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Bariatric Surgery as a Long-Term Treatment for Type 2 Diabetes/Metabolic Syndrome

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Keywords

metabolic surgery, bariatric surgery, type 2 diabetes, cardiovascular risk factor, weight loss, diabetes remission

Abstract

Metabolic surgery is increasingly becoming recognized as a more effective treatment for patients with type 2 diabetes (T2D) and obesity as compared to lifestyle modification and medical management alone. Both observational studies and clinical trials have shown metabolic surgery to result in sustained weight loss (20–30%), T2D remission rates ranging from 23% to 60%, and improvement in cardiovascular risk factors such as hypertension and dyslipidemia. Metabolic surgery is cost-effective and relatively safe, with perioperative risks and mortality comparable to low-risk procedures such as cholecystectomy, hysterectomy, and appendectomy. International diabetes and medical organizations have endorsed metabolic surgery as a standard treatment for T2D with obesity.

DIABETES AND OBESITY

Globally rising obesity and sedentary lifestyle have resulted in a tremendous increase in the global burden of type 2 diabetes mellitus (T2D). In 2015 there were an estimated 604 million adults with obesity and 414 million people with diabetes (1). The incidence of diabetes is expected to rise to 629 million by 2045 (2). Approximately 85% of all patients with T2D are either overweight or obese (3). Obesity is a major risk factor for T2D and cardiovascular (CV) diseases, such as hypertension and dyslipidemia. Recently, weight loss surgery (i.e., metabolic or bariatric surgery) has been shown to result in very good long-term glycemic control in patients with T2D and obesity. This review article presents evidence for metabolic surgery as a long-term, well-supported treatment for T2D.

CURRENT MANAGEMENT OF TYPE 2 DIABETES

For decades, the mainstay of T2D treatment has included lifestyle modifications and pharmacotherapy. First-line treatment for T2D patients involves diet, physical activity, and behavioral therapy, followed by pharmacotherapy (4, 5). Pharmacotherapy includes oral and injectable glucose-lowering medications and insulin. The choice of glucose-lowering medications is tailored to patients' body weight and comorbidities. In patients with T2D and obesity, oral antidiabetic agents with weight loss properties such as metformin and glucagon-like peptide-1 receptor agonists are preferred (6). Insulin therapy is usually started as the second- or third-line treatment if oral antidiabetic agents have been inadequate in achieving good glycemic control. Insulin therapy can be effective in glycemic control, reducing glycated hemoglobin (HbA1c) by 1.5–2% (7). However, some patients do not respond well to insulin therapy due to insulin resistance. Furthermore, insulin therapy is associated with hypoglycemia, especially in the elderly, and weight gain (6, 8). Difficulties of self-injection of insulin, lifestyle restrictions, and cost contribute further to the poor compliance associated with insulin therapy (9).

Achieving T2D remission (HbA1c < 6.5% off meds) with lifestyle modifications and short-term medical therapy is possible but uncommon, and remission is largely achieved by dietary weight loss in patients with mild T2D (10). In the DiRECT (Diabetes Remission Clinical Trial) study, patients with mild T2D (mean HbA1c 7.7%) treated with aggressive lifestyle intervention yielding 7.5% weight loss achieved 36% remission at two years, while the control group achieved 2.3% weight loss and 3.4% remission (11). Sustained T2D remission at four years after an intensive lifestyle intervention (ILI) in patients with mild T2D (mean HbA1c 7.3%) in the Look AHEAD (Action for Health in Diabetes) study was achieved in only 3.5% of treated patients versus 0.5% for the control group (12). At 10-year follow-up in Look AHEAD, the ILI group achieved 6% weight loss versus 3.5% in the control group, yet both groups had worse HbA1c compared to baseline (7.35% and 7.40%, respectively) (13). Sustained long-term T2D remission with lifestyle intervention and medical treatment has yet to be demonstrated.

Despite advances in medical therapy, successful management of T2D remains an important challenge globally (14). A 2018 meta-analysis (involving 369,251 patients from 20 countries) examining the achievement of guideline targets for controlling blood pressure, lipids, and glycemia in T2D patients showed that these targets were suboptimally achieved over 10 years (15). The pooled target achievements were as follows: for glycemic control, 43%; blood pressure, 29%; low-density lipoprotein cholesterol (LDL-C), 49%; high-density lipoprotein cholesterol (HDL-C), 58%; and triglycerides, 62%. According to a US survey (1988–2010), only 50% of patients on medication for T2D successfully achieved the American Diabetes Association–recommended glycemic targets (HbA1c < 7%); less than 20% met all three targets of medical therapy (HbA1c ≤ 7.0, LDL-C ≤ 100, blood pressure < 130/80 mm Hg) (16).

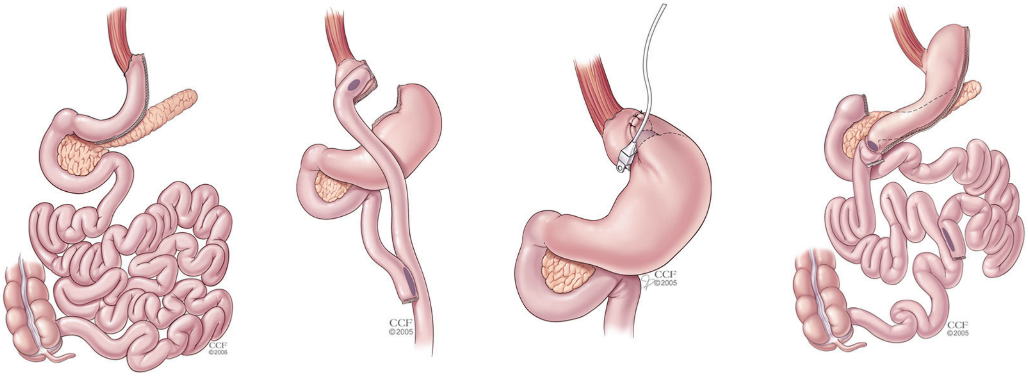

Figure 1

The most common metabolic surgical procedures in the United States. Left to right: Sleeve gastrectomy is the most common procedure (58%), followed by Roux-en-Y gastric bypass (19%), laparoscopic adjustable gastric band (3%), and biliopancreatic diversion with duodenal switch (0.6%). Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2017, all rights reserved (78, 79).

Several large long-term observational studies and clinical trials have compared metabolic surgery and medical treatment for T2D with obesity (6, 17, 18). Metabolic surgery has shown greater improvement in term of weight loss outcomes, T2D, and CV risk factors. These results have led metabolic surgery to be included in the management of T2D patients with obesity (19).

