Type 2 Diabetes Remission Rates After Laparoscopic Gastric Bypass and Gastric Banding: Results of the Longitudinal Assessment of Bariatric Surgery Study

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OBJECTIVE
The goals of this study were to determine baseline and postbariatric surgical characteristics associated with type 2 diabetes remission and if, after controlling for differences in weight loss, diabetes remission was greater after Roux-en-Y gastric bypass (RYGBP) than laparoscopic gastric banding (LAGB).

RESEARCH DESIGN AND METHODS
An observational cohort of obese participants was studied using generalized linear mixed models to examine the associations of bariatric surgery type and diabetes remission rates for up to 3 years. Of 2,458 obese participants enrolled, 1,868 (76%) had complete data to assess diabetes status at both baseline and at least one follow-up visit. Of these, 627 participants (34%) were classified with diabetes: 466 underwent RYGBP and 140 underwent LAGB.

RESULTS
After 3 years, 68.7% of RYGBP and 30.2% of LAGB participants were in diabetes remission. Baseline factors associated with diabetes remission included a lower weight for LAGB, greater fasting C-peptide, lower leptin-to-fat mass ratio for RYGBP, and a lower hemoglobin A1c without need for insulin for both procedures. After both procedures, greater postsurgical weight loss was associated with remission. However, even after controlling for differences in amount of weight lost, relative diabetes remission rates remained nearly twofold higher after RYGBP than LAGB.

CONCLUSIONS
Diabetes remission up to 3 years after RYGBP and LAGB was proportionally higher with increasing postsurgical weight loss. However, the nearly twofold greater weight loss–adjusted likelihood of diabetes remission in subjects undergoing RYGBP than LAGB suggests unique mechanisms contributing to improved glucose metabolism beyond weight loss after RYGBP.

Although weight loss by lifestyle and pharmacotherapy can substantially reduce progression from prediabetes to type 2 diabetes, improve glycemic control, and induce diabetes remission, a large and growing body of literature attests to the benefits of bariatric surgery for the treatment of diabetes (1–3). Because diabetes remission rates

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remission rates have been shown to decline and incidence rates rise during follow-up after bariatric surgery (4), identifying which surgical procedures and patient characteristics are predictive of durable diabetes remission could help clinicians when advising patients regarding the appropriateness of bariatric surgery to treat this condition.

Total postoperative weight loss is a significant predictor of diabetes remission after bariatric surgery (5,6). Immediately after Roux-en-Y gastric bypass (RYGBP), improvement in hyperglycemia typically occurs rapidly and is thought to be due, in part, to an acute reduction in calorie intake (7) as well as independent gastrointestinal hormonal effects unique to this operation as compared with laparoscopic gastric banding (LAGB) (8). However, longer-term studies have demonstrated that improvement in insulin sensitivity can be explained by weight loss alone after both RYGBP and LAGB (9), suggesting that the RYGBP procedure does not have unique effects on glucose metabolism once patients are matched for weight loss by surgery type.

To understand better the effects of bariatric surgery on diabetes status, we used the large prospective cohort study Longitudinal Assessment of Bariatric Surgery-2 (LABS-2) study to examine the diabetes incidence and remission rates after RYGBP and LAGB. In addition, we used the extensive dataset obtained as part of this study to understand baseline and postoperative patient factors predictive of diabetes remission, and whether or not diabetes remission rates were greater after RYGBP than LAGB even after accounting for weight loss difference between these procedures.

RESEARCH DESIGN AND METHODS

Study Design

LABS-2 is an observational cohort that enrolled and completed baseline studies in 2,458 adult participants between 2006 and 2009 at 1 of 10 centers in six geographically diverse U.S. centers. A total of 1,868 of these participants had complete data to assess diabetes status at both baseline and at least one follow-up visit (Supplementary Table 1). Of these, 627 (34%) were classified as having diabetes, 140 of whom underwent LAGB, 466 underwent RYGBP, and 21 underwent other surgical procedures. Participants with diabetes were studied prior to surgery and annually thereafter to assess comorbid disease status and obtain metabolic measurements. The institutional review board at each study center approved the protocol and consent forms, and all participants provided informed consent before enrollment.

