Optimizing bariatric procedures

Abel Boerboom

Propositions

1. The optimal Roux-en-Y gastric bypass has not yet been designed.
   (this thesis)

2. Revisional bariatric surgery is only effective in strictly selected patients.
   (this thesis)

3. Weight discrimination is one of the few forms of discrimination that is completely accepted in our society.

4. The General Practitioner curriculum should incorporate a course with interview techniques to discuss obesity and the related comorbidities.

5. To perform as a team, it is better to know each other's weaknesses than each other's strengths.

6. To matter is the most important factor for a good quality of life.

Propositions belonging to the thesis, entitled
Optimizing bariatric procedures

Abel Boerboom
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Optimizing bariatric procedures

Abel Boerboom

Thesis committee

Promotor
Prof. Dr E.J. Hazebroek
Special Professor Nutrition and Obesity Treatment
Wageningen University & Research

Co-promotors
Dr E.O. Aarts, Weightworks Amersfoort
Dr F.J. Berends, Weightworks Amersfoort

Other members
Prof. Dr E.J.M. Feskens, Wageningen University & Research
Prof. Dr J.W.M. Greve, Maastricht University
Dr S.W. Nienhuijs, Catharina Ziekenhuis Eindhoven
Dr M.J.M. Groenen, Rijnstate Ziekenhuis Arnhem

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Optimizing bariatric procedures

Abel Boerboom

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CHAPTER 1

General introduction, aim and outline thesis

Obesity is defined by the World Health Organization (WHO) as an "abnormal of excessive fat accumulation that presents a risk to health". In the last two decades, obesity has become a major health problem in most high-income countries. Due to the increasing number of patients with overweight, obesity is a worldwide challenge for the healthcare systems. In 2016 the WHO stated that almost 40% of the worldwide population, 18 years and older, were overweight and 650 million (13%) were obese[1]. In the Dutch population these percentages are even higher. Approximately 51% of the adult population is overweight and 14% suffers from obesity[2]. Future perspectives predict an increase in the prevalence of people with obesity worldwide with 33% over the next two decades[3].

To classify overweight and obesity, the body mass index (BMI) is mostly used. BMI is defined as a person's weight in kilograms divided by the square of his height in meters (kg/m^2):

$$\text{Body Mass Index } (kg/m^2) = \frac{\text{Weight (kg)}}{\text{(Length (meters) x Length (meters)}}$$

Currently, obesity is in the top three of causes resulting in loss of healthy life years. This is mainly due to its association with a disturbing high number of somatic and psychosocial comorbidities[4,5]. It is well known that obesity comes with higher risks for developing type 2 diabetes mellitus (T2DM), hypertension, hypercholesterolemia, obstructive sleep apnea syndrome (OSAS), musculoskeletal disorders and even certain types of cancer[6-9]. Less well known is the higher risk of developing anxiety disorders and depressions compared to people with a healthy weight[10,11]. Due to these somatic and psychosocial comorbidities the life expectancy of patients with obesity is significantly reduced, reaching up to 20 years in young patients with obesity[4,5].

Additionally, obesity has a significant effect on worldwide economics. The increasing number of people being overweight result in a higher number of unhealthy years of life spent. On average, people with obesity have four more sick days a year resulting in less productivity and an increase in health care costs[12-14].

Although challenging, it is important to counteract and decrease the number of patients with obesity, or at least prevent further growth of the percentage of people suffering from it. Prevention strategies installed by national governments would be the most logical solution. However it proofs to be a big challenge due to the obesogenic environment in which marketing of the food industry and economic systems are actually promoting consumption.

Conservative treatment of obesity by changing eating behavior and lifestyle may result in weight loss on the short term but maintaining these behavioral changes to prevent

weight regain on the long term is often challenging for most people[15,16]. When overweight or obesity has developed in addition to lifestyle changes, medication can be used to counteract obesity. Several studies have showed positive effects of glucagon-like peptide-1 receptor agonists on weight loss resulting in modest weight loss in the short term[17-19]. Although promising, long term results are lacking and data show there is a need for lifelong use of these medications to keep the weight off.

Since conservative and/or medicinal treatment is currently not sufficient to achieve significant long-term weight loss in the majority of patients with severe obesity, bariatric or metabolic surgery is regularly performed to induce weight loss. Metabolic surgery leads to more sustainable weight loss and reduces obesity-related comorbidities[16,20]. Due to these benefits the number of bariatric procedures performed each year has increased to a half million worldwide in the past decade[21].

To be eligible for metabolic surgery patients should meet the criteria that are stated by the National Institutes of Health (NIH). All patients with class three obesity (BMI≥40 kg/m^2) or with class two obesity (BMI ≥35 kg/m^2) with one or more obesity related comorbidities are candidates to undergo bariatric surgery. In addition to these basic criteria there are several in- and exclusion criteria to be eligible for bariatric surgery as a last resort in the treatment of obesity. The recently updated Dutch guideline for metabolic surgery even emphasizes to consider surgery in patients with class one obesity (BMI ≥30 kg/m^2) when T2DM is present because it is currently the most effective treatment option[22].

There are many types of metabolic surgery available. The choice of procedure depends on many factors, including BMI and specific patient characteristics. One of the most performed metabolic procedures is the Roux-en-Y Gastric Bypass (RYGB), and this procedure is the focus of this thesis.

During a laparoscopically performed RYGB procedure the stomach is reduced to a 30-45cc pouch and an alimentary limb (Roux limb) and biliopancreatic limb are created by creating a gastro-enterostomy and an entero-enterostomy. The clinical result is a small pouch from which food passes through the gastro-enterostomy into the alimentary limb. After the entero-enterostomy the ingested food comes in contact with the secretions from the gastric remnant, liver and pancreas. In the common channel, were food and the pancreatic enzymes and bile mix together, major digestion and absorption of nutrients occurs. No tissue is removed, but the duodenum and the proximal jejunum are completely bypassed for ingested food and drinks (**Figure 1**).

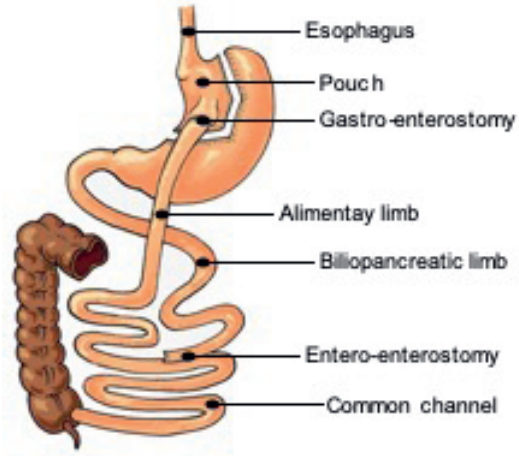

Figure 1. Roux-en-Y gastric bypass

Since the introduction of the gastric bypass in 1966 by Mason and Ito there have been only a few changes in its basic design[23,34]. The addition of the Roux-Y configuration by Griffin in 1977 was probably the most radical change[25]. But with every metabolic procedure there are possibilities to improve the design and the outcomes. The complex anatomical design of the RYGB suggests that there are a number of gripping points for improvement of its original design, ranging from a variety in pouch designs to variations in limb lengths.

