

Can Diabetes Be Surgically Cured?

Long-Term Metabolic Effects of Bariatric Surgery in Obese Patients with Type 2 Diabetes Mellitus

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Objective: Evaluate the long-term effects of bariatric surgery on type 2 diabetes (T2DM) remission and metabolic risk factors.

Background: Although the impressive antidiabetic effects of bariatric surgery have been shown in short- and medium-term studies, the durability of these effects is uncertain. Specifically, long-term remission rates following bariatric surgery are largely unknown.

Methods: Clinical outcomes of 217 patients with T2DM who underwent bariatric surgery between 2004 and 2007 and had at least 5-year follow-up were assessed. Complete remission was defined as *glycated hemoglobin* (A1C) less than 6% and fasting blood glucose (FBG) less than 100 mg/dL off diabetic medications. Changes in other metabolic comorbidities, including hypertension, dyslipidemia, and diabetic nephropathy, were assessed.

Results: At a median follow-up of 6 years (range: 5–9) after surgery (Roux-en-Y gastric bypass, $n = 162$; gastric banding, $n = 32$; sleeve gastrectomy, $n = 23$), a mean excess weight loss (EWL) of 55% was associated with mean reductions in A1C from $7.5\% \pm 1.5\%$ to $6.5\% \pm 1.2\%$ ($P < 0.001$) and FBG from 155.9 ± 59.5 mg/dL to 114.8 ± 40.2 mg/dL ($P < 0.001$). Long-term complete and partial remission rates were 24% and 26%, respectively, whereas 34% improved ($>1\%$ decrease in A1C without remission) from baseline and 16% remained unchanged. Shorter duration of T2DM ($P < 0.001$) and higher long-term EWL ($P = 0.006$) predicted long-term remission. Recurrence of T2DM after initial remission occurred in 19% and was associated with longer duration of T2DM ($P = 0.03$), less EWL ($P = 0.02$), and weight regain ($P = 0.015$). Long-term control rates of low high-density lipoprotein, high low-density lipoprotein, high triglyceridemia, and hypertension were 73%, 72%, 80%, and 62%, respectively. Diabetic nephropathy regressed (53%) or stabilized (47%).

Conclusions: Bariatric surgery can induce a significant and sustainable remission and improvement of T2DM and other metabolic risk factors in severely obese patients. Surgical intervention within 5 years of diagnosis is associated with a high rate of long-term remission.

Keywords: bariatric, diabetes, gastric banding, gastric bypass, LAGB, long term, metabolic, nephropathy, RYGB, sleeve gastrectomy

(*Ann Surg* 2013;258:628–637)

The growing pandemics of obesity and type 2 diabetes mellitus (T2DM) are closely associated and represent major global public

health threats.^{1–4} Although lifestyle modifications and medical therapy are the mainstays of management for obesity and T2DM, adequate glycemic control is difficult to achieve in most obese patients with T2DM. Currently, only 52% of diabetics in the United States are achieving the American Diabetes Association's (ADA) recommended glycated hemoglobin (A1C) goal of 7.0%.⁵ Many obese patients with T2DM also have hypertension and high low-density lipoprotein (LDL) and only 18.2% of patients in the United States are currently achieving the targeted goals of therapy for all 3 diseases.⁵

Since Pories et al⁶ described remission of T2DM after Roux-en-Y gastric bypass (RYGB) in morbidly obese patients, other groups have verified the benefits of commonly performed laparoscopic bariatric procedures on T2DM.^{7–11} Researchers have therefore become increasingly interested in the mechanisms that lead to these clinical results and the durability of these effects. The emergence of a large body of literature supporting surgical treatment of diabetes has led the International Diabetes Federation¹² and ADA¹³ to recognize bariatric surgery as an effective treatment option for obese patients with T2DM.

The majority of the published literature supporting diabetes remission after bariatric surgery has short- and medium-term follow-up, however. A meta-analysis by Buchwald et al¹⁴ reported an overall remission rate of 78% among diabetic patients undergoing bariatric surgery and similar remission rates for studies reporting outcomes less than 2 years and more than 2 years after surgery (80% and 75%, respectively). Currently, though, there are relatively few studies reporting long-term (≥ 5 years) diabetes remission rates substantiated by biochemical data. In addition, the long-term effects of different bariatric operations on T2DM need to be elucidated. It is generally accepted that bypass operations have more powerful effects on T2DM than non-bypass operations, but there are few long-term studies demonstrating this difference.

The ultimate effects of metabolic changes of bariatric surgery on end-organ complications of T2DM such as diabetic nephropathy also require further study, particularly because some patients with initial remission of T2DM will have recurrence and this may affect the course of nephropathy over time.

The primary aim of this study was to assess long-term metabolic effects of bariatric surgery in a type 2 diabetic cohort of patients and to identify predictive factors for long-term diabetes remission and recurrence. The secondary aims were to compare the metabolic effects of different bariatric procedures and to assess the long-term effect of surgery on diabetes-related nephropathy in a subgroup of gastric bypass patients.

METHODS

After institutional review board approval was obtained, a retrospective review was conducted for all patients who underwent bariatric surgery at the Cleveland Clinic Bariatric and Metabolic Institute between January 2004 and December 2007; had the diagnosis

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Disclosure: No funding was received for this work. The authors declare no conflicts of interest.

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ISSN: 0003-4932/13/25804-0628

DOI: 10.1097/SLA.0b013e3182a5034b

of T2DM preoperatively; and had at least 5 years of follow-up with documentation of fasting blood glucose (FBG), A1C levels, and body weight. Other clinical parameters including obesity-related comorbidities and medication use were obtained for the 2 years before surgery until the most recent follow-up. Baseline values are taken from the time of surgery. Patients who underwent reoperative bariatric surgery including conversion and revisional and reversal procedures within the 5 years of the index operation were excluded. International patients who were not expected to follow-up in our program after the initial postoperative evaluation were also excluded. Patients who had not continued long-term follow up with our program were contacted by telephone, e-mail, and letter mail and asked to return for routine clinical evaluation and laboratory testing. For patients who were unable to return to our clinic, we coordinated follow-up care with their primary care physician and requested documentation from the visit. No patient-reported data were included in the analysis. Therefore, all data included in the analysis were obtained from a clinical visit in our department or from source documentation from the patient's primary physician. Patients were considered "lost to follow-up" if no current contact information was available or if they did not respond to multiple inquiries by phone, e-mail, or mail or if they were unable or unwilling to provide outcome data. Search by social security number was conducted to determine death in patients who were not contacted directly.