TYPES OF METABOLIC SURGICAL PROCEDURES

A total of 216,000 metabolic procedures were performed in the United States in 2016 (20). Sleeve gastrectomy (SG) is the most common metabolic procedure (58%), followed by Roux-en-Y gastric bypass (RYGB, 19%), laparoscopic adjustable gastric band (LAGB, 3%), and biliopancreatic diversion with duodenal switch (BPD-DS, 0.6%) (**Figure 1**). Currently, more than 95% of metabolic procedures are performed laparoscopically (18), with 1–2 days of hospital stay and 2–4 weeks of recovery after surgery.

OUTCOMES OF METABOLIC SURGERY

Safety

Since minimally invasive surgery was introduced in the 1990s, there has been a significant decrease in perioperative morbidity and mortality rates associated with metabolic surgery. Most of the metabolic procedures are performed laparoscopically, and the mortality rates are ten times lower than those of the open procedures (21). The US Nationwide Inpatient Sample database showed an in-hospital morbidity rate of 9% and mortality risk of 0.1% (22). A systematic review reported that the perioperative complication rate among metabolic surgical patients ranges from 10% to 17%, and the 30-day mortality rate is 0.08% (23). The perioperative complication rate of metabolic surgery is approximately equivalent to that of laparoscopic cholecystectomy, appendectomy, or hysterectomy (24).

All surgical procedures have their postoperative complications, but these risks must be weighed against the benefits. Obesity and progression of T2D will eventually lead to micro- and macrovascular consequences in most T2D patients. The Agency for Healthcare Research and Quality reported that a surgical approach to metabolic conditions is associated with a relatively low rate of surgical complications (25), and that the postoperative complications were generally considered minor and rarely required major intervention (25).

Efficacy

Both observational studies and randomized trials have shown that metabolic surgery results in sustainable weight loss and improvement in T2D, CV risk factors, obesity-related comorbidities, and all-cause mortality. Metabolic procedures achieve T2D remission in 23–60% of patients at long-term follow-up, depending on the procedure and severity of T2D (26–30). Metabolic surgery has also been shown to reduce microvascular and macrovascular events in T2D as compared to a nonsurgical group (26, 31, 32). This observation strongly suggests that metabolic surgery contributes to neuroendocrine changes and preservation of β cell function to a much greater degree than medical treatment alone.

Observational and Controlled Clinical Trials

Observational and controlled clinical trials have shown that metabolic surgery results in sustainable weight loss and improvement of T2D and CV risk factors.

Weight loss. In the Swedish Obese Subjects (SOS) study with a 20-year follow-up, metabolic surgery (gastric bypass, gastric banding, and gastroplasty) resulted in durable long-term weight loss (20–30% loss) relative to the nonsurgical group (1% loss) (32). In contrast, long-term weight loss resulting from medical treatment rarely exceeds 5%, even with ILI (13). Adams et al. (27) showed sustained weight loss 12 years after RYGB as compared to two nonsurgical groups. The mean changes in weight from baseline in the RYGB group were −45 kg at 2 years, −36 kg at 6 years, and – 35 kg at 12 years, while mean changes in the nonsurgical groups at 12 years were −3 kg and 0 kg, respectively. Buchwald et al. (33) showed in a meta-analysis (involving 22,094 patients) that weight loss after LAGB, RYGB, and BPD-DS was 29 kg, 43 kg, and 46 kg, respectively.

The extent of weight loss varies according to the metabolic procedures. Maciejewski et al. (34) showed that at four-year follow-up, there was significant difference in weight loss depending on the procedure: 27.5% loss with RYGB, 17.8% with SG, and 10.6% with LAGB. A study involving 1,300 eligible patients showed an average weight loss of 28.4% with RYGB and 14.9% with LAGB at seven-year follow-up (29). LAGB has the slowest rate of weight loss and lowest amount of weight loss relative to other metabolic surgery procedures (35). The Finnish Sleeve versus Bypass (SLEEVEPASS) study, involving 240 patients with 80% five-year follow-up, showed that gastric bypass resulted in greater excess weight loss than SG (57% versus 50%) (36). The Swiss Multicenter Bypass or Sleeve Study (SM-BOSS), involving 217 patients with 95% five-year follow-up, reported that the percentage of excess body mass index (BMI) loss associated with gastric bypass and SG was 68% and 61%, respectively (37).

Diabetes. A meta-analysis on the impact of bariatric surgery in T2D patients (621 studies, 135,246 patients) showed an overall complete remission rate of 78%, and 87% of patients had either improvement or remission of T2D (38). Another study showed that usage of antidiabetic medications was reduced after metabolic surgery (−0.3 ± 1.4), but increased in the medical treatment group (0.8 ± 1.4) and other nonsurgical treatment group (1.1 ± 1.3) (28). The SOS (26) showed that bariatric surgery was associated with higher T2D remission rates and fewer

T2D complications than the nonsurgical group at a median follow-up of 18 years. The median follow-up time was 10 years for T2D assessment and 17 years for T2D complications. The T2D remission rate was higher for the surgical group than for the nonsurgical group ($p < 0.001$) at 2 years (72% versus 16%) and at 15 years (30% versus 7%). With long-term follow-up, the cumulative incidence of microvascular complications for the surgical group versus the nonsurgical group was 20.6 per 1,000 person-years [95% confidence interval (CI)17.0–24.9] versus 41.8 per 1,000 person-years [95% CI 35.3–49.5, hazard ratio (HR) 0.44; 95% CI 0.34–0.56; $p < 0.001$). Macrovascular complications were observed in 44.2 per 1,000 person-years (95% CI 37.5–52.1) in the nonsurgical group and 31.7 per 1,000 person-years (95% CI 27.0–37.2) in the surgical group (HR 0.68, 95% CI 0.54–0.85, $p = 0.001$).

A systematic review involving nine cohort studies showed that surgery significantly increased the T2D remission rate [relative risk (RR) 5.90, 95% CI 3.75–9.28), while reducing microvascular (RR 0.37, 95% CI 0.30–0.46) and macrovascular events (RR 0.52, 95% CI 0.44–0.61) and mortality (RR 0.21, 95% CI 0.20–0.21) as compared to nonsurgical treatment (30). A recent meta-analysis involving three randomized controlled trials (RCTs) and seven controlled clinical trials compared microvascular complications associated with metabolic surgery versus medical treatment in 17,532 T2D patients (31). The mean duration of T2D in the surgical and medical groups was 6.4 years and 6.9 years, respectively. The percentage of patients on insulin was 35% in the surgical group versus 34% in the medical group. Metabolic surgery significantly reduced the incidence of microvascular complications as compared to medical treatment [odds ratio (OR) 0.26, 95% CI 0.16–0.42, $p < 0.001$]. The incidence of nephropathy and retinopathy was also lower after metabolic surgery relative to medical treatment. There was a significant improvement of pre-existing diabetic nephropathy after metabolic surgery as compared to medical treatment (OR 15.41, CI 1.28–185.46, $p = 0.03$). However, there was no difference in the incidence of diabetic neuropathy between the two groups. More recently, a large Danish cohort study demonstrated that RYGB was associated with a 47% lower risk of microvascular complications compared to non-operated controls (HR 0.53, 95% CI 0.38–0.73), but a statistically nonsignificant 24% lower risk of macrovascular complications (HR 0.76, 95% CI 0.49–1.18) (39).

