Published in final edited form as:

Obes Surg. 2013 January ; 23(1): 93–102. doi:10.1007/s11695-012-0802-1.

A Multisite Study of Long-term Remission and Relapse of Type 2 Diabetes Mellitus following Gastric Bypass

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Abstract

Background—Gastric bypass has profound effects on glycemic control in adults with type 2 diabetes mellitus. The goal of this study was to examine the long-term rates and clinical predictors of diabetes remission and relapse among patients undergoing gastric bypass.

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Additional Contributions: The team would like to gratefully acknowledge the contributions of our project managers Rene Hawkes (Group Health Research Institute), Cathy Chou (Kaiser Permanente Northern California), and Mark Pierce (Kaiser Permanente Northern California) and programmers Mary Becker (HealthPartners), Mike Sorel (Kaiser Permanente Northern California), and Julie Liu (Kaiser Permanente Southern California). We would also like to acknowledge the scientific and clinical input of our Technical Expert Panel members: Edward H. Livingston, MD, FACS (University of Texas Southwestern); David R. Flum, MD, MPH, FACS (University of Washington); and Melinda Maggard Gibbons, MD (University of California at Los Angeles).

Prior presentation: The work described here was presented at the March 2011 annual meeting of the Health Maintenance Organization Research Network in Boston, MA.

Conflicts of Interest: Arterburn: None reported; Bogart: None reported; Coleman: None reported; Haneuse: None reported; Selby: None reported; Sherwood: None reported; Sidney: None reported; Theis: None reported; McCulloch: None reported; O'Connor: None reported

Methods—We conducted a retrospective cohort study of adults with uncontrolled or medication-controlled type 2 diabetes who underwent gastric bypass from 1995 to 2008 in three integrated health care delivery systems in the United States. Remission and relapse events were defined by diabetes medication use and clinical laboratory measures of glycemic control.

Results—We identified 4,434 adults with uncontrolled or medication-controlled type 2 diabetes who had gastric bypass. Overall, 68.2% (95% CI: 66%, 70%) experienced an initial complete diabetes remission within five years after surgery. Among these, 35.1% (95% CI: 32%, 38%) redeveloped diabetes within five years. The median duration of remission was 8.3 years. Significant predictors of complete remission and relapse were poor preoperative glycemic control, insulin use, and longer diabetes duration. Weight trajectories after surgery were significantly different for never remitters, relapsers, and durable remitters ($p=0.03$).

Conclusions—Gastric bypass surgery is associated with durable remission of type 2 diabetes in many but not all severely obese diabetic adults, and about one-third experience a relapse within five years of initial remission. More research is needed to understand the mechanisms of diabetes relapse, the optimal timing of surgery in effecting a durable remission, and the relationship between remission duration and incident microvascular and macrovascular events.

Keywords

gastric bypass; diabetes; remission; relapse

Introduction

Bariatric surgery has profound effects on glycemic control among people with type 2 diabetes mellitus, as documented by numerous reports, some of which suggest that surgery often produces a complete and durable remission.(1-5) A meta-analysis of 621 studies (mostly case series) of Roux-en-Y gastric bypass (RYGB), adjustable gastric banding (AGB), and biliopancreatic diversion/duodenal switch (BPD/DS) procedures estimated that 78.1% of diabetic patients undergoing these procedures experienced diabetes remission.(2) Three recent randomized controlled trials (RCTs) comparing bariatric operations vs. medical/behavioral therapy to treat T2DM, including among patients below the usual BMI threshold for surgery, reported that surgery yields better glycemic control, diabetes remission, and reduction of other cardiovascular risk factors, with acceptable complications (6-9). These remarkable anti-diabetes benefits result in part from mechanisms beyond just reduced food intake and body weight.(10-14) As a result of these studies, the Centers for Medicare and Medicaid Service and the American Diabetes Association recently concluded that bariatric surgery is an effective method for diabetes treatment.(15, 16)

