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ORIGINAL ARTICLE

Effects of Diet versus Gastric Bypass on Metabolic Function in Diabetes

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ABSTRACT

BACKGROUND

Some studies have suggested that in people with type 2 diabetes, Roux-en-Y gastric bypass has therapeutic effects on metabolic function that are independent of weight loss.

METHODS

We evaluated metabolic regulators of glucose homeostasis before and after matched (approximately 18%) weight loss induced by gastric bypass (surgery group) or diet alone (diet group) in 22 patients with obesity and diabetes. The primary outcome was the change in hepatic insulin sensitivity, assessed by infusion of insulin at low rates (stages 1 and 2 of a 3-stage hyperinsulinemic euglycemic pancreatic clamp). Secondary outcomes were changes in muscle insulin sensitivity, beta-cell function, and 24-hour plasma glucose and insulin profiles.

RESULTS

Weight loss was associated with increases in mean suppression of glucose production from baseline, by 7.04 μmol per kilogram of fat-free mass per minute (95% confidence interval [CI], 4.74 to 9.33) in the diet group and by 7.02 μmol per kilogram of fat-free mass per minute (95% CI, 3.21 to 10.84) in the surgery group during clamp stage 1, and by 5.39 (95% CI, 2.44 to 8.34) and 5.37 (95% CI, 2.41 to 8.33) μmol per kilogram of fat-free mass per minute in the two groups, respectively, during clamp stage 2; there were no significant differences between the groups. Weight loss was associated with increased insulin-stimulated glucose disposal, from 30.5 \pm 15.9 to 61.6 \pm 13.0 μmol per kilogram of fat-free mass per minute in the diet group and from 29.4 \pm 12.6 to 54.5 \pm 10.4 μmol per kilogram of fat-free mass per minute in the surgery group; there was no significant difference between the groups. Weight loss increased beta-cell function (insulin secretion relative to insulin sensitivity) by 1.83 units (95% CI, 1.22 to 2.44) in the diet group and by 1.11 units (95% CI, 0.08 to 2.15) in the surgery group, with no significant difference between the groups, and it decreased the areas under the curve for 24-hour plasma glucose and insulin levels in both groups, with no significant difference between the groups. No major complications occurred in either group.

CONCLUSIONS

In this study involving patients with obesity and type 2 diabetes, the metabolic benefits of gastric bypass surgery and diet were similar and were apparently related to weight loss itself, with no evident clinically important effects independent of weight loss. (Funded by the National Institutes of Health and others; ClinicalTrials.gov number, NCT02207777.)

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RANDOMIZED CLINICAL TRIALS HAVE shown that bariatric surgery is more effective than medical therapy for treatment of type 2 diabetes.¹⁻⁶ Moreover, several studies suggest that surgical procedures that involve bypass of the upper gastrointestinal tract, such as Roux-en-Y gastric bypass, have unique therapeutic effects on glycemic control, as evidenced by the higher incidence of diabetes remission after gastric bypass than after procedures that maintain intestinal continuity.⁷⁻⁹ However, the results from such studies are confounded by differences in weight loss among patients who undergo the procedures. The effects of gastric bypass, independent of weight loss, on the major factors involved in the pathogenesis of type 2 diabetes, namely multiorgan insulin resistance, alterations in the metabolic response to meal ingestion, and inadequate beta-cell function, are unclear because of conflicting results among studies^{10,11} and because data on several of these factors are limited.

The present study was designed to determine whether gastric bypass confers therapeutic metabolic effects independent of weight loss in people with obesity and type 2 diabetes. We compared the effects of marked weight loss induced by Roux-en-Y gastric bypass with the effects of the same weight loss induced by a low-calorie diet alone on hepatic insulin sensitivity (primary outcome) and muscle and adipose tissue insulin sensitivity; beta-cell function; the metabolic response to mixed-meal ingestion; 24-hour plasma glucose, free fatty acid, and insulin profiles; and body composition. We also evaluated several factors purported to be associated with benefits of gastric bypass independent of weight loss: alterations in plasma branched-chain amino acids, plasma bile acids, and the gut microbiome.¹²⁻¹⁵

METHODS

STUDY DESIGN AND OVERSIGHT

This matched prospective cohort study was conducted from November 2014 through October 2018. A comprehensive assessment of metabolic function was conducted before and after marked (16 to 24%) weight loss induced by Roux-en-Y gastric bypass (surgery group) or low-calorie diet therapy (diet group) in persons with obesity and type 2 diabetes. Participants provided written informed consent before participating in this study, which was approved by the Washington

University institutional review board. The last author had full access to all data and was responsible for the design and conduct of the study, the collection, analysis and interpretation of the data, and the preparation of the manuscript. The authors collaborated in preparing the manuscript, made the decision to submit the manuscript for publication, and vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol (available with the full text of this article at [NEJM.org](https://www.nejm.org)).

