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ORIGINAL CONTRIBUTIONS

A Longer Biliopancreatic Limb in Roux-en-Y Gastric Bypass Improves Weight Loss in the First Years After Surgery: Results of a Randomized Controlled Trial

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Abstract

Background Despite the fact that the RYGB is performed on a broad scale worldwide as a reliable treatment for morbid obesity, there is no uniform technique for this operation. A number of studies have tried to demonstrate an additional weight loss effect by lengthening the alimentary limb, but to no avail. At this moment in time, the role of the biliopancreatic limb on weight loss is for the greater part unknown. The aim of this randomized controlled trial was to compare the effect on weight loss of a long biliopancreatic limb Roux-en-Y gastric bypass (LBP-GB) with a standard RYGB (S-GB).

Methods A LBP-GB (BPL 150 cm, alimentary limb 75 cm) was compared with a S-GB (BPL 75 cm, alimentary limb 150 cm). One hundred forty-six patients were randomized in two groups. Weight loss, morbidity, reduction of comorbidities, nutritional status, and quality of life were measured during a period of 4 years.

Results Patient characteristics were comparable in both groups. Mean EWL in the LBP-GB group after 12, 24, 36, and 48 months was 81, 85, 78, and 72% respectively versus 71, 73, 68, and 64% in the S-GB group. The %EWL difference between groups was significant as soon as 9 months postoperatively and continued throughout the follow-up period.

Conclusions While LBP-GB achieved a significant increase in %EWL in the first years after surgery, no difference in long-term %TWL was observed after 4 years. In this study, the advantage of LBP-GB with respect to weight loss is modest, but shows promising gripping points for future improvements in RYGB design.

Keywords Morbid obesity · Bariatric surgery · Roux-en-Y gastric bypass · Long biliopancreatic limb · Weight loss

Introduction

Despite the fact that in recent years the sleeve gastrectomy has found itself being the most commonly performed bariatric procedure, the Roux-Y gastric bypass still holds its place as a prominent bariatric treatment, especially when type 2 diabetes (T2DM) is present as well as obesity [1–6]. The gastric bypass can boast a long standing surgical history but it is remarkable that since its introduction in 1966 by Mason and Ito there have been only a few changes in its basic design [7, 8]. The addition of the Roux-Y configuration by Griffin in 1977 was probably the most radical change throughout its working history [9]. There is no uniform technique to perform a Roux-Y gastric bypass (RYGB), but generally speaking, it is constructed using a relatively long alimentary (Roux) limb and a short biliopancreatic limb (BPL). In a survey by Madan among 215 American bariatric surgeons, the average alimentary limb (AL) length was 114 cm and the average BP limb length was 48 cm [10].

In the past, the common perception was that the working mechanism of the RYGB was based on malabsorption and it was a logical assumption that more exclusion of the intestine would lead to increased weight loss. There are numerous studies about limb length and on the attempts to achieve more weight loss. These studies usually focused on using a longer alimentary limb, yet mostly without demonstrating a significant effect on weight loss (a slight effect at BMI > 50 kg/m^2 expected) [11]. To a much lesser extent, the effect of the BP

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limb on weight loss was studied. Observational studies report better weight loss with a longer BPL, but remarkably, standardized RCTs are practically nonexistent [12–14]. The growing awareness of the metabolic aspects of the small intestine that contribute to weight loss justify more focus on the additive role of the BP limb in metabolic change.

The aim of the present study was to compare the effect on weight loss and reduction of obesity-related comorbidities of a long BPL RYGB (LBP-GB) with our "standard" RYGB (S-GB). As sustainable weight loss can only be evaluated after time, the study groups were followed up for an average of 4 years.

Methods

The study (the ELEGANCE trial) was designed as a randomized, controlled, parallel-group, single-center trial. The study protocol was reviewed and approved by the Central Medical Committee for Research in humans in Nijmegen, the Netherlands (CMO). The study was registered at the clinical trials registry of clinicaltrials.gov (NCT 01686997). This study was in accordance with the Declaration of Helsinki (originally adopted in 1964, with the last amendment before this trial in October 2008).

Patient Selection

All patients (aged ≥ 18 years) were evaluated by a multidisciplinary team, including a bariatric surgeon, a nutritionist, a psychologist, and a physiotherapist. Patients eligible for primary gastric bypass surgery according to the IFSO criteria (BMI > 40 kg/m^2 or > 35 kg/m^2 with the presence of at least 1 comorbidity) were asked to participate in the study if they met the inclusion criteria. The exclusion criteria according to Fried [15] were broadened with IBD, language barrier, and/or renal disease (GFS < 30 mL/min).

Patients were informed in detail about the potential risks and benefits of both operations. Written information was presented to the patient at the end of the consultation. Patients had 2 weeks to reflect on the possibilities before their final consent was given. In all cases, a written informed consent form was signed to officially confirm participation in the study.

Primary and Secondary End Points

The %EWL (defined as weight loss divided by excess weight before surgery above a normal BMI of 25 kg/m^2) was used to calculate the sample size and therefore also used to express the primary end point of the study. The %TBWL (defined as weight loss divided by weight before surgery) was also calculated and expressed. Differences between groups were documented over a period of 4 years. Secondary end points were reduction of obesity-related comorbidities (i.e., type 2 diabetes mellitus (T2DM), hypertension (HT), and dyslipidemia (DL), the rate of perioperative morbidity and mortality, nutritional status, and changes in quality of life (QoL).

