Is Roux-en-Y Gastric Bypass Surgery the Most Effective Treatment for Type 2 Diabetes Mellitus in Morbidly Obese Patients?

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Type 2 diabetes mellitus (T2DM) has a very strong association with obesity. The aim of our study was to analyze the effects of Roux-en-Y gastric bypass (RYGB) surgery on the glucose metabolism in morbidly obese patients with T2DM. Morbidly obese patients (n = 117) with T2DM underwent measurements of fasting serum glucose and glycosylated hemoglobin (HbA1C) at baseline, 6 months, and 12 months after laparoscopic RYGB surgery. Logistic regression was used in both univariate and multivariate modeling to identify independent variables associated with complete resolution of T2DM. Twelve months after surgery, fasting plasma glucose decreased from a preoperative mean of 164 ± 55 mg/dL to 101 ± 38 mg/dL (P = .001) and HbA1C decreased from a preoperative mean of 7.7% ± 1.5% to 6.0% ± 1.1% (P = .001). Resolution of T2DM was achieved in 72 patients (74%). All of the remaining 25 patients decreased the daily medication requirements. On univariate analysis, preoperative variables associated with resolution of T2DM were waist circumference, HbA1C, and absence of insulin treatment. Waist circumference (odds ratio 2.4; 95% confidence interval 1.4–4.1; P = .001) and treatment without insulin (odds ratio 42.2; 95% confidence interval 4.3–417.3; P = .002) remained significant predictors of T2DM resolution in the multivariate logistic regression model after adjusting for covariates. Laparoscopic RYGBP resulted in significant resolution of T2DM. Peripheral fat distribution (smaller waist circumference) and absence of insulin treatment were independent and significant predictors of complete resolution of T2DM. (J GASTROINTEST SURG 2005;9:1112–1118)

KEY WORDS: Morbid obesity, bariatric surgery, gastric bypass, diabetes, weight loss

Obesity causes an enormous burden for public health. Data from the 2001 Behavioral Risk Factor Surveillance System, a cross-sectional survey conducted by the Centers for Disease Control and state health departments, estimated incidence in obesity at 20.9% among U.S. adults.[1] Type 2 diabetes mellitus (T2DM) is strongly associated with obesity. Approximately 90% of individuals with T2DM are overweight or obese.[1] The lifetime risk of acquiring T2DM is 50% in subjects with morbid obesity, and 63.5% of patients with T2DM have a body mass index (BMI) $\geqslant$ 30 kg/m^2.[1] Diabetes is the leading cause of renal failure, blindness, and amputations, and is a major risk factor for heart disease and stroke.[2,3] An upper body or central distribution of body fat is a major risk factor for T2DM, regardless of the overall degree of obesity.[4] In obese patients with T2DM, weight loss that leads to reduction in visceral fat has been related to improvements in glycemic control, insulin sensitivity, and lipid profile.[5] Short-term studies lasting 12 months or less have demonstrated that weight loss in overweight or obese subjects with T2DM is associated with decreased insulin resistance, substantial improvements in measures of glycemic control, reduced lipemia, and reduced blood pressure.[6–9] However, long-term data substantiating that these improvements can be maintained are limited. Among the various modalities used to treat obesity, Roux-en-Y gastric bypass (RYGB) surgery represents the most effective for sustained weight loss.[10,11] RYGB in obese diabetic patients helps them to become normoglycemic,

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consequently decreasing the risk for vascular diseases, but prospective data regarding resolution of T2DM after RYGB have been scant.[10,11] Therefore, the aim of our study was to analyze the effect of RYGB in a prospective cohort of morbidly obese patients with T2DM and to identify patient factors associated with complete resolution of T2DM.