Short-term outcomes are defined as those clinical parameters recorded in the first 2 years after surgery, and *long-term outcomes* are defined as clinical parameters recorded more than 5 years after surgery. *Percent excess weight loss* (%EWL) was defined as [(operative weight – follow-up weight) / (operative weight – ideal weight)] × 100 with ideal weight based on body mass index (BMI) of 25 kg/m². *Percent total weight loss* was defined as (operative weight – follow-up weight / operative weight) × 100. To assess the effects of weight regain on recurrence of T2DM, *weight regain* was arbitrarily defined as an increase in BMI of 5 kg/m² or more above the weight loss nadir.

Definitions of T2DM remission and glycemic control used in this analysis are shown in Table 1. *Long-term remission* was defined as complete or partial remission at 5 years or more after surgery.

TABLE 1. Definitions of Glycemic Outcomes after Bariatric Surgery*

Outcome	Definition
Complete remission	Normal measures of glucose metabolism (A1C <6%, FBG <100 mg/dL) for 1 yr in the absence of antidiabetic medications.
Partial remission	Sub-diabetic hyperglycemia (A1C 6%–6.4%, FBG 100–125 mg/dL) for 1 yr in the absence of anti-diabetic medications.
Improvement	Significant reduction in A1C (by >1%) or FBG (by >25 mg/dL) OR reduction in A1C and FBG accompanied by a decrease in antidiabetic medication requirement (by discontinuing insulin or 1 oral agent, or 1/2 reduction in dose) for at least 1-yr duration.
Unchanged	The absence of remission or improvement as described earlier.
Recurrence	FBG or A1C in the diabetic range (≥126 mg/dL and ≥6.5%, respectively) OR need for antidiabetic medication after initial complete or partial remission.

*Criteria adapted from references 7 and 15.

Complete remission that continuously lasts for more than 5 years is operationally considered a "cure" on the basis of a 2009 ADA consensus statement.¹⁵ We attempted to obtain A1C, FBG, and diabetes medications status for all patients to determine the precise status of T2DM at short- and long-term follow-up. If we could not accurately determine the glycemic outcome for a patient because of missing data, we conservatively chose the worse outcome for that patient.

Control of other comorbidities was defined according to ADA criteria.⁵ *Hypertension control* is defined as systolic blood pressure (BP) less than 130 mm Hg and diastolic BP less than 80 mm Hg. Definitions of cholesterol and lipid control include LDL less than 100 mg/dL, high-density lipoprotein (HDL) more than 40 mg/dL in men, HDL more than 50 mg/dL in women, and triglycerides less than 150 mg/dL. Because of the retrospective nature of the data collection, we were unable to determine the precise indication for some nondiabetic medications (prophylactic, therapeutic, or other indication for a beta-blocker for example). Therefore, changes in BP and lipid-lowering medication were not analyzed and we used the definition of control according to ADA criteria with or without medication use. Framingham general cardiovascular risk score (10-year risk)¹⁶ was calculated at baseline and at the latest follow-up point.

Serum creatinine and random urinary albumin/creatinine ratio (uACR) were also evaluated to determine the long-term renoprotective effects of bariatric surgery. The *progression of diabetic nephropathy* was defined as an increase of 1 or more of the 3 stages of albuminuria: normo- (uACR <30 mg/g), micro- (uACR = 30–299 mg/g), and macroalbuminuria (uACR ≥300 mg/g). The use of angiotensin converting enzyme inhibitor and angiotensin II receptor blocker was analyzed for a subgroup of gastric bypass patients who had uACR data.

STATISTICAL ANALYSIS

Continuous variables with a normal distribution are presented as mean ± SD. Variables with a nonnormal distribution are reported as medians and interquartile ranges. Categorical variables are expressed as frequencies (%). Differences between groups were evaluated using parametric or nonparametric tests as appropriate (χ^2 test for categorical variables and analysis of variance with post hoc analysis or Kruskal-Wallis test for quantitative variables). A paired *t* test was used to analyze changes at the last follow-up point from baseline and *Z* test was utilized to compare 2 dependant proportions. Predictive factors of long-term remission and recurrence of T2DM were determined by multivariable logistic regression analysis. Receiver operating characteristic (ROC) curve analysis was performed to determine the cutoff value for predictive factors of outcomes, and the best cutoff was specified with Youden's *J* index. All analyses were performed using SPSS software, version 17.0 (SPSS Inc, Chicago, IL).

RESULTS

Of the 318 patients with T2DM who had bariatric surgery between 2004 and 2007, 18 reoperative bariatric surgery cases and 3 international patients were excluded on the basis of initial eligibility criteria. Of the remaining 297 eligible patients, 21 patients (7%) died during the study period and 59 (20%) were lost to follow-up. Therefore, data on 217 patients with a median follow-up of 6 years (range: 5–9) were included in the analysis.

Baseline characteristics of the patient population are shown in Table 2. The range of BMI, preoperative duration of T2DM, and A1C of the cohort was 32–73 kg/m², 1–30 years, and 5.1%–12%, respectively. Surgical procedures included RYGB (*n* = 162, 75%, laparoscopic in all except 4), laparoscopic adjustable gastric banding (LAGB, *n* = 32, 15%), and laparoscopic sleeve gastrectomy (LSG, *n* = 23, 10%). Gastric bypass patients were younger (*P* < 0.001)

and had shorter duration of T2DM than LAGB or LSG patients ($P = 0.004$).

