Roux-en-Y Gastric Bypass Increases Glycemic Variability and Time in Hypoglycemia in Patients With Obesity and Prediabetes or Type 2 Diabetes: A Prospective Cohort Study

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OBJECTIVE

Roux-en-Y gastric bypass (RYGB) is an established treatment for type 2 diabetes and obesity. The study objective was to establish RYGB's effects on glycemic variability (GV) and hypoglycemia.

RESEARCH DESIGN AND METHODS

This was a prospective observational study of 10 participants with obesity and prediabetes or type 2 diabetes who underwent RYGB. Patients were studied before RYGB (Pre) and 1 month, 1 year, and 2 years postsurgery with continuous glucose measurement (CGM). A mixed-meal test (MMT) was conducted at Pre, 1 month, and 1 year.

RESULTS

After RYGB, mean CGM decreased (at 1 month, 1 year, and 2 years), and GV increased (at 1 year and 2 years). Five of the 10 participants had a percent time in range (%TIR) <3.0 mmol/L (54 mg/dL) greater than the international consensus target of 1% at 1 or 2 years. Peak glucagon-like peptide-1 (GLP-1) and glucagon area under the curve during MMT were positively and negatively associated, respectively, with contemporaneous %TIR <3.0 mmol/L.

CONCLUSIONS

Patients undergoing RYGB are at risk for development of postbariatric hypoglycemia due to a combination of reduced mean glucose, increased GV, and increased GLP-1 response.

Bariatric and metabolic surgeries such as Roux-en-Y gastric bypass (RYGB) presently are the most effective means of achieving durable weight loss and remission of diabetes in obesity and type 2 diabetes (1). There is evidence that intraday glycemic variation (GV) may be exaggerated after surgery (2,3). Etiologically linked is the phenomenon of postbariatric hypoglycemia (PBH), in which patients present with disabling hypoglycemic episodes, sometimes necessitating hospital admission (4). Results of postoperative continuous glucose measurement (CGM) studies have suggested that hypoglycemic events can occur in 29%–75% of patients (5–7). For this study, our objective was to comprehensively profile the longitudinal evolution of GV

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and hypoglycemia before and after RYGB and to study their relationship to the postprandial glycemic and enteropancreatic hormone responses.

RESEARCH DESIGN AND METHODS

This was a prospective observational study conducted according to the principles of the Declaration of Helsinki (ClinicalTrials.gov NCT01945840; UK National Health Service Health Research Authority West London National Research Ethics Committee 13/LO/1510) (8). Participants underwent study visits prior to RYGB (Pre) and at 1 month, 1 year, and 2 years after surgery. Volunteers then had a 3 h mixed-meal test (MMT) (4) at the Pre, 1 month, and 1 year time points, using Ensure Compact (13 g of protein, 11.6 g of fat, 36 g of carbohydrates, 330 kcal, 137.5 mL; Abbott Nutrition). Blood was sampled at baseline and 15, 30, 60, 120, and 180 min from time of meal ingestion, via an indwelling cannula placed in the antecubital fossa. The participants were fitted with a blinded G4 Platinum or G6 CGM system (Dexcom) at each study visit; these CGM systems have been validated for accuracy (9) and comparability (10) in the hypoglycemic range. Data were collected for up to 7 days under free-living conditions and were analyzed using the EasyGV, version 10, calculator (Oxford University Innovation, Ltd.) for measures of GV and percent time in range (%TIR) (11,12). For details on statistical and assay methods, see the Supplementary Material.

RESULTS

The clinical characteristics of the 10 patients recruited are listed in Supplementary Table 1. After surgery, participants demonstrated substantial improvements in weight, hemoglobin A_{1c}, fasting glucose and insulin, and hepatic insulin sensitivity (Supplementary Fig. 1 and Supplementary Table 1), with stabilization between 1 year and 2 years in line with accepted experience after RYGB (1). No participant during this study reported any symptoms, nor were any participants admitted for treatment of hypoglycemia.

GV Increased After RYGB at 1 and 2 Years; the Combination of Reduced Mean Glucose and Increased GV Was Associated With Increased Time in Hypoglycemia

Supplementary Figure 2 shows a progressive reduction of mean CGM glucose, which stabilized between 1 and 2 years. GV, as measured by percent coefficient of variation (%CV), continuous overlapping net glycemic action, and mean absolute glucose, was not significantly different at 1 month but demonstrated significant increases at 1 year and 2 years; mean amplitude of glucose excursions was significantly increased at 2 years but not 1 year. In line with the substantial reduction of mean CGM glucose at 1 month, 1 year, and 2 years, the %TIR >10.0 mmol/L (180 mg/dL) was reduced (Supplementary Table 1). Notably, at 1 month, the combination of reduced mean glucose level with unchanged GV was associated with no significant change in %TIR <3.0 mmol/L (54 mg/dL) and <3.9 mmol/L (70 mg/dL). After 1 month, the combination of reduced mean glucose level and increased GV was associated with significant increases in %TIR <3.0 and <3.9 (Fig. 1 and Supplementary Table 1). Supplementary Figure 3 shows that six participants had a %TIR <3.9 above the Advanced Technologies & Treatments for Diabetes international consensus desired target of 4% and five had a %TIR <3.0 above the target of 1% (13), either at 1 year or 2 years. The %TIR <3.0 was negatively correlated with mean CGM glucose (Spearman correlation coefficient, −0.55) and positively correlated with %CV (0.61), mean absolute glucose (0.53), and continuous overlapping net glycemic action (0.42) but not mean amplitude of glucose excursions. In multivariable linear mixed-model analysis using these parameters as covariates, only %CV ($P = 0.034$) remained significantly associated with %TIR <3.0.