There are numerous studies about limb length and on attempts to achieve better results after gastric bypass surgery. These studies usually focused on using a longer alimentary limb[26]. From a historical perspective, this is understandable as the main purpose of the Roux-Y construction was traditionally to prevent biliary reflux. For this purpose, a short biliopancreatic limb measuring as little as 15 cm was considered to be sufficient. Although some (often retrospective) studies focus on the length of the biliopancreatic limb, the quality, standardization and follow-up of these studies are insufficient[27-29]. Additionally, many studies describe the effect of pouch size on weight loss and complications. The majority of studies are descriptive and observational, and it proves hard to draw any conclusions from them. Most studies focus on using a smaller pouch, yet mostly without demonstrating a correlation between pouch volume and weight loss[30-34].

When debating the design of the RYGB, many surgeons believe that placing a non-adjustable band around the pouch results in superior weight loss with acceptable complication rates[35]. It is hypothesized that by placing the ring around the pouch dilatation of the pouch is prevented and weight loss results could improve. However, there are concerns about long-term band related complications. Studies with a longer follow-up are necessary to determine the role of the banded RYGB in the field of bariatric and metabolic surgery.

Since metabolic surgery has been performed for approximately five decades now and the number of bariatric procedures is still increasing, there is also a rising demand for revisional metabolic surgery. This is because 10 to 35% of patient regain part of their weight after an initial good result or fail to achieve a sufficient amount of weight loss[36-38]. When conservative treatment to get these patients back on track do not improve results, revisional surgery can be taken into consideration after multidisciplinary evaluation.

Some revisional procedures, such as distalization of the gastric bypass, aim to induce hypoabsorption, whereas other interventions aim to increase restriction by adding an adjustable gastric band or by resizing ('trimming') the pouch[39,40]. Unfortunately, there is a paucity of high-quality studies on revisional surgery, and therefore, revisional surgery is mainly based on local experience. Therefore, there is a need for good clinical studies on this subject.

The aim of this thesis is to investigate how to improve clinical outcome by optimizing bariatric procedures, focusing on the laparoscopic Roux-en-Y Gastric bypass.

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CHAPTER 2

2

A longer biliopancreatic limb in Roux-en-Y gastric bypass improves weight loss in the first five year after surgery. Results of a randomized controlled trial.

Jens Homan, Abel Boerboom, Edo Aarts, Kemal Dogan, Kees van Laarhoven, Ignace Jansen, Frits Berends

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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 150cm, alimentary limb 75cm) was compared with a S-GB (BPL 75cm, alimentary limb 150cm). 146 Patients were randomized in two groups. Weight loss, morbidity, reduction of comorbidities, nutritional status and quality of life were measured during a period of four 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 difference between the groups was significantly as soon as 9 months postoperatively and continued throughout the follow up period.

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 four years. In this study the advantage of LBP-GB with respect to weight loss are modest, but show promising gripping points for future improvements in RYGB design.

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 it's 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 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 excepted)[11]. To a much lesser extent, the effect of the BP-limb on weight loss was studied. Observational studies report better weight loss with a longer BPL, but remarkably, standardized RCT's are practically non-existent[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 two 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, New Jersey, 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, New Jersey, USA) combined with running absorbable suture to close the stapling gap (V-loc, Medtronic, Minneapolis, Minnesota, 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-lock, Medtronic, Minneapolis, Minnesota, 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, New Jersey, 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 sized 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 two years, 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 two years, with a total of 15 follow-up moments. At 6 weeks, 3, 6, 12, 18 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 < 7mmol/L, HbA1c < 48mmol/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 (Fraxiparin 5700IU 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), 1500mg calcium and 2400 IU vitamin D3 lifelong on a daily base.

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 *t* tests for continue variables and Fisher exact-tests for categorical data. To adjust for the baseline covariates 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 to 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 endpoint 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 RCT's 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**).

Table 1. Baseline patient characteristics: no significant differences between patients with S-GB or LBP-GB

	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

S-GB standard Roux-en-Y gastric bypass, *LBP-GB* long biliopancreatic limb Roux-en-Y gastric bypass, *BMI* body mass index, ± standard deviation

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 four years and one patient withdrew for participation in the study after two 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 four years (**Figure 1**).

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 follow up with 85% versus 72% respectively (p=0.001). At this point, the difference in %TBWL was also significant. After four 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 two 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-GB group was still observed after four years, 70% in the LBP-GB group and 63% in the S-GB group (p=0.060), the difference was no longer significant.

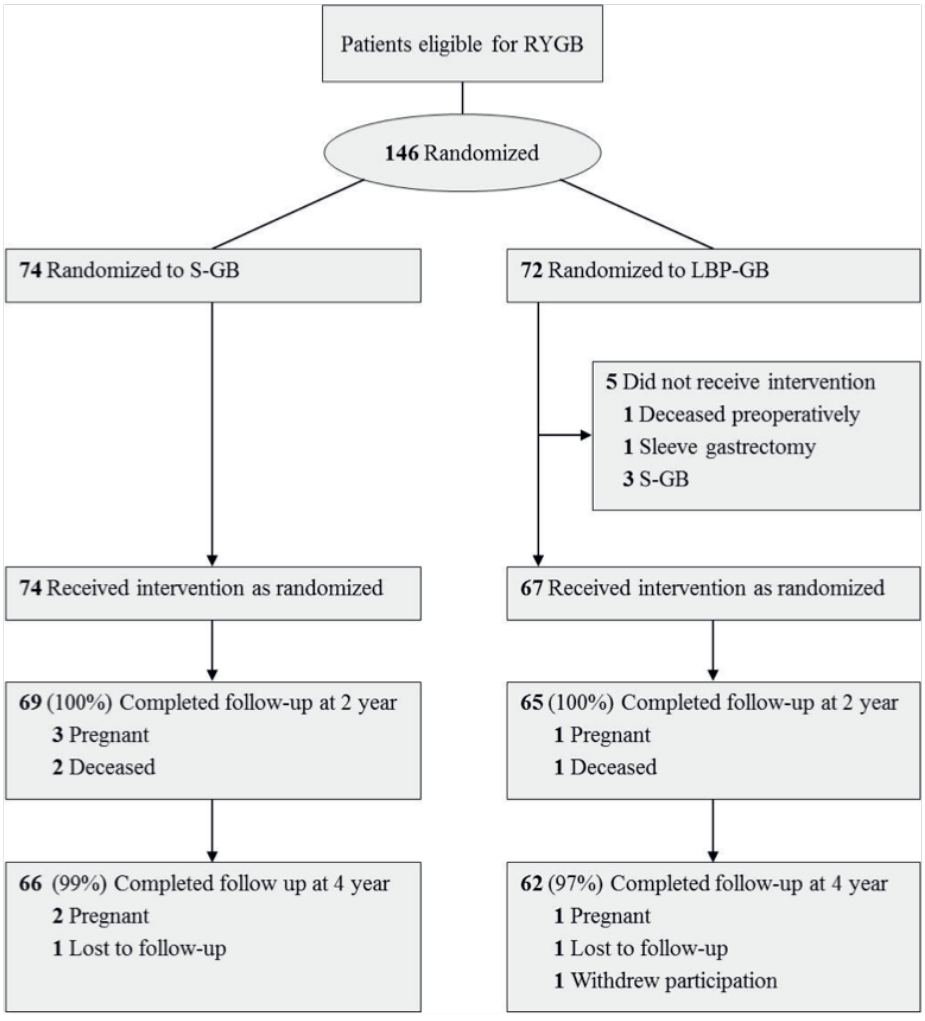

Figure 1. Flow diagram
S-GB standard Roux-en-Y gastric bypass. *LBP-GB* long biliopancreatic limb Roux-en-Y gastric bypass.

