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Long-Term Diabetic Response to Gastric Bypass

Stephen W. Davies, MD, MPH[1], **Jimmy T. Efird, PhD, MS**[2], **Christopher A. Guidry, MD, MS**[1], **Rachel I. Penn, BA**[3], **Robert G. Sawyer, MD**[1], **Bruce D. Schirmer, MD**[1], and **Peter T. Hallowell, MD**[1]

[1]University of Virginia School of Medicine, Department of General Surgery, Charlottesville, VA

[2]Biostatistics Unit, Center for Health Disparities, Brody School of Medicine, East Carolina University, Greenville, NC

[3]University of Miami Miller School of Medicine, Miami, FL

Abstract

BACKGROUND—As obesity and type II diabetes continue to rise, bariatric surgery offers a solution, but few long-term studies are available. The purpose of this study was to evaluate the long-term outcomes of diabetic patients following gastric bypass.

MATERIALS AND METHODS—This was a retrospective cohort study of all diabetic patients undergoing gastric bypass at our institution, from 1998–2012. Patients were compared by postoperative diabetic response to treatment (i.e., response=off oral medication/insulin vs. refractory=on oral medication/insulin) and followed at 1-, 3-, 5-, and 10-year intervals. Continuous data were analyzed using Student's t-test or Wilcoxon Rank Sum. Multivariable, Cox proportional-hazard regression was performed to compute diabetic cure ratios (CR) and 95% confidence intervals (CI).

RESULTS—A total of 2,454 bariatric surgeries were performed at our institution during the time period. 707 diabetic patients were selected by CPT codes for gastric bypass. Mean follow-up was 2.1 years. Incidence of diabetic response was 56% (1-year), 58% (3-year), 60% (5-year), and 44% (10-year). Postoperatively, responsive patients experienced greater percent total body weight loss [1-year ($p<0.0001$), 3-year ($p=0.0087$), and 5-year ($p=0.013$)], and less hemoglobin A1c levels [1-year ($p=0.035$) and 3-year ($p=0.040$)] at follow-up than refractory patients. Multivariable analysis

CORRESPONDING AUTHOR: Stephen Davies, **ADDRESS:** University of Virginia, School of Medicine, Department of General Surgery, PO Box 800679, Charlottesville, VA 22908-0679, **PHONE:** 919-414-6471, **FAX:** 434-243-5791, sd2wf@virginia.edu.

AUTHOR CONTRIBUTIONS:
Davies: analyzing and interpreting data, writing manuscript, approving the final version
Efird: analyzing and interpreting data, critical revision of manuscript, approving the final version
Guidry: analyzing and interpreting data, critical revision of manuscript, approving the final version
Penn: collecting data, critical revision of manuscript, approving the final version
Sawyer: analyzing and interpreting data, critical revision of manuscript, approving the final version
Schirmer: collecting data, critical revision of manuscript, approving the final version
Hallowell: conceiving and designing the study, collecting data, critical revision of manuscript, approving the final version

revealed a significant, independent inverse trend in incidence of diabetic cure as both age and BMI decreased (P_{trend}=0.0019 and <0.0001, respectively). Additionally, DJD was independently associated with responsive diabetes [CR=1.6 (95% CI=1.1–2.2)].

CONCLUSIONS—At follow-up, both groups in our study experienced substantial weight loss; however, a greater loss was observed among the response group. Further research is needed to evaluate methods for optimizing patient care preoperatively and improving patient follow-up.

Keywords

Diabetes; diabetes cure; gastric bypass; long-term follow-up

Introduction

According to the most recent National Health and Nutrition Examination Survey (NHANES), more than one-third of American adults (78 million) were obese [i.e., body mass index (BMI) > 30)] in 2009–2010 (1). As a result, the United States Department of Health and Human Services has classified obesity as one of the 12 leading health indicators of Healthy People 2020 (2). Obesity has previously been associated with an increased risk for heart disease, cancer, stroke, and diabetes (3).

Approximately 8.3% of Americans (25.8 million) suffer from diabetes with another 79 million Americans classified as pre-diabetic (4). Diabetes has been previously reported to be the leading cause of kidney failure, nontraumatic lower extremity amputations, blindness, heart disease, and stroke with total (direct and indirect) attributable costs amounting to $174 billion. Additionally, it is the 7th leading cause of death. Of these individuals, 90% can be classified as either obese or overweight (BMI>25) (5).

