, is widely accepted as the only known effective treatment for severe obesity. This procedure was introduced in the 1950s and involves surgical manipulation of the gastrointestinal tract to induce long-term weight loss in severely obese individuals.

Bariatric surgery has been shown to substantially improve or resolve many common obesity-related comorbid conditions, including type II diabetes, hypertension, sleep apnea, and dyslipidemia. A recent report with 10-year outcome data from the observational Swedish Obese Subjects (SOS) study showed marked benefits in patients treated surgically compared with matched control subjects treated medically, including recovery from diabetes, lipid abnormalities, sleep apnea, and quality of life.[6] Several studies have also shown that bariatric surgery improves long-term survival.[7–13]

According to the 1991 National Institutes of Health (NIH) consensus conference,[14] bariatric surgery is an effective option for treating individuals categorized as having morbid obesity. Nonsurgical treatment options in the severely obese population include a combination of low-calorie diets, behavioral therapy, exercise programs, and pharmacotherapy. However, limited success has been reported. In long-term follow-up, most patients did not maintain their reduced body weight. Even with pharmacotherapy, patients who experienced response to therapy usually regained weight when treatment stopped. A randomized controlled trial comparing bariatric surgery with nonsurgical treatment showed that the mean difference in weight loss at 24 months of follow-up greatly favored surgical therapy.[15]

Surgery is currently the best-established and most successful method for sustained weight loss in the morbidly obese.[16,17] Several bariatric operations were introduced in the past 4 decades, encompassing a spectrum from primarily restrictive, to combined restrictive/malabsorptive, to purely malabsorptive operations. Roux-en-Y gastric bypass is currently the most commonly performed operation for treating morbid obesity, representing approximately 70% to 75% of all bariatric procedures. The

past decade has seen a major growth in the number of bariatric operations performed in the United States. More patients are now seeking bariatric surgery, with the development of the laparoscopic approach an important factor in this growth. The public now views bariatric surgery as a less-invasive operation associated with less postoperative pain and a faster recovery. In addition, in June 2001 the U.S. Food and Drug Administration (FDA) approved laparoscopic adjustable gastric banding (LAGB; Lap-Band, Allergan, Irvine California) for clinical use. The LAGB represents approximately 20% to 25% of all bariatric operations in the United States and provides another minimally invasive surgical option that does not require gastric transection or gastrointestinal reconstruction. This article describes modern, commonly performed bariatric operations, outcomes of bariatric surgery regarding weight loss and morbidity and mortality, and the benefits of bariatric surgery for improvement or remission of obesity-related comorbidities.

PATIENT SELECTION AND WORKUP

Based on the 1991 NIH Consensus Development Conference Panel[14] for the treatment of severe obesity, individuals who have a BMI greater than 35 kg/m^2 with associated medical comorbidities or whose BMI is greater than 40 kg/m^2 qualify for bariatric surgery. Patients generally should have a chronic history of obesity with no underlying endocrine abnormality that can contribute to obesity. Nonsurgical means of weight loss should also have been attempted with failed results. These qualifications for bariatric surgery are endorsed by numerous professional societies and governmental agencies, including the Centers for Medicare and Medicaid Services.

Furthermore, numerous evidence-based reports support bariatric surgery as the preferred treatment for severe obesity.[18] However, most commercial insurance carriers currently do not cover or have very limited coverage of bariatric surgery. Thus, despite recent growth in bariatric surgery, patient access to the only known, broadly effective treatment for severe obesity is extremely limited.

Preoperative evaluation is considered critical to enhance outcomes. Most bariatric surgeons recommend psychological screening to ensure that patients have no severe, untreated psychological or psychosocial issues. In addition, most patients who have significant medical comorbidities often require preoperative cardiorespiratory clearance, because all medical conditions must be optimized before surgery. Other workup may include a sleep study to detect obstructive sleep apnea, arterial blood gas to detect obesity hypoventilation syndrome, and cardiac evaluation for patients suspected of having coronary heart disease.

Preoperative dietary education and the need for postoperative compliance with the comprehensive program are stressed in preoperative visits. Postoperative support group meetings are available and attendance is a common requirement among most bariatric practices, because patients who participate regularly in these meetings experience a significantly greater weight loss than those who do not.[19]

After appropriate patient selection, patients are counseled extensively on the various bariatric operations and the risks and benefits of each. The surgeon and patient select the appropriate bariatric procedure after extensive discussion of the pros and cons of each operation.

FACILITY REQUIREMENTS

For bariatric surgery to be safely performed, the health care facility must be able to accommodate morbidly obese patients in all aspects, starting with a system for

evaluation through follow-up. The institution should have a bariatric surgical team, skilled staff, appropriate operating room equipment, and sufficient institutional resources. A bariatric surgical team consists of experienced surgeons and physicians, anesthesiologists, nurses, psychologists, and nutritionists. Specialists in the field of cardiology, pulmonology, rehabilitation, and endocrinology should be available. The operating room must have operating tables and ancillary equipment to accommodate morbidly obese patients, and the staff should be familiar with this equipment and how to care for these patients. The hospital facility should have beds, commodes, chairs, and wheelchairs to accommodate the morbidly obese. In addition, radiology facilities should be capable of handling the radiologic needs of morbidly obese patients.

