

Effects of Gastric Bypass Surgery in Patients With Type 2 Diabetes and Only Mild Obesity

RICARDO V. COHEN, MD¹
JOSE C. PINHEIRO, MD¹
CARLOS A. SCHIAVON, MD¹

JOÃO E. SALLES, MD²
BERNARDO L. WAJCHENBERG, MD³
DAVID E. CUMMINGS, MD⁴

OBJECTIVE—Roux-en-Y gastric bypass (RYGB) ameliorates type 2 diabetes in severely obese patients through mechanisms beyond just weight loss, and it may benefit less obese diabetic patients. We determined the long-term impact of RYGB on patients with diabetes and only class I obesity.

RESEARCH DESIGN AND METHODS—Sixty-six consecutively selected diabetic patients with BMI 30–35 kg/m² underwent RYGB in a tertiary-care hospital and were prospectively studied for up to 6 years (median 5 years [range 1–6]), with 100% follow-up. Main outcome measures were safety and the percentage of patients experiencing diabetes remission (HbA_{1c} <6.5% without diabetes medication).

RESULTS—Participants had severe, longstanding diabetes, with disease duration 12.5 ± 7.4 years and HbA_{1c} 9.7 ± 1.5%, despite insulin and/or oral diabetes medication usage in everyone. For up to 6 years following RYGB, durable diabetes remission occurred in 88% of cases, with glycemic improvement in 11%. Mean HbA_{1c} fell from 9.7 ± 1.5 to 5.9 ± 0.1% ($P < 0.001$), despite diabetes medication cessation in the majority. Weight loss failed to correlate with several measures of improved glucose homeostasis, consistent with weight-independent antidiabetes mechanisms of RYGB. C-peptide responses to glucose increased substantially, suggesting improved β -cell function. There was no mortality, major surgical morbidity, or excessive weight loss. Hypertension and dyslipidemia also improved, yielding 50–84% reductions in predicted 10-year cardiovascular disease risks of fatal and nonfatal coronary heart disease and stroke.

CONCLUSIONS—This is the largest, longest-term study examining RYGB for diabetic patients without severe obesity. RYGB safely and effectively ameliorated diabetes and associated comorbidities, reducing cardiovascular risk, in patients with a BMI of only 30–35 kg/m².

Diabetes Care 35:1420–1428, 2012

The global spread of obesity is driving a parallel pandemic of type 2 diabetes, a disease afflicting >171 million people worldwide, causing ~3 million deaths per year (1). The therapeutic cornerstones for both obesity and type 2 diabetes are dieting, exercise, and medications. Long-term success rates

of lifestyle modifications can be disappointing (2), however, and despite an ever-increasing armamentarium of pharmacotherapeutics, adequate glycemic control often remains elusive (3). Moreover, most diabetes medications promote weight gain, and using them to achieve tight glycemic control increases risks of hypoglycemia (4).

In cases where lifestyle interventions and medications fail to promote adequate weight loss and/or glycemic control, gastrointestinal surgery offers a powerful alternative (5). Among patients with a BMI >35 kg/m², bariatric surgery causes profound weight loss and ameliorates virtually all obesity-related comorbidities, with acceptable surgical morbidity and mortality rates of ~5 and <1%, respectively, rates that are steadily declining as minimally invasive laparoscopic techniques evolve (6–11). The effect of Roux-en-Y gastric bypass (RYGB) on diabetes is especially impressive. Approximately 80–85% of severely obese patients with type 2 diabetes who undergo this operation experience full remission of diabetes, maintaining euglycemia without diabetes medications for ≥14 years thereafter (8,12,13). Among severely obese patients, bariatric surgery lowers overall long-term mortality, with a remarkable 92% reduction in diabetes-related deaths (7,14).

Such encouraging results in patients with diabetes and a BMI >35 kg/m², along with mounting evidence that RYGB engages weight-independent antidiabetes mechanisms (15,16), have prompted consideration of this operation in less obese individuals with type 2 diabetes (5). Routine clinical use of RYGB, however, remains bounded by a 1991 National Institutes of Health consensus statement, which set limits for the use of bariatric surgery (17). According to these criteria, a BMI ≥35 kg/m² with associated comorbidities, such as diabetes, is required to approve surgical obesity treatment.

Patients with a BMI between 30 and 35 kg/m² (class I obesity) constitute the most numerous class of obese persons (18). Millions of these individuals suffer from poorly controlled diabetes despite attempted lifestyle modifications and pharmacotherapy; yet this group does not meet existing criteria for bariatric surgery (17). We hypothesized that such patients might benefit from laparoscopic RYGB (LRYGB) and sought to evaluate this question carefully in a prospective, institutional review board–approved long-term study.

From ¹The Center of Excellence in Bariatric and Metabolic Surgery, Oswaldo Cruz Hospital, and Marcia Maria Braidó Hospital, São Paulo, Brazil; the ²Department of Endocrinology, Diabetes Division, Santa Casa Medical School, São Paulo, Brazil; the ³Diabetes Unit, Heart Institute, University of São Paulo, and Diabetes Center, Oswaldo Cruz Hospital, São Paulo, Brazil; and the ⁴Diabetes and Obesity Center of Excellence and Veterans Affairs Puget Sound Health Care System, University of Washington School of Medicine, Seattle, Washington.

Corresponding author: David E. Cummings, davidec@u.washington.edu.

Received 24 November 2011 and accepted 8 March 2012.

DOI: 10.2337/dc11-2289

A slide set summarizing this article is available online.

The Municipal Health Authority, Marcia Maria Braidó Hospital, São Paulo, Brazil, had no roles in any of the following: design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

© 2012 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

See accompanying commentary, p. 1399.

Accordingly, we evaluated the effect of LRYGB on patients with type 2 diabetes and class I obesity. We examined whether LRYGB in these less obese patients could safely improve glycemic control, leading to remission or amelioration of diabetes and related comorbidities. Over a 6-year follow-up period, we prospectively measured postoperative changes in body weight, fasting plasma glucose (FPG), HbA_{1c}, and diabetes medication requirements, as well as operative safety, as main outcome measures. Additional outcomes included changes in lipid profiles, blood pressure, waist circumference, and estimated 10-year cardiovascular risk.

