Does the length of the biliary limb influence medium-term laboratory remission of type 2 diabetes mellitus after Roux-en-Y gastric bypass in morbidly obese patients?

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Abstract

Introduction: The Roux-en-Y gastric bypass (RYGB) is an effective treatment of morbid obesity leading to type 2 diabetes mellitus (T2DM) resolution. However, evidence demonstrates that standard limb lengths can have a limited impact on long-term weight loss and durable T2DM remission.
Aim: The authors evaluated the impact of biliary limb (BL) length on the T2DM laboratory markers in 2-year follow-up.
Material and methods: The data of 93 obese patients with T2DM who underwent RYGB between 2008 and 2010 were collected from prospectively designed database. The length of BL was standard in one group of 51 patients (S-BL: 50–75 cm) and longer in another group of 42 patients (L-BL: 100–150 cm). The laboratory parameters defining T2DM remission – fasting plasma glucose (FPG) and glycosylated hemoglobin (HbA_{1c}) – were measured 3, 6, 12 and 24 months after surgery.
Results: The average level of FPG and HbA_{1c} remained non-diabetic 24 months after the RYGB in both groups. A statistical difference was not observed in direct FPG, HbA_{1c}, ΔFPG and ΔHbA_{1c} comparisons at any follow-up point. However, a significantly higher proportion of patients in L-BL than in S-BL reached the laboratory remission criteria without anti-diabetic medicaments. Additional analysis revealed a strong correlation between the measured T2DM parameters and length of the common limb (CL) in both groups.
Conclusions: A longer BL can intensify the anti-diabetic effect of RYGB. The length of CL rather than BL influences the medium-term T2DM remission. Long-term observation is needed to fully assess whether introduced technical aspects of RYGB provide a durable effect of T2DM resolution.

Key words: type 2 diabetes mellitus, Roux-en-Y gastric bypass, biliary limb, laboratory remission.

Introduction

The epidemic of obesity is associated with a rapid growth of type 2 diabetes mellitus (T2DM). It is estimated that over 300 million people will be affected with T2DM by the year 2025 [1, 2]. This stimulates the authorities of the health care systems to search for effective treatment of both obesity and T2DM. Bariatric surgery, particularly methods excluding the duodenum and the proximal part of the jejunum, represents the most effective treatment of morbid obesity [3–8]. Several recent publications have demonstrated the influence of Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion (BPD) on

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glycemia control [9–11]. Therefore it seems surgery should be considered as the most effective method of T2DM management. Roux-en-Y gastric bypass is the most frequently performed bariatric procedure worldwide and is accepted by many as the gold standard [12]. Although this method leads to substantial laboratory remission of T2DM in as many as 60–90% of cases and in consequence reduces the clinical presentations of the disease, its curative potential will be evaluated in long-term observations [8, 13, 14]. The large number of RYGB modifications demonstrates the limitation of the procedure originally introduced by Mason and Ito [15, 16]. Durable effectiveness of RYGB seems to be hampered mainly by the weight regain, resulting in the restoration of comorbidities including recurrence of glucose intolerance [17]. The reported higher impact of BPD than RYGB on both long-term weight loss and permanent T2DM resolution does not translate into more frequent usage of the procedure [10, 18]. Biliopancreatic diversion still remains less appealing and technically more demanding, with potentially higher risk of early and late adverse events. However, its highest effec-

tiveness of available bariatric options stimulates surgeons to modify RYGB using BPD metabolic assumptions. This is achieved by creating different lengths of alimentary (AL), biliary (BL) and finally the common limb (CL). Stefanidis *et al.* in an evidence-based review presented considerable variability of AL and BL length preferred by different bariatric centers in the range 35–250 cm (average 110 cm) and 10–250 cm (average 48 cm), respectively [16]. Although most surgeons use body mass index (BMI) as a decisive criterion to determine the limb lengths, much variability is observed even for patients with the same BMI [16]. Apart from the already widely acknowledged hybrid mechanism of RYGB, several endocrine hypotheses have been proposed in the most recent studies [19–21]. Therefore, the modern approach to bariatric solutions is not only limited to searching for the best balance between the degree of restriction, malabsorption and patients' safety [19–21]. The foregut and hindgut hypotheses after RYGB described by Rubino and Cummings explain the hormonal and metabolic benefits of bypassing the duodenum and proximal part of the jejunum, and accelerating the passage of undigested food to the distal intestine, all resulting in better glycemic control [13, 21, 22].