Cardiovascular risk and mortality outcomes. A recent systematic review (involving 73 studies and 19,543 patients at a mean follow-up of 58 months) showed long-term CV risk factor reduction after bariatric surgery. Hypertension and hyperlipidemia remission/improvement was seen in 63% and 65% of patients, respectively (40). Twelve cohort-matched nonrandomized studies comparing bariatric surgery with a nonsurgical group suggest that improvements in surrogate markers of disease such as body HbA1c, blood pressure, lipids, and body weight after surgery actually translate to reductions in macrovascular and microvascular events and in deaths (41).

Multiple cohort studies show all-cause mortality reduction with bariatric surgery. A study involving mostly higher-risk, male US military veterans associated surgery with a 42% reduction in mortality at 10 years as compared to medical therapy (42). In another study (43), 8,385 patients who underwent metabolic surgery (43% SG, 17% RYGB, 40% LAGB) were matched with 25,155 nonsurgical patients at a median follow-up of four years; metabolic surgery was associated with lower mortality (HR 2.02, 95% CI 1.6–2.5). However, there was no statistically significant difference in the rates of hospitalization and major cardiac events in both groups. Cardoso et al. (44) showed that bariatric surgery improves longevity and may reduce the risk of premature death by 41%. Another large cohort study from the United Kingdom, involving 187,061 patients and using multivariate analysis, found that bariatric surgery was associated with reduced risk of all-cause mortality (HR 0.49, $p < 0.001$) (45). A recent cohort study of 13,722 patients with obesity and diabetes (including 2,287 patients who underwent metabolic surgery and 11,435 matched controls) showed that metabolic surgery compared to usual care was associated with a significantly lower risk of major cardiovascular events including coronary events, cerebrovascular events, heart failure, atrial fibrillation, nephropathy and all-cause mortality (HR 0.61, 95% CI 0.55–0.69, $p < 0.01$) (46).

These observational cohort studies comparing metabolic surgery to medical treatment for T2D and obesity consistently demonstrate superiority of surgery; however, they are more likely to be subject to bias than RCTs.

Randomized Controlled Trials

In the last 10 years, randomized controlled clinical trials have shown that metabolic surgery achieves sustainable weight loss and improvement of T2D and CV risk factors compared to medical treatment alone (**Table 1**).

Weight loss. Meta-analysis of 11 RCTs involving 796 patients showed greater weight reduction (>26 kg) in the metabolic surgery group relative to the nonsurgical group ($p < 0.001$) (47). Three RCTs with five-year follow-up compared metabolic surgery versus intensive medical management in T2D patients and showed significant weight loss after metabolic surgery (28, 52, 55). Ikramuddin et al. (55) showed that cumulative weight loss after five years was 22.9% with RYGB as compared to 6.3% in the medical group. Schauer et al. (28) showed that at five years, weight reduction was greater after RYGB (–23 kg) than after SG (−17 kg) or medical therapy (–5 kg) ($p < 0.05$). At five years, there was a significantly greater reduction in body weight, BMI, waist circumference, and waist-to-hip ratio in both RYGB and SG groups as compared to the medical group ($p < 0.005$). Mingrone et al. (52) showed sustained weight loss at five years follow-up after BPD and RYGB relative to medical treatment ($p < 0.0001$).

Diabetes. Over the past decade, 12 RCTs comparing metabolic surgery with medical treatment of T2D have been reported (**Table 1**; 28, 48–64). All included patients with T2D and obesity (874 patients) with follow-up ranging from six months to five years. The severity of T2D among the studies varied significantly from mild (mean HbA1c 7.7%, <2 years duration, no insulin) (48) to advanced (mean HbA1c 9.3%, 8.3 years duration, 48% of patients on insulin) (28). All the trials included T2D patients with BMI ranging from 25 to 53 kg/m^2; 11 of 12 studies included patients with BMI < 35 kg/m^2. Surgical procedures included RYGB (6 studies), LAGB (3 studies), RYGB versus SG (1 study), RYGB versus LAGB (1 study), RYGB versus BPD (1 study), and SG versus RYGB versus LAGB (1 study). Five studies (53–56, 64) included a significant number of Asian patients. The primary or secondary endpoint of these RCTs was T2D remission, defined as achieving a HbA1c target (<6.0–6.5%) without requiring T2D medications.

Collectively, these RCTs showed that surgery was superior to medical treatment in reaching the designated glycemic target ($p < 0.05$ for all), except one study (62) that showed T2D remission rates of 33% with LAGB and 23% with medical treatment ($p = 0.46$). This result might be due to patients in this study having advanced T2D (HbA1c 8.2% ± 1.2%, with 40% on insulin), and they likely had significantly impaired β cell function. The surgical group experienced a decrease in HbA1c by 2–3.5%, whereas with medical treatment the decrease was only 1–1.5%. Most of these studies showed also the superiority of surgery over medical treatment in achieving secondary endpoints such as weight loss, remission of metabolic syndrome, reduction in T2D and CV medications, and improvement in triglycerides, HDL-C, and quality of life (18).

The durability of the effects of surgery was demonstrated by Mingrone et al. (52), Schauer et al. (28), and Ikramuddin et al. (55) in their five-year studies. The surgical groups showed durable weight loss and significant T2D remission or control relative to the medical group. The RCTs

Table 1 Randomized controlled trials comparing metabolic surgery to medical treatment in patients with type 2 diabetes mellitus (modified from table 1 in Reference 18 with permission)

References	Patients with BMI < 35 kg/m^2	Study design	*n*	Follow-up (months)	Remission criteria	Remission or change in HbA1c (%)[a]	*p*
Dixon et al. (48)	22%	LAGB versus control	60	24	HbA1c < 6.2%	73 versus 13	<0.001
Schauer et al. (28, 49, 50)	36%	RYGB versus SG versus control	150	60	HbA1c ≤ 6.0%	22 versus 15 versus 0	<0.05
Mingrone et al. (51, 52)	0%	RYGB versus BPD versus control	60	60	HbA1c ≤ 6.5%	42 versus 68 versus 0	0.003
Ikramuddin et al. (53–55)	59%	RYGB versus control	120	60	HbA1c < 6.0%	7 versus 0	0.02
Liang et al. (56)	100%	RYGB versus control	101	12	HbA1c < 6.5%	90 versus 0[b]	<0.0001
Halperin et al. (57)	34%	RYGB versus control	38	12	HbA1c < 6.5%	58 versus 16	0.03
Courcoulas et al. (58, 59)	43%	RYGB versus LAGB versus control	69	36	HbA1c < 6.5%	40 versus 29 versus 0	0.004
Wentworth et al. (60)	100%	LAGB versus control	51	24	FBG < 7.0 mmol/L	52 versus 8	0.001
Parikh et al. (61)	100%	(RYGB/LAGB/SG) versus control	57	6	HbA1c < 6.5%	65 versus 0	0.0001
Ding et al. (62)	34%	LAGB versus control	45	12	HbA1c < 6.5%	33 versus 23[c]	0.46
Cummings et al. (63)	25%	RYGB versus control	43	12	HbA1c < 6.0%	60 versus 5.9	0.002
Shah et al. (64)	85%	RYGB versus control	80	24	HbA1c < 6.5%	60 versus 2.5	<0.001