WEIGHT-LOSS INTERVENTIONS

Participants in the diet group received weekly education sessions on dietary practices and guidance on dietary behavior. All meals were provided throughout the study as liquid shakes and prepackaged entrees. The gastric bypass procedure involved creation of a 15-to-20-ml gastric pouch, a 75-to-150-cm Roux limb, and a 30-to-50-cm biliopancreatic limb.¹⁶ A study dietitian consulted with surgery patients weekly to monitor body weight and adjust dietary intake to meet weight-loss goals. After participants achieved the targeted weight loss, their energy intake was adjusted to maintain a constant body weight for 3 weeks before repeat testing was performed. The mean (\pm SD) coefficient of variation in weekly body weights during this period was $1.2\pm 0.5\%$ (range, 0.3 to 1.8) in the diet group and $1.2\pm 0.4\%$ (range, 0.7 to 1.8) in the surgery group.

STUDY OUTCOMES AND PROCEDURES

The primary outcome was the change in hepatic insulin sensitivity. Secondary outcomes were changes in insulin sensitivity in muscle and adipose tissue; beta-cell function; metabolic response to mixed-meal ingestion; 24-hour glucose, free fatty acid and insulin profiles; and body composition.

Glucagon-like peptide-1 receptor agonists were discontinued 2 weeks before each metabolic study, oral diabetes medications were discontinued 3 days before, and insulin was discontinued 1 day before to reduce their effects on metabolic outcomes. Diabetes medications were adjusted on the basis of twice-daily blood glucose measurements. A diabetes medication score was calculated on the basis of the number and dose of medications (scores ranged from 0 to 3.57, with a higher score indicating a greater number of medications, a higher dosage of medications, or both; details are provided in the Calculations

section in the Supplementary Appendix, available at NEJM.org).¹⁷

Participants were admitted to the research unit at Washington University School of Medicine in St. Louis for analysis of body composition¹⁸ and a 9-hour, three-stage hyperinsulinemic euglycemic pancreatic clamp procedure to assess hepatic, muscle, and adipose tissue insulin sensitivity. This procedure involved infusion of stable isotope tracers, octreotide to block insulin secretion, and insulin at increasing rates every 3 hours (from 15 to 25 to 50 mU per square meter of body-surface area per minute). Participants were readmitted to the research unit 1 to 2 weeks later for a 7-hour mixed-meal test to assess postprandial glucose and insulin kinetics¹⁶ and 24-hour plasma glucose, free fatty acid, and insulin profiles. Beta-cell function was assessed as the product of beta-cell glucose sensitivity (the ratio of postprandial insulin secretion rate to postprandial plasma glucose) during the mixed-meal test and whole-body insulin sensitivity assessed during the clamp procedure.^{16,19} Fecal samples were obtained during an inpatient visit to the research unit. (Details of all procedures and analyses are provided in the Supplementary Appendix.)

STATISTICAL ANALYSIS

An analysis of covariance, with the postintervention value as the dependent variable and the baseline value and group assignment as predictor variables, was used to assess the effects on outcomes of weight loss induced by diet as compared with surgery. Assumptions for all models were confirmed by regression residuals. (Additional details are provided in the Statistical Analysis section in the Supplementary Appendix.)

We assumed that weight loss would increase insulin-mediated suppression of glucose production from 43±13% at baseline to 62±13% after weight loss in the diet group and to 75±13% after weight loss in the surgery group.²⁰⁻²³ We calculated that 18 participants in each treatment group would be needed to give the study 83% power to detect this difference of 13 percentage points in hepatic insulin sensitivity between groups at a two-tailed alpha value of 0.05. On the basis of our previous experience, we anticipated that 25% of the participants would drop out because they did not achieve adequate weight loss or were unwilling to return for testing.

RESULTS

PARTICIPANTS

A total of 33 people with obesity and type 2 diabetes participated in this study: 18 in the diet group and 15 in the surgery group (inclusion and exclusion criteria are described in the Supplementary Appendix). Seven participants in the diet group and 4 in the surgery group withdrew or were withdrawn from the study because they did not achieve the target weight loss (Fig. S1 in the Supplementary Appendix). Accordingly, data from 11 participants (4 men and 7 women) in the diet group (mean age, 54±9 years; mean time since diagnosis of diabetes, 9.1±5.6 years) and 11 participants (3 men and 8 women) in the surgery group (mean age, 49±12 years; mean time since diagnosis of diabetes, 9.6±9.6 years) were analyzed before and after weight loss. The mean weight loss was 17.8±1.2% (range, 16.1 to 20.4) in the diet group and 18.7±2.5% (range, 16.0 to 24.4) in the surgery group. During the study, two adverse events occurred in the surgery group (one postoperative transfusion of 2 units of blood and one emergency department visit for food impaction), and no adverse events occurred in the diet group.

