CLIN CARE/EDUCATION/NUTRITION/PSYCHOSOCIAL

Late Relapse of Diabetes After Bariatric Surgery: Not Rare, but Not a Failure

Diabetes Care 2020;43:534–540 | https://doi.org/10.2337/dc19-1057

Ali Aminian,[1] Josep Vidal,[2,3,4] Paulina Salminen,[5,6,7] Christopher D. Still,[8] Zubaidah Nor Hanipah,[1,9] Gautam Sharma,[1] Chao Tu,[10] G. Craig Wood,[8] Ainitze Ibarzabal,[2] Amanda Jimenez,[2,4,11] Stacy A. Brethauer,[1,12] Philip R. Schauer,[1,13] and Kamal Mahawar[14]

OBJECTIVE

To characterize the status of cardiometabolic risk factors after late relapse of type 2 diabetes mellitus (T2DM) and to identify factors predicting relapse after initial diabetes remission following bariatric surgery to construct prediction models for clinical practice.

RESEARCH DESIGN AND METHODS

Outcomes of 736 patients with T2DM who underwent Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) at an academic center (2004–2012) and had ≥5 years' glycemic follow-up were assessed. Of 736 patients, 425 (58%) experienced diabetes remission (HbA_{1c} <6.5% [48 mmol/mol] with patients off medications) in the 1st year after surgery. These 425 patients were followed for a median of 8 years (range 5–14) to characterize late relapse of diabetes.

RESULTS

In 136 (32%) patients who experienced late relapse, a statistically significant improvement in glycemic control, number of diabetes medications including insulin use, blood pressure, and lipid profile was still observed at long-term. Independent baseline predictors of late relapse were preoperative number of diabetes medications, duration of T2DM before surgery, and SG versus RYGB. Furthermore, patients who relapsed lost less weight during the 1st year after surgery and regained more weight afterward. Prediction models were constructed and externally validated.

CONCLUSIONS

While late relapse of T2DM is a real phenomenon (one-third of our cohort), it should not be considered a failure, as the trajectory of the disease and its related cardiometabolic risk factors is changed favorably after bariatric surgery. Earlier surgical intervention, RYGB (compared with SG) and more weight loss (less late weight regain) are associated with less diabetes relapse in the long-term.

Bariatric surgery has now found a place in the algorithm of management of type 2 diabetes mellitus (T2DM) (1). At the same time, earlier suggestions that bariatric surgery might offer a permanent cure (2) for T2DM have had to be moderated as it became apparent that not all patients with T2DM experience a remission with bariatric surgery (3,4) and that a large number of those who experience a remission in the early period after surgery suffer a relapse on longer-term follow-up even with highly effective procedures such as biliopancreatic diversion (5,6).

[1]Bariatric and Metabolic Institute, Department of General Surgery, Cleveland Clinic, Cleveland, OH
[2]Obesity Unit, Hospital Clínic de Barcelona, Barcelona, Spain
[3]CIBER de Diabetes y Enfermedades Metabólicas Asociadas, Instituto de Salud Carlos III, Madrid, Spain
[4]Institut d'Investigacions Biomèdiques August Pi Sunyer, Barcelona, Spain
[5]Department of Surgery, University of Turku, Turku, Finland
[6]Division of Digestive Surgery and Urology, Turku University Hospital, Turku, Finland
[7]Satasairaala Central Hospital, Pori, Finland
[8]Obesity Research Institute, Geisinger Clinic, Danville, PA
[9]Department of Surgery, University Putra Malaysia, Selangor, Malaysia
[10]Department of Quantitative Health Sciences, Lerner Research Institute, Cleveland Clinic, Cleveland, OH
[11]Centro de Investigación Biomédica en Red de la Obesidad y la Nutrición (CIBEROBN), Instituto de Salud Carlos III, Madrid, Spain
[12]Department of Surgery, The Ohio State University Wexner Medical Center, Columbus, OH
[13]Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, LA
[14]Department of General Surgery, Sunderland Royal Hospital, Sunderland, U.K.

Corresponding author: Ali Aminian, aminiaa@ccf.org

Received 26 May 2019 and accepted 21 December 2019

This article contains Supplementary Data online at https://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc19-1057/-/DC1.

This article is featured in a podcast available at https://www.diabetesjournals.org/content/diabetes-core-update-podcasts.

Though relapse of T2DM after an initial remission following bariatric surgery is now well recognized (7–10), its exact incidence is difficult to comprehend, as most studies report outcomes on the total cohort and do not focus on only those patients who experienced an early remission. In addition, the severity of T2DM after late relapse is largely unknown. It is further known that bariatric surgery improves metabolic profile including lipid panel and blood pressure (3,4,6,8–12) in patients with diabetes, but the effect on lipid profile and hypertension in patients who experience a relapse of T2DM has not yet been adequately examined. It is therefore unclear whether these patients also experience a gradual reduction in other metabolic benefits, which would potentially diminish the long-term benefits of bariatric surgery in these individuals.

