

# Metabolic Effects of Bariatric Surgery in Patients With Moderate Obesity and Type 2 Diabetes

Analysis of a randomized control trial comparing surgery with intensive medical treatment

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**OBJECTIVE**—To evaluate the effects of two bariatric procedures versus intensive medical therapy (IMT) on  $\beta$ -cell function and body composition.

**RESEARCH DESIGN AND METHODS**—This was a prospective, randomized, controlled trial of 60 subjects with uncontrolled type 2 diabetes ( $HbA_{1c}$   $9.7 \pm 1\%$ ) and moderate obesity ( $BMI$   $36 \pm 2$   $kg/m^2$ ) randomized to IMT alone, IMT plus Roux-en-Y gastric bypass, or IMT plus sleeve gastrectomy. Assessment of  $\beta$ -cell function (mixed-meal tolerance testing) and body composition was performed at baseline and 12 and 24 months.

**RESULTS**—Glycemic control improved in all three groups at 24 months ( $N = 54$ ), with a mean  $HbA_{1c}$  of  $6.7 \pm 1.2\%$  for gastric bypass,  $7.1 \pm 0.8\%$  for sleeve gastrectomy, and  $8.4 \pm 2.3\%$  for IMT ( $P < 0.05$  for each surgical group versus IMT). Reduction in body fat was similar for both surgery groups, with greater absolute reduction in truncal fat in gastric bypass versus sleeve gastrectomy ( $-16$  vs.  $-10\%$ ;  $P = 0.04$ ). Insulin sensitivity increased significantly from baseline in gastric bypass (2.7-fold;  $P = 0.004$ ) and did not change in sleeve gastrectomy or IMT.  $\beta$ -Cell function (oral disposition index) increased 5.8-fold in gastric bypass from baseline, was markedly greater than IMT ( $P = 0.001$ ), and was not different between sleeve gastrectomy versus IMT ( $P = 0.30$ ). At 24 months,  $\beta$ -cell function inversely correlated with truncal fat and prandial free fatty acid levels.

**CONCLUSIONS**—Bariatric surgery provides durable glycemic control compared with intensive medical therapy at 2 years. Despite similar weight loss as sleeve gastrectomy, gastric bypass uniquely restores pancreatic  $\beta$ -cell function and reduces truncal fat, thus reversing the core defects in diabetes.

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Type 2 diabetes mellitus and obesity are closely interrelated chronic conditions growing in incidence worldwide, with diabetes-related deaths projected to double between 2005 and 2030 (1). The development of both insulin resistance and insulin secretory defects is the hallmark of type 2 diabetes, resulting in

progressive hyperglycemia, subsequent microvascular complications, and macrovascular complications. Although lifestyle modifications and oral hypoglycemic agents improve glycemic control, the majority of patients do not achieve the optimal glycohemoglobin ( $HbA_{1c}$ ) levels recommended by current guidelines ( $\leq 7.0\%$ ). The disease inexorably progresses in the majority of patients, ultimately requiring insulin replacement therapy. Most patients with type 2 diabetes are overweight or obese ( $BMI \geq 30$   $kg/m^2$ ), and abdominal adiposity, particularly, is tightly linked to induction of insulin resistance, metabolic syndrome, and increased cardiovascular risk. Many hypoglycemic agents, especially insulin, exacerbate weight gain and thwart lifestyle efforts, potentially contributing to the underlying pathophysiological disorder.

Because of the limitations to medical therapy, surgical approaches for the treatment of obesity have increased 10-fold in the past decade. Roux-en-Y gastric bypass surgery is the most commonly performed in the United States, followed closely by the sleeve gastrectomy (2). Recently, two randomized controlled trials (3,4) demonstrated improved glycemic control in patients undergoing bariatric surgery compared with intensive medical therapy, resulting in the ability to withdraw or reduce glucose-lowering medications. The rapid rate of glucose lowering, disproportionate to degree of weight loss, suggests that bariatric surgery reverses the fundamental pathophysiological defects of type 2 diabetes. Animal studies suggest that bariatric surgery increases insulin secretion or improves enteroinsular responses, specifically, the main incretin hormones glucagon like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP) (5–7). Previous small-scale studies from matched case-control and observational studies in severely obese diabetic individuals have reported that weight loss improves insulin sensitivity, reduces hyperinsulinemia, and improves pancreatic  $\beta$ -cell function by

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A slide set summarizing this article is available online.

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weight-independent mechanisms related to an incretin effect (8–10). However, there are no data from a randomized controlled trial examining the prolonged metabolic adaptations in conjunction with clinical efficacy outcomes after bariatric surgery relative to the effects of intensive medical therapy in moderately obese subjects with poorly controlled type 2 diabetes.

The STAMPEDE trial evaluated the efficacy and safety of intensive medical therapy (IMT) alone or intensive medical therapy combined with Roux-en-Y gastric bypass or sleeve gastrectomy to achieve a primary end point of HbA<sub>1c</sub> level of ≤6% (with or without medications) after 1 year of follow-up (11). The current report is a 2-year extension of a metabolic substudy of the STAMPEDE trial designed to thoroughly evaluate the effects of the three treatments on glucose regulation, pancreatic β-cell function (insulin secretion/sensitivity), and body composition in a subset of 60 subjects.