Table 2. Results on the weight loss parameters

		S-GB	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/m²	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

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

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.

Table 3. Resolution of obesity-related comorbidities

		S-GB	LBP-GB	*p*-value
Type 2 diabetes (%)		23 (31)	23 (34)	0.681
24 months	Remission	13 (59)	18 (78)	
	Improvement	8 (36)	5 (22)	0.290
	Unchanged	1 (5)	0	
	Type 2 diabetes de novo	0	0	
48 months	Remission	17 (77)	18 (78)	
	Improvement	4 (18)	5 (22)	0.572
	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)	
	Improvement	5 (21)	8 (24)	0.207
	Unchanged	3 (13)	10 (30)	
	Hypertension de novo	0	0	
48 months	Remission	14 (58)	18 (55)	
	Improvement	5 (21)	8 (24)	0.326
	Unchanged	3 (13)	7 (21)	
	re-Hypertension	2 (8)	0	
Dyslipidaemia (%)		66 (89)	58 (87)	0.797
24 months	Remission	25 (38)	30 (52)	
	Improvement	27 (41)	23 (40)	0.312
	Unchanged	9 (13)	3 (5)	
	Unknown	1 (2)	1 (2)	
	Dyslipidaemia de novo	4	1	
48 months	Remission	30 (50)	29 (52)	
	Improvement	20 (33)	24 (43)	
	Unchanged	10 (17)	1 (2)	**0,022**
	Unknown	0	2 (4)	
	Dyslipidaemia de novo	0	2	

S-GB standard Roux-en-Y gastric bypass, *LBP-GB* long biliopancreatic limb Roux-en-Y gastric bypass.

Table 4. Obesity-related comorbidities: biochemical and blood pressure changes

	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
Dyslipidaemia											
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

S-GB standard Roux-en-Y gastric bypass, *LBP-GB* long biliopancreatic limb Roux-en-Y gastric bypass, *BP* Blood pressure.
‡ 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 group
¶ 24 months postoperative scores between the S-GB and LBP-GB group
¶¶ 48 months postoperative scores between the S-GB and LBP-GB group

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 deceased. In the LBP-GB group 18 (78%) patients had a remission four 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 5**.

Table 5. Complete T2DM remission results with different guidelines

		S-GB	LBP-GB	*p*-value
24 months	Discontinuation of treatment and			
	HbA1c < 6.5% (%) [27]	13 (59)	18 (78)	0.165
	HbA1c < 6.0% (%) [22]	12 (55)	18 (78)	0.092
	HbA1c < 5.7% (%) [27,28]	10 (45)	14 (61)	0.300
48 months	Discontinuation of treatment and			
	HbA1c < 6.5% (%) [27]	17 (77)	18 (78)	0.936
	HbA1c < 6.0% (%) [22]	15(68)	17 (74)	0.672
	HbA1c < 5.7% (%) [27,28]	15 (59)	15 (65)	0.672

S-GB standard Roux-en-Y gastric bypass, *LBP-GB* long biliopancreatic limb Roux-en-Y gastric bypass

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 four 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 four 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 four 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 fraxiparin 5700IU 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 post mortem 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 whilst 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.

Table 6. Short-term complications. Patients could suffer from multiple complications

	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	

S-GB standard Roux-en-Y gastric bypass, *LBP-GB* long biliopancreatic limb Roux-en-Y gastric bypass.

Table 7. Complications that occurred after 30 days. Patients could suffer from multiple complications at the same time

	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 hypoglycaemia	1	0	
Mortality	1	0	

S-GB standard Roux-en-Y gastric bypass, *LBP-GB* long biliopancreatic limb Roux-en-Y gastric bypass.

Nutritional status

At year four of follow-up, 87% of the patients were using a Multi Vitamin Supplement (MVS) as prescribed. In addition, 75% of the patients were using calcium/cholecalciferol according to protocol. The percentage of patients with deficiencies after four years are 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.

Table 8. Anaemia and vitamin deficiencies: percentages preoperative and after 24 and 48 months

	S-GB			LBP-GB					
	0 m	**24 m**	**48 m**	**0 m**	**24 m**	**48 m**	***p****	***p*¶**	***p*¶¶**
Anaemia	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

S-GB standard Roux-en-Y gastric bypass, *LBP-GB* long biliopancreatic limb Roux-en-Y gastric bypass, *0 m* baseline, *m* months
p* (p-value) preoperative deficiency percentage between the S-GB and LBP-GB group
p¶ (p-value) 24 months postoperative deficiency percentage between the S-GB and LBP-GB group
p¶¶ (p-value) 48 months postoperative deficiency percentage between the S-GB and LBP-GB group

Quality of life

BAROS: To evaluate the results of both the S-GB and LBP-GB results of the 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.

Table 9. BAROS after 24 and 48 months postoperative

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

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.

Table 10. Outcomes in the RAND-36. The RAND-36 was measured preoperatively and 48 months postoperatively

	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

S-GB standard Roux-en-Y gastric bypass, *LBP-GB* long biliopancreatic limb Roux-en-Y gastric bypass.
* preoperative scores between the S-GB and LBP-GB group
¶ 24 months postoperative scores between the S-GB and LBP-GB group
‡ pre- versus 24 months postoperative scores of the total group
¶¶ 48 months postoperative scores between the S-GB and LBP-GB group
‡‡ pre- versus 48 months postoperative scores of the total group

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

It is no longer the 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 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 RCT's focused on comparison of alimentary limb length. However, despite maybe a slight effect on patients with higher BMI's (>50kg/m2) 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 RCT's on the BP-limb can be found, the quality of the studies lack 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 four 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[18]. In this group a "standard" BP limb length of 75 cm was chosen, which can be 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 meters wasn't detected in any of the patients that participated in the study.

It is notable that the favorable effects on weight loss in the first two 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 an 'one anastomosis gastric bypass' and in a SADI that on average is higher when compared to a standard gastric bypass in many reports[19-21]. 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 entero-enterostomy, 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[22-24]. This study fails to demonstrate these effects as outcomes were comparable between groups. Only the remission of DL 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 endpoint and probably underpowered for the secondary endpoints. 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 four years compares favorably to 72% found in a meta-analysis on this subject by Yu et al.[24]. This is illustrated by the change in HbA1c in both the S-GB and the LBP-GB groups (-2.1% and -1.9%), after four 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[25] found a higher concentration of bile acids in patients five 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.

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 Centre 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 hernia's. Although the mesenteric defect was routinely closed during surgery we did see internal hernia's, but there was no difference between groups.

Vitamin and mineral deficiencies are common after RYGB. Especially deficiencies for ferritin, vitamin B12 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.

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[26]. 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 relatively high 30-day mortality. It is a matter of debate if a difference in EWL of 13% has clinical significance as the equivalent in kilo's is on average no more than 3-5 kg's. At an average weight loss of 37 kg after two 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 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 number 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 meter 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 four years. In this study the advantage of LBP-GB with respect to weight loss and comorbid disease are modest but show promising gripping points for future improvement in gastric bypass design.