Similarly, there are some data to suggest that those with poor preoperative diabetes control, those with longer duration of T2DM, and those requiring insulin at the time of surgery—the clinical factors indicating diminished pancreatic β-cell reserve—are less likely to experience durable long-term remission (7,8,13). But we do not exactly know whether these factors can predict relapse. The predictors of diabetes relapse have been less well characterized. It is important to be able to predict relapse after an initial remission of T2DM to counsel patients accordingly, encourage closer monitoring, and institute appropriate medical management if and when needed in the long-term. Furthermore, the impact of late weight regain that can be seen several years after bariatric surgery in many patients on relapse of T2DM is not clear.

The purpose of this study was to determine the incidence of relapse of T2DM after initial remission following bariatric surgery at a high-volume academic center, characterize the status of metabolic profile and cardiovascular risk factors in these patients after late relapse, and identify factors predicting relapse of T2DM to construct and validate prediction models for clinical practice.

RESEARCH DESIGN AND METHODS

The institutional review board approved this retrospective study as minimal risk research and permitted us to conduct the study without obtaining the informed consent from patients. All patients with T2DM who underwent primary Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) at an academic center (Cleveland Clinic Main Campus, Cleveland, OH) between 2004 and 2012 were identified. Only patients with complete and documented baseline data who also had at least 5 years' postsurgery follow-up including data on body weight, fasting blood glucose (FBG), HbA_{1c} levels, and status of diabetes medications were included in this study. Patients who had reoperative bariatric surgery for conversion of SG to RYGB, conversion of SG to duodenal switch, or conversion of RYGB to distal gastric bypass with shortening of the common channel were excluded. Patients who died within the initial 5 years after the index procedure and international patients who were not expected to have a long-term follow-up at Cleveland Clinic were also not included in the analysis.

All outcome data included in the analysis were obtained from the electronic medical records from a clinical visit in Cleveland Clinic or from source documentation from the patient's primary physician. Data on body weight, BMI, diabetes status, blood pressure, lipid panel, and diabetes medications were extracted from the preoperative period until the most recent follow-up.

Diabetes status following bariatric surgery was characterized according to the definitions developed by the American Diabetes Association (14) and the American Society for Metabolic and Bariatric Surgery (15). Diabetes remission was defined as HbA_{1c} <6.5% (48 mmol/mol), FBG <126 mg/dL, and being off diabetes medications (3,4,14,15). Long-term remission was defined as meeting the criteria for remission at the last follow-up time, which was at least 5 years after surgery. According to the American Diabetes Association criteria, HbA_{1c} <7% (53 mmol/mol), irrespective of diabetes medications, was considered to indicate glycemic control. Percent total weight loss (TWL) was calculated as ([operative weight − follow-up weight]/operative weight) × 100. Late weight gain was assessed by ([weight 1st year after surgery − last follow-up weight]/weight 1st year after surgery) × 100. Values >5% were arbitrarily defined as significant late weight regain.

To characterize the subset of patients who developed late diabetes relapse, we first identified a group of patients who met the criteria for diabetes remission within the 1st year of surgery. These patients were then followed up to characterize late relapse of T2DM, which was defined as FBG or HbA_{1c} in the diabetes range (≥126 mg/dL and ≥6.5% [48 mmol/mol], respectively) or need for antidiabetes medication after initial remission.

Statistical Analysis

Categorical variables were presented as frequencies (%). Continuous variables with normal and nonnormal distributions were presented as mean ± SDs and median (interquartile range [IQR]), respectively.

To assess the metabolic status of patients who developed late diabetes relapse, a paired *t* test and Wilcoxon signed rank test were used to calculate the differences between the last follow-up point and baseline at the time of surgery. Two dependent proportions were compared with *Z* test.

All tests were two tailed and performed at a significance level of 0.05. Odds ratio (OR) and 95% CI were used as measures of the magnitude of the association. R software, version 3.5.0 (Vienna, Austria), was used for all analyses for this study.

Main Prediction Model

Independent baseline (before surgery) predictive factors of late relapse of T2DM were determined by multivariable logistic regression analysis. Univariate analysis (using χ^2, Fisher exact, and two-sample *t* tests) was performed to compare eight baseline characteristics in patients who developed late diabetes relapse compared with patients who stayed in diabetes remission long-term. Factors considered in univariate analysis included sex, age, known duration of T2DM before surgery, baseline BMI, HbA_{1c}, number of diabetes medications, insulin use, and type of bariatric surgery performed (RYGB vs. SG). Multivariable logistic regression models with stepwise variable selection were built to identify the independent predictors of diabetes relapse. Backward elimination was used to remove insignificant variables. The discriminatory capability of the model was assessed using the c-statistic, which is the same as the area under the receiver operating characteristic curve. The c-statistic with bootstrapping technique (internal validation) was also calculated.