SURGICAL OPERATIONS

Mason and Ito[20] conceived the original gastric bypass operation in the 1960s as a variation of gastric ulcer surgery. Weight loss was noted in a large percentage of patients who had undergone partial gastrectomy as primary treatment for peptic ulcer disease. The concept has since evolved through numerous modifications to achieve optimal weight loss while minimizing surgical morbidity and nutritional deficiency, with the emergence of a few safe operations. Although many surgical operations for weight loss currently exist, some have been relegated to historical perspective. Additionally, most modern bariatric surgery is performed laparoscopically unless it is revisional or cannot be performed for technical reasons.

Vertical Banded Gastroplasty

The vertical banded gastroplasty (VBG) consists of constructing a small gastric pouch based on the lesser curvature of the stomach, with the outlet restricted with a prosthetic band or mesh. The VBG is a purely restrictive bariatric procedure and the mechanism of weight loss is primarily related to caloric restriction. Although the NIH Consensus Panel proposed this operation as one of two acceptable bariatric procedures, it is not commonly performed because of its inferior weight loss compared with gastric bypass and its high incidence of late complications.

The VBG became popular because it is a simple operation and has a low perioperative risk profile. Although short-term results have been reported to be excellent, long-term results are less favorable.[21–25] The operative time for this procedure is generally short (1–2 hours), with an operative mortality of less than 1% in most series. Early complications included outlet stenosis and staple-line leak, whereas late complications included staple-line fistula, band erosion, stoma stenosis, food intolerance, and pouch dilation. Weight loss after VBG varies between reports. Morino and colleagues[24] reported a 61% excess weight loss at 4 years, whereas Kalfarentzos and colleagues[25] reported only a 37% excess weight loss at 5 years.

The advantages of VBG include its reversibility, preservation of the gastrointestinal tract, and maintained absorption of micronutrients. Disadvantages of VBG include lower weight loss compared with Roux-en-Y gastric bypass, long-term weight regain, high revisional rate, and development of maladaptive eating behavior.

Roux-en-Y Gastric Bypass

The modern Roux-en-Y gastric bypass operation is currently considered the safest and most efficacious operation combining a restrictive and malabsorptive component. It is the most widely performed bariatric operation today. The most common technique is the laparoscopic Roux-en-Y gastric bypass. Open surgery is reserved for difficult scenarios, such as patients who have high BMI, android body habitus, and a history

of gastrointestinal surgery, and is also performed by surgeons who are not comfortable with the laparoscopic technique.

Laparoscopic gastric bypass is performed using five or six abdominal ports of variable sizes. A liver retractor is used to retract the left lobe of the liver to expose the entire stomach. One goal is to construct a small gastric pouch that can hold approximately 15 to 20 mL of solid or liquid. The gastric pouch is constructed immediately below the gastroesophageal junction by applying a linear stapler horizontally across the lesser curve, and then turning the staples in a cephalad direction to the angle of His (**Fig. 1**).

The proximal jejunum is then addressed, where the jejunum and its mesentery are divided at 30 to 40 cm distal to the ligament of Treitz. The distal jejunal limb is brought up toward the new gastric pouch as the Roux limb, and the omentum is divided to create a valley through which the Roux limb is brought antecolic into apposition with the new gastric pouch. The length of the Roux limb is carefully measured at 75 to 150 cm, at which point the biliopancreatic limb of the jejunum is anastomosed to the Roux limb, typically using a linear stapler. The mesenteric defects are closed to prevent internal herniation. Finally, an anastomosis is constructed between the gastric pouch and the Roux limb using a circular stapler, which is further reinforced with several interrupted sutures to relieve tension from the gastrojejunal staple-line. Intraoperative endoscopy is performed with air insufflation while the anastomosis is submerged under water to ensure the anastomosis is airtight. Operative time is generally 2 to 4 hours.

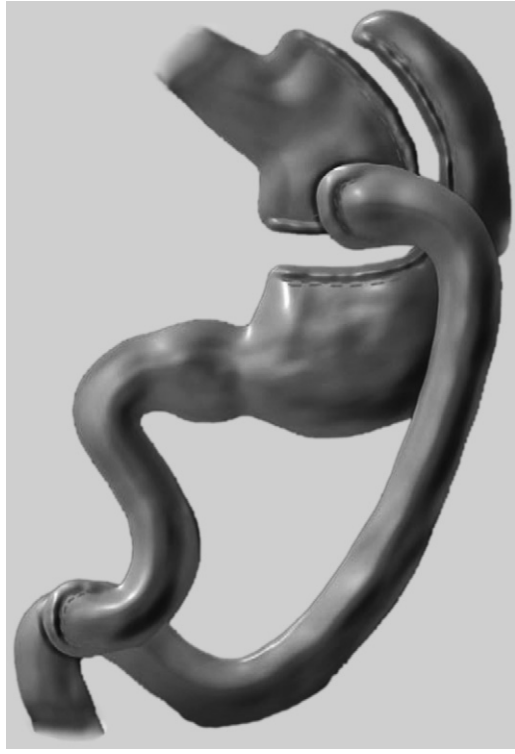

Fig. 1. Roux-en-Y gastric bypass.

