Incidence of Hypoglycemia After Gastric Bypass vs Sleeve Gastrectomy: A Randomized Trial

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Context: We compared the incidence of hypoglycemia after Roux-en-Y gastric bypass (RYGB) vs sleeve gastrectomy (SG).

Design, Setting, and Main Outcome Measures: Randomized, open-label trial conducted at the outpatient obesity clinic in a university hospital in Rome, Italy. The primary aim was the incidence of reactive hypoglycemia (<3.1 mmol/L after 75-g oral glucose load) at 1 year after surgery. Secondary aims were hypoglycemia under everyday life conditions, insulin sensitivity, insulin secretion, and lipid profile.

Results: Of 175 eligible patients, 120 were randomized 1:1 to RYGB or SG; 117 (93%) completed the 12-month follow-up. Reactive hypoglycemia was detected in 14% and 29% of SG and RYGB patients (P = 0.079), respectively, with the effect of treatment in multivariate analysis significant at P = 0.018. Daily hypoglycemic episodes during continuous glucose monitoring did not differ between groups (P = 0.75). Four of 59 RYGB subjects (6.8%) had 1 to 3 hospitalizations for symptomatic hypoglycemia vs 0 in SG. The static β-cell glucose sensitivity index increased after both treatments ($P < 0.001$), but the dynamic β-cell glucose sensitivity index increased significantly in SG (P = 0.008) and decreased in RYGB (P = 0.004 for time × treatment interaction). Whole-body insulin sensitivity increased about 10-fold in both groups.

Conclusions: We show that reactive hypoglycemia is no less common after SG and is not a safer option than RYGB, but RYGB is associated with more severe hypoglycemic episodes. This is likely due to the lack of improvement of β-cell sensitivity to changes in circulating glucose after RYGB, which determines an inappropriately high insulin secretion. **(*J Clin Endocrinol Metab* 103: 2136–2146, 2018)**

During the past 40 years, the prevalence of obesity has doubled worldwide, with >1.3 billion adults, equivalent to 39% of the world's population, being overweight, and >600 million, representing 13% of the population, being obese, in 2014 (1).

Long-term weight loss is difficult to maintain, despite dietary and behavioral changes; weight loss attained at 1 year in lifestyle modification trials is only 1.6 kg on average (2). In contrast, bariatric surgery is very effective in maintaining weight loss, with an average of 32 kg or greater weight reduction at 5 years after treatment (3).

Recently, sleeve gastrectomy (SG) outperformed in frequency the use of Roux-en-Y gastric bypass (RYGB) worldwide, representing 49% and 43% of global bariatric operations, respectively (4).

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Abbreviations: AUC, area under the curve; BMI, body mass index; CGM, continuous glucose monitoring; HDL, high-density lipoprotein; LDL, low-density protein; OGTT, oral glucose tolerance test; RYGB, Roux-en-Y gastric bypass; SE, standard error; SG, sleeve gastrectomy; T2D, type 2 diabetes; ϕ_1, decrement occurring during follow-up; ϕ_d, dynamic control of insulin secretion in the fed state; ϕ_s, glucose sensitivity index.

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Although bariatric/metabolic surgery has resulted in numerous health benefits, including type 2 diabetes (T2D) remission (5–7), it is also associated with serious metabolic side effects. Among these, hypoglycemia is a relevant and underestimated complication of RYGB leading to cognitive impairment when plasma glucose levels fall <3 mmol/L (54 mg/dL) (8). There is increasing evidence of severe hypoglycemia after RYGB, and some cases of postoperative nesidioblastosis have been described (9). Roslin *et al.* (10) found that, at 6 months after RYGB, 68% of patients had hypoglycemia at 2 hours during an oral glucose tolerance test (OGTT). Based on electronic medical record data, the incidence of clinical episodes of hypoglycemia was 13% in a retrospective study in nondiabetic RYGB patients (11). In contrast, studies based on inpatient hospitalization International Classification of Disease codes (12), or on self-reported data (13), show figures <1%. Yet, hospitalization is usually necessary only when severe hypoglycemia occurs.

Repeated hypoglycemic episodes have been shown to impair the normal counterregulatory stress responses to subsequent hypoglycemia in diabetic individuals (14). Similar changes have been shown after RYGB, with clinical symptoms and counterregulatory hormonal and sympathetic nerve responses to hypoglycemia significantly reduced (15).

Compared with RYGB, SG seems to have a much lower occurrence of reactive hypoglycemia, reported as ~20% (16). Conversion from RYGB to SG is currently used as an alternative to pancreatectomy to treat severe hypoglycemia after RYGB (17).

Although hypoglycemia following bariatric/metabolic surgery represents an important health issue, no randomized trials have been undertaken until now to compare the effect of SG with that of RYGB in relation to the incidence and severity of hypoglycemic episodes. The primary aim of our study was to conduct a 1-year randomized trial to compare the incidence of hypoglycemia after RYGB and SG. Secondary objectives were to measure the effects of these surgical procedures on metabolic processes associated with hypoglycemic risk, namely insulin sensitivity and insulin secretion, and on cardiovascular risk factors, body weight, and fat distribution.

Methods

Participants

From December 2012 to December 2014, we screened 175 patients eligible for bariatric surgery at the Day-Hospital of Obesity and Related Disorders of the Catholic University in Rome (Fig. 1). A total of 120 patients were enrolled and randomly assigned 1:1 to RYGB or to SG. The study was reviewed and approved by the institutional human ethics committee (A1534/CE/2012) in accordance with national guidelines and the provisions of the Helsinki Declaration, as revised in 2000. All patients provided written informed consent to participate in the study, and additional written informed consent was obtained before surgery.

Inclusion criteria were: age 25 to 65 years, body mass index (BMI) >40 or 35 to 40 kg/m^2 in the presence of obesity complications, or ability to understand and comply with the study process. Exclusion criteria were history of T2D; previous bariatric surgery; or history of medical problems such as mental impairment, cancer, major cardiovascular or gastrointestinal or respiratory diseases, hormonal disorders, infections, or pregnancy. Diabetic patients were excluded to avoid confounding factors such as need for hypoglycemic agents.

