ORIGINAL ARTICLE

Bariatric Surgery versus Intensive Medical Therapy for Diabetes — 3-Year Outcomes

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ABSTRACT

BACKGROUND

In short-term randomized trials (duration, 1 to 2 years), bariatric surgery has been associated with improvement in type 2 diabetes mellitus.

METHODS

We assessed outcomes 3 years after the randomization of 150 obese patients with uncontrolled type 2 diabetes to receive either intensive medical therapy alone or intensive medical therapy plus Roux-en-Y gastric bypass or sleeve gastrectomy. The primary end point was a glycated hemoglobin level of 6.0% or less.

RESULTS

The mean (±SD) age of the patients at baseline was 48±8 years, 68% were women, the mean baseline glycated hemoglobin level was 9.3±1.5%, and the mean baseline body-mass index (the weight in kilograms divided by the square of the height in meters) was 36.0±3.5. A total of 91% of the patients completed 36 months of follow-up. At 3 years, the criterion for the primary end point was met by 5% of the patients in the medical-therapy group, as compared with 38% of those in the gastric-bypass group (P<0.001) and 24% of those in the sleeve-gastrectomy group (P=0.01). The use of glucose-lowering medications, including insulin, was lower in the surgical groups than in the medical-therapy group. Patients in the surgical groups had greater mean percentage reductions in weight from baseline, with reductions of 24.5±9.1% in the gastric-bypass group and 21.1±8.9% in the sleeve-gastrectomy group, as compared with a reduction of 4.2±8.3% in the medical-therapy group (P<0.001 for both comparisons). Quality-of-life measures were significantly better in the two surgical groups than in the medical-therapy group. There were no major late surgical complications.

CONCLUSIONS

Among obese patients with uncontrolled type 2 diabetes, 3 years of intensive medical therapy plus bariatric surgery resulted in glycemic control in significantly more patients than did medical therapy alone. Analyses of secondary end points, including body weight, use of glucose-lowering medications, and quality of life, also showed favorable results at 3 years in the surgical groups, as compared with the group receiving medical therapy alone. (Funded by Ethicon and others; STAMPEDE ClinicalTrials.gov number, NCT00432809.)

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*The contributions of the authors and committee members in the Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial are listed in the Supplementary Appendix, available at NEJM.org.

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Bariatric surgery has recently emerged as a potentially useful treatment for type 2 diabetes mellitus.[1] Observational studies[2-5] and randomized, controlled trials[6-10] have shown that procedures including Roux-en-Y gastric bypass, sleeve gastrectomy, gastric banding, and biliopancreatic diversion significantly improve glycemic control and favorably affect cardiovascular risk factors.

In the Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial, we found that 1 year after randomization, gastric bypass and sleeve gastrectomy were superior to intensive medical therapy alone in achieving glycemic control and reducing cardiovascular risk factors while decreasing dependency on pharmacotherapy for diabetes management.[7] Although bariatric surgery yields short-term improvements in glycemic control, questions remain regarding the durability of the metabolic benefits of surgery, long-term safety, quality of life, and effects on diabetes-related end-organ disease. The current report provides results of the 3-year follow-up analyses from the STAMPEDE trial and addresses other unanswered questions about the durability of the benefits of bariatric surgery as compared with intensive medical therapy for treating diabetes mellitus.

METHODS

STUDY DESIGN

The rationale, design, and methods of the study have been reported previously.[7,11] The complete protocol was approved by the institutional review board at the Cleveland Clinic and is available with the full text of this article at NEJM.org. Briefly, the trial was a three-group, randomized, controlled, single-center study involving 150 obese patients, in which the effects of intensive medical therapy were compared with those of gastric bypass or sleeve gastrectomy. With the use of block randomization, patients were assigned, in a 1:1:1 ratio, to one of the three study groups, with stratification according to the baseline use of insulin. Eligibility criteria included an age of 20 to 60 years, a glycated hemoglobin level of more than 7.0%, and a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of 27 to 43. All patients provided written informed consent.

STUDY OUTCOMES

The primary outcome was a glycated hemoglobin level of 6.0% or less, with or without the use of diabetes medications.[7,11] This report provides 3-year outcomes in the study patients, including measures of glycemic control, weight loss, blood pressure, lipid levels, renal function, carotid intima–media thickness,[12] medication use, adverse events, disease-related complications, and quality of life (as evaluated with the use of the RAND 36-Item Health Survey).[13] The strategy for all three groups was the adjustment of medical therapy (every 3 months for 2 years and every 6 months thereafter) with the goal of achieving the therapeutic target of a glycated hemoglobin level of 6.0% or less, without unacceptable side effects associated with medical treatment.