RESEARCH DESIGN AND METHODS

We prospectively studied 66 consecutively selected patients who had type 2 diabetes and a BMI of 30–34.9 kg/m², who elected to undergo RYGB. There were 40 men and 26 women, mean age was 47 ± 12 years (range 31–63), and all were white. The cohort sample size was defined pragmatically in advance based on the number of patients we could study with the grant procured to fund this work. The diagnosis of diabetes was based on the following American Diabetes Association criteria: FPG ≥126 mg/dL (7.0 mmol/L), or symptoms of diabetes plus casual plasma glucose ≥200 mg/dL (11.1 mmol/L), or 2-h postload glucose ≥200 mg/dL during a 75-gm oral glucose tolerance test (19). Candidates were excluded if they had diabetes secondary to a specific disease (maturity-onset diabetes of the young, pancreatitis, or pancreatectomy), drug or alcohol addiction, recent vascular event (myocardial infarction, coronary angioplasty, or stroke within 6 months), internal malignancy, portal hypertension, inability to cooperate in long-term follow-up, poor understanding of the operation, or unrealistic expectations of outcomes or mental impairment (as judged by investigators during the first clinic visit).

Table 1—Preoperative patient characteristics

	Duration of diabetes (years)			
	<2	2–5	6–15	16–20
n	17	10	34	5
BMI (kg/m ²)	32.7 ± 1.1	31.9 ± 1.1	33.2 ± 1.4	30.7 ± 6.0
FPG (mg/dL)	162 ± 37	177 ± 21	138 ± 60	131 ± 16
HbA _{1c} (%)	9.1 ± 0.3	9.8 ± 0.5	10.0 ± 0.7	9.7 ± 0.2
Oral diabetes drugs (%)	100	70	85	60
Insulin usage (%)	0	30	15	40

Data are means ± SD, unless otherwise indicated.

Patients with type 1 diabetes or undetectable β-cell function were excluded (i.e., if any of the following were found upon testing in each candidate: diagnosed type 1 diabetes, anti-GAD or islet-cell autoantibodies, overnight-fasting C-peptide <1 ng/mL, or unresponsive to a standardized mixed-meal challenge). For this test, after a 10-h overnight fast, a mixed meal was consumed (8 kcal/kg; 45% carbohydrate, 15% protein, and 40% fat; containing 1 g/kg glucose). Plasma samples were collected at 0, 30, 60, and 120 min, and C-peptide, insulin, and glucose concentrations were measured. To avoid C-peptide negativity from glucotoxicity, fasting glucose levels were medically controlled to <120 mg/dL before this test.

All patients met American Diabetes Association criteria for diabetes, and none had merely impaired fasting glucose or impaired glucose tolerance. Diabetes was inadequately controlled (i.e., HbA_{1c} >8.0%) preoperatively in all cases, despite appropriate lifestyle modifications and use of oral antidiabetes medications and/or insulin for ≥1 year.

Participants underwent LRYGB and were serially followed postoperatively for up to 6 years. Table 1 shows preoperative patient characteristics pertaining to glucose homeostasis. The group had longstanding diabetes (mean duration 12.5 ± 7.4 years) under poor glycemic control (mean HbA_{1c} 9.7 ± 1.5%). Patients were evenly distributed across the BMI range from 30.0 to 34.9 kg/m². Mean waist circumference was 113 ± 4 cm for men and 101 ± 7 cm for women. Comorbidity rates included hypertension 39%, hypercholesterolemia 50%, and hypertriglyceridemia 47%.

Preoperative evaluation

All patients received an extensive preoperative evaluation, including history and physical examination, nutritional and psychiatric evaluations, and specialty consultations as indicated. Subjects were screened for

diabetes using FPG, careful history taking, and risk factor assessment; associated comorbidities also were recorded. Preoperative studies included complete blood count, urinalysis, serum chemistries, nutritional indices, pregnancy test (in women <50 years), electrocardiogram, chest roentgenogram, and abdominal sonogram. If gallstones were detected, cholecystectomy was performed during LRYGB.

Surgical preparation included a detailed explanation of LRYGB and its benefits, alternatives, and risks (including short- and long-term complications, adverse effects, nutritional sequelae, and possible conversion to open surgery). Written informed consent was obtained from all subjects. All studies were conducted according to the principles expressed in the Declaration of Helsinki and were approved by the institutional review board of Marcia Maria Braido Hospital, a tertiary-care institution in São Paulo, Brazil.

Surgical technique

Participants underwent a standard, proximal LRYGB, performed by one surgical team (lead surgeon, R.V.C.), as previously described (20). The operation involves an antecolic, antegastric Roux limb, a 100-cm bilio-pancreatic limb, a 150-cm alimentary limb, and a 25- to 30-mL gastric reservoir. A 12-mm gastro-jejunal anastomosis was created using a linear stapler. Thromboembolic prophylaxis consisted of perioperative pneumatic compression and low-molecular-weight heparin (40 mg) during anesthetic induction.

Postoperative management

Patients recovered postoperatively in the surgical ward unless they required intensive-care unit observation. Intravenous analgesia without opioids was prescribed. A clear liquid diet was started on postoperative day 1 if no complications were detected by physical examination and/or radiographic testing. Patients were discharged from the hospital when oral liquids were well tolerated and FPG was <120 mg/dL. Pureed food was started by postoperative week 2 and solids by week 3. The original surgical team performed all follow-up visits at 7, 30, and 90 days and then at 6, 12, 24, 48, 60, and 72 months after surgery. All of these examinations were conducted in person, rather than through nurses or telephone interviews. No patients from the original cohort have been lost to follow-up.

Each patient received standardized nutritional orientation, emphasizing dietary sources of protein, B vitamins, iron,

and calcium. From postoperative day 30 onward, patients received calcium citrate, cholecalciferol, and multivitamins plus trace elements. At 3 months, they initiated monthly intramuscular vitamin B injections. If micronutrient deficiencies were detected, additional supplementation was used.

Surgical safety outcomes classification

Surgical complications were defined as “major” according to standards from the multicenter Longitudinal Assessment of Bariatric Surgery study (10). Major complications include deep-vein thrombosis, venous thromboembolism, tracheal reintubation, endoscopy, tracheostomy, percutaneous drain placement, abdominal reoperation, or failure to be discharged within 30 days. Minor complications were other adverse outcomes deemed related to surgery but not requiring hospital readmission or continued intensive treatment (such as nausea, port-site hematomas, etc.) (10).

Diabetes outcomes classification

Diabetes remission was defined as HbA_{1c} <6.5% without use of any diabetes medications. Diabetes was considered improved if patients still required oral medication at lower dosages than at baseline (but no insulin) and had HbA_{1c} <7.0%.

Criteria for reduction or withdrawal of diabetes medications

Diabetes medications were titrated, with dosage decreased if fasting and postprandial glucose levels were <120 and <160 mg/dL, respectively. Diabetes medications were discontinued if HbA_{1c} levels remained <6.4%.