With use of the same enrollment criteria and outcomes definitions, a validation cohort was assembled by pooling the data from three external sources:

1) Hospital Clínic de Barcelona, *2*) patients with T2DM who were enrolled in the Sleeve vs Bypass (SLEEVEPASS) randomized clinical trial (16) from Finland, and *3*) patients from Geisinger Clinic in Danville, PA. Since the suggested minimum requirement for external validation is having at least 100 patients with the event (i.e., diabetes relapse) (17), data of three cohorts were combined to prevent possible overestimation of model performance by examining smaller cohorts individually.

The regression equation of the prediction model was programmed to construct an online version of the diabetes relapse calculator based on preoperative risk factors.

Second Prediction Model

To account for the effects of weight changes after bariatric surgery on late diabetes relapse, a second prediction model was developed utilizing the statistical methods described above. In the second prediction model, in addition to eight baseline variables (above), the role of percent weight loss within the 1 year after surgery and late weight regain (>5% weight gain from weight recorded at 1 year after surgery) were examined in multivariable logistic regression analysis. The second calculator was constructed, which can be used 1 year after surgery to predict late diabetes relapse utilizing both preoperative and weight change data.

RESULTS

Outcomes of 736 patients with T2DM who underwent primary RYGB or SG between 2004 and 2012 had ≥5 years' glycemic follow-up and who met other enrollment criteria (representing 80% of patients who would have been available for long-term follow-up) were assessed. Of 736 patients, 425 (58%) experienced diabetes remission in the 1st year after surgery including 62% after RYGB and 41% after SG.

The median postoperative follow-up time of the entire cohort was 8 years (range 5–14). The median postoperative follow-up time after RYGB was 8 years (IQR 6–9) and after SG was 8 years (IQR 5–9). Of those 425 patients who initially achieved diabetes remission in the short-term (Supplementary Table 1), 136 (32%) later relapsed with T2DM.

In patients who experienced late relapse (n = 136), statistically significant improvement in metabolic profile was still observed long-term compared with baseline values before surgery (Table 1). Despite experiencing diabetes relapse, 77% of them maintained adequate glycemic control (HbA_{1c} <7%), with a median HbA_{1c} of 6.4% (IQR 6.0–6.8) (46 mmol/mol [IQR 42–51]). A statistically significant reduction in the number of diabetes medications (median of 2 before surgery vs. 1 long-term, $P < 0.001$) and percentage of patients on insulin (29% before surgery vs. 12% long-term, $P < 0.001$) was observed. Similarly, there was a statistically significant improvement in systolic and diastolic blood pressure, LDL, HDL, and triglycerides compared with the baseline values before surgery.

Predictors of late diabetes relapse from univariate and multivariate analyses have been summarized in Tables 2 and 3, respectively. Independent baseline predictors of late relapse were preoperative number of diabetes medications (OR 2.04 [95% CI 1.54, 2.71], $P <$ 0.001), known duration of T2DM before surgery (OR 1.08 [95% CI 1.02, 1.14], $P =$ 0.005), and SG versus RYGB (OR 2.21 [95% CI 1.22, 4.01], $P = 0.009$) (Table 3).

Characteristics of external cohorts (Spain, 34.7% late diabetes relapse out of n = 196 with initial remission; U.S., 23.2% late relapse out of n = 82 with initial remission; and Finland, 31.7% late relapse out of n = 41 with initial remission) have been detailed in Table 2 and Supplementary Tables 2–4.

The c-statistics for the main model, bootstrapping validation, and external validation were 0.75, 0.74, and 0.73, respectively. The calibration curve on the external validation data suggested great accuracy (Supplementary Fig. 1).

The second model considers the impact of early weight loss and late weight regain on remission and relapse of T2DM. Patients with late relapse of T2DM lost less weight in their 1st year after bariatric surgery compared with patients who had durable diabetes remission (mean difference in weight loss ± SD 3.9 ± 0.8%, $P < 0.001$). In addition, patients with late relapse of T2DM had significantly higher weight gain long-term (11.6 ± 14.9%) compared with patients without late relapse (6.5 ± 15.5%, $P < 0.001$) (Supplementary Tables 5 and 6). Late weight gain was observed in 59% of the cohort. In model two, independent predictors of late relapse were preoperative number of diabetes medications, duration of T2DM before surgery, less weight loss in the 1st year after surgery, and greater late weight regain (Table 3). The model had a very good discrimination ability (c-statistic = 0.80 and bootstrap validation c-statistic = 0.79).