Intervention

Patients were evaluated by a multidisciplinary team (including endocrinologists, surgeons, dietitians, and nurses) at baseline and at 1,3,6,9, and 12 months after SG or RYGB. Dietary suggestions including multiple meals and reduction of simple carbohydrates were provided at the moment of the discharge from the hospital after metabolic surgery.

Hypoglycemia was assessed as follows:

1. OGTT: Plasma glucose measurements during a 3-hour standard (75 g) OGTT conducted at 1 year postsurgery. Blood samples were drawn at fasting and at 30, 60, 90, 120, 150, and 180 minutes after the OGTT. In a subset of 50 randomly selected subjects, more frequent blood sampling was performed (*i.e.*, at fasting and at 10, 20, 30, 40, 60, 80, 95, 120, 140, 155, and 180 minutes following the OGTT). OGTTs were performed at baseline and at 1, 3, 6, 9, and 12 months after surgery.
2. Hypoglycemia awareness questionnaire at each visit relative to episodes of hypoglycemia in the 30 days preceding the visit. Hypoglycemia awareness was assessed by the Gold score, in which participants rated their awareness of hypoglycemia from 1 (always aware) to 7 (never aware) on a linear analog scale (18) at each visit.
3. Episodes of severe hypoglycemia during the visit or during the previous 30 days, defined by Whipple triad (18), and confirmed by a finger prick blood glucose measurement, namely the association of neuroglycopenic and/or neurogenic symptoms, signs, or both, consistent with hypoglycemia, a plasma glucose concentration <3.9, <3.4, or 3.1 mmol/L assessed by finger prick test, and resolution of those symptoms or signs after plasma glucose increased. Hospitalization for hypoglycemia.
4. Blinded continuous glucose monitoring using Enlite Sensor (Medtronic), which participants wore for at least 5 days for 1 year. Fifty patients were randomly selected in each group; 25 at 1 year after RYGB and 25 at 1 year after SG were involved. An episode of hypoglycemia on continuous glucose monitoring (CGM) was defined as a single glycemic level <3.1 mmol/L, which is the average value of 5 minutes' registration.

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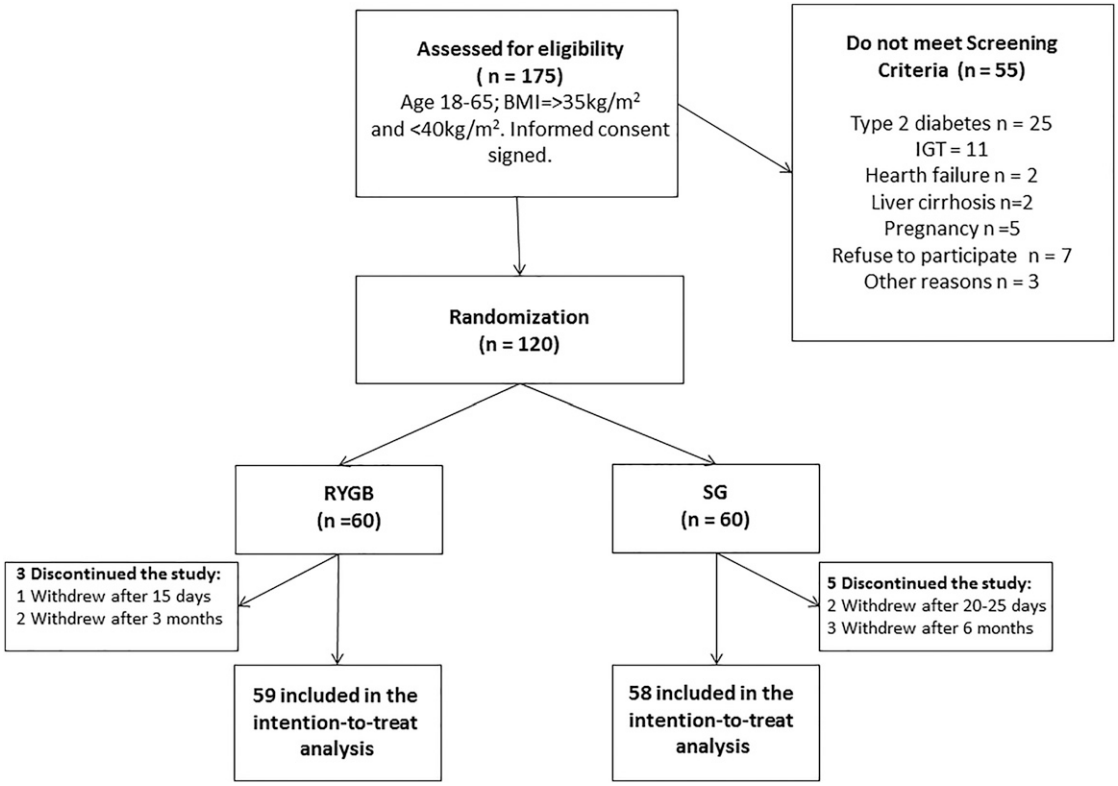

Figure 1. Flow diagram outlining patient enrollment and outcomes. IGT, impaired glucose tolerance.

Primary outcome

The primary end point was the incidence of hypoglycemia (≤55 mg/dL or 3.1 mmol/L within 3 hours after ingestion of glucose during a 75-g glucose OGTT) at 1 year after surgery.

Secondary outcomes

Secondary end points were changes of body weight, BMI, symptomatic hypoglycemia, lipid profile, insulin sensitivity, insulin secretion during OGTT, abdominal circumferences, and body composition 1 year after surgery. Hypoglycemic events during everyday life by CGM were added as a secondary outcome in October 2014.

Safety

Adverse events from bariatric surgery were noted by the study nurse at each visit and subsequently classified by the study physician for potential causality (unlikely, possibly, or likely).

Randomization

A total of 120 patients requiring bariatric surgery for medical reasons met the study inclusion criteria after physician screening, and were subsequently randomly assigned by a computer-generated blocked random sequence to the RYGB or SG groups in a 1:1 ratio.