Changes in diabetes-related conditions

We also assessed other metabolic syndrome components (hypertension, hypercholesterolemia, and hypertriglyceridemia) as defined by The Endocrine Society guidelines (21). Hypertension was considered resolved if a patient was normotensive (<130/80 mmHg) without blood pressure medication. Hypercholesterolemia and hypertriglyceridemia were considered resolved if serum levels of these lipids normalized without lipid-lowering medication (e.g., triglycerides <150 mg/dL; LDL <130 mg/dL in patients with resolved diabetes or <100 mg/dL in patients with persistent diabetes) (21). Predicted 10-year

risk of cardiovascular disease was calculated using the UK Prospective Diabetes Study (UKPDS) risk engine (22).

Statistical analyses

Continuous data are presented as means \pm SD or SE, as indicated. Changes from baseline in metabolic parameters were evaluated with Bonferroni-adjusted repeated-measures ANOVA. Statistical analyses were conducted using SPSS software, version 12. All tests were two sided, and *P* values <0.05 were considered significant.

RESULTS

Operative safety

There were no major intraoperative complications or conversions to laparotomy. Mean operative time was 46 ± 12 min (range 33–155). Postoperatively, there were eight port-site hematomas, one anastomotic ulcer, and one urinary tract infection (i.e., 15% minor complication rate). There were no major surgical complications (i.e., no deep-vein thrombosis, venous thromboembolism, tracheal reintubation, endoscopy, tracheostomy, percutaneous drain placement, abdominal reoperation, or failure to be discharged within 30 days) (10). There was no mortality. Mean hospital stay was 48 ± 16 h (range 1.5–4.0 days).

Main outcome measures: glycemic control

We remain in personal contact with, and have recent data from, all patients in the original cohort (i.e., follow-up rate is 100%). The median follow-up time is 5 years (range 1–6). Despite patients having severe, longstanding type 2 diabetes (disease duration 12.5 ± 7.4 years), mean HbA_{1c} for the entire cohort fell progressively throughout the study from 9.7 ± 1.5 to $5.9 \pm 0.1\%$, and FPG fell from 156 ± 11 to 97 ± 5 mg/dL (*P* < 0.001 for both) (Fig. 1). Most of these changes, especially for HbA_{1c}, occurred within the first 6 months. Likewise, insulin resistance, as roughly estimated by the homeostasis model assessment, fell markedly within the first 6 months then generally continued to decline more slowly thereafter (9.2 ± 2.3 at baseline, 3.4 ± 1.5 at 6 months, 3.3 ± 1.1 at 12 months, 2.5 ± 1.4 at 24 months, 2.0 ± 0.9 at 48 months, 2.2 ± 1.3 at 60 months, and 2.3 ± 0.8 at 72 months).

Remission of diabetes (i.e., HbA_{1c} <6.5% without diabetes medications)

was achieved in 88% of patients (58 of 66) (Fig. 1C), whose diabetes medications were discontinued 3–26 weeks after surgery. In this group, the mean duration of known diabetes was 8.0 ± 2.5 years (range 1.5–19). Seven subjects took insulin preoperatively, and the rest used oral diabetes medications. No patient who experienced diabetes remission based on a diabetes drug-free HbA_{1c} <6.5% subsequently exhibited an HbA_{1c} greater than that level or resumed diabetes medications in later evaluations. In other words, there was no recurrence of diabetes following remission during our 6-year follow-up.

Improvement of diabetes without full remission was observed in 11% of patients (7 of 66) (Fig. 1C). This group achieved diabetes control (HbA_{1c} <7.0%) with decreased usage of oral diabetes medications and withdrawal of insulin when previously used (at 3–14 weeks after surgery). The mean duration of known diabetes in this group was 7.2 ± 5.5 years (range 2–11). Preoperatively, two of the “improved” patients used insulin; the remainder used oral agents.

Only one patient, with 3 years of known diabetes, showed no clear postoperative disease improvement. Before surgery, he used insulin glargine 16 IU/day, pioglitazone 30 mg/day, and metformin 2 g/day. Insulin was withdrawn 7 months after surgery, and diabetes has subsequently been controlled with 50 mg vildagliptin b.i.d., pioglitazone 15 mg/day, and metformin 2 g/day. The patient experienced 72% excess weight loss at 48 months (his latest follow-up), similar to the weight loss in both the “resolved” and “improved” groups. Both at baseline and 48 months post-RYGB, his anti-GAD and islet-cell autoantibodies were negative, and his C-peptide levels were detectable (1.8 fasting and 2.8 ng/mL postmeal at baseline, 2.0 fasting and 2.1 ng/mL postmeal at 48 months).

Major, progressive reductions in waist circumference and total body weight were observed in all patients (*P* < 0.001 for both measures) (Fig. 1E–H). There were no apparent differences, however, in the magnitude of decrease in either parameter between patients who experienced diabetes remission and those who experienced only improved diabetes. Moreover, we could find no preoperative characteristics that predicted remission versus mere improvement in diabetes nor that influenced the kinetics of reduced glycemia, including baseline insulin usage and duration of diabetes. There also were no apparent preoperative characteristics distinguishing the