BODY COMPOSITION, BASAL METABOLIC VARIABLES, AND GLYCEMIC CONTROL

Weight loss was associated with changes in body composition, plasma glucose and hormone concentrations, and glycated hemoglobin levels, with no significant differences between the groups (Table 1). The diabetes medication score decreased from 0.93±0.55 to 0.23±0.29 (mean difference, -0.70; 95% confidence interval [CI], -1.06 to -0.33) in the diet group and from 1.64±1.15 to 0.60±0.78 (mean difference, -1.04; 95% CI, -1.70 to -0.40) in the surgery group, with no significant difference between the groups. Four participants in the diet group and two in the surgery group reached glycated hemoglobin levels lower than 6.0% without diabetes medications.

POSTPRANDIAL AND 24-HOUR GLUCOSE, FATTY ACID, AND INSULIN KINETICS

Areas under the curve for plasma glucose and insulin after ingestion of the identical breakfast mixed meal were lower after weight loss than before in both groups; the decrease in glucose, but not insulin, was greater in the diet group than in the surgery group (Table 2). The postprandial peak in plasma glucose after weight loss was

Table 1. Body Composition and Basal Metabolic Variables before and after Weight Loss.*

Variable	Diet Group			Surgery Group			Difference between Groups (95% CI)
	Before Weight Loss	After Weight Loss	Difference (95% CI)	Before Weight Loss	After Weight Loss	Difference (95% CI)	
Body weight (kg)	122.2±21.7	100.3±17.3	-21.9 (-25.0 to -18.8)	122.3±18.2	99.3±14.3	-23.0 (-26.5 to -19.4)	-1.1 (-3.4 to 1.2)
Body-mass index†	42.9±6.9	35.2±5.6	-7.7 (-8.6 to -6.7)	43.2±3.8	35.1±2.9	-8.1 (-9.1 to -7.1)	-0.39 (-1.18 to 0.39)
Fat mass (kg)	58.2±12.9	42.2±10.7	-16.0 (-18.3 to -13.7)	59.1±9.0	43.5±7.5	-15.6 (-18.2 to -13.0)	0.58 (-1.98 to 3.14)
Body fat (%)	48.4±7.6	42.4±8.2	-6.0 (-7.1 to -5.0)	48.9±4.6	44.0±5.9	-5.0 (-6.2 to -3.7)	1.00 (-0.47 to 2.47)
Fat-free mass (kg)	62.3±13.9	57.5±12.8	-4.8 (-6.3 to -3.2)	62.0±11.7	55.9±11.4	-6.1 (-7.3 to -4.8)	-1.32 (-3.06 to 0.43)
Intraabdominal adipose tissue volume (cm ³)	2306±752	1485±630	-821 (-1066 to -576)	2463±996	1749±675	-714 (-1082 to -346)	157 (-128 to 442)
Intrahepatic triglyceride content (%)	13.2±7.6	3.8±1.3	-9.4 (-15.0 to -3.7)	16.9±10.9	5.8±4.8	-11.1 (-18.8 to -3.4)	1.4 (-2.0 to 4.9)
Free fatty acids (mg/dl)	18.9±7.3	15.0±4.0	-4.0 (-8.8 to 0.84)	21.7±4.2	15.1±6.3	-6.5 (-9.5 to -3.6)	-0.9 (-5.6 to 3.9)
Glucose (mg/dl)	156±45	106±10	-51 (-78 to -23)	153±29	106±16	-47 (-62 to -32)	0.7 (-9.9 to 11.4)
Insulin (μU/ml)	20.3±6.7	11.9±2.9	-8.3 (-13.1 to -3.5)	27.0±11.3	9.3±5.0	-17.7 (-25.9 to -9.6)	-3.5 (-7.5 to 0.5)
Glycated hemoglobin (%)	8.0±2.1	5.6±0.7	-2.4 (-3.7 to -1.1)	7.2±1.3	6.0±0.7	-1.2 (-2.2 to -0.18)	0.52 (-0.11 to 1.14)
High-molecular-weight adiponectin (μg/ml)	1.88±1.12	2.65±1.51	0.77 (0.19 to 1.35)	1.31±0.98	2.31±1.75	1.0 (0.35 to 1.64)	0.07 (-0.08 to 0.22)
Leptin (ng/liter)	107±77	47±39	-61 (-91 to -31)	105±64	37±21	-68 (-100 to -36)	-8.5 (-23.1 to 6.1)

* 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 insulin to picomoles per liter, multiply by 6.0. To convert the values for free fatty acid to grams per liter, multiply by 0.01. The within-group difference is the mean with 95% confidence interval (CI) for the difference between the value before weight loss and the value after weight loss within each group. The difference between groups is the difference (and 95% CI) between the group means of the values after weight loss, adjusted for the values before weight loss by analysis of covariance.
 † The body-mass index is the weight in kilograms divided by the square of the height in meters.