## RESEARCH DESIGN AND METHODS

### Study design

The STAMPEDE study rationale and design have been previously reported (3,11). The first consecutive 60 subjects randomized in the main trial, with ~20 randomized to each treatment group, were included in the substudy. STAMPEDE was a single-center study that randomized patients in a 1:1:1 ratio to intensive medical therapy alone or intensive medical therapy combined with either Roux-en-Y gastric bypass or sleeve gastrectomy with stratification by use of insulin at screening. Intensive medical therapy included the use of the latest lifestyle guidelines by the American Diabetes Association, frequent home monitoring and titration strategies, and use of the latest U.S. Food and Drug Administration–approved drug therapy including incretin analogs or mimetics and insulin sensitizers for treatment of hyperglycemia. Patients were examined in the outpatient clinic every 3 months by a diabetes specialist at the Cleveland Clinic (S.R.K.). The bariatric procedures were performed by a single primary surgeon (P.R.S.).

During the screening period, all patients received nutritional counseling by a certified diabetes educator. Subjects were encouraged to participate in Weight Watchers for additional nutritional counseling. Patients underwent a psychological evaluation before randomization

to assess qualification for bariatric surgery. Subjects randomized to bariatric surgery had periodic evaluation by nutrition, psychology, bariatricians, and the surgery team as clinically indicated. The Data and Safety Monitoring Board convened yearly to review progress and safety of the trial. The protocol was developed with the assistance of the Cleveland Clinic Coordinating Center for Clinical Research and was approved by the Cleveland Clinic Institutional Review Board. All participants provided written informed consent.

After randomization at the baseline visit and at 12 and 24 months after randomization, subjects underwent metabolic assessment with a liquid mixed-meal tolerance test and body composition measurements with dual-energy X-ray absorptiometry (iDXA; Lunar Prodigy, Madison, WI) scan.

### Metabolic studies

The mixed-meal tolerance test was performed to assess glucose tolerance and metabolic measures of insulin sensitivity and secretion in response to a physiological stimulus. The liquid mixed meal consisted of a commercial product (Boost; 8 ounces, 350 kcal, 55% carbohydrate, 25% protein, 20% fat) and was consumed over 5 min after a 12- to 14-h overnight fast in a similar manner per protocol at baseline and 12 and 24 months. Fasting blood samples were obtained for glucose, C-peptide, insulin, lipids, HbA<sub>1c</sub>, adipokines, and a complete metabolic panel. Blood was drawn every 30 min for 120 min during the mixed meal tolerance testing for determination of glucose, insulin, C-peptide, and free fatty acid responses. Additional blood was drawn at fasting and at 60 min after ingestion for determination of GLP-1 and GIP responses. Glucagon levels were determined at fasting and at 120 min. Diabetes medications were withheld for 24 h before study, including insulin administration.

### Analytic determinations

Blood glucose was measured using the glucose oxidase method (YSI 2300 STAT Plus; YSI, Yellow Springs, OH). Plasma insulin was assayed by a double-antibody radioimmunoassay (RIA; Linco Research, St. Charles, MO). The intra-assay and interassay coefficients of variations were 2.6% and 3.0%, respectively. C-peptide was assayed using a chemiluminescence immunoassay (Linco Research). The intra-assay and interassay coefficients of variations were 3.5% and 7.2%, respectively. Blood

collected for GLP-1 (active) and GIP (total) analyses was treated immediately with a DPP4 and protease cocktail inhibitor (Sigma) and assayed using ELISA kits (ALPCO Diagnostics, Salem, NH). The intra-assay and interassay coefficients of variations were 3.6% and 9.3%, respectively. To correct for inter-assay variability, all premeasurements and postmeasurements for each individual were run on the same plate. Free fatty acid levels were determined by standard colorimetric methods (Wako Chemicals, Richmond, VA). The intra-assay and interassay coefficients of variation were 3.0% and 4.6%, respectively. Leptin was assayed using ELISA kits (R&D Systems, Minneapolis, MN). The intra-assay and interassay coefficients of variations were 3.6% and 5.3%, respectively.

### Calculations

Insulin secretion rate (ISR) in vivo was reconstructed by deconvolution of plasma concentrations of C-peptide, a peptide with linear kinetics that is cosecreted with insulin but is not extracted by the liver as previously described (8,12). ISRs over each sampling period were derived by using a well-accepted two-compartment model described by Van Cauter et al. (12) of C-peptide distribution and degradation and standard parameters for C-peptide clearance estimated for each subject, taking into account body surface area, sex, and age. ISR was related to the glucose stimulus by dividing the incremental area under curve (AUC) for ISR by the incremental AUC for plasma glucose. Pancreatic β-cell function measured by the insulin secretion/insulin resistance (disposition) index was determined by dividing the ΔISR/Δglucose by the severity of insulin resistance (ΔISR [AUC] / ΔG [AUC] ÷ IR), as measured by the inverse of the Matsuda index (13). The Matsuda index incorporates both hepatic and muscle components of insulin resistance, correlates well with euglycemic insulin clamp, and was calculated as follows:

$$\text{Matsuda index} = \frac{10,000}{\sqrt{(\text{FPG} \times \text{FPI}) \times (\text{mean PG} \times \text{mean PI})}}$$

Of note, the Matsuda index was performed in those subjects not using exogenous insulin. The incremental AUC for ISR (ΔISR [AUC]) and the incremental AUC for plasma glucose (ΔG

[AUC]) were calculated according to the trapezoid rule. The incretin response during meal testing subtracted the fasting value from the meal value at 60 min.