On the basis of the regression equations and the parameter estimates, two risk calculators for late relapse were developed. A free user-friendly version of the scoring systems is accessible at https://riskcalc.org/ and as a smartphone application (BariatricCalc, available on the Apple Store and Google Play). When the required values are entered into the calculator, the percent estimate of late relapse of T2DM following initial remission after bariatric surgery is calculated. The first model includes the preoperative factors only. However, in the second

Table 1—Long-term metabolic profile of post–bariatric surgery patients with late relapse of diabetes following initial remission (n = 136)

Variable	Baseline	Long-term	P
HbA_{1c} (%)	7.2 (6.3–8.7)	6.4 (6.0–6.8)	<0.001
HbA_{1c} (mmol/mol)	55 (45–72)	46 (42–51)	<0.001
Glycemic target*	52 (38.2)	103 (76.9)	<0.001
FBG (mg/dL)	138.5 (113.0–168.7)	114.0 (96.0–133.2)	<0.001
LDL (mg/dL)	93.7 ± 34.4	85.9 ± 31.7	0.031
HDL (mg/dL)	44.4 ± 11.2	56.9 ± 17.5	<0.001
Triglycerides (mg/dL)	156.0 (97.5–211.0)	98.5 (69.0–142.7)	<0.001
Systolic BP (mmHg)	134.2 ± 18.3	128.5 ± 15.3	0.003
Diastolic BP (mmHg)	77.3 ± 10.7	73.9 ± 9.5	0.004
Number of diabetes drugs	2 (1–3)	1 (1–1)	<0.001
On insulin therapy	40 (29.4)	16 (11.8)	<0.001

Data are median (IQR), mean ± SD, or n (%). BP, blood pressure. *Defined as HbA_{1c} <7% (53 mmol/mol), irrespective of diabetes medications.

Table 2—Univariate analyses in patients with and without diabetes relapse following initial remission after bariatric surgery in training and validating cohorts

	Cleveland Clinic cohort (n = 425)			Three external cohorts (n = 319)		
Baseline characteristics	Long-term diabetes remission	Late diabetes relapse after initial remission	P	Long-term diabetes remission	Late diabetes relapse after initial remission	P
N	289	136		219	100	
Female	205 (70.9)	90 (66.2)	0.38	148 (68.0)	70 (70.0)	0.82
Age (years)	49.9 ± 10.4	51.1 ± 9.4	0.25	49.8 ± 8.8	51.3 ± 9.5	0.20
BMI (kg/m^2)	47.7 ± 8.3	45.2 ± 9.0	0.005	48.0 ± 7.8	46.4 ± 6.1	0.046
Duration of diabetes (years)	4.2 ± 3.9	7.0 ± 5.0	<0.001	3.8 ± 2.7	6.3 ± 4.0	<0.001
Number of diabetes medications	1.4 ± 0.8	2.0 ± 0.9	<0.001	1.3 ± 0.8	1.9 ± 1.0	<0.001
Insulin use	39 (13.5)	40 (29.4)	<0.001	17 (7.8)	29 (29.3)	<0.001
HbA_{1c} (%)	7.0 ± 1.3	7.7 ± 1.6	<0.001	6.4 ± 1.0	7.6 ± 1.5	<0.001
HbA_{1c} (mmol/mol)	53 ± 14.2	61 ± 17.5	<0.001	46 ± 10.9	60 ± 16.4	<0.001
Type of surgery			0.053			0.040
SG	37 (12.8)	28 (20.6)		75 (34.2)	47 (47.0)	
RYGB	252 (87.2)	108 (79.4)		144 (65.8)	53 (53.0)	

Data are mean ± SD or n (%).

model, weight changes after bariatric surgery are among the independent predictors.

Below are two examples of the estimated probability of late relapse of T2DM after initial remission:

- Model 1: The estimated risk of relapse in a patient with T2DM for 5 years before bariatric surgery and on one diabetes medication would be 20% after RYGB and 36% after SG.
- Model 2: The estimated risk of relapse in a patient with T2DM for 10 years and on two diabetes medications before bariatric surgery who initially lost 30% of weight in 1 year after surgery would be 28% and 59% without and with significant long-term weight regain (>5% weight gain), respectively.

CONCLUSIONS

Over the last few years, it has become apparent that a large proportion of patients with T2DM who initially go into remission following a bariatric surgery experience a late relapse. As early as 2010, DiGiorgi et al. (18) and Chikunguwo et al. (19) observed that T2DM recurred or worsened from peak benefits in ~24% and 43% of their patients, respectively. New-onset T2DM after bariatric surgery has also been reported (20,21) in the scientific literature.