Definition of Diabetes and Diabetes Remission

The following criteria for diabetes at baseline were used: hemoglobin A1c (HbA1c) ≥6.5% (48 mmol/mol) or (if HbA1c was not available) fasting glucose >6.9 mmol/L; or self-report currently having diabetes and currently on a medication for diabetes; or self-report currently having diabetes and report ever hospitalized for treatment of a diabetes complication; or take any prescription antidiabetic medication in the 90 days before surgery. An exception was made for patients who self-reported use of metformin but no other diabetes medications, did not self-report a diagnosis of diabetes or report a diagnosis of polycystic ovarian syndrome, and had an HbA1c <6.5% (48 mmol/mol). Diabetes remission was defined using a modification of the American Diabetes Association Consensus Group as HbA1c <6.5% (48 mmol/mol) (or a fasting glucose ≤6.9 mmol/L if HbA1c was not available) and an absence of active pharmacologic therapy for diabetes (10). The decision to continue or discontinue diabetes medications was not standardized but instead left to the discretion of each patient and their clinician.

Weight and Weight Loss

Body weights, weight loss, and BMI were measured as previously reported (11). Percent body fat was measured by bioelectrical impedance analysis using a Tanita scale model TBF-310 (Tanita Corporation, Arlington Heights, IL) (12).

Laboratory Analyses

Glucose, alanine aminotransferase (ALT), and aspartate aminotransferase were measured using a Roche autoanalyzer (Roche Diagnostics Inc., Indianapolis, IN). Leptin and proinsulin levels were determined by radioimmunoassay kit (EMD Millipore, Inc., St Charles, MO). C-peptide and insulin levels were measured by a two-site immunoenzymometric assay using a Tosoh 2000 autoanalyzer (Tosoh Bioscience, South San Francisco, CA). HbA1c levels were measured by a dedicated analyzer (Tosoh Bioscience, South San Francisco, CA). Nonesterified fatty acid levels were determined using a Roche Hitachi Modular P analyzer.

Statistical Analysis

Analysis to determine whether there were any systematic mechanisms that gave rise to incomplete data on diabetes status at follow-up showed that the missing at random assumption was deemed reasonable, and a likelihood-based generalized linear mixed model (described below) that included age as a covariate was deemed appropriate. Differences between proportions of baseline characteristics by diabetes status during follow-up were assessed by the $\chi^2$ test.

Generalized linear mixed modeling approaches were used for subsequent analyses to account for repeated measures and within-subject correlations. Mixed-effects logistic regression models with robust error variance were used to estimate 1) changes in prevalence of diabetes over time in the full sample, 2) remission of diabetes among subjects with diabetes at baseline, and 3) incidence of diabetes among those without diabetes at study entry.

Relative risk (RR) regression models (generalized linear model with log link for remission as outcome) were used to 2) determine the association between demographic and clinical characteristics measured at baseline and remission of diabetes individually for RYGBP and LAGB and 2) evaluate the independent association between surgical procedure (RYGBP vs. LAGB) and remission of diabetes. Risk factor modeling involved both the identification of potential risk factors via a screening procedure and the inclusion of variables that did not reach statistical significance but were selected a priori, such as obstructive sleep apnea. Potential covariates were screened individually with a $P$ value of <0.20 and remained when the $P$ value was <0.10. The final adjusted models included the same variables across both surgical types so that the relative importance of each variable could be evaluated. Partial $F$ values from type III sum of squares were used to determine the relative contribution of
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Diabetes Care

In determining the independent association between surgical procedure and diabetes remission, a propensity score approach was used to balance factors associated with the non-random assignment of surgical procedure. The estimated propensity score for surgical procedure was obtained from the fit of a logistic regression model. This model included clinical site and participant demographic, clinical, and comorbid conditions measured prior to surgery as candidates predicting surgical assignment. The final propensity score model comprised clinical site and participant age, sex, education level, BMI, and number of concurrent comorbid conditions. The c-statistic for the model was 0.80, and the Hosmer and Lemeshow test indicated a good fit. The propensity score–adjusted models that assessed the association between surgical procedure and diabetes remission also included the covariate percent weight change.