MATERIAL AND METHODS

Patients

The study, after institutional review board approval, was conducted at Vanderbilt University Medical Center. Morbidly obese patients with T2DM who were undergoing laparoscopic RYGB were enrolled in the study. Eligibility criteria were age 18 to 60 years, diagnosis of T2DM with glycosylated hemoglobin (HbA1C) $\geq$ 6.5%, BMI $\geq$ 35 kg/m^2, stable weight for the previous 3 months, and constant doses of any oral diabetes medications or insulin for at least 1 month. Exclusionary criteria included use of any weight-loss product or participation in any formal weight-loss program in the previous month and diagnosis of type 1 diabetes mellitus. Diagnosis of T2DM was based on fasting plasma glucose concentrations according to criteria established by the American Diabetes Association.[12]

At baseline and each follow-up visit (6 and 12 months) body weight was recorded and blood samples for fasting glucose and HbA1C were obtained. Waist circumference, a surrogate marker of central obesity, was measured by a plastic tape meter at the level of the umbilicus at baseline.

Outcome Measures

The primary outcome measure was resolution of T2DM at 1-year follow-up visit. Complete resolution of T2DM was defined by normal levels of fasting plasma glucose and HbA1C after discontinuing medical treatment. Secondary end points measured included fasting serum glucose and HbA1C at 1-year follow-up visit. Fasting plasma glucose and HbA1C were determined in the Biochemistry Laboratory of Vanderbilt University Medical Center. Plasma glucose was determined by a glucose oxidase method. HbA1C was determined by high-pressure liquid chromatography using a Diamet Glycosylated Hemoglobin Analyzer (Bio-Rad Laboratories, Hercules, CA). One-year excess weight loss (EWL) was also calculated. EWL was defined as the excess weight over the ideal body weight calculated according to the Metropolitan Life Weight Tables (Source: Metropolitan Life Insurance Company).

Surgical Technique

All operations were performed laparoscopically using the same technique. A divided 15 to 20 mL gastric pouch was anastomosed with the roux limb in a retrocolic retrogastric fashion. The length of the roux limb varied according to the preoperative BMI (35–40: 75 cm, 40–50: 100 cm, $>$50: 150 cm).

Statistical Analysis

The data are presented as mean $\pm$ standard deviation for continuous variables, and as counts or proportions (%) for categoric variables. Binary logistic regression analysis was used in both univariate and multivariate modeling to identify independent preoperative variables associated with T2DM resolution. The following model-building strategy was used. Univariate analysis using logistic regression was applied to identify significant associations with the dependent variable (T2DM resolution). Transformed and untransformed data were used in the analysis. All independent variables with associations of P values of .05 or less then underwent multivariate analysis by simply entering them together using the backward stepwise method. The "best" model for each case definition was based on the strength (Hosmer and Lemeshow goodness-of-fit test), clinical utility, and biologic plausibility of the model. Model parameters were estimated by the maximum-likelihood method. From these estimates, odds ratios with 95% confidence intervals were computed.

The SPSS statistical software program (version 11.0, SPSS Inc., Chicago, IL) was used for all analyses. Statistical significance was set at P less than .05.

RESULTS

The study enrolled 117 consecutive patients over a 30-month period. Ninety-seven patients (83%) completed the 1-year follow-up clinic visit. The mean age was 44.6 $\pm$ 8.3 years, with 79 females and 18 males. Mean preoperative BMI was 49.3 $\pm$ 7.4 (range: 38–78). At 1-year follow-up, the mean EWL was 69.6% $\pm$ 16.3%.

As shown in Table 1, fasting plasma glucose and HbA1C levels significantly decreased after RYGB. However, 6- and 12-month postoperative levels of fasting plasma glucose and HbA1C were similar.