Aim

The authors, inspired by the importance of the hormonal hypothesis and based on their own long-term observation of BPD patients, modified the RYGB procedure by extending the biliary limb in order to evaluate its clinical effectiveness in T2DM resolution.

Material and methods

The data of 93 morbidly obese patients (BMI 35.2–55 kg/m^2, mean 44.2 kg/m^2, SD 5.52 kg/m^2) with T2DM who underwent RYGB between October 2008 and November 2010 were retrieved from a prospectively designed database. The standard short biliary limb (S-BL) was used in 51 cases. The majority of 42 patients with extended BL (L-BL) were operated on in 2010. The number of the cases included in the study was determined by the completion of a 2-year observation period with fixed follow-up visits 3, 6, 12 and 24 months postoperatively. Group characteristics are summarized in Table I. The preoperative period lasted 3–4 months and was based on cooperation with a psychologist, dietician, endocrinologist and bariatric surgeons. During this period

Table I. Profile of patients

Parameter	S-BL	L-BL
Number of cases	51	42
LRYGB/RYGB (ratio)	31/10 (1.55)	34/8 (1.33)
Male/female (ratio)	19/32 (0.59)	26/42 (0.62)
Average age [years]	46.2 ±5.67	47.8 ±5.81
Patients on insulin [%]	14/51 (27.5)	13/42 (30.9)
Average disease duration [years]	6.1 ±0.96	6.8 ±1.07
Average HbA$_{1c}$ [%]	8.6 ±0.84	8.9 ±1.32
Average FPG [mg%]	192.3 ±40.67	188.6 ±46.58
Average C-peptide level [μg/l]	2.4 ±0.27	2.6 ±0.31
Average BMI [kg/m^2]	43.3 ±5.67	45.1 ±5.46
Average size of pouch [ml]	35.8 ±5.91	36.2 ±5.66
Average length of alimentary limb [cm]	157.9 ±50.11	151.4 ±27.97
Average length of biliary limb [cm]	68.8 ±8.48	133.2 ±17.50
Average length of common limb [cm]	237 ±59.75	193.5 ±56.72

at least 2 meetings with each of the specialists were obligatory to ensure optimal general condition of the patients at the time of surgery and to prepare them to follow the postoperative dietary requirements. During the follow-up visits, among the basic metabolic tests, the most significant markers of glycemia control acknowledged by leading diabetes associations were assayed – glycosylated hemoglobin (HbA$_{1c}$, %) and fasting plasma glucose (FPG, mg/dl). The BMI calculated during the initial preoperative visit was used as baseline. In all cases, the preoperative HbA$_{1c}$ and FPG were determined. In addition, the use of antidiabetic agents was noted, as well as the duration of the disease.

All patients were qualified for RYGB. Fifty-five of them underwent a laparoscopic procedure (LRYGB). Regardless of the approach, the technical aspects of the procedures were the same. The size of the pouch was measured during the obligatory methylene blue test and ranged from 30 ml to 40 ml (average 36.01 ml, SD 5.79 ml). Because of the variable individual length of the small intestine (325–650 cm, average 470.9 cm, SD 108.23 cm), the total length was routinely measured before preparing the jejuno-jejunal anastomosis to reduce the risk of harmful malabsorption. The common limb was not shorter than 150 cm. The length of separated loops was basically adjusted to the patients' BMI; however, in some cases the intraoperative anatomical conditions defined the site of the intestinal anastomosis. The intraoperative measurement was carried out on the stretched bowel in the way used by the authors from the beginning of the bariatric activity. The anastomosis was performed after the exclusion of 50–75 cm of the biliary limb (average 68.8 cm, SD 8.48 cm) in the S-BL group and 100–150 cm (average 130.5 cm, SD 17.50 cm) in the L-BL group, with alimentary limb values of 100–200 cm (average 157.9 cm, SD 50.11 cm) and 75–200 cm (average 151.4 cm, SD 27.97 cm) in S-BL and L-BL, respectively.