Postoperatively, the authors' patients undergo an upper gastrointestinal contrast study with gastrograffin to check for leaks or obstructions before enteral feeds are initiated. Once the upper gastrointestinal study is negative, patients are started on a bariatric clear liquid diet consisting of no concentrated sweets and are instructed to ambulate extensively until discharge on postoperative day two or three. Follow-up is typically at 1 week postoperatively, at 1 month, and then at 3, 6, 9, and 12 months postoperatively.

Laparoscopic Adjustable Gastric Banding

The operation with the fastest rate of growth in recent years is LAGB. The two FDA-approved bands (Lap-Band, Allergan, Irvine, CA, USA, and Realize, Ethicon Endosurgery, Cincinnati, OH, USA) are made of silicone and have an inflatable ring on the inner surface that can be infused with saline (**Fig. 2**). Operative access is achieved with five abdominal ports. The band is placed around the proximal aspect of the stomach immediately below the gastroesophageal junction. Once in position, the band is tightened by closing the buckle and is secured through imbricating the band anteriorly with the gastric fundus to prevent band slippage or gastric herniation. The catheter attached to the band is then exteriorized through one of the port sites and connected to an infusion port, which is then secured to the rectus abdominus fascia. Operative time is usually approximately 1 to 2 hours.

Patients undergo a routine upper gastrointestinal study on the first postoperative day. After confirming easy passage of contrast through the band positioned at a 30° angle, patients are started on a bariatric clear liquid diet. They are typically discharged on postoperative day 1 when tolerating liquids and oral analgesics. Follow-up is similar to that for other bariatric operations; the first band adjustment occurs at 6 weeks postoperatively and then at 2- to 3-month intervals until the optimal level is achieved. Band

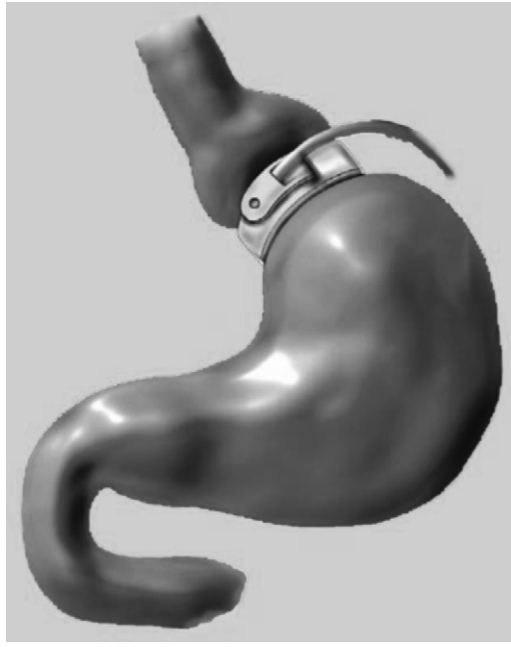

Fig. 2. Laparoscopic adjustable gastric banding.

adjustments are performed percutaneously in the office; however, some surgeons use fluoroscopy in the radiology suite.

Sleeve Gastrectomy

Sleeve gastrectomy has recently become an increasingly common and popular operation. The procedure originated as part of a duodenal switch operation and later evolved into a staging procedure for super-obese or high-risk patients. Patients in these categories would undergo an initial operation consisting entirely of a vertical resection of the lateral aspect of the gastric body and fundus (**Fig. 3**).

The operation begins with mobilization of the greater curvature of the stomach, with division of the short gastric vessels. Using the linear stapler, the greater curve of the stomach is transected approximately 6 cm proximal to the pylorus, and staples fired successively cephalad, parallel to the lesser curve and against a bougie, typically a 42-French. The resected stomach is removed through one of the large port sites. Operative time for this procedure is generally 1 to 2 hours. Postoperative course is similar to that of laparoscopic gastric bypass, with an upper gastrointestinal study on the first postoperative day and initiation of clear liquids when the study shows no leaks or obstruction. Patients typically are discharged on the first or second postoperative day after ambulating and tolerating oral analgesics.

Biliopancreatic Diversion and Duodenal Switch

The biliopancreatic diversion (BPD), developed by Scopinaro[26] in the late 1970s, is a malabsorptive operation whereby the small bowel is divided 250 cm proximal to the ileocecal valve and a subtotal gastrectomy performed, leaving a 400-mL gastric pouch. The distal (alimentary) limb is connected to the gastric pouch. The proximal (biliopancreatic) limb is connected end-to-side to the ileum 50 cm proximal to the ileocecal valve.

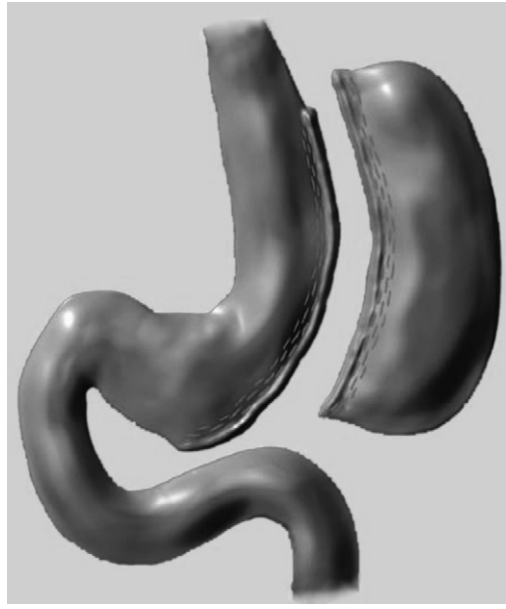

Fig. 3. Sleeve gastrectomy.