[a]Remission was primary or secondary end point; HbA1c value without diabetes medications, unless otherwise specified.
[b]Remission was not precisely defined; HbA1c < 6.5% by extrapolation.
[c]Intermittent diabetes medications.
Abbreviations: BMI, body mass index; BPD, biliopancreatic diversion; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; LAGB, laparoscopic adjustable gastric band; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy.

also predicted the common factors contributing to remission of T2D, including the duration of T2D, weight loss, and the requirement for insulin and disease status (HbA1c) (18).

The Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial (28) showed that at five years, patients who underwent either gastric bypass or SG had a significantly greater mean percentage reduction from baseline in HbA1c level than patients on medical therapy alone (2.1% versus 0.3%, $p = 0.003$). Both the surgical procedures were superior to intensive medical therapy alone with respect to achieving HbA1c of 6% or less with or without T2D medications, 6.5% or less without T2D medications, and 7.0% or less with T2D medications ($p < 0.05$). T2D remission rates were 22% with gastric bypass and 15% with

SG, and there were no remissions in the medical therapy group. Ikramuddin et al. (55) also showed that at five-year follow-up, T2D remission was significantly higher in the bypass group than in the lifestyle–medical management group (7% versus 0%, $p = 0.02$). HbA1c below 7.0% was achieved by 55% of the gastric bypass group as compared to 14% of the lifestyle–medical management group ($p = 0.002$).

Metabolic surgery decreased the medication requirement to maintain good glycemic control in 2 RCTs. The STAMPEDE trial (28) showed that patients in the surgical groups required significantly fewer medications than did patients in the medical therapy group ($p < 0.05$). At five years, ~89% of patients in the surgical groups were not on insulin and maintained an average HbA1c of 7.0%, whereas only 61% of patients in the medical therapy group were not on insulin, with an average HbA1c of 8.5%. Ikramuddin et al. (55) also showed similar findings at five years. Both insulin and noninsulin T2D medications were significantly lower in the gastric bypass group than in the lifestyle–medical management group; insulin use was 15% versus 37% ($p = 0.02$) and noninsulin T2D medication use was 42% versus 88% ($p < 0.001$).

The STAMPEDE trial (28) demonstrated that bariatric surgery (RYGB or SG) did not appear to worsen or improve retinopathy outcomes at five years compared to intensive medical management, but the sample size of 150 was probably too small for such assessment. Mingrone et al. (52) showed approximately 90% and 97% decrease in microvascular and macrovascular disease progression risk respectively in the surgical group relative to the medical group. Otherwise, none of the other RCTs was powered sufficiently to detect differences in macrovascular or microvascular complications or death, especially at relatively short follow-up (18).

Cardiovascular risk outcomes. Most of the RCTs showed improvement in the secondary endpoints after metabolic surgery relative to medical treatment. There was reduction in the need for CV medications and improvement in triglyceride and HDL-C levels after metabolic surgery as compared to medical treatment groups. However, the results of metabolic surgery were mixed regarding blood pressure and LDL-C (18). Ikramuddin et al. (55) showed at five years follow-up that 23% of the RYGB group, versus 4% in the medical treatment group, achieved the composite of triple endpoints (HbA1c < 7%, systolic blood pressure < 130 mm Hg, and LDL-C < 100 mg/dl, $p = 0.002$). Schauer et al. (28) showed similar findings at five-year follow-up; there were significant reductions in triglyceride and HDL-C levels after RYGB and SG relative to medical therapy. There were no significant differences in blood pressure and LDL-C among the surgical and medical groups, but there were significantly lower requirements of medications to treat hypertension and hyperlipidemia among the surgical groups relative to the medical group. The current RCTs involving metabolic surgery are insufficiently powered to evaluate clinical endpoints such as death, myocardial infarction, and stroke. Many investigators suggest that a multicenter RCT is imperative to definitively determine whether metabolic surgery reduces mortality as well as macro- and microvascular events. The overall outcomes of metabolic surgery are summarized in **Figure 2**.

Quality of Life

Long-term usage of insulin and other diabetic medication does have an effect on T2D patients' quality of life. RCTs (28, 50, 52) reported superior quality of life in the surgical groups as compared to the medical therapy group. STAMPEDE's five-year trial (28) showed a significant and durable decrease in bodily pain, improvement in the quality-of-life components, and improved overall general health in the surgical groups. The medical therapy group showed no improvement in bodily pain or quality of life and worsening of emotional well-being.