The follow-up visits were organized by a multidisciplinary team at the presented time points. The postoperative nutritional program arranged by the dieticians to prevent potential malnutrition was obligatory as after any bariatric procedures. The diabetologist determined the necessity of administration of anti-diabetic medications. The assays of the glycemia markers were all performed in the same laboratory.

The authors present the results of postoperative average change of HbA$_{1c}$, FPG and loss of BMI 3, 6,

12 and 24 months postoperatively, comparing group S-BL with group L-BL. The percentage of patients who met the non-diabetic laboratory norm without anti-diabetic medications at postoperative check points has been presented in a separate specification.

The criteria used for T2DM remission were The National Institutes of Health guidelines: normal FPG ≤ 100 mg% and "nondiabetic" range of HbA$_{1c}$ 4.0–6.0% [23–25].

The spectrum, methodology and assumptions of the study were accepted by the local bioethical committee of the Medical University of Gdansk, Poland.

Statistical analysis

Statistical analysis was performed using Statistica software. *T*-tests were used for comparisons of the groups at individual follow-up points. Pearson coefficient of correlation was used for the analysis of the length of CL.

Results

All 93 patients were followed up according to the established schedule. Gastrointestinal leak as the most serious complication was observed in 2 patients in the S-BL group. The first leakage was diagnosed in the site of the staple line of the remnant stomach and required reoperation and closure on the second postoperative day. The stenosis of the pouch-jejunal anastomosis 12 months after the procedure was the reason for late pouch–cutaneous fistula in another case. Endoscopic dilatation of the anastomosis and self-expanding covered stent implantation with intense nutrition for 8 weeks was an effective treatment. In the L-BL group 1 patient required re-operation after 3 months of insufficient conservative treatment of the low secreting pouch-cutaneous fistula.

Control endoscopy 1 year after RYGB demonstrated ulceration in the site of anastomosis in 3.9% and 4.8% of the patients in S-BL and L-BL groups respectively, which was successfully treated conservatively. Severe protein calorie malnutrition clinically expressing mainly with prolonged loose stools and lower extremities edema was laboratory proven in 1 patient 12 months after L-BL RYGB. Improvement of the nutritional parameters followed by symptoms' alleviation was observed 6 months later after intense dietary treatment.

The postoperative complications are listed in Table II with the most common adverse events reported during the postoperative visits.

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Table II. Serious complications and adverse events

Parameter	S-BL	L-BL
Number of cases	51	42
Gastrointestinal leak/fistula (%)	2 (3.9)	1 (2.3)
Anastomotic stenosis	1 (2)	0
Ulcer in anastomosis	2 (3.9)	2 (4.8)
Wound infection	2 (3.9)	2 (4.8)
Incisional hernia	1 (2)	1 (2.4)
Anemia Hb < 11 g%	1 (2)	2 (2.4)
Pneumonia	1 (2)	0
Hypoglycemic episode	22 (43.1)	20 (47.6)
Reoperation	2* (3.9)	2* (4.8)
Endoscopic intervention	2# (3.9)	0
Intense conservative treatment	2^ (3.9)	3^ (7.1)
Extensive vomiting	1 (2)	0
Dumping	3 (5.9)	3 (7.1)
Reflux symptoms	1 (2)	0
Prolonged diarrhea (> 6 months postop.)	1 (2)	2 (4.8)
Severe malnutrition	0	1 (2.4)

including one hernia repair in each group, one reoperation in each group due to leakage; #dilatation of the anastomosis, stenting of the pouch fistula; ^2 cases in each group due to hypoglycemic episode, parenteral nutrition in 1 case with fistula in L-BL group

More than 40% of the patients regardless of the BL length reported clinical symptoms of hypoglycemic episodes, but in only 2 patients, who required intensive medical treatment, was the accidental glucose level below 50 mg%.