Despite the mounting evidence, a few studies have suggested that diabetes remission might not be durable in all patients. The Swedish Obese Subjects study of more than 4,000 matched, severely obese patients receiving either nonsurgical care or bariatric surgery demonstrated that 72% experienced diabetes remission at 2 years after surgery, but only 36% remained diabetes-free at 10-year follow-up.(17) Two small, recent case series of adults with diabetes undergoing RYGB confirmed these findings. In the first study of 177

patients, 89% had an initial diabetes remission that eventually recurred in 43%.⁽¹⁸⁾ In the second series of 42 patients, 64% remitted with subsequent recurrence in 24%.⁽¹⁹⁾

Prior case series have found that patients with longer preoperative duration of diabetes, poorer glycemic control, and preoperative insulin use have a lower probability of diabetes remission.⁽²⁰⁾ Less is known about factors that predict subsequent recurrence, but one study suggested that advanced age, female sex, preoperative insulin use, and long-term weight regain were significant predictors of relapse.⁽¹⁸⁾

Motivated by the recent findings that bariatric surgery appears to be highly effective for diabetes control, at least in the short term, we investigated the durability of diabetes remission and incident relapse following RYGB surgery with a large, population-based study of three integrated health care delivery systems in the United States from 1995 to 2008. We examined two important clinical outcomes: 1) diabetes remission rate after surgery; and 2) diabetes relapse rate in patients who initially remitted. Finally, we investigated preoperative, patient-level predictors of these outcomes. We hypothesized that the severity of diabetes at baseline would be a strong predictor of diabetes remission and relapse.

Materials and Methods

We conducted a retrospective cohort study to describe the long-term outcomes of RYGB surgery among adults with uncontrolled or medication-controlled type 2 diabetes. Study subjects included adults enrolled from 1995 to 2008 in one of three integrated health care delivery systems in the United States: HealthPartners (HP) (Minnesota), Kaiser Permanente Northern California (KN), and Kaiser Permanente Southern California (KS). Analyses were conducted at the Group Health Research Institute (Seattle, Washington). All procedures were reviewed in advance and approved by the Institutional Review Boards of the four sites.

Primary inclusion criteria were: a) uncontrolled or medication-controlled diabetes; and b) a primary RYGB procedure occurring from 1995 to 2008 (identified using ICD-9 and CPT-4 procedure codes from inpatient hospitalizations). Uncontrolled diabetes was defined as a hemoglobin A1c (HbA1c) $\geq 6.5\%$ at the most recent measurement prior to surgery; medication-controlled diabetes was defined as a current prescription for diabetes medication at the time of surgery with the most recent HbA1c $<6.5\%$. The 6.5% threshold was chosen based on ADA guidelines.⁽²¹⁾ Electronic body mass index (BMI) data were not available at HP until 2002 and both Kaiser sites until 2005, so most cases had no preoperative BMI data in our electronic databases; therefore, BMI was not used as an eligibility criterion for our main analyses. We present separate BMI subgroup analyses below.

Exclusion criteria were gestational diabetes (if sole diabetes diagnosis) or prior gastrointestinal surgery for cancer or peptic ulcer disease. We also removed 406 who had undergone adjustable gastric banding, sleeve gastrectomy, or biliopancreatic diversion procedures, 1614 with diet-controlled type 2 diabetes (i.e., prior diagnosis, normal current hemoglobin A1c [HbA1c] $<6.5\%$ and no current diabetes medication use) at the time of surgery, 96 women with recent pre-surgical pregnancies, and 914 subjects who did not have an HbA1c measure within two years prior to surgery.

Using standardized data definitions and programming specifications, we extracted a comprehensive dataset for each eligible subject from administrative and clinical databases at each participating site. Data included demographic characteristics (age, sex), survival status, laboratory data related to glycemic control, pharmacy data, outpatient diagnoses, and inpatient hospitalizations including diagnoses and procedures. Survival status as of December 31, 2008 was ascertained through medical databases and by linking to state death indices in California and Minnesota.

