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Should Roux-en-Y gastric bypass biliopancreatic limb length be tailored to achieve improved diabetes outcomes?

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Abstract

The objective is to access the role of Roux-en-Y gastric bypass (RYGB) biliopancreatic limb (BPL) length in type 2 diabetes (T2D) outcomes.

RYGB is more effective than medical intervention for T2D treatment in obese patients. Despite the scarcity of available data, previous reports suggest that modifications of the RYGB limb lengths could improve the antidiabetic effects of the surgery.

A cohort of obese T2D patients (n = 114) were submitted to laparoscopic RYGB, either with a standard BPL (SBPL) (n = 41; BPL 84 ± 2 cm) or long BPL (LBPL) (n = 73; BPL = 200 cm) and routinely monitored for weight loss and diabetic status up to 5 years after surgery.

Baseline clinical features in the 2 patient subgroups were similar. After surgery, there was a significant reduction of body mass index (BMI) in both the groups, although the percentage of excess BMI loss (%EBMIL) after 5 years was higher for LBPL (75.50 ± 2.63 LBPL vs 65.90 ± 3.61 SBPL, $P = .04$). T2D remission rate was also higher (73% vs 55%, $P < .05$), while disease relapse rate (13.0% vs 32.5%; $P < .05$) and antidiabetic drug requirement in patients with persistent diabetes were lower after LBPL. Preoperative T2D duration predicted disease remission, but only for SBPL.

RYGB with a longer BPL improves %EBMIL, T2D remission, and glycemic control in those with persistent disease, while it decreases diabetes relapse rate over time. The antidiabetic effects of LBPL RYGB also are less influenced by the preoperative disease duration. These data suggest the RYGB procedure could be tailored to improve T2D outcomes.

Abbreviations: %EBMIL = percentage of excess body weight index loss, AL = alimentary limb, AUC = area under the curve, BMI = body weight index, BPD/DS = biliopancreatic diversion with duodenal switch, BPL = biliopancreatic limb, CL = common limb, GP = general practitioner, IDF = International Diabetes Federation, LBPL = long biliopancreatic limb, ROC = receiver operating characteristic, RYGB = Roux-en-Y Gastric Bypass, SBPL = short biliopancreatic limb, T2D = type 2 diabetes.

Keywords: biliopancreatic limb length, obesity, Roux-en-Y gastric bypass, type 2 diabetes

1. Introduction

Obesity prevalence has been increasing worldwide and accompanied by a parallel rise in type 2 diabetes (T2D).[1] Obesity is frequent in T2D, while 23% of morbid obese patients are also diabetic.[2]

Bariatric surgery, originally conceived for weight management, has soon demonstrated a dramatic ability to improve glycemic control,[3] reduce cardiovascular events and even mortality,[4,5] thus emerging also as an effective diabetes treatment. Weight loss, in overweight and obese individuals, plays an essential role in T2D improvement.[6–8] However, the unexpected magnitude of glycemic improvement observed after procedures such as Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion with duodenal switch (BPD/DS), which often precedes or goes beyond the expected from the weight loss achieved, has led to the hypothesis that additional mechanisms could be involved in the phenomena.

Biliopancreatic diversion (BPD), which was first described over 40 years ago by Scopinaro, is the bariatric procedure to allow better antidiabetic outcomes with a glycemic normalization rate of 98% for over 10 years.[9] The BPD procedure consists of a partial distal gastrectomy followed by transection of the small bowel 250 cm proximal to the ileocecal valve. The distal intestinal loop is then anastomosed to the stomach remnant to create the alimentary limb (AL), while the proximal biliopancreatic limb (BPL) is anastomosed side-to-side to the distal intestinal limb at 50 cm from the ileocecal valve, to originate the common limb (CL), where the major part of digestion occurs.[10] Thus, BPD or the modified BPD with DS, which is the BPD procedure currently most performed, results in the reduction of the gastric volume that restricts food intake as well as of the intestinal absorptive surface. A similar metabolic response with rapid correction of

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hyperglycemia, decrease in insulin secretion and normalization of insulin sensitivity, as observed after BPD and RYGB, was also reported after total or partial gastrectomy with gastrointestinal reconstruction excluding the duodenum, performed for conditions other than obesity and despite that the patients retained the same body weight.[11] In addition, the more distal the first contact of food with the small intestine mucosa occurs, the better seems to be the insulin sensitivity and glycemic control, as supported comparing the glucose excursion curves after direct nutrient infusion into the duodenum, proximal jejunum, or middle jejunum in T2D patients.[12]

Regardless being very effective, BPD is technically demanding when transposed to laparoscopy and associated with a significant percentage of early and late complications, when compared with other bariatric procedures. Therefore, for patients with a body mass index (BMI) under 50 kg/m^2, RYGB arises as a safe alternative,[13,14] as the occurrence of fat and protein malabsorption is less frequent,[15,16] and the incidence of micronutrients deficiencies, such as calcium and iron, is significantly lower and easier to correct with oral supplementation, as compared with what occurs after BPD.[17]

