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ORIGINAL CONTRIBUTIONS

Continuous Glucose Monitoring Captures Glycemic Variability After Roux-en-Y Gastric Bypass in Patients with and Without Type 2 Diabetes Mellitus: A Prospective Cohort Study

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Abstract

Purpose To evaluate glycemic variability (GV) using continuous glucose monitoring (CGM) in individuals with and without type 2 diabetes mellitus (T2DM) undergoing Roux-en-Y gastric bypass (RYGB).

Methods This prospective cohort study compared the CGM data of fourteen patients with T2DM ($n=7$) and without T2DM ($n=7$) undergoing RYGB. After 6 months, these patients were compared to a non-operative control group ($n=7$) matched by BMI, sex, and age to the T2DM group.

Results Fourteen patients underwent RYGB, with a mean BMI of 46.9 ± 5.3 kg/m^2 and an average age of 47.9 ± 8.9 years; 85% were female. After 6 months post-surgery, the total weight loss (TWL) was 27.1 ± 6.3%, with no significant differences between the groups. Patients without diabetes had lower mean interstitial glucose levels (81 vs. 94 and 98 mg/dl, $p<0.01$) and lower glucose management indicator (GMI) (5.2 vs. 5.6 and 5.65%, $p=0.01$) compared to the control and T2DM groups, respectively. The coefficient of variation (CV) significantly increased only in patients with diabetes (17% vs. 26.7%, $p<0.01$). Both groups with (0% vs. 2%, $p=0.03$) and without (3% vs. 22%, $p=0.03$) T2DM experienced an increased time below range with low glucose (54–69 mg/dL). However, patients without T2DM had significantly less time in rage (70–180 mg/dL) (97% vs. 78%, $p=0.04$).

Key Points
- We aimed to assess glycemic variability with CGM in individuals undergoing RYGB.
- Three groups were evaluated: RYGB with or without T2DM and a control group.
- Distinctive CV in the operated patients 6 months after RYGB.

CGM reveals an increase in glycemic variability after RYGB.

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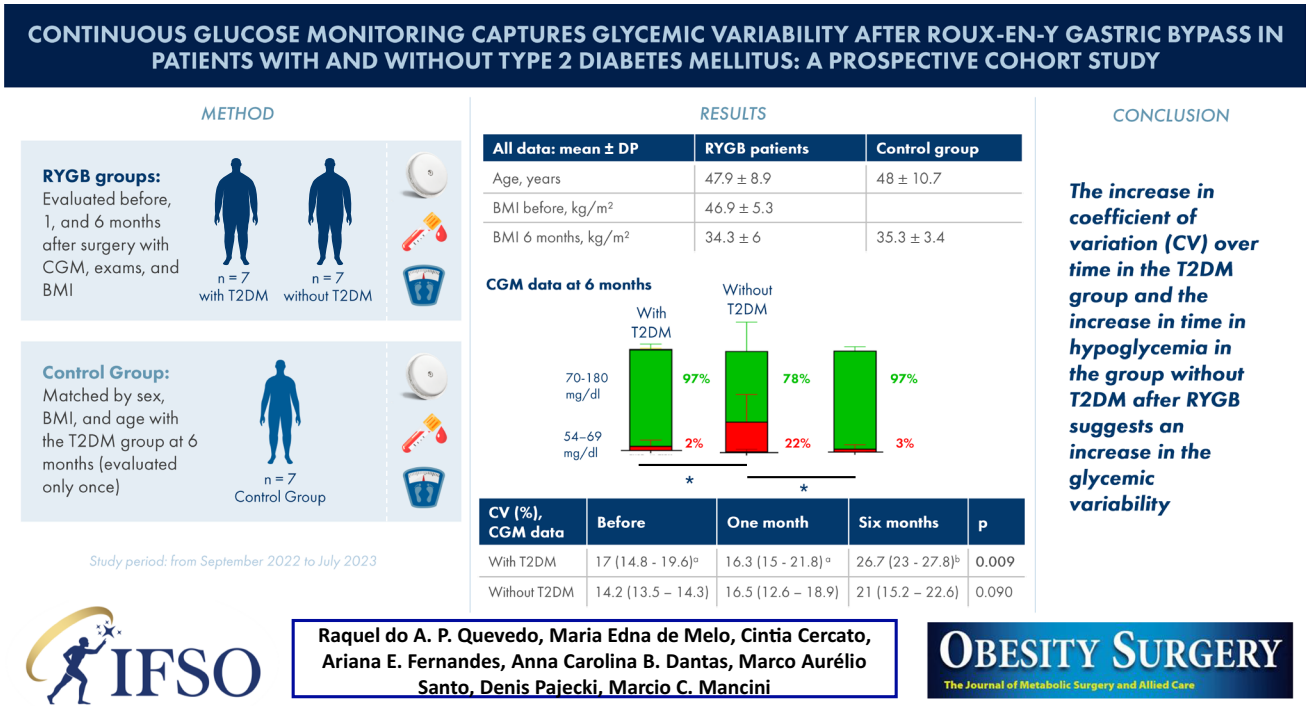
Conclusion Significant differences in CGM metrics among RYGB patients suggest an increase in glycemic variability after surgery, with a longer duration of hypoglycemia, especially in patients without T2DM.

