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Curing Diabetes Through Bariatric Surgery: Evolution of Our Understanding

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Abstract
Purpose of Review The goal of this review is to summarize available data on the impact of bariatric surgery on diabetes and to explore the mechanisms responsible for these outcomes.
Recent Findings In randomized controlled trials and when compared to standard medical management, bariatric surgery is consistently superior with regards to weight loss and remission of type 2 diabetes. Remission rates are proportional to weight loss. The likelihood of remission from type 2 diabetes after bariatric surgery can be estimated from several available clinical parameters.
Summary Bariatric surgery is superior in improving glycemic control when compared to standard medical management, but is associated with higher risk. However, for some patients with type 2 diabetes, the goal of sustained remission may only be achievable with surgery. The mechanisms by which this is achieved are multifold and continue to be the focus of ongoing studies.

Keywords Type 2 diabetes · Roux-en-Y gastric bypass · Bariatric surgery · Type 1 diabetes

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Introduction

Rising worldwide prevalence of obesity and its associated complications has led to the burgeoning popularity of bariatric surgery. Bariatric or weight loss surgery is currently the most durable method of weight loss for a variety of reasons; changes in appetite regulation, development of different food preferences, and alterations in gut transit that promote satiety are partly responsible for the relatively low risk of weight recidivism [1–3].

Bariatric surgery is also associated with the highest rates of type 2 diabetes (DM2) remission, with the likelihood of sustained remission (as defined variably over the years) most tightly associated with the degree of weight loss achieved [4]. Improvements in glycemic control, however, are seen before any significant weight loss is achieved, suggesting an alternative mechanism independent of weight loss by which bariatric surgery improves DM2. This review will summarize trial data supporting the role of bariatric surgery in the amelioration of DM2 and discuss the proposed mechanisms that facilitate glycemic improvement.

Clinical Data for Type 2 Diabetes

Key Meta-analysis or Non-randomized Trials

In evaluating the impact of bariatric surgery on DM2, Pories et al. first reported that 82.9% of patients with non-insulin-dependent diabetes and 98.7% of patients with impaired glucose tolerance experienced euglycemia without medications during an average follow-up of 7.6 years [5]. The Swedish Obese Subjects trial, which was a prospective case-controlled trial comparing obese subjects who underwent bariatric surgery to matched cohort, also showed similar results [6]. The procedures included in this trial were gastric banding, vertical banded gastroplasty (VBG), as well as Roux-En-Y gastric bypass (RYGB). The bariatric surgery patients were matched based on 18 variables including sex, age, weight, height, waist and hip circumference, systolic blood pressure, serum cholesterol and triglyceride levels, smoking status, diabetes, menopausal status, 4 psychological variables with documented associations with risk of death, and 2 personality traits related to treatment preferences. The incidence of diabetes was noted to be lower in the surgical group compared to control group at 2 years (1 vs. 8% respectively, p value < 0.001) and 10 years of follow-up (7 vs. 24% respectively, p value < 0.001). At 2 years, the control group had a 5.1% increase in their glucose levels compared to a 13.6% decrease in the surgical group, which amounted to a 16.6% difference in blood glucose levels between the two groups. This difference was greater at 10 years as the control group had an 18.7% increase in glucose, whereas the surgical group still had a 2.7% decrease compared to baseline [6].

Buchwald et al. conducted a meta-analysis of trials published from January 1, 1990 to April 30, 2006 [7]. They included 621 primary studies and also noted that 19 studies included data regarding diabetes resolution and weight loss for over 4000 patients with diabetes. The majority of the studies included were retrospective with only 4.7% being randomized clinical trials. Overall, there was resolution or improvement in 86.6% of patients with 78.1% of patients experiencing complete resolution of diabetes. Diabetes resolution was highest for patients undergoing biliopancreatic diversion/duodenal switch (BPD-DS; 95.1%), followed by RYGB (80.3%), VBG (79.7%), and then laparoscopic adjustable gastric banding (LAGB; 56.7%). Interestingly, weight loss also followed this particular order with the highest weight loss in BPD-DS followed by RYGB and VBG, and lowest in LAGB. After publication of this landmark meta-analysis, further meta-analyses have included newer trials and continued to show similar results [8, 9].