### Statistical analysis

This is a preplanned substudy with pre-specified analysis. However, because of the lack of published data in the literature regarding specified metabolic outcome measures at the time of trial design (2004–2005), and because of the exploratory nature of the substudy, no power calculations were performed for the substudy measures. Continuous variables with a normal distribution are reported as means and SDs. Variables with a non-normal distribution are reported as medians and interquartile ranges. Categorical variables were summarized using frequencies and were tested with the  $\chi^2$  statistic or Fisher exact test (two-tailed), as appropriate. One-way ANOVA was used to analyze continuous laboratory parameters, and comparisons between treatment groups were performed with either the Student *t* test or the Wilcoxon test. Glucose and insulin measures collected during the mixed-meal tolerance test were plotted graphically.

## RESULTS

### Patients

Sixty subjects enrolled in the substudy after randomization. At 24 months, 10% were lost to follow-up, with 17 subjects remaining in intensive medical therapy and 18 and 19 subjects remaining in the gastric bypass and sleeve gastrectomy groups, respectively. Baseline characteristics for the three study groups that were followed up for 24 months are shown in Table 1. The subjects were middle-aged, with a predominance of females, particularly in the sleeve gastrectomy group. The average BMI was 36 kg/m<sup>2</sup> with prolonged diabetes duration with mean baseline HbA<sub>1c</sub> levels of ~9%, indicating poor glycemic control despite using multiple glucose-lowering agents. Nearly half were insulin users, and a majority had hypertension and hyperlipidemia.

### Glycemic and cardiovascular risk control

Table 2 shows glycemic and lipid outcomes at 12 and 24 months. Although glycemic control improved in all three arms at 24 months as compared with baseline, the gastric bypass group had significantly greater reduction in fasting

glucose and HbA<sub>1c</sub> levels compared with IMT ( $P < 0.05$ ) (Table 2). At 24 months, the proportion of patients with HbA<sub>1c</sub>  $\leq 6\%$  attenuated in the sleeve gastrectomy group from 26% to 11% but persisted in the gastric bypass group. The percent of patients using insulin at 24 months was markedly lower in gastric bypass and sleeve gastrectomy groups as compared with IMT. Large increases in HDL cholesterol and reductions in levels of triglycerides and high-sensitivity C-reactive protein were noted in both surgery groups as compared with the IMT group. Other laboratory parameters and medication usage are available in Supplementary Table 1.

Three subjects randomized to bariatric surgery required reoperation, including laparoscopy to assess nausea and vomiting, for cholecystectomy and for jejunostomy for feeding access to treat a gastric leak after sleeve gastrectomy. There were no deaths or episodes of serious hypoglycemia requiring intervention, malnutrition, or excessive weight loss among the three groups.

### Body weight, body composition, and adipokines

Greater total body weight loss occurred after bariatric procedures compared with IMT at 12 months and was maintained at 24-month follow-up. A similar reduction in body weight, BMI, and absolute change in total body fat percent was observed between the sleeve gastrectomy and gastric bypass group at 24 months. However, despite similar weight loss, the absolute reduction in percent truncal fat was greater in the gastric bypass versus sleeve gastrectomy group ( $-16\%$  vs.  $-10\%$ ;  $P = 0.04$ ). Leptin levels reduced markedly after surgical weight loss, especially gastric bypass, compared with IMT. Suppression of free fatty acid concentration during mixed-meal testing was evident after both surgical procedures versus IMT (Supplementary Table 1).

### Mixed-meal tolerance

Figure 1 demonstrates the median glucose and C-peptide levels during the mixed-meal tolerance test at baseline and 24 months. At 24 months, the shape of the glucose tolerance curve for gastric bypass normalized with a marked reduction in fasting and postprandial glucose levels. Intermediate effects on postprandial glucose lowering were noted in sleeve gastrectomy, and IMT showed the least change. Large reductions in fasting C-peptide levels were observed in sleeve gastrectomy and gastric bypass at

24 months but did not change in the IMT group. Postprandial C-peptide levels and insulin secretion rate at 30 and 60 min increased by more than two-fold in gastric bypass and sleeve gastrectomy, with greater increases noted with gastric bypass. The average AUC for insulin secretion rate at 24 months was significantly greater with both gastric bypass ( $4.4 \pm 4$  pmol/min) and sleeve gastrectomy ( $3.3 \pm 2.5$  pmol/min) than IMT ( $1.7 \pm 2.4$  pmol/min; both  $P < 0.01$ ).