Graphical Abstract



Keywords Diabetes mellitus · Glycemic variability · Roux-en-Y gastric bypass · Continuous glucose monitor

Introduction

Bariatric surgery, particularly Roux-en-Y gastric bypass (RYGB), provides health benefits to patients with obesity and type 2 diabetes mellitus (T2DM), including disease remission and reduction of cardiovascular risk [1–4]. While there is great heterogeneity in remission criteria, its rate depends on factors such as type of surgery, disease duration, need for insulin therapy, and postoperative follow-up time [5]. Currently, the American Diabetes Association (ADA) T2DM remission criteria are glycated hemoglobin (HbA1c) below 6.5% 3 months after the suspension of hypoglycemic therapy, with some peculiarities related to the type of intervention and temporal factors [6].

The anatomical and physiological modifications caused by the RYGB are related to accelerated gastric emptying, which is known to interfere with the postprandial glycemic response in patients with and without T2DM [7]. Furthermore, the rapid transit of glucose in the small intestine causes a substantial release of the hormone glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide 1 (GLP-1), among others, which stimulate exaggerated insulin secretion, causing reactive hypoglycemia, aggravated by the inhibition of glucagon release by GLP-1 [8, 9]. Therefore, glycemic variability (GV) should also be assessed in RYGB patients since large oscillations of glucose levels may be involved in the pathogenesis of diabetic complications and mortality.

Continuous glucose monitoring (CGM) is a new technology that regularly monitors interstitial glucose levels every 1 to 5 min, overcoming the limitations of conventional glucose measurements such as HbA1c and providing insight into GV within or between days. Moreover, CGM-derived metrics have been used in diabetes care to improve glucose stability and avoid hypoglycemia events [10]. Recently, CGM use has been expanded to other vulnerable populations to dysglycemia, such as bariatric patients. Most studies focused on a very short monitoring interval [11]. This study aimed to evaluate glycemic variability after RYGB in patients with and without T2DM with CGM.

Methods

Study Design

We conducted a prospective cohort study from September 2022 to July 2023 at an academic referral hospital to evaluate glycemic variability after RYGB in patients with and without T2DM with CGM. Patients were distributed in two groups according to T2DM diagnosis. A non-operated control group was matched by sex, age, and BMI achieved by patients in the T2DM group after 6 months of surgery. The protocol was approved by the local research ethics committee. All patients provided written informed consent.

Study Population

Patients were eligible for enrollment if they were 18 or older, had a BMI greater than 35 kg/m^2, and planned to undergo RYGB. T2DM diagnosis was defined as the use of antidiabetic medication with a C-peptide level above 0.6 ng/ml. Critical exclusion criteria were pregnancy; psychiatric disorders such as dementia, psychosis, severe depression, alcohol, and drug abuse in the last 12 months; diagnosis of malignancy in the previous 5 years; anemia (defined as hemoglobin < 9 g/dl in women and < 11 g/dl in men); and severe acute or chronic renal failure, heart or liver failure, and other diseases that alter the interstitial volume, such as edema because these modifications can change the accuracy of interstitial blood glucose. Patients were excluded from the control group if they took any medication that interfered with blood glucose levels while using the CGM or had a history of gastrointestinal surgery.

Intervention and Management

Consecutive patient candidates for bariatric surgery who met the inclusion criteria were invited to participate in the study. After signing the informed consent, they had the CGM inserted during hospitalization before the procedure. During the preoperative period, they received a very low-calorie diet (VLCD) with 600 kcal/day. Oral hypoglycemic medications were stopped and were not reintroduced after surgery. Insulin was maintained in patients using a basal/bolus regimen, with insulin doses being adjusted according to frequent capillary blood glucose levels. Patients not using insulin before hospitalization had a correction regimen of just prandial regular insulin when capillary glucose values exceeded 180 mg/dl.

Clinical history, age, weight, height, and routine antidiabetic medications were informed before, after surgery, and at 1 and 6 months postoperatively for the RYGB groups and at a single time in the control group (Fig. 1).

Patients were reevaluated 30 days after surgery when a new sensor was inserted. After 6 months postoperatively, the patients replaced the sensor. They were on a regular diet and received nutrition guidelines. Laboratory tests were performed in addition to a new physical examination. We did not evaluate HbA1c 1 month after surgery because HbA1c depends on the half-life of the red blood cell, lasting about