RYGB results from the combination of a restrictive procedure with a moderate degree of malabsorption that derives from reducing the gastric volume and excluding the duodenum and proximal jejunum from the gastro-intestinal transit, creating 3 intestinal limbs: an AL, a BPL, and a CL.[18] After RYGB, most patients experience successful weight loss, as well as resolution of obesity-related comorbidities.[19,20] However, 5% to 15% of the patients submitted to RYGB fail to achieve either significant and sustained weight loss or improvement of associated medical conditions, including T2D.[21] Aiming to enhance the efficacy of RYGB surgery several modifications of the classical technique were empirically proposed, most of which involving alteration of the standardized intestinal limb lengths. The implementation of these experimental techniques has led to a series of reports using a wide range of AL and BPL lengths.[22–25] Data available is characterized by a high variability of procedures performed for the same BMI range, small patient cohorts, short-term follow-up, and use of different criteria for diabetes remission, which rend comparisons difficult to perform.[26,27] In the absence of head–head comparison studies, the ideal RYGB limb length to optimize the metabolic outcomes remains uncertain.[28] Nevertheless, previous reports including our own suggested that a longer BPL RYGB could improve diabetes control in the short term (< 5 years).[22,29,30] Thus, the aim of the herein study was to assess the influence of the BPL length in long-term T2D metabolic improvement, by comparing the clinical outcomes of patients submitted to a long BPL RYGB and the standard RYGB.

2. Methods

This was a prospective observational cohort study. Data concerning patients who underwent RYGB surgery for the primary treatment of obesity (BMI ≥35 kg/m^2 with comorbidities) at a single center based in a public hospital, which fulfilled the diagnosis criteria for T2D before surgery (International Diabetes Federation (IDF) diagnostic criteria: HbA1c ≥ 6.5% or fasting glucose ≥126 mg/dL on 2 different occasions) and completed 5 years of follow-up after surgery, was retrieved for analysis from our larger postbariatric cohort, comprised of a total of 2349 patients among whom 714 were submitted to RYGB between January of 2009 and December 2011. The study protocol and the patient information leaflet were approved by our Institutional Ethical Review Board. Written informed consent was obtained from all participants before enrolment in the cohort study, which has been conducted according to the National Data Protection regulations.

Patients (n = 114) were either submitted to a standard classical RYGB procedure (n = 41) or a longer BPL RYGB (n = 73). The 2 RYGB surgical procedures were done by laparoscopy and only diverged in the BPL length, with a median of 84 ± 2 cm (minimum 50 cm and maximum 90 cm) for the standard RYGB and of 200 cm for the long BPL RYGB variant, from herein designated as short biliopancreatic limb (SBPL) and long biliopancreatic limb (LBPL). In brief, the RYGB procedure consisted in performing a 15-mL gastric pouch by transecting the lesser curvature of the stomach distally to the cardia between the 2nd and 3rd vascular branches of the small gastric curvature, with a 45-mm endoscopic articulating linear cutter (Endopath ETS 3.5 mm, Johnson and Johnson, Somerville, NJ, USA), then the stomach was intubated with a 36-Fr bougie and transected again vertically in the direction of the cardia while avoiding the esophagus. Afterward, a calibrated (8–12 mm) gastro-enteric anastomosis, gastro-jejunal for SBPL, or gastro-ileal for LBPL was made with a 45-mm linear stapler (Endopath ETS 2.5 mm, Johnson and Johnson) and completed with a manual suture (Ethibond 2-0, ETHIBOND EXCEL*Polyester Suture, Johnson and Johnson). An ileal–ileal anastomosis was then executed with a 45-mm linear stapler (Endopath ETS 2.5 mm, Johnson and Johnson) and completed with a manual suture (Ethibond 2-0, ETHIBOND EXCEL* Polyester Suture, Johnson and Johnson), thus creating a 50 to 200 cm biliopancreatic limb depending on the procedure, with a 120 cm alimentary limb. This omega gastric bypass was then transformed in a Y-en-Roux gastric bypass by transsectioning the small intestine between the gastro-enteric and the entero-enteric anastomosis. Intestinal limb length measurements were performed with the aid of a grasper with a 10 cm mark. Petersen and mesenteric defects were closed with nonabsorbable sutures. Allocation to the surgical technique was conducted in a nonrandom way according to the surgeon preference (authors MN, MG, and RA) based on patients' anatomical and clinical features. Surgeons were equally proficient and likely to perform both the procedures with a similar ratio.