Weight loss data are summarized in Table 3. Short-term and long-term EWL of the entire cohort were $60.3 \pm 24.3\%$ and $54.9 \pm 26.7\%$, respectively. EWL at the last follow-up point was 11% higher for RYGB (60.5%) than for LSG (49.5%, $P = 0.047$) and was 20% higher for LSG than for LAGB (29.5%, $P = 0.004$). The mean A1C decreased from $7.5\% \pm 1.5\%$ to $6.5\% \pm 1.2\%$ ($P < 0.001$) and mean FBG decreased from 155.9 ± 59.5 mg/dL to 114.8 ± 40.2 mg/dL ($P < 0.001$). Long-term changes in BMI and A1C are shown in Figure 1. Twenty-four percent of the cohort achieved long-term complete remission of T2DM, and another 26% achieved partial remission. Thirty-four percent of all patients had improvement in long-term diabetes control, and 16% of patients had long-term glycemic control that was unchanged or worse. Of those patients who initially achieved remission ($n = 127$), 19% had recurrence of their diabetes at long-term follow-up. Remission and recurrence rates according to procedure are shown in Figure 2. Among the surgical procedures, the glycemic outcomes were significantly better after RYGB [remission rate of T2DM after RYGB vs LSG ($P = 0.006$), RYGB vs LAGB ($P < 0.001$), and LSG vs LAGB ($P = 0.04$)]. Among the RYGB patients who achieved complete remission long-term, 27% had continuously maintained complete remission for over 5 years.

Overall, patients were taking fewer numbers of diabetic medications long-term ($P < 0.001$), fewer patients were requiring insulin therapy ($P < 0.001$), and the number of patients who were taking no diabetic medications increased ($P < 0.001$). Furthermore, among the subgroup of patients who did not achieve long-term remission, there was a significant reduction in the number of patients receiving insulin

compared with baseline (32% vs 53%, $P = 0.001$) and in the median number of diabetic medications used (1 vs 2, $P < 0.001$).

Results of multivariate regression analysis on clinical features associated with remission and recurrence of T2DM after surgery are shown in Table 4. All analyses were adjusted for baseline clinical characteristics including gender, age, BMI, A1C, FBG, achieving the ADA glycemic goal, and use of insulin. Predictors of diabetes remission (complete or partial) among the entire cohort were shorter duration of T2DM, greater %EWL at last follow-up, and undergoing gastric bypass compared to banding. On the basis of our analysis, the cutoff point of 5 years or less of diabetes duration was the best time point to predict remission (sensitivity 76%, specificity 79%, area under ROC curve = 0.82). Patients with T2DM duration of 5 years or less had a 76% long-term remission rate (complete or partial) compared with a 21% remission rate for patients with duration of T2DM more than 5 years. Because of low numbers of complete remission for LSG and LAGB patients, regression analysis for complete remission and diabetes recurrence was performed for gastric bypass only. Predictors of complete remission for gastric bypass patients were shorter duration of diabetes and greater %EWL at last follow-up. Predictors of diabetes recurrence was longer duration of T2DM, lower %EWL at last follow-up, and weight regain as previously defined (Table 4). In our analysis of recurrence, preoperative duration of diabetes 5 years or more was the best time point to predict recurrence among gastric bypass patients (sensitivity 67%, specificity 70%, area under ROC curve = 0.65).

Table 5 shows the rates at which our cohort achieved the ADA's A1C, BP, and cholesterol goals. Framingham 10-year cardiovascular risk scores at baseline and long-term follow-up are also shown in

TABLE 2. Baseline Characteristics of Patients

	Whole Cohort (<i>n</i> = 217)	Gastric Bypass (<i>n</i> = 162)	Sleeve Gastrectomy (<i>n</i> = 23)	Gastric Banding (<i>n</i> = 32)	<i>P</i>
Female, <i>n</i> (%)	159 (73)	120 (74)	17 (74)	22 (69)	0.82
Age, mean \pm SD, y	51.4 \pm 10.2	49.4 \pm 9.5	57.7 \pm 10.2	57.3 \pm 10.0	<0.001
BMI, mean \pm SD, kg/m ²	48.8 \pm 7.8	48.8 \pm 7.6	50.7 \pm 10.6	47.5 \pm 7.5	0.35
Duration of diabetes, median (IQR), y	6 (3–12)	5 (2–10)	10.5 (5–15)	8 (4–16)	0.004
Diabetes pharmacotherapy, <i>n</i> (%)	207 (95)	154 (95)	22 (96)	31 (97)	0.90
Use of insulin, <i>n</i> (%)	71 (33)	47 (29)	11 (48)	13 (41)	0.12
No. diabetes medications, median (IQR)	2 (1–2)	2 (1–2)	2 (1–3)	1.5 (1–3)	0.12
A1C, mean \pm SD, %	7.5 \pm 1.5	7.6 \pm 1.6	7.8 \pm 1.6	7.3 \pm 1.3	0.61
FBG, median (IQR), mg/dL	137 (113–188)	139 (114–194)	137 (106–172)	136 (99–188)	0.56
Hypertension, <i>n</i> /total (%)	165/218 (76)	122/162 (75)	17/23 (74)	26/32 (81)	0.75
Dyslipidemia,* <i>n</i> /total (%)	175/186 (94)	128/137 (93)	21/23 (91)	26/26 (100)	0.36

*Presence of LDL > 100 mg/dL, HDL in men < 40 mg/dL, HDL in women < 50 mg/dL, or triglycerides > 150 mg/dL. IQR indicates interquartile range.

TABLE 3. Weight Loss Data by Procedure Type

	Whole Cohort	Gastric Bypass	Sleeve Gastrectomy	<i>P1</i>	Gastric Banding	<i>P2</i>
Total weight loss (%)						
Short-term	27.6 \pm 10.1	30.9 \pm 8.3	21.2 \pm 10.6	<0.001	16.5 \pm 7.6	0.068
Long-term	25.4 \pm 11.9	28.1 \pm 10.9	22.2 \pm 9.3	0.015	13.2 \pm 10.7	0.002
EWL (%)						
Short-term	60.3 \pm 24.3	66.8 \pm 20.4	49.7 \pm 32.5	0.029	37.0 \pm 17.8	0.112
Long-term	54.9 \pm 26.7	60.5 \pm 24.6	49.5 \pm 24.9	0.047	29.5 \pm 23.4	0.004

All values are mean \pm SD.

Short-term: 1–2 yrs after surgery; Long-term: 5 yrs or more after surgery.

P1: gastric bypass vs sleeve gastrectomy; *P2*: sleeve gastrectomy vs gastric banding.