To evaluate the role of weight loss after bariatric surgery, modeled probabilities and 95% CIs for diabetes remission were plotted for each postoperative year as a function of percent weight loss in participants by surgical type. A secondary analysis restricted the analysis sample to include only participants with overlapping percent weight loss in the first year postsurgery. In this analysis, a generalized linear mixed effect model was used to evaluate the association between surgical procedure and diabetes remission adjusting for other important covariates, including percent weight loss from baseline, baseline weight, HbA1c, insulin use for diabetes, and age.

Comparisons of median values of metabolic parameters by surgery type (LAGB or RYGBP) at baseline and subsequent time points were performed using Wilcoxon rank sum tests. Within each surgical type, linear mixed modeling was used to test whether or not each individual biomarker changed from baseline over time, accounting for within-subject repeated measures. Furthermore, Poisson mixed models were used to determine the association between remission of diabetes and changes in select biomarkers and anthropomorphic characteristics from baseline over three annual visits. Each model was separately fit and included time and the baseline value.

Analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC). All reported P values are two sided, and P values <0.05 were considered to be statistically significant.

RESULTS

The prevalence of type 2 diabetes at baseline in the LABS-2 cohort was 33.6% (Supplementary Tables 1 and 2), which declined to between 13 and 15% during the 3-year postoperative follow-up (Supplementary Table 2). Including all surgical procedures, diabetes remission was greatest by year 2 (63.2%) before dropping slightly by year 3 (60.2%). Remission of diabetes after RYGBP was 71.0% after 1 year and 68.7% after 3 years. Remission of diabetes after LAGB was 29.9% after 1 year, remaining stable at 30.2% after 3 years. The incidence of diabetes among participants without diabetes at baseline was low the first postoperative year after their bariatric procedure (0.4–0.8%) and remained low during the 3 years of postoperative follow-up after RYGBP but was significantly higher by year 3 (3.4%, P = 0.01) among the participants who underwent LAGB (Supplementary Table 2).

Analyzing the entire cohort, a number of baseline variables were identified that characterized those who achieved diabetes remission compared with those who did not (Supplementary Table 3). This included a younger age, having a higher percent body fat, using fewer noninsulin diabetes medications, not taking insulin, having a shorter duration of a diabetes diagnosis (although this latter finding was based on a sampling of only 50% of the eligible population), and the finding that remission rates were greater in those who underwent RYGBP or other bariatric procedures (sleeve gastrectomy, biliopancreatic diversion with duodenal switch, and banded gastric bypass) than LAGB. However, given that surgery type was not randomly assigned in LABS and that several baseline characteristics differed between surgical groups (Supplementary Table 4), diabetes remission was examined separately for patients undergoing RYGBP or LAGB (Table 1). Remission rates common to both procedures included diabetes treatment regimens lacking insulin and lower baseline HbA1c levels (Table 1). Diabetes remission was more likely after LAGB, but not RYGBP, for participants who weighed less and had higher levels of the liver enzyme ALT at baseline. On the other hand, diabetes remission was more likely after RYGBP, but not LAGB, if participants at baseline had higher fasting C-peptide levels and lower leptin levels adjusted for fat mass (leptin-to-fat mass ratio) (Table 1). Duration of diabetes was added to the data collection form midway into the study, and thus information on self-reported diabetes duration is missing on nearly half of the subjects included in this analysis. With this caveat, a sensitivity analysis including only subjects with nonmissing data for diabetes duration revealed that duration was inversely associated with diabetes remission among those undergoing RYGB surgery (RR 0.80 [95% CI 0.69–0.92], P = 0.003) after adjusting for the other covariates included in Table 1. Among the LAGB participants, however, there was no association between duration of diabetes and remission (RR 0.64 [95% CI 0.37–1.10], P = 0.10) after adjustment.

Next, we examined postsurgical changes in several metabolic parameters involved in glucose metabolism (Supplementary Table 5) and determined which of these were significantly associated with diabetes remission (Table 2). After both procedures, significant reductions were found in levels of HbA1c, C-peptide, proinsulin, free fatty acids, and leptin, as well as insulin use and the number of noninsulin medications needed to treat diabetes (Supplementary Table 5). Insulin sensitivity (HOMA-%S) significantly increased after both procedures, whereas insulin secretion (HOMA-%B) decreased after RYGBP but did not change significantly after LAGB. In parallel with greater weight loss, the changes in these variables were greater at each follow-up year in the RYGBP participants than the LAGB group, with the exception of fasting free fatty acid levels, which were not different between these two surgical groups at any follow-up year (Supplementary Table 5).