According to the National Heart Lung and Blood Institute (NHLBI), "weight loss surgery is an option for carefully selected patients with clinically severe obesity (i.e., BMI≥40 or ≥35 with comorbid conditions) when less invasive methods of weight loss have failed and the patient is at high risk for obesity-associated morbidity (e.g., diabetes) or mortality (Evidence Category B)" (6). Few studies are available evaluating long-term outcomes (10+ years) following bariatric surgery (7–12). The purpose of this study was to evaluate predictors of long-term, diabetic cure among patients at our institution following gastric bypass.

Materials and Methods

Patients and Follow-up

Institutional review board approval was obtained before review of the data was initiated. This was a retrospective cohort analysis of a prospectively maintained database of all patients undergoing bariatric surgery at the University of Virginia Health System, a tertiary care center, from 1985–2013. For the purposes of this study, diabetic patients who underwent gastric bypass from 1998–2012 were chosen based upon Current Procedural Terminology (CPT) code, electronic medical record (EMR), and follow-up availability (i.e., 1-, 3-, 5-, or 10-year follow-up). Patients were subsequently stratified and compared by diabetic response to treatment (i.e., response=off oral medication and/or insulin vs.

refractory=on oral medication and/or insulin) and procedural approach (i.e., laparoscopic vs. open). Patient demographics, comorbidities, perioperative outcomes, and follow-up data were collected.

Preoperative patient demographics and comorbidities evaluated included: age, gender, weight (pounds), body mass index (BMI), gastroesophageal reflux disease (GERD), degenerative joint disease (DJD), obstructive sleep apnea, hypertension (HTN), dyslipidemia, asthma, heart disease, and hemoglobin A1c (HgbA1c). Perioperative outcomes evaluated included: intensive care unit (ICU) admission, hospital length of stay (LOS), and mortality. Follow-up data evaluated at 1-, 3-, 5-, and 10-years included: weight (pounds), BMI, total weight loss, percent total body weight loss, and HgbA1c.

Definitions

Gastric bypass was defined as laparoscopic, open, or laparoscopic converted to open roux-en-Y. Separate analyses comparing laparoscopic and open gastric bypass, considered patients converted from laparoscopic to open gastric bypass as laparoscopic. GERD, DJD, HTN, dyslipidemia, asthma, and heart disease were defined by notation in the medical history or the presence of relevant medication within the EMR. Obstructive sleep apnea was determined by referral to sleep study center for evaluation. Mortality was defined as any cause occurring at any time, postoperatively. Total weight loss was defined as weight at follow-up subtracted from preoperative weight. Percent total body weight loss was defined as total weight loss divided by preoperative weight.

Statistical Analysis

Univariate analyses of continuous variables were performed using either Student’s t-test or Wilcoxon Rank Sum depending upon the normalcy of distribution. Probability of refractory diabetes following gastric bypass at 1-, 3-, 5-, and 10-year follow-up were computed using the Kaplan-Meier product limit method. Cox proportional-hazard regression was used to compute cure ratios (CR) and 95% confidence intervals (CI) for diabetic response to treatment. The test statistic of Grambsch and Therneau was used to check the proportional hazards assumption (13). Variables deemed clinically relevant and statistically significant were included in the multivariable model. P_{trend} were computed using the maximum likelihood trend test. Missing values were imputed using an iterative expectation-maximization (EM) algorithm (14–16). Propensity score matching was not used to control for confounding because of potential “non-collapsibility bias” inherent to logistic regression-based propensity scores (17). Statistical significance was defined as a p-value of less than 0.05. SAS© Version 9.3 (Cary, NC) was used for all analyses.

Results

A total of 2,850 bariatric surgeries were performed at our institution from 1985–2013. For the purposes of our study period, 707 diabetic patients were selected by CPT codes for gastric bypass between January 1998 and August 2012.

Preoperative patient demographics and comorbidities for all 707 diabetic patients are presented in Table 1. The mean age of our patient population was 46 ± 9.6 years, weight was 324 ± 71 pounds, BMI was 52 ± 10, and HgbA1c was 8.8 ± 36.