More recently, Arterburn et al. (7), in a large population-based study, examined 2,254 patients who experienced initial remission after RYGB. They found that 35% of their patients relapsed within 5 years of complete remission. The relapse rates of 32% in our primary cohort and 31% in external cohorts are similar to

Table 3—Independent predictors of late relapse of diabetes after bariatric surgery in multivariable analyses

	Main model*			Second model*		
Predictors	OR	95% CI	P	OR	95% CI	P
Preoperative number of diabetes medications	2.04	(1.54, 2.71)	<0.001	2.13	(1.58, 2.87)	<0.001
Preoperative duration of diabetes (years)	1.08	(1.02, 1.14)	0.005	1.10	(1.03, 1.16)	0.002
Type of surgery (SG vs. RYGB)	2.21	(1.22, 4.01)	0.009	—	—	—
Weight loss at 1 year (%)	—	—	—	0.92	(0.89, 0.95)	<0.001
Late weight regain#	—	—	—	3.69	(2.18, 6.24)	<0.001

	Main model*	Second model*
Multiple logistic regression equation^	L = −2.4917 + (0.0789 × preoperative duration of diabetes) + (0.714 × preoperative number of diabetes medications) + (0.7929 × [1, for SG, or 0, for RYGB])	L = −0.729 + (0.0919 × preoperative duration of diabetes) + (0.7565 × preoperative number of diabetes medications) − (0.0877 × short-term weight loss) + (1.3059 × [1, for late weight regain, or 0, for no weight regain])

*Main model to be used before surgery to predict late diabetes relapse based on preoperative characteristics; second model to be used 1 year after bariatric surgery to predict late relapse based on preoperative characteristics and weight changes. #Categorical variable defined as >5% weight regain from the weight recorded 1 year after bariatric surgery. ^Estimated probability of late relapse of diabetes after initial remission for a given patient (100%) = EXP [L]/(1 + EXP [L]). The notation EXP is equivalent to ex, where "e" is the base of the ln (2.718).

the findings of that study. In the Swedish Obese Subjects (SOS) study, of 342 patients with T2DM before bariatric surgery, 72% experienced diabetes remission at 2 years after surgery but only 36% remained diabetes free at 10-year follow-up (50% relapse rate) (10,22). The relatively higher relapse rate in the SOS study could be explained by the higher number of surgical procedures, which are less effective in improving T2DM. More than 85% of surgical procedures at that time in the SOS study were either vertical banded gastroplasty or gastric banding—the procedures that have fallen out of favor in recent years. In the Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial, out of 32 surgical patients (RYGB and SG) who initially met the study's end point (HbA_{1c} <6% [42 mmol/mol] without diabetes medications), 47% were not at this target 5 years after surgery (9).

The most frequently identified predictors of relapse in the scientific literature were signs of advanced T2DM at the time of surgery (23,24). Having a longer duration of T2DM before surgery, poorly controlled T2DM, or being on multiple glucose-lowering agents and insulin are all clinical factors that would reflect limited pancreatic β-cell reserve at baseline. In the investigations by Jiménez et al. (25,26), those experiencing a relapse had poorer β-cell function in comparison with those maintaining a durable remission. The independent baseline variables found to be significantly associated with late relapse on multivariate analysis in the current study were the preoperative number of diabetes medications, preoperative duration of T2DM, and type of bariatric surgery (SG vs. RYGB).

We also found higher short-term and long-term weight loss in patients with durable diabetes remission compared with patients with late relapse. Furthermore, we found that patients with late relapse of T2DM had significantly higher weight regain in the long-term compared with those without relapse. These observations mirror findings by Debédat et al. (13), who found that patients who relapsed with T2DM after 5 years exhibited more severe diabetes at baseline, lost significantly less weight during the 1st year after RYGB, and regained more weight afterward. Since postoperative weight trajectories of patients with durable remission and late relapse of T2DM were significantly different, we constructed a second prediction model to highlight the impact of weight loss on long-term diabetes status. Addition of weight change data could improve the c-statistic of the prediction model (from 0.75 to 0.80). Interestingly, with inclusion of weight trajectory data as independent predictive variables in the second model, type of surgical procedures (RYGB and SG) was no longer a significant predictor on multivariable analysis.