### Insulin sensitivity

Median values for the insulin sensitivity (Matsuda index) in noninsulin-using subjects increased at 24 months after gastric bypass ( $N = 9$ ) by 2.7-fold ( $3.8$  vs.  $1.4$ ;  $P < 0.001$ ) and 1.2-fold after sleeve gastrectomy ( $N = 10$ ;  $5.8$  vs.  $5.3$ ) and did not change with IMT ( $2.6$  vs.  $2.4$ ;  $P =$  not significant). The absolute change in median insulin sensitivity (Matsuda index) at 24 months tended to be higher in gastric bypass compared with sleeve gastrectomy ( $2.3$  [quartile 1:  $0.9$ ; quartile 3:  $3.1$ ] vs.  $0.9$  [quartile 1:  $-1.5$ ; quartile 3:  $4.6$ ]), despite equivalent weight loss.

### Pancreatic hormonal function

The absolute change in median values for pancreatic  $\beta$ -cell function (oral disposition index) at 24 months was markedly greater in gastric bypass than IMT ( $0.196$  [quartile 1:  $0.14$ ; quartile 3:  $0.29$ ] vs.  $0.027$  [quartile 1:  $-0.011$ ; quartile 3:  $0.074$ ];  $P = 0.001$ ) but not different between sleeve gastrectomy and medical therapy ( $0.058$  [quartile 1:  $-0.009$ ; quartile 3:  $0.416$ ] vs.  $0.027$  [quartile 1:  $-0.011$ ; quartile 3:  $0.074$ ];  $P = 0.30$ ). A median 5.8-fold (quartile 1:  $-7.00$ ; quartile Q3:  $11.29$ ) increase in  $\beta$ -cell function from baseline was noted in gastric bypass, with negligible increases in sleeve gastrectomy and IMT.

The change in  $\beta$ -cell function over 24 months for the substudy cohort correlated with the change in percentage of truncal fat ( $r = 0.43$ ;  $P = 0.0013$ ) and change in body weight ( $r = 0.49$ ;  $P < 0.001$ ). At 24 months, both percentage of truncal fat ( $r = -0.32$ ;  $P = 0.02$ ) and prandial free fatty acid levels ( $r = -0.48$ ;  $P = 0.0003$ ) were inversely correlated with  $\beta$ -cell function. In a multivariable analysis including both factors, prandial free fatty acid levels remained significant ( $P = 0.004$ ), whereas percentage of truncal fat was no longer significant ( $P = 0.41$ ).

Fasting glucagon concentrations were similar among the three groups at baseline. At 12 months, median glucagon

Table 1—Baseline characteristics

Parameter	All patients	IMT (N = 17)	Gastric bypass (N = 18)	Sleeve gastrectomy (N = 19)	P*
Age (years)	48.4 ± 9.3	50 ± 8.4	47.9 ± 9.7	47.5 ± 10.0	0.71
Female, n (%)	32 (59.3)	8 (47.1)	8 (44.4)	16 (84.2)	0.02
Caucasian, n (%)	39 (72.2)	14 (82.4)	11 (61.1)	14 (73.7)	0.37
Body weight (kg)	104.3 ± 15.1	107.9 ± 14.5	105.3 ± 13.6	100.0 ± 16.5	0.28
BMI (kg/m <sup>2</sup> )	36.1 ± 2.9	35.8 ± 3.0	36.1 ± 2.6	36.4 ± 3.2	0.83
Duration of diabetes (years)	8.4 ± 5.0	10.5 ± 5.0	7.4 ± 5.0	7.6 ± 4.5	0.12
N of diabetes medications					0.68
1	2 (3.7)	1 (5.9)	0 (0.0)	1 (5.3)	
2	11 (20.4)	5 (29.4)	3 (16.7)	3 (15.8)	
≥3	41 (75.9)	11 (64.7)	15 (83.3)	15 (78.9)	
Insulin users, n (%)	25 (46.3)	8 (47.1)	8 (44.4)	9 (47.4)	0.98
History of dyslipidemia, n (%)	44 (81.5)	14 (82.4)	15 (83.3)	15 (78.9)	1.0
History of hypertension, n (%)	34 (63.0)	10 (58.8)	13 (72.2)	11 (57.9)	0.61

\*P is for the overall comparison across treatment groups. The mean ± SD are reported for continuous variables. The BMI is calculated as weight in kilograms divided by the square of the height in meters. Race was self-reported.

levels tended to be lower in gastric bypass versus IMT (46 vs. 77 pg/mL;  $P = 0.07$ ) and were reduced in sleeve gastrectomy versus IMT (38 vs. 77 pg/mL;  $P < 0.02$ ). However, at 24 months fasting glucagon levels were not different among the three groups (~60 pg/mL).

Postprandial glucagon levels reduced in all three groups at 24 months from baseline values, but postprandial glucagon levels in gastric bypass were higher (77 pg/mL) than IMT (64 pg/mL;  $P < 0.05$ ) and not different between sleeve gastrectomy (65 pg/mL) and IMT.

