

## ORIGINAL ARTICLE

# Bariatric Surgery versus Conventional Medical Therapy for Type 2 Diabetes

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## ABSTRACT

**BACKGROUND**

Roux-en-Y gastric bypass and biliopancreatic diversion can markedly ameliorate diabetes in morbidly obese patients, often resulting in disease remission. Prospective, randomized trials comparing these procedures with medical therapy for the treatment of diabetes are needed.

**METHODS**

In this single-center, nonblinded, randomized, controlled trial, 60 patients between the ages of 30 and 60 years with a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of 35 or more, a history of at least 5 years of diabetes, and a glycated hemoglobin level of 7.0% or more were randomly assigned to receive conventional medical therapy or undergo either gastric bypass or biliopancreatic diversion. The primary end point was the rate of diabetes remission at 2 years (defined as a fasting glucose level of <100 mg per deciliter [5.6 mmol per liter] and a glycated hemoglobin level of <6.5% in the absence of pharmacologic therapy).

**RESULTS**

At 2 years, diabetes remission had occurred in no patients in the medical-therapy group versus 75% in the gastric-bypass group and 95% in the biliopancreatic-diversion group ( $P < 0.001$  for both comparisons). Age, sex, baseline BMI, duration of diabetes, and weight changes were not significant predictors of diabetes remission at 2 years or of improvement in glycemia at 1 and 3 months. At 2 years, the average baseline glycated hemoglobin level ( $8.65 \pm 1.45\%$ ) had decreased in all groups, but patients in the two surgical groups had the greatest degree of improvement (average glycated hemoglobin levels,  $7.69 \pm 0.57\%$  in the medical-therapy group,  $6.35 \pm 1.42\%$  in the gastric-bypass group, and  $4.95 \pm 0.49\%$  in the biliopancreatic-diversion group).

**CONCLUSIONS**

In severely obese patients with type 2 diabetes, bariatric surgery resulted in better glucose control than did medical therapy. Preoperative BMI and weight loss did not predict the improvement in hyperglycemia after these procedures. (Funded by Catholic University of Rome; ClinicalTrials.gov number, NCT00888836.)

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**T**HE PREVALENCE OF TYPE 2 DIABETES MELLITUS is rapidly increasing worldwide, in parallel with the current obesity epidemic. In 2010, the global prevalence of type 2 diabetes was estimated at 8.3% of the adult population, a proportion that is projected to increase to 9.9% by 2030.<sup>1</sup> As many as 23% of patients with morbid obesity have type 2 diabetes,<sup>2</sup> and the prevalence of screening-detected diabetes is 8%.<sup>2</sup> Global spending on diabetes was estimated to be at least \$376 billion in 2010 and projected to be \$490 billion in 2030.<sup>3</sup>

Conventional medical treatment of type 2 diabetes only partially achieves adequate glycemic control and a reduction in cardiovascular risk.<sup>4</sup> Management of diabetes is particularly challenging in obese patients. With the noted exception of agonists of the glucagon-like peptide 1 (GLP-1) receptor and inhibitors of dipeptidyl peptidase 4 (DPP-4), oral hypoglycemic agents and insulin therapy may result in weight gain, which may further impair metabolic control. Thus, other approaches are needed.

Although originally developed solely as a weight-reduction therapy, bariatric surgery has been reported to improve type 2 diabetes<sup>5</sup> and to reduce rates of cardiovascular disease<sup>6</sup> and death.<sup>7</sup> Furthermore, experimental studies in rodents<sup>8</sup> and humans<sup>9-12</sup> suggest that certain bariatric procedures may improve diabetes control through mechanisms beyond weight loss. Both a consensus meeting<sup>13</sup> and the International Diabetes Federation<sup>14</sup> have recommended consideration of bariatric surgery for control of type 2 diabetes. Yet, level 1 clinical evidence to support surgery as an alternative treatment option is lacking. In one randomized, controlled trial, patients with type 2 diabetes who underwent laparoscopic adjustable gastric banding (LAGB) had a higher rate of remission of hyperglycemia than did patients who were treated medically.<sup>15</sup> However, patients in that study had relatively mild diabetes of short duration (<2 years), and diabetes remission was predicted according to the degree of postoperative weight loss.

A meta-analysis<sup>16</sup> of studies on various bariatric procedures involving patients with type 2 diabetes showed an overall rate of remission of hyperglycemia of 78% among the various procedures. Remission occurred in approximately half of patients who underwent LAGB, 80% of those who underwent Roux-en-Y gastric bypass, and 95% of those

who underwent biliopancreatic diversion. Unlike LAGB, gastric bypass and biliopancreatic diversion reroute food through the upper small bowel, which may activate mechanisms of diabetes control that are independent of weight.<sup>10,17</sup> These observations suggest that gastric bypass and biliopancreatic diversion may be more effective than medical therapy in the treatment of obese patients with diabetes, including those with more severe diabetes and longer disease duration.