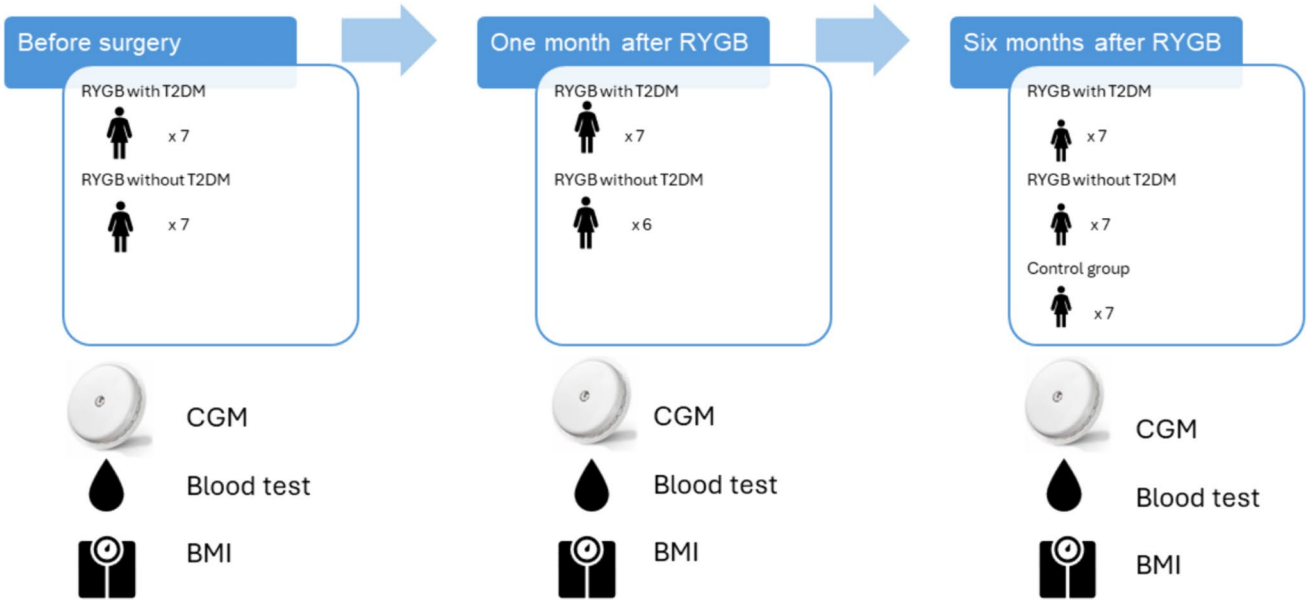


Fig. 1 Study design. BMI, body mass index; CGM, continuous glucose monitor; RYGB, Roux-en-Y gastric bypass; T2DM, type 2 diabetes mellitus

3 months, being, therefore, a poor indicator of acute dysglycemia [12]. We preferred the HbA1c estimation assessed by GMI in this period.

Surgical Technique

Laparoscopic RYGB was performed by a single experienced team at an academic referral center. It consisted of creating a 30-to-40-ml gastric pouch, a 100-cm alimentary limb, and a 100-cm biliopancreatic limb, with the closure of mesenteric and Petersen defects.

Glucose Monitoring Techniques and Devices

The FreeStyle Libre 14-day system, an unblinded mode and intermittently scanned CGM, comprises two components: a glucose sensor inserted into the back of the upper arm and a reading device. The sensor, featuring a filament immersed in interstitial fluid, incorporates the glucose oxidase enzyme. This enzyme catalyzes a reaction with glucose, producing hydrogen peroxide. Electrodes on the sensor detect the generated hydrogen peroxide, and its level correlates with interstitial fluid glucose concentration. The electrochemical reaction yields a measurable electric current directly proportional to glucose concentration [13]. It also works as a glucometer with strips for glucose and ketone. Its calibration is carried out at the factory. The sensor lasts up to 14 days. Patients were instructed to take frequent measurements since the sensor memory is only 8 h [14].

The sensor was removed when the patient was taken to the surgery center or after 14 days of use. According to the manufacturer, no studies guarantee the safety of the device during surgery. There is a manufacturer's recommendation for FreeStyle Libre removal before performing an MRI, CT scan, or high-frequency electrical heat treatment (diathermy) since the effects of these interventions on CGM system performance have not been evaluated [15]. For that reason, some patients did not complete the 14-day use of the sensor. Due to the low use of the sensor preoperatively, the GMI could not be obtained in these patients, so this metric was not used during this period.

The researcher downloaded all data obtained by CGM using the LibreView software (Newyu Inc., Orlando, FL, USA) and transformed them into Excel data files (Microsoft, Redmond, WA, USA) for analysis.

Glycemic variability was analyzed using metrics based on the consensus statement for the use of CGM in clinical trials [14], such as percentage of sensor data obtained, mean sensor glucose, coefficient of variation (CV), glucose management indicator (GMI), and time in ranges (time in range or TIR; time above range and time below range) when available.

The percentage of sensor data obtained provides a measure of confidence in all data-derived metrics and should be more or equal to 70%. The mean sensor glucose presents the mean 24-h glucose concentration calculated across all recorded glucose readings.

Statistical Analysis

The sample size was calculated using the website ClinCalc.com [16] and based on data obtained from the study by Hanaire et al. [17]. The result obtained was six individuals for each group.

Data analysis considers all information obtained using the CGM, physical examination, and laboratory tests. Continuous data were expressed as mean and standard deviation or median and interquartile range according to the normality; categorical variables were expressed as percentages. We used the Shapiro–Wilk and Levene tests to assess the assumptions of normality and homogeneity, respectively. For analyses where only two experimental groups were examined, we used the Student's *t*-test and Wilcoxon test. For three statistical groups, ANOVA or the Kruskal–Wallis test was executed. All results are presented as two-tailed values with statistical significance for p-values < 0.05. Data were analyzed using the R program for statistics.

Results

Nineteen patients were assessed for eligibility, but four declined to participate, and one was a candidate for another bariatric surgery. We remained with 14 patients, 85% female, who underwent RYGB, with a mean BMI of 46.9 ± 5.3 kg/m^2 and an age of 47.9 ± 8.9 years. The baseline demographical characteristics of the patients are summarized in Table 1.