Operation Techniques

The "standard" RYGB (S-GB): All patients were operated on using a standardized operation technique. A laparoscopic antecolic antegastric RYGB procedure was performed. A small gastric pouch of 40–50 mL was constructed using a linear stapler (Echelon, Ethicon, Johnson & Johnson, New Brunswick, NJ, USA). A BPL of 75 cm from the ligament of Treitz was measured with a measuring tape under medium stretch along the mesenteric border. It was pulled up antecolically and anastomosed end-to-side with the gastric pouch. The gastro-jejunostomy was performed with a 30-mm blue linear stapler (ETS, Ethicon, Johnson & Johnson, New Brunswick, NJ, USA) combined with running absorbable suture to close the stapling gap (V-loc, Medtronic, Minneapolis, MN, USA). The 150-cm AL was measured with a measuring tape under medium stretch along the mesenteric border. The entero-enterostomy was performed with a 60-mm white linear Endo stapler combined with running absorbable suture (V-loc, Medtronic, Minneapolis, MN, USA). At the end of the procedure, both mesenteric defects were closed with a double layer of hernia staples (EMS, Ethicon, Johnson & Johnson, New Brunswick, NJ, USA) The integrity of the gastro-jejunostomy and gastric pouch staple line were tested intraoperatively for anastomotic leak with a burst test.

Long BPL RYGB (LBP-GB): The long BP limb procedure was performed in exactly the same way as the standard procedure. The only differences were a 150-cm BPL and a 75-cm AL. In both procedures, a total of 225 cm of small intestine was excluded.

Randomization

Randomization was performed by the local study coordinator using a web-based randomization module. Computer-generated permutated block randomization with a 1:1 allocation ratio and concealed carrying permuted block size of two and four patients was used. Owing to the invasive nature of the intervention and the logistics involved to perform the procedures, the investigators could not be masked to group allocation. The trial participants were masked to their procedure. This RCT was thus a single-blinded study. Based on the assumption that a LBP-GB would lead to a 10% higher EWL after 2 years, this leads after power analysis to two groups of 63 patients. Anticipating a percentage of 10% lost to follow-up a little over 140 patients were randomized.

Assessment

Preoperatively, all patients underwent anesthesiological evaluation (including standard laboratory blood tests). Blood sampling consisted of a complete blood count, ferritin, folic acid, vitamin B12, 25-hydroxyvitamin D (25-OHD), and parathyroid hormone (PTH). Additional investigations were performed according to the risk profile of each individual patient. When a preoperative deficiency was found, it was corrected before surgery.

All patients had seven educational lifestyle group sessions prior to their operation, counseling them on nutritional, physical activity, and motivation. Postoperatively, these sessions continued during the first 2 years, with a total of 15 follow-up moments. At 6 weeks, 3 months, 6 months, 12 months, 18 months, and 24 months, a medical consult was added to these sessions and thereafter on an annual basis. Weight, BMI, comorbidities, eating behavior, blood samples, and a QoL assessment were routinely performed. Comorbidities were defined using the following criteria: for T2DM a fasting plasma glucose ≥ 7.0 mmol/L and/or HbA1c ≥ 48 mmol/mol (HbA1c ≥ 6.5%) or the use of oral antidiabetic/insulin medication; HT: systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or antihypertensive drug therapy; DL: impaired high-density lipoprotein < 1.03 mmol/L for men, < 1.29 mmol/L for women, and/or triglycerides > 1.69 mmol/L, and/or low-density lipoprotein > 2.59 mmol/L, or the use of statins. Remission and/or improvement of comorbidities were documented by the endocrinologist or physician responsible for follow-up and the following definitions were defined: *remission*, for T2DM a fasting glucose < 7 mmol/L, HbA1c < 48 mmol/mol and discontinuation of treatment for at least a year, for HT a systolic blood pressure < 140 mmHg, diastolic blood pressure < 90 mmHg and discontinuation of treatment and for DL an impaired high-density lipoprotein > 1.03 mmol/L for men, > 1.29 mmol/L for women, triglycerides < 1.69 mmol/L, low-density lipoprotein < 2.59 mmol/L, and discontinuation of treatment; *improvement*, reduction in treatment such as lowering of medication dosage or cessation of insulin use; *unchanged*, no difference to the preoperative situation; de novo, postoperative newly diagnosed disease. Every year, standard laboratory blood tests were performed. Vitamin deficiencies were defined as serum levels falling below the lower normal limit. Quality of life was assessed using the Bariatric Analysis and Reporting Outcome System (BAROS) [16] and the RAND-36.

Postoperative Management

Ambulation and clear liquids were started on the day of the operation, oral feeding was resumed the first day postoperative. Thrombosis prophylaxis (Fraxiparine 5700 IU anti-Xa, once daily) was started day one postoperative and continued for 4 weeks. All patients were advised to take 150% RDA multivitamins (Fit For Me, Rotterdam, The Netherlands), 1500 mg calcium, and 2400 IU vitamin D_3 lifelong on a daily basis.

Statistical Analysis

Data were analyzed using IBM® SPSS® (version 21.0 for Windows). Results are presented as mean values ± standard deviation (SD), unless specified otherwise. Descriptive statistics were used for demographic variables. Differences between groups were analyzed by Student's *t* tests for continue variables and Fisher's exact tests for categorical data. To adjust for the baseline covariates, i.e., age, sex, preoperative BMI, and preoperative diabetes, a linear regression analysis was performed. All tests were two tailed and a p value < 0.05 was considered as statistically significant.