After both surgical procedures, greater likelihood of diabetes remission was associated with greater reductions in body weight, waist circumference, and
mference (Table 2). Because participants in the parent LABS-2 study lost more weight after RYGBP than LAGB (11), we compared diabetes remission likelihood ratios while controlling for weight loss differences and a propensity score that accounted for baseline imbalances between the two surgical groups. We found that as a function of percent weight loss, the mean (and 95% CIs) adjusted probability of diabetes remission was greater at each postoperative follow-up year after RYGBP than LAGB (adjusted RRs [aRRs] were 1.91, 1.72, and 1.92 at years 1, 2, and 3, respectively; all \( P \leq 0.001 \)) (Fig. 1 and Supplementary Table 6). When 3-year changes in metabolic variables were examined separately by surgical procedure, greater diabetes remission likelihood after LAGB was associated with postsurgical reductions in C-peptide, insulin, proinsulin levels, and leptin levels, as well as improvements in insulin sensitivity (HOMA-%S) (Table 2). Although the only incremental postsurgical metabolic parameter change significantly associated with diabetes remission after RYGBP was a reduction in the proinsulin-to-insulin ratio (Table 2), a selective decline in the baseline predictor of diabetes remission, the leptin-to-fat mass ratio (Table 1), was found after RYGBP but not LAGB (Fig. 2).

**CONCLUSIONS**

In this report, we expand on previous data by our group (11) to include yearly diabetes remission and incidence rates and explore both baseline and postsurgical changes in patient characteristics and metabolic parameters that predicted diabetes remission by surgical procedure type. Regardless of surgery type, diabetes remission rates remained mostly stable during the 3 years of follow-up. Analyzing RR likelihoods, we confirmed that

### Table 1—Baseline risk factors related to remission of type 2 diabetes status among participants undergoing either RYGBP or LAGB surgeries

| Risk factors                                      | Type 2 diabetes remission |
|---------------------------------------------------|---------------------------|
|                                                   | RYGBP \((n = 466)\) | LAGB \((n = 140)\) |
| Weight, per under 5 kg                            | RR: 1.00, 95% CI: 0.99–1.01, \( P = 0.91 \) | RR: 0.92, 95% CI: 0.86–0.98, \( P = 0.02 \) |
| Age, per 10 years older                           | RR: 0.95, 95% CI: 0.89–1.01, \( P = 0.13 \) | RR: 0.96, 95% CI: 0.77–1.19, \( P = 0.70 \) |
| Insulin use                                        | RR: 0.66, 95% CI: 0.49–0.88, \( P = 0.005 \) | RR: 0.27, 95% CI: 0.11–0.63, \( P = 0.003 \) |
| Number noninsulin medications, per one medication | RR: 0.93, 95% CI: 0.85–1.02, \( P = 0.13 \) | RR: 0.65, 95% CI: 0.43–0.99, \( P = 0.04 \) |
| HbA1c, per under 0.9% (10 mmol/mol)                | RR: 1.05, 95% CI: 1.00–1.11, \( P = 0.05 \) | RR: 1.99, 95% CI: 1.52–2.62, \( P < 0.001 \) |
| Insulin, per under 20 pmol/L                       | RR: 0.99, 95% CI: 0.98–1.01, \( P = 0.39 \) | RR: 0.90, 95% CI: 0.77–1.04, \( P = 0.16 \) |
| C-peptide, per increase under 1 nmol/L             | RR: 1.40, 95% CI: 1.19–1.66, \( P < 0.001 \) | RR: 0.99, 95% CI: 0.75–1.33, \( P = 0.97 \) |
| Proinsulin, per increase under 10 pmol/L/L         | RR: 0.99, 95% CI: 0.97–1.02, \( P = 0.70 \) | RR: 1.07, 95% CI: 1.01–1.14, \( P = 0.03 \) |
| HOMA-%S, per increase under 10 units               | RR: 1.02, 95% CI: 0.99–1.05, \( P = 0.28 \) | RR: 0.80, 95% CI: 0.53–1.19, \( P = 0.27 \) |
| HOMA-%B, per increase under 20 units               | RR: 1.01, 95% CI: 0.999–1.014, \( P = 0.08 \) | RR: 1.03, 95% CI: 0.97–1.08, \( P = 0.34 \) |
| Leptin/fat mass, per increase under 1 µg/L/kg      | RR: 1.46, 95% CI: 1.20–1.78, \( P < 0.001 \) | RR: 1.12, 95% CI: 0.996–1.27, \( P = 0.06 \) |
| Leptin, per 10 µg/L                                | RR: ––, 95% CI: ––, \( P = –– \) | RR: 1.01, 95% CI: 0.62–1.17, \( P = 0.95 \) |
| Obstructive sleep apnea                            | RR: 0.95, 95% CI: 0.84–1.08, \( P = 0.46 \) | RR: 1.01, 95% CI: 1.004–3.00, \( P = 0.99 \) |
| Baseline ALT, per under 1 µkat/L                   | RR: 1.02, 95% CI: 0.86–1.21, \( P = 0.79 \) | RR: 1.90, 95% CI: 1.23–2.92, \( P = 0.004 \) |