Our primary outcomes of interest were time to diabetes remission and time to relapse and were based on recently published consensus definitions.(22) We defined partial diabetes remission as co-occurrence of: 1) diabetes medication discontinuation and 2) fasting glucose values <126 and/or HbA1c levels <6.5% occurring 180 days after last prescription fill. We defined complete diabetes remission as co-occurrence of: 1) diabetes medication discontinuation and 2) fasting glucose values <100 and/or HbA1c levels <6.0% occurring 180 days after last prescription fill. We examined the diabetes relapse rate among subjects who initially experienced a diabetes remission after surgery. Relapse of type 2 diabetes was defined as one or more of the following conditions: a) restarting diabetes medication; b) one or more HbA1c measures ≥6.5%; and/or c) one or more fasting glucose measures ≥126 mg/dL.

Occurrence and timing of complete or partial remission and relapse were investigated using the Cox proportional hazards framework.(23) Subjects were censored for one of the following: a) health plan disenrollment (loss to follow-up of medication and laboratory data); b) disenrollment from pharmacy coverage (loss to follow-up of medication data); c) pregnancy; d) death; or e) end of the study period (December 31, 2008). We examined unadjusted, minimally adjusted (demographic characteristics), and fully-adjusted models, reporting unadjusted and fully adjusted approach results. Covariates in the fully adjusted model were age at surgery, sex, year of surgery, type of surgery, HbA1c at the time of surgery, diabetes medication use at time of surgery, and diabetes duration. Diabetes duration was defined as the time since the subject was first observed to meet one or more of the following criteria in a defined 12-month (calendar) period: a) 1+ fills for diabetes-specific medication (oral or insulin); b) HbA1c ≥7.0% on one or more occasions; c) fasting blood glucose ≥126 mg/dL on two or more occasions; d) random blood glucose ≥200 mg/dL on two or more occasions; e) one fasting blood glucose ≥126 mg/dL plus one random glucose ≥200 mg/dL; f) one or more inpatient hospital discharge ICD-9 code related to diabetes; g) two or more outpatient ICD-9 codes related to type 2 diabetes..

We also conducted additional, secondary analyses to examine the relationships between BMI and outcomes among the 2,116 patients who had a total of 41,784 BMI measures recorded in the electronic medical record between 2002-2008. Initial analyses of BMI over time indicated that they follow a highly non-linear trajectory (Appendix Figure 2; left panel). As such, we modeled BMI as a function of time using a natural smoothing spline. (24, 25) Briefly, similar to adding quadratic and cubic terms to the model, natural smoothing splines provide a flexible framework for modeling smooth non-linear associations. They provide a parsimonious alternative to categorizing BMI that would require making restrictive, arguably arbitrary, decisions regarding the cut-points. The model covariates of

primary interest were indicators of diabetes status after surgery a) never remitted diabetes, b) remitted their diabetes and later relapsed, or c) durably remitted their diabetes. Models were further adjusted age at surgery, sex, year of surgery, type of surgery, HbA1c at the time of surgery, diabetes medication use at time of surgery, and diabetes duration. For the analysis of BMI trajectories, parameter estimates were obtained via Generalized Estimating Equations (GEE), with intensity-based weighting to accommodate the heterogeneity in the number of weights recorded across individuals. (26) Standard errors were obtained via the bootstrap on 1000 replications of the model fit. Based on the parameter estimates and standard errors, we constructed plots of the adjusted predicted BMI values as a function of time relative to the time of surgery (Appendix Figure 2; right panel). All analyses were conducted using SAS 9.2 (SAS Institute Inc., Cary, NC, USA) and R 2.12 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Our study criteria yielded 4 434 eligible adults. Baseline characteristics of our sample are in Table 1. Appendix Figures 1A and 1B show the flow of subjects through the study, including which subjects experienced each outcome of interest (complete and partial remission and relapse) during follow-up and the reasons for censoring (end of study, death, end of insurance and/or drug coverage, or pregnancy). Subjects were predominantly women (77.1%) and the average age was 49.6 years. The number of subjects identified at each site differed, with 6.5% from Site 1, 45.1% from Site 2, and 48.5% from Site 3. The mean duration of post-surgery follow-up for all subjects was 1,122 days (3.1 years; range 1 to 4,655 days). The overall 1, 3, and 5-year retention rates were 91.4% (n=4,052), 78.1% (n=3,462), and 67.8% (n=3,006) of the total eligible subjects were still available for follow up at each of these time points. The number of cases performed per year increased dramatically between 1995-96 (9 cases) to 2007-08 (1227 cases). The majority of bariatric procedures performed were open RYGB (55.5% open; 44.5% laparoscopic).