Early laboratory remission of T2DM was observed in some of the patients from both groups. In the vast majority of these patients FPG level lower than 100 mg% was observed after the surgery while they were still in hospital. A statistical difference was not observed in direct FPG, HbA_{1c}, ΔFPG and ΔHbA_{1c} comparisons at any follow-up point (Table III, Figures 1 and 2). However, a significantly higher percentage of patients in the L-BL group reached the laboratory remission criteria for both DM parameters at all follow-up points (Table IV, Figure 3).

The results of the diabetic parameters 1 year and 2 years postoperatively demonstrated the stabilization of the downward trend with minimal T2DM restoration tendency at the last follow-up point in the S-BL group (in 3/51 patients HbA_{1c} increased above the non-diabetic level). About 80% of all cases presented HbA_{1c} and FPG below or equal to the threshold established as non-diabetic.

The average level of HbA_{1c} and FPG remained non-diabetic 24 months after the RYGB in both studied groups. Loss of BMI did not significantly differ between the studied S-BL and L-BL groups (Table V, Figure 4). The dynamics of change in both diabetic markers observed in all patients after RYGB parallel the change of BMI.

Table III. Average FPG and HbA_{1c} level

Parameter	Preop.		3 months		6 months		12 months		24 months	
	S-BL	L-BL	S-BL	L-BL	S-BL	L-BL	S-BL	L-BL	S-BL	L-BL
FPG [mg/dl]	188.6 ±40.67	192.3 ±46.58	108.8 ±21.15	100.6 ±18.88	97.2 ±15.19	90.6 ±10.57	96.6 ±13.01	92.2 ±11.14	99.8 ±12.89	93.4 ±11.11
Value of *p*	0.833		0.307		0.211		0.365		0.173	
ΔFPG (%)	0	0	−42.3 ±13.72	−47.7 ±16.15	−48.5 ±12.38	−52.9 ±13.05	−48.8 ±12.95	−51.7 ±14.62	−47.1 ±12.77	−51.4 ±14.17
Value of *p*	−		0.707		0.726		0.931		0.744	
HbA_{1c} (%)	8.6 ±0.84	8.9 ±1.32	6.2 ±041	6 ±0.19	5.8 ±0.44	5.6 ±0.38	5.7 ±0.51	5.4 ±0.48	5.9 ±0.48	5.4 ±0.50
Value of *p*	0.413		0.099		0.174		0.130		0.163	
ΔHbA_{1c} (%)	0	0	−27.9 ±7.88	−30.2 ±10.54	−32.5 ±8.52	−34.9 ±12.84	−33.7 ±9.90	−39.3 ±14.32	−31.4 ±9.84	−39.3 ±14.80
Value of *p*	−		0.707		0.778		0.933		0.873	
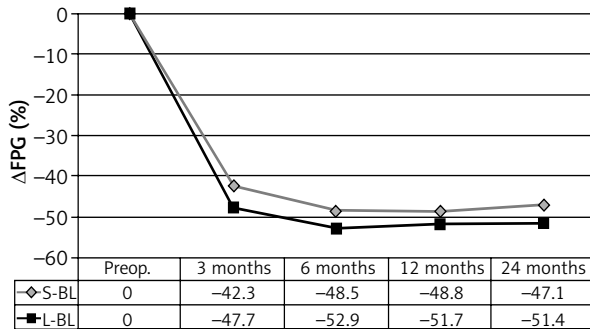
Figure 1. Change in average FPG level