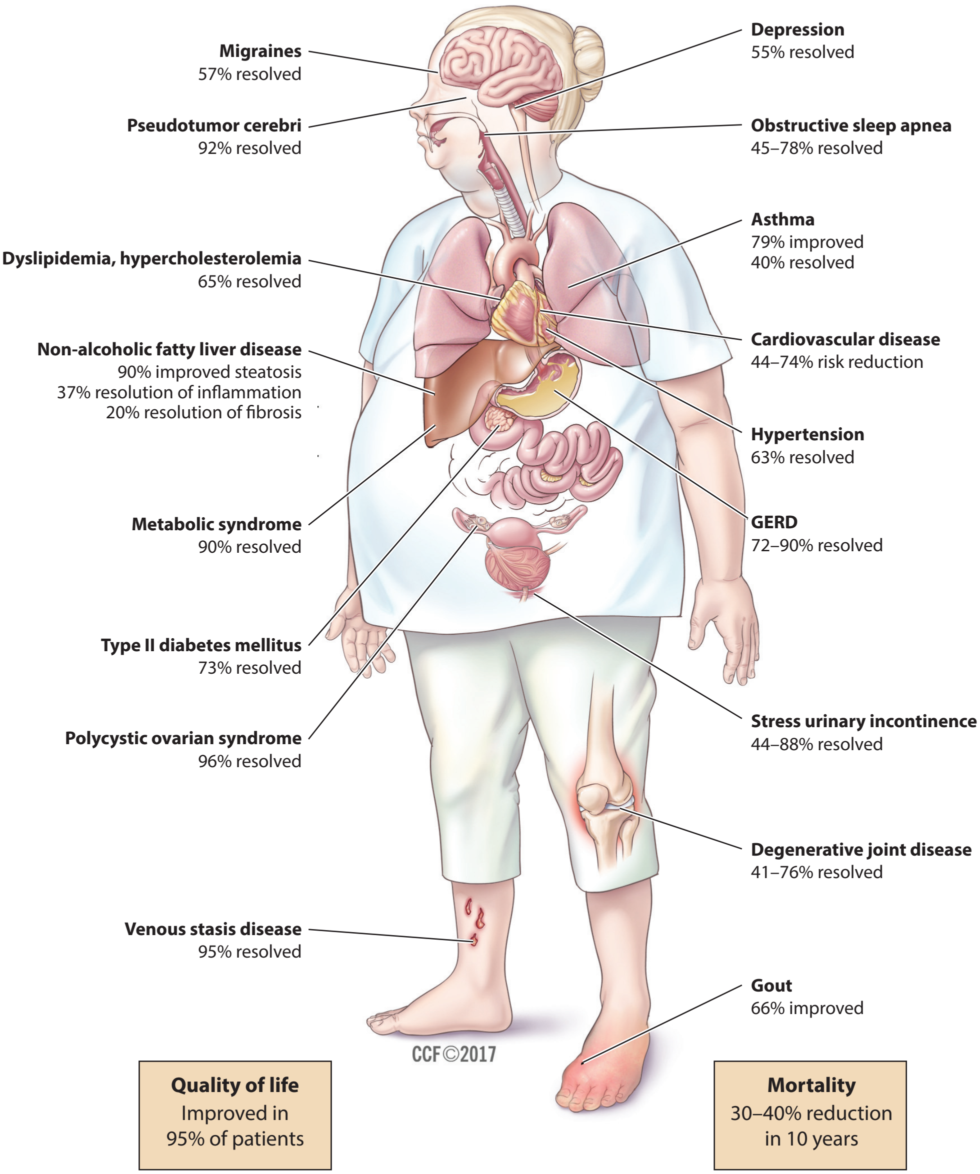

Figure 2

Metabolic surgery outcomes. In addition to increased quality of life and reduced mortality, outcomes of metabolic surgery include improvement in type 2 diabetes and obesity-related comorbidities. Adapted from Reference 35 with permission from Cleveland Clinic Center for Medical Art & Photography © 2017, all rights reserved.

Cost

The long-term effectiveness of metabolic surgery reduces the subsequent costs of medication and outpatient care, as well as long-term T2D complications. Retrospective and modeling studies have shown that metabolic surgery is cost-effective and even cost-saving in T2D patients, with a break-even time of 5–10 years (65, 66). Metabolic surgery is cost-effective in the obese T2D population, with a price per quality-adjusted life-year (QALY) ranging from \$7,000 to \$13,000, as compared to an intensive medical glycemic and lipid control cost of \$41,384/QALY and \$51,889/QALY, respectively (67).

CURRENT GUIDELINES FOR DIABETES MANAGEMENT

The new international guidelines for T2D management in obese patients have endorsed metabolic surgery as another option to assist in achieving treatment goals (4, 19). Metabolic surgery has historically been selected on the basis of the patient's body weight using BMI (68); patients with obesity and BMI > 40, or BMI > 35 with comorbidity, are candidates for surgery if they are psychologically stable and have no active substance abuse. However, metabolic surgery in patients with T2D should be tailored according to the class of obesity and inadequate glycemic control despite optimal medical treatment. Based on strong evidence from randomized trials, metabolic surgery was recently recommended in the treatment algorithm for T2D in the second Diabetes Surgery Summit (19, **Figure 3**). The American Diabetes Association has incorporated these guidelines

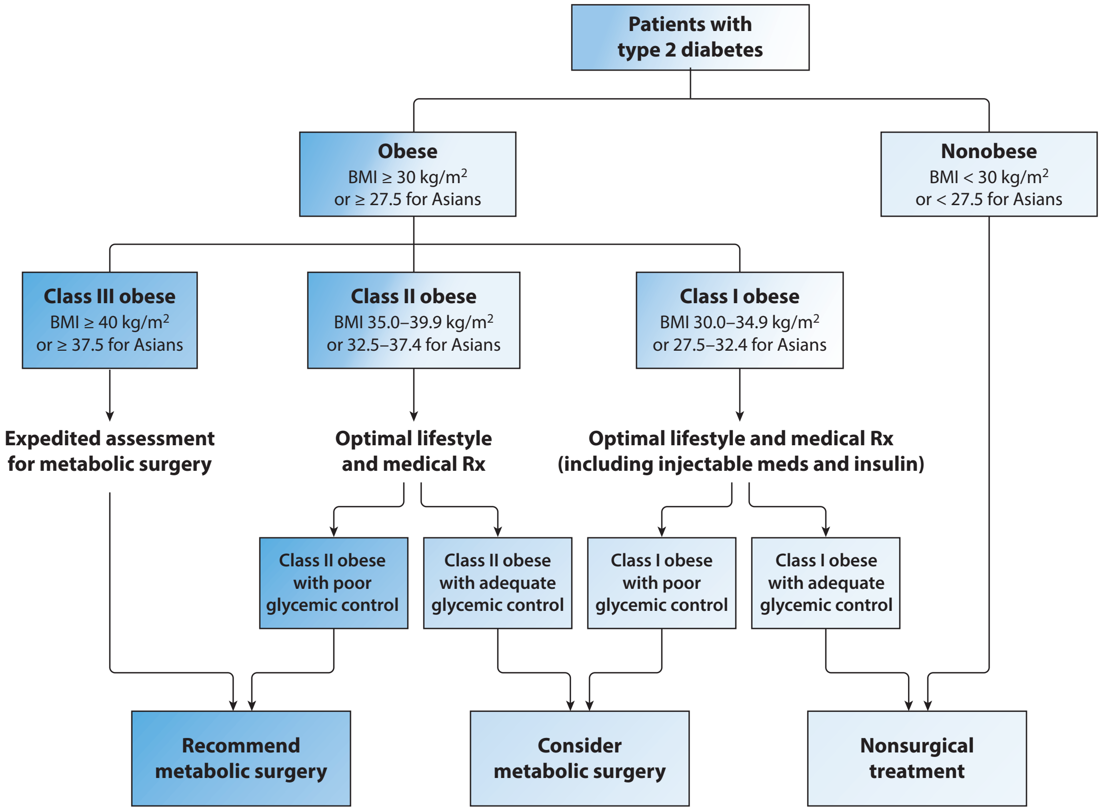

Figure 3

Treatment algorithm for type 2 diabetes endorsed by the second Diabetes Surgery Summit. This guideline was published in collaboration with five international diabetes organizations: the American Diabetes Association, the International Diabetes Federation, Diabetes UK, the Chinese Diabetes Society, and Diabetes India. It was endorsed by 53 leading professional diabetes and surgical societies worldwide. Adapted from Reference 72 with permission from the American Diabetes Association (copyright and all rights reserved).

into its annual Standards of Care guidelines since 2017 (69). Similarly, the 2018 American Diabetes Association/European Association for the Study of Diabetes algorithm endorses metabolic surgery to treat T2D in patients with obesity (70).