The prediction models would assist in shaping patient expectations, informed consent process, decision-making, and evidence-based bariatric procedure selection. Our first model can be used before surgery to estimate the risk of late relapse based on severity of diabetes and can help in procedure selection between RYGB and SG. Procedure selection, however, should not be solely based on diabetes-related outcomes. Diabetes is one outcome—one of many outcomes and conditions that need to be considered in decision making. The surgical risk (generally lower after SG), differential impact of each procedure on body weight and other obesity-related conditions, presence of other medical and mental problems, and patient's values and goals should be considered in procedure selection (27). The second model can be used at 1st year after surgery in patients with diabetes remission to estimate their risk of late relapse with or without significant weight regain in future. In addition to our model, Debédat et al. (13) recently published their prediction model of diabetes relapse after RYGB (mean follow-up time of 5 years), originated from 94 patients with persistent remission and only 27 patients with late relapse of T2DM. Their model, which is accessible at https://5y-ad-diarem.nutriomics.org/, incorporates both preoperative variables at baseline (duration of T2DM, number of glucose-lowering agents, and HbA_{1c}) and postoperative variables at 1 year (glucose-lowering agents, FBG, and short-term weight loss) to estimate the rate of late relapse after RYGB (c-statistic = 0.90) (13). Our main model, originated from 289 patients with durable remission and 136 patients with late relapse and subsequently validated on an external cohort of 319 patients (100 patients with relapse), considered only baseline variables to predict the risk of relapse in a median 8-year follow-up after RYGB and SG. Our second prediction model, constructed based on data of 425 patients, can inform the patients of their long-term diabetes status with or without weight gain. When the patient's values are entered into the calculators (accessible at https://riskcalc.org/ and as a smartphone application), the percent estimate of late relapse of T2DM after RYGB and SG is calculated.

This is one of the first studies in the scientific literature to show statistically significant improvement in glycemic control, diabetes medication requirements, and other cardiovascular risk factors in the patients experiencing a relapse of T2DM. In addition, these patients may further benefit from the beneficial effect of the time period spent in diabetes remission on end-organ complications. This beneficial effect of time spent with better control of diabetes on long-term complications, irrespective of diabetes control on long-term follow-up, has variously been described as the "legacy effect" or "metabolic memory" (3,28). In some of the large diabetes trials, continued posttrial follow-up showed that glycemic differences between the groups disappeared early after the trials ended. Nonetheless, treatment effects persisted with respect to the end-organ complications of T2DM. Therefore, it is possible that patients who eventually relapse with T2DM after bariatric surgery will still continue to experience reduced micro- and macrovascular complications in the long-term (3,29,30). In an effort to support the concept of legacy effect after bariatric surgery, Coleman et al. (31) studied 4,683 patients with T2DM who had undergone bariatric surgery in four health care systems in the U.S. Among patients who experienced a late relapse after initial remission, the length of time spent in remission was inversely related to the risk of incident microvascular disease; for each additional year of time spent in remission prior to relapse, the risk of microvascular disease was reduced by 19% compared with that for patients who never achieved remission.

Although some would consider the late relapse of T2DM a treatment failure, these findings must be viewed against the known risks of poorly controlled T2DM in patients who do not undergo bariatric and metabolic surgery. In patients with late relapse, glycemic control and cardiovascular risk are significantly improved compared with baseline and the trajectory of these chronic conditions has been changed by surgery. Furthermore, the possible benefit from the legacy effect of improved glycemic control provides support to look at these long-term results in a positive light (3,32).

This study has several limitations that must be acknowledged. There are obvious limitations of a retrospective design, but the difficulties of prospectively following up any large cohort for a long enough time mean that there is no prospective large study in the scientific literature specifically focusing on the relapse of T2DM after bariatric surgery. For construction and validation of prediction models, a large sample size is needed, which is usually only possible with retrospective studies. This is particularly important for research on diabetes relapse after bariatric surgery, as patients not experiencing remission (~40% of patients) would necessarily have to be excluded from analysis, leading to reduced sample size. Since this study only includes patients undergoing RYGB or SG, its findings cannot necessarily be extrapolated to patients undergoing other bariatric procedures. But the fact that these two procedures between themselves account for >95% of the primary bariatric procedures worldwide in patients with T2DM (33,34) means that the findings of this study will be relevant to the practice of most of the bariatric surgeons globally. Another weakness of this study is that only 15% of our patients in the training cohort underwent SG. But in the external cohorts, 38% had SG. Limited follow-up is another problem with this study, but a median follow-up of 8 years (with at least 5-years' follow-up for all patients) on such a large cohort would still be regarded as acceptable. Nonetheless, it is possible that a longer follow-up time may increase the relapse rate and change the study findings. Loss to long-term follow-up of 20% in the base cohort would be associated with selection bias. After RYGB and SG operations, patients may achieve their nadir weight at different time points. Identification of nadir weight depends on the frequency weight measurement. Therefore, we opted to calculate late weight regain from year 1 after surgery and not from the nadir weight. We have not been able to study biochemical parameters like insulin, C-peptide, and incretin hormones at baseline and during follow-up. This means we are not able to consider them for our prediction models and to offer scientific explanations based on these markers for relapse of T2DM in these patients. However, these markers are not available in every clinical practice. Future studies in this area will need to address this. In addition to bootstrap validation, we could pool data of three external cohorts from the U.S. and Europe to assemble a validation cohort with 100 cases with the study event (relapse), which is the requirement for meaningful validation (17). Nonetheless, external validation in other cohorts, especially in different patient populations (e.g., Asian ethnicity or class I obesity), should be considered in future.