Here we report the results of a single-center, nonblinded, randomized, controlled trial comparing the efficacy of two types of bariatric surgery (gastric bypass and biliopancreatic diversion) with conventional medical therapy in severely obese patients with type 2 diabetes.

## METHODS

### PATIENTS

From April 30, 2009, through October 31, 2011, we enrolled 72 patients at the Day Hospital of Metabolic Diseases and Diabetology of the Catholic University in Rome. Two teams of bariatric surgeons, one with expertise in laparoscopic gastric bypass and the other with expertise in open biliopancreatic diversion, performed the procedures.

The study was reviewed and approved by the institutional human ethics committee in accordance with national guidelines and the provisions of the Helsinki Declaration, as revised in 2000. All patients provided written informed consent to participate in the study, and additional written informed consent was obtained before any surgical procedure. The study protocol is available with the full text of this article at [NEJM.org](http://NEJM.org).

Inclusion criteria were an age of 30 to 60 years, a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of 35 or more, a history of type 2 diabetes of at least 5 years, a glycated hemoglobin level of 7.0% or more (as confirmed by at least three analyses), and an ability to understand and comply with the study protocol.

Exclusion criteria were a history of type 1 diabetes, diabetes secondary to a specific disease or glucocorticoid therapy, previous bariatric surgery, pregnancy, other medical conditions requiring short-term hospitalization, severe diabetes complications, other severe medical conditions, and geographic inaccessibility.

**RANDOMIZATION**

The patients were assigned to one of three study groups — gastric bypass, biliopancreatic diversion, or medical therapy — by simple randomization in a 1:1:1 ratio with the use of a computerized system for generating random numbers.

**TREATMENTS***Medical Therapy*

Patients in the medical-therapy group were assessed and treated by a multidisciplinary team that included a diabetologist, a dietitian, and a nurse, with planned visits at baseline and at 1, 3, 6, 9, 12, and 24 months after study entry.

Oral hypoglycemic agents and insulin doses were optimized on an individual basis with the aim of reaching a glycated hemoglobin level of less than 7%. Programs for diet and lifestyle modification, including reduced overall energy and fat intake (<30% total fat, <10% saturated fat, and high fiber content) and increased physical exercise ( $\geq 30$  minutes of brisk walking every day, possibly associated with moderate-intensity aerobic activity twice a week), were designed by an experienced diabetologist with assistance from a dietitian.

*Bariatric Surgery*

Patients who were assigned to undergo either gastric bypass or biliopancreatic diversion were evaluated by a multidisciplinary team (including a diabetologist, a dietitian, and a nurse) at baseline and at 1, 3, 6, 9, 12, and 24 months after surgery. (A detailed description of the surgical procedures is provided in the Supplementary Appendix, available at NEJM.org.) Medical therapy was adjusted according to the seven-point glycemic profile during the first 3 months and according to glycated hemoglobin levels thereafter. Discontinuation of medical therapy was considered in cases of normalization of the glycemic profile, glycated hemoglobin levels, or both.

Daily multivitamin and mineral supplementation was prescribed to the surgical groups; patients undergoing biliopancreatic diversion received additional vitamin D and calcium supplementation.

**LABORATORY ANALYSES**

Fasting plasma glucose was measured by means of the glucose oxidase method (Beckman) and plasma insulin by microparticle enzyme immunoassay (Abbott), with a sensitivity of 1  $\mu\text{U}$  per milliliter and an intraassay coefficient of variation of 6.6%.

Serum glycated hemoglobin levels were measured by high-performance liquid chromatography (normal range, 3.5 to 6.5%), and total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured by means of standard enzymatic assays. Low-density lipoprotein (LDL) cholesterol was calculated with the use of the Friedewald formula. The level of HDL cholesterol was defined as low if it was less than 40 mg per deciliter (1.0 mmol per liter) in men or less than 50 mg per deciliter (1.3 mmol per liter) in women.

**END POINTS**

The primary end point was the difference in the rate of remission of type 2 diabetes among patients undergoing either gastric bypass or biliopancreatic diversion, as compared with medical therapy. Remission of diabetes was defined as a fasting plasma glucose level of less than 100 mg per deciliter (5.6 mmol per liter) and a glycated hemoglobin level of less than 6.5% for at least 1 year without active pharmacologic therapy. This definition is in agreement with the recommendations from an expert consensus meeting organized by the American Diabetes Association,<sup>18</sup> in which partial remission of diabetes was defined as a fasting glucose level of 100 to 125 mg per deciliter (5.6 to 6.9 mmol per liter) and a glycated hemoglobin level of less than 6.5% for at least 1 year without active pharmacologic therapy; complete remission was defined as a fasting glucose level of 100 mg per deciliter and a glycated hemoglobin level of less than 6.0% for at least 1 year without active pharmacologic therapy. This study was neither designed nor powered to evaluate differences between two surgical procedures.