Patients were periodically monitored by the same Obesity Treatment Multidisciplinary Team for a minimum of 3 years after surgery and by their general practitioner (GP) thereafter. In addition, patients with more than 3 years after surgery were invited to attend a hospital clinic for weighing and reassessment of the diabetic status.

Recorded data included height, weight, HbA1c, fasting plasma glucose, fasting insulin, and ongoing diabetes treatment. Anthropometric and biochemical parameters were used to calculate BMI, percentage of excess BMI loss (% EBMIL, calculated as [[(preoperative BMI – postoperative BMI) ÷ (preoperative BMI-25)] × 100]), % total weight loss (TWL) (calculated as [[(preoperative weight – postoperative weight) ÷ (preoperative weight) × 100], HOMA-IR (calculated as [(insulin (mU/L) × fasting glucose (mg/dL)) ÷ 405]) and HOMA-β (obtained by [(360 × Insulin (mU/L)) ÷ (Fasting glucose (mg/dL) − 63)]). After surgery, patients were instructed to withdraw all antidiabetic drugs except for insulin, until instructed otherwise during the postoperative period clinical reassessment based on glucose monitoring records. T2D was considered to be in remission if HbA1c was under 6.5% while off any antidiabetic drugs for at least the previous 6 months, according to IDF criteria.

2.1. Statistical analysis

Qualitative variables are expressed as number of cases and percentage (%), and the quantitative variables are expressed as mean and standard error of the mean. The difference between 2 independent experimental groups was evaluated using the unpaired Student *t* test for normally distributed variables, and the Mann–Whitney *U* test for variables that did not meet the normal parameters. To compare 3 or more independent groups with normal distribution we used a simple analysis of variance (1-way ANOVA) with post-hoc Newman Keuls test. Kruskal–Wallis ANOVA with Dunns post hoc was used to compare 3 or more groups when a sample did not meet the criteria of normality. To compare 2 or more nominal variables, we used a χ^2 test. To correlate the different groups, a Pearson or Spearman correlation was used as the normality of the samples. The diagnostic prediction power of several parameters was evaluated using the receiver operating characteristic (ROC) curve. In a ROC curve, the true positive rate (sensitivity) is represented as a function of the false positive rate (1 − specificity) for different cut-off points of a parameter. In summary, the area under the ROC curve (AUC) was used to measure how well a marker can predict the diabetes diagnosis. Based on the AUC, the test was considered excellent between 0.90 and 1.00; good between 0.80 and 0.90; fair between 0.70 and 0.80; and poor between 0.60 and 0.70, and the test was considered to have failed if the value was below 0.60.

A P value $<.05$ was considered statistically significant. All statistical analyses were performed with the aid of the Graphpad Prism software version 7.00 and IBM SPSS Statistics version 24, both for Windows.

3. Results

Before surgery there were no significant differences in age, BMI, HbA1c, diabetes duration, antidiabetic therapy, HOMA-IR, HOMA-β, blood pressure, or fasting lipid profile between the 2 groups of patients (Table 1).

After surgery, there was a significant and sustained weight loss for both the procedures. BMI was significantly lower after 36 and 48 months (Fig. 1A), while %EIBML (Fig. 1B) and %TWL were significantly higher (Fig. 1C), in LBPL RYGB as compared with SBPL RYGB.

T2D metabolic control also improved significantly after both the surgical procedures. The rate of T2D clinical remission at 36, 48, and 60 months after surgery was significantly higher in LBPL versus SBPL (74.6%, 72.7%, and 72.5% vs 43.2%, 44.4% and 55%, respectively ($P<.05$)) (Fig. 2A), while the disease relapse rate was significantly lower at the same follow-up times (10.4%, 12.7%, and 13.0% vs 37.8%, 38.9%, and 32.5% in LBPL vs SBPL, respectively ($P<.05$)) (Fig. 2B) after LBPL RYGB when compared with SBPL RYGB. The proportion of patients with over 5 years of preoperative duration of T2D undergoing disease remission at 60 months after surgery was significantly higher in the LBPL group (Fig. 2C).

Both surgeries led to a significant HbA1c reduction. Patients with persistent or relapsing T2D had higher HbA1c levels (Table 2), while there were not significant differences between patients submitted to either procedure (Table 3), although the number and/or dosage of antidiabetic drugs at 48 and 60 months was significantly lower in patients submitted to LBPL than in those submitted to SBPL RYGB (see Figure, Supplemental Digital Content 1, http://links.lww.com/MD/B984). After surgery, HOMA-IR and HOMA-β were not significantly different between the 2 surgical groups (see Figure, supplemental Digital Content 2, http://links.lww.com/MD/B984). Yet, BMI, % EBMIL, HOMA-IR, and HOMA-β at 60 months after the procedure were significantly different when comparing patients' clinical remission and those with T2D. Overall, patients experiencing T2D remission regardless the procedure had a higher preoperative HOMA-β, while those undergoing remission after LBPL RYGB were also characterized by having a greater % EBMIL and lower HOMA-IR (Tables 1 and 2). To infer whether the glucose homeostasis improvement could be accounted for the weight loss, the correlation between EBMIL and HOMA-IR has been assessed and found to be weak ($r=0.42$, $P<.05$), regardless the surgical procedure, time after surgery or T2D status. ROC curve analysis showed that previous T2D duration and HOMA-β were good predictors of the diabetes status at 60 months, but only for patients submitted to SBPL RYGB, while previous T2D duration was not a good predictor for patients submitted to LBPL RYGB (Table 3; see Figure, Supplemental Digital Content 3, http://links.lww.com/MD/B984).