	Preop.	3 months	6 months	12 months	24 months
S-BL	0	−42.3	−48.5	−48.8	−47.1
L-BL	0	−47.7	−52.9	−51.7	−51.4
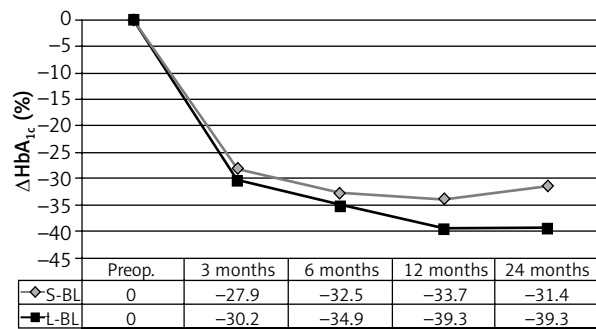
Figure 2. Change in average HbA$_{1c}$ level

	Preop.	3 months	6 months	12 months	24 months
S-BL	0	−27.9	−32.5	−33.7	−31.4
L-BL	0	−30.2	−34.9	−39.3	−39.3

Table IV. Percentage of patients in laboratory T2DM remission (without anti-diabetic medications)

	% Patients							
	3 months		6 months		12 months		24 months	
	S-BL	L-BL	S-BL	L-BL	S-BL	L-BL	S-BL	L-BL
FPG < 100 mg%	20/51 (35.3%)	24/42 (57.1%)	35/51 (68.6%)	36/42 (85.7%)	39/51 (76.5%)	40/42 (95.2%)	37/51 (72.5%)	39/42 (92.9%)
Value of p	0.018		0.028		0.009		0.007	
HbA$_{1c}$ < 6%	21/51 (41.2%)	26/42 (61.9%)	37/51 (72.6%)	37/42 (88.1%)	41/51 (80.4%)	40/42 (95.2%)	38/51 (74.5%)	40/42 (95.2%)
Value of p	0.023		0.038		0.018		0.005	

Table V. Loss of BMI

Parameter	Loss of BMI			
	3 months	6 months	12 months	24 months
S-BL	−6.3 ±1.98 (−14.5%)	−10.2 ±4.54 (−23.6%)	−12.8 ±4.68 (−29.6%)	−12 ±5.36 (−27.7%)
L-BL	−8 ±2.67 (−17.7%)	−12.5 ±2.73 (−27.7%)	−16.1 ±3.13 (−35.7%)	−17.3 ±4.18 (−38.4%)
Value of p	0.349	0.331	0.270	0.154

Additional analysis revealed a statistically significant strong or very strong correlation between the measured T2DM parameters' average values and length of CL at all follow-up points. There was also a statistically significant strong or very strong negative correlation between the measured T2DM parameters' Δs and the length of CL (Table VI).

Discussion

In the face of the global growing burden of T2DM, both the patients afflicted with the disease and the physicians committed to the treatment await with hope the results of modern potentially sufficient therapy. Although bariatric surgery was designed primarily to facilitate weight loss, numerous studies present its exceptional high effectiveness in improving obesity-related comorbidities [6–9, 26]. In 1995, Pories et al. demonstrated long-term results of more
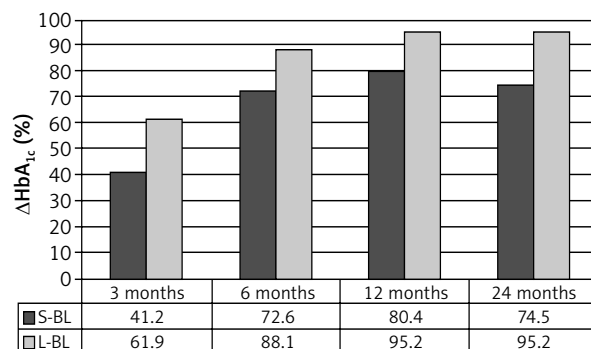