Secondary end points were changes from baseline in levels of fasting plasma glucose and glycated hemoglobin, the average glycated hemoglobin level, body weight, waist circumference, arterial blood pressure, and levels of plasma cholesterol, HDL cholesterol, and triglycerides at 2 years.

**STATISTICAL ANALYSIS**

The study was powered to detect an absolute difference of 65 percentage points in the rate of remission of type 2 diabetes between the gastric-bypass group and the medical-therapy group (on the basis of a remission rate of 15% for medical therapy and of 80% for gastric bypass) and a difference of 75 percentage points in the rate of re-

mission between the biliopancreatic-diversion group and the medical-therapy group (on the basis of a remission rate of up to 90% for biliopancreatic diversion), with a statistical power of 90% at a two-sided *P* value of 0.025. Because the study was not powered to assess differences among treatments on all the analyzed variables, results that are not related to the primary outcome should be considered as merely indicative. Analysis of the primary end points was performed on an intention-to-treat basis.

The assumptions on effect determined the need for 15 patients who would receive medical therapy, 15 who would undergo gastric bypass, and 11 who would undergo biliopancreatic diversion. However, assuming an attrition rate of 25% over the course of the study, we determined that we would need to enroll 60 patients (20 per study group).

We compared continuous variables in baseline characteristics using one-way analysis of variance. We used a chi-square test to study the association between study group and the rate of remission. In a secondary analysis, we used a Kaplan–Meier procedure with a log-rank test to compare surgical treatments for the time to remission. Logistic regression was applied to study the dependence of diabetes remission on some of the recorded variables. Changes at 2 years for continuous variables were expressed as percent changes as compared with baseline and were tested by a planned sequential procedure in which an analysis of variance was performed first and Bonferroni pairwise analyses were performed to compare treatments in case of global significance. Repeated-measurements analysis of variance was also used to test changes in continuous variables over time as being dependent on the study group. For these analyses, missing data were handled with the use of listwise deletion of missing data. Continuous variables are reported as means  $\pm$ SD and categorical variables as numbers and percentages. A *P* value of less than 0.05 was considered to indicate statistical significance.

## RESULTS

### PATIENTS

Overall, 60 of 72 screened patients underwent randomization (Fig. 1). Reasons for screening failure included abnormal results on electrocardiography,

chronic renal failure, geographical distance, and patients' preference to undergo bariatric surgery.

The retention rate was greater than expected, with 56 patients (93%) completing the 2-year follow-up (Fig. 1). Follow-up compliance was 100% in the three study groups among patients who did not drop out.