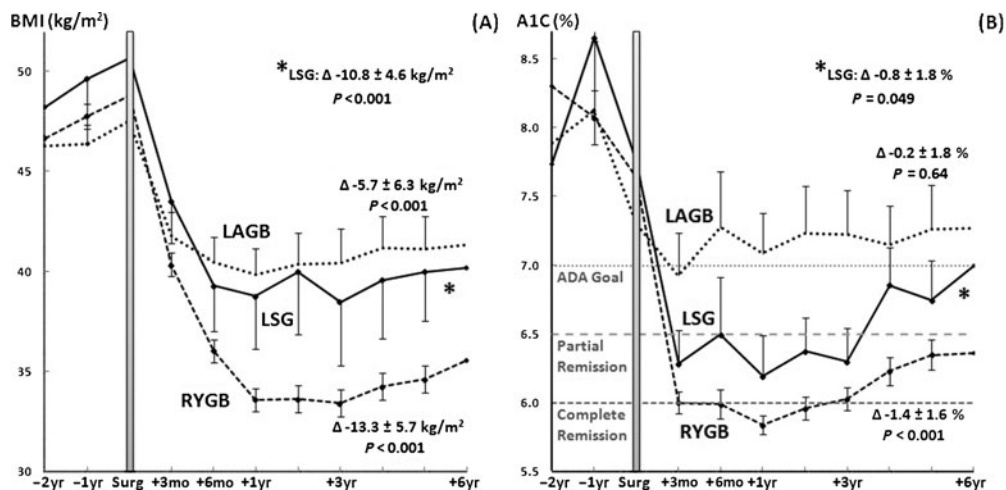


FIGURE 1. Changes in BMI (A) and A1C (B) according to procedure type. Δ: Mean ± SD at the last follow-up point—baseline at time of surgery.

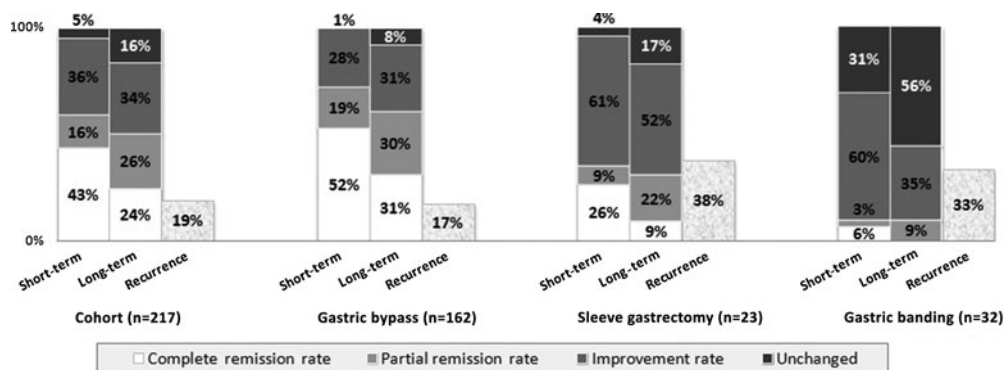


FIGURE 2. Short- and long-term diabetes remission and recurrence rates according to procedure type.

TABLE 4. Logistic Regression Analysis of Predictive Factors of Long-term Remission and Recurrence of T2DM After Bariatric Surgery*

	Remission of T2DM (Whole Cohort)		Complete Remission of T2DM (Gastric Bypass)		Recurrence of T2DM (Gastric Bypass)	
	Odds Ratio (95% CI)	P	Odds Ratio (95% CI)	P	Odds Ratio (95% CI)	P
Duration of T2DM, y	0.76 (0.7–0.9)	<0.001	0.8 (0.6–0.9)	<0.001	1.30 (1.02–1.6)	0.031
EWL at the last follow-up, %	1.03 (1.01–1.06)	0.006	1.02 (1.0–1.1)	0.044	0.93 (0.88–0.99)	0.023
Type of surgery (gastric bypass as reference)	For LAGB: 0.07 (0.01–0.73)	0.025	—	—	—	—
Weight regain after initial diabetes remission	—	—	—	—	12.74 (1.2–98.8)	0.015

*All analyses were adjusted for baseline clinical characteristics including gender, age, BMI, A1C, FBG, achieving the ADA glycemic goal, and use of insulin. CI indicates confidence interval.

Table 5. Overall, there was a 25% reduction in predicted cardiovascular risk over the course of the study. Figure 3 shows the mean changes in FBG, triglycerides, LDL, HDL, and BP for the entire cohort over the 6-year follow-up period.

The last follow-up data of patients with recurrence of T2DM (n = 24) was significantly improved from baseline values in terms of reduction in A1C (−1.1% ± 1.6%, P = 0.004); FBG (−35.6 ±

66.7 mg/dL, P = 0.02); number of diabetes medications (−1.0 ± 1.1, P < 0.001); use of insulin (0% vs 25%, P = 0.006); and achievement of ADA’s glycemic goal (75% vs 42%, P = 0.01), BP goal (57% vs 12%, P < 0.001), and LDL goal (84% vs 24%, P < 0.001).

Baseline and long-term data of serum creatinine and uACR were available on 59 patients after RYGB. In this subgroup, at a median follow-up of 6 years, a mean EWL of 61.1% ± 24.8% was

TABLE 5. Long-term and Short-term Metabolic Profile of Diabetic Patients After Bariatric Surgery

Metabolic Parameter	Baseline	Short-term	Long-term	P	
				Short-term vs Baseline	Long-term vs Baseline
American Diabetes Association goals					
A1C < 7%, n/total (%)	93/217 (43)	190/217 (88)	173/217 (80)	<0.001	<0.001
Gastric bypass, n/total (%)	66/162 (41)	151/162 (93)	139/162 (86)	<0.001	<0.001
Sleeve gastrectomy, n/total (%)	10/23 (43)	16/23 (70)	17/23 (74)	0.074	0.036
Gastric banding, n/total (%)	17/32 (53)	23/32 (72)	17/32 (53)	0.121	1.00
BP < 130/80 mm Hg, n/total (%)	37/217 (17)	90/182 (49)	130/209 (62)	<0.001	<0.001
LDL < 100 mg/dL, n/total (%)	84/163 (52)	92/130 (71)	114/158 (72)	0.001	<0.001
All the above 3 parameters, n/total (%)	6/212 (3)	45/168 (27)	53/187 (28)	<0.001	<0.001
HDL > 50 mg/dL in women and >40 mg/dL in men, n/total (%)	79/170 (46)	91/133 (68)	120/164 (73)	<0.001	<0.001
Triglycerides < 150 mg/dL, n/total (%)	71/171 (42)	107/133 (80)	129/162 (80)	<0.001	<0.001
Diabetes medications					
Number of drugs, median (IQR)	2 (1–2)	0 (0–1)	0 (0–1)	<0.001	<0.001
On Insulin therapy, n (%)	71 (33)	31 (14)	35 (16)	<0.001	<0.001
Without medication, n (%)	10 (5)	133 (61)	117 (54)	<0.001	<0.001
Framingham 10-yr cardiovascular risk score, mean ± SD	28.0 ± 18.1	—	21.6 ± 15.3	—	<0.001