Conflict of interest

All authors declare to have no conflict of interest

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CHAPTER 3

A longer biliopancreatic limb results in more weight loss in revisional RYGB surgery. Outcomes of the ELEGANCE trial.

Abel Boerboom, Jens Homan, Edo Aarts, Theo Aufenacker, Ignace Janssen, Frits Berends

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Abstract

Background

For a number of years, the laparoscopic adjustable gastric band (LABG) has been one of the leading bariatric procedures with good short term outcomes. However, inadequate weight loss, weight regain and other band-related complications in the long term led to an increase in revisional Roux-en-Y gastric bypass procedures. Lengthening the biliopancreatic limb, a relatively simple and safe adjustment of the standard technique, could improve the results of the revisional procedure.

Objectives

The aim of this randomized controlled trial was to evaluate the effect of a long biliopancreatic limb Roux-en-Y gastric bypass (LBP-GB) and standard Roux-en-Y gastric bypass (S-GB) as revisional procedure after LAGB.

Setting

General hospital specialized in bariatric surgery

Methods

146 patients were randomized in two groups; 73 patients underwent a S-GB (alimentary/biliopancreatic limb 150/75 cm) and 73 patients a LBP-GB (alimentary/biliopancreatic limb 75/150). Weight loss, remission of comorbidities, quality of life and complications were assessed during a period of four years.

Results

Baseline characteristics between the groups were comparable. At 48 months, follow up rate was 95%. Mean TBWL after 24 months was 27% for LBP-GB versus 22% S-GB ($p=0.015$) and after 48 months 23% and 18% respectively ($p=0.036$). No significant differences in other parameters were found between the groups.

Conclusions

A LBP-GB as revisional procedure after a failing LAGB improves short- and long-term TBWL compared to a S-GB. Together with future modifications this technically simple adjustment of the RYGB could significantly improve disappointing results after revisional surgery.

Introduction

For a number of years the laparoscopic adjustable gastric band (LABG) has been one of the leading bariatric procedures with good short term outcomes [1,2]. However, inadequate weight loss, weight regain and other band-related complications in the long term led to the fast worldwide decrease in LAGB procedures[3,4]. Most failed LABG are converted to a Roux-en-Y gastric bypass (RYGB), as band removal alone results in weight regain and deterioration of comorbidities in most patients, even when patients had reached an adequate weight loss at time of explantation[3,5,6,7]. The RYGB as revisional surgery can be technically demanding but can be performed with acceptable perioperative morbidity as a one stage procedure when performed by experienced surgeons[3]. Compared to better results after primary procedures, Fournier et al[8] reported a total body weight loss (TBWL) of 28-30% after two years of follow up and Aarts[3] et al an excess weight loss (EWL) of 53% after revisional RYGB. Especially patients who did not achieved sufficient weight loss with a LAGB seem to have a lower success rate after revisional RYGB compared to good responders after LAGB[8].

The basic design of the RYGB has hardly been changed since the introduction in 1966 by Mason[10] and a relatively longer alimentary (Roux) limb (AL) and a short biliopancreatic limb (BPL) are still used in most primary and revisional procedures[11]. Research from our center suggests that lengthening the BPL results in significantly more weight loss in primary RYGB [not yet published data]. This advantage of a relatively simple and safe adjustment of the standard technique could improve the inferior results of the revisional procedure. To this date, no other studies compared limb length in revisional surgery.

The aim of this single blind randomized controlled trial was to evaluate the effect of a long biliopancreatic limb Roux-en-Y gastric bypass (LBP-GB) and standard Roux-en-Y gastric bypass (S-GB) as revisional procedure after LAGB.

Methods

The protocol of this randomized, controlled, parallel-group, single-center trial was reviewed and approved by the central medical committee for research in humans in Nijmegen, the Netherlands (CMO) and registered at the clinical trials registry of clinicaltrials.gov (NCT 01686997) and 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 adult patients (age ≥ 18 years) with a failing LAGB due to insufficient weight loss, weight regain or other band-related complication that were planned to be converted to a RYGB

were approached and informed about trial design. After receiving explanation of the study setup, risks and possible benefits during consultation and through a written information brochure, patients were given two weeks time to consider participation, written informed consent was documented thereafter. All patients were evaluated if in- and exclusion criteria according to the IFSO guidelines ((Body Mass Index (BMI) >40 kilogram (kg)/meter (m)^2 or >35 kg/m^2 with the presence of at least one comorbidity) were considered applicable by a multidisciplinary team, including a bariatric surgeon, a nutritionist, a psychologist, endocrinologist and a physiotherapist before being fully approved for revisional surgery. A form of inflammatory bowel disease, a language barrier and renal dysfunction (GFS <30min) were additional exclusion criteria for this study.

Primary and secondary endpoints

Primary endpoint of the study was percentage total body weight loss (%TBWL) over a period of four years. The %TBWL was defined as weight loss divided by total body weight before revisional RYGB. The weight before revisional surgery was used since weight loss due to revisional surgery was analyzed regardless of the initial weight before primary surgery. Secondary endpoints were reduction of obesity related comorbidities (type 2 diabetes (T2DM), hypertension (HT) and dyslipidemia (DL)), perioperative complications and quality of life (QoL).

Surgical procedures/operation techniques

Standard revisional RYGB (S-GB)

Four experienced bariatric surgeons (>1000 RYGB cases) performed the procedures. A standardized operation technique was used in which the band was removed and a RYGB was performed. All revisional operations were performed laparoscopically. After introduction of the trocars in the abdominal cavity adhesions were carefully released and the anatomic structures were identified. On the anterior side the band was released from the stomach, opened and removed. Fibrotic tissue on the stomach due to the band was released by cleaving the fibrotic ring on the anterior side of the stomach. Distal of the former position of the band a gastric pouch was constructed using a linear stapler (Echelon, Ethicon, Johnson & Johnson, New Brunswick, New Jersey, USA). The BPL of 75cm was measured from the ligament of Treitz using a tapeline under medium stretch along the mesenteric border. The AL was placed antecolic and antegastric and the end-to-side gastro-jejunostomy was created using a linear stapler (ETS, Ethicon, Johnson & Johnson, New Brunswick, New Jersey, USA) combined with a running suture to close the stapling gap (V-loc, Medtronic, Minneapolis, Minnesota, USA). The AL of 150cm was measured with a tapeline under medium stretch and a side-to-side entero-enterostomy was made using a 60 mm linear stapler combined with a running suture. The gastric pouch staple-line and the gastro-jejunostomy were tested intraoperative for integrity for leakage with an air leakage

test and mesenteric defects were closed with a double layer of hernia staples (EMS, Ethicon, Johnson & Johnson, New Brunswick, New Jersey, USA).

Long biliopancreatic limb revisional RYGB (LBP-GB)
The same standardized operation as described above was performed, but with different limb lengths. A 150cm BPL and a 75cm AL was used. In both procedures a combined total length of 225 cm of small intestine was used for the BPL and AL.

Randomization

The local study coordinator performed the randomization of patients. A web-based randomization module (Research Manager, Nova Business Software, Zwolle) with a 1:1 allocation ratio and concealed carrying permuted block size of two and four patients was used. Due to the invasive nature of the procedure and the logistics investigators and surgeons were not blinded for group allocation. The patients however were not aware which procedure they had received during operation and during the complete follow up, making this a single blind randomized controlled trial.