The role of metabolic surgery was extended to T2D patients with BMI 30–34.9 and the BMI threshold was lowered by 2.5 in patients of Asian origin. These current guidelines provide greater emphasis on surgical treatment for patients with BMI > 40 regardless of glycemic control (4, 19). Metabolic surgery should be performed in high-volume centers with a multidisciplinary team including the bariatric surgeon, endocrinologist/diabetologist, cardiologist, anesthetist, psychologist, and dietitian with expertise in T2D care.

IDEAL CANDIDATES FOR METABOLIC SURGERY

Metabolic surgery has proven to result in significant T2D remission and improvement. Studies have shown that patients with early T2D without insulin usage have better remission rates, due in part to greater preservation of beta cell function (19, 71, 72). Based on the recent guidelines, metabolic surgery should also be recommended for patients with uncontrolled T2D and obesity (**Figure 3**).

Recently, the Individualized Metabolic Surgery (IMS) score was developed to predict the success of T2D remission after metabolic surgery (SG and RYGB) (73). This IMS scoring system was generated from a database of ∼900 T2D patients who had greater than five-year follow-up after SG or RYGB. This score predicts T2D remission based on preoperative T2D severity. It includes duration of T2D ($p < 0.0001$), number of T2D medications ($p < 0.0001$), insulin use ($p = 0.002$), and HbA1c < 7% ($p = 0.002$). The score assists in choosing the metabolic procedure (SG or RYGB) based on a specific patient's T2D severity. The IMS scoring tool, available online at **http://riskcalc.org/Metabolic_Surgery_Score/**, should only be used as a guide. There are other predictive models available for T2D remission, such as the ABCD and DeaRem scores (74–76).

CHOICE OF METABOLIC SURGICAL PROCEDURE

The choice among metabolic surgical procedures is based on assessment of risk versus benefit for each procedure. Long-term postoperative complications of surgery versus effectiveness of glycemic control and CV risk reduction should be discussed with each patient. A number of factors should be individualized for each T2D patient. These include the following: (*a*) the expertise and experience of the surgical team; (*b*) the patient's BMI and other comorbid illness; (*c*) the patient's risk factors that could be associated with high perioperative morbidity and mortality; and (*d*) the follow-up regimen for the procedure and the patient's commitment to adhere to it.

Bypass procedures (such as RYGB and BPD-DS) generally achieve greater and more sustainable weight loss than do SG and LAGB. Even though metabolic surgery achieves good and sustainable weight loss for most patients, it may result in poor weight loss or weight regain in some patients. The occurrence of poor long-term weight loss (within 5% of preoperative weight) appears to vary according to the procedure: 30.5% with LAGB, 14.6% with SG, and 2.5% with RYGB (35). Similarly, recurrence of T2D at five years has been reported in 17% with RYGB, 38% with SG, and 33% with LAGB and is likely related in part to weight gain (77).

CONCLUSION

Both observational studies and clinical trials have shown metabolic surgery to result in sustained weight loss, T2D remission rates ranging from 23% to 60%, and improvement in CV risk factors such as hypertension and dyslipidemia. Metabolic surgery is cost-effective and relatively safe, with perioperative risks and mortality comparable to cholecystectomy and appendectomy. International diabetes and medical organizations have endorsed metabolic surgery when available, as a standard T2D treatment regime in patients with T2D and obesity.

DISCLOSURE STATEMENT

Dr. Schauer serves on the Advisory Boards of GI Dynamics. He serves as a consultant to Ethicon, Medtronic, WL Gore, and BD Surgical. He receives research support from Ethicon, Medtronic, and Pacira.

LITERATURE CITED

1. Afshin A, Forouzanfar MH, Reitsma MB, et al. 2017. Health effects of overweight and obesity in 195 countries over 25 years. *N. Engl. J. Med.* 377(1):13–27
2. International Diabetes Federation. 2017. IDF Diabetes Atlas, 8th ed. **http://www.diabetesatlas.org/**
3. Bays HE, Chapman RH, Grandy S, et al. 2007. The relationship of body mass index to diabetes mellitus, hypertension and dyslipidaemia: comparison of data from two national surveys. *Int. J. Clin. Pract.* 61:737–47
4. American Diabetes Association. 2018. 7. Obesity management for the treatment of type 2 diabetes: *Standards of Medical Care in Diabetes—2018*. *Diabetes Care* 41(Suppl. 1):S65–72
5. American Diabetes Association. 2018. 6. Glycemic targets: *Standards of Medical Care in Diabetes—2018*. *Diabetes Care* 41(Suppl. 1):S55–64
6. Pareek M, Schauer PR, Kaplan LM, et al. 2018. Metabolic surgery: weight loss, diabetes, and beyond. *J. Am. Coll. Cardiol.* 71(6):670–87
7. Chatterjee S, Khunti K, Davies MJ. 2017. Type 2 diabetes. *Lancet* 389(10085):2239–51
8. Barnett AH. 2013. Complementing insulin therapy to achieve glycemic control. *Adv. Ther.* 30:557–76
9. Davies MJ, Gagliardino JJ, Gray LJ, et al. 2013. Real-world factors affecting adherence to insulin therapy in patients with type 1 or type 2 diabetes mellitus: a systematic review. *Diabet. Med.* 30:512–24
10. Taylor R, Barnes AC. 2019. Can type 2 diabetes be reversed and how can this best be achieved? James Lind Alliance research priority number one. *Diabet. Med.* 36(3):308–15
11. Lean ME, Brosnahan N, Kean S, et al. 2019. Two-year results of the randomised Diabetes Remission Clinical Trial (DiRECT). *Lancet Diabetes Endocrinol.* 7(5):344–55
12. Gregg EW, Chen H, Wagenknecht LE, et al. 2012. Association of an intensive lifestyle intervention with remission of type 2 diabetes. *JAMA* 308(23):2489–96
13. Wing RR, Bolin P, Brancati FL, et al. 2013. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N. Engl. J. Med.* 369:145–54
14. Kahn SE, Cooper ME, Del Prato S. 2014. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. *Lancet* 383(9922):1068–83
15. Khunti K, Ceriello A, Cos X, De Block C. 2018. Achievement of guideline targets for blood pressure, lipid, and glycaemic control in type 2 diabetes: a meta-analysis. *Diabetes Res. Clin. Pract.* 137:137–48
16. Casagrande SS, Fradkin JE, Saydah SH, et al. 2013. The prevalence of meeting A1C, blood pressure, and LDL goals among people with diabetes, 1988–2010. *Diabetes Care* 36(8):2271–79
17. Cummings DE, Rubino F. 2018. Metabolic surgery for the treatment of type 2 diabetes in obese individuals. *Diabetologia* 61(2):257–64
18. Schauer PR, Mingrone G, Ikramuddin S, Wolfe B. 2016. Clinical outcomes of metabolic surgery: efficacy of glycemic control, weight loss, and remission of diabetes. *Diabetes Care* 39(6):902–11
19. Rubino F, Nathan DM, Eckel RH, et al. 2016. Metabolic surgery in the treatment algorithm for type 2 diabetes: a joint statement by international diabetes organizations. *Diabetes Care* 39(6):861–77
20. English WJ, DeMaria EJ, Brethauer SA, et al. 2018. American Society for Metabolic and Bariatric Surgery estimation of metabolic and bariatric procedures performed in the United States in 2016. *Surg. Obes. Relat. Dis.* 14(3):259–63