associated with a significant reduction in A1C ($P < 0.001$), FBG ($P < 0.001$), systolic blood pressure ($P = 0.003$), and diastolic blood pressure ($P < 0.001$). Long-term remission and complete remission rate of T2DM was 47% and 24%, respectively. The proportion of patients who were taking angiotensin converting enzyme inhibitors or angiotensin II receptor blockers was comparable at baseline and follow-up (76% vs 63%, $P = 0.16$). Of the 40 normoalbuminuric patients at baseline, 2 developed albuminuria (5%) at follow-up. Of the 19 albuminuric patients (including 2 cases of macroalbuminuria) at baseline, diabetic nephropathy regressed in 10 (53%) and remained stable in 9 (47%) patients without any case of progression. Of the 2 macroalbuminuric patients at baseline, diabetic nephropathy resolved in 1 patient and albuminuria regressed to the microalbuminuria range in the other. The follow-up creatinine of this cohort was significantly lower than the baseline values with a mean difference of 0.05 ± 0.2 mg/dL ($P = 0.039$).

DISCUSSION

There is now a substantial body of evidence describing the short- and medium-term effects of bariatric surgery on T2DM, including 3 recent randomized trials.^{8,17,18} The percentage of patients who achieve T2DM remission after surgery in these studies depends on the type of procedure performed, the duration and severity of T2DM at the time of surgery, the length of follow-up, and, importantly, the definitions of remission and improvement used by the authors. There is generally agreement among the published studies that gastrointestinal bypass procedures achieve higher rates of remission than procedures involving restriction of the gastric fundus only and that patients who have long-standing T2DM or require insulin at the time of surgery have lower remission rates.^{7,19–22} Currently, though, there are relatively few studies reporting long-term T2DM remission rates after bariatric surgery and fewer still that report long-term biochemical evidence of remission (Table 6).

Our study reports durable weight loss in type 2 diabetic patients with an overall T2DM remission rate (complete and partial) of 50% with a median follow-up period of 6 years after bariatric surgery. Although the term “cure” with respect to T2DM is still controversial,

our study demonstrated that 24% of all patients and 31% of gastric bypass patients achieved long-term complete remission with an A1C less than 6.0% and that 27% of the gastric bypass patients sustained that level of glycemic control off medication continuously for more than 5 years. This level of long-term glycemic control represents a cure according to a consensus of ADA experts.¹⁵ An additional 34% of the entire cohort had improvement in their glycemic status as defined in Table 1.

Our data are consistent with others who have demonstrated that RYGB has a higher long-term rate of diabetes remission than restrictive procedures.¹⁴ Although there is evidence that sleeve gastrectomy is a metabolic operation with incretin effects resulting in excellent short-term diabetes control,^{20,23} long-term data on the metabolic effects of LSG are scarce. At a mean follow-up period of 73 months after LSG, Eid et al²⁴ reported 77% remission or improvement in diabetes of 35 patients, but long-term biochemical data were not reported and further studies are necessary with regard to the long-term effects of LSG on metabolic disease. Similarly, there are few long-term studies reporting biochemical evidence of T2DM remission after gastric banding.^{25,26} A study by Sultan et al²⁵ reported 5-year diabetes outcomes in 95 patients who had LAGB with a reduction of A1C from 7.5% to 6.6% and a complete remission rate of 40% among the 58 patients with long-term biochemical data. Buchwald et al's¹⁴ meta-analysis of diabetic patients undergoing bariatric surgery found an overall T2DM remission rate of 56.7% after LAGB with no difference in studies reporting more than 2 year follow-up.

The number of non-bypass procedures in our study was low, however, which makes it difficult to draw any definitive conclusions about these procedures. The lower numbers from that period in our program likely represent our limited use of the LSG because of insurance coverage at the time, the use of banding as a lower risk procedure in older patients with greater comorbidities and surgical risk, and a bias in our practice to recommend bypass procedures to diabetic patients. This selection bias, in part, is responsible for the lower remission and higher recurrence rates for those groups of patients. Moreover, in our study, patients who had gastric banding or sleeve gastrectomy were older and had a longer duration of T2DM,