Complete resolution of T2DM was achieved in 72 patients (74%). All of the remaining 25 patients decreased the daily medication requirements (partial resolution). Our cohort of patients was then divided into two groups: (1) complete T2DM resolution (n = 72) and (2) partial T2DM resolution (n = 25). Preoperative demographics, anthropometric

Table 1. Effect of gastric bypass on the glucose metabolism

Variables	Baseline	6 months	12 months	Two-sided *P* value
Fasting plasma glucose mg/dL	164 ± 55*	104 ± 43	101 ± 38	.0001
HbA1C (%)	7.7 ± 1.5	6.1 ± 1.3	6.0 ± 1.1	.0001

HbA1C = glycosylated hemoglobin; T2DM = type 2 diabetes mellitus.
*Preoperative period off T2DM medications.

measures, diabetes-related data, and weight-loss data for the two groups are listed in Table 2. Preoperative waist circumference was a significant predictor for resolution of T2DM. The complete response group had a significantly smaller waist circumference than the partial response group (47.5 ± 3.8 vs. 53.2 ± 3.0; $P = .0001$). Type of medical treatment was also a significant predictor of successful outcome, with patients treated only with oral hypoglycemic medications achieving a higher percentage of complete response than patients treated with insulin. Complete resolution of T2DM was also associated with lower preoperative levels of HbA1C. BMI had a noticeable but not statistically significant effect; patients with a lower BMI achieved a higher percentage of complete response. EWL at 1-year follow-up was similar ($P = .4$) in the two groups (complete resolution: 70.3 ± 17.1; partial resolution: 67.3 ± 19.4).

According to the group's outcome distribution and assumptions of the logistic regression, we entered the two most significant variables into the logistic regression model. We tested the model for goodness of fit using the Hosmer and Lemeshow ($P = .21$) test and concluded that the model fit well. Waist circumference and preoperative treatment without insulin remained significant predictors of T2DM resolution after gastric bypass surgery in the multivariate logistic regression model after adjusting for covariates (BMI, gender, and preoperative HbA1C). As shown in Table 3, for 1-inch change in waist circumference, the associated odds ratio was 2.4. The absence of preoperative insulin treatment increased the chance to have T2DM resolution after RYGB by 42 times. In Figure 1, the calculated probability of T2DM resolution by logistic regression equation is plotted as a continuous dependent variable against the independent variables: waist circumference and preoperative use of insulin.

Table 2. Preoperative demographic, clinical, and laboratory findings

	Complete DM resolution (n = 72)	Partial DM resolution (n = 25)	Two-sided *P* value
Age	44.0 ± 8.9	46.4 ± 6.1	.22
Gender (M/F)	12/60	19/6	.41
No preoperative use of insulin (%)	62/72 (86.1)	8/25 (32)	.0001
BMI (kg/m2)	48.5 ± 7.5	51.7 ± 6.9	.06
Waist circumference (inches)	47.5 ± 3.8	53.2 ± 3.0	.0001
HbA1C (%)	7.5 ± 1.3	8.6 ± 1.7	.001
Duration of T2DM (y)	3.5 ± 2.8	4.3 ± 3.9	.27

DM = diabetes mellitus; BMI = body mass index; HbA1C = glycosylated hemoglobin; T2DM = type 2 diabetes mellitus.

DISCUSSION

The results from our study definitively demonstrate that RYGB achieves better biochemical glycemic control than the most effective medical treatment reported. RYGB induced a significantly greater weight loss, decrement in HbA1C, and decreased requirement for diabetes medications than a low-calorie diet combined with sibutramine treatment.[7] Twelve months after surgery, patients who underwent RYGB experienced a mean HbA1C decrease of 1.7%, and 74% of subjects were not taking any antidiabetic medication. Patients treated with a low-calorie diet and sibutramine experienced a mean HbA1C decrease of 0.6%, and only 26% of subjects were taking reduced doses of diabetes medications; none of the patients were able to discontinue antidiabetic medication.

The relationship between weight loss and improvement in glycemia in subjects with T2DM has not been clearly defined. Caloric restriction and weight loss produce rapid improvements in glycemia, which are mitigated with the passage of time, even when weight loss is maintained.[6,7] Possible explanations for this include acute effects of caloric restriction on glycemia, which lessen as caloric

Table 3. Result of binary logistic regression analysis

Variable	Odds ratio (95% CI)	Coefficient (SE)	Two-sided *P* value
Waist circumference	2.4 (1.4–4.1)	0.9 (0.3)	.001
No preoperative use of insulin	42.2 (4.3–417.3)	3.74 (1.17)	.001

CI = confidence interval; SE = standard error.