STUDY OVERSIGHT

This investigator-initiated trial was financially supported by Ethicon, with additional support from LifeScan, the Cleveland Clinic, and the National Institutes of Health. The sponsors participated in discussions regarding study design but had no role in data accrual, data analysis, or manuscript preparation. The first author wrote the first draft of the manuscript. All the authors had full and independent access to all the data and vouch for the integrity and the accuracy of the analysis and its fidelity to the protocol. Complete study governance is outlined in the Supplementary Appendix, available at NEJM.org.

STATISTICAL ANALYSIS

We report all continuous variables with a normal distribution as means and standard deviations. Variables with a non-normal distribution are reported as medians and interquartile ranges. Categorical variables are summarized with the use of frequencies. We used the chi-square test to evaluate the primary end point of a glycated hemoglobin level of 6.0% or less at 3 years. We used an analysis of variance to analyze continuous laboratory measurements and to perform comparisons among the three study groups. For glycemic measures and body weight, a mixed model for repeated measures was used to analyze the change from baseline, and least-square means with corresponding standard errors were plotted graphically.

A stepwise multivariable logistic model was used to determine factors associated with achiev-

ing the primary end point. Factors that were considered in the model included age, sex, insulin use, duration of diabetes, baseline glycated hemoglobin and glucose levels, C-peptide levels, baseline BMI, change in BMI, blood pressure, and lipid measures. No adjustments were made for multiple comparisons, since these were exploratory analyses. Analyses were performed with the use of SAS software, version 9.2 (SAS Institute).

RESULTS

STUDY PATIENTS

Of the 150 patients who underwent randomization from March 2007 through January 2011, a total of 9 patients withdrew from the trial immediately after randomization or during the initial 6 months (8 patients in the medical-therapy group and 1 patient who did not undergo sleeve gastrectomy because of severe anemia); 4 patients were lost to follow-up. The remaining 137 patients (91.3%) were evaluated in the 3-year assessment of safety and efficacy.

The baseline characteristics of the 150 patients were reported previously.[7] In the current analysis, 68% of the patients were women, and 74% were white. The mean (±SD) age was 48±8 years, and the mean BMI was 36±3.5; 49 patients (36%) had a BMI of less than 35. The mean glycated hemoglobin level was 9.3±1.5%, and the average duration of diabetes was 8.3±5.1 years, with 43% of patients requiring insulin at baseline. There

Table 1. Primary and Secondary End Points at 3 Years.*

End Point	Medical Therapy (N=40)	Gastric Bypass (N=48)	Sleeve Gastrectomy (N=49)	P Value		
				Gastric Bypass vs. Medical Therapy	Sleeve Gastrectomy vs. Medical Therapy	Gastric Bypass vs. Sleeve Gastrectomy
Glycated hemoglobin						
Level — no. of patients (%)						
≤6%	2 (5)	18 (38)	12 (24)	<0.001	0.01	0.17
≤6% without diabetes medications	0	17 (35)	10 (20)	<0.001	0.002	0.10
≤6.5%	7 (18)	23 (48)	23 (47)	0.003	0.003	0.92
≤6.5% without diabetes medications	0	22 (46)	14 (29)	<0.001	<0.001	0.08
≤7%	16 (40)	31 (65)	32 (65)	0.02	0.02	0.94
≤7% without diabetes medications	0	28 (58)	16 (33)	<0.001	<0.001	0.01
At baseline — %	9.0±1.4	9.3±1.4	9.5±1.7			
At 3 yr — %						
Mean	8.4±2.2	6.7±1.3	7.0±1.3	<0.001	<0.001	0.42
Median (IQR)	7.7 (6.7 to 9.6)	6.6 (5.8 to 7.4)	6.6 (6.1 to 7.5)			
Change from baseline — percentage points	−0.6±2.5	−2.5±1.9	−2.5±2.1	<0.001	<0.001	0.99
Relapse — no./total no. (%)†						
Glycemic control	4/5 (80)	5/21 (24)	9/18 (50)	0.03	0.34	0.09
Diabetes	NA	8/21 (38)	6/13 (46)	NA	NA	0.64
Median (IQR) fasting plasma glucose — mg/dl						
At baseline	157 (115 to 199)	193 (142 to 236)	164 (132 to 224)			
At 3 yr	132 (104 to 179)	100 (87 to 141)	106 (86 to 136)	0.001	0.007	0.92
Change from baseline‡	−6.0 (−68.5 to 56.0)	−85.5 (−122.0 to −21.5)	−46.0 (−113.0 to −21.0)	0.001	0.006	0.24
Body weight						
At baseline — kg	104.5±14.2	106.8±14.9	100.6±16.5			
At 3 yr — kg	100.2±16.6	80.6±15.5	79.3±15.1	<0.001	<0.001	0.69
Change from baseline — kg	−4.3±8.8	−26.2±10.6	−21.3±9.7	<0.001	<0.001	0.02
% Change from baseline	−4.2±8.3	−24.5±9.1	−21.1±8.9	<0.001	<0.001	0.06