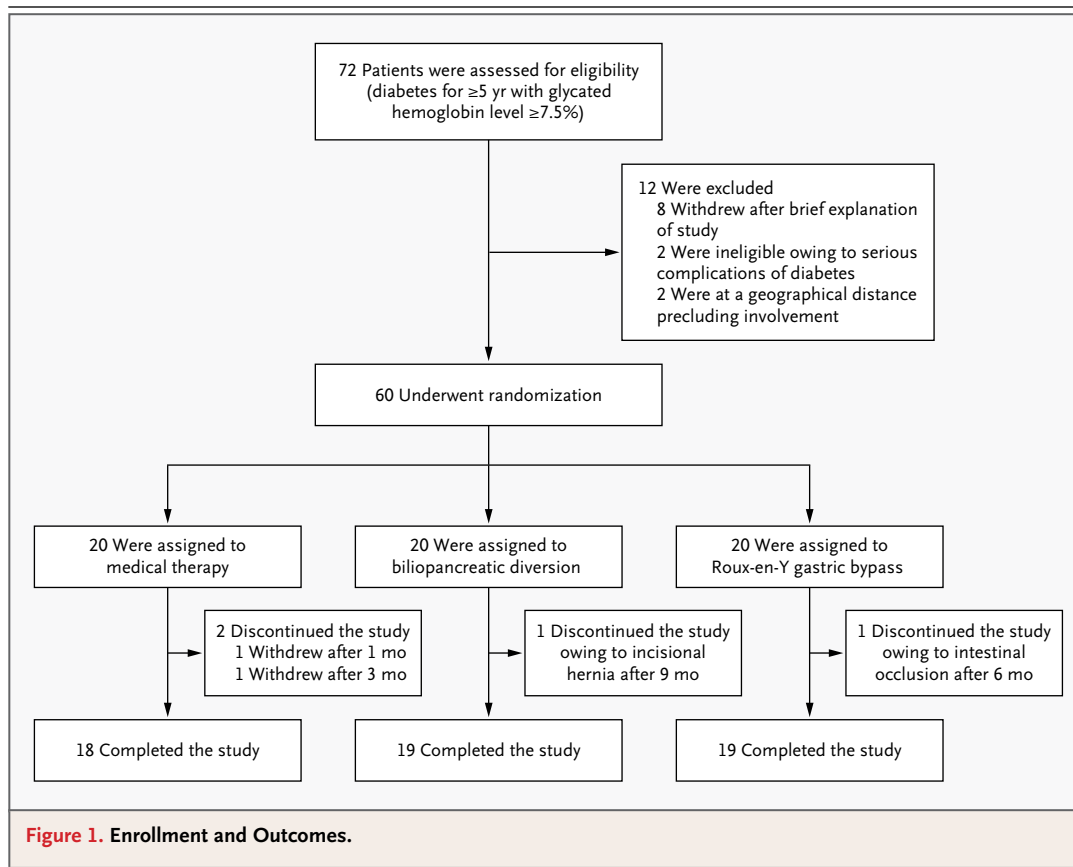
### LIPID CONTROL AT BASELINE

There were no significant differences among the study groups in baseline characteristics except for levels of total cholesterol, LDL cholesterol, and triglycerides (*P*=0.01 for all comparisons) (Table 1). Post hoc analyses showed that the medical-therapy group had higher values than the gastric-bypass group at baseline for total cholesterol (237 $\pm$ 60 mg per deciliter [6.12 $\pm$ 1.55 mmol per liter] vs. 182 $\pm$ 35 mg per deciliter [4.71 $\pm$ 0.91 mmol per liter], *P*=0.005), for LDL cholesterol (154 $\pm$ 54 mg per deciliter [3.99 $\pm$ 1.40 mmol per liter] vs. 109 $\pm$ 32 mg per deciliter [2.83 $\pm$ 0.84 mmol per liter], *P*=0.008), and for triglycerides (221 $\pm$ 71 mg per deciliter [2.49 $\pm$ 0.80 mmol per liter] vs. 147 $\pm$ 76 mg per deciliter [1.66 $\pm$ 0.86 mmol per liter], *P*=0.03), probably because most patients (approximately 65%) who underwent gastric bypass were already receiving hypolipidemic agents at the time of enrollment. Eligibility criteria for this study did not include cutoffs for hyperlipidemia or arterial blood pressure. Eligible patients underwent randomization as they presented, and there was no effort to optimize lipid and blood-pressure measurements before randomization.

### GLYCEMIC CONTROL

All patients in the surgical groups discontinued pharmacologic treatment (oral hypoglycemic agents and insulin) within 15 days after the operation on the basis of daily seven-point glucose profiles (premeal, postmeal, and bedtime).

At 2 years, diabetes remission had occurred in none of the patients receiving medical therapy, as compared with 15 of 20 (75%) undergoing gastric bypass and 19 of 20 (95%) undergoing biliopancreatic diversion (*P*<0.001 for both comparisons). There was a significant association between study group and rate of remission. However, since there were no remissions in the medical-therapy group, risk ratios were computed in a more conservative fashion on the assumption that remission had occurred in the 2 patients in the medical-therapy



group who dropped out. On the basis of this hypothesis, the relative risk of diabetes remission was 7.5 in the gastric-bypass group (95% confidence interval [CI], 1.97 to 28.61;  $P < 0.001$ ) and 9.5 in the biliopancreatic-diversion group (95% CI, 2.54 to 35.51;  $P < 0.001$ ), as compared with the medical-therapy group.

In the Kaplan–Meier analysis of levels of fasting glucose and glycated hemoglobin in the two surgical groups, the average time to normalization differed significantly, with  $10 \pm 2$  months for gastric bypass versus  $4 \pm 1$  months for biliopancreatic diversion ( $P = 0.01$ ).

Age, sex, baseline BMI, diabetes duration before study enrollment, and weight changes were not significant predictors of diabetes remission at 2 years or of normalization of levels of fasting glucose and glycated hemoglobin at 1 and 3 months on the basis of logistic-regression analysis.

At 2 years, average percent changes in glycated hemoglobin levels from the baseline value of  $8.65 \pm 1.45\%$  were smaller in the medical-therapy

group ( $-8.39 \pm 9.93\%$ ) than in the gastric-bypass group ( $-25.18 \pm 20.89\%$ ) and the biliopancreatic-diversion group ( $-43.01 \pm 9.64\%$ ) (Fig. 2). All post hoc between-group comparisons in glycated hemoglobin levels were significant, including the comparison between medical therapy and gastric bypass ( $P = 0.003$ ), between medical therapy and biliopancreatic diversion ( $P < 0.001$ ), and between gastric bypass and biliopancreatic diversion ( $P = 0.001$ ). Changes and trends in the fasting plasma glucose levels over time resembled those for glycated hemoglobin levels:  $-14.37 \pm 11.93\%$  in the medical-therapy group,  $-37.81 \pm 33.75\%$  in the gastric-bypass group, and  $-56.23 \pm 10.01\%$  in the biliopancreatic-diversion group (Table 2).