Results

Between July 2012 and March 2013, 146 patients were enrolled in the study; 72 patients were randomized to a LBP-GB and 74 to a S-GB. In the LBP-GB group, five patients were excluded: in one patient, a sleeve gastrectomy was performed owing to firm adhesions in the upper abdomen; three patients that were randomized to receive a LBP-GB got a S-GB as a result of too much traction on the mesentery of the small intestine while creating the BPL; and one patient was preoperatively diagnosed with a metastasized melanoma. As the primary end point was %EWL as a result of the RYGB and patients were blinded for their treatment, making it unlikely that they could influence outcomes, we chose to exclude these patients from the analysis. This "per protocol" analysis is in accordance with the CONSORT 2010, update on guidelines for parallel group RCTs, and is used instead of "the intention to treat" principle [17]. However, for reference purposes, intention to treat outcomes are reported as well. The baseline characteristics between the groups did not differ significantly (Table 1).

Follow-up

During follow-up, seven female patients became pregnant, five in the S-GB group and two in the LBP-GB respectively. Four women became pregnant before 24 months and three women became pregnant in the fourth year of their follow-up. Two patients were lost to follow-up at 4 years and one patient withdrew for participation in the study after 2 years of follow-up. The data of all these patients was used until the time they became pregnant, were lost to follow-up, or withdrew from participation. A total follow-up percentage of 98% was achieved after 4 years (Fig. 1).

Table 1 Baseline patient characteristics: no significant differences between patients with S-GB or LPB-GB. *S-GB* standard Roux-en-Y gastric bypass, *LBP-GB* long biliopancreatic limb Roux-en-Y gastric bypass, *BMI* body mass index, ± standard deviation

	S-GB	LBP-GB
Number of patients	74	67
Caucasian (%)	97	99
Female (%)	62 (84)	58 (87)
Age (years)	43 ± 10	44 ± 9
Length (cm)	171 ± 7	171 ± 9
Weight (kg)	132 ± 19	128 ± 18
BMI (kg/m^2)	45 ± 5	43 ± 5

Weight Loss

Patients with a LBP-GB achieved significantly more %EWL compared to a S-GB. This difference occurred as soon as 9 months after surgery and continued throughout the follow-up period. The difference between groups was the largest after 24 months of follow-up with 85% versus 72% respectively ($p = 0.001$). At this point, the difference in %TBWL was also significant. After 4 years, the significant difference in %EWL was still present, but due to weight regain in both groups, values dropped to 72 and 64% respectively and the significant difference in %TBWL disappeared. After adjustment for age, sex, preoperative BMI, and preoperative T2DM, the difference in %EWL between LBP-GB and S-GB was 9.2% ($p = 0.004$) after 24 months and 6.1% ($p = 0.12$) after 48 months. The outcomes of all weight parameters are shown in Table 2.

When applying "the intention to treat" principle, the LBP-GB group still had superior results compared to the S-GB group. After 2 years the LBP-GB group achieved a %EWL of 84% versus 73% in the S-GB group ($p = 0.002$). Although an advantage in the LBP-group was still observed after 4 years, 70% in the LBP-GB group and 63% in the S-GB group ($p = 0.060$), the difference was no longer significant.

Resolution of Comorbidities

Table 3 gives an overview of the number of patients that achieved remission of the studied obesity-related comorbidities. In addition, Table 4 shows changes in biochemical parameters and blood pressure.

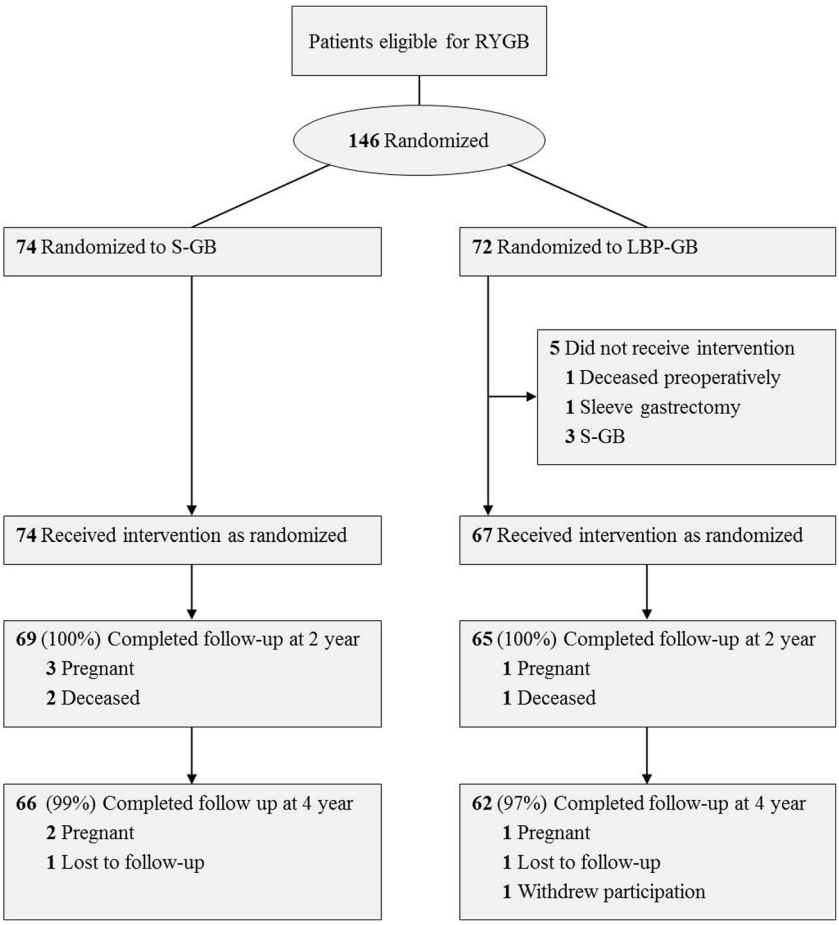

Fig. 1 Flow diagram. S-GB, standard Roux-en-Y gastric bypass; LBP-GB, long biliopancreatic limb Roux-en-Y gastric bypass