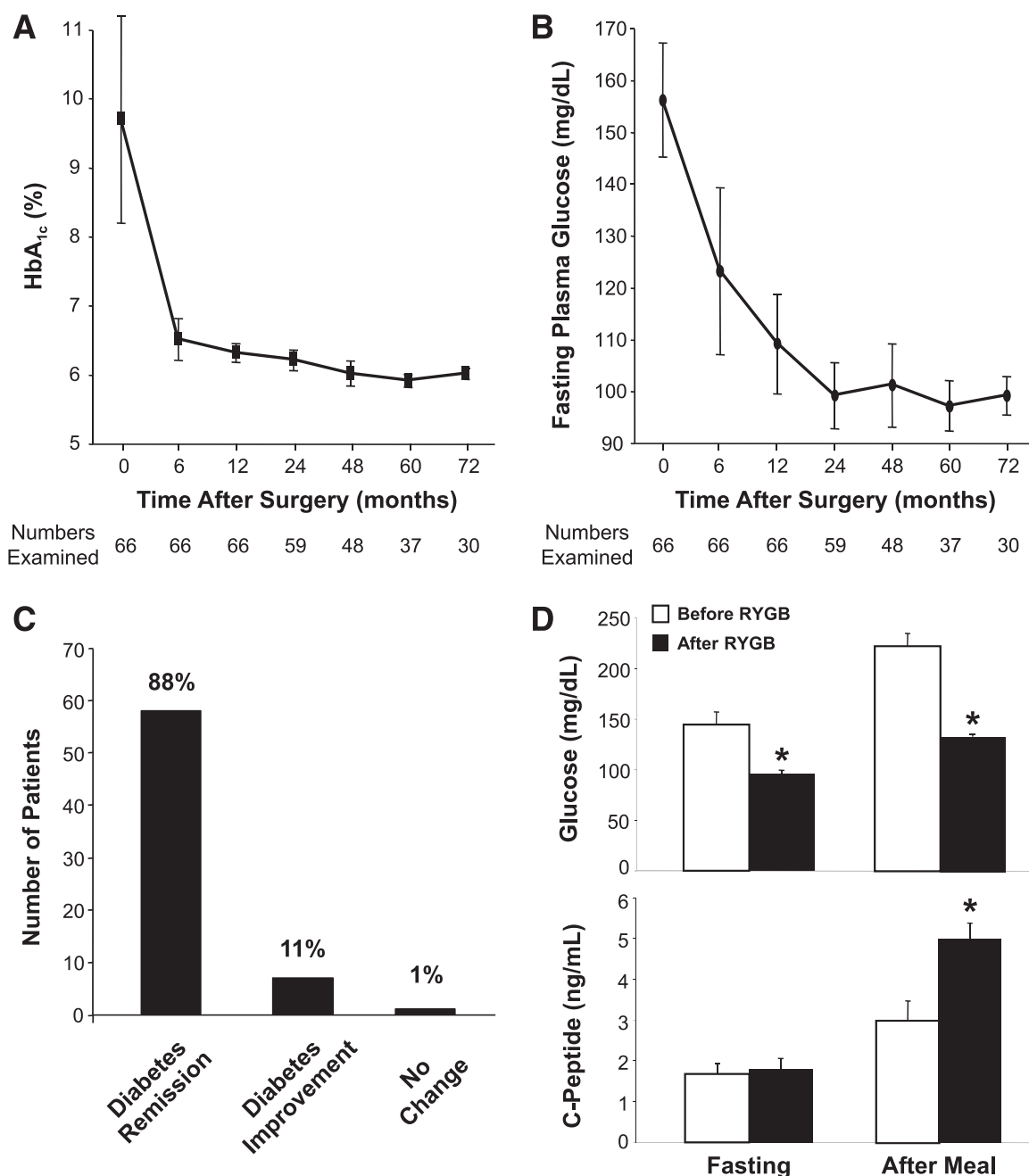


Figure 1—Improvement in glycemic control during 6 years following RYGB. Mean (\pm SE) HbA_{1c} (A) and FPG (B) for the entire cohort decreased from values representing poorly controlled diabetes, despite all patients being on diabetes medications at baseline, to the nondiabetic or normal range from 6 months through 6 years after RYGB, with 88% of patients discontinuing all diabetes medications. $n = 66$ at 0, 6, and 12 months; 59 at 24 months; 48 at 48 months; 37 at 60 months; and 30 at 72 months (i.e., 6 years). These n values decrease over time because not all patients have yet made it to the longer follow-up times; no one from the original cohort has been lost to follow-up. C: At the time of the latest follow-up, 88% of patients experienced remission of diabetes (i.e., HbA_{1c} < 6.5% off all diabetes medications), 11% had improved diabetes, and only 1 individual did not display a clear change in glycemic control. Remission occurred between 3 and 26 weeks after RYGB, and no one in the “diabetes remission” group has subsequently experienced a recrudescence of diabetes during follow-up. Classification as “diabetes improved” was based on participants’ status at the time of the latest follow-up. All patients who used insulin at baseline discontinued insulin usage between 3 and 14 weeks after surgery. D: Plasma glucose and C-peptide levels after an overnight fast and 120 min after a standardized mixed-macronutrient test meal, assessed before and after RYGB. Postoperative values are shown at the longest time point of individual follow-up. *Significant difference between equivalent preoperative and postoperative measurements ($P < 0.004$ in all cases). E–H: There was similar loss of adiposity over 6 years among patients who experienced full remission vs. only improvement of diabetes. Waist circumference (E and G) and total body weight (F and H) decreased markedly in both the “resolved” ($n = 58$) and “improved” ($n = 7$) diabetic groups. Reductions in both parameters were highly significant over the course of the study ($P < 0.001$ for all four panels shown in E–H), but there were no apparent differences in the magnitude of change in waist circumference or body weight between patients who experienced remission vs. only improvement of diabetes. Although mean waist circumference and body weight in the entire cohort increased modestly toward the end of the study, diabetes did not recur in any case where it had resolved. T2DM, type 2 diabetes. Data represent means \pm SE.

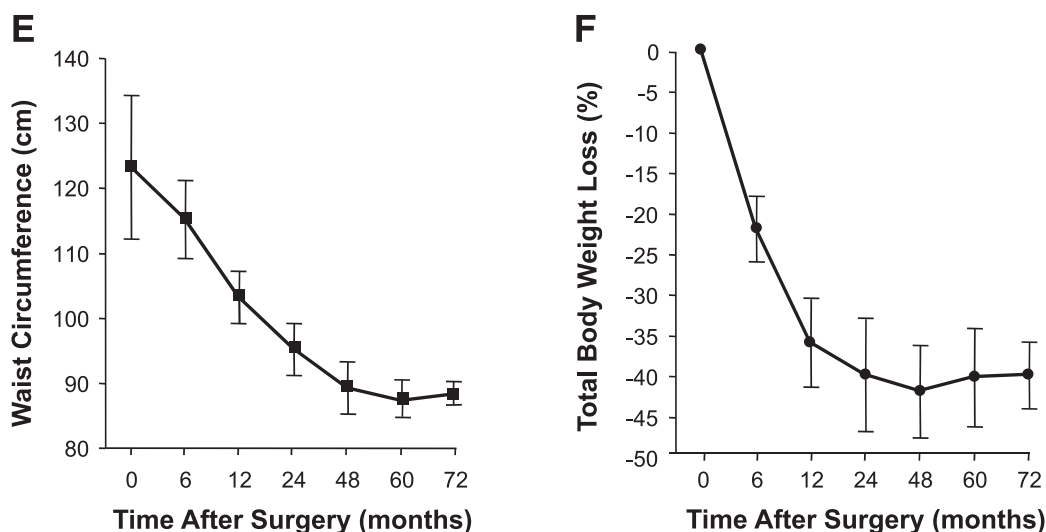
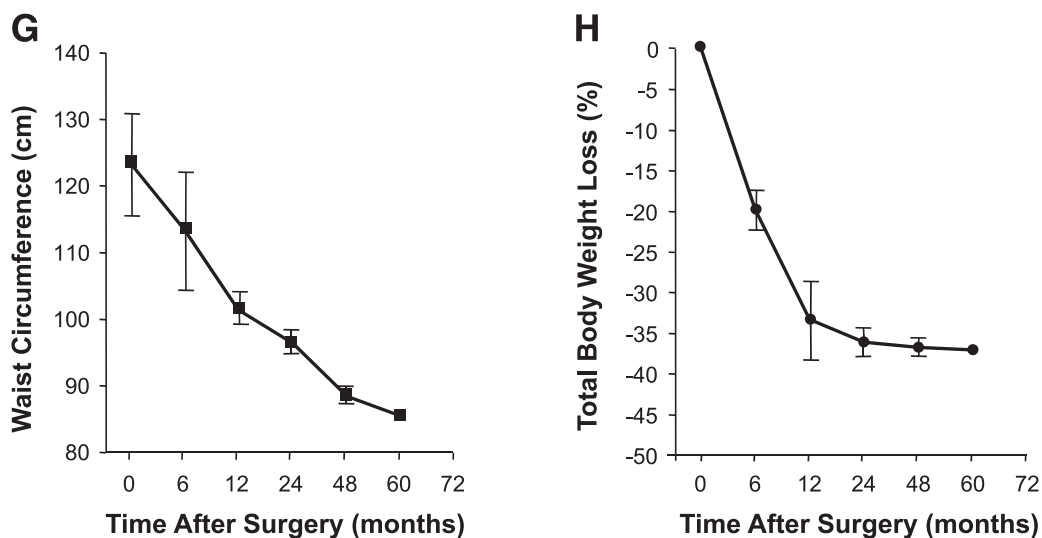
T2DM Resolved**T2DM Improved**