The hypothesis that the LBP-GB leads to a 5% higher TBWL after two years was used for sample size calculation. Using a 80% power, an alpha of 5%, a SD of 10% and taking into account 10% lost to follow up 70 patients were needed in both groups. Finally, slightly more than 146 patients were randomized.

Assessment

Preoperatively all patients underwent anesthesiological screening and blood samples were taken, in which serum levels of ferritin, folic acid, vitamin B12, 25-hydroxyvitamin D (25-OHD) and parathyroid hormone (PTH) were determined. When any deficiencies were detected they were corrected before surgery.

To prepare patients for the different lifestyle required postoperatively they followed obligatory sessions at the Dutch Obesity Clinic where they received nutritional, psychological and physical counseling. In the postoperative phase these sessions continue until six years after surgery. Additionally, patients came for a medical control on a regular basis (6 weeks, 3,6,9,12,18 and 24 months) after surgery. After two years the medical controls were scheduled annually. During these control visits the patients' weight, BMI, medication use, eating habits and blood values were assessed. Deficiencies in vitamins were defined as a value below the lower normal limit as stated in the ASMBS guidelines[12]. The Bariatric Analysis and Reporting Outcome System (BAROS)[13] and the RAND-36 were used to evaluated the changes in the Quality of Life (QoL).

Obesity related comorbidities that were investigated were T2DM, HT and DL. T2DM was defined as a fasting plasma glucose ≥ 7 mmol/L and/or HbA1c ≥48 mmol/mol (HbA1c ≥ 6.5%) or the use of oral antidiabetic medication or insulin, HT was defined as the use of antihypertensive medication and DL was defined as the use of statins. Changes in T2DM was defined as *remission* when a fasting glucose < 7 mmol/L, a HbA1c < 48 mmol/mol (Hba1c < 6.5%) and a discontinuation of all T2DM medication for at least a year was achieved. *Improvement* was defined as a reduction in treatment medication and *unchanged* when no difference to the preoperative status was seen. Remission of HT was defined as *remission* when a discontinuation of medical treatment was achieved, *improvement* as reduction in treatment and *unchanged* when no difference to the preoperative status. The same definitions for remission of DL were used. However, *improvement* is not a sensible outcome measure in DL since partial reduction of treatment is not really possible.

Postoperative medication and supplements

After the operation the patient started intake with clear liquids as soon as two hours after surgery. The first postoperative day oral feeding was expanded. Postoperative fraxiparin 5700IU anti-XA once daily as thrombosis prophylaxis for four weeks and 20 mg of omeprazole for seven months to protect the gastroenterostomy were prescribed. Patients were also prescribed specialized bariatric supplements for RYGB patients (FitforMe, Rotterdam, The Netherlands), 1500mg calcium and 2400IU vitamin D3 lifelong on a daily base.

Statistical analysis

All data was analyzed using IBM® SPSS® (version 21.0 Windows). Primary and secondary outcomes are presented as mean values with standard deviation. Continuous variables were analyzed using an independent *t* test and categorical data were analyzed using Fisher exact-test. All tests were two-tailed and a p-value <0.05 was considered statistically significant.

Results

From July 2012 to December 2013, 146 adult patients with a failing LABG who were scheduled to undergo revisional RYGB were entered in the study. 73 Patients were randomized to undergo a S-GB and 73 a LBP-GB. In both groups one patient was excluded. In the S-GB group one patient because during surgery it turned out that the patient had not received an earlier LAGB in a different center despite the report in the medical file and in the LBP-GB group one patient appeared to have a intestinal malrotation during surgery making the LBP-GB she was scheduled for impossible to perform. These protocol violations were excluded for the 'per protocol' analysis of the primary and secondary outcomes. In the 'intention to treat' analysis all patients were included. The baseline characteristics did

not differ significantly between groups. The major reason for conversion of the LAGB to a RYGB was weight regain, 67% in the S-GB group and 76% in the LBP-GB group (**table 1**). At 48 months the follow up rate was 95%. Despite our persistent efforts seven (5%) patients were lost to follow up after four years (**figure 1**).

Table 1. Baseline patient characteristics

	S-GB	LBP-GB
Number of patients	72	72
Female (%)	57 (79)	61 (85)
Age, years	47±7	47±9
Height, cm	170±8	170±9
Weight, kg	121±16	123±20
BMI, kg/m^2	42±4	43±5
BMI pre-LAGB, kg/m^2	47±6	47±6
Indication revision (%)		
Insufficient weight loss	10 (14)	12 (17)
Weight regain	55 (76)	48 (67)
Band intolerance	5 (7)	10 (14)
Band related complications	2 (3)	2 (3)

S-GB standard Roux-en-Y gastric bypass, *LBP-GB* long biliopancreatic limb Roux-en-Y gastric bypass, *BMI* Body Mass Index, *LAGB* laparoscopic adjustable gastric band, ± standard deviation

Weight loss

The LBP-GB group achieved a significantly higher percentage TBWL after six months postoperatively. This significant difference was seen throughout the complete follow up period of four years. After 24 months both groups reached their maximum TBWL, 22% in the S-GB group and 27% in the LBP-GB group (p=0.015). Although both groups regained weight a significant difference in favor of the LBP-GB group was still seen after four years, 18% versus 23% (p=0.036). The results of the weight parameters are shown in **table 2**. When applying the 'intention to treat' principle results remain significant at the same time-points.