Among all patients, 62% were diagnosed with systemic arterial hypertension (four in the RYGB group with T2DM, five in the other RYGB group, and four in the GC), 20% were taking lipid-lowering drugs (one, two, and one, respectively), 9% with chronic obstructive pulmonary disease (one in each RYGB group), and 9% were diagnosed with obstructive sleep apnea (one in each RYGB group).

In the T2DM group, six patients were taking metformin in the maximum dose (2550 mg per day), three were taking sulfonylureas, one was on an insulin regimen with 0.5 IU/kg a day, and only one was not using hypoglycemic drugs. Two were diagnosed within 5 years, three patients between 5 and 10 years, and two more than 10 years. The mean HbA1c was $7.1\% \pm 1.3\%$.

Table 2 describes the data obtained in the evaluation when the patients were hospitalized for surgery, such as preoperative BMI and collected blood tests, for groups of patients with and without T2DM. The patients in both

Table 1 Demographic data of the patients

	Control group	RYGB groups		*p*-value
		Without T2DM	With T2DM	
Sex	5F:2 M	7F	5F:2 M	
Age	48 ± 10.7	46.3 ± 2.0	49.4 ± 10.7	0.929
Height	165.6 ± 7.9	160.3 ± 9.6	165.6 ± 5.9	0.430
Max weight (kg)	113.9 ± 24.7	136.7 ± 18.4	143 ± 23.6	0.087
Max BMI (kg/m^2)	41.3 ± 7.7^a	53.7 ± 9.5^b	51.9 ± 6.2^{ab}	**0.030**

BMI body mass index, *F*, female, *M* male, *Max* maximum, *RYGB* Roux-en-Y gastric bypass, *T2DM* type 2 diabetes mellitus. Data for each variable is presented as mean ± standard deviation (SD) based on the Shapiro-Wilk test for normality. The significance of the p-value (p <0.05 in bold) was determined using ANOVA or Kruskal-Wallis test for comparisons among three groups. The distinction between groups was indicated by identical letters for no significant difference or distinct letters for significant differences

Table 2 Baseline patient data

	RYGB groups		*p*-value
	Without T2DM	With T2DM	
BMI (kg/m^2)	45 ± 4.3	48.8 ± 5.6	0.210
Total cholesterol (mg/dl)	188.9 ± 34.9	187.9 ± 24.8	0.955
LDL cholesterol (mg/dl)	122.9 ± 29	114.1 ± 16.1	0.535
HDL cholesterol (mg/dl)	42.4 ± 7.9	43.9 ± 9.6	0.784
Triglyceride (mg/dl)	105 (96.5–159)	147 (114–219.5)	0.318
Fasting blood glucose (mg/dl)	92.1 ± 14.8	141.1 ± 37.2	**0.017**
Fasting insulin (µU/ml)	27.7 ± 17.9	28.8 ± 9.3	0.895
HOMA-IR	6.8 ± 5.4	10.1 ± 4.4	0.278
HbA1c (%)	5.6 ± 0.4	7.1 ± 1.3	**0.028**
C-peptide (ng/ml)	4.3 ± 1.7	4.6 ± 0.6	0.753
Hemoglobin (g/dl)	13.7 ± 0.9	13.8 ± 1.3	0.862
Creatinine (mg/dl)	0.74 (0.68–0.75)	0.74 (0.69–0.80)	0.607
TSH (µIU/ml)	1.18 (1.0–1.86)	1.65 (1.38–2.35)	0.383

BMI body mass index, *HbA1c* glycated hemoglobin, *HOMA-IR* homeostatic model assessment for insulin resistance, *RYGB* Roux-en-Y gastric bypass, *T2DM* type 2 diabetes mellitus, *TSH* thyroid stimulating hormone. Data for each variable is presented as mean ± standard deviation (SD) or median (interquartile range, IQR) based on the results of the Shapiro-Wilk test for normality. The significance of the p-value (p < 0.05 in bold) was determined using the Student's t-test or Wilcoxon test for comparisons between two groups.

groups were similar in all parameters except fasting blood glucose (FBG) and HbA1c, which were higher in the T2DM group.

Table 3 compares CGM data, BMI, and other laboratory tests of the three groups (6 months after surgery in RYGB groups and a single time in the control group). At this time, the sensor usage percentage was 71.4% of all assessments. The time in ranges obtained by the CGM is shown in Fig. 2, while the data obtained by CGM in RYGB groups over time are represented in Table 4.

In the temporal analysis of the RYGB group without T2DM, significant changes were observed in various parameters 6 months postoperatively compared to the preoperative period. Notably, BMI, FBG, fasting insulin, HOMA-IR, HbA1c, and C-peptide levels showed significant reductions ($p < 0.05$). Mean interstitial glucose levels also decreased significantly ($p = 0.016$). Sensor usage percentage was initially low before surgery due to early removal, with some patients not completing the 14-day use of the sensor. The time in range decreased due to an increase in time below range with low glucose at 6 months, both with $p < 0.05$.