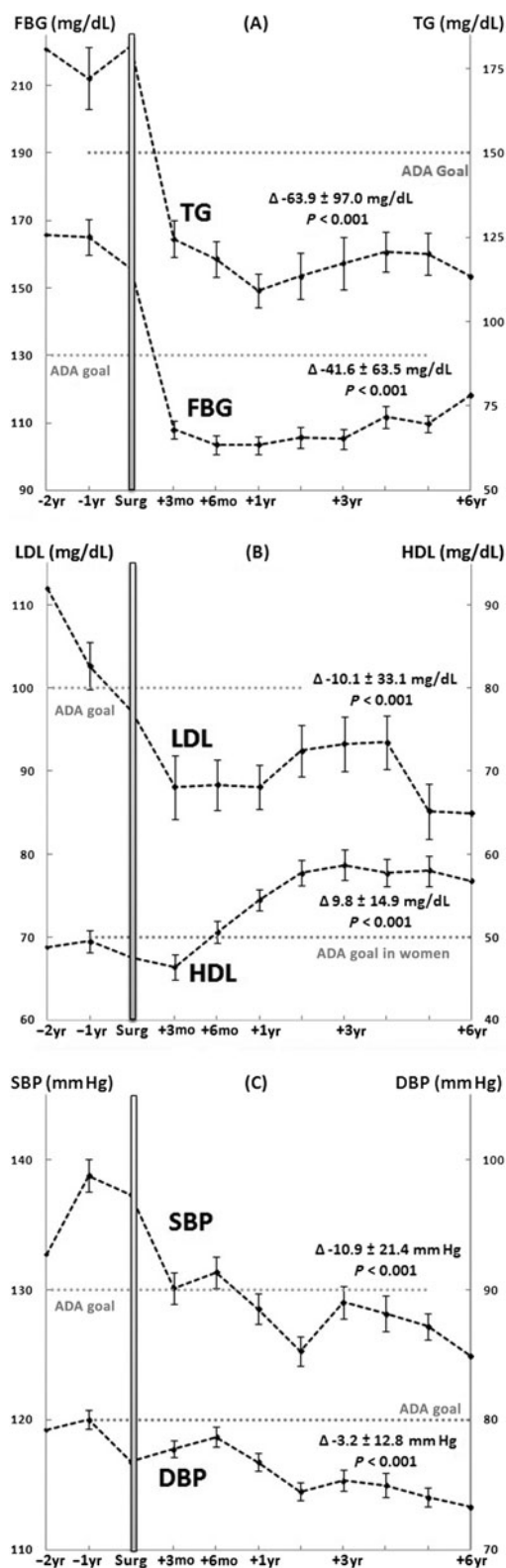


FIGURE 3. Long-term changes in triglycerides (TG) and FBG (A), LDL and HDL (B), and BP for the entire study cohort (C). Δ : Mean \pm SD at the last follow up point—baseline at time of surgery.

which may have accounted for the inferior glycemic outcomes with those restrictive operations as opposed to purely procedure-related factors.

A recent prospective study by Adams et al²¹ reported 6-year outcomes for 418 patients who underwent RYGB and compared outcomes with 2 nonsurgical groups. Between 2 years and 6 years after surgery, mean total weight loss in the surgical group changed from 35% to 28% and diabetes remission changed from 75% to 62% [93 patients (22%) of the surgical group was diabetic at baseline]. Despite a 7% weight regain over time and some recurrence of T2DM, these outcomes were significantly better than the nonsurgical control groups (417 patients who sought but did not receive bariatric surgery and 321 randomly selected population-based patients). Six-year remission rates for hypertension (42%), low HDL (67%), and high LDL (53%) were also significantly higher than the nonsurgical controls. Maintenance of diabetes remission is higher in Adams' study than our entire cohort (50% in our study overall for similar criteria of A1C < 6.5%, FBG < 126 mg/dL) but is the same as the remission rate among our gastric bypass patients (61%).

The recurrence rate in our RYGB group was 17%, which is lower than a recently published retrospective cohort study utilizing data from 3 integrated health care systems by Arterburn et al.²⁷ In that study, 4434 patients who underwent gastric bypass had an overall complete remission rate of 68% within 5 years of surgery (68% follow-up) and one third of those patients had recurrent diabetes. Predictors of relapse after remission were poor preoperative glycemic control, longer duration of diabetes, and insulin use. Our study demonstrated similar findings with respect to duration of diabetes but also found less weight loss and weight regain to predict recurrence. In our analysis, poor preoperative glycemic control and insulin use did not predict remission or recurrence of T2DM. There were relatively few patients in our study with very poor control (mean A1C of 7.5%, only 18% with A1C > 9%) compared with some other studies and this may explain why preoperative A1C was not predictive of remission.

Now that data are emerging showing long-term remission rates less than 80% as seen with short-term studies; it is important to address these remission and recurrence rates in terms of micro- and macrovascular endpoints. Large studies such as the United Kingdom Prospective Diabetes Study (UKPDS),²⁸ Diabetes Control and Complications Trial (DCCT), and Epidemiology of Diabetes Interventions and Complications (EDIC, long-term follow-up of DCCT patients)²⁹ trials have demonstrated a "legacy effect" after periods of tight glycemic control.³⁰ Continued long-term follow-up of patients after the trial periods ended demonstrated that glycemic differences between groups disappeared early after the trials ended. Despite this, treatment effects persisted with respect to the microvascular benefits and macrovascular benefits later emerged. Specifically, there was a reduced risk for any diabetes-related endpoint, long-term all-cause mortality and myocardial infarction (UKPDS) and a reduction in any cardiovascular event, myocardial infarction, stroke, or cardiovascular death (DCCT/EDIC) that were closely associated with intense glycemic control and A1C levels achieved during the studies.

Cardiovascular events and mortality are also reduced after bariatric surgery. The Swedish Obese Subjects (SOS) study is a large prospective, matched cohort study in which 2010 patients underwent bariatric surgery (most were vertical banded gastroplasty) and 2027 patients (contemporaneously matched according to 18 variables) received usual care in the community for weight and comorbidity management. At 10 years, the SOS study demonstrated a reduction in all-cause mortality,³¹ cardiovascular deaths, and first-time (fatal and nonfatal) cardiovascular events (myocardial infarction and stroke) in the surgery group.³² Among patients who had T2DM at their baseline examination for the SOS study, there was a significant reduction

TABLE 6. Long-term Bariatric Surgery Studies Reporting Biochemical Evidence of Type 2 Diabetes (T2DM) Remission

Author	Study Design	N Procedure	Follow-up Time (yr) and Rate (%)	A1C Definition of Complete Remission	Remission Rates
Adams et al ²¹	P	418 RYGB (93 T2DM) 417 nonsurgical obese control (106 T2DM) 321 population-based control (92 T2DM)	6 (93%) 6 (73%) 6 (97%)	<6.5%	62% complete 8% complete 6% complete
Sjostrom et al ³⁴	P	641 band, VBG, RYGB 627 matched controls	10 (75%) 10 (74%)	NR	36% 13%
Arterburn et al ³⁰	R	4434 RYGB	5 (68%)	<6.0%	68% complete 9% partial
Cohen et al ¹¹	P	66 RYGB	6 (100%)	<6.5%	88% complete 11% partial
Lakdawala et al ²²	P	52 RYGB	5 (100%)	<7.0%	58% complete 38% partial
Heneghan et al ³⁶	R	52 RYGB, LSG, LAGB	5 (NR)	<6.5%	44% complete 33% partial
Sultan et al ²⁸	R	95 LAGB	5 (85%)	<6.0%	40% complete 40% partial
Scopinaro et al ²³	R	312 BPD	10 (85%)	NR	97%
Pontiroli et al ²⁴	R	23 BPD 78 LAGB 37 Control	5.5 (NR)	NR	100% 66% None
Marceau et al ²⁵	R	1356 DS (377 T2DM)	7 (97%)	NR	92%
Brethauer et al (current study)	R	217 RYGB, LSG, LAGB	6 (79%)	<6.0%	24% complete 26% partial

