

## Review Article

# Safety, Effectiveness, and Cost Effectiveness of Metabolic Surgery in the Treatment of Type 2 Diabetes Mellitus

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Remission of type 2 diabetes mellitus with metabolic surgery is a field of active investigation and development. The extraordinary results obtained in diabetic patients with BMI  $> 35 \text{ kg/m}^2$  have led investigators to query if similar results could be achieved in patients with BMI  $< 35 \text{ kg/m}^2$ . A few studies have been recently conducted to evaluate the safety, effectiveness, and cost effectiveness of bariatric surgery in diabetic patients with BMI  $< 35 \text{ kg/m}^2$ . However, stronger evidence would be required before insurance coverage is extended for bariatric surgery to all type 2 diabetic patients, in addition to those with BMI  $\geq 35 \text{ kg/m}^2$  for whom eligibility is already established. In addition, the hormonal and metabolic mechanisms of diabetes remission after gastrointestinal surgery are yet to be determined. This paper will review the evidence about safety, effectiveness, and cost effectiveness of bariatric surgery in type 2 diabetes mellitus remission and the potential socioeconomic impact of offering bariatric surgery to diabetic patients with BMI  $< 35 \text{ kg/m}^2$ .

## 1. Introduction

Type 2 Diabetes Mellitus (T2DM) is a major cause of morbidity and mortality around the world. The prevalence of T2DM in the US was 8% in 2008 [1]. According to the American Diabetes Association, the total estimated cost of diabetes in 2007 was \$174 billion [2]. The traditional goal for medical treatment of T2DM has been to delay the appearance of end-organ complications. In contrast, surgical treatment for T2DM is currently being evaluated as a potential “cure” for T2DM. Several studies have demonstrated that obese diabetic patients who undergo bariatric surgery experience complete T2DM remission, maintaining euglycemia without medications for more than 10 years [3]. Additionally, following some gastrointestinal (GI) procedures, T2DM resolves within days to weeks, long before the occurrence of major weight loss [4]. Bariatric surgery as a modality to treat obesity in the US is reserved for patients with BMI  $\geq 35 \text{ kg/m}^2$  and the presence of serious comorbidities (T2DM, moderate or severe obstructive sleep apnea (OSA), pseudotumor cerebri, and severe steatohepatitis), or BMI  $> 40 \text{ kg/m}^2$  and minor comorbidities (mild OSA, hypertension

(HTN), insulin resistance, glucose intolerance, dyslipidemia, impaired quality of life, or activities of daily living) [5]. However, some recent publications also suggest that conventional bariatric surgery results in remission of T2DM in patients with BMI  $< 35 \text{ kg/m}^2$  [6, 7]. In addition, novel antidiabetic GI procedures have been developed by groups outside the US to treat T2DM patients with BMI  $< 35 \text{ kg/m}^2$  [8, 9]. In view of the growing enthusiasm for surgical interventions to treat T2DM, the 1st diabetes surgery summit (DSS) was held in Rome in March 2007 to develop guidelines for the use of GI surgery to treat T2DM. The DSS position statement included that a surgical approach may be appropriate as a nonprimary alternative to treat inadequately controlled T2DM in suitable surgical candidates with BMI 30–35  $\text{kg/m}^2$  and that novel GI surgical techniques (duodenal-jejunal bypass, ileal interposition, sleeve gastrectomy, and endoluminal sleeves) should be used only in the context of IRB-approved trials [10]. The growing interest in offering surgical therapy to T2DM patients with BMI  $< 35 \text{ kg/m}^2$  within the world surgical community has not yet spread to the US surgical community. A major limitation for the development of the field of metabolic surgery in the US is

the absence of insurance coverage for bariatric procedures in T2DM patients with BMI < 35 kg/m<sup>2</sup>. Several studies have demonstrated that adjustable gastric banding (AGB) and Roux-en-Y gastric bypass (RYGB) are cost effective at 5-year followup in comparison to conventional treatment (CT) for T2DM in patients with BMI ≥ 35 kg/m<sup>2</sup> [11–14]. One study has also shown cost effectiveness of bariatric surgery in patients with T2DM and BMI ≥ 30 and <40 kg/m<sup>2</sup> [15]. The purpose of this paper is to review the existing literature about safety, effectiveness, and cost effectiveness of bariatric surgery in T2DM remission and the potential socioeconomic impact of offering bariatric surgery to diabetic patients with BMI < 35 kg/m<sup>2</sup>.