At the time of surgery, subjects had diabetes for an average of 4.5 years, 70.1% were on oral diabetes medications, and 21.8% were on insulin. Sulfonylurea medications were found among 40.6% of subjects; metformin among 48.0%; and thiazolidinediones among 13.9%. Combined, 77.4% were on oral medications, insulin, or both at the time of surgery. For the last HbA1c prior to surgery, 73.6% were 6.5% and 27.8% were 8%.

A total of 108 subjects (2.4%) died after surgery through the study end date (December 31, 2008). Survival probability estimates were 98.9%, 98.2%, and 96.6% at 1, 3, and 5 years after surgery. In multivariable Cox models, significant predictors of death were older age (HR for 5-year increase in age: 1.28; 95% CI: 1.10 to 1.40) and female sex (HR: 0.55; 95% CI: 0.36 to 0.82), and duration of diabetes (HR for 1-year increase: 1.09; 95% CI: 1.01 to 1.18).

Remission of diabetes

The upper left panel of Figure 1 shows the complete diabetes remission rates in our study population by time with point-wise 95% confidence intervals. We observe that 47.2% (95% CI: 45.6%, 48.8%), 72.5% (95% CI: 70.9, 74.1%), and 76.9% (95% CI: 75.3%, 78.6%) of

study subjects achieved the partial type 2 diabetes remission threshold or better within 1, 3, and 5 years after bariatric surgery, and 37.1% (95% CI: 35.6%, 38.7%), 63.3% (95% CI: 61.5, 65.0%), and 68.2% (95% CI: 66.4%, 70.0%) of study subjects achieved complete type 2 diabetes remission within 1, 3, and 5 years after bariatric surgery. Median time to partial remission threshold was 389 days (95% confidence interval [CI]: 376 to 407 days), and median time to complete remission threshold was 537 days (95% confidence interval [CI]: 507 to 566 days).

Table 2 presents the clinical predictors of complete type 2 diabetes remission after bariatric surgery based on our unadjusted and multivariable adjusted Cox models. In our multivariable adjusted models, women were significantly less likely to remit than men (hazard ratio [HR]: 0.81; 95% CI: 0.74 to 0.90). Complete remission rates with laparoscopic RYGB were not significantly different than with open RYGB. Subjects with poor preoperative glycemic control (HbA1c $\geq 6.5\%$) were less likely to experience complete remission than those with good preoperative control, and subjects treated with either insulin or oral hypoglycemic agents before surgery were less likely to completely remit than uncontrolled diabetic subjects who were not on those medications. Finally, longer duration of diabetes was significantly associated with a lower complete remission rate (HR for each additional year of diabetes: 0.91; 95% CI: 0.90 to 0.93). The lower left panel of Figure 1 shows diabetes remission rates stratified by preoperative insulin use and level of glycemic control. This figure illustrates that subjects receiving insulin and those having HbA1c $\geq 6.5\%$ prior to surgery were much less likely to experience complete diabetes remission during follow-up. Similar relationships were found between baseline patient level characteristics and the likelihood of achieving at least the partial threshold for remission, so those data are not shown.