21. Flum DR, Belle SH, King WC, et al. 2009. Perioperative safety in the longitudinal assessment of bariatric surgery. *N. Engl. J. Med.* 361:445–54
22. Khan S, Rock K, Baskara A, et al. 2016. Trends in bariatric surgery from 2008 to 2012. *Am. J. Surg.* 211(6):1041–46
23. Chang SH, Stoll CR, Song J, et al. 2014. The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003–2012. *JAMA Surg.* 149(3):275–87
24. Aminian A, Brethauer SA, Kirwan JP, et al. 2015. How safe is metabolic/diabetes surgery? *Diabetes Obes. Metab.* 17:198–201
25. Maglione MA, Gibbons MM, Livhits M, et al. 2013. *Bariatric surgery and nonsurgical therapy in adults with metabolic conditions and a body mass index of 30.0 to 34.9 kg/m^2*. Comparative Effectiveness Reviews No. 82. Rockville, MD: US Agency for Healthcare Research and Quality. **https://www.ncbi.nlm.nih.gov/books/NBK148685/**
26. Sjöström L, Peltonen M, Jacobson P, et al. 2014. Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. *JAMA* 311:2297–304
27. Adams TD, Davidson LE, Litwin SE, et al. 2017. Weight and metabolic outcomes 12 years after gastric bypass. *N. Engl. J. Med.* 377(12):1143–55
28. Schauer PR, Bhatt DL, Kirwan JP, et al. 2017. Bariatric surgery versus intensive medical therapy for diabetes—5-year outcomes. *N. Engl. J. Med.* 376:641–51
29. Courcoulas AP, King WC, Belle SH, et al. 2018. Seven-year weight trajectories and health outcomes in the Longitudinal Assessment of Bariatric Surgery (LABS) study. *JAMA Surg.* 153(5):427–34
30. Sheng B, Truong K, Spitler H, et al. 2017. The long-term effects of bariatric surgery on type 2 diabetes remission, microvascular and macrovascular complications, and mortality: a systematic review and meta-analysis. *Obes. Surg.* 27(10):2724–32
31. Billeter AT, Scheurlen KM, Probst P, et al. 2018. Meta-analysis of metabolic surgery versus medical treatment for microvascular complications in patients with type 2 diabetes mellitus. *Br. J. Surg.* 105(3):168–81
32. Sjöström L, Peltonen M, Jacobson P, et al. 2012. Bariatric surgery and long-term cardiovascular events. *JAMA* 307:56–65
33. Buchwald H, Avidor Y, Braunwald E, et al. 2004. Bariatric surgery: a systematic review and metaanalysis. *JAMA* 292:1724–37
34. Maciejewski ML, Arterburn DE, Van Scoyoc L, et al. 2016. Bariatric surgery and long-term durability of weight loss. *JAMA Surg.* 151:1046–55
35. Brethauer SA, Chand B, Schauer PR. 2006. Risks and benefits of bariatric surgery: current evidence. *Cleve. Clin. J. Med.* 73(11):993
36. Salminen P, Helmiö M, Ovaska J, et al. 2018. Effect of laparoscopic sleeve gastrectomy versus laparoscopic Roux-en-Y gastric bypass on weight loss at 5 years among patients with morbid obesity: the SLEEVEPASS randomized clinical trial. *JAMA* 319(3):241–54
37. Peterli R, Wölnerhanssen BK, Peters T, et al. 2018. Effect of laparoscopic sleeve gastrectomy versus laparoscopic Roux-en-Y gastric bypass on weight loss in patients with morbid obesity: the SM-BOSS randomized clinical trial. *JAMA* 319(3):255–65
38. Buchwald H, Estok R, Fahrbach K, et al. 2009. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am. J. Med.* 122:248–56
39. Madsen LR, Baggesen LM, Richelsen B, Thomsen RW. 2019. Effect of Roux-en-Y gastric bypass surgery on diabetes remission and complications in individuals with type 2 diabetes: a Danish population-based matched cohort study. *Diabetologia* 62(4):611–20
40. Vest AR, Heneghan HM, Agarwal S, et al. 2012. Bariatric surgery and cardiovascular outcomes: a systematic review. *Heart* 98:1763–77
41. Vest AR, Heneghan HM, Schauer PR, Young JB. 2013. Surgical management of obesity and the relationship to cardiovascular disease. *Circulation* 127(8):945–59
42. Arterburn DE, Olsen MK, Smith VA, et al. 2015. Association between bariatric surgery and long-term survival. *JAMA* 313:62–70