Key Randomized Trials

The Diabetes Surgery Study, a multi-site randomized controlled trial, randomized 120 patients with DM2 (HbA1c $\geq$ 8.0%) and BMI between 30 and 40 kg/m^2 from 4 teaching hospitals to either surgery (RYGB) or intense lifestyle intervention and medical management [10]. Intense lifestyle program was modeled after the Diabetes Prevention Program (DPP) [11] and Look AHEAD [12] trials consisting of weekly sessions for the first 6 months followed by bi-weekly sessions for 3 months and then monthly sessions. Weight loss medications (orlistat and sibutramine) were used along with medications for glycemic control (metformin, glucagon-like peptide-1 analog, dipeptidyl peptidase 4 inhibitor, sulfonylurea or pioglitazone, and insulin, in that order). The bariatric surgery group underwent 2 weeks of meal replacements prior to surgery and the surgical procedure was standardized across all centers (20 ml gastric pouch, 100-cm biliopancreatic limb, and 150-cm Roux limb). At 12 months, they noted that mean HBA1c was 7.8% in the lifestyle group and 6.3% in the surgery group. Only 32% of participants in the lifestyle group, compared to 75% in the RYGB group, achieved an HbA1c of less than 7% [10].

Courcoulas et al. randomized 61 obese subjects (BMI 30–40 kg/m^2) with DM2 to one of three groups: RYGB, LGAB, or intense lifestyle intervention for 1 year [13]. Intense lifestyle intervention was again modeled after the DPP and Look AHEAD trials as noted above. All the three groups received low-intensity lifestyle intervention for years 2 and 3 consisting of twice-monthly contact and regular refresher group classes. Patients with BMI between 30 and 40 kg/m^2 were eligible. Of the 52 participants evaluated at 3 years, complete or partial DM2 remission was noted to occur in 40% of RYGB (n = 8), 29% of LAGB (n = 6), and none of the lifestyle group. The RYGB group had the highest change in HBA1c (− 1.42%) compared to LAGB (− 0.8%) and the intense lifestyle (+ 0.2%) groups. These changes in DM2 control occurred in the surgical groups requiring fewer medications, whereas the lifestyle group had no significant change in medication use. It is important to note that baseline HbA1c for the RYGB group was higher (8.56%) compared to the LAGB (7.87%) and intense lifestyle (7.03) groups [13].

With a similar three-arm design, Schauer et al. randomized 150 obese patients with uncontrolled DM2 to either intensive medical management alone or intensive medical management plus RYGB or sleeve gastrectomy (SG) [14]. They included the lowest range of BMI with subjects with BMI of 27–43 kg/m^2 being eligible. This is an important point since most insurance plans in the United States cover bariatric surgery in patients with a BMI of 40 kg/m^2 or higher without significant medical co-morbidities, or those with BMI of 35 kg/m^2 or higher in those with medical co-morbidities such as diabetes. Baseline HbA1c was also higher than the above trials at 9.3 ± 1.5%. After 3 years, the primary end-point of HbA1c of 6.0% or less was achieved in 5% of patients in intensive medical management compared to 38% of RYGB group and 24% of SG group. Reduction in BMI and duration of diabetes were significant predictors of achieving primary end-point in the surgical arms. There was also a significant reduction in number of medications required in both the surgical arms at 3 years compared to intense medical therapy group

(RYGB 0.48 ± 0.80; SG 1.02 ± 1.01; Medical therapy 2.60 ± 1.10). At 5 years, 5% of patients who received medical therapy alone, versus 29% who underwent gastric bypass and 23% after SG, had an HbA1c of < 6%, highlighting the long-term durability of bariatric surgery in improving diabetes (Table 1) [15•].