## 2. Morbidity and Mortality of Bariatric Surgery

Trends in mortality in bariatric surgery were reported by Buchwald et al. [16] in 2007. This systematic review and meta-analysis included 360 studies for a total of 85,000 patients with a mean BMI of 47.4 kg/m<sup>2</sup>. In contrast to the popular belief that bariatric surgery is a drastic measure to treat obesity because of its associated risks, this study demonstrates that mortality from laparoscopic RYGB (LRYGB) is comparable to mortality from laparoscopic cholecystectomy, which is considered to be a safe operation by the general public. Mortality rates from LRYGB in this study were 0.16% within 30 days and 0.09% from 30 days to 2 years. Similarly, a 30-day postoperative mortality of 0.3% after RYGB or laparoscopic AGB (LAGB) was reported by the Longitudinal Assessment of Bariatric Surgery (LABS) Consortium, a 10-center prospective trial involving 4776 patients undergoing bariatric surgery. This study also reported a composite end point of death or serious complication of 4.1% within 30 days after surgery [17]. Gastric bypass surgery has been associated with decreased long-term total mortality in severely obese patients, as demonstrated by Adams et al. [18] in 2007. This retrospective cohort study compared the long-term mortality of 7925 patients who underwent gastric bypass surgery matched for age, sex, and BMI to severely obese control subjects who applied for driver's licenses, using the National Death Index. During a mean followup of 7.1 years, adjusted long-term mortality from any cause in the surgery group decreased by 40%, as compared with that in the control group (37.6 versus 57.1 deaths per 10,000 person-years,  $P < .001$ ); cause-specific mortality in the surgery group decreased by 56% for coronary artery disease (2.6 versus 5.9 per 10,000 person-years,  $P = .006$ ), by 92% for diabetes (0.4 versus 3.4 per 10,000 person-years,  $P = .005$ ) and by 60% for cancer (5.5 versus 13.3 per 10,000 person-years,  $P < .001$ ). However, rates of death not caused by disease, such as accidents and suicide, were 58% higher in the surgery group than in the control group (11.1 versus 6.4 per 10,000 person-years,  $P = .04$ ). Sjöström et al. [19] also reported a survival benefit of bariatric surgery over conventional treatment for obesity. This prospective controlled study compared 2010 patients who underwent bariatric surgery (AGB: 376; RYGB: 265; vertical banded gastroplasty: 1369) to 2037 patients who received conventional treatment (matched control group). The unadjusted overall hazard ratio was 0.76

in the surgery group ( $P = .04$ ), as compared with the control group, and the hazard ratio adjusted for sex, age, and risk factors was 0.71 ( $P = .01$ ). The most common causes of death were myocardial infarction and cancer. Perioperative complications were experienced by 13% of patients, which included bleeding (0.9%), thromboembolic events (0.8%), wound complications (1.8%), abdominal infection (2.1%), pulmonary symptoms (6.2%), and miscellaneous (4.8%). Postoperative complications requiring reoperation were experienced by 2.2%.