Table 2. Metabolic Response to Mixed-Meal Ingestion and 24-hour Plasma Glucose, Free Fatty Acid, and Insulin Profile before and after Weight Loss.*

Variable	Diet Group		Surgery Group		Difference between Groups (95% CI)
	Before	After	Before	After	
4-Hr meal glucose AUC — mg/dl × min × 10 ³	53.9±18.9	33.1±6.7	50.5±14.3	40.4±12.0	-10.1 (-17.7 to -2.6)
4-Hr meal insulin AUC — μU/ml × min × 10 ³	16.5±8.8	10.9±3.7	17.0±8.3	12.4±6.6	-4.6 (-9.3 to 0.06)
Total glucose RA 4-hr AUC — μmol/kg FFM/ min × min	6270±1204	5500±867	6050±1010	5530±1030	-520 (-1250 to 202)
Ingested glucose RA 4-hr AUC — μmol/ kg FFM/min × min	3780±834	3910±728	3560±956	3790±749	230 (-572 to 1020)
Endogenous glucose RA 4-hr AUC — μmol/ kg FFM/min × min	2500±751	1590±313	2490±979	1750±406	-740 (-1481 to -9)
24-Hr glucose AUC — mg/dl × min × 10 ³	311±132	169±25	322±99	204±61	-118 (-172 to -64)
24-Hr free fatty acid AUC — mg/ dl × min × 10 ³	18.6±5.9	12.9±2.1	22.0±6.1	17.1±5.4	-4.9 (-6.9 to -2.9)
24-Hr insulin AUC — μU/ml × min × 10 ³	84±54	46±14	85±32	47±27	-38 (-63 to -12)
24-Hr insulin secretion rate AUC — pmol/ min × 10 ³	940±377	779±214	929±231	742±281	-187 (-345 to -29)
24-Hr insulin clearance rate — liters/min	2.14±0.22	2.91±0.18	1.90±0.13	2.90±0.25	1.0 (0.46 to 1.54)

* Plus-minus values are means ±SD. To convert the values for C-peptide to nanograms per milliliter, multiply by 0.331. The within-group differences are the mean and 95% CI for the difference between the value before weight loss and the value after weight loss within each group. The difference between groups is the difference (and 95% CI) between the group means of the values after weight loss, adjusted for the values before weight loss by analysis of covariance. The area under the curve (AUC) was calculated with data from the time ingestion of the breakfast meal began to either 4 hours or 24 hours later. Glucose rate of appearance (RA) 4-hr AUC is the AUC for the total glucose RA (i.e., the sum of ingested glucose RA and endogenous glucose RA) into the systemic circulation from the time meal ingestion began until 4 hours after the meal. FFM denotes fat-free mass.