This operation is considerably more complex and technically more challenging than the previously described operations. The duodenal switch is a modification of the BPD, whereby a sleeve gastrectomy is performed rather than a subtotal gastrectomy. The duodenum is divided immediately beyond the pylorus. The alimentary limb is connected to the duodenum while the biliopancreatic limb is connected to the ileum 75 cm proximal to the ileocecal valve.

The role of malabsorptive procedures for treating morbid obesity is limited to selected centers. These procedures may have a role in treating patients who are extremely obese (BMI $\geq$60 kg/m^2) or for whom other bariatric operations have failed.

SURGICAL OUTCOMES

Bariatric surgical outcomes have become a significant area of scrutiny, predominately because of higher-than-expected morbidity and mortality rates that accompanied the introduction of laparoscopic gastric bypass at the turn of this century. It became evident that certain groups of patients, including men, elderly individuals, and the super-morbidly obese were at an increased risk for death from this operation, and a steep learning curve exists for laparoscopic gastric bypass.

Studies covering the early period of laparoscopic bariatric surgery tend to reflect higher morbidity and mortality rates, whereas more recent studies show improved perioperative outcomes. Recent national outcome data for bariatric surgery from the Agency for Health Research and Quality showed a 78% decrease in inpatient mortality from 1998 to 2004 (0.89%–0.19%).

For laparoscopic gastric bypass, most series report a mean BMI ranging between 44 and 51 kg/m^2.[27–35] The mean operative time ranges from 90 to 260 minutes, with a low conversion rate to open surgery in 0.5% to 2.0% of cases. The mortality rate after laparoscopic gastric bypass is between 0% and 1.1%.

Results of the recent national analysis of bariatric surgery performed by the University HealthSystem Consortium, a multi-institutional consecutive cohort study conducted among 29 academic institutions, are more reflective of current data for laparoscopic gastric bypass.[36] For gastric bypass procedures (n = 1049), the overall complication rate was 16%, with an anastomotic leak rate of 1.6% and a 30-day mortality rate of 0.4%. For restrictive procedures, the overall complication and 30-day mortality rates were 3.2% and 0%, respectively. Early perioperative complications included anastomotic leak, wound infection, early bowel obstruction, deep venous thrombosis, and gastrointestinal hemorrhage, whereas late complications included bowel obstruction from internal hernia, marginal ulcers, and anastomotic stricture.

Weight loss after laparoscopic gastric bypass is believed to be equivalent to that after open gastric bypass, because the only difference between the techniques is the method of access. Wittgrove and Clark[27] reported long-term weight loss after laparoscopic gastric bypass to be more than 80% of excess body weight loss at 5 years.

Data are emerging on the outcomes of laparoscopic gastric banding.[37–45] The operative time tends to be shorter than that of laparoscopic gastric bypass, ranging between 80 and 105 minutes. Conversion to open laparotomy is low (<1%), with a low mortality rate ranging from 0% to 0.5%. Perioperative complications included gastric or esophageal perforation and bleeding. Late complications included food intolerance, band slippage, pouch dilatation, and band erosion. Esophageal dilatation was also reported.[37] Weight loss after laparoscopic gastric banding was reported to be 56% to 59% at 5 years and 59% at 8 years.[37,39,40]

A recent study evaluated two multicenter, prospective trials that collectively evaluated 485 laparoscopic gastric banding procedures.[46] No perioperative mortalities were seen and complications averaged approximately 12% and consisted predominately of band slippage, stoma obstruction, port displacement, gastroesophageal reflux, esophageal dilation, and wound infections. Weight loss was excellent in both trials.[46]

For sleeve gastrectomy, the largest published study (n = 216) reported a 59% excess weight loss at 1 year,[47] with complications including leaks, nausea and vomiting, pulmonary embolism, and hemorrhage. No studies document long-term results for sleeve gastrectomy.

For malabsorptive operations, Rabkin and colleagues[26] reported the largest study of laparoscopic duodenal switch in 345 patients. The mean BMI in their study was 50 kg/m^2, with a mean operative time of 201 minutes. Conversion occurred in 2% of patients and no operative mortalities occurred. The mean percent of excess weight loss at 2 years was 91%.

COMPARISON OF GASTRIC BANDING, GASTRIC BYPASS, AND SLEEVE GASTRECTOMY

Three case-controlled studies have compared the outcomes of laparoscopic gastric banding with laparoscopic gastric bypass. Jan and colleagues[48] reported the outcomes of 219 patients who underwent laparoscopic gastric bypass compared with 154 patients who underwent Lap-Band. One death occurred in each group. The incidence of major and minor complications was similar, although the reoperation rate was higher in the Lap-Band group and weight loss was greater with gastric bypass.

In a matched control study of 103 patients undergoing Lap-Band and 103 undergoing laparoscopic gastric bypass, Weber and colleagues[49] reported that laparoscopic gastric bypass was superior to Lap-Band. BMI at 2 years decreased from 48.0 to 36.8 kg/m^2 in the Lap-Band group and from 47.7 to 31.9 kg/m^2 in the gastric bypass group. In addition, the gastric bypass procedure was associated with a significantly better reduction of medical comorbidities.