	3 months	6 months	12 months	24 months
S-BL	41.2	72.6	80.4	74.5
L-BL	61.9	88.1	95.2	95.2

Figure 3. Percentage of patients with HbA$_{1c}$ ≤ 6%

Table VI. Correlation between length of CL and laboratory markers of T2DM

Parameter	3 months	6 months	12 months	24 months
HbA$_{1c}$ (%)	$r = 0.48$	$r = 0.76$	$r = 0.86$	$r = 0.81$
ΔHbA$_{1c}$ (%)	$r = -0.74$	$r = -0.77$	$r = -0.78$	$r = -0.75$
FPG [mg/dl]	$r = 0.42$	$r = 0.52$	$r = 0.68$	$r = 0.65$
ΔFPG (%)	$r = -0.77$	$r = -0.78$	$r = -0.79$	$r = -0.79$

All correlations were statistically significant with p < 0.05

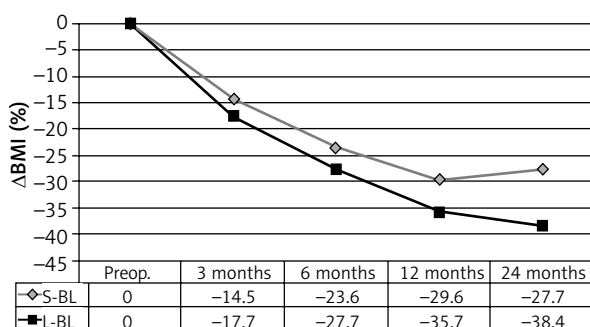|	Preop.	3 months	6 months	12 months	24 months
S-BL	0	−14.5	−23.6	−29.6	−27.7
L-BL	0	−17.7	−27.7	−35.7	−38.4

Figure 4. Change in average BMI

than 600 obese patients who underwent RYGB with a follow-up period of 14 years [14]. Eighty-three percent of these individuals experienced durable normoglycemia without anti-diabetic medications. Even more impressive effects of bariatric treatment were published by Scopinaro *et al.* after BPD [18]. The results recently published in "New England Journal of Medicine" of direct comparison of best available conservative vs. surgical treatment (sleeve gastrectomy, RYGB and BPD) in T2DM remission revealed the distinct advantage of surgery bypassing the duodenum and proximal jejunum in up to 2 years observation [9, 10]. Though gastric bypass is recognized by many as the gold standard of bariatric procedures, its initial model introduced by Mason and Ito was modified over the years in the search for long-term improvement of weight loss and durable resolution of related comorbidities [12, 16]. The definition of RYGB as a hybrid restrictive and malabsorptive procedure seemed to be inadequate, since several studies highlighted the important hormonal role in metabolic homeostasis of anatomically reconstructed intestine [13, 19, 20–22, 27, 28].

Several mechanisms mediate the anti-diabetic impact of RYGB, including induced by restricted pouch and limited intestinal absorption lower caloric intake, hyper-stimulation of the distal ileum to pro-

duction of incretins, compromised ghrelin secretion or, though credited to the fast postoperative glucose control, the still unidentified phenomenon related to duodenum exclusion from contact with ingested food [13, 14, 29, 30].

The fast improvement of glucose tolerance presented in this study (even during the hospital stay) confirms the effectiveness of the weight loss independent mechanisms reported previously by other researchers in both animal and human models [22, 31–33]. Approximately 40% of patients were discharged from hospital with the FPG level ≤ 100 mg/dl but this number was as high as 80% in other reports [13]. This rapid improvement was not observed after purely restrictive procedures, which emphasizes the exceptional impact of bypassed duodenum and proximal jejunum [9, 34–37]. The accelerated transmission of the undigested food to the distal ileum observed in BPD because of the ultra-short alimentary and long biliary limb alters the intensity of incretins (e.g. glucagon-like peptide-1) secretion, impacting beta-cell stimulation to insulin production and therefore influencing glycemia control [13, 18]. Moreover, it was suggested that a long part of the intestine excluded from passage influences higher "recycling" of the undiluted bile, which additionally enhances the desired metabolic effect [14, 18, 29].