In conclusion, consistent with previous studies, our data show that ~60% of patients with T2DM experience diabetes remission within the 1st year after bariatric surgery. Furthermore, this study, with the largest cohort examining diabetes relapse to date, indicates that while late relapse is a real phenomenon (one-third of our cohort), relapse of T2DM years after bariatric surgery should not be considered a failure, since the trajectories of cardiometabolic risk factors, diabetes severity, and medication requirements are altered favorably after surgery.

Earlier surgical intervention, RYGB (compared with SG), and better weight loss outcomes (less late weight regain) are associated with lower diabetes relapse in the long-term. Understanding pathophysiology of durable remission and late relapse could aid patient and procedure selection. Further research is also needed to study the potential effect bariatric surgery might have on the subsequent incidence of diabetes micro- and macrovascular complications in those who experience a late relapse of T2DM.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.
Author Contributions. A.A. designed the study and contributed to data acquisition, data analysis and interpretation, literature search, and writing the manuscript. K.M. contributed to literature search and writing the manuscript. J.V., P.S., C.D.S., Z.N.H., G.S., G.C.W., A.I., and A.J. contributed to data acquisition. C.T. analyzed the data. All authors reviewed the manuscript and edited it for intellectual content and gave final approval for this version to be published. A.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Prior Presentation. Parts of this study were presented in abstract form at the 35th American Society for Metabolic and Bariatric Surgery Annual Meeting at ObesityWeek, Nashville, TN, 11–15 November 2018.

References

1. Rubino F, Nathan DM, Eckel RH, et al.; Delegates of the 2nd Diabetes Surgery Summit. Metabolic surgery in the treatment algorithm for type 2 diabetes: a joint statement by international diabetes organizations. Surg Obes Relat Dis 2016;12:1144–1162
2. Rubino F, Gagner M. Potential of surgery for curing type 2 diabetes mellitus. Ann Surg 2002; 236:554–559
3. Brethauer SA, Aminian A, Romero-Talamás H, et al. Can diabetes be surgically cured? Long-term metabolic effects of bariatric surgery in obese patients with type 2 diabetes mellitus. Ann Surg 2013;258:628–636; discussion 636–637
4. Aminian A, Brethauer SA, Andalib A, et al. Can sleeve gastrectomy "cure" diabetes? Long-term metabolic effects of sleeve gastrectomy in patients with type 2 diabetes. Ann Surg 2016;264: 674–681
5. Adami GF, Camerini G, Papadia F, et al. Type 2 diabetes remission and control in overweight and in mildly obese diabetic patients at long-term follow-up after biliopancreatic diversion. Obes Surg 2019;29:239–245
6. Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial. Lancet 2015;386:964–973
7. Arterburn DE, Bogart A, Sherwood NE, et al. A multisite study of long-term remission and relapse of type 2 diabetes mellitus following gastric bypass. Obes Surg 2013;23:93–102
8. Andalib A, Aminian A. Sleeve gastrectomy and diabetes: is cure possible? Adv Surg 2017;51:29–40
9. Schauer PR, Bhatt DL, Kirwan JP, et al.; STAMPEDE Investigators. Bariatric surgery versus intensive medical therapy for diabetes - 5-year outcomes. N Engl J Med 2017;376:641–651
10. Sjöström L, Peltonen M, Jacobson P, et al. Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. JAMA 2014;311:2297–2304
11. Aminian A, Zelisko A, Kirwan JP, Brethauer SA, Schauer PR. Exploring the impact of bariatric surgery on high density lipoprotein. Surg Obes Relat Dis 2015;11:238–247
12. Aminian A, Zajichek A, Arterburn DE, et al. Association of metabolic surgery with major adverse cardiovascular outcomes in patients with type 2 diabetes and obesity. JAMA 2019; 322:1271–1282
13. Debédat J, Sokolovska N, Coupaye M, et al. Long-term relapse of type 2 diabetes after Roux-en-Y gastric bypass: prediction and clinical relevance. Diabetes Care 2018;41:2086–2095