Relapse of diabetes

All 2,254 subjects who experienced complete diabetes remission after bariatric surgery were considered eligible for relapse analyses. The upper right panel of Figure 1 shows the rate of type 2 diabetes relapse over time with point-wise 95% confidence intervals, with 7.9% (95% CI: 6.8%, 9.2%), 22.1% (95% CI: 20.1%, 24.3%), and 35.1% (95% CI: 32.0%, 38.4%) of subjects experiencing a relapse of type 2 diabetes within 1, 3, and 5 years after initial complete remission. Median time to relapse was 8.3 years (3,019 days; 95% CI: 2,507 to 3,281 days).

Table 3 presents the clinical predictors of type 2 diabetes relapse after initial complete remission based on our unadjusted and multivariable adjusted Cox models. In our multivariable adjusted models, older age at surgery was associated with higher risk of relapse (HR for 5-year increase in age: 1.09; 95% CI: 1.04 to 1.15). Subjects with poor preoperative glycemic control (HbA1c $\geq 6.5\%$) were significantly more likely to experience relapse than those with good preoperative control, and subjects treated with insulin were significantly more likely to experience relapse than uncontrolled diabetic subjects not using insulin before surgery. Finally, longer diabetes duration was significantly associated with higher relapse rate (HR for each additional year of diabetes: 1.13; 95% CI: 1.09 to 1.17). The lower right panel of Figure 1 shows the rate of relapse stratified by preoperative insulin

use and glycemic control. This figure displays the strong association between of pre-operative insulin use and risk of type 2 diabetes relapse.

The rate of type 2 diabetes relapse over time were higher when the partial remission threshold was used after RYGB surgery, with 12.9% (95% CI: 11.2%, 13.9%), 27.8% (95% CI: 25.7%, 30.0%), and 40.2% (95% CI: 37.3%, 43.3%) of subjects experiencing a relapse of type 2 diabetes within 1, 3, and 5 years after achieving either partial or complete remission (data not shown). And the median time to relapse after partial or complete remission was shorter at 6.8 years (2,507 days; 95% CI: 2,259 to 3,019 days). Similar relationships were found between baseline patient level characteristics and the likelihood of partial or complete remission, so those data are not shown.

Finally, to explore the relationship between pre-operative BMI, BMI change after surgery, and the occurrence of remission and relapse, we conducted a series of analyses on a subpopulation of 2,116 RYGB cases (47% of our total sample) with uncontrolled or medication controlled type 2 diabetes that also had available BMI data (i.e., had RYGB surgery after we had implemented our electronic medical record systems from 2005-2008). We found that the pre-operative BMI values were not significantly different ($p=0.93$) between 1,224 cases who never completely remitted their diabetes (BMI 45.5 kg/m²), 103 cases who completely remitted but relapsed (BMI 45.8 kg/m²), and 789 cases who durably remitted their diabetes (BMI 45.6 kg/m²). Appendix Figure 2 provides graphical representations of the BMI trajectories of these three groups of surgical subjects. The left hand figure presents the unadjusted lowess smoothed trajectories for each group, and the right hand figure presents the multivariable adjusted and intensity-weighted plots for each group. In our multivariable analyses we found that the postsurgical BMI trajectories for these three groups of patients were significantly different (global test; chi square(4df) = 10.42; $p=0.034$). The trajectory plots suggest that the 1,234 bariatric cases that never remit their diabetes after surgery appear to have slightly less weight loss and greater weight regain over time than the cases that do remit their diabetes. However, we find that 103 cases who relapsed their diabetes after initial remission appear similar if not slightly superior BMI maintenance after surgery than the 789 who have durable remission.