## 3. Effectiveness of Bariatric Surgery in T2DM Remission in Patients with T2DM and BMI ≥ 35 kg/m<sup>2</sup>

The bariatric literature has consistently demonstrated a significant effect of bariatric surgery in T2DM remission in patients with BMI ≥ 35 kg/m<sup>2</sup>. T2DM resolution or remission has usually been defined as HbA<sub>1c</sub> values ranging from <6% to <7% in the absence of antidiabetic medications. The prospective, controlled Swedish Obese Subjects Study by Sjöström et al. [20] reported a significant difference in the prevalence of diabetes between the surgery group and the conventional treatment group (2 years: 1% versus 8%,  $P < .001$ ; 10 years: 7% versus 24%,  $P < .001$ ). Participants who underwent surgery were more likely to recover from diabetes (2 years: 72% versus 21%,  $P < .001$ ; 10 years: 36% versus 13%,  $P < .001$ ). A systematic review and meta-analysis of bariatric surgery by Buchwald et al. [3] included 136 studies for a total of 22,094 patients; mean baseline BMI was 46.9 kg/m<sup>2</sup> (32.3–68.8). The studies that reported resolution of T2DM included a total of 1846 patients. Diabetes resolution rates were 98.9% after biliopancreatic diversion (BPD), 83.7% after RYGB and 47.9% after AGB. Another systematic review by Levy et al. [21] confirmed that bariatric surgery was highly effective in obtaining weight reduction in morbidly obese patients of up to 60% of the excess weight, along with resolution of preoperative diabetes in more than 75% of the cases.

## 4. Cost Effectiveness of Bariatric Surgery in Patients with T2DM and BMI ≥ 35 kg/m<sup>2</sup>

Ackroyd et al. [11] established a payer-perspective cost effectiveness and budget impact (BI) model of AGB and RYGB versus CT in patients with BMI ≥ 35 kg/m<sup>2</sup> and T2DM in Germany, UK, and France (Table 1). The base case time scope was 5 years, and the annual discount rate for utilities and costs was 3.5%. In Germany and France, both RYGBP and AGB yielded a cost decrease and were thus dominant in terms of incremental cost-effectiveness ratio (ICER) compared to CT. In the UK, RYGBP and AGB yielded a cost increase but were cost-effective. The authors concluded that, in patients with T2DM and BMI ≥ 35 kg/m<sup>2</sup>, AGB and RYGBP are effective at 5-year followup in cost-saving in Germany and France and are cost effective in the UK with a moderate BI versus CT. Anselmino et al. [12] replicated this model in Austria, Italy, and Spain. In Austria

TABLE 1: Cumulative cost per patient over 5 years including cost of therapy, cost of complications, and cost of prevalent T2DM [11].

Study	Conventional therapy	Laparoscopic adjustable gastric banding	Laparoscopic gastric bypass
Germany	€17197	€13610	€12166
France	€19276	€14796	€13399
United Kingdom	£7083	£9072	£9121

TABLE 2: Summary results for the base-case analysis [13].

35-year time horizon	Bariatric surgery	Medical management	Difference
Life expectancy, y	11.536 (0.424)	10.870 (0.187)	+0.6666 (0.460)
Quality-adjusted life expectancy, y	6.782 (0.479)	5.883 (0.105)	+0.8999 (0.493)
Total costs (2007, dollars)	83,482 (3191)	63,722 (2296)	+19,760 (3861)
Management	9117	11,621	−2504
Cardiovascular disease	34,811	37,824	−3013
Renal	3592	4539	−947
Eye	3769	3963	−194
Ulcer/neuropathy/amputation	5915	5776	+139
Surgery	23,131	0	+23,131
Incremental cost per life-year gained (2007, dollars)	—	—	29,676
Incremental cost per QALY gained (2007, dollars)	—	—	21,973

and Italy, both AGB and RYGBP are cost saving and are thus dominant in terms of ICER compared to CT. In Spain, AGB and RYGBP yield a moderate cost increase but are cost effective, assuming a willingness to-pay threshold of 30,000 euro per quality adjusted life year (QALY). Under worst-case analysis, AGB and RYGBP remain cost saving or around breakeven in Austria and Italy and remain cost effective in Spain.