Clinical Data for Type 1 Diabetes

In contrast to DM2, there is a paucity of data available for impact of bariatric surgery on Type 1 Diabetes (DM1). Czupryniak et al. reported 5–8-year follow-up data in three poorly controlled DM1 patients [16]. The first patient was a 23-year-old female with DM1 since age 15. Her BMI was 38.3 kg/m^2 and HbA1c was 9.5% despite 68 units of insulin per day. She underwent RYGB and after 8 years, her BMI was 30.5 kg/m^2 and HBA1c was 6.9% with her insulin being reduced to 43 units per day. Similar patterns were noted with the other two cases as well. In fact, all three patients had an improvement in HbA1c with surgery as well as a reduction in required daily insulin usage (Case 1: 0.60–0.53 IU/kg, Case 2: 0.95–0.83 IU/kg, Case 3: 0.7–0.3 IU/kg). Fuentes-Zamorano et al. reported two very similar cases of patients with DM1 undergoing bariatric surgery [17]. Both these patients however had moderately well controlled HbA1c prior to surgery (< 8%). They noted a > 50% reduction in insulin dose with a HbA1c reduction in one of the cases. Mendez et al. also reported a case series of 3 patients with initial HbA1c ranging from 7.6 to 8.2% [18]. In this series, one patient had an improvement in their HbA1c, whereas the other two did not despite weight loss. Insulin requirements also only improved in one of the three cases.

In addition to these smaller case series, two groups have reported a larger case series of 10 patients, which highlight the difficulty of interpreting the data available for DM1 as opposed to DM2. Brethauer et al. reported a series of 10 patients with DM1 who underwent bariatric surgery (RYGB n = 7, LAGB n = 2, and SG n = 1) [19]. They noted an improvement in HbA1c from 10.0 ± 1.6% to 8.9 ± 1.1% (p value = 0.039) with reduction in insulin dose from 0.74 units/kg ± 0.32 units to 0.40 units/kg ± 0.15 units (p- value = 0.004) after surgery. It is important to note that HbA1c of 8.9% would not be assessed as good control and again contrasts some of the benefit of bariatric surgery in DM2 patients. Maraka et al. analyzed all insulin-dependent DM patients undergoing bariatric surgery from May of 2008 to April of 2013 allowing for a direct comparison of 118 insulin-requiring patients with DM2 versus 10 patients with DM1 [20]. There was no significant difference between the groups at baseline in BMI, age, and HbA1c. The DM1 group had a longer duration of disease compared to patients with DM2, 20.6 ± 11.4 vs. 12.8 ± 7.9 years (p = <0.01). At both 1 and 2 years of follow-up post-operatively, patients with DM2 had significant decrease in A1c going from 7.8 ± 1.4% at baseline to 6.5 ± 1.3% at 1 year and 6.8 ± 1.4% at year 2. The DM1 group on the other hand did not experience a significant improvement (Baseline 8.2 ± 1.6%; 1 year 8.3 ± 1.3%; 2 year 7.8 ± 0.9%). A sub-analysis was subsequently performed with patients matched for duration of diabetes and again the results revealed an improvement in patients with insulin-dependent DM2 but not in those with DM1.

Table 1 Randomized controlled trials comparing standard medical management to RYGB in the remission of type 2 diabetes

	Definition of type 2 diabetes remission	Remission of type 2 diabetes		Follow-up (months)
		Medical management (%)	Roux-en-Y gastric bypass (%)	
Diabetes Surgery Study [10]	HbA1c < 7%[a]	11/60 (19)	28/60 (49)	12
STAMPEDE [14, 15•]	HbA1c ≤ 6% ± use of medications	2/40 (5)	18/48 (38)	36
		2/38 (5)	14/49 (29)	60
Halperin et al. [41]	HbA1c < 6.5% + FPG < 126 mg/dL	3/19 (16)	11/19 (58)	12
Courcoulos et al. [13]	HbA1c < 6.5% + FPG < 125 mg/dL + no diabetes medications	0/20 (0)	8/20 (40)	36
Mingrone et al. [42]	HbA1c < 6.5% +FPG < 100 mg/dL + no diabetes medications	0/15 (0)	7/19 (37)	60
Cummings et al. [43]	HbA1 < 6% + no diabetes medications	1/17 (5.9)	9/15 (60)	12