Discussion

In this large, population-based retrospective study of bariatric operations performed over a 13-year period in three integrated care delivery systems in the United States, we found that the 5-year rate of complete type 2 diabetes remission was 68.2%, which is lower than prior reports from academic bariatric centers that used more liberal HbA1c cutpoints (usually 7.0%).(2, 3, 8) A recent report by Pournaras and colleagues also found lower rate of remission using the new complete diabetes remission criteria .(27) The 5-year rate of partial diabetes remission (76.9%) that we observed is more consistent with those prior published estimates. (2, 3, 8) Most notably, however, longer-term follow-up of our cohort revealed that 35.1% of subjects who completely remitted their diabetes after surgery experienced a relapse within five years. Among those who initially remitted, the median remission duration was 7.5 years. As one might expect, the rate of relapse was even higher (40.1%) when the partial remission threshold was used. These findings are consistent with a few smaller reports of

diabetes remission and relapse.(17-19) Contrary to some published opinions,(1) our current study indicates that many patients do not experience a durable remission of type 2 diabetes after bariatric surgery.

The results presented here shed new light on the importance of preoperative patient selection and counseling when one of the goals of surgical intervention is durable diabetes remission. We consistently found that those treated with insulin were less likely to remit and more likely to relapse than those not on insulin prior to surgery. The lower rate of durable remission in insulin-treated subjects is likely related to greater pancreatic beta-cell loss and lower endogenous insulin secretion at the time of surgery.(12) However, not all patients receiving insulin fail to remit their diabetes, and further research is needed to determine whether patients who experience early initiation of insulin therapy have similar outcomes after bariatric surgery. Similarly, we found that worse preoperative glycemic control and longer duration of diabetes were associated with lower remission rates and higher relapse risk. Overall, these data suggest that when the main goal of surgical treatment is durable diabetes remission, earlier surgical intervention is likely to be more effective. This is not to say that more advanced and insulin-dependent patients cannot benefit from bariatric surgery, (28) but further study is needed to understand the effects bariatric surgery might have on diabetes severity, medication requirements, or subsequent incidence of diabetes complications, such as nephropathy and retinopathy in those who experience diabetes relapse. Furthermore, these patients may obtain other important benefits from surgery, such as improvement in quality of life, remission and/or improvement of other obesity associated diseases (hypertension, sleep apnea, hyperlipidemia, and osteoarthritis), reduction in cardiovascular risk, and reduced mortality. (3, 29-31) Finally, the UKPDS and DCCT/EDIC studies demonstrated that a transient period of aggressive glycemic control can induce a beneficial “metabolic memory” effect and reduce incident microvascular events.(32-36) Thus, it is possible that patients who eventually relapse their type 2 diabetes after bariatric surgery will still continue to experience reduced microvascular and macrovascular complications long-term compared to those never experience a relapse of type 2 diabetes.

Our study was not designed to identify mediators of diabetes remission and subsequent relapse. In particular, due to the late implementation of electronic medical records at each of the study sites, we lacked electronic BMI measures for most subjects, which limited our ability to examine the relationship between weight changes and outcomes. However, our subpopulation analyses involving 2,116 subjects with BMI measures from our electronic medical records yield some interesting results that deserve further study. We found that the mean pre-operative BMI values were not significantly different across groups defined by whether they had achieved remission or relapse. This finding is consistent with prior studies in the field.(37, 38) Furthermore, we confirmed prior studies which have suggested that the amount of initial weight loss is likely to be related to the rate of remission.(37-40) In our current analysis, we found that patients who never completely remitted their diabetes lost less weight than those who achieve complete remission (Appendix Figure 2). However, our data do yield some surprising and provocative results for the association between weight regain and diabetes relapse after complete remission– we found no clear difference in the weight trajectories between these two groups and, although the sample size was small (n=103) there was a slight trend towards relapsing patients having more durable weight loss

over time. This finding is counter-intuitive and deserves further confirmation in other samples, but could be explained by the relatively short follow-up time in our 2,116 cases with available BMI data (4 years) or by non-weight mediated factors, such as progressive beta-cell loss with age. This finding for weight change and relapse is at odds with two recent small case series with 3- and 5-year follow-up data, which found that greater weight regain increased the likelihood of diabetes recurrence, so our findings deserves replication in other studies.(18, 19) Buchwald and colleagues' review of 621 studies suggested that patients with diabetes actually lose more weight in the first 2 years after bariatric surgery than those without diabetes.(2) Beyond 2 years post surgery, those with diabetes had weight loss similar to those without. Other studies refute this claim, suggesting that those with diabetes lose less weight in the first 2 years after surgery than patients who do not have diabetes. (41-43) Clearly more work is needed in this area to clarify the relationship between long-term changes in body weight and durable diabetes remission.