A similar study was conducted in the US by Ikramuddin et al. [13]. The analysis showed that compared with medical management, RYGB surgery for obese diabetic patients has a cost effectiveness ratio of \$22,000 per QALY gained (Table 2). The authors concluded that, in the US, RYGB surgery is cost-effective from a payer's perspective. From a third-party payer's perspective, Crémieux et al. [14] evaluated the return on investment for bariatric surgery in the United States. Morbidly obese patients aged 18 years or older were identified in an employer claims database of more than 5 million beneficiaries. Each of the 3651 patients who underwent bariatric surgery during this period was matched to a control subject who was morbidly obese and never underwent bariatric surgery. Total healthcare costs for bariatric surgery patients and their controls were recorded for 6 months before surgery through the end of their continuous enrollment. The study suggested that the total cost of laparoscopic bariatric surgery is fully recovered after 25 months. These returns on investment result from reductions in prescription drug costs, physician visit costs, and hospital costs (including emergency department visits and inpatient and outpatient visits). The reduced costs are associated with multiple major diagnosis categories, including diabetes mellitus, coronary

artery disease, hypertension, and sleep apnea. Similarly, a review of 15 years of experience in a French university hospital reported that bariatric surgery is cost effective after 3.5 years [22].

## 5. Effectiveness of Bariatric Surgery in T2DM Remission in Patients with BMI < 35 kg/m<sup>2</sup>

Recent publications suggest that the beneficial effects of bariatric surgery in type 2 diabetic patients are not limited to patients with BMI  $\geq 35$  kg/m<sup>2</sup>. O'Brien et al. [23] completed a randomized clinical trial that included 80 adults with BMI between 30 kg/m<sup>2</sup> and 35 kg/m<sup>2</sup>. They reported a significant resolution of the metabolic syndrome in patients undergoing laparoscopic adjustable gastric banding. Patients in this study were assigned to a program of very-low-calorie diets, pharmacotherapy, and lifestyle change for 24 months (non-surgical group) or to placement of a laparoscopic adjustable gastric band. The metabolic syndrome was initially present in 38% of patients in each group and was present in 24% of nonsurgical patients and 3% of surgical patients at the completion of the study ( $P < .002$ ). A second nonblinded randomized controlled trial was conducted by Dixon et al. [24] from December 2002 through December 2006, which included 60 obese patients with BMI  $>30$  and  $<40$  recently diagnosed with type 2 diabetes. CT reflected the best available medical management including consultation with a diabetes educator every 6 weeks, medical therapies as determined by an experienced endocrinologist specialized in diabetes, and lifestyle modification programs. In addition to all aspects of CT, surgical therapy involved the placement

of a LAGB. Remission of T2DM (fasting glucose level  $<126$  mg/dL and  $\text{HbA}_{1\text{C}} < 6.2\%$  while taking no glycemic therapy) was observed in 73% of patients in the surgical group and in 13% of patients in the conventional therapy group. Remission of T2DM was related to weight loss and lower baseline  $\text{HbA}_{1\text{C}}$ .

Cohen et al. [25] also demonstrated that obese patients with a BMI of  $<35$  kg/m<sup>2</sup> and severe comorbidities can benefit from LRYGB. A total of 37 patients (mean BMI 32.5 kg/m<sup>2</sup>) who had tried to lose weight with no success and had been undergoing clinical treatment with no resolution or improvement of their life-threatening comorbidities (T2DM, HTN, lipid disorder, GERD, and sleep apnea) underwent LRYGB. After extensive explanation and documentation, the Brazilian insurance companies approved the procedure in 3 cases, and international (nonAmerican) insurance companies approved the procedure in 4 cases. The followup range was 6–48 months. The mean excess weight loss was 81%. Thirty-six patients had total remission of their comorbidities. One patient still had mild hypertension, but with a reduction in the number of antihypertensive drugs used. No surgery-related complications were reported.