For the group with T2DM, the temporal analysis showed a significant decrease in FBG, fasting insulin, HOMA-IR, and C-peptide levels 1 month postoperatively compared to the preoperative time ($p < 0.05$). The BMI and HbA1c exhibited significant reduction at 6 months, with $p = 0.007$ and 0.037, respectively. Mean interstitial glucose levels significantly decreased ($p = 0.06$). The CV revealed an increase at 6 months ($p = 0.09$). The sensor usage percentage was

Table 3 Comparison of results 6 months after surgery with the control group

	Control group	RYGB group		*p*-value
		Without T2DM	With T2DM	
BMI (kg/m^2)	35.4 (30.2–39.2)	32.6 (30.8–34.8)	33.2 (31.3–42.4)	0.600
TWL	NA	27.4 ± 7.0	26.7 ± 5.5	0.848
Fasting blood glucose (mg/dl)	80.4 ± 10.8	73.9 ± 6.9	86.6 ± 12.9	0.147
Fasting insulin (µU/ml)	17 (9–18)[a]	4 (2.3–5)[b]	5 (4–8.5)[b]	**0.014**
HOMA-IR	2.7 ± 1.0	0.8 ± 0.5	1.4 ± 1.0	0.051
HbA1c (%)	5.1 ± 0.4	5.2 ± 0.2	5.2 ± 0.6	0.927
C-peptide (ng/ml)	2.2 (1.7–2.4)	2.3 (1.4–2.5)	3.3 (2.5–4.3)	0.095
Fructosamine (µmol/l)	227.8 ± 7.6	242.2 ± 25.6	238.7 ± 30.9	0.680
CGM data				
Mean sensor glucose (mg/dl)	94 (88.5–96)[a]	81 (72.5–85)[b]	98 (95–100)[a]	**< 0.001**
Sensor use (%)	73 (48.3–89)	79 (43–98)	93 (77–94.5)	0.472
GMI (%)	5.6 (5.4–5.7)[a]	5.2 (5.2–5.3)[b]	5.65 (5.6–5.7)[a]	**0.015**
CV (%)	14 (13.1–14.2)[c]	21.1 (15.2–22.6)[b]	26.7 (23.3–27.8)[a]	**0.001**
Time in ranges (%)				
Very low glucose	0	0 (0–1)	0	0.119
Low glucose	3 (0–4)[b]	22 (8.5–45)[a]	2 (1.5–4.5)[b]	**0.004**
TIR	97 (95.5–100)[a]	78 (51.5–91.5)[b]	97 (95–97.5)[a]	**0.004**
High glucose	0[b]	0[b]	0 (0–1)[a]	**0.036**
Very high glucose	0	0	0	NA

BMI body mass index, *CV* coefficient of variation, *GMI* glucose management indicator, *HbA1c* glycated hemoglobin, *HOMA-IR* homeostatic model assessment for insulin resistance, *NA* not applicable, *RYGB* Roux-en-Y gastric bypass, *T2DM* type 2 diabetes mellitus. Time in ranges: very low glucose (< 54 mg/dl); low glucose (between 54 and 69 mg/dl); TIR or time in range (between 70 and 180 mg/dl); high glucose (between 181 and 250 mg/dl); very high glucose > 250 mg/dl). Data for each variable is presented as mean ± standard deviation (SD) or median (interquartile range, IQR) based on the results of the Shapiro-Wilk test for normality. The significance of the p-value (p <0.05 in bold) was determined using ANOVA or the Kruskal-Wallis test for comparisons among the three groups. The distinction between groups was indicated by identical letters for no significant difference or distinct letters for significant differences

similarly low during the perioperative period for the same reason observed in the group without T2DM. The time below range with low glucose increased at 6 months ($p = 0.027$). Figure 3 shows the temporal analysis in the time in ranges of each group of patients undergoing RYGB.

Discussion

Continuous glucose monitoring is a valuable diagnostic tool for evaluating glycemic variability in patients undergoing RYGB with or without symptoms of hypoglycemia. Our study has shown greater glycemic variability with the increase in time below range with low glucose after 6 months of RYGB compared with the preoperative period in patients with and without T2DM.

Halperin et al. [18] evaluated post-RYGB patients with neuroglycopenic symptoms, comparing CGM to the mixed meal test (MMT). They showed that CGM had a significantly higher sensitivity and specificity for detecting clinical hypoglycemia than MMT [18].

The combination of rapid gastric emptying, increased rate of glucose appearance, excessive postprandial insulin secretion, elevated gastrointestinal peptides (like GLP-1 and GIP), and improved insulin sensitivity can create an environment where blood glucose levels drop rapidly, leading to hypoglycemia. Treating hypoglycemic episodes with glucose can trigger subsequent spikes in glucose levels, creating a cycle of recurrent hypoglycemia, often referred to as a "roller coaster" of hypoglycemia [19].

Other mechanisms leading to hypoglycemia beyond GLP-1 and GIP include (a) the lack of reduction of β-cell mass which was constitutively increased during the preoperative obese state; (b) increased insulin sensitivity following weight loss; (c) inappropriate β-cell secretion following early entry of ingested nutrients into the small intestine (late dumping syndrome); and (d) abnormal counter-regulatory hormonal (glucagon) responses. Alterations in other gastrointestinal hormones, including ghrelin, peptide YY, and leptin levels, have also been implicated in glycemic patterns following RYGB. Nevertheless, the impact of their altered secretion patterns in post-RYGB hypoglycemia remains unclear [20].