Figure 1—Continued

one individual who experienced no clear change in diabetes status from those whose diabetes remitted or improved. This outlier patient did not seem to have misdiagnosed type 1 diabetes, given his persistently negative autoantibody studies, as well as detectable fasting and meal-stimulated C-peptide levels, both at baseline and his latest follow-up.

To investigate the relationship between the magnitude of weight loss and the degree of improved glycemia, we generated regression lines for change in body weight compared with changes in both FPG and HbA_{1c}, with each comparison made at 6 months and also at 1, 2, 4, 5, and 6 years after RYGB. There were no significant

correlations between the amount of weight loss and the magnitude of decrease in either FPG or HbA_{1c} at any time point before 5 years (data not shown). Only at 5 and 6 years did we observe significant correlations between weight loss and decrease in FPG ($r = 0.541$, $P = 0.001$ at 5 years; $r = 0.431$, $P = 0.017$ at 6 years). There were no such correlations between weight loss and decrease in HbA_{1c} at any time point.

Overnight-fasting and meal-stimulated plasma C-peptide levels were measured preoperatively to help exclude patients with type 1 diabetes. These parameters were reassessed postoperatively to estimate whether RYGB affected β -cell

function. In response to a standardized test meal, the ratio of change in C-peptide to change in glucose increased from 18.0 preoperatively to 78.5 [ng/mL][mg/dL]⁻¹ at the longest time of individual follow-up ($P < 0.001$) (Fig. 1D), suggesting increased β -cell secretory function and sensitivity to glucose. There was no correlation between the magnitude of increase in this measure of β -cell sensitivity to glucose and the amount of body weight lost ($r = 0.03$, $P = \text{NS}$).

Additional outcome measures: other cardiovascular risk parameters

Among patients with other metabolic syndrome features, hypertension resolved in

58% (15 of 26), hypercholesterolemia resolved in 64% (21 of 33), and hypertriglyceridemia resolved in 58% (18 of 31). Mean blood pressure for the entire cohort decreased progressively over 6 years ($P < 0.05$ for diastolic and systolic) (Fig. 2), with reductions in diastolic pressure reaching statistical significance by 6 months and thereafter and reductions in

systolic pressure becoming significant by 48 months and thereafter. Mean lipid parameters for the group also improved steadily for 6 years (Fig. 2). There were clear, progressive reductions in total cholesterol ($P < 0.001$), LDL cholesterol ($P < 0.001$), and triglycerides ($P = 0.003$) as well as an increase in HDL cholesterol ($P = 0.002$).

Predicted 10-year risk of cardiovascular disease, calculated using the UKPDS risk engine (22), fell substantially after surgery, with the following changes in risk of events (Table 2): 71% decrease in coronary heart disease (CHD, $P = 0.001$), 84% decrease in fatal CHD ($P = 0.001$), 50% decrease in stroke ($P = 0.01$), and 57% decrease in fatal stroke ($P = 0.009$).