14. Buse JB, Caprio S, Cefalu WT, et al. How do we define cure of diabetes? Diabetes Care 2009; 32:2133–2135
15. Brethauer SA, Kim J, El Chaar M, et al.; ASMBS Clinical Issues Committee. Standardized outcomes reporting in metabolic and bariatric surgery. Obes Surg 2015;25:587–606
16. Salminen P, Helmiö M, Ovaska J, et al. Effect of laparoscopic sleeve gastrectomy vs laparoscopic Roux-en-Y gastric bypass on weight loss at 5 years among patients with morbid obesity: the SLEEVEPASS randomized clinical trial. JAMA 2018;319:241–254
17. Steyerberg EW. Validation in prediction research: the waste by data splitting. J Clin Epidemiol 2018;103:131–133
18. DiGiorgi M, Rosen DJ, Choi JJ, et al. Reemergence of diabetes after gastric bypass in patients with mid- to long-term follow-up. Surg Obes Relat Dis 2010;6:249–253
19. Chikunguwo SM, Wolfe LG, Dodson P, et al. Analysis of factors associated with durable remission of diabetes after Roux-en-Y gastric bypass. Surg Obes Relat Dis 2010;6:254–259
20. Yamaguchi CM, Faintuch J, Hayashi SY, Faintuch JJ, Cecconello I. Refractory and new-onset diabetes more than 5 years after gastric bypass for morbid obesity. Surg Endosc 2012;26:2843–2847
21. Nor Hanipah Z, Punchai S, Brethauer SA, Schauer PR, Aminian A. Development of de novo diabetes in long-term follow-up after bariatric surgery. Obes Surg 2018;28:2247–2251
22. Sjöström L. Review of the key results from the Swedish Obese Subjects (SOS) trial - a prospective controlled intervention study of bariatric surgery. J Intern Med 2013;273:219–234
23. Aminian A, Brethauer SA, Andalib A, et al. Individualized metabolic surgery score: procedure selection based on diabetes severity. Ann Surg 2017;266:650–657
24. Aminian A, Brethauer SA, Daigle CR, et al. Outcomes of bariatric surgery in type 2 diabetic patients with diminished pancreatic secretory reserve. Acta Diabetol 2014;51:1077–1079
25. Jiménez A, Casamitjana R, Flores L, et al. Long-term effects of sleeve gastrectomy and Roux-en-Y gastric bypass surgery on type 2 diabetes mellitus in morbidly obese subjects. Ann Surg 2012;256:1023–1029
26. Jiménez A, Casamitjana R, Flores L, Delgado S, Lacy A, Vidal J. GLP-1 and the long-term outcome of type 2 diabetes mellitus after Roux-en-Y gastric bypass surgery in morbidly obese subjects. Ann Surg 2013;257:894–899
27. Aminian A. Bariatric procedure selection in patients with type 2 diabetes: choice between Roux-en-Y gastric bypass or sleeve gastrectomy. Surg Obes Relat Dis. 2 December 2019 [Epub ahead of print]. DOI: 10.1016/j.soard.2019.11.013
28. Murray P, Chune GW, Raghavan VA. Legacy effects from DCCT and UKPDS: what they mean and implications for future diabetes trials. Curr Atheroscler Rep 2010;12:432–439
29. Carlsson LMS, Sjöholm K, Karlsson C, et al. Long-term incidence of microvascular disease after bariatric surgery or usual care in patients with obesity, stratified by baseline glycaemic status: a post-hoc analysis of participants from the Swedish Obese Subjects study. Lancet Diabetes Endocrinol 2017;5:271–279
30. O'Brien R, Johnson E, Haneuse S, et al. Microvascular outcomes in patients with diabetes after bariatric surgery versus usual care: a matched cohort study. Ann Intern Med 2018; 169:300–310
31. Coleman KJ, Haneuse S, Johnson E, et al. Long-term microvascular disease outcomes in patients with type 2 diabetes after bariatric surgery: evidence for the legacy effect of surgery. Diabetes Care 2016;39:1400–1407
32. Madsen LR, Baggesen LM, Richelsen B, Thomsen RW. Effect of Roux-en-Y gastric bypass surgery on diabetes remission and complications in individuals with type 2 diabetes: a Danish population-based matched cohort study. Diabetologia 2019;62:611–620
33. Khorgami Z, Shoar S, Andalib A, Aminian A, Brethauer SA, Schauer PR. Trends in utilization of bariatric surgery, 2010-2014: sleeve gastrectomy dominates. Surg Obes Relat Dis 2017; 13:774–778
34. Angrisani L, Santonicola A, Iovino P, et al. IFSO worldwide survey 2016: primary, endoluminal, and revisional procedures. Obes Surg 2018;28:3783–3794