Sample size

Previous studies reported an absolute difference in the occurrence of hypoglycemia between the two surgical procedures of ~50%, expecting an incidence of 68% in the RYGB group (10) vs 20% in the SG group (16). With a more conservative approach, the sample size was computed to detect a 30% difference between treatments, expecting an incidence of 50% in the RYGB group vs 20% in the SG group. Under this hypothesis, with two-tailed $P < 0.05$ and a power of 0.90, a sample size of 50 patients per group would have been sufficient. Considering an attrition rate of 20%, the number of patients in each group was set to 60 and, thus, overall to 120.

Body composition

Body weight was measured to the nearest 0.1 kg with a beam scale and height to the nearest 0.5 cm using a stadiometer. Hip and waist circumferences were measured in duplicate, with patients standing in underwear, as the maximal circumference over the buttocks and between the iliac crest and the lower ribcage, respectively. Body composition was measured by dual-energy X-ray absorptiometry (Lunar-iDXA).

Laboratory analyses

Fasting plasma glucose was measured by the glucose-oxidase method (Analox) and plasma insulin by microparticle enzyme immunoassay (Abbott), with 1 μU/mL sensitivity and 6.6% intra-assay coefficient of variation. Architect C-peptide (Abbott) assay precision of ≤10% total coefficient of variation was used to measure C-peptide levels. Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were measured by standard enzymatic assays. Low-density lipoprotein (LDL) cholesterol was calculated by the Friedewald formula.

Mathematical modeling

Insulin sensitivity and secretion were computed in the subset of 50 patients by the oral glucose minimal model (19). Changes

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over time of the indices were compared by a repeated measurement analysis of variance with time as within-factor and treatment as between-factor.

Statistics

Hypoglycemia during OGTT at 1 year after surgery was defined as any value of plasma glucose <3.1 mmol/L (55 mg/dL). During CGM, the average number of hypoglycemic episodes per day, defined as any glucose value <3.1 mmol/L, was also computed and compared between treatments by Mann-Whitney *U* test. Associations between treatments and presence/absence of hypoglycemic events were analyzed by χ^2 or Fisher exact tests. For continuous variables means and standard deviations were computed.

Student *t* tests were used to assess differences between groups at baseline. Percent changes at 1 year were computed as the differences between 1 year and baseline values divided by the baseline values, multiplied by 100. Deltas in the two groups were then compared by *t* test. Logistic regression with stepwise elimination was applied to identify possible predictors of hypoglycemic incidence.

To study the possible relationship between the dependent binomial variable, presence/absence of hypoglycemia, and its regressors (independent variables), we used a logistic regression model with a multivariate variable selection procedure and a forward selection method; the latter was used to take into account multicollinearity. In particular, we included sex, age, BMI, triglycerides and total cholesterol, insulin sensitivity and insulin secretion at baseline, as well as variations in BMI, triglycerides, total cholesterol, insulin sensitivity and insulin secretion at 1 year after surgery, including the type of treatment as a possible explanatory variable.

A logistic model relating presence/absence of hypoglycemia (glycemia <3.1 mmol/L) and baseline characteristics was carried out. The variables entering the model were age, sex, BMI, insulin sensitivity, and insulin secretion at baseline. The analysis was performed considering either all patients together, independent of the type of surgery, or separately (RYGB and SG).

A nonlinear mixed-effects model was applied to both glycemic "trough" and "peak" variables. The model describing the trend over time of both the variables (y) is:

$$y = \phi_1 \times \exp(-\lambda \times \text{time}) + (\phi_3 - \phi_1)$$

Parameter ϕ_3 represents the values of the dependent variables at baseline, parameter λ represents the decreasing rate of the variables, and ϕ_1 represents the decrement that occurred during the follow-up.

$P < 0.05$ was considered significant. All analyses were performed in R and Matlab (R2009b).

Results

Overall, 120 of 175 screened patients underwent randomization (Fig. 1).The follow-up at 1 year was 92.5%. Three patients withdrew their consent before the first visit after surgery and were excluded from the analysis. Two of the 3 patients who withdrew their consent in the SG arm after the visit at 6 months and 2 patients in the RYGB arm who withdrew after the visit at 3 months did so because of job-related changes in location. One patient withdrew consent in the SG arm after the 6-month visit did because of family problems. These patients were included in the intention-to-treat analysis.

Three patients who abandoned the study immediately after surgery, 1 in the RYGB and 2 in the SG arm, respectively, did not give reasons for withdrawing prematurely from the trial and did not undergo the OGTT at 1 month and were therefore not included in the study. A total of 117 patients were therefore evaluated for the primary and secondary end points: 59 who underwent RYGB, age 43.07 ± 9.17 years, and 58 who underwent SG, age 45.76 ± 9.68 years.

Between-groups baseline variables (Table 1) as well as sex (33.3% men and 66.7% women) did not differ significantly between treatment groups ($P = 0.133$).

Primary outcome

Percentages of patients experiencing hypoglycemia (<55 mg/dL or 3.1 mmol/L) after OGTT at 1 year were 14% and 29% in the SG and RYGB groups, respectively ($P = 0.079$). The percentages of patients experiencing hypoglycemia after OGTT over time was higher in RYGB than in the SG group, with a maximum at 6 and 3 months, respectively (Fig. 2).

About 5% of the RYGB and none of the SG patients referred to symptoms of hypoglycemia in their questionnaire (Table 1). Absence of Whipple triad associated with glycemia <3.9, < 3.4, or 3.1 mmol/L, as assessed by finger-prick test, excluded symptomatic hypoglycemia during the periodic visits and OGTT in all patients.

In a mixed-effects model, with the occurrence of hypoglycemia as the dependent variable, both time and treatment were significant contributory factors ($P < 0.001$ and $P = 0.01$, respectively). When postsurgery weight was introduced as a covariate, time was no longer significant, with estimates of the regression coefficients of 1.50 ($P = 0.018$) for RYGB vs SG, 0.04 ($P = 0.5$) for time, and −0.04 ($P = 0.020$) for weight. The odds ratio for hypoglycemia was 4.5 times higher for RYGB than for SG ($P = 0.018$).