There were no significant differences between the 2 groups in early major morbidity (3.2%) or mortality 30 and 90 days (0%) after surgery. No protein deficiencies occurred and there were no differences in the rate of mineral and vitamin deficiencies between the 2 groups.

Table 1

Baseline patient's demographic, anthropometric, and clinical features.

	Short BP limb (n = 41)	Long BP limb (n = 73)	*P*
Gender			
F	38	65	.82
M	5	8	
Age, y	49 ± 1	49 ± 1	.67
BMI, kg/m^2	42.22 ± 0.66	41.09 ± 0.54	.10
Fasting glucose, mg/dL	166 ± 9	148 ± 6	.09
HbA1c, %	7.7 ± 0.3	7.1 ± 0.2	.14
Antidiabetic drugs, %	38 (92.68)	65 (89.04)	
OAD	32 (78.05)	53 (72.54)	.79
Insulin+OAD	6 (14.63)	12 (18.46)	
Diabetes duration, y	8 ± 2	6 ± 1	.88
Fasting insulin, uU/mL	17.48 ± 4.40	16.26 ± 2.16	.72
HOMA IR	7.23 ± 1.73	5.39 ± 0.78	.21
HOMA B	100.2 ± 23.20	101.9 ± 14.22	.44
Systolic BP, mm Hg	148 ± 2	148 ± 2	.85
Diastolic BP, mm Hg	87 ± 2	85 ± 1	.24
Total cholesterol, mg/dL	196.67 ± 8.66	198.95 ± 4.38	.79
Triglycerides, mg/dL	159.37 ± 16.13	154.39 ± 8.95	.95
HDL, mg/dL	45.96 ± 2.29	47.68 ± 1.48	.58
LDL, mg/dL	111.50 ± 10.50	120.71 ± 4.13	.33

Presented results as number, percentage, or mean ± SEM.
OAD = oral antidiabetic drugs.

4. Discussion

Bariatric surgery allows a significant and sustained weight loss that plays an important role in glycemic control, being more effective than intensive medical interventions for the treatment of T2D associated with severe obesity [8,31–33]. Clinical remission of T2D occurs at different rates according to the surgical procedure, ranging from 47% after gastric banding to 98% after BPD, while averaging 83% for RYGB. This implicates that the antidiabetic effects of bariatric surgery are likely complex and comprise a