Follow-up data stratified by diabetic response is presented in Table 2. Mean follow-up for patients who returned to our clinic postoperatively was 2.1 (0.53–11) years (not represented in Table 2). At 1-, 3-, 5-, and 10-year follow-up, 289 [lost to follow-up (LTFU)=394], 125 (LTFU=459), 70 (LTFU=403), and 48 (LTFU=83) patients were present, respectively. When evaluating patients present for follow-up, patients whose diabetes was responsive to gastric bypass surgery experienced significantly greater total weight loss [5-year follow-up (p=0.039)] and percentage of total body weight loss [1-year (p<0.0001), 3-year (p=0.0087), and 5-year follow-up (p=0.013)], and significantly less HgbA1c [1-year (p=0.035) and 3-year follow-up (p=0.040)] as compared with patients whose diabetes was refractory to gastric bypass. No appreciable difference was present between laparoscopic and or open gastric bypass patients regarding percent of total body weight loss or HgbA1c at each follow-up period (not presented in Table 2).

Independent predictors of diabetic patients who were responsive to gastric bypass surgery are presented in Table 3. Multivariable, Cox proportional-hazard modeling revealed that younger age at time of surgery (≤40) was independently associated with diabetic cure. Furthermore, a significant inverse trend in incidence of diabetic cure can be appreciated as age decreases (P_{trend}=0.0019). Additionally, lower BMI at time of surgery (≤50) was independently associated with diabetic cure. Likewise, a significant inverse trend in incidence of diabetic cure can be appreciated as BMI decreases (P_{trend}<0.0001). Finally, DJD was independently associated with responsive diabetes as well.

Discussion

Our study observed a postoperative, diabetic cure rate of 56% at 1-year follow-up, 58% at 3-year follow-up, 60% at 5-year follow-up, and 44% at 10-year follow-up among diabetic patients undergoing gastric bypass. Previous studies have observed similar if not slightly higher percentages of diabetic cure rates ranging from 41–100% at 1-year (18–23), 75% at 2-year (24), 44–88% at 5-year (25–28), and 71–89% at 10-year follow-up (7–9). One possible explanation for this discrepancy may involve attrition rates, which are known to impact observed health outcomes (26, 29). The previously mentioned studies were able to obtain rates of follow-up ranging from 83–99% at 1-year (8, 9, 19–22, 28), 53–87% at 3-year (8–10, 28), 46–100% at 5-year (8, 9, 26–28), and 2–69% at 10-year (7–10) compared with our follow-up rates of 42%, 21%, 15%, and 37%, respectively. Possible explanations for this discrepancy in follow-up include our sole use of in-person, bariatric clinic reminders compared with a combination of in-person, phone, primary care provider, and/or EMR reminders. Our lower follow-up rates may have introduced selection bias, as patients may be more or less inclined to follow-up based upon their surgical outcome. However, while a substantial number of patients were LTFU, the distribution between the two study groups at each follow-up period was similar, indicating that the data was “missing at random.”

Responsive diabetic patients were more likely to experience greater total weight loss, greater percent total body weight loss, and less HgbA1c compared to diabetic patients refractory to gastric bypass in our study. Our results may partially be explained by the fact that on multivariable analysis, lower preoperative BMI was independently observed to be associated with diabetes responsive to surgery. Previous studies have observed similar associations between preoperative weight (25), postoperative weight loss (21), and diabetic cure. This association is presumed to occur secondary to changes in gut hormonal physiology (i.e., incretins, ghrelin, and glucagon-like peptide-1) induced by and in addition to the restrictive and upper gastrointestinal excluding properties intrinsic to gastric bypass (20, 30–42).