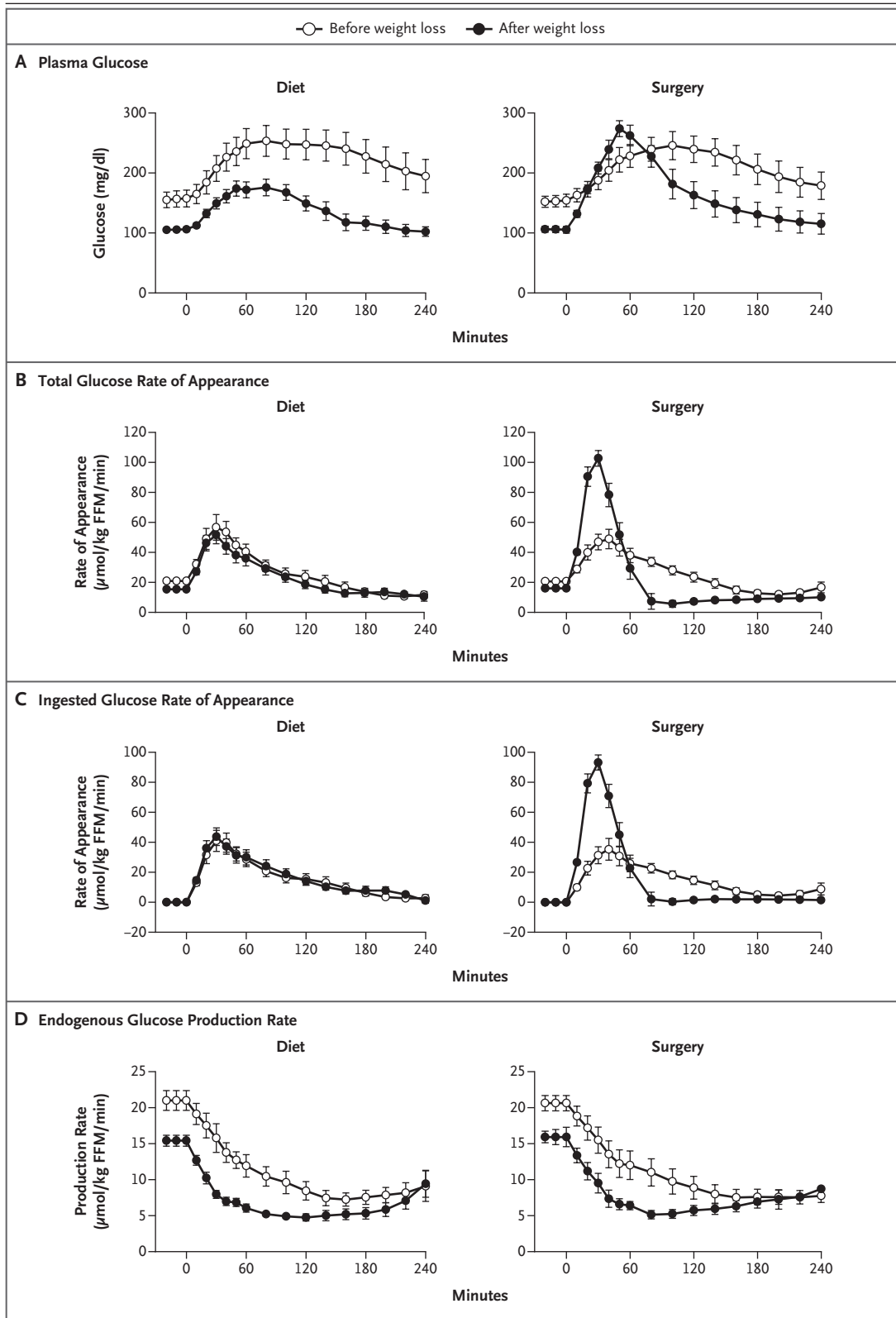


Figure 1 (facing page). Effects of Weight Loss Induced by Diet and Gastric Bypass on Postprandial Glucose Kinetics.

Shown are mean levels of plasma glucose (Panel A), total glucose rate of appearance in the systemic circulation (Panel B), ingested glucose rate of appearance (Panel C), and endogenous glucose production rate (Panel D) after ingestion of an identical mixed meal (consumed from time 0 to 30 minutes) before (white circles) and after (black circles) weight loss induced by low-calorie diet therapy (Diet, 11 participants) or gastric bypass (Surgery, 9 participants). Decreases in postprandial areas under the curve after weight loss for plasma glucose concentration, total glucose rate of appearance, and endogenous glucose production rate were not significantly different between the two groups. To convert the values for glucose to millimoles per liter, multiply by 0.05551. I bars indicate standard errors. FFM denotes fat-free mass.

greater in the surgery group than in the diet group, a difference caused by a marked increase in the rate of delivery of ingested glucose into the circulation (Fig. 1). The effect of weight loss on meal-induced suppression of endogenous glucose production did not differ significantly between the two groups (Table 2 and Fig. 1).

Although the composition of the meals provided during the 24-hour study was the same before and after weight loss, the energy content was individualized on the basis of each participant's measured resting energy expenditure. Therefore, energy consumption was lower after weight loss (2091 ± 136 kcal per day) than before weight loss (2520 ± 183 kcal per day). Weight loss decreased the 24-hour areas under the curve for glucose, free fatty acids and insulin, and insulin secretion rate, with no significant differences between the diet and surgery groups (Table 2). The shape of the plasma concentration curves differed between the groups, manifested by higher peaks in both substrate and hormone concentrations immediately after meal ingestion in the surgery group than in the diet group (Fig. 2).

MULTIORGAN INSULIN SENSITIVITY AND BETA-CELL FUNCTION

Insulin sensitivity in the liver (suppression of glucose production during stages 1 and 2 of the clamp procedure), skeletal muscle (stimulation of glucose disposal during stage 3 of the clamp procedure), and adipose tissue (suppression of lipolysis during stages 1 and 2 of the clamp procedure) increased after weight loss in both