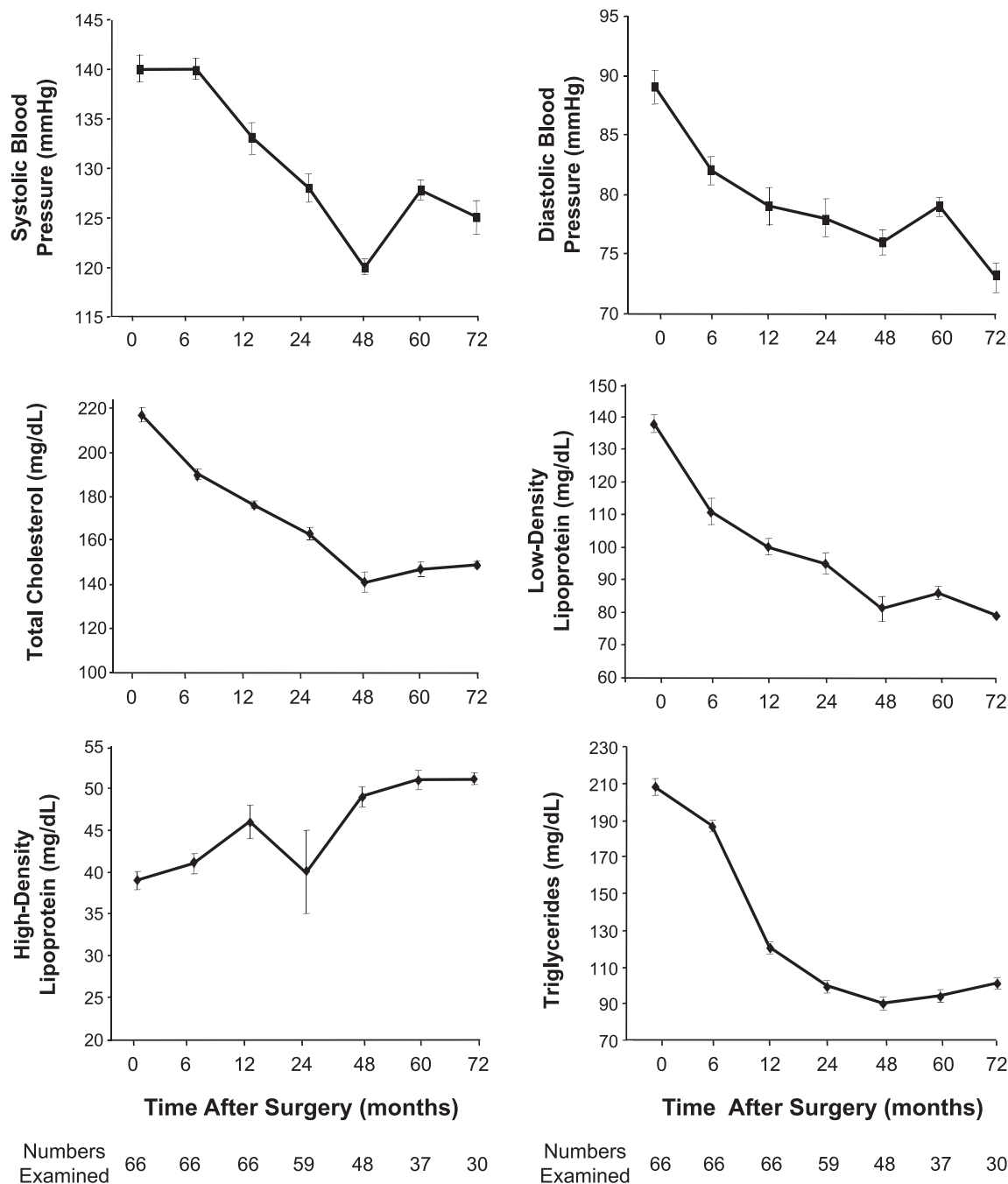


Figure 2—Improvements in blood pressure and lipid levels during 6 years following RYGB. There were significant, progressive decreases in average systolic and diastolic blood pressure ($P < 0.05$ for both) in the entire cohort over the course of the study. There also were significant, progressive decreases over the course of the study in total cholesterol ($P < 0.001$), LDL cholesterol ($P < 0.001$), and triglycerides ($P = 0.003$), as well as an increase in HDL cholesterol ($P = 0.002$). Data represent means \pm SE for all patients; n values are the same as in Fig. 1.

Table 2—Estimated 10-year cardiovascular risk before vs. after surgery

Cardiovascular event	Presurgery mean risk	Postsurgery mean risk*	Absolute risk reduction (%)	95% CI	Relative risk reduction (%)	P†
n	66	66				
CHD	35.3 ± 10.0	10.3 ± 2.6	25	8.2–13.3	71	0.001
Fatal CHD	26.2 ± 8.1	5.4 ± 1.9	21	3.7–8.0	84	0.001
Stroke	5.0 ± 0.4	2.5 ± 1.7	2.5	1.7–6.0	50	0.01
Fatal stroke	0.7 ± 0.3	0.4 ± 0.2	0.3	0.03–0.1	57	0.009

Data are means ± SD (%), unless otherwise indicated. The UKPDS risk engine equations use several patient characteristics, including duration of diabetes, and all of our subjects had type 2 diabetes at baseline. In cases where diabetes resolved during the study, we used the duration of diabetes at the time of remission for UKPDS calculations at time points thereafter, although diabetes remission was durable throughout the study in all cases where it occurred. This conservative approach, in which a component of cardiovascular risk is assigned because of duration of diabetes even in cases following diabetes remission, should underestimate the actual risk reduction following RYGB. *At the time of the longest individual follow-up. †P considered significant if ≤ 0.05 . Thus, decreases in all four components of cardiovascular risk are significant.

CONCLUSIONS—Because RYGB typically promotes complete remission of type 2 diabetes in severely obese patients (8,12,13), and because mounting evidence indicates that this results from hormonal and metabolic mechanisms beyond just the consequences of weight loss (5,15,16,23), evaluating the use of RYGB to treat diabetes in less obese patients is logical (5,23). Here we report the largest and longest-term study to date examining the efficacy and safety of RYGB to treat type 2 diabetes in patients with class I obesity (i.e., below the BMI cutoff for bariatric surgery by existing standards) (17). Our 6-year results are favorable regarding this novel surgical approach to diabetes care among less obese patients. Complete diabetes remission was achieved in 88% of cases, with improvement in an additional 11%. Only 1 patient among 66 showed no clear amelioration of diabetes. Postoperative changes in the C-peptide and glucose responses to test meals demonstrated improved β -cell function, despite patients aging, suggesting that RYGB can reverse the progressive β -cell failure that characterizes type 2 diabetes. The impressive improvement in glycemic control we observed was accompanied by substantial reductions in hypertension and dyslipidemia, yielding major improvements in predicted cardiovascular disease risk from fatal and nonfatal CHD and strokes. There was no mortality, significant surgical morbidity, excessive weight loss, or malnutrition, emphasizing the safety and efficacy of RYGB in patients with type 2 diabetes and a BMI of 30–35 kg/m².

Because we did not directly compare the safety and efficacy of RYGB in patients with class I obesity to results in more obese patients who would traditionally

qualify for bariatric surgery, we cannot make strong conclusions regarding contrasts between these two populations. Nevertheless, the 88% diabetes remission rate we found in patients with BMI < 35 kg/m² seems at least comparable to that observed among conventional bariatric surgery patients with BMI > 35 kg/m², in whom diabetes remission rates are historically 80–85% (8,9,12,13). Likewise, the operation seemed to be at least as safe, or perhaps safer, in our less obese cohort as in heavier patients. Our rates of mortality, major morbidity, and minor morbidity were 0, 0, and 15%, respectively, compared with expected rates of 0.2, 4–5, and 10–15% in patients with BMI > 35 kg/m² undergoing LRYGB (8,10,11). Although excessive weight loss is a theoretical concern for less obese individuals undergoing weight-reducing surgery, this did not occur in our study. The lowest postoperative BMI we observed was 23.6 kg/m² (solidly within the healthy-weight range), and evidence of malnutrition was not manifest in any subject. In summary, among our patients with BMI 30–35 kg/m², both the safety and efficacy of LRYGB to treat type 2 diabetes seemed to be at least as good or perhaps better than is typically expected in patients with BMI > 35 kg/m².