Additional demographics found to be independently associated with diabetes responsive to gastric bypass on multivariable analysis in our study included younger age. Previous studies have observed similar findings (9, 21, 25) and also report shorter preoperative diabetic duration (9, 20, 28), gender (25, 28), and lack of antidiabetic medication use preoperatively (25). Conversely, other studies have not identified this association (24, 27). For example, a recent prospective study by Cohen, et al., evaluating 62 consecutively selected diabetic patients undergoing gastric bypass did not observe a significant correlation between preoperative diabetic duration, preoperative HgbA1c, degree of postoperative weight loss, and diabetic remission (27). The authors attributed this finding to the fact that the BMI range of their patient population was between 30 and 35 kg/m^2. Thus, suggesting that while the traditional benefits of gastric bypass (i.e., weight loss, decreased hyperglycemia, decreased hyperlipidemia, decreased hypertension, and decreased cardiovascular disease risk) (7, 8, 12, 26, 27) are still realized by most patients, the degree of benefit may be affected by the degree of obesity. Interestingly, our study observed that DJD was independently associated with diabetic cure. While counterintuitive, this comorbidity may serve as motivation to arthritically debilitated patients, helping them to lose weight through postoperative diet and exercise adherence and thus regain mobility.

Finally, patients in our study usually experienced rapid weight loss and diabetic cure within their 1-year, follow-up appointment; however, as time progressed, some experienced an increase in postoperative weight gain and a concomitant increase in diabetic relapse. Resolution of diabetes has previously been observed to occur within days to weeks following gastric bypass and may even occur prior to hospital discharge (23, 36, 37, 42). Long-term remission (i.e., euglycemia without use of antidiabetic medication) has previously been observed to last for at least 14 years (7, 8, 12, 37); however, diabetic relapse (i.e., backsliding) has been known to occur (7, 9, 10, 28). For example, a retrospective, multisite study by Arterburn, et al., evaluating 4,434 adults with uncontrolled or medication-controlled diabetes following gastric bypass observed that 68% experienced diabetic cure within five years (28). Of those, 35.1% experienced diabetic relapse within five years. On multivariable analysis, the authors observed that poor preoperative glycemic control, insulin use, and longer diabetic duration independently predicted relapse. The Swedish Obese Subjects (SOS) study observed 1658 obese, non-diabetic patients who underwent bariatric surgery and 1771 obese, non-diabetic matched controls over a 15-year period and evaluated incidence of new-onset diabetes (10). Postoperatively, 110 bariatric surgery patients and 392 matched controls developed diabetes. On multivariable analysis, the authors observed that

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older age, increased blood glucose, and increased waist to hip ratio, preoperatively, were independently predictive of postoperative diabetic incidence.

Strengths and Limitations

Our study is strengthened by its large sample size and long-term follow-up; however, may be limited by its retrospective design. Retrospective studies are known to be susceptible to recall and selection bias. We acknowledge that our study had a high attrition rate and may not reflect the generalized population of bariatric surgery patients. However, we feel that our data characterizes the population of patients that return to our clinic and provides useful information for postoperative management of this group. Furthermore, as previously mentioned, the LTFU appears to have been evenly distributed between study groups at each follow-up time period. Additionally, although our analyses adjusted for demographic and other relevant variables, unmeasured factors could have influenced our results due to the non-randomized, nature of the study. Finally, this was a single center study, and thus external validity may be limited in generalizing results to other centers as the demographics and comorbidities of our patient population may differ.

Conclusion

At 10-yr follow-up, both groups in our study (i.e., diabetic cure and diabetes refractory to surgery) experienced substantial weight loss and diabetes prevalence, overall, was greatly reduced. Multimodal reminders may need to be incorporated to improve our comparatively low, postoperative follow-up. Further research is needed to evaluate pre- and postoperative optimization of patient comorbidities and postoperative compliance issues in this population.

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Table 1

Demographics and Comorbidities among Type II Diabetic Patients Undergoing Gastric Bypass Surgery (N=707)

Variables	DMII n (%)
Age (years)	
Q1 (≤40)	198 (28)
Q2 (41–47)	162 (23)
Q3 (48–53)	173 (24)
Q4 (>53)	174 (25)
Mean ± SD	46 ± 9.6
Median (IQR)	47 (13)
Gender	
Female	538 (76)
Male	168 (24)
Weight (lbs)	
Q1 (≤274)	177 (25)
Q2 (275–312)	178 (25)
Q3 (313–363)	178 (25)
Q4 (>363)	174 (25)
Mean ± SD	324 ± 71
Median (IQR)	312 (89)
Body Mass Index	
Q1 (≤44)	179 (25)
Q2 (45–50)	192 (27)
Q3 (51–57)	162 (23)
Q4 (>57)	174 (25)
Mean ± SD	52 ± 10
Median (IQR)	50 (13)
GERD	246 (35)
DJD	366 (52)
Apnea	286 (40)
Hypertension	562 (79)
Dyslipidemia	211 (30)
Asthma	80 (11)
Heart Disease	51 (7)
HgbA1c*	

Variables	DMII n (%)
Q1 (≤2.6)	177 (25)
Q2 (2.7–7.7)	178 (25)
Q3 (7.8–15)	175 (25)
Q4 (>15)	177 (25)
Mean ± SD	8.8 ± 36
Median (IQR)	7.7 (12)

* Missing values imputed using expectation-maximization algorithm (n=10 simulations; relative efficiency=0.92).