Other factors also constrain interpretation of our findings. First, the rates of diabetes remission that we observed in the first year after surgery (37%) were significantly lower than those reported in prior prospective studies (70-80%). This is likely due to our use of the recent, consensus-based, but relatively conservative definition of diabetes remission,(22) and our reliance on electronic medical record data to identify clinical laboratory evidence of glycemic control occurring 90 days after the last filled diabetes medication prescription for an individual. While we cannot observe the exact timing of medication discontinuation and euglycemia in our databases, we believe that our definition of accurately identifies subjects who experienced true clinical remission of type 2 diabetes. Second, our study cannot identify whether variations in the RYGB surgical approach over time or across sites that may have impacted our rates of remission and relapse. Future research should assess whether diabetes response to surgery is influenced by RYGB approach. Third, we did not have sufficient data to analyze differences in outcomes by race/ethnicity, changes in body weight, incident end organ damage, or diabetes-related mortality. Future analyses should examine the long-term impact of bariatric procedures on these important outcomes among diverse populations, particularly among those who experience relapse. Our 1-, 3-, and 5-year retention rates were quite high at 91.4%, 78.1%, and 67.8%, and we feel that these rates of disenrollment are unlikely to significantly influence our findings since most patients disenroll due to changes in employer. Finally, our diabetes duration variable was limited because it was defined as the time since first meeting one of seven diabetes criteria, so some subjects with long-term diabetes who recently enrolled in our systems may have been misclassified as having more recent onset.

Despite these limitations, we believe that our results have a number of significant clinical and research implications for diabetes care. This is the largest community-based study of long-term diabetes outcomes after bariatric surgery to date. Although bariatric surgery induced initial complete diabetes remission within five years in 68% of severely obese adults, one-third relapsed within five years of initial remission. Patients should be counseled that bariatric surgery alone does not reliably "cure" diabetes.(22) However, the remission rates achieved by RYGB appear to be far better than what could be achieved by any other behavioral or drug treatment. Finally, our data suggest that the effect of bariatric surgery on durable diabetes remission is likely to be strongest among those who are earlier in the course

of their diabetes, although this finding should be confirmed in future prospective, randomized controlled studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Funding/Support: This research was conducted by Group Health Research Institute, HealthPartners, Kaiser Permanente Northern California, Kaiser Permanente Southern California, and the University of Wisconsin. This project was funded under Contract No. HHS290-2005-0033-I-TO10-WA1 from the Agency for Healthcare Research and Quality, US Department of Health and Human Services as part of the Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) program.

Role of the Sponsor: The authors of this article are responsible for its content. No statement may be construed as the official position of the Agency for Healthcare Research and Quality of the U. S. Department of Health and Human Services. The sponsor provided feedback to the authors on the preliminary study design and analysis as well as review of the manuscripts. However, the sponsor had no role in the conduct of the study; collection, management, analysis, and interpretation of the data; or preparation and approval of the manuscript.

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Figure 1.
Right-hand Panels. Time to relapse of diabetes following bariatric surgery and initial complete remission, overall and by baseline control status
Figure 1. Left-hand Panels. Time to complete diabetes remission following bariatric surgery, overall and by baseline control status