Table 2 Results on the weight loss parameters. *S-GB* standard Roux-en-Y gastric bypass, *LBP-GB* long biliopancreatic limb Roux-en-Y gastric bypass, *BMI* body mass index, *%EWL* percentage excess weight loss, *%TBWL* percentage total body weight loss, *sd* standard deviation

		S-GB	sd	LBP-GB	sd	*p* value
Weight (kg)	Baseline	132	19	128	18	0.188
	6 weeks	118	17	114	16	0.234
	3 months	109	17	106	15	0.281
	6 months	100	16	96	15	0.155
	9 months	94	15	90	15	0.067
	12 months	91	15	86	15	*0.037*
	24 months	91	16	83	14	*0.004*
	36 months	93	17	87	16	*0.028*
	48 months	96	18	90	17	*0.042*
BMI (kg/m^2)	Baseline	45	5	43	5	0.085
	6 weeks	40	5	39	5	0.106
	3 months	37	4	36	5	0.158
	6 months	34	4	33	5	0.068
	9 months	32	4	30	4	*0.021*
	12 months	31	4	29	4	*0.009*
	24 months	31	5	28	4	*0.001*
	36 months	32	5	30	5	*0.009*
	48 months	33	6	30	5	*0.015*
%EWL	6 weeks	25	8	26	8	0.344
	3 months	41	11	43	12	0.378
	6 months	56	16	61	16	0.083
	9 months	66	17	74	19	*0.020*
	12 months	71	19	81	21	*0.007*
	24 months	73	21	85	21	*0.001*
	36 months	68	22	78	23	*0.021*
	48 months	64	23	72	24	*0.049*
%TBWL	6 weeks	10	3	11	3	0.924
	3 months	17	4	17	4	0.768
	6 months	24	5	25	5	0.392
	9 months	28	5	30	6	0.097
	12 months	31	6	33	7	*0.042*
	24 months	31	8	35	7	*0.006*
	36 months	29	8	32	9	0.087
	48 months	27	9	30	10	0.152

Italic values represent significant outcomes

Type 2 Diabetes Mellitus At baseline, 46 (33%) patients were diagnosed with T2DM, 23 (31%) in the S-GB group versus 23 (34%) in the LBP-GB group respectively. One of the T2DM patients in the S-GB is deceased. In the LBP-GB group, 18 (78%) patients had a remission 4 years after their RYGB and 17 (77%) patients in the S-GB ($p > 0.05$). It is notable that there were no patients that developed T2DM de novo in this 4-year period. The definition of remission of T2DM differs between studies. To enable comparison of T2DM remission result with other studies, outcomes for the different levels of HbA1C are shown in Table Table 5.

Hypertension Despite randomization more patients suffered from hypertension in the LBP-GB group, 33 (49%) patients versus 24 (32%) in the S-GB group ($p = 0.086$). In total, 32 (55%) patients achieved remission of their HT after 4 years, 14 (58%) in the S-GB group versus 18 (55%) in the LBP-GB group ($p > 0.05$). The decrease in systolic and diastolic blood pressure was the same in both groups.

Dyslipidemia Based on the medical histories and drug use, 36 (26%) patients appeared diagnosed with DL at baseline. However, when reviewing the baseline lipid spectrum of all patients, the total number of patients which met the criteria for DL increased to 124 (88%), of whom 66 (89%) in the S-GB group versus 58 (87%) in the LBP-GB group. After 4 years, 59 (48%) patients achieved remission of their dyslipidemia. Significantly, more patients achieved remission or improved in the LBP-GB group ($p = 0.022$). Remission after 4 years was achieved in 52% of patients in the LBP-GB group and 50% in the S-GB group.

Complications

In total, 11 patients suffered from a short-term complication, 4 (5%) in the S-GB group and 7 (10%) in the LBP-GB group ($p > 0.05$). No anastomotic leakage occurred in either of the two groups. All short-term complications are listed in Table 6. Despite the low short-term complication rate, two patients died within 30 days after surgery, one in each group. In the LBP-GB group, a patient acutely died at home from an unknown cause. Most likely, this was due to a pulmonary embolism, despite the postoperative thrombosis prophylaxis regiment of Fraxiparine 5700 IU once a day for four consecutive postoperative weeks. As far as we know, this patient used this prophylaxis according to protocol. Her family did not concede in a postmortem examination. The patient in the S-GB group underwent a laparotomy for a postsurgical bleeding (which was packed and coiled), and was resuscitated with packed cells and plasma while in the intensive care unit. Despite cessation of the bleeding and all interventions, the patient developed multi-organ failure and died 25 days after surgery.

In the long term, 41 (29%) patients developed a complication or underwent surgery a second time. Thirty patients underwent a repeat surgery, 18 of them for symptomatic gallstones. All long-term complications are listed in Table 7. One patient died during the follow-up due to a lung carcinoma.