DJD=degenerative joint disease. DMII=type II diabetes. GERD=gastroesophageal reflux disease. HgbA1c=hemoglobin A1c. IQR=interquartile range. Lbs=pounds. Q1=first quartile. Q2=second quartile. Q3=third quartile. Q4=fourth quartile. SD=standard deviation.

Table 2

Postoperative Outcomes at Each Follow-up Visit Stratified by Diabetic Response to Gastric Bypass Surgery

Variables	Response Mean ± SD; Median (IQR)	Refractory Mean ± SD; Median (IQR)	P-Value*
Overall [n (%) within each F/u period]			
1-Year F/u	161 (56)	128 (44)	---
3-Year F/u	72 (58)	53 (42)	---
5-Year F/u	42 (60)	28 (40)	---
10 Year F/u	21 (44)	27 (56)	---
Weight (lbs)			
1-Year F/u	207 ± 52; 196 (55)	235 ± 53; 230 (74)	<0.0001
3-Year F/u	210 ± 54; 204 (64)	234 ± 52; 229 (74)	0.012
5-Year F/u	221 ± 55; 212 (80)	236 ± 51; 232 (54)	0.23
10-Year F/u	242 ± 74; 229 (61)	252 ± 59; 239 (57)	0.34
Body Mass Index			
1-Year F/u	33 ± 7.3; 31 (8.0)	38 ± 8.0; 37 (11)	<0.0001
3-Year F/u	33 ± 7.8; 33 (10)	38 ± 7.4; 36 (11)	0.0012
5-Year F/u	35 ± 7.9; 34 (12)	38 ± 6.8; 38 (9.5)	0.17
10-Year F/u	40 ± 12; 35 (12)	41 ± 8.6; 40 (14)	0.43
Total Weight Loss (lbs)			
1-Year F/u	108 ± 34; 102 (39)	102 ± 34; 99 (46)	0.13
3-Year F/u	121 ± 55; 109 (53)	108 ± 49; 97 (60)	0.22
5-Year F/u	116 ± 49; 98 (60)	97 ± 54; 82 (77)	0.039
10-Year F/u	110 ± 59; 96 (59)	82 ± 53; 75 (42)	0.065
PTBWL			
1-Year F/u	34 ± 7.0; 34 (7.2)	30 ± 7.6; 30 (11)	<0.0001
3-Year F/u	36 ± 10; 36 (14)	31 ± 10; 31 (14)	0.0087
5-Year F/u	34 ± 10; 33 (12)	28 ± 10; 26 (11)	0.013
10-Year F/u	31 ± 13; 29 (17)	24 ± 13; 25 (13)	0.070
HgbA1c			
1-Year F/u	5.7 ± 0.60; 5.7 (0.55)	6.6 ± 1.5; 6.0 (1.8)	0.035
3-Year F/u	5.7 ± 0.76; 5.6 (0.45)	6.8 ± 1.5; 6.0 (2.3)	0.040
5-Year F/u	5.4 ± 0.47; 5.4 (0.80)	6.8 ± 1.6; 6.4 (2.6)	0.13
10-Year F/u	5.1 ± 1.4; 5.1 (2.0)	7.3 ± 1.3; 7.2 (0.60)	0.056

*P-Values do not account for patients who were lost to follow-up between the two groups.

Student's T-test or Wilcoxon Rank Sum was used for continuous variables depending upon the normalcy of distribution.

F/u=follow-up. HgbA1c=hemoglobin A1c. IQR=interquartile range. Lbs=pounds. LTFU=lost to follow-up. SD=standard deviation. PTBWL=percent total body weight loss.