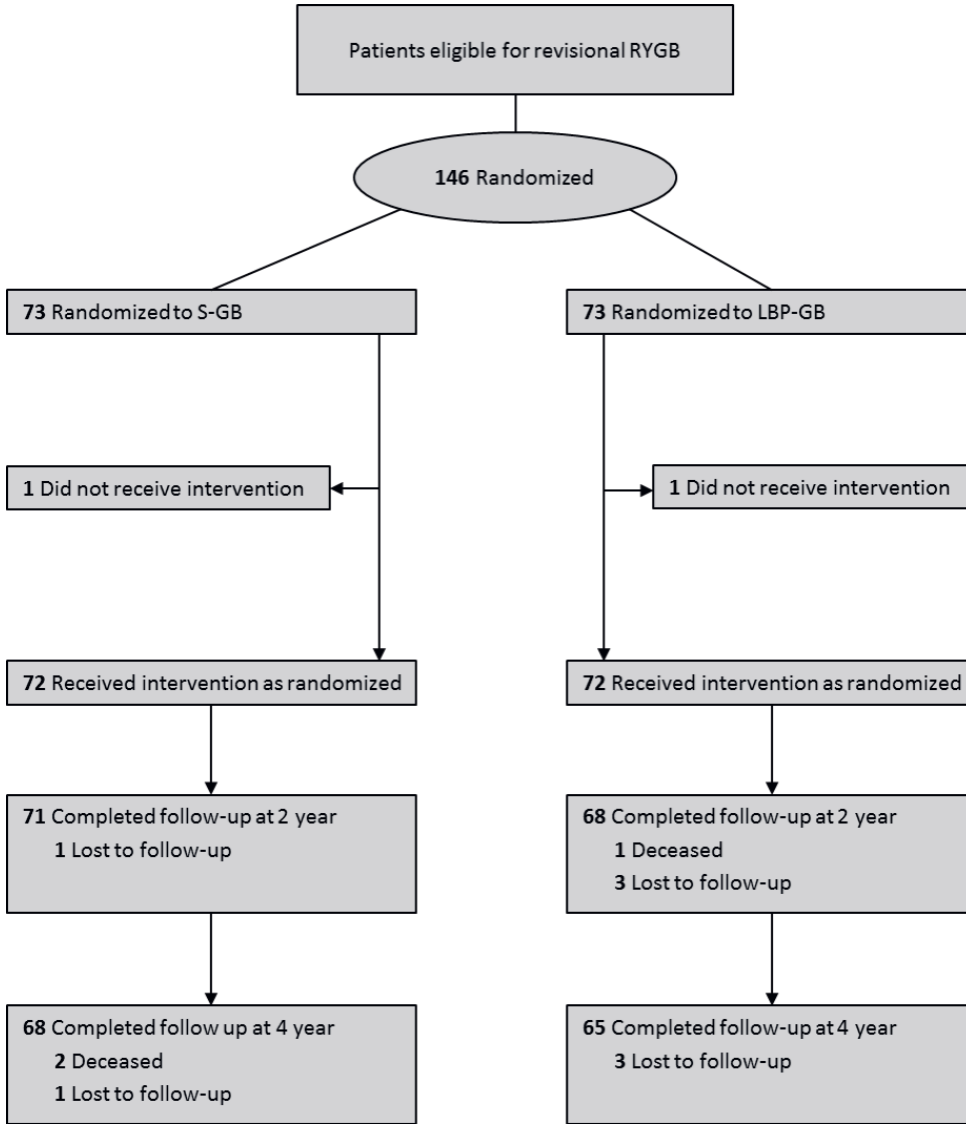

Figure 1. Flow diagram: number of patients during follow-up
S-GB standard Roux-en-Y gastric bypass, *LBP-GB* long biliopancreatic limb Roux-en-Y gastric bypass

Table 2. Weight loss parameters

		S-GB	sd	LBP-GB	*sd*	*p*-value
%EWL	12 months	59	23	66	21	0.094
	24 months	58	27	67	26	**0.045**
	36 months	51	29	61	29	**0.043**
	48 months	47	28	57	32	0.078
%TBWL	12 months	23	8	26	9	**0.021**
	24 months	22	10	27	11	**0.015**
	36 months	20	11	24	12	**0.014**
	48 months	18	10	23	12	**0.036**

S-GB standard Roux-en-Y gastric bypass, *LBP-GB* long biliopancreatic limb Roux-en-Y gastric bypass, *EWL* excess weight loss, *TBWL* total body weight loss, *sd* standard deviation

Resolution of comorbidities

The patients that achieved resolution of the most common obesity related comorbidities are listed in **table 3** and the changes in biochemical parameters and blood pressure are shown in **table 4**.

Type 2 diabetes mellitus: at baseline 24 (17%) patients were diagnosed with T2DM, fifteen (21%) in the S-GB group and nine (13%) in the LBP-GB group. Both groups included patients, four in the S-GB and three in the LBP-GB group, with a glucose intolerance (fasting serum glucose ≥ 7mmol/L and/or HbA1c ≥48 mmol/mol) at screening without using oral antidiabetic medication or insulin. In 73% of the patients in the S-GB and in 67% in the LBP-GB group surgery resulted in at least an *improvement* after 48 months. Remission of T2DM two years after surgery, when maximum weight loss was achieved, was achieved in 67% in the S-GB and 78% in the LBP-GB (p=0.824). No significant difference was found between the groups.

Hypertension: In the S-GB group 21 (29%) patient were diagnosed with HT and surgery resulted in remission in 5 (28%) patients after 48 months. In the LBP-GB group 24 (33%) patients were diagnosed with hypertension and remission occurred in 7 (29%). No significant difference was found between the groups after 48 months, nor after 24 months. The mean systolic and diastolic blood pressure significantly decreased in both groups without significant differences between the groups.

Dyslipidemia: Based on the use of statin a total of 20 (14%) patients suffered of DL at baseline. After four years 12 (60%) patients achieved remission, 8 (62%) in the S-GB group

and 4 (57%) in the LBP-GB group. No significant differences in remission rate or in improved lipid biochemical chemical parameters were found between the groups.

Table 3. Remission of co-morbidities

		S-GB	LBP-GB	*p*-value
Type 2 diabetes (%)		15 (21)	9 (13)	0.180
24 months	Remission	10 (67)	7 (78)	
	Improvement	3 (20)	1 (11)	0.824
	Unchanged	2 (13)	1 (11)	
48 months	Remission	9 (60)	5 (56)	
	Improvement	2 (13)	1 (11)	0.791
	Unchanged	1 (7)	0	
	Unknown	3 (20)	3 (33)	
Hypertension (%)		18 (25)	24 (33)	0.271
24 months	Remission	7 (39)	12 (50)	
	Improvement	5 (28)	2 (8)	0.332
	Unchanged	6 (33)	9 (38)	
	Unknown	0	1 (4)	
48 months	Remission	5 (28)	7 (29)	
	Improvement	4 (22)	3 (13)	0.587
	Unchanged	3 (17)	8 (33)	
	Unknown	6 (33)	6 (25)	
Dyslipidemia (%)		13 (18)	7 (10)	0.242
24 months	Remission	9 (69)	5 (71)	0.843
	Unchanged	4 (31)	2 (29)	
48 months	Remission	8 (62)	4 (57)	0.640
	Unchanged	5 (39)	3 (43)	

S-GB standard Roux-en-Y gastric bypass, *LBP-GB* long biliopancreatic limb Roux-en-Y gastric bypass

Complications

A total number of 14 (10%) patients suffered a short term complication, 6 (8%) patients in the S-GB group versus 8 (11%) patients in the LBP-GB group ($p>0.05$). In total 3 (4%) patients underwent a reoperation. One anastomotic leakage occurred in in both groups. One patient in the LBP-GB group underwent reoperation because of the suspicion of a bleeding however a focus was not found. All the short-term complications are listed in **table 5**.

A long term complication occurred in 30 (21%) patients, fifteen patients in both groups. In total, 30 reoperations were performed, most (nine) of which were cholecystectomies, which is a common phenomenon after bariatric surgery. Four patients in both groups were re-operated because of a suspicion of an internal herniation, which was confirmed and corrected is one patient in the S-GB group and in in three patients the LBP-GB group.

During the follow up period three patients (4%) died. In the S-GB group one patient died from a cerebral hemorrhage and in the LBP-GB group as a result of a metastasized cervix carcinoma. In the S-GB one patient underwent a laparoscopy for reasons of weight regain and was converted to a distal RYGB. One week postoperatively this patient underwent a laparotomy because of a blow-out of the stomach remnant. Despite all efforts this patient developed multi-organ failure and died two weeks after. All long-term complications are listed in **table 5**.