Nutritional Status

At year four of follow-up, 87% of the patients were using a multivitamin supplement (MVS) as prescribed. In addition,

Table 3 Resolution of obesity-related comorbidities. *S-GB* standard Roux-en-Y gastric bypass, *LBP-GB* long biliopancreatic limb Roux-en-Y gastric bypass

		S-GB	LBP-GB	*p* value
Type 2 diabetes (%)		23 (31)	23 (34)	0.681
24 months	Remission	13 (59)	18 (78)	0.290
	Improvement	8 (36)	5 (22)	
	Unchanged	1 (5)	0	
	Type 2 diabetes de novo	0	0	
48 months	Remission	17 (77)	18 (78)	0.572
	Improvement	4 (18)	5 (22)	
	Unchanged	1 (5)	0	
	Type 2 diabetes de novo	0	0	
Hypertension (%)		24 (32)	33 (49)	0.086
24 months	Remission	16 (67)	15 (46)	0.207
	Improvement	5 (21)	8 (24)	
	Unchanged	3 (13)	10 (30)	
	Hypertension de novo	0	0	
48 months	Remission	14 (58)	18 (55)	0.326
	Improvement	5 (21)	8 (24)	
	Unchanged	3 (13)	7 (21)	
	Hypertension de novo	2 (8)	0	
Dyslipidemia (%)		66 (89)	58 (87)	0.797
24 months	Remission	25 (38)	30 (52)	0.312
	Improvement	27 (41)	23 (40)	
	Unchanged	9 (13)	3 (5)	
	Unknown	1 (2)	1 (2)	
	Dyslipidemia de novo	4	1	
48 months	Remission	30 (50)	29 (52)	*0.022*
	Improvement	20 (33)	24 (43)	
	Unchanged	10 (17)	1 (2)	
	Unknown	0	2 (4)	
	Dyslipidemia de novo	0	2	

Italic values represent significant outcomes

75% of the patients were using calcium/cholecalciferol according to protocol. The percentage of patients with deficiencies after 4 years is listed in Table 8. The only notable difference that was found between the two groups was a higher percentage of patients in the LBP-GB group with ferritin deficiency after 24 months but not after 48 months.

Quality of Life

Bariatric Analysis and Reporting Outcome System To evaluate the results of both the S-GB and LBP-GB, results of the Bariatric Analysis and Reporting Outcome System (BAROS) scores are presented in Table 9. At year four of follow-up, the LBP-GB showed a mean BAROS score of 2.42 compared to 2.29 in the S-GB group ($p > 0.05$). In total, 88% of patients had a result of "fair" or better. At the "high point" of weight loss around 24 months, there was a significant difference in the BAROS score in favor of the LBP-GB that disappeared thereafter.

RAND-36 The results of the RAND-36 of both the S-GB and LBP-GB are presented in Table 10. As might be expected, there was a significant improvement 24 months and 48 months postoperative in all patients in several domains compared to preoperative values. A significant difference between groups in favor of LBP-GB was seen after 24 months in the domains: role functioning/emotional and pain. The baseline scores and the scores after 48 months were not significantly different between the two groups.

Discussion

In the last two decades, there has been a growing understanding of the enormous potential of bariatric procedures on metabolic and weight loss control. Although the number of procedures have rocketed to over half a million worldwide and some new procedures show great promise, the sleeve

Table 4 Obesity-related comorbidities: biochemical and blood pressure changes. *S-GB* standard Roux-en-Y gastric bypass, *LBP-GB* long biliopancreatic limb Roux-en-Y gastric bypass, *BP* blood pressure

	S-GB			LBP-GB							
	Baseline	24 months	48 months	Baseline	24 months	48 months	*p* value[†]	*p* value[‡]	*p* value*	*p* value[¶]	*p* value[¶¶]
Type 2 diabetes											
HbA1c (mmol/mol)	63	41	40	62	39	42	*< 0.001*	*0.001*	0.971	0.610	0.987
HbA1c (%)	7.8	5.9	5.8	7.8	5.7	5.9	*< 0.001*	*0.001*	0.980	0.590	0.873
Fasting glucose (mmol/L)	9.0	6.0	6.2	9.8	5.7	6.3	*0.003*	*0.027*	0.491	0.807	0.737
Hypertension											
Systolic BP (mm Hg)	148	130	143	157	140	147	0.942	0.501	0.054	0.066	0.611
Diastolic BP (mm Hg)	89	83	88	95	85	86	*0.040*	*0.012*	0.078	0.474	0.539
Dyslipidemia											
HDL cholesterol (mmol/L)	1.14	1.46	1.49	1.18	1.54	1.63	*< 0.001*	*< 0.001*	0.462	0.250	0.095
Triglycerides (mmol/L)	1.83	1.19	1.39	1.79	1.11	1.21	*< 0.001*	*< 0.001*	0.848	0.540	0.420
LDL cholesterol (mmol/L)	2.92	2.38	2.63	2.76	2.29	2.63	*< 0.001*	*0.003*	0.199	0.482	0.897

Italic values represent significant outcomes

[†] Pre- versus 24 months postoperative scores of the total group

[‡] Pre- versus 48 months postoperative scores of the total group

*Preoperative scores between the S-GB and LBP-GB groups

[¶] 24 months postoperative scores between the S-GB and LBP-GB groups

[¶¶] 48 months postoperative scores between the S-GB and LBP-GB groups

gastrectomy and the Roux-en-Y gastric bypass are still the two prevalent surgical procedures.