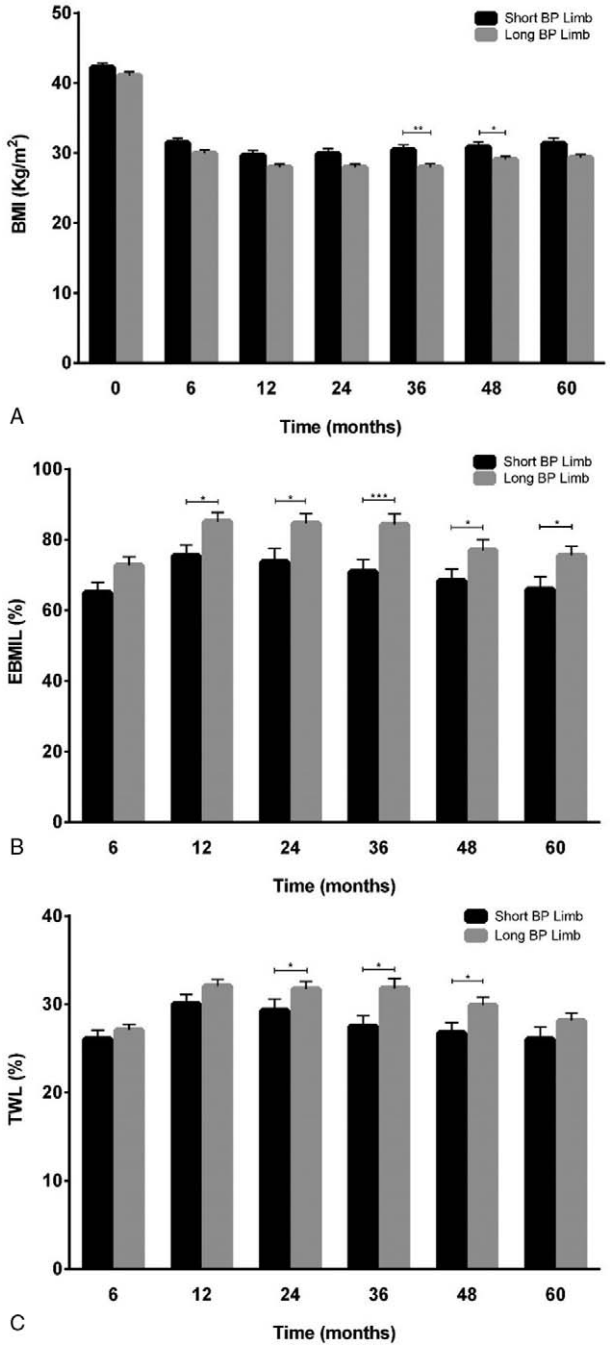

Figure 1. BMI, EBMIL, and percentage of TWL after SBPL and LBPL RYGB (SBPL vs LBPL) at each follow-up time. Results presented as mean ± SEM ($^{*}-P<.05$, $^{**}-P<.01$, $^{***}-P<.001$). In LBPL RYGB as compared with SBPL RYGB, BMI was significantly lower after 36 and 48 months (28.14 ± 0.51 vs 30.43 ± 0.69 [$P=.008$] and 28.81 ± 0.51 vs 30.76 ± 0.72 [$P=.03$] in LBPL vs SBPL, respectively) (A). The %EIBML was significantly higher after 12, 24, 36, 48, and 60 months (85.18 ± 2.53 vs 75.40 ± 3.08 [$P=.02$]; 84.65 ± 2.72 vs. 73.73 ± 3.77 [$P=.02$]; 84.28 ± 3.03 vs 70.90 ± 3.49 [$P=.006$]; 76.97 ± 3.01 vs 68.37 ± 3.22 [$P=.05$]; 75.50 ± 2.63 vs 65.90 ± 3.61 [$P=.04$] in LBPL and SBPL) (B). The %TWL was significantly higher after 24, 36, and 48 months (31.72 ± 0.88 vs 29.29 ± 1.30 [$P=.05$], 31.81 ± 1.12 vs 27.52 ± 1.19 [$P=.002$] and 29.86 ± 0.95 vs 26.73 ± 1.22 [$P=.03$] in LBPL and SBPL, respectively) (C). Results presented as mean ± SEM. (%EBMIL = percentage of excess body weight index loss, BMI = body mass index, BP = biliopancreatic, EBMIL = excess of body mass index loss, LBPL = long biliopancreatic limb, RYGB = Roux-en-Y Gastric Bypass, SBPL = short biliopancreatic limb, TWL = total weight loss).