An OGTT plasma glucose value ≤3.9 mmol/L was recorded in 67.2% of SG and in 91.5% of RYGB patients ($P = 0.002$). Glucose levels ≤3.3 mmol/L were 36.2% and 61% in the SG and RYGB group, respectively ($P = 0.012$). Glycemia ≤2.8 mmol/L was recorded in 5.2% of SG and in 18.6% of RYGB patients ($P = 0.050$). Glycemia ≤2.2 mmol/L occurred only in 2 RYGB patients ($P = 0.50$).

Four of 59 subjects who completed the 1-year follow-up in the RYGB group had 1 to 3 hospitalizations for symptomatic, neuroglycopenic hypoglycemia between month 9 and 12 after surgery.

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Table 1. Variables Averages and Their SD at Baseline and 1 y After Bariatric Surgery, With Percentage Changes

		SG (n = 58)		RYGB (n = 59)		Overall (n = 117)		
		Mean	SD	Mean	SD	Mean	SD	*P* Value
Weight, kg	Baseline	121.57	18.32	124.19	13.30	122.89	15.96	0.390
	After 1 y	84.04	16.33	81.13	9.95	82.57	13.51	0.262
	% Δ at 1 y	−30.93	7.38	−34.47	6.81	−32.72	7.28	0.010
BMI, kg/m^2	Baseline	43.44	4.25	43.10	3.96	43.27	4.09	0.666
	After 1 y	30.02	3.93	28.27	3.81	29.14	3.95	0.019
	% Δ at 1 y	−30.74	7.20	−34.33	6.89	−32.55	7.24	0.008
HbA1c, mmol/mol	Baseline	38.17	3.13	40.00	7.40	39.12	5.80	0.095
	After 1 y	34.62	2.44	34.91	4.61	34.77	3.69	0.706
	% Δ at 1 y	−8.85	7.89	−10.29	11.70	−9.58	9.99	0.488
Glycemia, mmol/L	Baseline	5.15	0.50	5.09	0.56	5.12	0.53	0.590
	After 1 y	4.54	0.51	4.48	0.50	4.51	0.50	0.517
	% Δ at 1 y	−11.06	12.63	−11.34	12.76	−11.20	12.64	0.911
Total cholesterol, mmol/L	Baseline	5.11	0.94	4.89	0.97	5.00	0.96	0.250
	After 1 y	4.25	0.74	4.00	0.77	4.12	0.77	0.128
	% Δ at 1 y	−14.56	19.80	−15.51	28.62	−15.05	24.62	0.855
HDL cholesterol, mmol/L	Baseline	1.29	0.29	1.26	0.27	1.28	0.28	0.669
	after 1 year	1.34	0.26	1.49	0.30	1.42	0.29	0.024
	% Δ at 1 y	8.42	25.15	20.92	43.23	14.83	35.92	0.121
LDL cholesterol, mmol/L	Baseline	3.02	0.88	2.97	0.70	2.99	0.79	0.742
	After 1 y	2.48	0.74	2.13	0.61	2.29	0.69	0.023
	% Δ at 1 y	−14.99	28.21	−29.25	15.84	−22.31	23.68	0.008
Triglycerides, mmol/L	Baseline	1.56	0.91	1.35	0.77	1.45	0.84	0.194
	After 1 y	1.13	0.44	0.97	0.44	1.05	0.45	0.083
	% Δ at 1 y	−14.97	40.08	−5.55	77.56	−10.15	61.97	0.479
Systolic blood pressure, mm Hg	Baseline	127.53	10.27	129.25	15.08	128.39	12.87	0.495
	After 1 y	122.36	9.68	125.55	8.77	124.05	9.30	0.078
	% Δ at 1 y	−3.81	8.91	−2.22	8.20	−2.98	8.54	0.352
Diastolic blood pressure, mm Hg	Baseline	80.72	6.97	83.68	10.01	82.20	8.71	0.080
	After 1 y	78.54	6.96	80.54	5.45	79.59	6.26	0.102
	% Δ at 1 y	−2.38	9.28	−2.82	12.18	−2.61	10.85	0.839
Hypoglycemia assessed by OGTT, %	Baseline	0		0		0		—
	At 1 y	14		29		21.4		0.047
Episodes of severe hypoglycemia assessed by questionnaire, %	Baseline	0		0		0		—
	At 1 y	0		5.1		2.6		0.082
Episodes of nonsevere hypoglycemia (Whipple triad plus glycemia <3.9, <3.4, or 3.1 mmol/L assessed by finger prick test) during the visit at 1 y	Baseline	0		0		0		—
	At 1 y	0		0		0		—
Hypoglycemia assessed during CGM[a]	At 1 y	32		24		28		0.533

Abbreviation: HbA1c, glycosylated hemoglobin.

[a]CGM was performed only on a subsample of 50 subjects, 25 per group, and only after surgery.

Incidence of hyperglycemia during OGTT

Hyperglycemia (≥10 mmol/L) during OGTT occurred in 13.8% of SG and 22% of RYGB patients ($P = 0.36$). The association at 1 year between hypoglycemic and hyperglycemic episodes, independent of treatment, was not significant ($P = 0.56$).

Glycemic trough and peak after OGTT

The values of both plasma glucose trough and peak during the OGTT were evaluated for each patient. Trough values decreased at 1 year and Δ was significantly different between groups (−30.9 ± 24.7 in RYGB vs −21.7 ± 21.7 in SG, $P = 0.040$). Also, the mixed-effects model showed a significantly greater decrement of the trough values in RYGB patients: $\phi_1 = 21.0 \pm 2.22$ [standard error (SE)] for SG vs $\phi_1 + 6.0 \pm 1.88$ for RYGB, $P = 0.0006$.

Peak glycemic values decreased less in RYGB than in SG with Δ of −29.9 ± 44.06 and of −47.7 ± 30.55 ($P = 0.015$), respectively. RYGB patients had a numerically lower ($P = 0.094$) glycemic peak value at baseline, which did not reach significance, and experienced a significantly smaller decrement in the attained maximum values of glycemia: $\phi_1 = 46.60 \pm 4.5$ (SE) for SG vs $\phi_1 - 16.67 \pm 6.3$ for RYGB, $P = 0.0087$.