[a]Composite score of HbA1c < 7%, LDL < 100 mg/dl, systolic blood pressure < 130 mmHg

Mechanism of Benefit from Bariatric Surgery

The mechanisms by which bariatric surgery leads to improvements in glucose control are still not fully elucidated. Calorie restriction itself, as seen immediately after bariatric surgery, is known to improve insulin action and glucose control. Several decades ago, very low calorie diets (VLCD, 400–800 kcal/day) were utilized for the specific treatment of type 2 diabetes. Before the onset of weight loss, patients would exhibit significant improvements in fasting glucose and hepatic glucose output as a consequence of improved hepatic insulin action [21]. In the early 1990s, Kelley et al. showed that approximately half the improvement in hepatic glucose production, insulin sensitivity, and insulin secretion expected with substantial weight loss is seen after 7 days of calorie restriction alone [22]. However, there does seem to be a threshold beyond which calorie restriction ceases to improve glucose tolerance, as seen in this study where calorie restriction for 6 or 12 weeks produced equivalent results [23]. There is evidence to suggest that at least in the short term, when patients with type 2 diabetes are placed on a similar calorie restriction program to that seen immediately post RYGB, there is similar improvement in endogenous glucose production between the two groups. For example in this cohort of patients with type 2 diabetes, 8 weeks of a VLCD resulting in 15% weight loss (followed by weight maintenance) resulted in sustained fasting plasma glucose of < 126 mg/dL at 6 months [24•]. However, whether the mechanism by which this is achieved in the two groups is similar is unknown. Moreover, sustaining this degree of calorie restriction is not practically feasible for the vast majority of patients with type 2 diabetes.

When bariatric surgery was first recognized to result in improvements in glucose control, several hypotheses were generated based on the anatomical alterations created by surgery. The 'foregut hypothesis' is based on the idea that there may a 'diabetogenic' factor in the foregut which, if bypassed and therefore not exposed to a nutrient stimulus, is not secreted. This would occur, for example, after RYGB wherein the proximal duodenum is bypassed. The corollary to this theory is the 'hindgut hypothesis', wherein a substance in the hindgut (or distal small intestine) is now exposed more rapidly to nutrients, resulting in an 'anti-diabetogenic' factor that improves glucose control. The incretin hormones glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide (GIP) were proposed to be those factors based in particular on the observation that post-prandial GLP-1 concentrations are about 10-fold higher in patients who have undergone RYGB compared to weight-matched controls [25]. Although GLP-1 concentrations are elevated post-prandially following a sleeve gastrectomy, it is not of a similar magnitude [26]. After RYGB, GLP-1 exerts its glucose-lowering effect mostly through improvement in beta cell functioning, and less so through improvements in peripheral insulin action [25, 27]. However, the relative contribution of GLP-1 to the improvements in glucose metabolism seen after RYGB is small and inadequate to explain the profound improvements in glucose metabolism post-surgery.

It is now recognized that there is probably a wider physiologic 'bariatric surgery-driven enteroplasticity' (capacity of the small intestine to adapt to stimuli) that results in adaptation of the small intestinal environment to the surgical manipulation it is subject to [28•]. In animal models of bariatric surgery, there are changes in villi length and number, crypt length depth, increased sensitivity of entero-endocrine cells to nutrients, and alterations in neuronal activity, which are all thought to contribute to the metabolic benefits of bariatric surgery [29]. Another putative mechanism is via changes in bile acid circulation. The farnesoid X receptor (FXR) responds to bile acid binding. In knock-out animal models, absence of FXR led to faster weight regain and higher body fat accumulation than wild-type mice following sleeve gastrectomy [30]. Interestingly, these knock-out mice also exhibited greater difficulty regulating glucose, suggesting that changes in bile acid binding following bariatric surgery may be partly responsible for the improvements seen in glucose metabolism.