It is no longer a question if these procedures have a significant effect on metabolic control but rather how to make the outcomes of bariatric procedures more pronounced and sustainable. It is often argued that a percentage EWL of more than 50% is already considered a successful treatment, but extra weight loss above this threshold is associated with more resolution of comorbidities and higher patient satisfaction. In addition, when weight regain occurs, a higher primary weight loss will provide an extra buffer against weight loss failure. It is for these reasons that our study was conducted.

It is strange that while the operative technique of the sleeve gastrectomy has been studied intensively in the last years in order to maximize its effectiveness, the gastric bypass has remained basically unchanged. This is particularly striking given that the anatomical design of a gastric bypass is more complex than that of a sleeve gastrectomy, suggesting a greater number of gripping points for improvement of design, ranging from a variety in pouch and stoma sizes to variations in limb lengths. Most research into the effect of limb length on weight loss is focused on the alimentary limb. From a historical perspective, this is understandable for the main purpose of Roux-Y construction, was traditionally to prevent biliary reflux. For this purpose, a short BP limb measuring a little over 15 cm was sufficient. For many years, the mechanical effect of the bypassing long alimentary limb was held responsible for most of the weight loss effect. It is therefore no surprise that many studies and RCTs focused on comparison of alimentary limb length. However, despite maybe a slight effect on

Table 5 Complete T2DM remission results with different guidelines

		S-GB	LBP-GB	*p* value
24 months	Discontinuation of treatment and			
	HbA1c < 6.5% (%) [18]	13 (59)	18 (78)	0.165
	HbA1c < 6.0% (%) [19]	12 (55)	18 (78)	0.092
	HbA1c < 5.7% (%) [18, 20]	10 (45)	14 (61)	0.300
48 months	Discontinuation of treatment and			
	HbA1c < 6.5% (%) [18]	17 (77)	18 (78)	0.936
	HbA1c < 6.0% (%) [19]	15(68)	17 (74)	0.672
	HbA1c < 5.7% (%) [18, 20]	15 (59)	15 (65)	0.672

Table 6 Short-term complications. Patients could suffer from multiple complications. *S-GB* standard Roux-en-Y gastric bypass, *LBP-GB* long biliopancreatic limb Roux-en-Y gastric bypass

	S-GB	LBP-GB	*p* value
Total number of patients (%)	4 (5)	7 (10)	0.265
Reoperation	1	1	
Anastomotic leakage	0	0	
Bleeding	1	0	
Iatrogenic serosal injury	0	1	
Conservative-treated bleeding	1	2	
Superficial wound infection	1	1	
Readmission	3	3	
Mortality	1	1	

patients with higher BMIs (> 50 kg/m^2), a longer alimentary limb does not seem to contribute to any weight loss [11].

The effect of the BP limb on weight loss has been studied to a much lesser extent. Although a few RCTs on the BP limb can be found, the quality of the studies lacks sufficient relevance, standardization, and follow-up. At the same time, some non-randomized studies report exceptional weight loss in patients with long BP limbs [13]. The present RCT demonstrates that a LBP-GB results in a significantly higher %EWL than a S-GB. This significant difference is still present 4 years postoperatively, although at that time there is no longer a difference in %TBWL. An EWL of 85% in the LBP-GB group is exceptionally good compared to all standards and exceeds by far most reported outcomes after both gastric bypass and sleeve gastrectomy. But even in the S-GB group, an average EWL of 72% was observed after 2 years, which is higher than observed in many other gastric bypass studies [21]. In this group, a "standard" BP limb length of 75 cm was chosen, which can also be considered long to some standards. The thought arises if results would have been even more pronounced if a shorter BP limb was chosen in the standard group. And in the same line of reasoning an even longer BP limb could theoretically, lead to even more weight loss. However, lengthening the BP limb is not limitless as at some point it will affect the remaining length of the common channel which carries the additional risk of introducing detrimental effects associated with malabsorptive procedures. The length of the remaining common channel was not routinely measured in this study, however we acquired data from about 46% of patients (data not shown). The average length was comparable between the groups, 425 cm in the S-GB group and 462 cm in the LBP-group. A common channel shorter than 2 m was not detected in any of the patients that participated in the study.

It is notable that the favorable effects on weight loss in the first 2 years after gastric bypass surgery decrease in the years thereafter. Weight regain is a well-known phenomenon after all bariatric procedures and in this study it was equally distributed in both groups. Apparently, the mechanisms that lead to weight regain seem not related or influenced by limb length. However, since the LBP-GB group started off with a higher %EWL, after 4 years, there is still a significant advantage noticeable in this group compared to the S-GB group. Only %TBWL was no longer significant after 48 months.

It is not yet fully clear how the enhanced weight loss effect of a longer BP limb is explained. It is feasible that the same beneficial effect on weight loss can be found in other procedures such as a "one anastomosis gastric bypass" and in a SADI-S that on average is higher when compared to a standard gastric bypass in many reports [22–24]. Both procedures share the longer BP-limb construction with the LBP-GB. Although hard evidence is lacking, from a theoretical point of view a longer BP limb has a more pronounced "hind gut" effect. This theory describes the mechanism that the rapid delivery of food to a more distal part of the bowel induces the upregulation of the number of L-cells in the intestinal wall. L-cells produce the gut hormones among which GLP-1, that is in turn, shown to induce anorexia, the incretin effect and the "ileal brake," eventually leading to weight loss. When a longer BP limb is measured and divided at the level of the enteroenterostomy, the adjacent distal part is pulled up to be attached to the gastric pouch. It is this more distal part of the small intestine that receives first the food bolus passing through the gastric pouch. Studies on blood gut hormone levels to examine this hypothesis are well underway but prove to be both complicated and expensive [ClinicalTrials.gov number NCT03384303].