Peak Glucagon-Like Peptide 1 and Glucagon Area Under the Curve During MMT Were Associated With Time in Hypoglycemia

Figure 1 and Supplementary Table 2 show the postsurgical enhancements in postprandial glucagon-like peptide 1 (GLP-1) and a reduction of glucagon secretion during the MMT, paralleling the improvement in glucose tolerance (14). We hypothesized that the following parameters, derived from the MMT study at each time point, might be associated with the contemporaneous %TIR <3.0 and <3.9: fasting levels of glucose, GLP-1, insulin, and glucagon; the highest concentrations of glucose, GLP-1, insulin, and glucagon; overall and incremental area under the curve from 0 to 180 min ($AUC_{0–180}$) for each of these hormones; and the nadir value of glucose achieved during the MMT.

The %TIR <3.9 was positively correlated with peak value of GLP-1 (0.68) and GLP-1 $AUC_{0–180}$ (0.63) and negatively with fasting glucose (correlation coefficient, −0.59) and glucagon $AUC_{0–180}$ (−0.50).

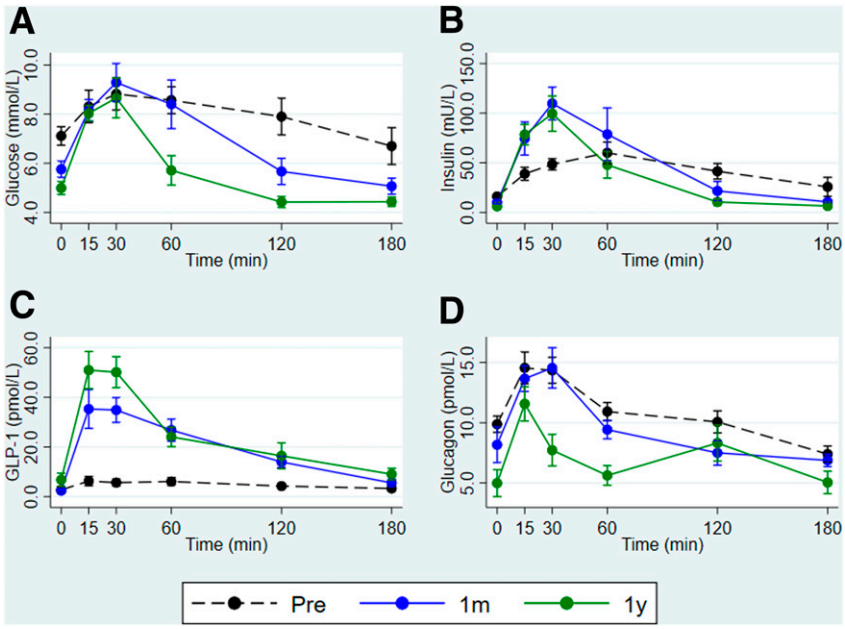

Figure 1—Response of glucose (*A*), insulin (*B*), GLP-1 (*C*), and glucagon (*D*) to MMT given at time 0, plotted as mean and SEM over time. Dashed black line, Pre; solid blue line, 1 month (1m) postsurgery; solid green line, 1 year (1y) postsurgery.

Given the a priori collinearity of GLP-1 peak and GLP-1 $AUC_{0–180}$, these parameters were tested individually in the multivariable models. Only the peak value of GLP-1 and glucagon $AUC_{0–180}$ remained significantly associated with % TIR <3.9 ($P = 0.0129$ and 0.003, respectively). When tested for associations with %TIR <3.0, these parameters were also significantly associated (GLP-1 peak, $P = 0.024$; glucagon $AUC_{0–180}$, $P = 0.01$).

CONCLUSIONS

In this study, we show that RYGB is followed by increases in GV at the 1- and 2-year time points; the combination of the decrease in mean glucose level with increased GV is associated with significant increases in time in hypoglycemia. Limitations of the study include the relatively short duration of CGM at 7 days, which limits the interpretation of the GV and %TIR compared with those established by longer-term CGM studies (15), the small number of participants studied, and that most participants had well-controlled glycemia by lifestyle measures alone. Strengths include the metabolic homogeneity of the cohort, use of a standardized surgical technique in a single center, and the prospective design with serial MMT studies that allowed us to relate the emergence of CGM-detected hypoglycemia to contemporaneous postprandial glycemic and enteropancreatic hormone responses. Our data support the hypothesis that PBH is associated with excessive GLP-1 secretion and, additionally, a possible association with reduced glucagon secretion during the MMT. Consistent with this, both the GLP-1 receptor antagonist exendin (9-39) (16) and glucagon itself (17) are being investigated as potential therapies for PBH.

We highlight two fundamental challenges in the diagnosis of PBH. First, there is a symptomatic "gap" between CGM-detected hypoglycemia and PBH; although many of our participants had CGM-detected hypoglycemia, none reported symptoms diagnostic of PBH. Second, there is currently no gold standard test for PBH. Our data suggest the nadir glucose during an MMT is not predictive of CGM-detected hypoglycemia. Defining PBH either via symptoms or hospital admission for hypoglycemia, via provocation tests such as MMT or via CGM-detected hypoglycemia, presents a diagnostic challenge.

We conclude that a substantial proportion of patients undergoing RYGB for treatment of diabetes and obesity are at risk for development of hypoglycemia and this should be disclosed during presurgical counseling as a common adverse effect. On the other hand, it should be noted that in an equal proportion of patients, CGM-detected hypoglycemia did not develop in the long term, and it is unclear why this phenomenon occurs in some patients and not others. More research is required in the form of long-term longitudinal studies of patients undergoing RYGB, focusing on risk factors for increased GV and the development of symptomatic and asymptomatic hypoglycemia, and relating these phenomena to their clinical outcomes. The data from such studies will have important implications for the diagnosis and management of PBH.

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