Lastly, in a comparative study of 1200 cases (456 gastric bypasses versus 805 Lap-Band procedures), Biertho and colleagues[32] reported that excess body weight loss at 18 months was superior in the gastric bypass group.

Only one prospective randomized trial has compared the outcomes of laparoscopic gastric banding to those of laparoscopic gastric bypass. Angrisani and colleagues[43] reported on 51 patients who were randomized to undergo laparoscopic gastric banding (n = 27) or laparoscopic gastric bypass (n = 24). At 5-year follow-up, patients who underwent laparoscopic gastric bypass had a higher percentage of excess body weight loss. Weight loss failure (BMI >35 kg/m^2) was observed in 35% of patients in the gastric banding group but only 4% of patients in the gastric bypass group.

In a randomized study comparing gastric banding with sleeve gastrectomy (n = 80), Himpens and colleagues[50] found that the median percentage of excess weight loss at 3 years was 48% for gastric banding and 66% for sleeve gastrectomy.

EFFECTS OF BARIATRIC SURGERY ON MORTALITY

Several studies have shown improved survival for patients who undergo bariatric surgery compared with a control cohort of severely obese patients who did not.[12,51,52] Christou and MacLean[51] compared a cohort of patients (n = 1035) who underwent bariatric surgery with a control cohort (n = 5746) of age- and gender-matched severely obese patients who did not undergo weight-reduction surgery. At

a maximum of 5-year follow-up from inception, the mortality rate in the bariatric surgery cohort was 0.68% compared with 6.17% in controls, which translates to an 89% reduction in the relative risk for death.

In another study, Adams and colleagues[12] determined the long-term mortality of 7925 patients who underwent bariatric surgery and 7925 severely obese control subjects matched for age, sex, and BMI. During a mean follow-up of 7.1 years, adjusted long-term mortality from any cause decreased by 40% in the surgery group compared with the controls. Cause-specific mortality in the surgery group decreased by 56% for coronary artery disease, 92% for diabetes, and 60% for cancer.

Lastly, Sjostrom and colleagues[52] reported on the effects of bariatric surgery on mortality in 4047 obese subjects from the SOS study, of which 2010 underwent bariatric surgery and 2037 conventional treatment. During an average of 10.9 years of follow-up, 6.3% of subjects in the matched control group died, compared with 5% in the surgery group, representing a 29% adjusted (all-cause) mortality reduction associated with surgery.

EFFECTS OF BARIATRIC SURGERY ON OBESITY-RELATED COMORBIDITIES

In addition to the well-documented long-term efficacy of bariatric surgery in achieving sustainable weight loss, numerous studies have also evaluated the efficacy of bariatric surgery in ameliorating specific obesity-related comorbidities, particularly type 2 diabetes, hypertension, and dyslipidemia. However, because standards for evaluating the effect of surgery on metabolic diseases have not been established, results should be interpreted with the understanding that many studies lack important determinants, including designation of disease severity in the study population (eg, mild versus severe diabetes), uniform methods of measuring effect of surgery (eg, hemoglobin A1c [HbA1c] versus fasting plasma glucose versus medication withdrawal), and standard definitions of treatment end points (resolution versus remission versus improvement). Some studies, for example, define diabetes resolution as HbA1c of 7.0% or less, whereas others consider it as HbA1c of 6.0% or less. Because *resolution* implies cure, *remission* was chosen as a more accurate term in this article. *Remission* indicates absence of disease indicators, such as normal fasting plasma glucose and HbA1c, blood pressure recordings, and serum lipid levels, but does not imply that the normalization is necessarily permanent. Some of the more noteworthy and well-designed studies are reviewed briefly.

Few studies have examined outcomes of bariatric surgery for patients who have type 1 diabetics, presumably because of the relative infrequency of obesity in this population.[53] However, one small series examining obese patients who had type 1 diabetes showed significant reductions in insulin requirements and glycosylated Hb levels after surgical weight loss.[54]

Much more evidence exists to substantiate remission or improvement of type 2 diabetes after bariatric surgery. In the landmark prospective controlled SOS study involving obese subjects who underwent bariatric surgery and matched obese controls, the surgery group had lower 2- and 10-year incidence rates and remission rates of diabetes, hypertriglyceridemia, and hyperuricemia than the control group.[6] Multiple retrospective cohort studies have shown that all major bariatric procedures result in diabetes remission rates from 45% to nearly 100% (**Tables 1–3**)[55–65] with significant durability. These studies suggest that the bypass procedures (Roux-en-Y and BPD) yield greater weight loss and diabetes remission rates than the purely restrictive procedures.