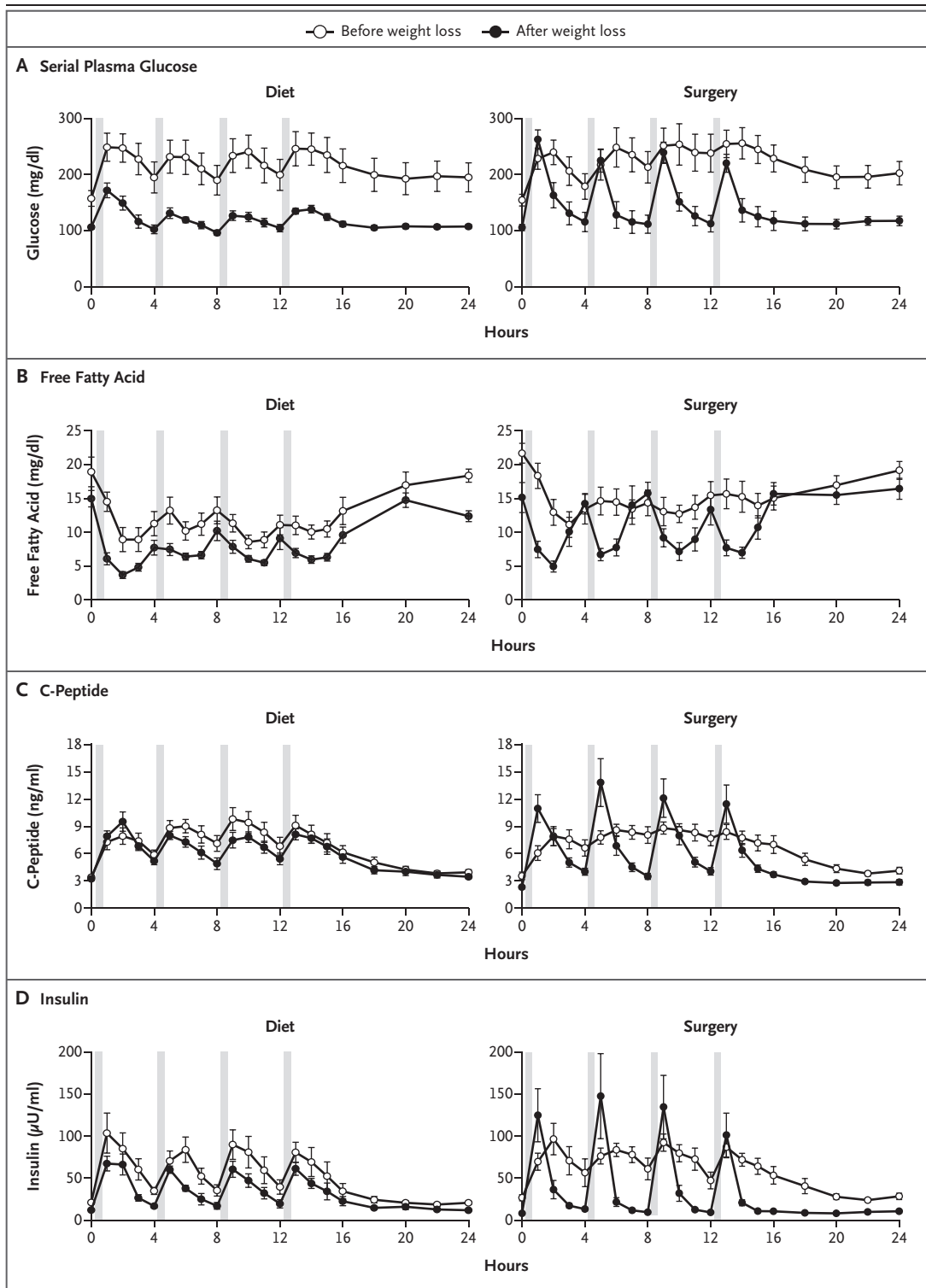
the diet and surgery groups, with no significant differences between the groups (Table 3). Weight loss increased beta-cell function in both groups, which appeared to be caused by an increase in beta-cell glucose sensitivity and whole-body insulin sensitivity (Table 3).

OTHER WEIGHT-LOSS-INDEPENDENT THERAPEUTIC EFFECTS OF GASTRIC BYPASS

Several factors are purported to result in therapeutic effects of gastric bypass that are independent of weight loss. The decreases in 24-hour plasma branched-chain amino acid and C3 and C5 acylcarnitine concentrations after weight loss were greater in the surgery group than in the diet group. Plasma bile acids after weight loss were decreased from baseline in the diet group, but were increased from baseline in the surgery group. Weight loss caused changes in the composition of the gut microbiome in both treatment groups, but the changes were greater in the surgery group than in the diet group. (For additional details, see Fig. S2).