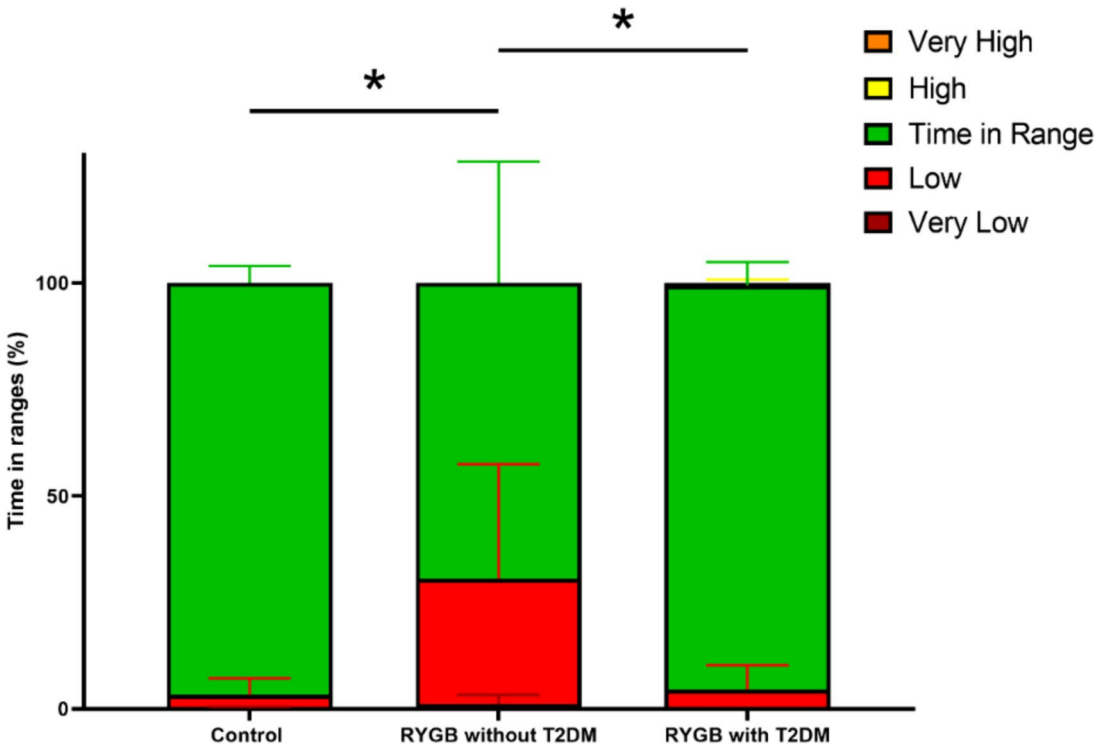


Fig. 2 Comparison of interval times obtained by CGM of patients operated on 6 months after surgery and in the control group. RYGB, Roux-en-Y gastric bypass; T2DM, type 2 diabetes mellitus. Time in ranges: very low glucose (< 54 mg/dl); low glucose (between 54 and 69 mg/dl); TIR or time in range (between 70 and 180 mg/dl); high glucose (between 181 and 250 mg/dl); very high glucose > 250 mg/dl). Data is presented as mean ± standard deviation (SD). *$p < 0.05$ RYGB without T2DM vs. RYGB with T2DM and CG

It has been demonstrated that after RYGB, the secretion of GLP-1 and GLP-2 increases proportionally with insulin secretion and glucose absorption [21]. Since these hormones are derived from proglucagon cleavage after secretion by ileal L cells, their postprandial circulating levels should exhibit similar patterns. Some studies suggest that GLP-2 might help reduce inflammation and potentially decrease hypoglycemia incidence [21]. While incretin levels were not measured in our research, there could be a correlation between increased incretin secretion and reduced hypoglycemia, with higher GLP-2 secretion possibly associated with shorter hypoglycemic episodes.

We believe that non-T2DM individuals experience prolonged hypoglycemia post-RYGB due to improved insulin sensitivity, unlike those with prior T2DM and the control group. Increased gastrointestinal peptides, postprandial insulin, and a more favorable insulin response contribute to this prolonged hypoglycemia, whether symptomatic or not. Our study, however, could not correlate prolonged hypoglycemia episodes to postprandial or fasting because patients did not record a food diary on the CGM reader.

Wysocki M. et al. [22] have compared CGM between sleeve gastrectomy (SG) and RYGB, showing that the latter was associated with a more frequent and longstanding hypoglycemic state only in patients with T2DM over 10 days of monitoring after surgery [22]. Our study evaluated patients 1 month after RYGB and found no statistically significant difference between the time in ranges (TIR, below, or above range) in the two groups. However, our patients with T2DM had worse clinical control, with different mean preoperative HbA1c between groups.

In a study using the FreeStyle Libre Pro system, the sensor failure rate was 7%, and the detachment rate was 16% [23]. Our study had failure and detachment rates of 4.2% and 12.5%, respectively, across 48 instances of new sensor use in 21 patients. Given that some of our patients had BMI > 50 kg/m^2, a question arises regarding whether sensor failure rates might differ compared to individuals with lower BMI levels.