BPD indicates biliopancreatic diversion; DS, duodenal switch; NR, not reported; P, prospective; R, retrospective; VBG, vertical banded gastroplasty.

in the number of myocardial infarctions at 13 years for the surgery cohort compared with the standard treatment group. This beneficial effect was strongest among patients who also had high cholesterol and triglycerides at their baseline examination.³³ It is important to recognize that the 2-year diabetes remission rate of 72% in the SOS study declined to a 36% remission rate at 10 years.³⁴ Despite this 50% recurrence rate of diabetes in the surgery group, there remained significant reductions in macrovascular events overall.

Although some would consider the recurrence of T2DM a failure, our data and others must be measured against the known risks of poorly controlled diabetes in patients who do not undergo bariatric surgery. Patients who experience long-term remission or improvement and those who have recurrence but benefit from the legacy effect of improved glycemic control provide support to look at these long-term results in a positive light. Our data suggest that, even for those patients who have recurrence of T2DM based on strict criteria, their glycemic control and cardiovascular risk is significantly improved compared with their baseline and the trajectory of these chronic conditions has been changed by surgery. In fact, 75% of patients in our cohort who had recurrence of T2DM still met the ADA goal of A1C less than 7%.

According to the most current National Health and Nutrition Examination Surveys (NHANES), 52% of patients with T2DM treated in the United States achieve the ADA's therapeutic goal of A1C less than 7.0%.⁵ Only 40% of patients in our study met that goal at baseline, but 80% met the goal at a median of 6 years after surgery (86% of the gastric bypass patients). In addition, long-term control of other cardiovascular risk factors in our study exceeds that of the general population. Sixty-two percent met the BP goal after surgery (vs 51% in NHANES) and 72% of our patients met the LDL goal (vs 56% in NHANES). Only 18.2% of patients in the NHANES study met all 3 goals (A1C, BP, and LDL), whereas 28% of the patients in our study met all 3 goals at long-term follow-up.

Long-term studies after bariatric surgery reveal the emergence of microvascular and macrovascular risk reduction.^{35–37} We have previously published our results in a different group of patients demonstrating the long-term renoprotective effect of bariatric surgery in diabetic patients.³⁶ Studies on incidence of diabetic nephropathy have reported an annual transition rate from normoalbuminuria to albuminuria between 2% and 4% per year. For instance, in a study by Gall et al,³⁸ the 5-year cumulative incidence of microalbuminuria was 23% and in the UKPDS trial, 38% of patients developed albuminuria after a median of 15-year T2DM duration.³⁹ Interestingly, only 5% of our diabetic patients developed albuminuria at a median of 6 years after RYGB (<1% per year). In addition, once microalbuminuria develops, there is a relatively greater chance of progression of kidney disease. For example, in one study 22% of patients with microalbuminuria developed proteinuria after 9 years.⁴⁰ In the Casale Monferrato Study with a median follow-up of 5.3 years, the annual rate of transition from microalbuminuria to proteinuria was 5.4% per year.⁴¹ In our patients with albuminuria at baseline, it regressed in 53% and remained stable in 47% of patients without any case of progression. Similarly, in a 10-year case-control study by Iaconelli et al⁴² in which surgical patients with recent onset T2DM underwent biliopancreatic diversion, all surgical patients recovered from microalbuminuria whereas microalbuminuria appeared or progressed to macroalbuminuria in matched control subjects. Our current results extend these findings and suggest a favorable effect of gastric bypass procedure on diabetic nephropathy rates.

The limitations of this study include its retrospective design, single-center experience, predominance of RYGB over restrictive procedures, lack of accurate cardiovascular medication data, and the loss to follow-up rate of 20%. A selection bias can occur because the group lost to follow-up might be associated with poorer weight loss and glycemic outcomes that were not included in analyses. However, generally, there is less reason for concern regarding validity of study

when the baseline characteristics, risk factors, and disease severities are similar between the group lost and the group completing the study.⁴³ We could demonstrate that demographics including diabetes duration and severity (A1C level, insulin dependency) did not differ significantly between study patients and patients lost to follow-up at baseline. Furthermore, the short-term outcomes after surgery in terms of weight loss and glycemic outcomes were comparable among the 2 groups (data not shown). On the basis of these findings, one can potentially assume that long-term outcomes would be comparable. In the worst case scenario, if any diabetic patient whose long-term glycemic data are missing is considered “unchanged or worse,” the long-term remission and improvement rate of T2DM for our study would be 39% and 26%, respectively, which still constitutes nearly two thirds of our cohort.

CONCLUSIONS

In summary, bariatric surgery can induce a significant and sustainable remission and improvement of T2DM and other metabolic risk factors in severely obese patients. The criteria for T2DM cure was met in 27% of gastric bypass patients. Surgical intervention within 5 years of diagnosis is associated with a high rate of long-term remission.

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DISCUSSANTS

W.J. Pories (MacClesfield, NC):

I want to point out that this is a really important contribution. And let me explain that assessment.

Even in ancient India, it was known that if somebody's urine was sweet, so sweet that it attracted flies, that patient would die, all too often blind with failed kidneys. Since then, despite the great advances in the therapy of type 2 diabetes, with newer drugs and more expensive insulins, the morbidity and mortality for the disease continues to explode, with a doubling of the disease over the last decade.

Today, in the United States, one out of every 4 adults older than 65 years has diabetes. One would have thought that our medical colleagues would have been ecstatic at the news that an operation on the gut, a safe procedure that can be performed in about an hour, could produce full and durable remission of diabetes, with complete prevention of amputations, blindness, and kidney failure.

But that was not the case. All we heard were cries for more evidence, more evidence. We've got to have the evidence.