### Incretin responses

Median levels of GLP-1 60 minutes after mixed-meal ingestion (taking into account fasting levels) increased dramatically 24 months after gastric bypass (12.5 vs. 2 pmol/L;  $P < 0.001$ ) and sleeve gastrectomy (7.3 vs. 2.4 pmol/L;  $P < 0.01$ ) and did not change with IMT (1.5 vs. 1.4 pmol/L;  $P =$  not significant). In contrast, median levels of GIP in response to mixed meal were reduced 24 months after gastric bypass (13.5 vs. 30.7 pmol/L;  $P < 0.01$ ) and were significantly different ( $P < 0.01$ ) from sleeve gastrectomy (36.9 pmol/L) and IMT (29.7 pmol/L). Both surgical groups had an overall increase in the incremental change in median GLP-1 response to mixed meal as compared with IMT at 24 months (gastric bypass 10.0 pmol/L [quartile 1: 5.2; quartile 3: 15.2] vs. sleeve gastrectomy 4.5 pmol/L [quartile 1: 2.9; quartile 3: 8.2];  $P = 0.07$ ; vs. IMT -0.4 pmol/L [quartile 1: -1.8; quartile 3: 1.1];  $P < 0.001$  for

both). However, a reduction in GIP response was noted in gastric bypass only at 24 months (gastric bypass, -20 pmol/L [quartile 1: -44.2; quartile 3: -10.2] vs. IMT 5.4 pmol/L [quartile 1: -6.3; quartile 3: 30.4];  $P < 0.001$  vs. sleeve gastrectomy 0.6 pmol/L [quartile 1: -18.6; quartile 3: 33.2];  $P =$  NS).

### Metabolic determinants of HbA<sub>1c</sub> ≤6% at 24 months

A multivariate logistic model of metabolic parameters that were associated with HbA<sub>1c</sub> ≤6% at 24 months in the substudy cohort demonstrated that the fold increase in the oral disposition index ( $\beta$ -cell function) was associated with an increased odds ratio of 1.67 (CI 1.012–1.124;  $P = 0.016$ ), and the increase in truncal fat was associated with a lower odds ratio of 0.878 (CI 0.777–0.991;  $P = 0.036$ ) to achieve glycemic control at 24 months.

**CONCLUSIONS**—Two recent bariatric surgery studies have shown markedly improved glycemic control in surgically treated patients with obesity and type 2 diabetes compared with medical therapy (3,4). In one of those studies, the STAMPEDE trial, 1 year after randomization, patients assigned to bariatric surgery were significantly more likely to achieve an HbA<sub>1c</sub> level of 6% compared with patients treated using IMT alone (3). In the current metabolic substudy, we extended follow-up of the STAMPEDE trial patients to 2 years and sought to determine the durability of the initial results and to examine the metabolic adaptations responsible

for the improved glycemic control observed with bariatric surgery. We measured a wide range of metabolic parameters at three time points, at baseline, after the original 1-year follow-up, and repeated measurements 2 years after initial randomization.