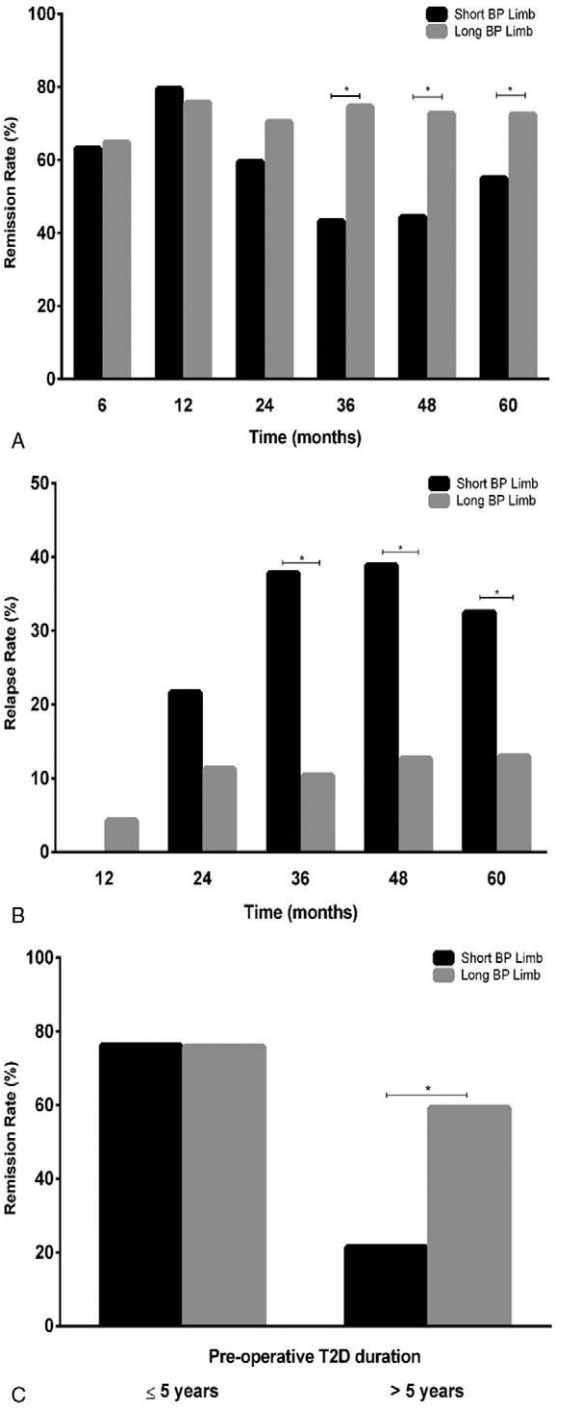

Figure 2. T2D remission and relapse rates (%) at each follow-up time in patients submitted to SBPL or LBPL RYGB; T2D remission rates at 60 months postsurgery according to preoperative duration of disease (< 5 or >5 years of diagnosis, $^{*}P<.05$). T2D clinical remission rate was significantly higher in LBPL vs SBPL RYGB at 36, 48, and 60 months after surgery (74.6%, 72.7%, and 72.5% vs 43.2%, 44.4%, and 55%, respectively ($P<.05$)) (A). T2D relapse rate was significantly lower at 36, 48, and 60 months after surgery in LBPL versus SBPL RYGB (10.4%, 12.7%, and 13.0% vs 37.8%, 38.9%, and 32.5%, respectively ($P<.05$)) (B). The proportion of patients with over 5 years of preoperative duration of T2D that undergoing T2D remission 60 months after surgery was also significantly higher in the LBPL RYGB group (C). BP = biliopancreatic, LBPL = long biliopancreatic limb, RYGB = Roux-en-Y Gastric Bypass, SBPL = short biliopancreatic limb, T2D = type 2 diabetes.

Table 2

Mean and SEM of BMI, %EBMIL, HbA1c, HOMA-IR and HOMA-β of SBPL, and LBPL patients according to diabetic status along the follow-up time.

	SBPL		LBPL	
	No T2D	T2D	No T2D	T2D
Time (mo)	Mean ± SEM	Mean ± SEM	Mean ± SEM	Mean ± SEM
6				
BMI	31.05 ± 0.84	32.17 ± 1.18	29.81 ± 0.58	30.04 ± 0.97
%EBMIL	68.01 ± 3.46	59.20 ± 5.06	73.12 ± 2.80	73.30 ± 4.83
HbA1c	5.5 ± 0.2	6.1 ± 0.3	5.5 ± 0.1	6.5[‡] ± 0.3
HOMA-IR	1.39 ± 0.13	1.97 ± 0.38	1.49 ± 0.13	1.81 ± 0.26
HOMA-β	86.74 ± 11.95	55.05[*] ± 11.25	92.75 ± 8.91	64.27[‡] ± 13.49
12				
BMI	28.98 ± 0.72	30.63 ± 1.22	27.80 ± 0.52	28.20 ± 1.03
%EBMIL	79.36 ± 3.34	66.37 ± 6.10	86.35 ± 2.78	83.28 ± 6.47
HbA1c	5.4 ± 0.1	6.5[*] ± 0.2	5.4 ± 0.1	6.8[‡] ± 0.3
HOMA-IR	1.20 ± 0.11	1.07 ± 0.23	1.05 ± 0.06	2.31[†,‡] ± 0.36
HOMA-β	89.56 ± 13.35	26.35[*] ± 4.84	88.74 ± 10.07	64.18[†] ± 12.72
24				
BMI	29.30 ± 0.86	30.42 ± 1.42	27.27[*] ± 0.47	29.71[‡] ± 0.99
%EBMIL	77.93 ± 4.35	68.82 ± 7.31	88.54 ± 2.76	74.90[‡] ± 6.46
HbA1c	5.5 ± 0.1	6.3[*] ± 0.2	5.5 ± 0.1	6.7[‡] ± 0.3
HOMA-IR	1.47 ± 0.15	1.52 ± 0.15	1.08[*] ± 0.06	2.43[‡] ± 0.36
HOMA-β	98.39 ± 10.04	55.49[*] ± 8.84	89.86 ± 12.14	74.33 ± 9.77
36				
BMI	29.72 ± 1.27	31.06 ± 0.79	27.69 ± 0.51	29.46 ± 1.26
%EBMIL	76.44 ± 6.17	66.15 ± 3.57	86.01 ± 2.75	73.72 ± 8.40
HbA1c	5.6 ± 0.1	6.5[*] ± 0.1	5.4 ± 0.1	6.7[‡] ± 0.3
HOMA-IR	1.53 ± 0.19	1.66 ± 0.14	1.31 ± 0.08	3.84[‡] ± 1.40
HOMA-β	93.68 ± 8.21	67.85[*] ± 12.16	115.10 ± 26.79	75.39 ± 16.35
48				
BMI	29.61 ± 1.00	31.63 ± 1.00	28.52 ± 0.51	29.87 ± 1.42
%EBMIL	74.67 ± 4.74	63.34 ± 4.20	80.57 ± 2.78	73.28 ± 8.20
HbA1c	5.5 ± 0.1	6.4[*] ± 0.2	5.3 ± 0.1	6.9[‡] ± 0.3
HOMA-IR	1.31 ± 0.07	1.72 ± 0.19	1.21 ± 0.11	1.84 ± 0.43
HOMA-β	73.41 ± 7.06	63.06 ± 8.59	59.67[*] ± 4.69	91.16 ± 50.73
60				
BMI	31.34 ± 1.23	30.72 ± 0.89	28.86[*] ± 0.49	30.70 ± 1.07
%EBMIL	67.64 ± 5.45	65.63 ± 4.60	78.47[*] ± 2.52	66.94[‡] ± 6.52
HbA1c	5.7 ± 0.1	6.5[*] ± 0.2	5.5 ± 0.1	6.7[‡] ± 0.2
HOMA-IR	1.43 ± 0.11	1.82 ± 0.32	1.29 ± 0.11	1.86[‡] ± 0.20
HOMA-β	83.73 ± 6.68	60.45[*] ± 12.05	94.04 ± 19.30	46.52[‡] ± 9.42