And for the members who are not in bariatric surgery, let me point out that your group, headed by Dr Schauer, provided that evidence, typed and solid, in a prospective randomized trial published in the *New England Journal of Medicine* in April that provided clear proof that surgery was far superior to medical therapy.

Today's paper adds even more proof. Not only does it work, but it works 5 years later. It is not totally new. We reported good results in 10 years. The Swedish colleagues reported at 20 years. But your paper was far more elegant and far more detailed.

So, my first question is, why would you choose a cutoff of 6.0 for A1C when the American Diabetes Association considers 7 as their cutoff point? If you accepted their metric, your results would show that even after 5 years 84% of the patients were either cured or improved, with only 16% unchanged. Furthermore, if you had limited the review to gastric bypasses, instead of diluting with bands and sleeves, the outcomes would be even better. By any measure, you provided even more valuable evidence.

My second question is, is it not time for our medical colleagues to show us their evidence?

Response from S.A. Brethauer (Cleveland, OH):

In terms of the cutoff point that we used for the study, there are authors who use 6.5 and some that even use 7 in their publications to define remission rates. I think when we raise this issue of cure, which is still quite controversial and somewhat provocative, particularly with our endocrinology colleagues, we must find the strictest and most conservative criteria that we can try to make our point, and be as granular as possible in how we present our data.

We had some guidance from the 2009 ADA consensus statement that defined what would operationally be considered a cure of diabetes, which is complete remission with an A1C less than 6 for a duration of more than 5 years.

So, when we posed the question of cure for the study, we used that criteria and demonstrated that we are able to achieve that in some of our patients.

In terms of the different operations, I agree that gastric bypass patients did do well. And we know there are certainly different

outcomes with different procedures in terms of diabetes. I think that the large difference in our study may in part be due to the selection bias. In 2004 to 2007, we used the band and the sleeve somewhat differently than we do now.

In terms of the sleeve, we did not have widespread insurance coverage. And we were still thinking of it more as a staging procedure for higher risk, higher BMI patients, not so much as a diabetic or metabolic operation. The band was frequently used as a low-risk operation for higher risk and older patients who may not have been the best candidates for this operation as it turns out.

I think the way we would use those operations has changed over time. Therefore, we need to continue to look at long-term results in terms of the types of patients who are undergoing these operations now.

I agree with you completely that we need to continue to provide data to support the concept that this is a surgically treated disease. It is a major paradigm shift for our endocrinology colleagues to accept. And I think it is going to require time and a new generation of endocrinologists before they fully embrace this. But I think we have to keep working on it and provide high-quality data. I could not agree with you more that we need to see some data from their side to provide any sort of counterpoint to what we are providing.

DISCUSSANTS

W.O. Richards (Mobile, AL):

This is a study that I think is incredibly important as we go forward for surgical treatment of type 2 diabetes.

I have one comment and several questions. It looks like the changes in HgBA1c closely follow the weight loss, and recurrence of diabetes closely follows weight regain.

So, I question if you have any evidence that gastric bypass in particular increases insulin secretion or works through other modalities other than just the weight loss in these patients to affect the diabetes? Is it something more than just the caloric restriction and the weight loss?

In our own clinic, we carefully look at body composition of fat and muscle mass in our postoperative patients. Do you have any evidence to show that the patients that really do well with the diabetes lose more fat mass while maintaining their lean muscle mass?

Do you have any evidence to show that insulin resistance is changed?

Response from S.A. Brethauer (Cleveland, OH):

In terms of the mechanisms that play here, we know there are weight-loss independent mechanisms that improve glycemic control after gastric bypass and these are absent or exist to a lesser degree after non-bypass procedures. There are certainly incretin effects with gut hormone production, GLP1, and probably a lot of incretin effects that we do not fully understand related to bypassing the foregut. In this retrospective study, though, we did not provide any mechanistic data.

In terms of body composition in this particular study, we have no evidence to support the effect of body composition changes related to changes in glycemic control. Those types of data are coming from other prospective mechanistic studies.

We have recently reported that with gastric bypass compared with the sleeve gastrectomy, in a subgroup of the Stampede trial, that we are seeing decreases in truncal fat in the gastric bypass patients, which exceeds that after a sleeve gastrectomy. And that, along with the known incretin effects, may certainly increase the diabetes remission rate and improved glycemic control in the gastric bypass compared with a restrictive operation.

We did not present any data in this retrospective study on insulin resistance, but that is something that we are looking at in our prospective studies. I think it is important, particularly when we are talking to endocrinologists, that we provide that type of data as well.

DISCUSSANTS

L.E. Ratner (New York, NY):

My question pertains to your looking at the diabetic nephropathy. Not surprisingly, you saw a decrease in the creatinine. But did you just look at creatinine clearance, or glomerular filtration rate (GFR), and did you see any improvement there?

Response from S.A. Brethauer (Cleveland, OH):

We did not delve any deeper than what I presented in terms of other functional studies of renal function. That is an excellent point. It is something we should look at in terms of focusing more on the microvascular effects of these operations. But, we clearly showed that we have arrested or even improved some of these nephropathy patients who we would expect to have progressed over time. So, I think your point is excellent, and we can certainly start looking at some of these issues in a more detailed way.

DISCUSSANTS

S.G. Mattar (Indianapolis, IN):

I would like to focus on your sleeve population. Your results for the sleeve gastrectomy will not reassure proponents of the sleeve gastrectomy. I wonder if, during the course of the study, was the sleeve gastrectomy operation itself in evolution, or did you have a standardized method of constructing your gastric tube?

Response from S.A. Brethauer (Cleveland, OH):

I do not think there have been any major changes in how we have done the sleeve gastrectomy since that time. We do it using an endoscope for calibration. We oversee the staple line. And that has not changed since 2004. So, our study did not encompass a period of time where we started with a larger bougie and then continued over time to make it tighter.

I think the technique is consistent throughout the course of this study. What I do not think is the same is the patient selection. We are doing more sleeves now as primary operations. There is some evidence to suggest the sleeve gastrectomy has metabolic effects and some L-cell stimulation. So, we do consider the sleeve a metabolic operation, although we do not consider it as powerful a tool in fighting diabetes as the gastric bypass, as evidenced in some of our other studies.