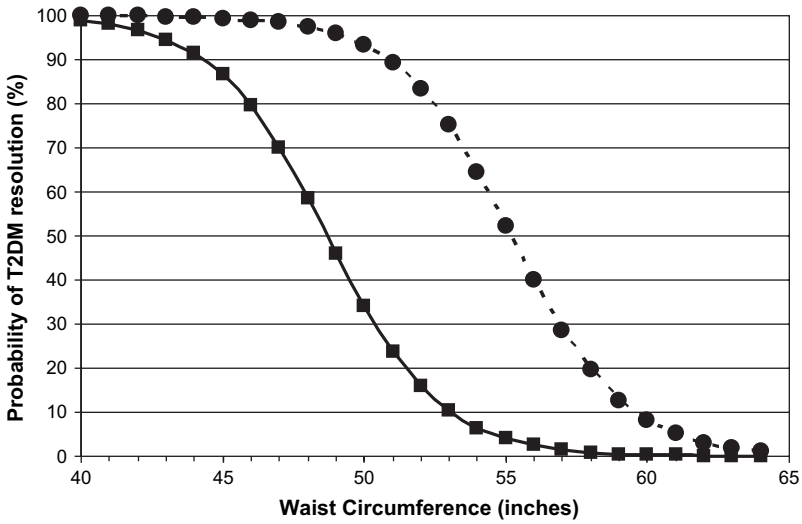

Fig. 1. Prediction of type 2 diabetes mellitus (T2DM) resolution by the logistic regression model. Smooth curves are plots of the probability of T2DM resolution 12 months after Roux-en-Y gastric bypass (RYGB) for patients with (*solid line*) and without (*dotted line*) preoperative insulin use in relation to waist circumference (in inches).

intake returns toward baseline. Currently, bariatric surgery seems to be the only modality that results in sustained weight loss, resolution of diabetes, improvements in cholesterol biosynthesis, lipoprotein metabolism, and decreased cardiovascular risk factors in morbidly obese patients. Long-term follow-up studies by Pories et al[13] showed that patients undergoing RYGB lost 75% of the excess body weight within 24 months, with approximately only a 10% regain after 14 years. The weight loss achieved with RYGB exceeds that with any medical approach, accounting for its higher use in the treatment of morbid obesity. Our results are consistent with recent studies demonstrating significant and sustained improvement in T2DM (up to 10–20 years) after RYGB.[10,11,13] However, direct comparison of these studies can lead to analytic bias because they are different in terms of the study design (retrospective vs. prospective) and methodology of evaluating metabolic outcome by biochemical or clinical assessment. The higher rate of diabetes resolution achieved by Schauer et al.[10] (80%) versus our data (74%) is most readily explained by the exclusion in our series of individual with impaired glucose tolerance (7% in Schauer et al.'s series). In our experience, individuals with impaired glucose tolerance experience early normalization of fasting plasma glucose and HbA1C after RYGB. In our study, the percentage of EWL was similar in patients with resolved and unresolved diabetes. In the Schauer et al.[10] and Sugerman et al.[11] series, the magnitude of EWL positively correlated with T2DM resolution. A plausible explanation of this difference may be that net weight loss may not necessarily be the dominant mechanism driving T2DM resolution because many patients after RYGBP are rendered euglycemic before significant weight loss occurs.