The mean preoperative interstitial glucose values for patients with T2DM and those without T2DM are very close to the FBG values collected in the same period before surgery. This similarity between the values may have occurred because the patients were on a VLCD during hospitalization, with little carbohydrate available, affecting the average glucose values. Furthermore, the patients already had a history of weight loss even before admission, which may justify the

Table 4 Temporal analysis of each group of patients undergoing RYGB

	Before RYGB	One month after RYGB	Six months after RYGB	*p*-value
RYGB without T2DM				
BMI (kg/m^2)	45 ± 4.3[a]	40.4 ± 4.8[a]	32.7 ± 4.9[b]	**0.005**
Fasting blood glucose (mg/dl)	92.1 ± 14.8[a]	84.2 ± 10.9[ab]	73.9 ± 6.9[b]	**0.044**
Fasting insulin (μU/ml)	27.7 ± 17.9[a]	10.2 ± 4.8[ab]	4.3 ± 2.5[b]	**0.006**
HOMA-IR	6.8 ± 5.4	2.2 ± 1.2	0.8 ± 0.5	**0.005**
HbA1c (%)	5.6 ± 0.4[a]	5.2 ± 0.2[ab]	5.2 ± 0.2[b]	**0.028**
C-peptide (ng/ml)	4.3 ± 1.7[a]	3.3 ± 1.1[ab]	1.9 ± 0.7[b]	**0.014**
CGM data				
Mean sensor glucose (mg/dl)	92 (88–97.5)[a]	88.5 (82.5–90.8)[ab]	81 (72.5–85)[b]	**0.016**
Sensor use (%)	27 (23.5–28.5)[b]	84 (66.8–93)[a]	79 (43–98)[a]	**0.017**
GMI (%)	…	5.5 (5.2–5.5)	5.2 (5.2–5.3)	0.277
CV (%)	14.2 (13.5–14.3)	16.5 (12.6–18.9)	21 (15.2–22.6)	0.090
Time in ranges (%)				
Very low glucose	0 (0–1)	0	0 (0–1)	0.684
Low glucose	3 (1–7)[b]	5 (1.75–9)[b]	22 (8.5–45)[a]	**0.029**
TIR	97 (92–99)[a]	94 (91–97)[a]	78 (51.5–91.5)[b]	**0.036**
High glucose	0	0	0	0.311
Very high glucose	0	0	0	NA
RYGB with T2DM				
BMI (kg/m^2)	48.8 ± 5.6[a]	42.5 ± 6.3[ab]	36 ± 6.6[b]	**0.007**
Fasting blood glucose (mg/dl)	141.1 ± 37.2[a]	96.6 ± 20[b]	86.6 ± 12.9[b]	**0.018**
Fasting insulin (μU/ml)	28.8 ± 9.3[a]	9.4 ± 4.6[b]	6.5 ± 3.2[b]	**< 0.001**
HOMA-IR	10.1 ± 4.4[a]	2.4 ± 1.5[b]	1.4 ± 0.9[b]	**0.001**
HbA1c (%)	7.1 ± 1.3[a]	5.8 ± 1.4[ab]	5.2 ± 0.6[b]	**0.037**
C-peptide (ng/ml)	4.6 ± 0.6[a]	2.8 ± 0.9[b]	2.1 ± 0.5[b]	**0.003**
CGM data				
Mean sensor glucose (mg/dl)	132 (115.5–159)[a]	96 (92–101)[b]	98 (95–100)[b]	**0.006**
Sensor use (%)	32 (29.5–60)[b]	84 (69.5–88.5)[a]	93 (77–94.5)[a]	0.174
GMI (%)	…	5.65 (5.5–5.8)	5.65 (5.6–5.7)	0.869
CV (%)	17 (14.8–19.6)[a]	16.3 (15–21.8)[a]	26.7 (23–27.8)[b]	**0.009**
Time in ranges (%)				
Very low glucose	0	0	0	NA
Low glucose	0 (0–0.5)[b]	1 (0–3)[ab]	2 (1.5–4.5)[a]	**0.027**
TIR	91 (82.5–98.5)	99 (96.5–100)	97 (95–7.5)	0.199
High glucose	8 (0–17.5)	0	0 (0–1)	0.115
Very high glucose	0 (0–0.5)	0	0	0.122

BMI body mass index, *CV* coefficient of variation, *GMI* glucose management indicator, *HbA1c* glycated hemoglobin, *HOMA-IR* homeostatic model assessment for insulin resistance, *NA* not applicable, *RYGB* Roux-en-Y gastric bypass, *T2DM* type 2 diabetes mellitus. Time in ranges: very low glucose (< 54 mg/dl); low glucose (between 54 and 69 mg/dl); TIR or time in range (between 70 and 180 mg/dl); high glucose (between 181 and 250 mg/dl); very high glucose > 250 mg/dl). Data for each variable is presented as mean ± standard deviation (SD) or median (interquartile range, IQR) based on the results of the Shapiro-Wilk test for normality. The significance of the p-value (p <0.05 in bold) was determined using ANOVA or the Kruskal-Wallis test for comparisons among the three groups. The distinction between groups was indicated by identical letters for no significant difference or distinct letters for significant differences