Table 5. Short and long term complications

	S-GB	LBP-GB	*p*-value
Short term			
Total number of patients (%)	6 (8)	8 (11)	0.780
Reoperation	3	3	
Leakage	1	1	
Bleeding	2	0	
Other	0	2	
Conservative treated bleeding	1	0	
Superficial wound infection	3	2	
Readmission	1	3	
Mortality	0	0	
Long term			
Total number of patients (%)	15 (21)	15 (21)	1.000
Reoperation	14	16	
Cholecystectomy	4	5	
Internal herniation	1	3	
Adhesion	2	2	
Suspicion of internal herniation	3	1	
Perforation gastroenterostomy	0	1	
Hernia cicatricalis	2	2	
Other	2	2	
Stomach ulcer	2	1	
Dysphagia	2	0	
Mortality	2	1	

S-GB standard Roux-en-Y gastric bypass, *LBP-GB* long biliopancreatic limb Roux-en-Y gastric bypass

Nutritional status

The percentage of patients using multivitamins as prescribed according to protocol decreased from 62% after two year to 55% after four years. After 48 months 66% of the non-users developed a deficiency compared to 34% of the users according to protocol. The number of patients with a deficiency preoperative and after two and four years are listed in **table 6**. No significant differences were found between the groups.

Table 6. Nutritional and vitamin deficiencies

	S-GB			LBP-GB					
Deficiency %	**0 m**	**24 m**	**48 m**	**0 m**	**24 m**	**48 m**	***p****	***p****	***p****
Hemoglobin	8	5	4	4	6	4	0.494	0.719	1.000
Folic acid	1	0	2	0	0	2	1.000	1.000	1.000
Vitamin B_{12}	19	19	15	21	20	9	1.000	0.827	0.572
Ferritin	22	24	29	11	22	29	0.116	0.836	1.000
Vitamin D	63	20	11	54	19	9	0.307	1.000	1.000

S-GB standard Roux-en-Y gastric bypass, *LBP-GB* long biliopancreatic limb Roux-en-Y gastric bypass, *0 m* Baseline, *m* months
* (p-value) preoperative scores between the S-GB and LBP-GB group
** (p-value) 24 months scores between the S-GB and LBP-GB group
*** (p-value) 48 months scores between the S-GB and LBP-GB group

Quality of life

BAROS: The results of the BAROS scores are presented in **table 7**. At the point of maximum weight loss at two years the mean BAROS score in both groups was 3.4 ($p>0.05$). Still after four years a total of 80% of the patients had a result of 'fair' and up with a mean BAROS score of 3.2 in the S-GB group and 3.0 in the LBP-GB group ($p>0.05$).

RAND-36: A significant improvement in several domains is seen after 24 and 48 months in all patients compared to the preoperative values. Only after 24 months there is a significant difference seen between the S-GB group and the LBP-GB group in the domain physical functioning (*****) in favor of the LBP-GB group. Results of the RAND-36 scores are presented in **figure 2**.

Table 7. BAROS score

	S-GB	LBP-GB	*p*-value
BAROS 24 months postoperative			
Excellent	3%	0	0.981
Very good	28%	29%	
Good	39%	26%	
Fair	10%	34%	
Failure	21%	11%	
BAROS 48 months postoperative			
Excellent	6%	0%	0.822
Very good	22%	18%	
Good	22%	31%	
Fair	31%	33%	
Failure	19%	18%	

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

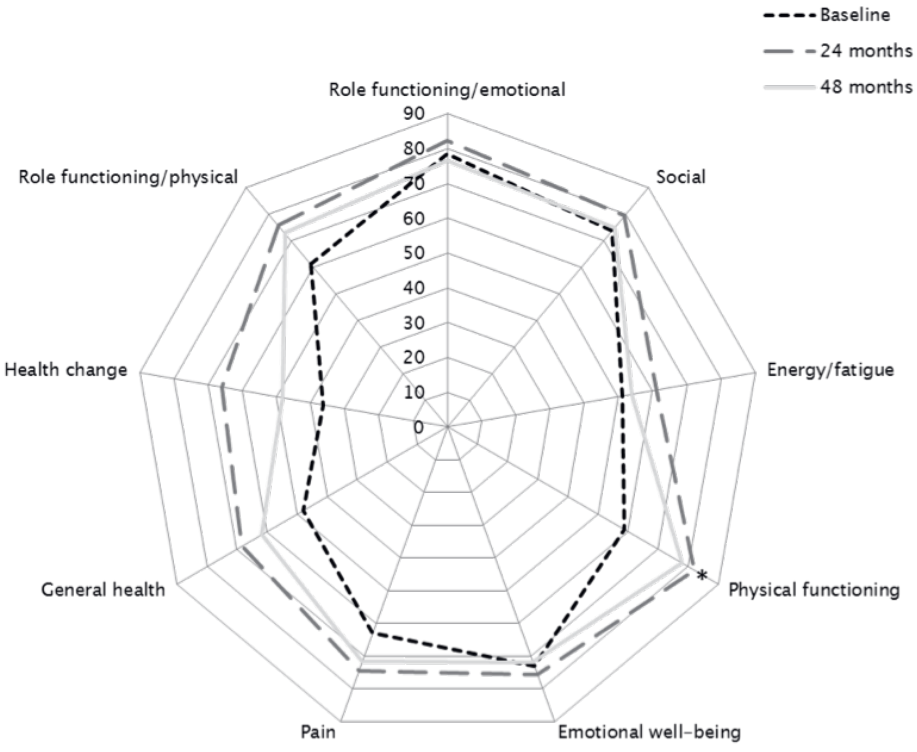

Figure 2. RAND-36 score total group

Discussion

Poor mid- and long-term results after LAGB resulted in an increase of revisional bariatric surgery worldwide[3,4]. To prevent weight regain after band removal or to obtain secondary weight loss, removal is often combined with conversion to another bariatric procedure, most often a RYGB [3,5-7]. It is notable that weight loss results after conversion of LAGB to a RYGB are on average worse than after primary procedures[3,8]. The mechanisms leading to this observation are not fully understood but one of the factors may well be patient selection, since revision is often considered only after either insufficient weight loss or weight regain. To improve weight loss outcomes after revisional surgery an adjustment in RYGB design could help to produce results that are more pronounced and sustainable.

Gripping points for adjustments in RYGB design are limb lengths, pouch size and gastro-enterostomy passage by adding a non-adjustable gastric band[14-17]. For many years AL length is held responsible for weight loss results after RYGB and is therefore studied most. However, several RCT's and a systematic review on AL limb length show that lengthening the AL does not result in additional weight loss after RYGB, except maybe in e selected group of patients with BMI > 50 kg/m2[14].

The length of the BPL is studied to a much lesser extent. An exceptional good weight loss is described in some none-randomized studies, but most studies lack sufficient standardization and follow up[15,18,19]. To our knowledge, this is the first study in which the length of the BPL in revisional RYGB is studied and moreover, the first randomized controlled trial in which results of revisional surgery after a failed LAGB are described.

In this RCT a significantly better %TBWL was seen from 6 months to 4 year postoperatively, with a maximum of 27% in the LBP-GB group versus 22% in the S-GB group after 24 months. Both the %TBWL after LBP-GB and after S-GB at two years in the present studies are high compared to results after revisional surgery published in literature. A possible explanation could lie in the fact that even for our S-GB an already relatively long BPL of 75 cm is used, which is more than in most other studies[3,8].

A possible explanation for the above average results in the LBP-GB group could be a more pronounced 'hindgut' effect that arises with lengthening of the BPL. Due to the delivery of nutrients to a more distal L-cell rich part of the small intestine an increased postprandial GLP-1 response arises[20,21], which theoretically reduces appetite and gastrointestinal motility eventually leading to better weight loss in the LBP-GB group. Alternatively, the results in the LBP-GB group could be explained using the 'foregut' hypothesis. Creating a longer BPL results in a larger part of the small intestine that is excluded from ingested nutrients

with the result less production of foregut hormones that contribute to the development of obesity and diabetes.