Remission of T2DM in patients with BMI  $< 35$  kg/m<sup>2</sup> after LRYGB was also published by Lee et al. [26]. This was a retrospective study of prospectively collected data that included 201 patients with impaired fasting glucose or T2DM. Among the 201 patients, 44 (21.9%) had BMI  $< 35$  kg/m<sup>2</sup> and 157 (78.1%) had BMI  $\geq 35$  kg/m<sup>2</sup>. One year after surgery, fasting plasma glucose returned to normal in 89.5% of BMI  $< 35$  kg/m<sup>2</sup> T2DM and 98.5% of BMI  $\geq 35$  kg/m<sup>2</sup> patients ( $P = .087$ ). The treatment goal of T2DM ( $\text{HbA}_{1\text{C}} < 7.0\%$ , LDL  $< 150$  mg/dL, and triglyceride  $< 150$  mg/dL) was met in 76.5% of BMI  $< 35$  kg/m<sup>2</sup> and 92.4% of BMI  $\geq 35$  kg/m<sup>2</sup> patients ( $P = .059$ ). Major perioperative complications occurred in 4.5% of patients with BMI  $< 35$  kg/m<sup>2</sup> and no perioperative mortality. The authors concluded that despite a slightly lower response rate of T2DM treatment, patients with include BMI  $< 35$  kg/m<sup>2</sup> still had an acceptable T2DM resolution, and this treatment option can be offered to this group of patients. A recent study demonstrated T2DM remission and reduced cardiovascular risk after gastric bypass in Asian Indians with BMI  $< 35$  kg/m<sup>2</sup>. A total of 15 consecutive patients with T2DM and a BMI of 22–35 kg/m<sup>2</sup> underwent RYGB. The data were prospectively collected before surgery and at 1, 3, 6, and 9 months postoperatively. The BMI decreased postoperatively by 20%, from  $28.9 \pm 4.0$  kg/m<sup>2</sup> to  $23.0 \pm 3.6$  kg/m<sup>2</sup> ( $P < .001$ ). All antidiabetic medications were discontinued by 1 month after surgery in 80% of the subjects. At 3 months and thereafter, 100% were euglycemic and no longer requiring diabetes medication. The fasting blood glucose level decreased from  $233 \pm 87$  mg/dL to  $89 \pm 12$  mg/dL ( $P < .001$ ), and the  $\text{HbA}_{1\text{C}}$  decreased from  $10.1\% \pm 2.0\%$  to  $6.1\% \pm 0.6\%$  ( $P < .001$ ). Their waist circumference, presence of dyslipidemia, and hypertension improved significantly. The predicted 10-year cardiovascular disease risk (calculated using the United Kingdom Prospective Diabetes Study equations) decreased substantially for fatal and nonfatal coronary heart disease and stroke. No

mortality, major surgical morbidity, or excessive weight loss occurred [27].

## 6. Cost Effectiveness of Bariatric Surgery in Patients with T2DM and BMI $< 35$ kg/m<sup>2</sup>

Cost effectiveness of surgically induced weight loss for the management of T2DM has also been demonstrated for patients with BMI  $>30$  and  $<40$  kg/m<sup>2</sup>. Keating et al. [15] published the within-trial cost efficacy of surgical therapy relative to CT for achieving remission of recently diagnosed T2DM in class I and II obese patients. The efficacy results were derived from a 2-year randomized controlled trial conducted by Dixon et al. [24]. Trial intervention costs included LAGB surgery, mitigation of surgical complications, outpatient medical consultation, pathology, medical investigations, weight loss assisted therapies, and medication. During the first 6 months of the trial, mean intervention costs per patient were approximately sevenfold greater for surgical patients than for CT patients. The difference between costs in each intervention group decreased with each subsequent 6-month period until the last 6 months of the trial, when intervention costs were equivalent in both groups. The ICER for surgical therapy (relative to CT, 16,600 Australian dollars) was lower than the comparable ICER for CT (relative to no intervention, 25,500 Australian dollars). Modeling cost effectiveness over a longer time period, Keating et al. [28] concluded that after 10 years the return on investment of surgical therapy is fully recovered through savings in health care costs to treat T2DM in the surgical group.