BMI = body mass index, EBMIL = excess of body mass index loss, HbA1c = hemoglobin A1c, HOMA β = HOMA of β-cell function, HOMA IR = HOMA of insulin resistance, LBPL = long biliopancreatic limb, SBPL = short biliopancreatic limb, T2D = type 2 diabetes.

[*] Versus SBPL no T2D, $P < .05$.

[†] Versus SBPL T2D, $P < .05$.

[‡] Versus LBPL no T2D, $P < .05$.

Table 3

Area under the curve values (AUC) for receiver operating characteristic (ROC) curves using preoperative and time-point specific parameters as predictors of the diabetic status.

	SBPL			LBPL		
Preop	6 mo	36 mo	60 mo	6 mo	36 mo	60 mo
T2D duration	0.769	0.662	0.780	0.615	0.671	0.618
HOMA-β	0.762	0.917	0.625	<0.600	0.679	<0.600
Time specific	**6 mo**	**36 mo**	**60 mo**	**6 mo**	**36 mo**	**60 mo**
HOMA-IR	<0.600	0.620	<0.600	<0.600	0.746	0.750
HOMA-β	0.750	0.765	0.744	0.728	0.622	0.819
%EBMIL	0.622	0.614	<0.600	<0.600	< 0.600	0.635

Strength as a predictor based on ROC AUC values: under 0.6—bad; 0.6 to 0.7—weak; 0.7 to 0.8—fair; 0.8 to 0.9—good; 0.9 to 1—excellent.

EBMIL = excess of body mass index loss, Homa β = homa of β-cell function, HOMA IR = HOMA of insulin resistance, LBPL = long biliopancreatic limb, Preop = preoperative, SBPL = short biliopancreatic limb, T2D = type 2 diabetes.

variety of anatomical, physiological, and molecular changes.[34,35] As metabolic improvement often occurs early after surgery,[3] weight loss is probably only one among several factors driving the phenomena.

The technical variant of LBPL RYGB herein described was empirically implemented by us (MN) with the specific goal of ameliorating the surgical outcomes in obese T2D patients. The underlying rationale to perform a longer biliopancreatic limb was to apply the concept introduced by Scopinaro when designing BPD, while merging the "foregut" and "hindgut" hypothesis, the 2 prevailing hypotheses to explain the glycemic improvement after bariatric procedures. These theories postulate that the endocrine changes leading to glucose homeostasis are either triggered by the exclusion of the duodenum and proximal jejunum from the intestinal transit[36] or the early arrival of undigested nutrients to the distal ileum,[37] respectively. Therefore, a longer BPL RYGB would harbor the potential to combine the anatomical modifications proposed in the 2 theories by promoting a duodenal–jejunal exclusion and allowing the early arrival of nutrients to the distal ileum by creating a gastro-ileal anastomosis. Thus, the ultimate goal of this procedure would be to achieve metabolic outcomes more similar to those observed after BPD, while eliminating the risk of early and late complications associated with the former technique.