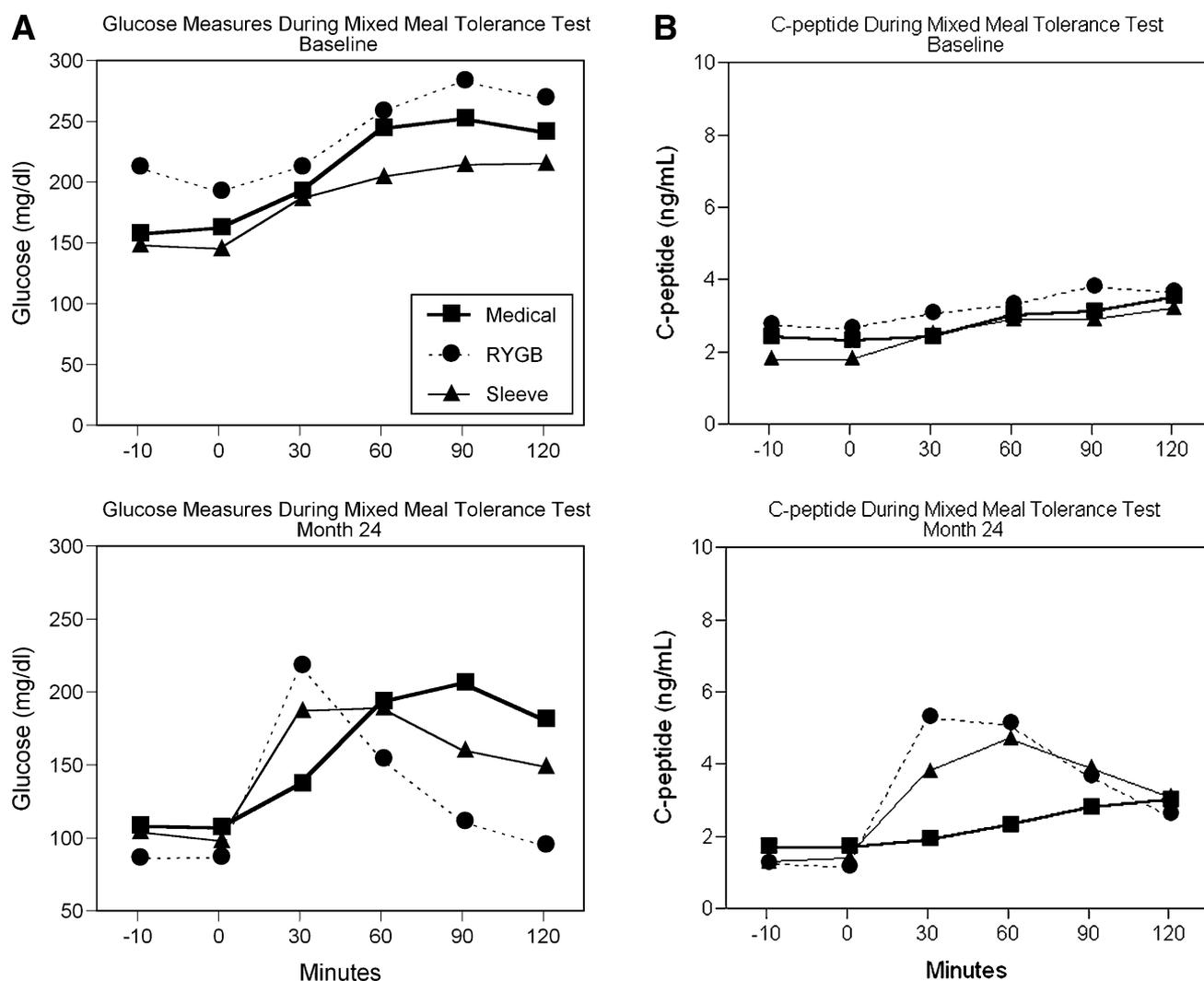
After 2 years, gastric bypass provided more durable glycemic control with little or no need for glucose-lowering agents in patients randomized to this strategy. Despite comparable weight loss compared with sleeve gastrectomy, more durable glycemic control was achieved in patients randomized to gastric bypass, with a substantially greater percentage of patients attaining the target HbA<sub>1c</sub> levels of ≤6%. Attenuation of improvement in diabetes control was noted in the sleeve gastrectomy treatment group despite persistent weight loss. Other long-term observational studies have documented greater relapse rates for glycemic control after gastric restrictive procedures such as sleeve gastrectomy, suggesting that surgical weight loss from enforced caloric restriction itself is insufficient to halt the disease (14,15). Our results extend the findings from our initial 12-month report and suggest factors beyond weight loss that are specific to intestinal bypass patients help regulate glucose levels and restore pancreatic  $\beta$ -cell function.

Striking metabolic changes were observed in patients randomized to bariatric surgery compared with intensive medical therapy, particularly in the gastric bypass treatment group. At baseline, all randomized patients exhibited poor pancreatic secretory function. After both 1 and 2