#### WEIGHT LOSS

At 2 years, patients in the two surgical groups had greater percent reductions in average body weight from baseline than did patients receiving medical therapy ( $-4.74 \pm 6.37\%$ ), with  $-33.31 \pm 7.88\%$  for gastric bypass and  $-33.82 \pm 10.17\%$  for biliopancreatic

**Table 1. Baseline Characteristics of the Patients.\***

Characteristic	Medical Therapy (N=20)	Biliopancreatic Diversion (N=20)	Gastric Bypass (N=20)	P Value†
Age — yr	43.45±7.27	42.75±8.06	43.90±7.57	0.90
Fasting glucose — mmol/liter	9.94±3.43	9.70±3.44	9.55±3.35	0.93
Glycated hemoglobin — %	8.51±1.24	8.88±1.71	8.56±1.40	0.69
Cholesterol — mmol/liter				
Total	6.12±1.55	5.54±1.50	4.71±0.91	0.01
High-density lipoprotein	0.99±0.21	0.99±0.21	1.13±0.23	0.07
Low-density lipoprotein	3.99±1.40	3.41±1.21	2.83±0.84	0.01
Triglycerides — mmol/liter	2.49±0.80	2.49±1.21	1.66±0.86	0.01
Blood pressure — mm Hg				
Systolic	155.20±34.18	154.50±29.73	145.75±20.54	0.51
Diastolic	96.00±17.52	95.90±12.87	91.50±14.15	0.56
Weight — kg	136.40±21.94	137.85±30.35	129.84±22.58	0.57
Height — cm	172.95±10.66	174.35±9.59	169.75±10.10	0.34
Body-mass index‡	45.62±6.24	45.14±7.78	44.85±5.16	0.93
Waist — cm	126.90±14.68	130.35±19.73	125.40±16.58	0.65
Diabetes duration — yr	6.08±1.24	6.00±1.26	6.03±1.18	0.98
Male sex — no. (%)	10 (50)	10 (50)	8 (40)	0.77

\* Plus-minus values are means ±SD. To convert the values for glucose to milligrams per deciliter, divide by 0.05551. To convert the values for cholesterol to milligrams per deciliter, divide by 0.02586. To convert the values for triglycerides to milligrams per deciliter, divide by 0.01129.

† P values are for all comparisons.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

diversion ( $P<0.001$  for both comparisons). Post hoc analysis showed a significant difference in weight loss between the surgical and medical-therapy groups ( $P<0.001$ ), with no significant difference between the two surgical groups. Changes in weight were reflected by BMI changes, which decreased from  $45.62\pm6.24$  to  $43.07\pm6.44$  in the medical-therapy group, from  $44.85\pm5.16$  to  $29.31\pm2.64$  in the gastric-bypass group, and from  $45.14\pm7.78$  to  $29.19\pm4.90$  in the biliopancreatic-diversion group. Waist circumference was significantly reduced after both types of surgery (Table 2).

#### LIPID PROFILE

Significant differences among the three groups were found for levels of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides at 2 years (Table 2). Apart from HDL cholesterol levels, post hoc analysis did not show significant differences between medical therapy and gastric bypass. Conversely, all lipid-profile measures (ex-

cept for HDL cholesterol) were significantly lower among patients undergoing biliopancreatic diversion than among those receiving medical therapy. All analyzed variables decreased over time except for HDL cholesterol, which increased in all three study groups. Overall, changes were larger for patients undergoing biliopancreatic diversion. However, HDL cholesterol levels increased significantly more among patients undergoing gastric bypass (by  $29.66\pm18.21\%$ ) than among those receiving medical therapy ( $6.03\pm6.25\%$ ) or undergoing biliopancreatic diversion ( $12.98\pm20.66\%$ ) ( $P<0.001$  for both comparisons). After 2 years, total cholesterol levels normalized in 27.3% of patients in the medical-therapy group, as compared with 100% of those in both the gastric-bypass and biliopancreatic-diversion groups ( $P<0.001$  for both comparisons); triglyceride levels normalized in 0%, 85.7%, and 92.3% of patients, respectively ( $P<0.001$ ), and HDL cholesterol levels in 11.1%, 100%, and 72.7% ( $P=0.005$ ).



**BLOOD PRESSURE**

Systolic and diastolic blood-pressure levels were significantly reduced in all three study groups. Antihypertensive therapy was reduced or discontinued in 70% of patients receiving medical therapy, 80% of those undergoing gastric bypass, and 85% of those undergoing biliopancreatic diversion.