We observed impressive effects of RYGB on diabetes even though our subjects had very severe diabetes. A previous 2-year examination of laparoscopic adjustable gastric banding (LAGB) to treat type 2 diabetes in adults with BMI 30–40 kg/m² reported an excellent 73% diabetes remission rate; but those subjects had very mild diabetes, with disease duration of < 2 years in all cases, only 3% taking insulin, and average preoperative HbA_{1c} 7.7% (24,25). In contrast, we observed an even higher

88% diabetes remission rate after RYGB in patients with class I obesity, despite our subjects having very severe diabetes (disease duration 12.5 ± 7.4 years, 15% taking insulin, and preoperative HbA_{1c} poorly controlled at $9.7 \pm 1.5\%$). Duration of disease and insulin usage are the strongest predictors of diabetes persisting after RYGB in patients with BMI > 35 kg/m² (9,12,13); yet although our study subjects had longstanding, poorly controlled diabetes, and many were insulin requiring, the large majority achieved disease remission. In short, among patients with BMI < 35 kg/m², we found a higher diabetes remission rate with longer follow-up and more subjects than has been observed following LAGB, despite our patients having far more severe diabetes.

Although weight loss undoubtedly plays an important long-term role in improving glycemia after RYGB, several of our findings are consistent with additional weight-independent antidiabetes effects of this operation, as has previously been proposed (5,15,16,23). We found no relationship between change in body weight and change in HbA_{1c} at any postoperative time point from 6 months through 6 years. Likewise, we found no correlation between changes in body weight and FPG until 5 years after surgery, even though all of the patients who experienced diabetes remission had achieved such remission by just 6 months. There also was no relationship between the amount of weight lost and the magnitude of improvement in β -cell sensitivity to glucose. Finally, there were no apparent differences in the time-course curves for loss of either body weight or waist circumference among patients who experienced full remission versus only improvement of diabetes.

Lowering of HbA_{1c} in our study seemed to occur more rapidly than did reduction of FPG (Fig. 1A and B). Differences in the maximum possible speed of change in these two parameters would predict the opposite results, and, moreover, the earliest post-RYGB follow-up time point still is late enough to reflect steady-state responses in both measurements to any immediate postoperative changes. Theoretically, the difference in kinetics suggests that perhaps post-RYGB improvements in daytime and/or postprandial glucose levels (reflected in HbA_{1c}) occurred unexpectedly earlier than did changes in fasting values.

Our favorable results confirm and extend observations made in smaller, shorter pilot studies exploring RYGB in patients with BMI < 35 kg/m². These

preliminary investigations also reported beneficial effects on type 2 diabetes and dyslipidemia in Indian (26), Chinese (27), and South American (28) populations, as well as among scattered cases throughout the U.S. (29), although sample sizes were small and observation periods relatively short. Importantly, as in our cohort, excessive post-RYGB weight loss was not observed in any of these studies of less obese patients. Early explorations of LAGB (24,30), biliopancreatic diversion (31), and experimental gastrointestinal operations (32–34) to treat type 2 diabetes among patients with BMI <35 kg/m² also have reported promising results, although additional studies are required to judge these approaches' risks versus benefits. However, available evidence suggests that a BMI cutoff of 35 kg/m² is not an accurate parameter to predict the potential of gastrointestinal surgery to induce glycemic and metabolic control (5,23).

Our results have potentially broad implications for health policy. Bariatric surgery is currently restricted to patients with BMI >40 kg/m², or BMI >35 kg/m² with obesity-related comorbidities such as type 2 diabetes. These guidelines derive from a 20-year-old National Institutes of Health consensus statement (17), which was written before the impact of RYGB on diabetes was generally known and before the development of many recent advances in minimally invasive RYGB techniques, which have greatly improved safety. Recently, worldwide experts in the field have offered new consensus suggestions, carefully crafted but unofficial, as articulated by delegates of the Diabetes Surgery Summit, the World Congress on Interventional Therapies for Type 2 Diabetes, and the International Diabetes Federation (5,23,35). These thought leaders recommended that RYGB be considered to treat poorly controlled type 2 diabetes in patients with BMI 30–35 kg/m². However, that recommendation was based on limited, short-term data then available (5). Our study, which is by far the largest and longest on this topic to date, helps affirm this new guideline.

Although lowering the BMI threshold for RYGB in patients with type 2 diabetes from 35 to 30 kg/m² would be a modest numerical change, it would affect a very large population because the BMI distribution peak among diabetic patients lies within this range (18). In the U.S., more than one-fourth of people with diabetes have class I obesity (BMI 30–35 kg/m²) (18,36), which was our study's focus. Thus, a modest alteration of RYGB criteria

to include this population would have far-reaching implications for diabetes care. Insufficient data exist to judge the utility of RYGB to treat diabetes in patients with BMI <30 kg/m².

Our results, however, indicate that RYGB is a safe, effective procedure to ameliorate type 2 diabetes and associated comorbidities, thereby reducing predicted cardiovascular disease risk, in patients with a BMI of 30–35 kg/m². Additional data are needed from randomized controlled trials before routinely recommending RYGB in patients with BMI <35 kg/m². However, our favorable findings from a relatively large, long-term study help justify such trials to clarify whether standard indications for RYGB should be broadened and whether this operation might be viewed primarily as “metabolic,” rather than “bariatric,” surgery.

Acknowledgments—This work was supported by the Municipal Health Authority, Marcia Maria Braidó Hospital, São Paulo, Brazil (research grant no. 22/02).

R.V.C. and D.E.C. have received funding for studies unrelated to this one from Covidien and Ethicon Endo-Surgery, respectively. No other potential conflicts of interest relevant to this article were reported.

R.V.C. primarily was responsible for carrying out the study, including performing all gastric bypass operations, and he contributed to the manuscript. J.C.P. and C.A.S. researched data and contributed to the manuscript. J.E.S. and B.L.W. contributed to study conception and design and reviewed and edited the manuscript. D.E.C. contributed to study design, data analysis, and interpretation; he was the major author of the final manuscript. D.E.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Parts of this study were presented in oral form at the Asia-Pacific Workshop on Metabolic Surgery for Type 2 Diabetes, Singapore, 6 February 2012; at the 1st International Symposium on Metabolic Surgery, São Paulo, Brazil, 5 May 2012; and at the 72nd Scientific Sessions of the American Diabetes Association, Philadelphia, Pennsylvania, 8–12 June 2012.

The authors thank Silvia Lamas, MSc, from PGS Medical Statistics, for her expert, paid statistical consultation.

