Preserved Insulin Secretory Capacity and Weight Loss Are the Predominant Predictors of Glycemic Control in Patients With Type 2 Diabetes Randomized to Roux-en-Y Gastric Bypass

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Improvement in type 2 diabetes after Roux-en-Y gastric bypass (RYGB) has been attributed partly to weight loss, but mechanisms beyond weight loss remain unclear. We performed an ancillary study to the Diabetes Surgery Study to assess changes in incretins, insulin sensitivity, and secretion 1 year after randomization to lifestyle modification and intensive medical management (LS/IMM) alone (n = 34) or in conjunction with RYGB (n = 34). The RYGB group lost more weight and had greater improvement in HbA1c. Fasting glucose was lower after RYGB than after LS/IMM, although the glucose area under the curve decreased comparably for both groups. Insulin sensitivity increased in both groups. Insulin secretion was unchanged after LS/IMM but decreased after RYGB, except for a rapid increase during the first 30 min after meal ingestion. Glucagon-like peptide 1 (GLP-1) was substantially increased after RYGB, while gastric inhibitory polypeptide and glucagon decreased. Lower HbA1c was most strongly correlated with the percentage of weight loss for both groups. At baseline, a greater C-peptide index and 90-min postprandial C-peptide level were predictive of lower HbA1c at 1 year after RYGB. β-Cell glucose sensitivity, which improved only after RYGB, and improved disposition index were associated with lower HbA1c in both groups, independent of weight loss. Weight loss and preserved β-cell function both predominantly determine the greatest glycemic benefit after RYGB.

RESEARCH DESIGN AND METHODS

Study Participants

Details of the study methods have been published (5,6). Key inclusion criteria included BMI 30–39.9 kg/m²; HbA1c < 8% (64 mmol/mol) or < 14% (130 mmol/mol); and C-peptide > 1 ng/mL 90 min after a standardized meal challenge. The 68 patients in this ancillary study...
were from two of the five study sites that recruited a total of 120 participants.

**Interventions**
Details of the RYGB and LS/IMM intervention, including the protocol for intensification of medical therapy, have been described (5). Blood specimens were collected before and 15, 30, 60, 90, and 120 min after ingestion of Ensure over 15 min in the morning while upright. Insulin was held the prior evening, and other diabetes medications were held the morning of testing.

**Assays**
Assays used for determination of hormone concentrations were as follows: 1) insulin and C-peptide were measured using the Immulite Analyzer; 2) total glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2), and gastric inhibitory polypeptide (GIP) were measured by ELISA (Millipore); and 3) glucagon was measured by randoimmunoassay (Millipore).

**Calculations and Statistical Analysis**
The insulinogenic index and C-peptide index were quantified as the change in insulin or C-peptide relative to the change in glucose from 0 to 30 min. The insulin secretion rate (ISR) was calculated by deconvolution of C-peptide through the Chronological Series Analyzer software (7,8). HOMA-insulin resistance (IR) was calculated as reported by Matthews, et al. (9). The Matsuda index (MI) was calculated as 10,000/(glucose0 × insulin0 × mean glucose × mean insulin)0.5 (10,11). The oral disposition index (oDI) was calculated as the product of the MI and the ratio of insulin secretion relative to glucose. Insulin clearance was calculated as the ratio of fasting C-peptide to fasting insulin. The metabolic clearance rate (MCR) of insulin was calculated as the ratio of fasting C-peptide to fasting insulin with peak insulin or C-peptide levels (data not shown). There were greater changes in HOMA-IR and MI after RYGB (Fig. 1). A higher MI correlated with a greater percentage weight loss for both LS/IMM and RYGB (Fig. 1). The oDI increased threefold for LS/IMM and sixfold for RYGB and also correlated with the percentage of weight loss (Fig. 1). BCGS increased significantly only for RYGB and was relatively unchanged in LS/IMM.

**Gut Hormones**
Values for GLP-1, GIP, and GLP-2 are presented in Table 1 and Fig. 2. The GLP-1 AUC increased after RYGB but not after LS/IMM. Despite an early postprandial increase in GIP levels, there was an overall significant decrease in the GIP AUC after RYGB. There was no change in GIP after LS/IMM. Peak GLP-1 or GIP levels were not associated with peak insulin or C-peptide levels (data not shown). The GLP-2 AUC decreased in LS/IMM patients but increased in RYGB patients.