Table 3

Probability of Diabetes Refractory to Surgery at Each Follow-Up Period and Corresponding, Unadjusted and Adjusted Cure Ratio (N=707)

Variables	DMII Refractory to Surgery (%)*				Univariable CR (95%CI)	Multivariable CR (95%CI)
	1-Year	3-Year	5-Year	10-Year		
Age (years)						
Q1 (≤40)	0.69	0.33	0.26	0.22	1.5 (0.99–2.2)	2.0 (1.3–3.2)
Q2 (41–47)	0.77	0.32	0.28	0.14	1.3 (0.83–2.0)	1.4 (0.90–2.2)
Q3 (48–53)	0.79	0.39	0.36	0.36	1.1 (0.73–1.8)	1.2 (0.76–1.9)
Q4 (>53)	0.82	0.45	0.41	0.35	1.0 Referent	1.0 Referent
Mean ± SD					$P_{trend}=0.043^{\delta}$	$P_{trend}=0.0019^{\delta}$
Median (IQR)						
Gender						
Female	0.79	0.38	0.31	0.26	1.0 Referent	1.0 Referent
Male	0.66	0.35	0.35	0.35	1.1 (0.80–1.7)	1.4 (0.96–2.1)
Body Mass Index						
Q1 (≤44)	0.64	0.17	0.13	---β	2.2 (1.5–3.3)	2.6 (1.7–4.0)
Q2 (45–50)	0.78	0.37	0.31	0.31	1.4 (0.89–2.1)	1.6 (1.01–2.5)
Q3 (51–57)	0.81	0.47	0.47	0.42	0.90 (0.57–1.4)	0.95 (0.60–1.5)
Q4 (>57)	0.83	0.49	0.39	0.31	1.0 Referent	1.0 Referent
Mean ± SD					$P_{trend}=0.0001^{\delta}$	$P_{trend}<0.0001^{\delta}$
Median (IQR)						
GERD						
No	0.76	0.35	0.34	0.31	1.0 Referent	1.0 Referent
Yes	0.77	0.42	0.28	0.20	1.0 (0.73–1.4)	1.0 (0.72–1.4)
DJD						
No	0.78	0.43	0.41	0.38	1.0 Referent	1.0 Referent
Yes	0.75	0.33	0.26	0.21	1.3 (0.93–1.7)	1.6 (1.1–2.2)

Variables	DMII Refractory to Surgery (%)*				Univariable CR (95%CI)	Multivariable CR (95%CI)
	1-Year	3-Year	5-Year	10-Year		
Apnea						
No	0.75	0.33	0.28	0.23	1.0 Referent	1.0 Referent
Yes	0.79	0.43	0.38	0.35	0.80 (0.59–1.1)	0.97 (0.68–1.4)
Hypertension						
No	0.70	0.34	0.30	0.20		1.0 Referent
Yes	0.78	0.38	0.34	0.29	0.91 (0.61–1.4)	0.98 (0.64–1.5)
Dyslipidemia						
No	0.80	0.35	0.30	0.24	1.0 Referent	1.0 Referent
Yes	0.72	0.40	0.35	0.33	0.97 (0.72–1.3)	1.0 (0.76–1.4)
Asthma						
No	0.76	0.36	0.30	0.28	1.0 Referent	1.0 Referent
Yes	0.78	0.45	0.45	0.30	0.80 (0.53–1.2)	0.86 (0.56–1.3)
Heart Disease						
No	0.76	0.35	0.29	0.25	1.0 Referent	1.0 Referent
Yes	0.78	0.56	0.56	0.46	0.62 (3.7–1.03)	0.74 (0.43–1.3)

*Kaplan-Meier probability of refractory diabetes following gastric bypass at indicated follow-up period.

$^{\beta}$Follow-up time for respected category less than indicated period.

$^{\delta}$$P_{trend}$ computed using the maximum likelihood trend test.

CI=confidence interval. CR=cure ratio (instantaneous cure rate of diabetes relative to referent category; computed using Cox proportional-hazard model). DJD=degenerative joint disease. DMII=type II diabetes. GERD=gastroesophageal reflux disease. IQR=interquartile range. Lbs=pounds. Q1=first quartile. Q2=second quartile. Q3=third quartile. Q4=fourth quartile. SD=standard deviation.