Table 1
Laparoscopic adjustable gastric banding and type 2 diabetes mellitus

Author	N	Preoperative BMI	Type 2 Diabetes Mellitus Severity	Follow-up (y)	Weight Loss	Pre- versus Postoperative Fasting Plasma Glucose (mmol/L)	Pre- versus Postoperative Hemoglobin A1c	Response
Dixon et al,[55]	500	48	67 IGF 51 DC 4 IU	1	38% EWL	9.4 vs 6.2	7.8 vs 6.2	R = 64% I = 26% U = 10%
Pontiroli et al,[56]	143	45	47 IGF 19 T2DM	3	BMI (45–37)	6.2 vs 5.4	8.3 vs 5.3	R = 80%
Ponce et al,[57]	413	49	53 T2DM	3	52.6% EWL	N/A	7.2 vs 5.33	R = 80% I = 20%
Pontiroli et al,[58]	73	46	17 T2DM	4	BMI (46–38)	N/A	9.4 vs 8.0	R = 45%
	LAGB	—	20 IGF	—	—	—	—	—
	49	45	20 T2DM	—	No change	—	8.6 vs 8.6	R = 4%
	Controls	—	10 IGF	—	—	—	—	—

Abbreviations: BMI, body mass index; EWL, excess weight loss; I, improved; IGF, insulin-like growth factor; LAGB, laparoscopic adjustable gastric banding; N/A, not applicable; R, remission; T2DM, types 2 diabetes mellitus; U, unchanged.

Table 2
Roux-en-Y gastric bypass and type 2 diabetes mellitus

Author	N	Preoperative Weight	Type 2 Diabetes Mellitus Severity	Follow-up (y)	Weight Loss	Pre- versus Postoperative Fasting Plasma Glucose (mg/dL)	Pre- versus Postoperative Hemoglobin A1c	Response
Pories et al,[59]	608	134 kg	165 IGF 165 DC/OA	10	54% EWL	213 vs 117	12.3 vs 6.6	R = 89% I = 7% U = 4%
Schauer et al,[60]	1160	50.4 BMI	14 IGF 32 DC 93 OA 52 IU	4	60% EWL	180 vs 98	8.2 vs 5.6	R = 83% I = 17%
Torquati et al,[61]	117	49 BMI	117 T2DM	1	69% EWL	N/A	7.7 vs 6.0	R = 74% I = 26%
Morinigo et al,[62]	34	49 BMI	12 IGF 5 DC 4 OA 1 IU	1	32% IBW	155 vs 91	6.9 vs 4.6	R = 80% I = 20%

Abbreviations: BMI, body mass index; EWL, excess weight loss; I, improved; IBW, ideal body weight; IGF, insulin-like growth factor; N/A, not applicable; R, remission; T2DM, types 2 diabetes mellitus; U, unchanged.

Table 3
Biliopancreatic diversion and type 2 diabetes mellitus

Author	N	Weight (BMI)	Follow-up (y)	Weight Loss	Pre- versus Postoperative Fasting Plasma Glucose (mg/dL)	Pre- versus Postoperative Hemoglobin A1c	Response
Scopinaro et al,[63]	312	50.1	10	BMI (50–32)	178 vs 89	N/A	R = 98%
Marinari et al,[64]	268	49	5	BMI (49–31)	178 vs 86	N/A	R = 100% (71% follow-up)
Marceau et al,[65]	72	47	4	BPD = 61% EWL DS = 73% EWL	N/A	N/A	R = 96% I = 2.5% U = 1.5%

Abbreviations: BMI, body mass index; BPD, biliopancreatic diversion; EWL, excess weight loss; I, improved; IGF, insulin-like growth factor; N/A, not applicable; R, remission; U, unchanged.

The observation that the bypass procedures enable rapid remission before significant weight loss suggests the existence of an antidiabetic effect independent of weight loss. In one study by Schauer and colleagues,[60] 1160 patients underwent bypass, of which 240 (21%) had impaired fasting glucose or type 2 diabetes. Of the diabetic patients, fasting plasma glucose and glycosylated Hb concentrations returned to normal levels in 83% of patients or markedly improved in 17%. Factors found to be predictive of complete diabetes remission included duration of disease less than 5 years, mildest form of the disease (diet-controlled diabetes), and significant weight loss after surgery.[60]

MacDonald and colleagues[7] compared 154 patients who underwent gastric bypass with 78 control patients. With an average of 9 years of follow-up, the percentage of control subjects treated with oral hypoglycemics or insulin increased from 56% to 87%, whereas the percentage of surgical patients requiring medical management for diabetes decreased from 32% to 9%. In a systematic review of the literature involving 2738 citations and 22,094 patients between 1990 and 2002, Buchwald and colleagues[66] showed an overall diabetes remission rate of 48% for restrictive procedures, 84% for Roux-en-Y, and 98% for BPD.

In a recent randomized controlled trial, Dixon and colleagues[67] compared medical treatment of type 2 diabetes mellitus (eg, lifestyle modification and antidiabetic medications) with LAGB and equal medical treatment. All patients in the study had a BMI between 30 to 40 kg/m^2 and mild diabetes (<2-year history, no insulin requirement, and mean HbA1c of 7.7). After 2 years, the surgical group had a remission rate (normal fasting plasma glucose, HbA1c, and no medications) of 73% and weight loss of 20.7% of ideal body weight versus 13% and 1.7% of ideal body weight for the control group, respectively (P<.001). No serious side effects occurred in either group. This randomized controlled trial, along with the previous studies, provides strong evidence that bariatric surgery is an effective therapy for treating type 2 diabetes mellitus in patients who have mild to severe obesity.