DISCUSSION

We evaluated whether Roux-en-Y gastric bypass has therapeutic effects independent of weight loss on the major physiologic factors that regulate glycemic control in people with obesity and type 2 diabetes. To this end, we assessed the metabolic response to mixed-meal ingestion, 24-hour glucose, free fatty acid and insulin profiles, multiorgan insulin sensitivity, and beta-cell function before and after matched (approximately 18%) weight loss induced by gastric bypass surgery or diet therapy alone. A three-stage hyperinsulinemic euglycemic pancreatic clamp was used to control both portal and systemic plasma insulin concentrations to provide a reliable assessment of hepatic, muscle, and adipose tissue insulin sensitivity across a physiologic range of plasma insulin concentrations. Our data show that after marked weight loss induced by either diet therapy or gastric bypass, there were considerable improvements in body composition (body fat mass, intraabdominal adipose tissue volume, and intrahepatic triglyceride content); 24-hour plasma glucose, free fatty acid, and insulin profiles; beta-cell function; and insulin sensitivity in the liver, skeletal muscle, and adipose tissue,



with no significant differences between the groups in any of these variables. These results underscore the potent therapeutic effects of weight loss on metabolic function and show that

the metabolic benefits of gastric bypass surgery are probably the result of weight loss alone.

In contrast to weight loss induced by diet alone, weight loss induced by gastric bypass was

Figure 2 (facing page). Effects of Weight Loss Induced by Diet and Gastric Bypass on 24-hour Plasma Glucose, Free Fatty Acid, C-Peptide, and Insulin Concentrations.

Shown are mean levels of concentrations of plasma glucose (Panel A), free fatty acid (Panel B), C-peptide (Panel C), and insulin (Panel D) from serial samples obtained for 24 hours before (white circles) and after (black circles) weight loss induced by low-calorie diet therapy (Diet, 11 participants) or gastric bypass (Surgery, 8 participants). Gray bars represent the time of mixed-meal consumption. Average 24-hour plasma glucose, free fatty acid, and insulin concentrations were lower after treatment than before treatment in both the diet and surgery groups, with no significant difference between the groups. To convert the values for free fatty acids to grams per liter, multiply by 0.01; to convert the values for C-peptide to nanograms per milliliter, multiply by 0.331. I bars indicate standard errors.

associated with marked alterations in the pattern of the metabolic response to mixed-meal ingestion, manifested by a rapid delivery of ingested glucose into the systemic circulation and a concomitant large early rise and fall in plasma glucose and insulin concentrations. Despite these differences, weight loss had the same beneficial effects on overall postprandial glucose and insulin kinetics in the two groups. In addition, weight loss decreased the integrated 24-hour plasma glucose and insulin concentrations by about 40% from baseline in both the diet and surgery groups, even though the total dose of diabetes medications for participants in both groups decreased by approximately 75%. The improved 24-hour metabolic profile was presumably caused by improvements in beta-cell function and multiorgan insulin sensitivity, in conjunction with a decrease from baseline in total carbohydrate and energy intake.

Multiorgan insulin resistance is a universal feature of type 2 diabetes and is involved in the pathogenesis of cardiometabolic diseases associated with diabetes.²⁴⁻²⁷ Hepatic glucose production is more sensitive to insulin than is skeletal muscle glucose uptake.²⁸ Accordingly, the assessment of hepatic insulin sensitivity requires low doses of insulin to partially suppress glucose production, whereas higher doses are needed to adequately stimulate muscle glucose disposal. The assessment of hepatic insulin sensitivity is particularly complicated because portal vein insulin is higher than systemic plasma insulin,²⁹ and the feedback suppression of insulin secre-

tion by circulating insulin is blunted in people with obesity.³⁰ Therefore, we infused octreotide during the clamp procedure to block endogenous insulin secretion in order to ensure that similar portal vein insulin concentrations were achieved before and after weight loss. Moreover, we provided a comprehensive assessment of hepatic insulin sensitivity by infusing insulin at two rates that spanned the physiologic range needed to partially suppress hepatic glucose production. Our data showed that weight loss caused considerable improvement in the ability of insulin to suppress both glucose production and lipolysis and to stimulate glucose disposal, with no significant differences between the diet and surgery groups.

The ability of beta cells to secrete an adequate amount of insulin in response to a glucose challenge is critical for normal glucose homeostasis and is an important predictor of diabetes remission after weight loss induced by gastric bypass.^{31,32} We assessed beta-cell function as the product of beta-cell glucose sensitivity after mixed-meal ingestion and whole-body insulin sensitivity assessed during the clamp procedure. The interpretation of insulin secretion in relation to insulin sensitivity is necessary because the amount of insulin needed for glycemic control depends on the effectiveness of insulin. Weight loss markedly increased beta-cell function because of an increase in both beta-cell glucose sensitivity and whole-body insulin sensitivity in both the diet and surgery groups, with no significant differences between the groups.