References

- King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. *Diabetes Care* 1998;21:1414–1431
- Norris SL, Zhang X, Avenell A, et al. Long-term effectiveness of lifestyle and behavioral

weight loss interventions in adults with type 2 diabetes: a meta-analysis. *Am J Med* 2004;117:762–774

- Norris SL, Zhang X, Avenell A, et al. Efficacy of pharmacotherapy for weight loss in adults with type 2 diabetes mellitus: a meta-analysis. *Arch Intern Med* 2004;164:1395–1404
- Hemmingsen B, Lund SS, Gluud C, et al. Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2011 June 15;6:CD008143
- Rubino F, Schauer PR, Kaplan LM, Cummings DE. Metabolic surgery to treat type 2 diabetes: clinical outcomes and mechanisms of action. *Annu Rev Med* 2010;61:393–411
- Sjöström L, Lindroos AK, Peltonen M, et al.; Swedish Obese Subjects Study Scientific Group. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med* 2004;351:2683–2693
- Sjöström L, Narbro K, Sjöström CD, et al.; Swedish Obese Subjects Study. Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med* 2007;357:741–752
- Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. *JAMA* 2004;292:1724–1737
- Buchwald H, Estok R, Fahrenbach K, et al. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am J Med* 2009;122:248e5–256e5
- Flum DR, Belle SH, King WC, et al.; Longitudinal Assessment of Bariatric Surgery (LABS) Consortium. Perioperative safety in the longitudinal assessment of bariatric surgery. *N Engl J Med* 2009;361:445–454
- Buchwald H, Estok R, Fahrenbach K, Banel D, Sledge I. Trends in mortality in bariatric surgery: a systematic review and meta-analysis. *Surgery* 2007;142:621–632; discussion 632–635
- Pories WJ, Swanson MS, MacDonald KG, et al. Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. *Ann Surg* 1995;222:339–350; discussion 350–352
- Schauer PR, Burguera B, Ikramuddin S, et al. Effect of laparoscopic Roux-en-Y gastric bypass on type 2 diabetes mellitus. *Ann Surg* 2003;238:467–484; discussion 84–85
- Adams TD, Gress RE, Smith SC, et al. Long-term mortality after gastric bypass surgery. *N Engl J Med* 2007;357:753–761
- Thaler JP, Cummings DE. Minireview: hormonal and metabolic mechanisms of diabetes remission after gastrointestinal surgery. *Endocrinology* 2009;150:2518–2525
- Cummings DE. Endocrine mechanisms mediating remission of diabetes after

- gastric bypass surgery. *Int J Obes (Lond)* 2009;33(Suppl. 1):S33–S40
17. Consensus Development Conference Panel. NIH conference: gastrointestinal surgery for severe obesity. *Ann Intern Med* 1991; 115:956–961
 18. Bays HE, Chapman RH, Grandy S; SHIELD Investigators' Group. The relationship of body mass index to diabetes mellitus, hypertension and dyslipidaemia: comparison of data from two national surveys. *Int J Clin Pract* 2007;61:737–747
 19. American Diabetes Association. Diagnosis and classification of diabetes mellitus (Position Statement). *Diabetes Care* 2010; 33(Suppl. 1):S62–S69
 20. Pinheiro JS, Schiavon CA, Pereira PB, Correa JL, Noujaim P, Cohen R. Long-long limb Roux-en-Y gastric bypass is more efficacious in treatment of type 2 diabetes and lipid disorders in super-obese patients. *Surg Obes Relat Dis* 2008;4:521–525; discussion 526–527
 21. Rosenzweig JL, Ferrannini E, Grundy SM, et al.; Endocrine Society. Primary prevention of cardiovascular disease and type 2 diabetes in patients at metabolic risk: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2008;93:3671–3689
 22. Stevens RJ, Kothari V, Adler AI, Stratton IM; United Kingdom Prospective Diabetes Study (UKPDS) Group. The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). *Clin Sci (Lond)* 2001;101:671–679
 23. Rubino F, Kaplan LM, Schauer PR, Cummings DE; Diabetes Surgery Summit Delegates. 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
 24. 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: 316–323
 25. Cummings DE, Flum DR. Gastrointestinal surgery as a treatment for diabetes. *JAMA* 2008;299:341–343
 26. Shah SS, Todkar JS, Shah PS, Cummings DE. Diabetes remission and reduced cardiovascular risk after gastric bypass in Asian Indians with body mass index < 35 kg/m². *Surg Obes Relat Dis* 2010;6: 332–338
 27. Lee WJ, Wang W, Lee YC, Huang MT, Ser KH, Chen JC. Effect of laparoscopic mini-gastric bypass for type 2 diabetes mellitus: comparison of BMI > 35 and < 35 kg/m². *J Gastrointest Surg* 2008;12:945–952
 28. Cohen R, Pinheiro JS, Correa JL, Schiavon CA. Laparoscopic Roux-en-Y gastric bypass for BMI < 35 kg/m²: a tailored approach. *Surg Obes Relat Dis* 2006;2:401–404; discussion 404
 29. Demaria EJ, Winegar DA, Pate VW, Hutcher NE, Ponce J, Pories WJ. Early postoperative outcomes of metabolic surgery to treat diabetes from sites participating in the ASMBS bariatric surgery center of excellence program as reported in the Bariatric Outcomes Longitudinal Database. *Ann Surg* 2010;252:559–566; discussion 566–567
 30. Angrisani L, Favretti F, Furbetta F, et al. Italian Group for Lap-Band System: results of multicenter study on patients with BMI $<$ or $= 35$ kg/m². *Obes Surg* 2004;14:415–418
 31. Scopinaro N, Papadia F, Marinari G, Camerini G, Adami G. Long-term control of type 2 diabetes mellitus and the other major components of the metabolic syndrome after biliopancreatic diversion in patients with BMI < 35 kg/m². *Obes Surg* 2007;17:185–192
 32. DePaula AL, Macedo AL, Rassi N, et al. Laparoscopic treatment of type 2 diabetes mellitus for patients with a body mass index less than 35. *Surg Endosc* 2008;22: 706–716
 33. Ramos AC, Galvão Neto MP, de Souza YM, et al. Laparoscopic duodenal-jejunal exclusion in the treatment of type 2 diabetes mellitus in patients with BMI < 30 kg/m² (LBMI). *Obes Surg* 2009;19:307–312
 34. Tarnoff M, Rodriguez L, Escalona A, et al. Open label, prospective, randomized controlled trial of an endoscopic duodenal-jejunal bypass sleeve versus low calorie diet for pre-operative weight loss in bariatric surgery. *Surg Endosc* 2009;23:650–656
 35. Dixon JB, Zimmet P, Alberti KG, Rubino F; International Diabetes Federation Taskforce on Epidemiology and Prevention. Bariatric surgery: an IDF statement for obese type 2 diabetes. *Diabet Med* 2011;28:628–642
 36. Leibson CL, Williamson DF, Melton LJ 3rd, et al. Temporal trends in BMI among adults with diabetes. *Diabetes Care* 2001; 24:1584–1589