The main aim of this study was then to evaluate the influence of the RYGB BPL length in long-term weight loss, metabolic improvement, and remission of T2D. By comparing the outcomes of a cohort of T2D diabetic patients allocated to 2 surgical procedures only differing in the BPL length, we demonstrated that a longer BPL RYGB enhanced long-term weight loss, metabolic improvement, and T2D remission rate as previously suggested.[22,38] However, most of the former data supporting the enhanced antidiabetic effects of RYGB with longer BPL limbs only refer to shorter follow-up times up to 2 years,[22,38] in contrast to studies evaluating the metabolic effects over 5 years after surgery that are limited to the classical RYGB.[31,39] In further support of these findings is our previous report that GLP-1 producing L-cell density is higher at 200 cm from the duodenal angle onward.[40] Moreover, RYGB was reported to increase circulating GLP-1 levels early since after surgery, while GLP-1 is well known for its weight loss and hypoglycemic effects.[41] Therefore, elongating the BPL to 200 cm may favor early stimulation of GLP-1 producing cells by nutrients[42] and consequently potentiate the weight loss and the antidiabetic effects of the surgery.

Assessing insulin resistance (HOMA-IR) and pancreatic function (HOMA-β) of the patients who underwent T2D remission and remained diabetic after each procedure, yielded 2 distinct profiles. After SBPL, HOMA-β was significantly higher in patients in T2D remission, while after LBPL, HOMA-IR was significantly lower. These results suggest that the classical RYGB procedure relies mainly on the remaining pancreatic functional reserve to overcome insulin resistance. However, an additional improvement of insulin resistance, as observed after LBPL patients, also leads to a higher T2D remission rate despite similar HOMA-β. Moreover, our results showed that the correlation between the BMI or %EBMIL and HOMA-IR, was rather weak, suggesting that the additional decrease in HOMA-IR observed

after LBPL RYGB was not entirely weight dependent. Although weight loss is associated with a decrease in insulin resistance,[43] weight-independent improvement of insulin sensitivity both in T2D patients and controls was recently reported.[32] This could be attributed to the bypass of the duodenum or proximal jejunum, avoiding the production of insulin resistance factors, as well as the earlier delivery of nutrients to the distal small intestine, similar to what we observed in patients submitted to LBPL RYGB.[44]

Several different short and long-term predictors of T2D status after bariatric surgery were identified by previous series. These included patient age, preoperative duration of the disease, insulin treatment dose requirements and duration, C-peptide levels, HbA1c, HOMA-IR, and HOMA-B.[43,45,46] In our cohort, preoperative duration of T2D was the only solid predictor of T2D at 5 years after SBPL. In fact, a shorter preoperative duration of T2D seems to be determinant for the likelihood of disease remission after SBPL, while being not significantly relevant after LBPL. T2D is characterized by being a progressive disease starting with increased insulin resistance that is incrementally difficult to overcome by augmenting insulin secretion, which results in progressive decline of pancreatic function and β cell-mass (HOMA-β) with subsequent deterioration of the glycemic control.[47] LBPL seems to be more effective in altering the diabetic status by promoting an additional decrease in insulin resistance, thus less dependent on β-cell status, which could explain the differences found in remission rates of the 2 surgeries, especially when the preoperative duration of T2D is taken into account.

Although the molecular mechanisms for improved antidiabetic effects of the modified RYGB surgery were not subject of detailed investigation, several theories can be proposed based on findings from previous studies.[15] These hypothesis span from changes in the hormonal milieu, immunological profiles,[8,48] altered intestinal circulation of bile acids and alterations of gut microbiota, all induced by the anatomical modification produced by the surgical procedure.[49–51] Additionally, it is also plausible that the endocrine and molecular effects induced by the RYGB are able not only to ameliorate the pancreatic function,[8] but also to improve insulin sensitivity by acting in the peripheral tissues (Reviewer#3Comment#1).[49]

The major strength of the current study was having assessed the impact of BPL length on T2D metabolic improvement 5 years. This allowed concluding on the significant improvement of diabetes glycemic control and T2D remission rate after a long follow-up time. The fact that all patients were treated on a single surgical center and medically managed by the same team, not only decreased the variability of the surgical procedure as performed by different surgeons, but also decreased the variability in antidiabetic drug prescription practices among different diabetes physicians, thus increasing the robustness of the results. One of major limitations of this study was being conducted in a nonrandomized manner, as the choice for the procedure was based on the surgeon preference for each technique and therefore does not allow entirely excluding the potential bias in patient allocation. In addition, the fact that no hormone profile assessments, as well as fat and protein absorption measurements, were performed in this specific cohort of patients further limits the extent of our conclusions.

In conclusion, LBPL RYGB that can be distinguished from the classic RYGB by the length of the biliopancreatic limb is associated with a higher rate of T2D remission, a lower percentage of disease relapse, and a decreased need for antidiabetic drugs in those patients with persistent diabetes. These antidiabetic outcomes seem to be achieved at the expense of an additional HOMA-IR reduction, not entirely weight dependent and less influenced by the preoperative duration of the T2D.

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