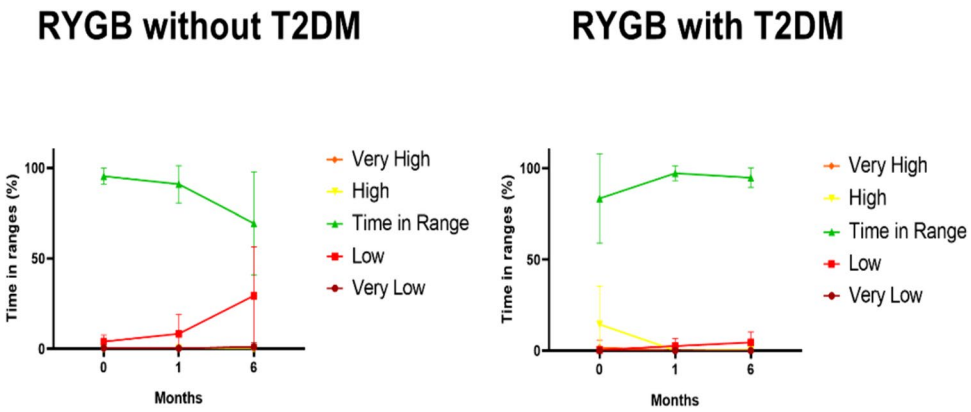


Fig. 3 Temporal analysis of each group of patients undergoing RYGB. RYGB, Roux-en-Y gastric bypass; T2DM, type 2 diabetes mellitus. Time in ranges: very low glucose (< 54 mg/dl); low glucose (between 54 and 69 mg/dl); TIR or time in range (between 70 and 180 mg/dl); high glucose (between 181 and 250 mg/dl); very high glucose > 250 mg/dl). Data is presented as mean ± standard deviation (SD)

good control of T2DM in patients with a longer diagnosis of the disease.

In the literature, few studies compare CGM data before and after bariatric surgery. In one of them, Kim K et al. [24] have shown that mean interstitial glucose decreased significantly after surgery, with values comparable to 1-month follow-up in our study. The TIR increased significantly in a subgroup of individuals with HbA1c 8.0% or above before surgery. The time below range with low and very low glucose increased significantly overall, especially in a subset of individuals with HbA1c below 8.0% before surgery. They also showed that CV decreased significantly after surgery, whereas our study found a significant difference between groups, with higher GV after 6 months. We believe that CV tends to increase over time after surgery. After 1 month, the CV did not differ significantly from the preoperative period. However, there was an apparent increase in the group with T2DM at 6 months and a rising trend in the group without T2DM.

All groups maintained an average sensor usage of over 70% during these periods. Per the consensus on CGM use in clinical trials, prolonged sensor use may be recommended when participants are expected to experience more hypoglycemia or greater glucose variability than usual [14]. An alternative to the standard 70% data acquisition over 14 days is 80–100% over 10 consecutive days, with acceptance of potential accuracy loss associated with a shorter review period [14]. We met these criteria despite sensor failures, detachments, or inappropriate use in our study at 6 months postoperatively and in the sole control group assessment. Despite that, the low percentage of sensor data obtained could impact the increase in time below range and the CV metric.

One study reports suboptimal accuracy of the FreeStyle Libre sensor for measuring glucose concentrations compared to values obtained from venous plasma samples, especially during hypoglycemia and glycemic swings [25]. However, another study revealed that, with increased frequency and amplitude of hypoglycemic events, CGM exhibited high accuracy in distinguishing individuals who had undergone RYGB with and without hypoglycemia. Additionally, the calculated low blood glucose index (LBGI) obtained through CGM was significantly higher in symptomatic individuals than in asymptomatic individuals, implying that CGM is an effective method for clinicians to diagnose hypoglycemia in RYGB individuals [26]. Future studies should explore the potential of CGM technology in assisting patients with elevated glycemic variability after RYGB for a more prolonged time.

This study was limited by its small sample size, male minority, and heterogeneity in preoperative diabetes control, all of which could impact the external validity of our findings. Additionally, there were limitations related to the usage of the FreeStyle Libre system, as some patients required early sensor removal for safety concerns during surgery. Furthermore, no specific recommendations or literature exist on its use in patients with a BMI of 50 kg/m^2 or higher.

Conclusions

Patients with T2DM undergoing RYGB, and even those without T2DM, present greater glycemic variability due to an increase in time in hypoglycemia 6 months after the procedure.

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Data Availability The data that support the findings of this study are available at the request of the corresponding author. The data are not publicly available due to medical confidentiality and to not compromise the privacy of research participants.

Declarations

Ethics Approval All procedures performed in studies involving human participants were approved by the ethical standards of the institutional

and/or national research committee and in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The research project has a Certificate of Presentation of Ethical Appreciation issued by the Research Ethics Committee of the HCFMUSP under number 17127119.0.0000.0068.

Consent to Participate Informed consent was obtained from all individual participants included in the study.

Conflict of Interest Raquel do Amaral Prado Quevedo declares no conflict of interest. Maria Edna de Melo has received consulting fees and support for travel from Novo Nordisk and BracePharma. Cintia Cercato has served as an advisory board for Novo Nordisk and reports having received research grants from Eli-Lilly, Novo Nordisk, Merck, Boehringer Ingelheim, Eurofarma, Fractyl, BracePharma, and EMS. Ariana Ester Fernandes declares no conflict of interest. Anna Carolina Batista Dantas declares no conflict of interest. Marco Aurélio Santo declares no conflict of interest. Denis Pajecki declares no conflict of interest. Marcio C. Mancini has received consulting fees, honoraria, and support for meetings or travel from Merck, Lilly, Novo Nordisk, Takeda, EMS, Eurofarma, BracePharma, Science Valley, and Aché.

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