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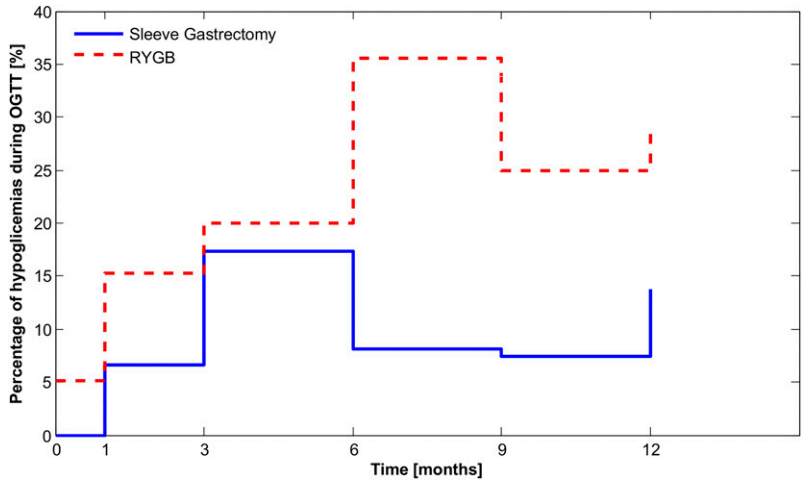

Figure 2. Average number of hypoglycemic episodes (glycemia ≤3.1 mmol/L) following the OGTT at 1 year after sleeve gastrectomy (blue solid line) and after gastric bypass (red dashed line).

Supplemental Figs. 1 and 2 report the average (dashed lines) and predicted values (continuous lines) of the trough and peak variables for SG and RYGB, respectively.

Glycated hemoglobin

Glycated hemoglobin decreased significantly at 1 year: changes were −10.29 ± 11.70% ($P < 0.001$) in RYGB and −8.85 ± 7.89% ($P < 0.001$) in the SG groups, with no significant difference between groups ($P = 0.50$). Also, fasting glycemia decreased significantly in both groups without significant differences between groups: % Δ −11.34 ± 12.76 in RYGB ($P < 0.001$) and −11.06 ± 12.63, $P < 0.001$ in SG; absolute values: 4.48 ± 0.50 vs 4.54 ± 0.51 mmol/L in RYGB and SG, respectively ($P = 0.52$).

Incidence of hypoglycemia during CGM

The average daily glycemic values ≤3.1 mmol/L did not differ between groups: 5.47 ± 11.35 in the SG vs 2.76 ± 6.64 in RYGB ($P = 0.75$) groups.

Eight patients in the SG group and 6 in the RYGB group experienced 1 to 4 hypoglycemic episodes (continuous periods of hypoglycemia during CGM); overall, 14 hypoglycemic episodes were recorded in SG and 9 in RYGB patients, with an average duration of 48.1 ± 37.2 and 45.6 ± 32.8 minutes, respectively ($P = 1$ by Mann-Whitney U test). Fifty-seven percent of the hypoglycemic episodes in the SG group were postprandial, whereas 43% were nocturnal. In the RYGB group, however, most occurred during the night (55%), and two were postprandial and two occurred in the afternoon at some distance from meal consumption. The daily average number of hypoglycemic episodes was 1.26 ± 0.81 and 1.77 ± 2.14 ($P = 0.95$ by Mann-Whitney U test) in the SG and RYGB groups, respectively.

The mean glycemic values during hypoglycemic episodes in the 8 SG and 6 RYGB patients were 2.73 ± 0.27 and 2.98 ± 0.06 mmol/L, respectively ($P = 0.10$ by Mann-Whitney U test). We report in Supplemental Table 1 the study variables for patients with and without hypoglycemia. The only significantly different variables between the two groups were weight percent changes as well as 1-year total cholesterol and triglyceride levels that were lower in the group with hypoglycemia.

Insulin sensitivity and insulin secretion during OGTT

Results from the minimal model analysis are reported in Table 2. The static β-cell glucose sensitivity index ϕ_s increased after both treatments (50.99 ± 33.68 at baseline vs 120.43 ± 98.90 $\times 10^9/\text{min}^{-1}$ at 1 year, $P < 0.001$), whereas there were no significant difference between RYGB and SG. A similar trend was recorded for the global β-cell glucose sensitivity. In contrast, dynamic β-cell glucose sensitivity had a different outcome; it increased significantly ($P = 0.008$) in the SG group (from 324 ± 481 to 933 ± 1064 $\times 10^9$/min), but decreased in the RYGB group (from 646 ± 733 to 415 ± 470 $\times 10^9$/min) ($P = 0.004$ for time × treatment interaction). Whole-body insulin sensitivity increased from 3.76 ± 3.09 to 36.26 ± 57.09 $\times 10^5$ dL/kg/min^{-1} $(\text{pmol/L})^{-1}$, whereas insulin secretion rate (ISR) area under the curve (AUC) decreased from 140.6 ± 54.8 to 64.6 ± 24.2 nmol.

The ratio between the incremental AUCs of OGTT C-peptide and glycemia increased with time (from 127.52 ± 39.39 to 204.17 ± 150.40 nmol/mmol, $P < 0.001$).

Figure 3 reports the mean concentrations of plasma glucose, C-peptide, and insulin after OGTT in the SG and RYGB groups at baseline and 1 year. The disposition index increased significantly with both treatments (from 209.62 ± 229.71 to 4130.75 ± 5677.94 $\times 10^{14}$ dL/kg/min^{-1} per pmol/L^{-1}, $P < 0.001$).

Weight loss and BMI

The highest weight loss change was observed at 1 year after RYGB: −34.47 ± 6.81% after RYGB and −30.93 ± 7.38% after SG ($P = 0.010$). Changes in weight reflected changes in BMI (Table 1) with significant between-groups difference ($P = 0.008$).