FXR signaling also targets the gut bacterial community [31]. The human host has approximately 10^{14} microbes in the colon, which contain about tenfold more genes than the human genome. These bacteria have diverse functions, and following RYGB, changes in acid exposure to the gastric remnant and proximal small bowel, dietary restriction, intestinal dysmotility along with a degree of nutrient malabsorption lead to changes in the composition of the gut microbiome [32]. This has been shown in cross-sectional and longitudinal human studies and holds true for both sleeve gastrectomy and RYGB [32, 33]. Interestingly, there is less of a difference in gut bacterial composition between obese patients and those undergoing sleeve gastrectomy versus obese patients and those undergoing RYGB, and the gut bacterial composition following RYGB generally tends to be more similar to that of lean, non-diabetic individuals [33]. Whether this is relevant to the improvements seen in glucose metabolism is still unknown. In one study, when fecal microbiota from RYGB patients were transferred to germ-free mice, the mice accumulated 43% less body fat than mice that had been colonized with stool from obese donors [33]. No glucose tolerance studies were performed on the mice, however. There is some evidence that changing the gut microbiome in humans with an intervention (fecal transplant) leads to small improvements in insulin sensitivity in the short term [34]. Some proposed mechanisms include less systemic absorption of lipopolysaccharides, increased short chain fatty acid production (e.g., butyrate), decreased synthesis and absorption of branched chain amino acids that lead to insulin resistance and bacterial metabolism of bile acids, e.g., stimulation of FGF-19 which has metabolic effects on FXR in the β cells and liver. There continues to be a robust interest in the role of the post-bariatric gut microbiome in the amelioration of type 2 diabetes, which in turn will contribute to our understanding of how bariatric surgery results in better metabolic health.

Likelihood of Remission

We have known for some time that the likelihood of achieving remission of type 2 diabetes after bariatric surgery is influenced by the degree of weight loss achieved, pre-operative duration of diabetes, and pre-surgical treatment [35–37]. The latter is particularly relevant if the patient is on high doses of insulin, suggesting limited beta cell reserve. In fact, retrospective data estimates show that 5 years post RYGB, 90.1% (95% CI 86.6–93.6%) of non-insulin-using patients achieve remission, compared with 31.1% (23.5–38.6%) of those who had been using insulin prior to surgery [38]. There are now several predictive scoring systems available that can help predict the likelihood of diabetes remission following RYGB. The externally validated DiaRem clinical predictive score uses four pre-operative clinical variables (age, HbA1c, other diabetes medications, and treatment with insulin) to predict the probability of remission of diabetes after RYGB [38]. Low scores predict a high probability of remission for both partial and complete remission of diabetes. An alternative scoring system, the Diabetes Surgical Score utilizes BMI, C-peptide level, T2DM duration, and patient age to construct a multidimensional 10-point scale in which higher scores indicate a better chance of T2DM remission [39]. This may have better discriminatory value at predicting remission in patients with poor scores when compared to DiaRem, but has not been externally validated [40]. Thus, utilizing a scoring system may predict the likelihood of diabetes remission after RYGB with moderate accuracy, and can help guide decision-making with the patient. No clinical predictive scoring system exists for sleeve gastrectomy at this time.

Conclusions

The twin epidemics of obesity and type 2 diabetes are targets of metabolic surgery. Bariatric surgery is superior in improving glycemic control when compared to standard medical management, but is associated with higher risk. However, for some patients with type 2 diabetes, the goal of sustained remission may only be achievable with surgery. Therefore, a conversation about the advantages, disadvantages, and alternatives to surgery, perhaps aided by a clinical diabetes remission score, makes for an informed decision by both parties.

Author Contributions MM and MS formulated an outline of the manuscript and created the first draft. AP and VG critically appraised the manuscript. All authors agree to be responsible for its content.

Compliance with Ethical Standards

Conflict of interest Meera Shah, Angela Pham, Victoria Gershuni, and Manpreet S. Mundi declare that they have no conflict of interest.

Research Involving Human and Animal Participants This article does not contain any studies with human or animal subjects performed by any of the authors.

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