43. Reges O, Greenland P, Dicker D, et al. 2018. Association of bariatric surgery using laparoscopic gastric banding, Roux-en-Y gastric bypass, or laparoscopic sleeve gastrectomy versus usual care obesity management with all-cause mortality. *JAMA* 319(3):279–90
44. Cardoso L, Rodrigues D, Gomes L, Carrilho F. 2017. Short- and long-term mortality after bariatric surgery. *Diabetes Obes. Metab.* 19(9):1223–32
45. Moussa OM, Erridge S, Chidambaram S, et al. 2019. Mortality of the severely obese: a population study. *Ann. Surg.* 269(6):1087–91
46. Aminian A, Zajichek A, Arterburn DE, et al. 2019. Association of metabolic surgery with major adverse cardiovascular outcomes inpatients with type 2 diabetes and obesity. *JAMA* 322:1271–82
47. Gloy VL, Briel M, Bhatt DL, et al. 2013. Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomized controlled trials. *BMJ* 347:f5934
48. Dixon JB, O'Brien PE, Playfair J, et al. 2008. Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. *JAMA* 299:316–23
49. Schauer PR, Kashyap SR, Wolski K, et al. 2012. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. *N. Engl. J. Med.* 366:1567–76
50. Schauer PR, Bhatt DL, Kirwan JP, et al. 2014. Bariatric surgery versus intensive medical therapy for diabetes—3-year outcomes. *N. Engl. J. Med.* 370:2002–13
51. Mingrone G, Panunzi S, De Gaetano A, et al. 2012. Bariatric surgery versus conventional medical therapy for type 2 diabetes. *N. Engl. J. Med.* 366:1577–85
52. Mingrone G, Panunzi S, De Gaetano A, et al. 2015. Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial. *Lancet* 386:964–73
53. Ikramuddin S, Korner J, Lee WJ, et al. 2013. Roux-en-Y gastric bypass versus intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia: the Diabetes Surgery Study randomized clinical trial. *JAMA* 309:2240–49
54. Ikramuddin S, Billington CJ, Lee WJ, et al. 2015. Roux-en-Y gastric bypass for diabetes (the Diabetes Surgery Study): 2-year outcomes of a 5-year, randomized, controlled trial. *Lancet Diabetes Endocrinol.* 3:413–22
55. Ikramuddin S, Korner J, Lee WJ, et al. 2018. Lifestyle intervention and medical management with versus without Roux-en-Y gastric bypass and control of hemoglobin A1c, LDL cholesterol, and systolic blood pressure at 5 years in the Diabetes Surgery Study. *JAMA* 319(3):266–78
56. Liang Z, Wu Q, Chen B, et al. 2013. Effect of laparoscopic Roux-en-Y gastric bypass surgery on type 2 diabetes mellitus with hypertension: a randomized controlled trial. *Diabetes Res. Clin. Pract.* 101:50–56
57. Halperin F, Ding SA, Simonson DC, et al. 2014. Roux-en-Y gastric bypass surgery or lifestyle with intensive medical management in patients with type 2 diabetes: feasibility and 1-year results of a randomized clinical trial. *JAMA Surg.* 149:716–26
58. Courcoulas AP, Goodpaster BH, Eagleton JK, et al. 2014. Surgical versus medical treatments for type 2 diabetes mellitus: a randomized clinical trial. *JAMA Surg.* 149:707–15
59. Courcoulas AP, Belle SH, Neiberg RH, et al. 2015. Three-year outcomes of bariatric surgery versus lifestyle intervention for type 2 diabetes mellitus treatment: a randomized clinical trial. *JAMA Surg.* 150:931–40
60. Wentworth JM, Playfair J, Laurie C, et al. 2014. Multidisciplinary diabetes care with and without bariatric surgery in overweight people: a randomised controlled trial. *Lancet Diabetes Endocrinol.* 2:545–52
61. Parikh M, Chung M, Sheth S, et al. 2014. Randomized pilot trial of bariatric surgery versus intensive medical weight management on diabetes remission in type 2 diabetic patients who do not meet NIH criteria for surgery and the role of soluble RAGE as a novel biomarker of success. *Ann. Surg.* 260:617–22
62. Ding SA, Simonson DC, Wewalka M, et al. 2015. Adjustable gastric band surgery or medical management in patients with type 2 diabetes: a randomized clinical trial. *J. Clin. Endocrinol. Metab.* 100:2546–56
63. Cummings DE, Arterburn DE, Westbrook EO, et al. 2016. Gastric bypass surgery versus intensive lifestyle and medical intervention for type 2 diabetes: the CROSSROADS randomized controlled trial. *Diabetologia* 59:945–53

64. Shah SS, Todkar J, Phadake U, et al. 2016. *Gastric bypass versus medical/lifestyle care for type 2 diabetes in South Asians with BMI 25–40 kg/m^2: the COSMID randomized trial [261-OR]*. Oral paper presented at the American Diabetes Association's 76th Scientific Session. June 10–14, New Orleans, LA
65. Fouse T, Schauer P. 2016. The socioeconomic impact of morbid obesity and factors affecting access to obesity surgery. *Surg. Clin. North Am.* 96:669–79
66. Rubin JK, Hinrichs-Krapels S, Hesketh R, et al. 2016. Identifying barriers to appropriate use of metabolic/bariatric surgery for type 2 diabetes treatment: policy lab results. *Diabetes Care* 39:954–63
67. Hoerger TJ, Zhang P, Segel JE, et al. 2010. Cost-effectiveness of bariatric surgery for severely obese adults with diabetes. *Diabetes Care* 33(9):1933–39
68. Consensus Development Conference Panel. 1991. Gastrointestinal surgery for severe obesity. *Ann. Intern. Med.* 115:956–61
69. American Diabetes Association. 2019. Standards of medical care in diabetes—2019. *Diabetes Care* 42(Suppl. 1)
70. Davies MJ, D'Alessio DA, Fradkin J, et al. 2018. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 61(12):2461–98
71. Ghio B, Jiménez A, Corcelles R, et al. 2017. Midterm effects of bariatric surgery in patients with insulin-treated type 2 diabetes. *Surg. Obes. Relat. Dis.* 13(12):2004–9
72. Rubino F, Nathan DM, Eckel RH, et al. 2016. Metabolic surgery in the treatment algorithm for type 2 diabetes: a joint statement by international diabetes organizations. *Diabetes Care* 39:861–77
73. Aminian A, Brethauer SA, Andalib A, et al. 2017. Individualized metabolic surgery score: procedure selection based on diabetes severity. *Ann. Surg.* 266(4):650–57
74. Still CD, Wood GC, Benotti P, et al. 2014. Preoperative prediction of type 2 diabetes remission after Roux-en-Y gastric bypass surgery: a retrospective cohort study. *Lancet Diabetes Endocrinol.* 2(1):38–45
75. Lee WJ, Hur KY, Lakadawala M, et al. 2013. Predicting success of metabolic surgery: age, body mass index, C-peptide, and duration score. *Surg. Obes. Relat. Dis.* 9(3):379–84
76. Lee WJ, Chong K, Chen SC, et al. 2016. Preoperative prediction of type 2 diabetes remission after gastric bypass surgery: a comparison of DiaRem scores and ABCD scores. *Obes. Surg.* 26(10):2418–24
77. Brethauer SA, Aminian A, Romero-Talamás H, et al. 2013. Can diabetes be surgically cured? Long-term metabolic effects of bariatric surgery in obese patients with type 2 diabetes mellitus. *Ann. Surg.* 258:628–36
78. Hanipah ZN, Schauer PR. 2017. Surgical treatment of obesity and diabetes. *Gastrointest. Endosc. Clin. N. Am.* 27(2):191–211
79. Schauer PR, Nor HZ, Rubino F. 2017. Metabolic surgery for treating type 2 diabetes mellitus: now supported by the world's leading diabetes organizations. *Cleve. Clin. J. Med.* 84(7 Suppl. 1):S47