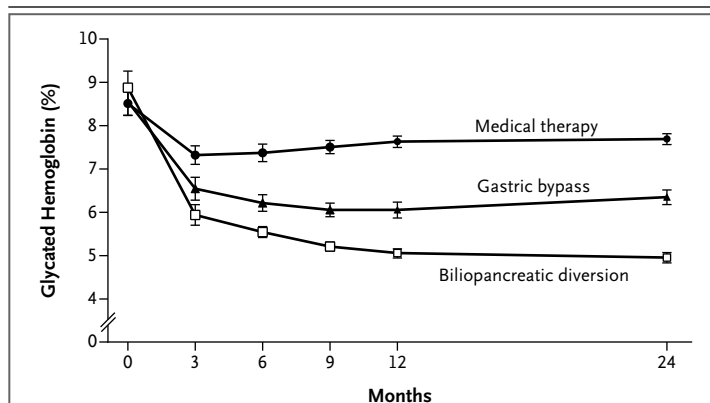
**SAFETY AND ADVERSE EVENTS**

There were no operative deaths among patients undergoing either gastric bypass or biliopancreatic diversion. An incisional hernia requiring reoperation 9 months after surgery developed in a patient undergoing biliopancreatic diversion, and one patient undergoing gastric bypass had an intestinal obstruction requiring reoperation 6 months after surgery. Two patients who were receiving medical therapy had persistent diarrhea associated with metformin, a condition that resolved when the drug was discontinued and another oral hypoglycemic agent was substituted. All surgical complications and side effects are listed in Table 3.

**DISCUSSION**

In our study, we compared optimized conventional medical therapy with two types of bariatric surgery (gastric bypass and biliopancreatic diversion) in patients with type 2 diabetes with a BMI of 35 or more. Our results indicated that at 2 years, the two types of bariatric surgery were far more effective than conventional medical therapy in the control of hyperglycemia in such patients with severe obesity. Gastric bypass and biliopancreatic diversion were associated with increased rates of remission of hyperglycemia (relative risk, 7.5 and 9.5, respectively) and greater reductions from baseline in levels of fasting glucose and glycated hemoglobin, as compared with medical therapy. These results were obtained in the framework of the most conservative analyses.

Although the degree of postoperative weight loss appears to be the major driver of the improvement in glucose control after LAGB,<sup>15</sup> there was no correlation between normalization of fasting glucose levels and weight loss after gastric bypass and biliopancreatic diversion, findings that are consistent with results of previous studies,<sup>8-12,19</sup> which suggests that such surgeries may exert effects on diabetes that are independent of weight.



**Figure 2.** Glycated Hemoglobin Levels during 2 Years of Follow-up.

The preoperative BMI did not predict control of diabetes after either surgical procedure, which calls into question the current use of a strict BMI cutoff as a stand-alone criterion for surgical indications.

The timing of diabetes remission differed between the two surgical groups in spite of similar weight loss, possibly because of the substantial malabsorption of fat that is characteristic of biliopancreatic diversion, which may translate to lower levels of circulating triglycerides and cholesterol. Indeed, we previously showed that intramyocellular lipid accumulation dramatically decreased 6 months after biliopancreatic diversion, and this decrease was associated with a large increase in the expression of glucose transporter type 4 (GLUT4) and with normalization of whole-body insulin resistance.<sup>20</sup> In one study, reductions in levels of triglycerides and LDL cholesterol after biliopancreatic diversion helped to normalize insulin sensitivity and to reduce rates of cardiovascular events.<sup>21</sup> However, intestinal malabsorption after biliopancreatic diversion can increase the incidence of late nutritional complications, such as hypoalbuminemia and deficiencies in vitamin D and calcium, even with vitamin and mineral supplementation, which raises concern about the potential of this operation to cause long-term nutritional side effects requiring rigorous and careful postoperative monitoring and care. In other studies, lifestyle modifications and bariatric surgery were associated with similar effects on blood-pressure control.<sup>5,15</sup>

Most studies show less weight loss with gastric bypass than with biliopancreatic diversion.<sup>16</sup>