Table 2—Clinical changes at 12 and 24 months: glycemic and lipid control

	IMT (N = 17)	Gastric bypass (N = 18)	Sleeve gastrectomy (N = 19)	P*	P†	P‡
HbA <sub>1c</sub> ≤6 (12 months)	1/16 (6.25)	8/18 (44.44)	5/19 (26.32)	0.02	0.19	0.25
HbA <sub>1c</sub> ≤6 (24 months)	1/17 (5.9)	6/18 (33.3)	2/19 (10.5)	0.09	1.00	0.12
HbA <sub>1c</sub> (%)						
Baseline	9.5 ± 1.73	9.8 ± 1.35	9.7 ± 1.95	0.54	0.74	0.84
12 months	8.1 ± 2.34	6.3 ± 0.78	6.9 ± 1.11	0.004	0.05	0.08
24 months	8.4 ± 2.33	6.7 ± 1.23	7.1 ± 0.84	0.01	0.04	0.18
Change from baseline	-1.1 ± 1.99	-3.1 ± 1.38	-2.5 ± 2.39	0.001	0.06	0.37
Fasting plasma glucose, median, IQR (mg/dL)§						
Baseline	180 (159–241)	211 (181–252)	164 (112–224)	0.19	0.30	0.04
12 months	129 (103–212)	93 (78–133.0)	97 (81–137)	0.05	0.09	0.81
24 months	134 (90–160)	87 (75–105)	104 (80–113)	0.03	0.04	0.34
Change from baseline	-33.0 (-96 to -4)	-124 (-157 to -100)	-70 (-116 to -8.0)	0.001	0.31	0.03
N of subjects using insulin at 24 months	10 (59)	1 (5.6)	2/18 (11.1)	0.001	0.003	1.0
HDL cholesterol (mg/dL)						
Baseline	45.4 ± 11.9	40.5 ± 9.6	40.7 ± 8.2	0.19	0.17	0.95
24 months	50.2 ± 9.2	54.3 ± 13.5	57.5 ± 16.4	0.30	0.12	0.53
Change from baseline	4.8 ± 7.2	13.8 ± 8.8	16.8 ± 13.0	0.002	0.002	0.43
Triglycerides (mg/dL), median (IQR)§						
Baseline	155 (118–221)	161 (97–257)	154 (104–176)	0.99	0.69	0.61
24 months	127 (94–145)	126 (63–153)	119 (82–158)	0.49	0.89	0.45
Change from baseline	-56.0 (-81 to -8)	-56.0 (-131 to -11)	-2.0 (-61 to 9)	0.41	0.36	0.06
High-sensitivity C-reactive protein (mg/L), median (IQR)§						
Baseline	3.6 (2.4–5.1)	3.8 (2.0–5.8)	6.0 (2.9–9.9)	0.99	0.05	0.10
24 months	3.1 (2.1–5.5)	0.5 (0.3–2.0)	1.5 (0.6–3.6)	0.001	0.02	0.04
Change from baseline	-0.1 (-0.8 to 2.1)	-2.6 (-4.4 to -0.6)	-2.4 (-8.4 to -1.4)	0.001	0.002	0.75
Body weight (kg)						
Baseline	107.9 ± 14.5	105.3 ± 13.6	100.0 ± 16.5	0.58	0.14	0.30
12 months	106.3 ± 14.7	77.6 ± 10.0	75.8 ± 12.5	<0.001	<0.001	0.63
24 months	107.4 ± 14.9	79.9 ± 11.7	77.5 ± 14.3	<0.001	<0.001	0.58
Change from baseline	-0.5 ± 4.09	-25.4 ± 10.32	-22.5 ± 8.79	<0.001	<0.001	0.37
BMI (kg/m <sup>2</sup> )						
Baseline	35.8 ± 2.9	36.1 ± 2.6	36.4 ± 3.2	0.74	0.57	0.77
12 months	35.3 ± 3.3	26.7 ± 2.5	27.6 ± 2.5	<0.001	<0.001	0.27
24 months	35.6 ± 3.1	27.4 ± 2.9	28.2 ± 3.1	<0.001	<0.001	0.46
Change from baseline	-0.2 ± 1.41	-8.7 ± 3.13	-8.2 ± 3.01	<0.001	<0.001	0.66
Total body fat (%)						
Baseline	42.2 ± 4.5	41.1 ± 4.7	46.1 ± 4.9	0.48	0.02	0.003
12 months	42.0 ± 6.7	27.0 ± 8.5	36.0 ± 6.3	<0.001	0.01	0.001
24 months	43.3 ± 5.2	30.5 ± 8.5	38.4 ± 6.1	<0.001	0.01	0.003
Change from baseline	1.1 ± 1.7	-10.6 ± 6.6	-7.7 ± 3.5	<0.001	<0.001	0.11
Truncal fat (%)						
Baseline	49.1 ± 4.23	50.0 ± 5.45	51.8 ± 4.62	0.59	0.07	0.27
12 months	47.9 ± 6.65	29.7 ± 10.02	39.1 ± 6.49	<0.001	<0.001	0.002
24 months	50.0 ± 5.04	34.1 ± 9.66	41.7 ± 5.93	<0.001	<0.001	0.006
Change from baseline	0.9 ± 2.3	-15.9 ± 10.7	-10.1 ± 5.0	<0.001	<0.001	0.04
Leptin (ng/mL)§						
Baseline	24.9 (15.6–30.8)	24.0 (15.1–31.0)	29.6 (21.4–49.5)	0.93	0.18	0.10
12 months	24.9 (16.2–33.4)	4.9 (3.1–12.8)	10.4 (7.6–21.5)	<0.001	0.003	0.02
24 months	29.3 (21.2–37.8)	7.2 (3.1–15.3)	19.1 (11.2–26.8)	<0.001	0.006	0.01
Change from baseline	4.7 (1.9–10.0)	-11.2 (-22.3 to -8.8)	-16.2 (-21.1 to -4.6)	<0.001	<0.001	0.99

Unless otherwise specified, data are expressed as mean ± SD. IQR, interquartile range. \*P for IMT vs. gastric bypass. †P for IMT vs. sleeve gastrectomy. ‡P for gastric bypass vs. sleeve gastrectomy. §P values were generated using the Wilcoxon test; otherwise, the Student t test was used.



**Figure 1**—Glucose (A) and C-peptide (B) during the mixed-meal tolerance test performed at time of randomization (baseline) and at 24 months after randomization for IMT, sleeve gastrectomy, and gastric bypass. Mixed meal consisted of Boost (8 ounces) with 30-min interval blood sampling for glucose and C-peptide values. Data are shown in median values. RYGB, Roux-en-Y gastric bypass.

years of follow-up, gastric bypass patients achieved near-normal glucose tolerance after a physiological liquid mixed meal. These effects were associated with a remarkable 5.8-fold increase in overall pancreatic  $\beta$ -cell function. In gastric bypass patients, both insulin sensitivity and secretion components increased, but despite comparable weight loss in sleeve gastrectomy, insulin sensitivity was only partially restored and pancreatic  $\beta$ -cell function did not improve. Both bariatric surgery procedures stimulated incretins with markedly increased postprandial GLP-1 levels as noted in previous observational studies in obese patients with type 2 diabetes (8,9,16). However, divergence in postprandial GIP levels was noted, with a reduction seen only in gastric bypass that may be related to anatomical exclusion of the duodenum (which

produces GIP) or may be reflective of improved GIP action that is noted to be defective in type 2 diabetes (17).