**Correlation Analyses**
Various factors were examined to determine predictors of HbA1c at 12 months (Table 2). At 12 months, weight loss was significantly correlated with HbA1c in both groups. Baseline HbA1c was predictive of HbA1c at 1 year in LS/IMM. Baseline 90-min C-peptide and greater early-phase (30 min) insulin secretion were associated with lower...
Table 1—Clinical characteristics and changes in glucostatic parameters and gut hormones

<table>
<thead>
<tr>
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<th>Baseline 12 months</th>
<th>12 months</th>
<th>P*</th>
<th>P†</th>
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<tr>
<td><strong>BMI (kg/m^2)</strong></td>
<td>35.7</td>
<td>35.8</td>
<td>—</td>
<td>—</td>
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<tr>
<td><strong>Weight (kg)</strong></td>
<td>105.7</td>
<td>96.3</td>
<td>0.0001 0.0001</td>
<td>0.5 §</td>
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<tr>
<td><strong>HbA1c (mmol/mol)</strong></td>
<td>8.1</td>
<td>7.4</td>
<td>0.0001 0.0004</td>
<td>0.2 §</td>
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<tr>
<td><strong>Glucose 120m (mg/dL)</strong></td>
<td>252</td>
<td>14 117</td>
<td>0.0001 0.005 0.0001</td>
<td>6 §</td>
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<tr>
<td><strong>HOMA-IR</strong></td>
<td>2.9</td>
<td>0.5</td>
<td>0.0001 268, 0.01 0.0001</td>
<td>9 §</td>
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<td><strong>40-min CGR index</strong></td>
<td>0.3</td>
<td>1.4</td>
<td>0.0001 2.2 § 0.0001</td>
<td>0.04 0.01</td>
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<td><strong>Weight loss (%)</strong></td>
<td>—</td>
<td>9.2</td>
<td>2.1 1.3</td>
<td>—</td>
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<tr>
<td><strong>All T2DM medications</strong></td>
<td>34 (100)</td>
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Note: § P = 0.05 between groups at baseline; * P = 0.05 between groups at 12 months. Differences in the changes over time between groups: P = 0.05 between groups at baseline. 

Values are mean ± SEM or n (%). All is calculated from 0 to 120 min. More ratios for insulin/glucagon are presented. C — C-peptide; F — fasting; I — insulin. *

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Values are mean ± SEM or n (%). All is calculated from 0 to 120 min. More ratios for insulin/glucagon are presented. C — C-peptide; F — fasting; I — insulin. *
Figure 1 — Glucostatic and pancreatic hormone changes. Changes in glucose (A), insulin (B), C-peptide (C), and glucagon (D). E: Changes in insulin secretion relative to glucose. F: Changes in metabolic insulin clearance. G: MI at baseline. H: MI after 1 year. I: Regression analysis of MI after 1 year and percentage of weight loss. J: Regression analysis of oDI after 1 year and percentage of weight loss. LS/IMM is depicted in blue and RYGB is depicted in red. Open shapes and dashed lines denote baseline values, and closed shapes and solid lines denote values at 1 year. Hatched bars denote baseline values, and solid bars denote values at 1 year. AUC is calculated from 0 to 120 min and is expressed $\times 10^3$. M0, month 0 (baseline); M12, month 12. * $P < 0.05$ for within-group change. §$P < 0.05$ for difference in change between groups.
HbA$_{1c}$ at 1 year in RYGB. A higher C-peptide index was correlated with lower HbA$_{1c}$ for RYGB patients, and greater early postprandial insulin secretion at 1 year continued to correlate with lower HbA$_{1c}$. The oDI was correlated with lower HbA$_{1c}$ for both LS/IMM and RYGB. BCGS correlated with HbA$_{1c}$ at 1 year for both groups; this association was independent of weight loss. BCGS did not correlate with weight loss, GLP-1 at 30 min, or total GLP-1 AUC (data not shown). Neither HOMA-IR nor MI were correlated with HbA$_{1c}$ at 1 year for either group, but higher adiponectin levels at 1 year in RYGB patients correlated with lower HbA$_{1c}$. After taking into account weight loss, adiponectin was no longer predictive of HbA$_{1c}$ at 1 year in either group. Gut hormone levels before and after either intervention were not correlated with HbA$_{1c}$.

**DISCUSSION**

We assessed pancreatic function and gut hormone changes after LS/IMM, alone or with RYGB, to determine factors associated with glycemic improvement after RYGB.
that may help identify patients most likely to derive the greatest glycemic benefit from surgery. As expected, fasting glucose and HbA1c improved in both groups but more so after RYGB; unexpectedly, the glucose AUC decreased similarly in both groups. We found that when insulin and gut hormone responses are compared between treatment groups, it is important to consider altered dynamics after RYGB that are likely due to accelerated transit and absorption of nutrients (12–14). Therefore, the discussion below considers both fasting and postprandial changes.