**Table 2. Average Absolute Values and Percentage Changes at 2 Years.\***

Variable	Medical Therapy (N=18)	Biliopancreatic Diversion (N=19)	Gastric Bypass (N=19)	P Value†			
				Overall	Biliopancreatic Diversion vs. Medical Therapy	Gastric Bypass vs. Medical Therapy	Gastric Bypass vs. Bilio- pancreatic Diversion
Glucose (mmol/liter)	7.83±1.66	3.89±0.67	5.69±3.07	<0.001	<0.001	0.005	0.03
Change from baseline (%)	-14.37±11.93	-56.23±10.01	-37.81±33.75				
Glycated hemoglobin (%)	7.69±0.57	4.95±0.49	6.35±1.42	<0.001	<0.001	0.003	0.001
Change from baseline (%)	-8.39±9.93	-43.01±9.64	-25.18±20.89				
Cholesterol (mmol/liter)							
Total	4.91±0.87	2.77±0.81	4.27±0.77	<0.001	<0.001	0.31	<0.001
Change from baseline (%)	-16.82±11.60	-49.25±11.52	-6.83±27.03				
High-density lipoprotein	1.05±0.20	1.08±0.16	1.47±0.31	<0.001	0.61	<0.001	0.01
Change from baseline (%)	6.03±6.25	12.98±20.66	29.66±18.21				
Low-density lipoprotein	2.98±0.83	1.25±0.71	2.20±0.72	<0.001	<0.001	1.00	<0.001
Change from baseline (%)	-20.31±15.24	-64.63±15.93	-17.21±36.21				
Triglycerides (mmol/liter)	1.91±0.39	0.96±0.32	1.15±0.48	<0.001	<0.001	1.00	0.001
Change from baseline (%)	-18.28±7.84	-56.79±16.70	-21.17±41.23				
Blood pressure (mm Hg)							
Systolic	134.44±10.97	129.21±8.04	132.11±10.45	0.32	1.00	1.00	0.40
Change from baseline (%)	-11.15±12.71	-14.55±12.63	-9.02±7.51				
Diastolic	87.28±9.32	82.37±4.21	84.21±4.79	0.13	0.23	1.00	0.24
Change from baseline (%)	-7.14±11.51	-13.06±8.97	-7.30±9.42				
Weight (kg)	128.06±19.77	89.53±17.84	84.29±13.35	<0.001	<0.001	<0.001	1.00
Change from baseline (%)	-4.74±6.37	-33.82±10.17	-33.31±7.88				
Excess weight lost (%)	9.29±12.94	69.36±17.60	68.08±12.70	<0.001	<0.001	<0.001	1.00
Body-mass index	43.07±6.44	29.19±4.90	29.31±2.64	<0.001	<0.001	<0.001	1.00
Change from baseline (%)	-4.73±6.37	-33.82±10.17	-33.31±7.88				
Waist (cm)	116.33±12.14	103.53±16.94	98.58±13.06	<0.001	<0.001	<0.001	1.00
Change from baseline (%)	-7.69±7.80	-20.70±8.34	-19.91±8.44				

\* Plus-minus values are means ±SD.

† P values for the overall comparisons were calculated with the use of analysis of variance. P values for the comparisons between each of the two surgical procedures and medical therapy and for the comparison between the two types of surgery were calculated with the use of the Bonferroni method in post hoc analyses.

However, those findings seem to apply particularly to markedly obese patients (BMI, >50). In our study, the similar weight-loss outcome between the two procedures may reflect the fact that most patients had a BMI of less than 50 and also a relatively short-term follow-up for assessment of weight-loss maintenance. The adverse events observed in our trial were in line with those that have been reported previously.<sup>22-24</sup>

Our study has several limitations. The number of patients, although fulfilling the sample-size

requirement, was relatively small; larger multi-center studies will be required to confirm our findings. The study did not have sufficient power to analyze safety or to detect differences in other important end points, such as rates of death or cardiovascular events and differences in long-term morbidity between the two surgical procedures. Eligibility criteria did not include cutoffs for dyslipidemia or arterial blood pressure, and eligible patients underwent randomization as they presented. The observed significant differences in



**Table 3. Late Complications of Surgical Procedures.\***

Complication	Biliopancreatic Diversion (N=19)	Gastric Bypass (N=19)
Incisional hernia (9 mo)	1 Male patient (5%)	0
Intestinal occlusion (6 mo)	0	1 Male patient (5%)
Iron-deficiency anemia	2 Female patients (11%) <sup>†</sup>	2 Female patients (11%)
Hypoalbuminemia (albumin, <3.5 g/dl)	1 Female and 1 male patient (11%) <sup>†</sup>	0
Osteopenia (BMD T score, -2)	1 Female patient (5%)	0
Osteoporosis (BMD T score, -2.7)	1 Female patient (5%) <sup>†</sup>	0

\* The listed metabolic complications developed 9 to 18 months after the operations. BMD denotes bone mineral density at the femoral neck on dual-energy x-ray absorptiometry.

<sup>†</sup> One female patient had multiple complications.

lipid profile among the study groups at baseline reflect random allocation of patients to the three study groups. Although these differences had no direct implication for the primary end point, they may have influenced secondary outcome measures. Since our study was designed to evaluate medium-term benefits of bariatric surgery, the longer-term outcome is unclear because of the potential for recurrence of hyperglycemia.<sup>5,25</sup>

In conclusion, our findings indicate that bariatric surgery, specifically gastric bypass and biliopancreatic diversion, may be more effective than conventional medical therapy in controlling hyperglycemia in severely obese patients with type 2 diabetes.