Lipid profile

Total and LDL cholesterol decreased significantly in both groups ($P = 0.001$ and $P < 0.001$ in RYGB patients;

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Table 2. OGTT Minimal Model β-cell Glucose Sensitivity, Whole Body Insulin Sensitivity Indices, and Body Composition

		SG (n = 25)		RYGB (n = 25)		Overall (n = 50)		
Variables		**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	***P* Value**
Static β-cell glucose sensitivity, $\times 10^9$/min^{-1}	Baseline	53.67	35.55	48.30	32.22	50.99	33.68	0.58
	After 1 y	114.45	100.61	126.41	98.86	120.43	98.90	0.67
Dynamic β-cell glucose sensitivity, 10^9	Baseline	323.93	480.87	645.69	733.21	484.81	634.81	0.07
	After 1 y	933.32	1063.86	414.90	469.87	674.11	855.01	0.03
Global β-cell glucose sensitivity, $\times 10^9$/min^{-1}	Baseline	57.32	35.51	54.71	34.44	56.01	34.65	0.79
	After 1 y	130.37	104.36	135.74	99.97	133.06	101.17	0.85
Whole body insulin sensitivity, 10^5 dL/kg per min per pmol/L	Baseline	3.28	2.80	4.24	3.34	3.76	3.09	0.28
	After 1 y	36.87	59.75	35.66	55.54	36.26	57.10	0.94
Insulin secretion rate AUC, nmol	Baseline	136.11	52.26	145.20	58.02	140.65	54.84	0.56
	After 1 y	66.5	22.21	62.51	26.35	64.63	24.21	0.54
Disposition index, 10^{14} dL/kg/min^{-2} per pmol/L	Baseline	202.00	259.66	217.25	200.46	209.62	229.71	0.82
	After 1 y	4532.68	6329.19	3728.83	5042.44	4130.75	5677.94	0.62
C-peptide AUC over glucose AUC above basal levels, nmol/pmol	Baseline	135.39	36.87	119.66	41.00	127.52	39.39	0.16
	After 1 y	179.70	118.98	228.63	175.45	204.17	150.40	0.25
C-peptide AUC over glucose AUC, nmol/pmol	Baseline	118.79	33.29	112.84	36.42	115.81	34.66	0.55
	After 1 y	100.32	28.17	114.40	49.09	107.36	40.25	0.22
Waist circumference, cm	Baseline	125.76	8.50	127.64	11.53	126.70	10.07	0.515
	After 1 y	101.52	9.97	97.84	10.75	99.68	10.43	0.215
	% Δ at 1 y	−19.29	5.40	−23.32	5.29	−21.31	5.67	0.010
Hip circumference, cm	Baseline	131.68	9.76	133.52	10.37	132.60	10.01	0.521
	After 1 y	106.12	9.80	102.72	12.23	104.42	11.10	0.283
	% Δ at 1 y	−19.40	4.57	−23.16	6.08	−21.28	5.65	0.017
Lean mass, kg	% Δ at 1 y	−17.03	9.95	−15.87	10.35	−16.45	10.06	0.688
Fat mass, kg	% Δ at 1 y	−36.11	14.27	−47.81	14.77	−41.96	15.54	0.006

$P < 0.001$ and $P = 0.003$ in SG patients, respectively). Although total cholesterol Δ did not reach statistical significance between groups, changes in LDL cholesterol differed between the two surgical procedures at 1 year: -29.25 ± 15.84 in RYGB and -14.99 ± 28.21 in SG ($P = 0.008$). HDL cholesterol increased in both groups; although changes in RYGB were highly significant (20.92 ± 43.23, $P = 0.004$), they were borderline in the SG group (8.42 ± 25.15, $P = 0.046$). Δ differences between groups were not significant. Triglycerides decreased significantly only in the SG group (-14.97 ± 40.08, $P = 0.019$).

Arterial blood pressure

Systolic and diastolic blood pressure slightly decreased in both groups, with no substantial difference between groups. Only the change in Δ systolic blood pressure was significantly different from zero for SG patients (-3.81 ± 8.91, $P = 0.005$). At baseline, 9 RYGB and 12 SG patients had hypertension; 44% RYGB and 50% SG hypertensive patients normalized blood pressure at 1 year without changes in type and dose of medications.

Stepwise regressions

No variable significantly predicted the binomial outcome presence/absence of hypoglycemia of any severity, whereas Δ BMI was borderline (β = −1.70e-01, SE = 9.25e-02, $P = 0.07$). Instead, when the primary end point (*i.e.* glycemia <3.1 mmol/L) was considered, both treatments ($\beta = 2.33$, SE = 1.07, $P = 0.03$) and Δ-BMI ($\beta = -0.21$, SE = 0.10, $P = 0.03$; with the probability of hypoglycemic events increasing in the RYGB group) were significant predictors of hypoglycemia. In other words, the larger the BMI reduction, the higher the number of hypoglycemic events in response to the OGTT.

For each minimal model index, ϕ_s and dynamic control of insulin secretion in the fed state (ϕ_d), a regression model was built with a stepwise procedure to take into account multicollinearity to test if these parameters could be related to some baseline variables or to variable values recorded at 1 year. Each model parameter was related to age and sex and to their baseline values, BMI, glycemia, insulinemia, and to BMI, glycemia, insulinemia, and insulin sensitivity, at 1 year. In the model for the variable ϕ_s, only Δ BMI was significant ($\beta = 4.33$, SE = 1.79, $P = 0.020$).

The ϕ_d was related significantly to the type of surgery ($\beta = -601.35$, SE = 226.27, $P = 0.011$), decreasing if the patients underwent RYGB, to baseline fasting insulinemia ($\beta = -55.98$, SE = 17.42, $P = 0.0025$) and to the BMI at 1 year after surgery ($\beta = 56.72$, SE = 23.94, $P = 0.022$).