Table 1. (Continued.)

End Point	Medical Therapy (N=40)	Gastric Bypass (N=48)	Sleeve Gastrectomy (N=49)	P Value		
				Gastric Bypass vs. Medical Therapy	Sleeve Gastrectomy vs. Medical Therapy	Gastric Bypass vs. Sleeve Gastrectomy
Other risk factors						
% Change from baseline in low-density lipoprotein cholesterol	2.5±29.9	16.9±54.5	14.5±52.2	0.14	0.20	0.82
% Change from baseline in high-density lipoprotein cholesterol	4.6±20.7	34.7±27.3	35.0±31.0	<0.001	<0.001	0.96
Median % change from baseline in triglycerides (IQR)	−21.5 (−45.4 to 16.4)	−45.9 (−61.0 to −7.5)	−31.5 (−52.1 to −6.9)	0.01	0.01	0.18
Change from baseline in blood pressure — mm Hg						
Systolic	0.63±22.63	1.29±20.38	−4.43±20.69	0.88	0.27	0.17
Diastolic	−6.48±12.33	−4.25±10.57	−6.27±13.30	0.36	0.94	0.41

* Plus–minus values are means ±SD. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. IQR denotes interquartile range, and NA not applicable.

† Relapse of glycemic control was defined as having met the primary end point for glycated hemoglobin of 6% or less at 1 year but not at 3 years. Relapse of diabetes was defined as having met the primary end point for glycated hemoglobin of 6% or less with the use of no antidiabetic medications at 1 year but not at 3 years. None of the patients in the medical-therapy group had a complete remission of diabetes, and thus, these patients were not evaluated for relapse.

‡ For skewed data, the median of the change is not the numerical difference between the group-level median at baseline and the median value at 3 years.

were no significant differences between the study groups at baseline (Table S1 in the Supplementary Appendix).

PRIMARY END POINT

At 3 years, the target glycated hemoglobin level of 6.0% or less was achieved in 5% of the patients in the medical-therapy group, as compared with 38% of those in the gastric-bypass group (P<0.001) and 24% of those in the sleeve-gastrectomy group (P=0.01) (Table 1). The percentage of patients who had a glycated hemoglobin level of 6.0% or less at 1 year but did not maintain this level of glycemic control at 3 years (which was defined as a glycemic relapse) was 80% in the medical-therapy group, as compared with 24% in the gastric-bypass group (P=0.03) and 50% in the sleeve-gastrectomy group (P=0.34). In the entire cohort, a reduction in the BMI was the only significant predictor of achieving the primary end point (odds ratio for each 1-unit decrease in BMI, 1.41; 95% confidence interval [CI], 1.22 to 1.64; P<0.001) (Table S2 in the Supplementary Appendix). In the two surgical groups, meeting the criterion for the primary end point was predicted both by a reduction in the BMI (odds ratio, 1.33; 95% CI, 1.15 to 1.56; P<0.001) and by a duration of diabetes of less than 8 years (odds ratio, 3.3; 95% CI, 1.2 to 9.1; P=0.02).