Our study, like others, highlights the pivotal role played by central obesity in the pathogenesis of T2DM. However, we are the first to show that central obesity negatively influences the likelihood of T2DM resolution after RYGB. Not all types of obesity are associated with increased risk of metabolic and cardiovascular complications. Individuals with peripheral fat distribution in the gluteofemoral regions are less prone to develop T2DM and cardiovascular disease than individuals with abdominal fat distribution.[14]

Furthermore, the amount of visceral fat strongly correlates with insulin resistance and can account for most of the variability in insulin sensitivity in the obese population.[15] A major reason behind this correlation is that visceral fat compared with subcutaneous fat is a more important producer of cytokines that are involved in the pathogenesis of insulin resistance.[16,17] In addition, the omentum is the major downloader of free fatty acid into the portal circulation leading to inappropriately elevated hepatic glucose production and hyperinsulinemia.[18] Stolic and coworkers[19] investigated basal and insulin-stimulated deoxyglucose uptake in omental and subcutaneous adipose tissue explants from obese patients. They found that insulin-responsive deoxyglucose transport was significantly lower in the omental adipose tissue of subjects with central obesity, compared with that of subjects with peripheral obesity.

Thorne and coworkers[20] randomized 50 nondiabetic subjects with morbid obesity to either adjustable gastric banding alone or adjustable gastric banding plus removal of the greater omentum (omentectomy). The improvements in oral glucose tolerance, insulin sensitivity, and fasting plasma glucose and insulin were 2 to 3 times greater in omentectomized subjects compared with control subjects. The striking effect of omentectomy on insulin sensitivity raises the argument for removing the omentum during an RYGB in morbidly obese patients with T2DM. We recently started a National Institutes of Health-funded randomized trial aimed to explore the effect of omentectomy combined with RYGB on glucose metabolism. We hypothesize that the combined procedure will be more effective in reversing insulin resistance in obese patients with T2DM than TYGB alone.

CONCLUSIONS

The goal of our study was to determine whether RYGB would result in improved glycemic control in a prospective cohort of morbidly obese subjects with T2DM. The study clearly demonstrated that laparoscopic RYGB is highly effective in achieving excellent glycemic control in patients with T2DM. Six months after surgery, most patients are able to withdraw from all antidiabetic medications including insulin. Improvement in glucose metabolism occurs early after LRYGB and therefore is not entirely related to weight loss. Our study is the first to show that central obesity negatively influences the likelihood of T2DM resolution after RYGB. Last, the comparison of our data with the best results obtained by medical treatment[7] suggests that RYGB should be considered standard treatment of T2DM in morbidly obese patients who are appropriate surgical candidates.

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Discussion

Dr. Jon Gould (Madison, WI): I congratulate Dr. Torquati and his colleagues at Vanderbilt University for conducting this very interesting study. Thank you for getting me the article ahead of time.

As you pointed out, we are currently in the midst of two very closely linked epidemics here in the United States, type 2 diabetes and obesity. These two epidemics are so closely linked, in fact, that the term "diabesity" has been coined. You have demonstrated an impressive 100% response rate of type 2 diabetes to Roux-en-Y gastric bypass in a large prospectively identified cohort. No known medical treatment of type 2 diabetes has demonstrated the kind of consistent results attained in studies such as yours that examine the impact of surgically induced weight loss on this debilitating and progressive disease.

My first question for you is, considering the fact that patient morbidity is significantly decreased with current minimally invasive techniques, why do you think that bariatric technique isn't yet a universally accepted first-line treatment for type 2 diabetes in obese patients in the early stages of this disease?

I have a couple of additional questions. I wonder if you could hypothesize for me an explanation as to why patients with increased waist circumference tend to respond less uniformly to surgically induced weight loss than other patients do.

And finally, I am curious as to the rest of your surgical population, whether your diabetic patients differed from your nondiabetic patients in terms of waist circumference, BMI, age, things like that?

Dr. Torquati: Thank you for your questions. Definitely bariatric surgery is gaining popularity among internal medicine practitioners and the family practitioner, but still there are concerns in terms of morbidity and mortality. Articles like the one recently published by Flum and colleagues, in the *Journal of American College of Surgeons*, report a mortality of 1.75% after bariatric surgery in Washington State. These data support the common opinion of your internal medicine colleagues who consider bariatric surgery still a very risky treatment for this type of patient. Also we don't have level 1 or 2 data regarding the long-term follow-up of these patients in terms of potential weight regain and evolution of comorbidities. I think it is very important for us to continue to follow up patients with type 2 diabetes for 10 and more years after gastric bypass surgery.