### Table 2—The association between changes from baseline over 3 years’ postsurgical follow-up in select biomarkers and anthropomorphic characteristics and type 2 diabetes remission rates among participants undergoing either RYGBP or LAGB surgeries

| Risk factors                                      | Type 2 diabetes remission |
|---------------------------------------------------|---------------------------|
|                                                   | RYGBP \((n = 466)\) | LAGB \((n = 140)\) |
| Percent weight change, per under 10%              | RR: 1.14, 95% CI: 1.07–1.20, \( P < 0.001 \) | RR: 1.31, 95% CI: 1.12–1.55, \( P = 0.002 \) |
| Percent change in waist circumference, per under 10% | RR: 1.11, 95% CI: 1.05–1.18, \( P < 0.001 \) | RR: 1.37, 95% CI: 1.12–1.68, \( P = 0.002 \) |
| Percent change in neck circumference, per under 10% | RR: 1.17, 95% CI: 1.08–1.27, \( P < 0.001 \) | RR: 1.29, 95% CI: 1.01–1.66, \( P = 0.04 \) |
| Change in C-peptide, per increase under 1 nmol/L  | RR: 0.98, 95% CI: 0.93–1.02, \( P = 0.28 \) | RR: 1.63, 95% CI: 1.11–2.39, \( P = 0.01 \) |
| Change in insulin, per increase under 10 pmol/L    | RR: 1.00, 95% CI: 0.99–1.01, \( P = 0.59 \) | RR: 1.07, 95% CI: 1.01–1.12, \( P = 0.01 \) |
| Change in proinsulin, per increase under 10 pmol/L | RR: 1.02, 95% CI: 0.96–1.09, \( P = 0.46 \) | RR: 1.10, 95% CI: 1.01–1.20, \( P = 0.025 \) |
| Change in proinsulin-to-insulin ratio, per under 1 unit | RR: 1.71, 95% CI: 1.20–2.44, \( P = 0.003 \) | RR: 0.90, 95% CI: 0.35–2.32, \( P = 0.83 \) |
| Change in fatty acids, per increase under 0.5 mmol/L | RR: 1.01, 95% CI: 0.92–1.11, \( P = 0.76 \) | RR: 0.97, 95% CI: 0.74–1.29, \( P = 0.85 \) |
| Change in leptin, per under 10 µg/L                 | RR: 0.99, 95% CI: 0.99–1.03, \( P = 0.99 \) | RR: 1.13, 95% CI: 1.01–1.26, \( P = 0.034 \) |
| Change in leptin-to-fat mass ratio, per under 1 µg/L/kg | RR: 0.89, 95% CI: 0.77–1.05, \( P = 0.16 \) | RR: 1.11, 95% CI: 0.65–1.90, \( P = 0.70 \) |
| Change in HOMA-%S, per increase under 30 units     | RR: 1.01, 95% CI: 0.999–1.021, \( P = 0.054 \) | RR: 1.22, 95% CI: 1.03–1.43, \( P = 0.02 \) |
| Change in HOMA-%B, per increase under 30 units     | RR: 1.004, 95% CI: 0.99–1.01, \( P = 0.51 \) | RR: 0.98, 95% CI: 0.95–1.00, \( P = 0.059 \) |