The metabolic changes observed in these bariatric surgical patients are markedly different from previous studies performed in medically treated patients with type 2 diabetes and highlight the clinical value of improving  $\beta$ -cell function to achieve glycemic control. The UK Prospective Diabetes Study (UKPDS) demonstrated that pancreatic  $\beta$ -cell function continues to deteriorate over time despite diet, exercise, and administration of hypoglycemic agents (18). In UKPDS, the natural history of type 2 diabetes was characterized by an average increase in HbA<sub>1c</sub> level of 1% over 2 years despite the use of medications. In patients with well-controlled diabetes prescribed a single oral hypoglycemic agent, the mean

time of deterioration of glycemic control was 33–60 months (19). For patients using metformin and additionally prescribed a sulfonylurea, median HbA<sub>1c</sub> levels deteriorated as early as 6 months at a rate similar to that observed with metformin alone (20). These findings suggest that with continuing decline in  $\beta$ -cell function, single or even multiple agents are no longer sufficient to control blood glucose levels, which is why many patients ultimately require insulin therapy. For those who initiate insulin therapy, less than half achieve a desired HbA<sub>1c</sub> of  $\leq 7\%$  (21).

Although weight loss associated with hypocaloric diet has been shown to reduce insulin resistance, reduce hyperinsulinemia, and improve  $\beta$ -cell function (22–24), both bariatric surgery procedures displayed much larger postprandial insulinotropic effects compared with IMT. Greater insulin

secretory effects of gastric bypass coupled with a nearly threefold improvement in insulin sensitivity likely account for complete normalization of postprandial glucose tolerance seen uniquely with gastric bypass patients. Lack of suppression of glucagon is known to contribute to postprandial hyperglycemia in diabetes (25), and, contrary to our expectation, bariatric surgery did not restore this defect. A slight increase in postprandial glucagon level was noted in gastric bypass, a finding consistent with a previous study (26).

Massive weight loss and reduction of adipose tissue mass clearly contribute to the major improvements in insulin sensitivity and cardiovascular risk profile observed after bariatric surgery. However, the marked improvements in insulin sensitivity and glycemic control observed in the gastric bypass group suggest factors specifically linked to the presence of abdominal (truncal) fat. Ectopic abdominal fat presence has long been recognized to induce insulin resistance, subclinical inflammation, and cardiovascular risk specific to type 2 diabetes (27,28). Previous studies also have demonstrated greater improvements in insulin sensitivity with intestinal bypass procedures (i.e., gastric bypass and biliopancreatic diversion) compared with BMI-matched nonsurgical patients, presumably because these procedures produce greater nutrient and fat malabsorption (29,30). In the current study, adipogenic inflammation was significantly reduced after both bariatric procedures, especially gastric bypass, mediated by factors such as free fatty acids, leptin, and C-reactive protein, which impair glucose uptake by insulin-dependent tissues (muscle and liver).

Although modest improvement in glycemic control, glucose metabolism, and clinical parameters was noted with IMT in our trial, more vigorous and behavioral/lifestyle modification strategies as used in the Look AHEAD trial (31) that aggressively target weight loss are clearly needed. Future randomized control trials are needed to compare such strategies results with bariatric surgery. However, maintaining weight loss in patients with diabetes who require insulin and other hypoglycemic agents is difficult in the "real world" clinical setting because conventional drug therapy generally results in weight gain. In addition, fear of hypoglycemia and patient burdens related to administration of multiple drugs

for diabetes and cardiovascular risk control presents significant barriers to implementing and adhering to IMT.

A limitation of this study is the validity of the incretin hormone responses that were obtained after the assigned interventions. Concentrations of GLP-1 and GIP were obtained at fasting and at 60 min after meal ingestion, and this likely underestimates the incretin surge that normally occurs rapidly (within 15 min) after meal ingestion. Nevertheless, large incremental changes in prandial GLP-1 levels and corresponding C-peptide levels were noted 2 years after both bariatric procedure types that were not observed with IMT. Further studies are warranted to thoroughly investigate the long-term effects of bariatric surgery on incretin responses and action to modulate insulin secretion. Additionally, insulin sensitivity determined by the Matsuda index was performed only in a subset of subjects not using exogenous insulin at baseline and followed trends similar to the whole cohort because insulin administration was withheld 24 h before meal testing.

In summary, bariatric surgery induces powerful metabolic effects in moderately obese patients with advanced type 2 diabetes inadequately controlled with currently available drug therapy. Bariatric surgery, particularly gastric bypass surgery, uniquely restores normal glucose tolerance and pancreatic  $\beta$ -cell function, presumably by targeting the truncal fat that represents the core metabolic defect involved in diabetes pathogenesis. Longer-term multicenter studies with safety outcomes are warranted to test the durability of these metabolic benefits.

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