Fewer data exist on amelioration of hypertension after bariatric surgery. A recent study from Michigan compared preoperative and postoperative diabetes, hypertension, lipids, and 10-year estimates of coronary heart disease based on Framingham risk scores.[68] Men and women were analyzed separately, and both groups and the collective group showed significant improvement in all categories. Another important study involving 1025 patients who underwent gastric bypass showed an average loss of 66% of excess body weight and hypertension remission in 69% of patients at 1-year follow-up. At 5-year follow-up, remission of hypertension was 66%.[69]

Data also support improvement and normalization of lipid profiles after bariatric surgery. In a group of 400 patients who underwent gastric bypass, hyperlipidemia either resolved or improved postoperatively in 80% to 100%,[70] whereas another group of 650 patients who underwent gastric banding showed a 72% rate of hypertriglyceridemia normalization within 18 months.[71] Across studies, however, the rates of normalization do not always reach statistical significance.[52]

Nevertheless, an important trend toward normalization is seen even in these data sets. When these data are considered collectively with the results of diabetes and hypertension remission rates, it becomes increasingly clear that bariatric surgery plays an important role in reversing the metabolic syndrome responsible for coronary heart disease. Many studies have documented the long-term efficacy of bariatric operations in treating the comorbidities of obesity, including sleep apnea, obesity hypoventilation, pseudotumor cerebri, nonalcoholic liver disease, polycystic ovary syndrome, gastroesophageal reflux, urinary incontinence, degenerative joint disease, and venous stasis disease.[72]

MECHANISMS FOR DIABETES REMISSION

Type 2 diabetes mellitus has long been and continues to be a significant source of morbidity and mortality and a substantial economic burden on worldwide health care.[73] Development of type 2 diabetes is rooted in two fundamental pathophysiologic processes: decreased production of endogenous insulin and cellular insulin resistance. Bariatric surgery has been shown to resolve or substantially improve glucose control.[60,74] Although no clear understanding exists of the mechanisms through which bariatric surgery facilitates remission of type 2 diabetes, numerous possible mechanisms for altering either insulin production or resistance have been proposed as potential explanations for improved or resolved diabetes after bariatric surgery. However, it is becoming increasingly clear that remission of diabetes is multifactorial.[60]

Caloric Restriction

Early improvement or remission of type 2 diabetes after bariatric surgery, before significant weight loss, support postoperative fasting and restriction of caloric intake as important mechanisms. Glucose and insulin requirements have been shown to significantly decline immediately after bariatric surgery.[75] Other small but similar studies showed comparable early changes in insulin resistance after gastric bypass, typically occurring within the first week postoperatively.[76] These results are consistent in most series, suggesting that weight loss alone is not the key factor in improving diabetes. Some authors have also noted a decline in glucose and insulin requirements that began 1 day before surgery,[76] providing the most compelling argument that caloric restriction that begins with the preoperative fast and continues with a bariatric clear liquid diet postoperatively results in significant normalization of these parameters. However, the lasting positive effects on the glucose profile at least partially suggest that the mechanism is far more complex than simply decreased caloric intake.

Weight Loss

The SOS study is one of the best-designed and most compelling studies supporting weight loss as the mechanism for improvement or remission of diabetes.[6] This study compared diabetes prevalence in patients who underwent bariatric surgery and controls, showing a steady prevalence in the former over 8 years, whereas controls had a significantly increased prevalence over the same period.

This finding suggests that in high-risk or early diabetic patients, weight loss from interventions such as bariatric surgery could potentially arrest progression of disease, and the type of bariatric operation is not critical. Compelling data also suggest a 58% reduction in new diabetes diagnoses in high-risk populations when modest weight loss is achieved.[77,78] Again, the data support the notion that weight loss ultimately halts progression of type 2 diabetes.

Conversely, a slightly more specific study evaluated improvement in glycemic control after laparoscopic gastric banding. This study showed a closer association with improved β cell function and duration of diabetes,[79] suggesting that a duration of the disease exists beyond which weight loss cannot overcome dysfunctional β-cell production of insulin. However, the same study also found weight loss to be more closely associated with improved insulin sensitivity,[79] suggesting that weight loss as a final end point can, when experienced sufficiently early in the disease process, reverse diabetes.

Several other studies have helped refute weight loss as the sole cause of diabetes remission. In a well-designed study with impressive long-term follow-up, Pories and

colleagues[80] found significantly improved glycemic control within only 1 week of surgery, before any meaningful achievement in weight loss. These and other findings have prompted further research into hormonal and other factors as a mechanism for reversal of diabetes independent of any substantial weight loss.

Endocrine Changes

A substantial body of evidence shows improvement or remission of diabetes before significant weight loss after bariatric surgery.[6,75,81] These data support a mechanism of action mediated by hormonal changes that occur as a direct result of bypassing the fore- or midgut from feeding. Numerous studies have examined preoperative and postoperative gut hormone levels after bariatric surgery. The results have been somewhat mixed and resulted in even further speculation regarding interpretation of the results. A brief summary of hormonal changes after bariatric surgery is provided in the next sections.

Insulin

Good data show a significant decrease in postoperative circulating insulin levels after Roux-en-Y gastric bypass.[73,82] A corresponding decrease in insulin-like growth factor 1 (IGF-1) has also been shown. These hormone alterations occurred despite an expected incremental increase caused by surgical stress.[75] However, despite these changes, mean serum glucose levels decreased significantly to normal levels. These findings raise further questions regarding possible mechanisms and what role incretins play in these hormone alterations.