Total insulin secretion was predicted directly by baseline BMI (β = 1.87e+03, SE = 8.431e+02, $P = 0.032$)

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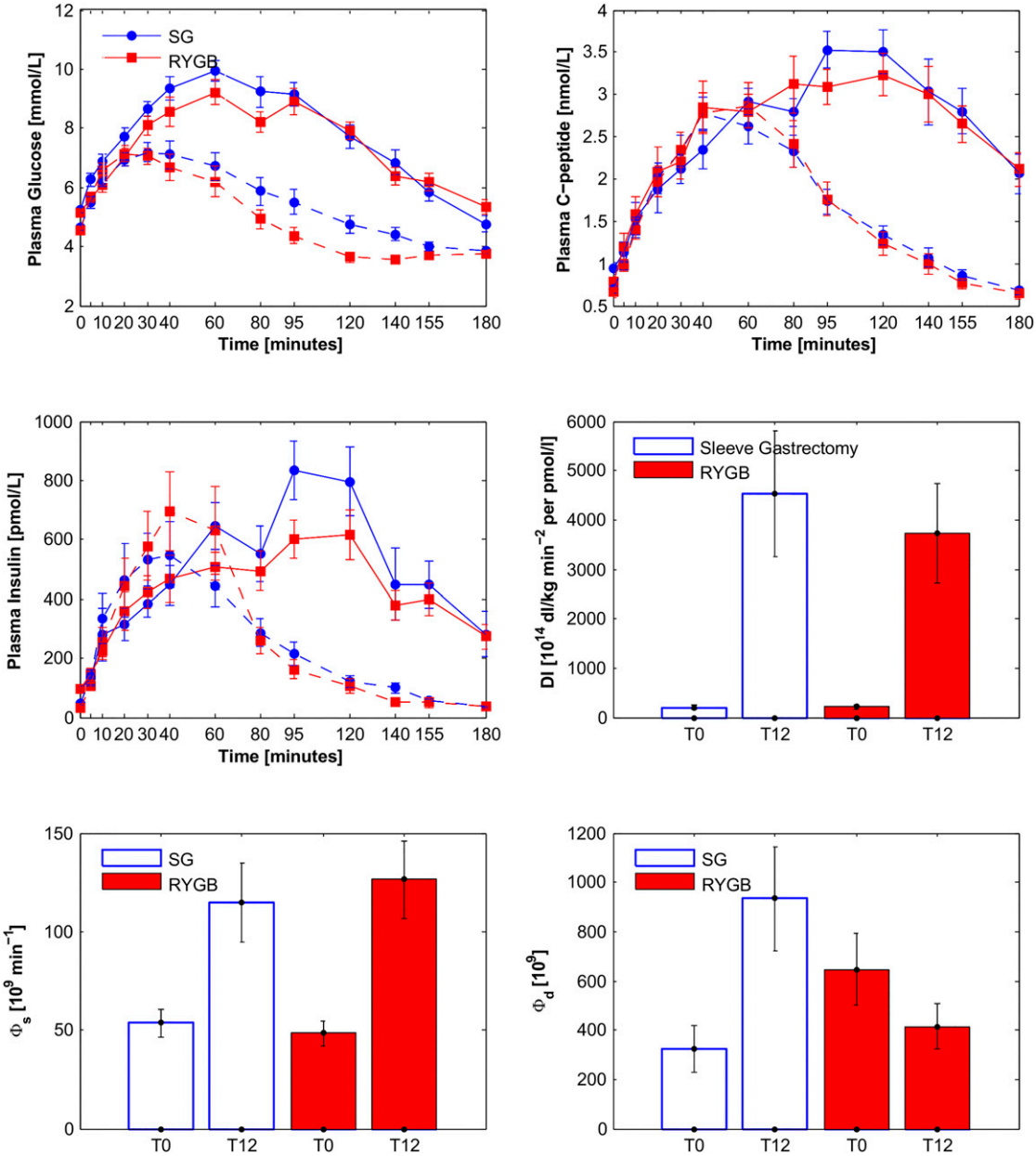

Figure 3. Plasma glucose, C-peptide, and insulin concentrations before (solid line) and after (dashed line) sleeve gastrectomy (solid circle) or gastric bypass (solid square). Disposition index (*i.e.,* the product between β-cell glucose insulin sensitivity and whole body insulin sensitivity) and Φ_D and Φ_S (*i.e.,* the dynamic and static components of the insulin secretion) before and after SG (open bar) or gastric bypass (filled bar).

and inversely by insulin sensitivity at 1 year (β = −1.78e+02, SE=5.35e+01, P = 0.002).

Insulin sensitivity at one year was predicted by sex (β = 48.94, SE = 15.84, P = 0035), being higher in women, baseline BMI (β = 6.78, SE = 2.58, P = 0.012) and BMI at 1 year after surgery (β = −4.42, SE = 2.21, P = 0.052).

Finally, we checked for baseline characteristics that could predict hypoglycemia after surgery.

When patients were considered altogether, the only significant predictor was age (β = −0.061, SE = 0.025 and P = 0.015). Age was also a significant predictor in the RYGB group (β = −0.084, SE = 0.036, P = 0.021), whereas in the SG group the baseline BMI was the only significant predictor (β = 0.19, SE = 0.097, P = 0.044).

Adverse events

There were no deaths or excessive weight loss in any group. Reintervention was not needed. Intravenous treatment of dehydration was necessary in 4 patients after RYGB and in 3 patients after SG. Cholelithiasis occurred in 2 RYGB patients.

Nutritional deficiencies (*i.e.,* anemia, low serum ferritin, hypoalbuminemia, hypocalcaemia, raised parathyroid hormone, and low vitamin D) were noted in 18 patients of the RYGB group and in 11 of the SG group.

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Discussion

Our study demonstrates that the 1-year incidence of hypoglycemia (defined as <3.1 mmol/L or <55 mg/dL) after an OGTT was not significantly different between RYGB and SG (29% vs 14%, P = 0.079). Everyday hypoglycemic events, as measured with CGM, were also not significantly different. Yet, our multivariate analysis showed more hypoglycemia in the RYGB group as well as differences in hypoglycemia after OGTT using higher cutoffs (≤3.9 or ≤3.3 mmol/L). A more rapid recovery in the glycemic trough was also observed in SG as compared with RYGB subjects. Severe hypoglycemia that required hospitalization occurred in 6.8% of RYGB treatments, but never in SG-treated patients. We found substantial differences on the impact of both surgeries on parameters of insulin secretion that may contribute to hypoglycemia.