All models include time and the baseline value for the characteristic.
presurgical characteristics associated with a greater likelihood of diabetes remission after both LAGB and RYGBP include having shorter diabetes duration and better glucose control (13,14), whereas use of insulin reduced the likelihood of remission by 73% after LAGB and by 34% after RYGBP. Other baseline predictors differed by surgical procedure. Lower baseline weight was associated with improved diabetes remission after LAGB but not RYGBP, whereas greater insulin secretory function, as indicated by an elevated fasting C-peptide level, and a lower leptin-to-fat mass ratio were more likely to be associated with diabetes remission after RYGBP but not LAGB.

Similar to other reports, we found that amount of postoperative weight loss (5,6) and reductions in abdominal fat mass (15,16) after both RYGBP and LAGB were associated with greater probability of diabetes remission. However, postsurgical changes in metabolic parameters closely related to body weight were associated with a greater likelihood of diabetes remission after LAGB, but not RYGBP. For example, proportionally greater reductions in leptin (reflecting loss of fat mass) and insulin sensitivity (15,16) after both RYGBP and LAGB were associated with greater probability of diabetes remission.

Figure 1—Modeled probabilities and 95% CIs for diabetes remission for each postoperative year of follow-up as a function of percent weight loss in participants undergoing LAGB (red lines) and RYGBP (blue lines). aRR estimates and 95% CIs for the association between surgical type (RYGBP vs. LAGB) and diabetes remission are adjusted for percent weight change from baseline and a propensity score consisting of baseline demographic and clinical characteristics associated with type of bariatric surgical procedure. aRR is greater for RYGBP than LAGB at each postoperative year; P = 0.001 for each time point.

Figure 2—Box plots displaying levels of leptin adjusted for fat mass before and yearly for 3 years after undergoing LAGB (left graph, red bars) and RYGBP (right graph, blue bars). Overall test for change from baseline over time accounting for within-participant correlation: P < 0.001 for RYGBP and P = 0.40 for LAGB.
which tracks closely with weight loss) were associated with diabetes remission after LAGB only. In turn, improved insulin sensitivity would then be expected to reduce demand on islet cell secretion, many parameters of which (including lower fasting levels of insulin, C-peptide, and proinsulin) showed significant associations with diabetes remission after LAGB.

These same metabolic parameters were not, however, associated with diabetes remission after RYGBP. This was somewhat unexpected because of a previous report demonstrating that postsurgical improvements in insulin sensitivity and islet cell secretion were similar when subjects undergoing LAGB and RYGBP were matched for weight loss (9). When we examined the relationships between degree of weight loss and likelihood of diabetes remission more closely, we found a nearly twofold greater likelihood of diabetes remission after RYGBP compared with LAGB in each year of follow-up, even accounting for weight loss differences between these procedures. This finding could potentially be explained by several factors. Shortly after surgery and before significant weight loss has occurred, the proportionally greater reductions in caloric intake that accompany RYGBP (7) as well as the immediate increases in postprandial secretion of the incretin GLP-1 (17) are thought to lead to lower fasting and postprandial glucose levels compared with LAGB. Animal models and human studies have also demonstrated rapid reversal of hyperglycemia simply by surgically or mechanically excluding nutrients from the duodenum (18,19), although the mechanisms for this phenomenon remain unclear. Longer-term, factors that may beneficially impact glucose metabolism after RYGBP compared with LAGB include higher levels of circulating bile acid levels (20), differential effects on the microbiome (21), and alterations in jejunal nutrient sensing (22).