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#### REFERENCES

1. IDF diabetes atlas. 5th ed. Brussels: International Diabetes Federation, 2011 (<http://www.idf.org/diabetesatlas>).
2. Hofso D, Jensen T, Hager H, Røislien J, Hjelmestaeth J. Fasting plasma glucose in the screening for type 2 diabetes in morbidly obese subjects. *Obes Surg* 2010;20:302-7.
3. Zhang P, Zhang X, Brown J, et al. Global healthcare expenditure on diabetes for 2010 and 2030. *Diabetes Res Clin Pract* 2010;87:293-301. [Erratum, *Diabetes Res Clin Pract* 2011;92:301.]
4. Liebl A, Mata M, Eschwège E. Evaluation of risk factors for development of complications in Type II diabetes in Europe. *Diabetologia* 2002;45:S23-S28.
5. Sjöström L, Lindroos AK, Peltonen M, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med* 2004;351:2683-93.
6. Sjöström L, Narbro K, Sjöström CD, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med* 2007;357:741-52.
7. Sjöström L, Peltonen M, Jacobson P, et al. Bariatric surgery and long-term cardiovascular events. *JAMA* 2012;307:56-65.
8. Rubino F, Forgione A, Cummings DE, et al. The mechanism of diabetes control after gastrointestinal bypass surgery reveals a role of the proximal small intestine in the pathophysiology of type 2 diabetes. *Ann Surg* 2006;244:741-9.
9. Salinari S, Bertuzzi A, Asnaghi S, Guidone C, Manco M, Mingrone G. First-phase insulin secretion restoration and differential response to glucose load depending on the route of administration in type 2 diabetic subjects after bariatric surgery. *Diabetes Care* 2009;32:375-80.
10. Guidone C, Manco M, Valera-Mora E, et al. Mechanisms of recovery from type 2 diabetes after malabsorptive bariatric surgery. *Diabetes* 2006;55:2025-31.
11. Laferrère B, Teixeira J, McGinty J, et al. Effect of weight loss by gastric bypass surgery versus hypocaloric diet on glucose and incretin levels in patients with type 2 diabetes. *J Clin Endocrinol Metab* 2008;93:2479-85.
12. Pories WJ, Caro JF, Flickinger EG, Meelheim HD, Swanson MS. The control of diabetes mellitus (NIDDM) in the morbidly obese with the Greenville Gastric Bypass. *Ann Surg* 1987;206:316-23.
13. Rubino F, Kaplan LM, Schauer PR, Cummings DE. The Diabetes Surgery Summit consensus conference: recommendations for the evaluation and use of gastrointestinal surgery to treat type 2 diabetes mellitus. *Ann Surg* 2010;251:399-405.
14. Dixon JB, Zimmet P, Alberti KG, Rubino F. Bariatric surgery: an IDF statement for obese Type 2 diabetes. *Diabet Med* 2011;28:628-42.
15. Dixon JB, O'Brien PE, Playfair J, et al. Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. *JAMA* 2008;299:316-23.
16. Buchwald H, Estok R, Fahrback K, et al. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am J Med* 2009;122(3):248.e5-256.e5.
17. Rubino F, Gagner M. Potential of surgery for curing type 2 diabetes mellitus. *Ann Surg* 2002;236:554-9.
18. Buse JB, Caprio S, Cefalu WT, et al. How do we define cure of diabetes? *Diabetes Care* 2009;32:2133-5.
19. Pories WJ. Bariatric surgery: risks and rewards. *J Clin Endocrinol Metab* 2008;93:Suppl 1:S89-S96.
20. Mingrone G, Henriksen FL, Greco AV, et al. Triglyceride-induced diabetes associated with familial lipoprotein lipase deficiency. *Diabetes* 1999;48:1258-63.
21. Iaconelli A, Panunzi S, De Gaetano A, et al. Effects of bilio-pancreatic diversion on diabetic complications: a 10-year follow-up. *Diabetes Care* 2011;34:561-7.
22. Maggard MA, Shugarman LR, Suttorp M, et al. Meta-analysis: surgical treatment of obesity. *Ann Intern Med* 2005;142:547-59.
23. Scopinaro N, Adami GF, Marinari GM, et al. Biliopancreatic diversion. *World J Surg* 1998;22:936-46.
24. Søvik TT, Aasheim ET, Taha O, et al. Weight loss, cardiovascular risk factors, and quality of life after gastric bypass and duodenal switch: a randomized trial. *Ann Intern Med* 2011;155:281-91.
25. DiGiorgi M, Rosen DJ, Choi JJ, et al. Re-emergence of diabetes after gastric bypass in patients with mid- to long-term follow-up. *Surg Obes Relat Dis* 2010;6:249-53.

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