We used <3.1 mmol/L to define hypoglycemia as our primary end point based on evidence that glucose concentrations under 3 mmol/L are associated with clinical harm. Cognitive impairment during both experimental and spontaneous hypoglycemia in people with T1D is detectable at 3 mmol/L or less (20), and exposure to 3 mmol/L can induce symptoms as well as counter-regulatory hormonal responses to hypoglycemia in clamp studies (21, 22). T2D subjects who fail to recognize hypoglycemic symptoms until their glucose falls below 3 mmol/L (54 mg/dL) are nearly 8 times more likely to experience severe episodes of hypoglycemia (23) (blood glucose below 2.8 to 3 mmol/L). A recent conjunct position statement of the American Diabetes Association and of the European Association for the Study of Diabetes supports this definition, opting for the slightly stricter criterion of <3 mmol/L or 54 mg/dL (24). We also looked at <3.9 mmol/L, or 70 mg/dL, as this value is associated with the start of counter-regulatory response in health and has been defined as hypoglycemia by many authorities in the past.

In the literature, RYGB reversal was associated with resolution of hypoglycemia in 13/17 (76%) (25) and 3/4 (75%) (26) of the patients with severe hypoglycemia. Conversion from RYGB to SG is currently used as an alternative treatment strategy to pancreatectomy for severe hypoglycemia following RYGB (27, 28). However, this conversion not only often fails to resolve the hypoglycemic symptoms but is also associated with high rates of major complications and hospital readmissions, and with needs for supplemental nutrition (29).

Our study shows that SG is not a safer option than RYGB when assessed in terms of incidence rate of hypoglycemia after OGTT 1 year after surgery.

In a recent study Salehi *et al.* (30) administered a liquid mixed meal during a hyperinsulinemic-hypoglycemic clamp with a target of 3 to 3.5 mmol/L in patients who underwent RYGB, in obese patients and in healthy controls. In spite of similar glycemic levels, insulin secretion was suppressed in controls but unsuppressed in RYGB subjects (30).

The minimal model estimates two indexes, the static and the dynamic sensitivity to glucose. The static sensitivity ϕ_s measures the effect of glucose on β-cell secretion and is the ratio between insulin secretion rate and glucose concentrations, above a threshold level, at steady state. The ϕ_d is a measure of the stimulatory effect on insulin secretion of the rate at which glucose increases or decreases.

We found that ϕ_d was reduced after RYGB, whereas the static control, ϕ_s, was improved. Therefore, after RYGB, the patients had an increased insulin secretion in response to increased plasma glucose concentrations, but were unable to reduce the secretion of insulin when glucose concentrations were falling.

The hyperglycemic peak that follows an OGTT or a meal after RYGB or SG has been attributed to the accelerated gastric emptying associated with both types of operations (31). About one-third of the variability in the glycemic response to an OGTT, either in subjects with normal glucose tolerance or T2D, is due to the variability of the gastric emptying rate (32).

Gastric emptying has been described to be equally accelerated after both RYGB and SG. In fact, in rats in which gastric emptying was evaluated by ^{99m}Tc-scintigraphy, the liquid meal mixture was fully (100%) emptied in only 5 minutes after both RYGB and SG, whereas only about 6% was emptied in sham-operated animals in the same period (33).

In humans (34), the half-emptying time evaluated by scintigraphy was significantly reduced after SG compared with baseline, down to <30 minutes. After RYGB, the scintigraphic gastric emptying time for both liquids and solids was also found to be <30 minutes (35).

However, our data suggest that the postprandial hyperinsulinemia observed after RYGB is not the consequence of the rapid glycemic rise but rather the result of an inappropriately high insulin secretion. In fact, the hypoglycemic events were uncorrelated with the hyperglycemic peaks, which were observed after both RYGB and SG.

The dysregulation in insulin secretion in conjunction with an impressive improvement of insulin sensitivity can help to explain why RYGB patients had an overall larger number of reactive hypoglycemic episodes than SG.

Recently, Abrahamsson *et al.* (15) found significantly reduced symptoms and counterregulatory hormonal response to hypoglycemia 23 weeks after RYGB. The repeated episodes of hypoglycemia in our series can help

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explain why these patients are generally unaware of low glycemic levels. In fact, repeated hypoglycemia or a state of chronic hypoglycemia, such that occurring during a continuous hyperinsulinemic-hypoglycemic clamp for 4 consecutive days, are associated with a glycemic threshold for cognitive impairment that is lowered from 3.0 to 2.5 mmol/L (36). This suggests a progressive adaptation to hypoglycemia. Also, in patients with T2D, recurrent hypoglycemia reduces the glucose concentration needed for the counterregulatory response (37,).

Although hypoglycemia is regarded as a life-threatening complication in diabetic individuals, very few data for nondiabetic subjects are reported in the literature. The increasing use of bariatric surgery, leading to frequent hypoglycemic episodes, makes it necessary to rethink the need for lifelong nutritional support for these patients, possibly together with a modification of the surgical technique such as, for example, a longer alimentary limb in RYGB. In fact, biliopancreatic diversion is rarely associated with hyper- and hypoglycemia (38).

Looking for a predictor of hypoglycemia after gastrointestinal surgery, we found that the higher the reduction of BMI at 1 year, the higher the number of hypoglycemic events triggered by the oral glucose load. The minimal model parameter ϕ_d was more reduced in those RYGB patients who had the largest reduction in BMI at 1 year after surgery, suggesting that insulin secretion dysregulation is more likely in those subjects who experienced the largest weight loss. Women had a better improvement of insulin sensitivity than men; this might be a reason they were subjected to more hypoglycemic episodes. However, new, larger trials are necessary to identify those factors that can predict reactive hypoglycemia before surgery.

Although the power of our study is high, an important limitation consists of the relatively short duration of follow-up (12 months), with evidence that a difference in the rate of OGTT hypoglycemia starts to appear at 6 months. In addition, we note the single-center, open-label nature of our study. However, we are continuing patient follow-up and we plan to publish the results at 3 and 5 years. Finally, lack of glucagon-like peptide 1 levels data during the OGTT is a limitation of our study because it is a major glucoregulatory player that improves β-cell glucose sensitivity.

In conclusion, RYGB induced a rate of reactive hypoglycemia (<3.1 mmol/L) similar to that of SG, but more hypoglycemic events using glycemic higher cutoffs and 6.8% severe hypoglycemia with hospitalization. Hypoglycemic episodes increased in frequency over time after RYGB and appeared to be associated with an imbalance between impaired β-cell dynamic glucose sensitivity and dramatically enhanced total body insulin sensitivity.

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