In this report, we identified a potentially novel metabolic relationship that may play a role in the greater likelihood of diabetes remission after RYGBP compared with LAGB, that of changes in fat-adjusted leptin levels after surgery, lower levels of which were identified as a baseline predictor of diabetes remission after RYGBP but not LAGB. Several recent studies have reported lower than expected leptin and leptin-to-fat mass ratio levels after RYGBP compared with LAGB and weight loss controls (23,24). Given the sustained reduction in caloric intake and high success rates of long-term weight loss maintenance for many after RYGBP (4,25), it has been suggested that this reduction in leptin-to-fat mass ratio is indicative of enhanced central leptin sensitivity (24,26). As leptin has been demonstrated to influence glucose metabolism through mechanisms thought to be mediated by both central and peripheral leptin signaling (27–29), it is possible that enhanced leptin sensitivity leads to improved glucose metabolism independent of weight loss after RYGBP. Support for this hypothesis comes from recent studies demonstrating that leptin administration to patients with diabetes reduced HbA1c levels in the absence of body weight change (30) or improvement in measured insulin sensitivity by an insulin clamp (31).

Our study has several limitations. As a multicenter, observational cohort study, biases may have been introduced as a result of participants and surgeons electing one surgical procedure over another, by regional variation in surgical approach, and by the fact that the surgical groups did not undergo a formal matching process. On the other hand, the RYGBP and LAGB groups did not differ in many of the baseline factors identified as key factors predicting diabetes remission, such as diabetes duration and insulin use, the surgical sites agreed to standardized procedural approaches, and having large numbers of participants allowed for statistical adjustment for many demographic or other differences between groups. Other baseline factors indicative of severity of glucose metabolism impairment were also not different between the groups, such as HbA1c levels and fasting levels of glucose, insulin, C-peptide, and proinsulin. Estimates of insulin sensitivity and islet cell secretion were calculated using the HOMA model and were also not different between the groups, but as these equations are based on fasting levels of glucose and insulin, potentially significant effects representing dynamic insulin responses and action on diabetes remission could have been missed in our study. Finally, another limitation to our analysis is the lack of a standardized approach to diabetes management across the study sites, leaving decisions regarding if and when to start (or stop) diabetes medications up to the patients and their primary care providers. For example, a patient may have continued metformin even though their HbA1c fell into the normal range after surgery if they felt it benefited them by preventing weight regain or diabetes recurrence. Indeed, we found patients with HbA1c levels <6.5% while on an oral diabetes medication in both surgical groups, decreasing in frequency over the 3-year follow-up (Supplementary Table 2). Roughly twice as many were in the LAGB than RYGBP group, but overall, the numbers in this category are relatively small and remission rates remained significantly higher after RYGBP than LAGB even if these subjects were included as remitters in the analysis (Supplementary Fig. 1).

In summary, better glucose control without need for insulin use prior to surgery, as well as greater postsurgical weight loss and reductions in waist circumference, were associated with a greater likelihood of diabetes remission for up to 3 years after both RYGBP and LAGB. The likelihood of diabetes remission after LAGB was associated primarily with metabolic parameters that closely track with weight loss. However, diabetes remission rates after RYGBP were higher than predicted by weight loss alone (by nearly twofold compared with LAGB) and were not related to changes in weight-associated metabolic factors. These data suggest that factors unique to RYGBP may have added benefits beyond weight loss on glucose control. Longer-term studies are needed that confirm the relationships of these metabolic factors with durability of diabetes remission status after bariatric surgery.

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Duality of Interest. J.O.P. serves on an advisory board for Novo Nordisk and is site investigator for a Sanofi-sponsored clinical trial. A.P. receives honoraria for participating in the speaker’s bureau for Medtronic (formerly Covidien) and W.L. Gore & Associates, Inc. C.M. receives research grant funding from Allergan. D.E.C. is the principal investigator on the COSMID (Comparison of Surgery vs. Medicine for Indian Diabetes) trial, which is funded by Johnson & Johnson. D.R.F. serves on a medical advisory board for Pacira Pharmaceuticals, Inc. B.M.W. is a site investigator for a clinical trial of vagal blocking (Enteromedics). A.C. has received research grants from the NIH-NIDDK, Nutrisystem, Ethicon, Inc., Johnson & Johnson, and Covidien, is a project consultant for Apollo Endosurgery, and was a project consultant for Ethicon, Inc. No other potential conflicts of interest relevant to this article were reported.

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