Table 1

Patient characteristics at date of bariatric surgery

All patients N = 4,434	
Age at surgery, mean (sd)	49.6 (9.3)
Female, n (%)	3419 (77.1%)
Site, n (%)	
Site 1	286 (6.5%)
Site 2	1999 (45.1%)
Site 3	2149 (48.5%)
Year of surgery, n (%)	
1995-1996	9 (0.2%)
1997-1998	62 (1.4%)
1999-2000	253 (5.7%)
2001-2002	640 (14.4%)
2003-2004	1266 (28.6%)
2005-2006	977 (22%)
2007-2008	1227 (27.7%)
Bariatric Surgery Type	
Open RYGB	2463 (55.5%)
Laparoscopic RYGB	1971 (44.5%)
HbA1c, n (%)	
Below 6.5%	1170 (26.4%)
[6.5%, 8%)	2031 (45.8%)
[8%, 9%)	573 (12.9%)
[9%, 10%)	313 (7.1%)
10% and higher	347 (7.8%)
On oral medication at surgery, n (%)	3109 (70.1%)
On insulin at surgery, n (%)	966 (21.8%)
Years since diabetes diagnosis, mean (sd)	4.5 (3.4)

^aRYGB, roux-en-y gastric bypass; HbA1c, hemoglobin A1c; diabetes type 2 diabetes mellitus

Table 2

Predictors of complete type 2 diabetes remission (Cox proportional hazards modeling of time until complete remission)^{a, b}

	Unadjusted Hazard Ratio Estimates	Adjusted Hazard Ratio Estimates
N	4,434	4,434
Age at surgery, 5 year increase	0.92 (0.90, 0.94)	0.98 (0.96, 1.01)
Female	0.89 (0.80, 0.98)	0.81 (0.74, 0.90)
HbA1c Category at surgery		
Below 6.5%	1 (referent)	1 (referent)
[6.5%, 8%)	0.76 (0.69, 0.84)	0.73 (0.66, 0.81)
[8%, 9%)	0.56 (0.48, 0.65)	0.69 (0.59, 0.80)
[9%, 10%)	0.47 (0.39, 0.58)	0.56 (0.46, 0.69)
10% and higher	0.47 (0.39, 0.56)	0.54 (0.44, 0.65)
On oral medication at surgery	0.70 (0.64, 0.77)	0.66 (0.60, 0.73)
On insulin at surgery	0.28 (0.25, 0.32)	0.37 (0.32, 0.43)
Years since diabetes diagnosis, 1 year increase	0.87 (0.85, 0.88)	0.91 (0.90, 0.93)

^aUnadjusted and adjusted models each stratified the baseline hazard function on year of surgery and study site. The adjusted model additionally includes all covariates shown

^bHbA1c = hemoglobin A1c; diabetes = type 2 diabetes mellitus

Table 3

Predictors of relapse of type 2 diabetes following complete remission (Cox proportional hazards modeling of time from initial complete remission until relapse) ^{a,b}

N	Unadjusted Hazard Ratio Estimates	Adjusted Hazard Ratio Estimates
	2,254	2,254
Age at surgery, 5 year increase	1.13 (1.08, 1.19)	1.09 (1.04, 1.15)
Female	0.99 (0.8, 1.23)	1.14 (0.91, 1.42)
HbA1c Category at surgery		
Below 6.5%	1 (referent)	1 (referent)
[6.5%, 8%)	1.19 (0.94, 1.52)	1.34 (1.04, 1.71)
[8%, 9%)	1.47 (1.07, 2.03)	1.43 (1.03, 1.97)
[9%, 10%)	2.05 (1.41, 2.97)	1.95 (1.34, 2.84)
10% and higher	2.19 (1.52, 3.15)	2.07 (1.42, 3.02)
On oral medication at surgery	1.39 (1.13, 1.72)	1.37 (1.10, 1.70)
On insulin at surgery	2.54 (2.00, 3.21)	1.91 (1.48, 2.45)
Years since DM diagnosis, 1 year increase	1.18 (1.14, 1.22)	1.13 (1.09, 1.17)

^aUnadjusted and adjusted models each stratified the baseline hazard function on year of surgery and study site. The adjusted model additionally includes all covariates shown

^bHbA1c, hemoglobin A1c; diabetes type 2 diabetes mellitus