Many studies exhibit better outcomes in terms of resolution of comorbidities and QoL when weight loss increases [19, 25, 26]. This study fails to demonstrate these effects as outcomes were comparable between groups. Only the remission of DL

Table 7 Complications that occurred after 30 days. Patients could suffer from multiple complications at the same time. *S-GB* standard Roux-en-Y gastric bypass, *LBP-GB* long biliopancreatic limb Roux-en-Y gastric bypass

	S-GB	LBP-GB	*p* value
Total number of patients (%)	22 (30)	19 (28)	0.858
Reoperation	17	13	
Cholecystectomy	10	8	
Internal herniation	4	3	
Adhesion	1	0	
Suspicion of internal herniation	2	1	
Incisional hernia	0	1	
Stomach ulcer	0	1	
Admission for unexplained abdominal pain	3	5	
Hyperinsulinemic hypoglycemia	1	0	
Mortality	1	0	

Table 8 Percentages of anemia and vitamine deficiencies at baseline, after 24 and after 48 months

	S-GB			LBP-GB					
	Baseline (%)	24 months (%)	48 months (%)	Baseline (%)	24 months (%)	48 months (%)	*p* value*	*p* value¶	*p* value¶¶
Anemia	3	15	9	5	16	12	1.000	1.000	0.753
Folic acid	0	0	6	0	0	6	–	–	1.000
Vitamin B_{12}	19	27	20	24	15	10	0.539	0.128	0.182
Ferritin	5	9	30	15	21	26	0.088	0.080	0.827
Vitamin D	9	15	16	10	15	12	1.000	1.000	0.589

*Preoperative deficiency percentage between the S-GB and LBP-GB groups

¶ 24 months postoperative deficiency percentage between the S-GB and LBP-GB groups

¶¶ 48 months postoperative deficiency percentage between the S-GB and LBP-GB groups

was significantly better in the LBP-GB group after 48 months. No differences between groups were seen in the remission of T2DM and HT after 24 and 48 months. It must be mentioned however that this study was powered for weight loss as a primary end point and probably underpowered for the secondary end points. Nevertheless the excellent resolution of T2DM and especially the absence of new patients with T2DM in a period of 4 years is quite remarkable. A mean remission rate of 78% after 4 years compares favorably to 72% found in a meta-analysis on this subject by Yu et al. [26]. This is illustrated by the change in HbA1c in both the S-GB and the LBP-GB groups (− 2.1% and − 1.9%), after 4 years, which is much better than − 1.1% reported in the same meta-analysis.

Only the remission of DL was significantly better in the LBP-GB group after 48 months. Risstad et al. [27] found a higher concentration of bile acids in patients 5 years after RYGB and an inverse correlation between bile acids and total cholesterol. An even higher concentration of bile acids together with a greater reduction in total cholesterol, LDL cholesterol, and triglycerides were found in patients after biliopancreatic diversion with duodenal switch (BPD/DS). This suggested that the long biliopancreatic limb, used in a BPD/DS, may be important for the metabolic improvement due to differences in intestinal absorption of bile acids in the biliopancreatic limb. Finding a significantly better remission in the LBP-GB group, is in accordance with these conclusions.

Table 9 BAROS after 24 and 48 months postoperative. *S-GB* standard Roux-en-Y gastric bypass, *LBP-GB* long biliopancreatic limb Roux-en-Y gastric bypass, *BAROS* Bariatric Analysis and Reporting Outcome Scale

	S-GB (%)	LBP-GB (%)	*p* value
BAROS 24 months postoperative			
Failure	0	0	*0.03*
Fair	24	7	
Good	43	46	
Very good	19	28	
Excellent	14	20	
BAROS 48 months postoperative			
Failure	12	9	0.347
Fair	49	45	
Good	35	41	
Very good	4	5	
Excellent	0	0	

Italic values represent significant outcomes

The LBP-GB procedure is not more difficult to perform, which is illustrated by comparable complication rates in both groups. However, in some patients with a relatively short mesentery it could prove to be slightly more difficult to pull up the longer BP limb up to the level of the gastric pouch. This was the case in three patients in the LBP-GB group. The death of one patient in each group, adding up to a 30-day mortality rate of 1.4% is high. However, the surgeons performing the operations in this study each have extensive experience in bariatric surgery and as the overall mortality rate in our high-volume center of excellence (> 1200 procedures annually) is approximately 0.2% (data not shown), this can probably be attributed to an unfortunate coincidence. There is some evidence in literature suggesting that longer (BP) limbs in gastric bypass surgery could lead to more internal hernias. Although the mesenteric defect was routinely closed during surgery, we did see internal hernias, but there was no difference between groups.

Vitamin and mineral deficiencies are common after RYGB. Especially deficiencies for ferritin, vitamin B_{12}, and folic acid which are frequently found. Since ferritin uptake takes place in the duodenum and proximal jejunum, a longer BPL could theoretically result in a higher risk of developing a ferritin deficiency. A higher ferritin deficiency percentage was seen in the LBP-GB group after 24 months, but disappeared after 48 months. As patients generally receive an adjustment of their vitamin regimen when a deficiency is apparent during follow-up, it is possible that any difference between groups was corrected in this way. As this was not sufficiently recorded no conclusion can be drawn from this.