Incretins are gastrointestinal hormones that directly stimulate insulin release from β cells of the pancreas, and whose reduced secretion is theorized to significantly contribute to type 2 diabetes.[83] Two examples of incretins are gastric inhibitory peptide (GIP) and glucagon-like peptide-1 (GLP-1). Exenatide is the first drug in a new class of incretin-mimetics, and is administered as a twice-daily, long-acting subcutaneous injection.

Endogenous GLP-1 is made by L cells of the colon and ileum.[83] Mechanisms of action include direct stimulation of insulin secretion, inhibition of glucagon secretion, augmentation of the β cell mass, delayed gastric emptying and acid production, and increased satiety. Levels increase after carbohydrate intake and have been shown to increase in a nonstatistically significant way after gastric bypass.[75,83] This finding implies at least a partial role for GLP-1 in normalizing diabetes after surgery.

GIP is made by mucosal K cells of the duodenum and jejunum, and functions in a glucose-dependent manner to stimulate insulin release.[84,85] However, its stimulation of insulin secretion is blunted in patients who have diabetes, and serum levels after Roux-en-Y have been anything but consistent.[83,86,87] More recent data measuring levels of GLP-1 and GIP in response to both oral and intravenous glucose stimulation 1 month after gastric bypass showed significant increases in both hormone levels.[88] This finding corresponds to improved β cell function and resultant normalization of serum glucose, but fails to explain how bypassing the foregut, where GIP is synthesized, increases its secretion. Although much literature supports the notion that ablating the insulin-stimulating effects of GIP contributes to diabetes remission after gastric bypass, the mechanisms of incretin augmentation as a result of foregut bypass remain unclear.

Ghrelin

Ghrelin is produced by A cells in the gastric fundus and functions primarily to stimulate appetite. Other actions of ghrelin include stimulation of growth hormone and

gastrointestinal motility. Levels of ghrelin decrease when insulin levels are elevated, and correspondingly increase with normalization of insulin. Receptors for ghrelin are predominately located in the brain, and a correlation seems to exist between serum levels and food intake.[89] However, obese patients have shown lower plasma levels, making the role of this hormone in weight management unclear. Reports have also conflicted on postbypass serum ghrelin levels,[90,91] further confusing its role in improving diabetes after surgery. Despite these findings, ongoing interest and research continues to attempt to clarify the role of this apparent key hormone in both pre- and post–bariatric surgery weight management.

Peptide YY

Peptide YY (PYY) is a peptide derived from intestinal endocrine L cells, which predominately line the distal small intestine and colon.[92] Most studies in animals and humans have shown reduced food intake through PYY stimulation of hypothalamic neuropeptide Y receptors.[93] The anorexic properties of this hormone are currently theorized to play a role in the termination of feeding. Recent work by le Roux and colleagues[94] showed attenuated levels of fasting and postprandial PYY in obese humans and rodents, who also had diminished plasma levels of PYY in response to graded oral challenges. The authors concluded that obese individuals have a PYY deficiency that effectively reduces postprandial satiety, and that this deficiency may be a consequence of obesity rather than a cause.

Leptin

Leptin is an adipose-derived hormone that functions to decrease appetite and inhibits glucose-stimulated insulin secretion.[93] Receptors for leptin reside in the hypothalamus, and levels have been shown to significantly and consistently decrease after gastric bypass.[76,82,88] Neuropeptide Y is believed to be the effector of leptin stimulation of the hypothalamus, and its levels markedly decrease and result in appetite reduction with elevated leptin levels.[94] Increased serum leptin also significantly inhibits glucose-induced insulin secretion and promotes insulin resistance, providing an important potential explanation for the diabetogenic nature of obesity.[83] Therefore, relative decreases in leptin levels from moderate weight loss would rapidly improve diabetes and promote sustained remission. However, definitive data sustaining this theory remain to be seen.

On a collective and larger scale, it is entirely conceivable that hormonal changes are what permit long-term maintenance of weight loss after surgery. Given the relatively poor longevity of diet-induced weight loss, it is certainly intuitive that these hormonal changes, which result from alterations in native intestinal anatomy, result in lasting endocrine changes that promote normalization of the enteroendocrine axis and sustained weight loss.

SUMMARY

As the obesity epidemic continues to grow in the Unites States, so does the search for the ideal nonsurgical or surgical solution. Bariatric surgery continues to be the most sustainable form of weight loss available to morbidly obese patients. In addition, bariatric surgery has established an acceptable safety profile with respect to morbidity and mortality. With the number of elective bariatric cases growing in recent years, it is unsurprising that results have improved and better data are emerging regarding improvement of obesity-related comorbid conditions. Additionally, ample evidence suggests that bariatric surgery may increase longevity, particularly through reducing cardiovascular deaths.

Although the specific mechanisms involved in the remission of these medical conditions remain to be fully elucidated, it has become clear that bariatric surgery has established a significant and firm role in the treatment of medical comorbidities that result directly from obesity. However, until commercial insurance carriers provide improved coverage for bariatric surgery, patient access to these treatments will remain limited.

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