For the second question, usually waist circumference is an index of central obesity, and we found that omentum is a very important endocrine organ. Omentum produces a lot of cytokines called adipokines, and we know these are very important in terms of creating the milieu for insulin resistance. Also we know that omentum is a major downloader of free fatty acid to the liver and that high levels of free fatty acid in the portal circulation are associated with insulin resistance.

Regarding the last question, we didn't analyze the data in terms of comparing waist circumference in patients with or without diabetes because our enrolled patients were all diabetic. However, this represents a great idea for a future study.

Dr. Michael Zenilman (Brooklyn, NY): I think this is great that we can now focus on basic physiology rather than the technical issues of bariatric surgery; it has been a long time coming in surgery and medicine. Having Frank Moody and others comment on articles like this is really great.

My question is in terms of the pathophysiology of your observations. Why do you think that actual obesity is the issue? My understanding is that insulin sensitivity and glucose tolerance improve almost immediately after Roux-en-Y bypass surgery; patients can be discharged on less insulin than on admission. Some investigators postulate that incretins secreted from the upper GI tract are involved in this phenomenon. So, why did you study patients at 6 months? You should be looking at this effect a day or two after surgery.

Dr. Torquati: I definitely agree with your statement. We can observe a patient having resolution a few days after gastric bypass surgery. I have a comment that there is an article from Rubino and collaborators, published recently in *Annals of Surgery*, using an animal model showing that you can achieve a very good resolution of diabetes by just bypassing the duodenum and the first portion of the jejunum. I agree with your statement that there is something else that can justify why these patients have resolution of diabetes. It is not only the calorie restriction or the weight loss but some unknown factors that we are looking forward to studying.

Dr. J. Christopher Eagon (St. Louis, MO): Others have shown a relationship between the duration of diabetes preoperatively and its resolution. Did you not see the effect at all or was it not statistically significant in your data?

Did you do any sort of measurements of insulin sensitivity among your patient population, or at least

in subgroups of it? Might insulin sensitivity be a more precise measure than waist circumference?

Dr. Torquati: In previous articles from Schauer and Sugerman, both published in *Annals of Surgery*, short duration of the diabetes was correlated with a good metabolic response to gastric bypass. In our article, we found only a trend, maybe because we had 100 patients compared with the 400 and 500 patients who were included in the Dr. Sugerman and Dr. Schauer article.

It is very important to measure insulin sensitivity in these patients. The best method to assess insulin sensitivity is the minimal model or the insulin clamp study. As you know, they are very invasive studies to perform. Right now in our randomized clinical trial we are assessing insulin sensitivity by insulin clamp studies before surgery and 4 weeks, 3 months, 6 months, and 12 months after surgery. Definitely in the future we are going to have some good data about how insulin sensitivity changes over time.

Dr. Michel Murr (Tampa, FL): I want to echo the previous discussants. I think I would be a little bit more careful about extrapolating resolution of diabetes based on the fasting plasma glucose rather than an invasive test like the intravenous glucose tolerance test. I would look into the just to solidify your argument.

You have shown us that there is a decrease in the plasma glucose and better control of diabetes, and you linked it to central adiposity, but you didn't show us data that the central adiposity has resolved. You only looked at waist circumference. Is there a better way to quantify that?

Dr. Torquati: Regarding the first question, we used the glycosylated hemoglobin as the primary endpoint of your study, not fasting plasma glucose. In fact, low levels of glycosylated hemoglobin have been validated in several studies as an excellent marker of good long-term diabetes control. Regarding the second question, waist circumference has been extensively validated as a great surrogate measurement for central adiposity. However, there is a potential better method: the computed tomography scan of the abdomen with a slice level at the umbilicus. This study allows the measurement of fat distribution between the subcutaneous and intra-abdominal compartment. But this test takes more time and money to do, and at the end, several studies did not provide a better indication of central obesity than waist circumference.