Several mechanisms have been purported to cause metabolic benefits of gastric bypass that are independent of weight loss, including decreased plasma branched-chain amino acids and their acylcarnitines,¹² increased circulating bile acids,¹³ and alterations in the gut microbiome.^{14,15} We found that patients in the surgery group had a greater decline in plasma concentrations of branched-chain amino acids and C3 and C5 acylcarnitines and a greater increase in plasma bile acids than patients in the diet group — a finding consistent with results from previous studies.^{12,13} The changes observed in the gut microbiome of persons in the surgery group are also consistent with the results from most studies^{15,33-39} and were much greater than the changes observed in the diet group. These results confirm that gastric bypass causes alterations in spe-

Table 3. Multiorgan Insulin Sensitivity and Beta-cell Function before and after Weight Loss.*

	Diet Group			Surgery Group			Difference between Groups (95% CI)
	Before	After	Difference (95% CI)	Before	After	Difference (95% CI)	
Glucose RA (Stage 1) — $\mu\text{mol}/\text{kg}$ FFM/min	17.07 \pm 2.36	10.03 \pm 3.08	-7.04 (-9.33 to -4.74)	17.44 \pm 4.99	10.42 \pm 4.30	-7.02 (-10.84 to -3.21)	0.25 (-3.08 to 3.59)
Glucose RA (Stage 2) — $\mu\text{mol}/\text{kg}$ FFM/min	8.84 \pm 3.91	3.45 \pm 2.74	-5.39 (-8.34 to -2.44)	8.84 \pm 4.08	3.47 \pm 0.77	-5.37 (-8.33 to -2.41)	0.02 (-2.00 to 2.04)
Glucose RD (Stage 3) — $\mu\text{mol}/\text{kg}$ FFM/min	30.5 \pm 15.9	61.6 \pm 13.0	31.0 (22.5 to 39.6)	29.4 \pm 12.6	54.5 \pm 10.4	25.1 (16.4 to 33.8)	-6.5 (-15.7 to 2.7)
Palmitate RA (Stage 1) — $\mu\text{mol}/\text{kg}$ FFM/min	1.78 \pm 0.55	0.81 \pm 0.41	-0.97 (-1.30 to -0.64)	2.24 \pm 1.13	1.17 \pm 0.74	-1.07 (-2.11 to -0.03)	0.33 (-0.26 to 0.91)
Palmitate RA (Stage 2) — $\mu\text{mol}/\text{kg}$ FFM/min	1.14 \pm 0.76	0.65 \pm 0.40	-0.49 (-1.06 to 0.08)	1.41 \pm 0.75	0.64 \pm 0.31	-0.77 (-1.23 to -0.31)	-0.04 (-0.39 to 0.31)
Beta-cell function†	0.93 \pm 0.94	2.76 \pm 1.20	1.83 (1.22 to 2.44)	0.99 \pm 0.82	2.10 \pm 1.24	1.11 (0.08 to 2.15)	-0.71 (-1.75 to 0.34)

* Plus-minus values are means \pm SD. The within-group difference is the mean with 95% CI for the difference between the value before weight loss and the value after weight loss within each group. The difference between groups is the difference (and 95% CI) between the group means of the values after weight loss, adjusted for the values before weight loss by analysis of covariance. RD denotes rate of disposal from the systemic circulation.

† Beta-cell function was assessed as the product of beta-cell glucose sensitivity (the ratio of postprandial total area under the curve of insulin secretion rate to total area under the curve of postprandial plasma glucose) and whole-body insulin sensitivity (glucose infusion rate divided by the plasma insulin concentration during stage 3 of the hyperinsulinemic euglycemic pancreatic clamp procedure).

cific plasma metabolites and the gut microbiome that are independent of weight loss but showed that these changes were not associated with greater improvements in metabolic function.

Our study has several limitations. First, treatment assignment was not randomized, so potential confounding differences between groups cannot be ruled out. Second, it is possible that unique benefits of surgery were not detected because of inadequate statistical power and the large proportion of dropouts. However, this possibility is unlikely because the method used to assess our primary outcome can detect small differences in a small number of participants, and there was no evidence of even a trend in differences between groups in any outcome. Third, we evaluated a variety of secondary outcomes that require confirmation because there was no adjustment for multiple testing. Fourth, metabolic outcomes were assessed after a weight loss of 16 to 24%, so we cannot exclude the possibility of different results with lesser or greater amounts of weight loss. Fifth, we cannot exclude the possibility that gastric bypass has unique effects on other important clinical outcomes not assessed in this study.

The results from our study underscore the profound effect that marked weight loss can have on metabolic function in people with diabetes. The similar findings in participants in the two groups challenge the current belief that upper gastrointestinal bypass has clinically meaningful effects on key metabolic factors involved in glucose homeostasis and the pathogenesis of diabetes that are independent of weight loss. However, the difficulty in achieving successful long-term weight loss with lifestyle therapy often renders gastric bypass surgery far more effective than diet therapy for most patients with obesity and type 2 diabetes.

We found nearly identical benefits of matched weight loss induced by gastric bypass or diet alone on multiorgan insulin sensitivity, beta-cell function, 24-hour plasma glucose and insulin profiles, and body composition.

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