Table 10 Outcomes in the RAND-36. The RAND-36 was measured preoperatively and 48 months postoperatively. *S-GB* standard Roux-en-Y gastric bypass, *LBP-GB* long biliopancreatic limb Roux-en-Y gastric bypass

	Total preop	S-GB preop	LBP-GB preop	*p*-value*	Total 2 year postop	S-GB 2 year postop	LBP-GB 2 year postop	*p* value¶	*p* value‡	Total 4 year postop	S-GB 4 year postop	LBP-GB 4 year postop	*p* value¶¶	*p* value‡‡
Physical functioning	47.3	50.1	44.2	0.153	85.9	83.6	88.2	0.282	*< 0.001*	79.0	76.1	82.1	0.318	*< 0.001*
Role functioning/-physical	46.2	52.0	56.6	0.51	81.2	75.4	86.8	0.068	*< 0.001*	68.0	61.9	74.4	0.184	0.087
Role functioning/-emotional	81.0	78.1	84.4	0.304	82.0	73.2	90.6	*0.007*	0.653	77.2	77.8	76.7	0.895	0.789
Energy/fatigue	46.2	46.0	46.4	0.905	60.8	60.8	60.8	0.997	*< 0.001*	57.0	56.8	57.3	0.92	*0.001*
Emotional well-being	73.3	73.0	73.6	0.818	73.8	73.9	73.7	0.947	0.972	73.8	72.6	75.1	0.547	0.487
Social functioning	67.5	65.2	70.1	0.29	79.6	78.1	81.1	0.535	*0.01*	74.7	71.7	77.8	0.319	0.311
Pain	57.9	56.9	59.1	0.645	73.5	68.1	78.8	*0.031*	*< 0.001*	68.6	65.9	71.4	0.372	*< 0.001*
General health	39.0	39.8	38.1	0.609	68.7	68.7	68.8	0.978	*< 0.001*	64.2	63.1	65.4	0.667	*< 0.001*
Health change	32.8	32.5	33.2	0.873	74.1	73.7	74.6	0.867	*< 0.001*	48.8	47.0	50.6	0.473	*< 0.001*
Total physical health	46.2	46.2	46.3	0.99	76.7	73.9	79.4	0.137	*< 0.001*	65.7	62.8	68.8	0.252	*< 0.001*
Total mental health	67.0	65.6	68.6	0.33	74.1	71.5	76.6	0.204	*0.032*	70.7	69.7	71.7	0.687	0.278

Italic values represent significant outcomes

*Preoperative scores between the S-GB and LBP-GB groups

¶ 24 months postoperative scores between the S-GB and LBP-GB groups

‡ Pre- versus 24 months postoperative scores of the total group

¶¶ 48 months postoperative scores between the S-GB and LBP-GB groups

‡‡ Pre- versus 48 months postoperative scores of the total group

Weight reduction after bariatric surgery is associated with the improvement of QoL scores. The improvements of the physical aspects are more distinct compared to the mental aspects of QoL [28]. Finding a significant higher mean BAROS-QoL score at 24 months in the LBP-GB group, when maximum weight loss was achieved, and finding a significant improvement in almost all mean scores in the physical domains of the RAND-36 are in accordance with these findings. It is well documented that there is a high correlation between the amount of weight loss and patient satisfaction with the procedure. Therefore, it is conceivable that a weight regain of about 10% after 24 months (equally present in both groups) weakens the QoL outcome thereafter.

In retrospect, the study design with 146 randomized patients proved to be sufficient to demonstrate an attributed effect on excess weight loss of a LBP-GB, but has its limitations in other aspects of the study. The numbers proved to be too small to show a distinct advantage in resolution of comorbidities or QoL. Although a trend was seen in terms of %TBWL, it was not enough to be significant after 4 years. A smaller study group also has the risk of introducing a type II error, which can be reflected in the relative high 30-day mortality. It is a matter of debate if a difference in EWL of 13% has clinical significance as the equivalent in kilos is on average no more than 3–5 kg. At an average weight loss of 37 kg after 2 years, this does not seem a lot. Still we want to emphasize that this RCT was meant to demonstrate one of the many possible improvements in the RYGB design. Several other trials are underway looking for example at pouch length and a banded bypass concept that not only could add to weight loss but simultaneously aim at preventing weight regain after several years [CilicalTrials.gov numbers NCT02218957 and NCT02545647]. An additional consideration is that the ideal length for the BP limb has not been determined. In the present study, an arbitrary length of 150 cm was chosen as a long alternative to the existing standard RYGB design. When indeed the BP limb has a more pronounced effect on weight loss than the alimentary limb one could argue that a bypass with a 2-m BP limb and only 75 cm of alimentary limb is more rational. If all the alterations in the basic RYGB design, prove over time to be improvements, it is very likely that this cumulative effect will be considered clinically significant.

Conclusion

While LBP-GB achieved a significant increase in %EWL in the first years after surgery, no difference in long-term %TBWL was observed after 4 years. In this study, the advantage of LBP-GB with respect to weight loss and comorbid disease is modest, but shows promising gripping points for future improvement in gastric bypass design.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent The study protocol was reviewed and approved by the Central Medical Committee for Research in humans in Nijmegen, the Netherlands (CMO). The study was registered at the clinical trials registry of clinicaltrials.gov (NCT 01686997). This study was in accordance with the Declaration of Helsinki (originally adopted in 1964, with the last amendment before this trial in October 2008).

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