GLYCEMIC CONTROL

After 3 years, each of the two surgical procedures was superior to intensive medical therapy alone in achieving exploratory targets for glycated hemoglobin of 6.5% and 7.0%, with or without the use of diabetes medications (P<0.05 for all comparisons) (Table 1). Median levels of fasting plasma glucose were significantly lower in the two surgical groups than in the medical-therapy group (P<0.01 for both comparisons) (Table 1). There were more rapid, larger, and more sustained reductions in levels of glycated hemoglobin and fasting plasma glucose and in the use of glucose-lowering medications in the two surgical groups than in the medical-therapy group (Table 2, Fig. 1A and 1C, and Fig. S1 in the Supplementary Appendix). The reductions in glycated hemoglobin levels, medication use, and BMI in the surgical groups were similar in patients with

Table 2. Medication Use at Baseline and at 3 Years.*

Medication	At Baseline			At 3 Years		
	Medical Therapy (N=40)	Gastric Bypass (N=48)	Sleeve Gastrectomy (N=49)	Medical Therapy (N=40)	Gastric Bypass (N=48)	Sleeve Gastrectomy (N=49)
Diabetes medications						
No. of medications	2.80±1.11	2.50±1.15	2.45±1.19	2.60±1.10	0.48±0.80†	1.02±1.01†‡
Insulin — no. of patients (%)	21 (52)	22 (46)	22 (45)	22 (55)	3 (6)†	4 (8)†
Not taking this class of medication — no. of patients (%)	1 (2)	1 (2)	1 (2)	1 (2)	33 (69)†	21 (43)†‡
Cardiovascular medications						
No. of medications	2.70±1.22	2.73±1.32	2.18±1.09	2.63±1.31	0.96±1.15†	1.35±1.40†
ACE inhibitor or ARB — no. of patients (%)	25 (62)	36 (75)	30 (61)	22 (55)	11 (23)§	13 (27)§
Not taking this class of medication — no. of patients (%)	0	3 (6)	2 (4)	1 (2)	20 (42)†	19 (39)†
Any medication						
No. of medications	5.50±1.71	5.23±1.76	4.63±1.67	5.23±1.86	1.44±1.49†	2.37±1.82†‡
Difference from baseline to 3 yr — no.				−0.28±2.03	−3.79±1.81†	−2.27±1.99†‡

* Plus–minus values are means ±SD. All P values are for the comparison with the medical-therapy group unless otherwise indicated. ACE denotes angiotensin-converting enzyme, and ARB angiotensin-receptor blocker.
† P<0.001.
‡ P<0.05 for comparison between gastric bypass and sleeve gastrectomy.
§ P<0.01.

a BMI of less than 35 and those with a BMI of 35 or more, and the reductions in both BMI subgroups of the surgical group were greater than the reductions in either BMI subgroup of the medical-therapy group (Fig. 1B, and Fig. S2 and S3 in the Supplementary Appendix).

DIABETES MEDICATIONS

At 3 years, the use of glucose-lowering medications including insulin was reduced from baseline in the two surgical groups (Table 2). Patients in the gastric-bypass group required fewer glucose-lowering medications per day than did those in the sleeve-gastrectomy group (0.48±0.80 vs. 1.02±1.01). The proportion of patients who were not taking any glucose-lowering medications was significantly higher in the gastric-bypass group than in the sleeve-gastrectomy group (Table 2).

WEIGHT LOSS

At 3 years, reductions in body weight, BMI, waist circumference, and waist-to-hip ratio were greater after gastric bypass and sleeve gastrectomy than after intensive medical therapy (Table 1, Fig. 1D, and Table S3 in the Supplementary Appendix). The reduction in body weight was greater after gastric bypass than after sleeve gastrectomy (P=0.02).

CARDIOVASCULAR BIOMARKERS AND MEDICATIONS

The decrease in triglyceride levels and increase in high-density lipoprotein (HDL) cholesterol levels that had been observed after the two surgical procedures, as compared with intensive medical therapy, were sustained at 3 years (Table 1). There were no significant differences in blood pressure and low-density lipoprotein (LDL) cholesterol levels among the three study groups, although there

Figure 1 (facing page). Mean Changes in Measures of Diabetes Control from Baseline to 3 Years.

Shown are the percentage change in glycated hemoglobin levels (Panel A), the percentage change in glycated hemoglobin levels according to body-mass index (BMI) (Panel B), the average number of diabetes medications during the study period (Panel C), and the changes in BMI (Panel D) over a 3-year period among patients receiving intensive medical therapy only, sleeve gastrectomy, or gastric bypass. I bars indicate standard errors. Mean values in each group are provided below the graphs; in Panels A and B, median values are also provided in parentheses. P values are for the comparison between each surgical group and the medical-therapy group in Panels A, C, and D. In Panel B, P=0.008 for the comparison between the surgical groups and the medical-therapy group for the subgroup of patients with a BMI of less than 35; P<0.001 for the comparison for the subgroup with a BMI of 35 or more.