The significant decline in total insulin response after RYGB disguises a greater early postprandial peak in insulin secretion. RYGB patients experienced a rapid insulin increase early after meal ingestion, followed by a precipitous decline, whereas insulin secretion increased in LS/IMM patients and remained elevated. The early postprandial increase in insulin secretion after RYGB was significantly associated with lower HbA1c. C-peptide and insulinogenic indices both increased and were correlated with lower HbA1c after RYGB but remained unchanged after LS/IMM. Although higher insulin secretion may be the expected response to an early glycemic stimulus with altered nutrient transport, the correlation between early insulin secretion and improved HbA1c suggests that RYGB improves intrinsic β-cell glucose sensitivity.

Greater early improvement in hepatic insulin sensitivity may be partly responsible for improved insulin clearance after RYGB, as noted by others (15); however, postprandial metabolic clearance was similar in both groups. Insulin sensitivity was several-fold greater after RYGB than after LS/IMM. The MI, used as a measure of peripheral insulin sensitivity (10), was associated with weight loss in both groups but did not correlate with HbA1c after 1 year. β-Cell function (oDI) showed greater improvement after RYGB and was significantly associated with glycemia and weight loss at 1 year in both groups. BCGS, although unchanged after LS/IMM and markedly increased after RYGB at 1 year, correlated significantly with improved HbA1c for both treatment groups, even after adjusting for weight loss. Taken together, the significant association of BCGS and oDI with improved HbA1c after 1 year highlights the importance of β-cell function and sensitivity in determining glycemic control, regardless of weight loss.

Altered gut hormone secretion has been proposed as an important mechanism for improved glycemia after RYGB (2). Postprandial secretion of GLP-1 has been shown to substantially and durably increase after RYGB but not after laparoscopic adjustable gastric banding or diet-induced weight loss (16,17). Our results corroborate earlier studies demonstrating an exaggerated increase in the GLP-1 AUC after RYGB without a significant change in LS/IMM. GLP-1 levels did not correlate with HbA1c at 1 year, in contrast to other studies that have implicated GLP-1 as a predictor of remission (18). Some studies have implicated an exaggerated GLP-1 response as a mediator of improved β-cell function after RYGB (14,19), but BCGS was not associated with GLP-1 in our study. Measurements of peripheral levels of GLP-1, however, may not reflect GLP-1 receptor action (20).

The insulin-to-glucagon molar ratio in RYGB patients decreased, which is consistent with relative hyperglucagonemia after RYGB, as proposed by Camastra, et al. (21). Given that glucagon and GLP-1 are both derived from preproglucagon, it is possible that relative hyperglucagonemia is due to aberrant cleavage within the intestinal L cells after RYGB and/or lack of α-cell suppression (22). GLP-2, another product of preproglucagon that is cosecreted with GLP-1 in equimolar amounts, is similarly increased after RYGB. GLP-2 directly affects bowel mucosa by increasing the absorptive surface area, which may limit malabsorption and account for how well surgery is tolerated (23). GLP-2 has also been shown to stimulate glucagon secretion (24).

HbA1c at 12 months correlated most strongly with weight loss for both intervention groups. BCGS and oDI also correlated with lower HbA1c in both groups, and the association was independent of weight loss. Before surgery, a greater C-peptide index and greater 90-min postprandial C-peptide level were predictive of lower HbA1c at 1 year, suggesting that residual β-cell function plays an important role in remission. After 1 year, these parameters and greater early insulin secretion continued to correlate with lower HbA1c in RYGB patients. C-peptide and insulinogenic indices were essentially unchanged in LS/IMM patients, consistent with continued impaired insulin secretion. For LS/IMM patients, the only baseline predictor of lower HbA1c at 1 year was HbA1c, showing that aside from weight loss, different mechanisms mediate improvement in glycemia in LS/IMM versus RYGB patients.

In summary, we have shown that improved β-cell function and BCGS contribute significantly to improved glycemia regardless of weight loss and intervention. Greater insulin secretory capacity is predictive of outcome after RYGB, which may be used to identify surgical candidates most likely to achieve the greatest glycemic benefit. Optimization of the surgical procedure to maximize weight loss in combination with targeted therapies that enhance β-cell function are likely to improve surgical outcomes.

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References