The short nutrients pathway and extended biliary limb is also constructed in the Ω-loop gastric bypass, where the total length of excluded jejunum is localized proximally to the pouch-jejunum anastomosis. This variation of gastric bypass, popular in some bariatric centers, is considered by some authors as one of the most sufficient second-stage procedures after sleeve gastrectomy [38].

A higher T2DM remission rate was demonstrated in patients after gastric bypass modified with a longer biliary limb, but not with an elongated alimentary limb [15, 16]. Clear-cut evidence of superiority of elongated BL modification over standard RYGB was

reported recently by Pinheiro *et al.* [30]. To enhance the antidiabetic mechanism, this technical solution learned from BPD was partially adopted into RYGB also in our study, by extending the biliary limb from 50–80 cm to 135–150 cm without changing any other anatomical aspects of the procedure. In order to reduce the risk related to the high degree of malabsorption from too short common limb, the length of CL was set as described by many authors as safe at 150 cm [16, 18].

In our study we observed a higher percentage of patients (free from anti-diabetic agents) in the L-BL group who achieved the laboratory non-diabetic criteria of HbA_{1c} and FPG values 3, 6, 12, 24 months after RYGB, than patients from the S-BL group. However, the average change in the value and Δ of diabetic markers did not differ significantly between the studied groups at any follow-up points. Analyzing the anatomical proportions of the intestine arranged in our procedures and considering the individual diversity of the intestinal length, we realized that elongating the BL in some of the patients led to the common limb shortening even below 200 cm. An interesting finding of the study was that the length of CL strongly correlates with the metabolic effect of the surgery in both groups. A more significant effect of the surgery was observed in patients with shorter CL.

The number of long-term adverse events was comparable in both groups and seemed to be more the consequence of complications than the long-term result of anatomical variations. The rate of the malnutrition burden was related to shorter CL but principally accompanied such complications as anastomosis strictures or prolonged gastrointestinal fistulas and was minimized by a strict postoperative monitoring schedule provided by a multidisciplinary team, which is recommended in several guidelines.

Episodes of postoperative hypoglycemia were experienced by nearly half of the operated patients in both groups, which corresponds with Schauer's observations, but still this phenomenon is less frequent than in the group of patients treated conservatively with insulin [9].

According to what has previously been investigated, the persistent effect of glucose metabolism improvement depends on the growth of insulin sensitivity mainly in peripheral tissues which occurs 6 months after duodenal bypass surgery with a peak 2 years after surgery [39]. This dynamic process is correlated with reduction of lipid content in the muscles or liver and is supposed to be proportional to weight loss [17, 40–42]. Moreover, this anti-diabetic mechanism is supplemented with over-stimulation of beta islets to endogenous insulin production [14, 43].

Providing the most intensive adipose tissue reduction, BPD is favored as the most effective bariatric procedure, which also influences the long-term glucose metabolism [44]. However, potentially serious malnutrition and relatively higher risk, mostly in patients whose compliance to the therapy is inadequate, may limit the indications to the super-obese population of patients. Deriving the experiences from BPD, in the first place, bariatric surgeons should focus on common limb length in designing the gastric bypass procedure to obtain more durable benefits [16]. Long-term observations of patients after modified RYGB with extended biliary limb alone are required to estimate its effect in patients with T2DM. The combination of relevant lengths of the BL and CL in RYGB seems to be a promising solution which can reduce the necessity of more malabsorptive surgical arrangements such as BPD.

Conclusions

A longer biliary limb can intensify the anti-diabetic effect of RYGB. However, the length of the common limb rather than the biliary limb influences the laboratory T2DM remission in obese patients after RYGB. A long-term observational study is needed to fully assess whether introduced technical solutions in RYGB would provide a durable effect of T2DM resolution.

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