## 7. Discussion

A significant existing body of literature has proven that bariatric surgery is safe, effective, and cost effective as a treatment for T2DM in patients with BMI  $\geq 35$  kg/m<sup>2</sup>. A rapidly growing body of literature has demonstrated that bariatric surgery is also safe, effective and cost-effective as a treatment for T2DM in patients with BMI  $> 30$  and  $<35$  kg/m<sup>2</sup>. However, most data collection on weight loss surgery has relied on administrative data sets, single-institution studies, and other sources that are not weight loss surgery specific. The results from weight loss surgery specific databases, which have been implemented since 2004 (i.e., NIH-sponsored longitudinal assessment of bariatric surgery consortium, the ACS-Bariatric Surgery Center Network, and the ASMBS/SRC Centers of Excellence Program), could identify areas for improvement and optimize outcomes and patient care [29].

There is still controversy in the US health system about extending coverage for bariatric surgery to all obese patients with diabetes, in addition to those with BMI  $\geq 35$  kg/m<sup>2</sup> for whom eligibility is already established. This approach would result in immediate costs of several hundred billion dollars. There is concern that such expenditures would redirect scarce resources away from prevention efforts [30]. Although the studies quoted above refute this argument, opponents to expanding metabolic surgery argue that at least one recent study suggests that maintenance of weight loss over time may



be no better in surgical patients than in those who lost weight without surgery [31]. Weight regain may be associated with deceleration in the rate of recovery from comorbidities after bariatric surgery [20].

It is important to promote funding for projects that study the safety, effectiveness, and cost effectiveness of metabolic surgery in T2DM patients. The Surgical Therapy and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial was designed to evaluate the efficacy of two bariatric surgery procedures (laparoscopic sleeve gastrectomy and RYGB) in comparison to advanced medical therapy in patients with T2DM with modest obesity with BMI of 27–42 kg/m<sup>2</sup>. This single site, prospective, randomized controlled trial will enroll 150 subjects who will be followed. The primary end point will be the rate of biochemical resolution of T2DM at 1 year as measured by HbA1c < 6%. The safety and adverse event rates will also be compared between the three arms of the study [32]. The creation and development of similar parallel trials would help to validate the results derived from STAMPEDE.

It is also important to promote funding for projects that investigate the hormonal and metabolic mechanisms of diabetes remission after gastrointestinal surgery. It appears that other mechanisms besides weight loss contribute to the higher rates of T2DM remission after RYGB in comparison with AGB [33]. Potential mechanisms underlying the direct antidiabetic impact of RYGB include enhanced nutrient stimulation of lower intestinal hormones (e.g., glucagon-like peptide-1), altered physiology from excluding ingested nutrients from the upper intestine, compromised ghrelin secretion, modulations of intestinal nutrient sensing, and regulation of insulin sensitivity, and other changes yet to be fully characterized [34]. Elucidation of the antidiabetic mechanisms of RYGB may help develop more potent and efficacious drugs in the future treatment of T2DM.

Although cost effectiveness of bariatric surgery in patients with T2DM and BMI < 35 kg/m<sup>2</sup> have been reported in at least 2 well-conducted studies, more good quality evidence is required before extending coverage for all T2DM patients. It is unclear if all T2DM would be potential candidates for metabolic surgery or if only patients that meet certain criteria (e.g., duration of T2DM, BMI, established cardiovascular disease, insulin dependency, C-peptide levels, etc.) would benefit while others would not. The socioeconomic impact of obtaining T2DM remission via metabolic surgery is yet to be determined and should be an area of active investigation.

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