Results of this study raise the question if an even longer BP limb of 200-250 cm would also lead to even more weight loss, yet an ideal length for all limbs is still a matter of debate. However, it should be kept in mind that that at some point the total length of excluded intestine would lead to a short common channel and subsequent malabsorptive issues. In the present study the mean length of the common channel was 395 cm (measured in 27% of the patients), leaving room for a longer BP limb in most cases, especially if it is combined with a shorter AL. As AL-limb length does not seem to influence weight loss a minimum of 60cm, just to prevent reflux theoretically suffices.

Although a significant difference is found in weight loss between the groups, this study fails to demonstrate a significant difference in secondary outcomes such as: remission of type 2 diabetes, hypertension and dyslipidemia. This is in contrast with literature in which an improved remission of co-morbidities is found when weight loss increases[22-24]. However, this study was powered for weight loss and is probably underpowered for finding a significant differences in these secondary endpoints. Still, the results of the remission of especially type 2 diabetes and hypertension in this study are good compared to other studies reporting results after revisional surgery.

The LBP-GB is not technically more difficult to perform, which is illustrated by comparable complication rates in both groups. Although revisional surgery after a failed LAGB seems safe, a higher complication rate compared to primary procedures is described[25]. In this study a complication rate of 21% in both groups seems high, but that is partly attributed to the fact that cholecystectomy is counted as a complication after bariatric surgery. When cholecystectomies are left out the overall complication rate in this study decreases to 15% which is in line with results from the literature. In the past it is was suggested that lengthening the BPL results in a higher incidence of internal herniation's. The total number of only four cases in this study does not seem to confirm that claim.

Theoretically lengthening the BPL could lead to more vitamin and mineral deficiencies due to exclusion of a longer part of duodenum and proximal jejunum. Ferritin uptake for example takes place in the first part of the small intestine. However, no differences in deficiencies were found between the procedures during follow-up. Although only 55% of patients was using the specialized multivitamins after four years as prescribed no increase of the total number of deficiencies was seen. This may be a result from the fact that patients with an established deficiencies during follow-up received additional supplementation. It is very likely that possible differences between groups were corrected in this way.

Weight loss after bariatric surgery is associated with improvement of QoL, especially where the physical aspects are concerned[26]. In this study, the RAND-36 showed significant improvement in almost all physical domains after 24 and still after 48 months. In contrast to the significant difference in weight loss found in this study no differences were seen between groups in QoL using the BAROS score, not even after two years when weight loss was at his 'high' point. Perhaps the slightly inferior weight loss results, only taken into account in the BAROS score, compared to primary RYGB patients and the already adjusted expectations of bariatric surgery in revisional RYGB patients could play a role in this.

Patients with a LAGB eligible for revisional surgery often have a history of severe symptoms or disappointing results prior to revisional surgery. Given the fact that revisional surgery on average has worse outcomes in terms of weight loss it seems wise to manage unrealistic expectations in an early phase. It is questionable if an additional 5% TBWL, which roughly translates to a weight of 5 kilograms, has great clinical relevance. However, limb length is not the only gripping point for RYGB adjustment. Other factors, among which pouch design, length and pouch-banding are studied in a primary RYGB RCT in our center, in search of the optimal design [CilicalTrials.gov number NCT02218957 and NCT02545647]. Also, the diameter of the gastrojejunal anastomoses could be the subject of debate. When proven effective in primary RYGB patients all adjustment together may further improve weight loss in revisional RYGB surgery.

Conclusion

A LBP-GB as revisional procedure after a failing LAGB improves short- and long-term TBWL compared to a S-GB. Together with future modifications this technically simple adjustment of the RYGB could significantly improve disappointing results after revisional surgery.

Conflict of interest

All authors declare to have no conflict of interest

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CHAPTER 4

An extended pouch in a Roux-en-Y gastric bypass reduces weight regain: three year results of a randomized controlled trial.

Abel Boerboom, Mellody Cooiman, Edo Aarts, Theo Aufenacker, Eric Hazebroek, Frits Berends

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Abstract

Background

Although the Roux-en-Y gastric bypass (RYGB) is considered a standard procedure, many variations exist in the basic design. In order to achieve more pronounced and sustainable results after RYGB, factors such as diameter of the gastroenterostomy, limb length and pouch size are gripping points for improvement of design. Extending the pouch could improve results by altering food passage through the pouch.

Objective

The aim of this randomized controlled trial was to evaluate the effect of an extended pouch RYGB (EP-GB) and standard pouch RYGB (S-GB).

Methods

In total, 132 patients were randomized in two groups: 68 patients received an EP-GB (pouch length 10 cm) and 64 a S-GB (pouch length 5 cm). Subsequently, weight loss, remission of comorbidities, nutritional status, complications, quality of life and GERD-symptoms were assessed during a follow-up of three years.

Results

During the first two years of follow-up no significant differences in terms of weight loss were observed. In the third year of follow-up the S-GB group regained 3 kg, while in the EP-GB group no weight regain was observed. The mean TBWL after 36 months in the EP-GB group was 31% versus 27% in the S-GB group (p=0.023). Additionally, besides a better remission rate of hypertension in the EP-GB group, no differences in complications, quality of life and GERD-symptoms were found.

Conclusion

Creation of an extended gastric pouch is a safe and effective modification in RYGB design. An EP-GB improves mid-term weight loss, potentially driven by a lower occurrence of weight regain.

Introduction

Since the introduction of the gastric bypass in 1966 by Mason there only have been a few changes in its basic design. After adding the Roux-en-Y construction in 1977 no other essential alterations are done to the original design[1,2]. Although the gastric sleeve is currently the most popular bariatric procedure worldwide, over the years the RYGB has been performed in most patients. Especially when type 2 diabetes is present, the RYGB is often the preferred bariatric treatment[3,4]. Although the RYGB is considered a standard procedure, many different versions of the same procedure are used. No international standards or guidelines exist for possibly relevant anatomical features such as: stoma size, limb length, pouch size and volume[5,6]. The growing awareness about the metabolic rather than mechanical effects of bariatric surgery have warranted a more critical look at gastric bypass construction. In this study we looked specifically at pouch shape and length.

There are numerous studies regarding pouch size and the influence on weight loss and complications, but the majority are descriptive and observational studies and it proves hard to draw any conclusions from them[7-11]. Many studies focus on using a smaller pouch, yet mostly without demonstrating a correlation between pouch volume and weight loss[7-9]. Observational studies do report a reduced risk of marginal ulcers in patients with a small pouch, which is attributed to the scarcity of parietal cells proximal in the stomach[12,13].

In the past it was postulated that the combination of restriction and malabsorption was the working mechanism of the RYGB. However, further research led to a growing awareness of the metabolic effect of the small intestine contributing to weight loss and reduction of comorbidities after bariatric surgery. Duration of pouch passage and gastric emptying seem to affect this metabolic mechanism, since Deden et al found a relatively fast pouch emptying in patients with poor weight loss after RYGB surgery[14]. Following established laws of physics a longer pouch may delay passage which in turn could affect intestinal function[6]. In that respect pouch size could be one of the gripping points for RYGB design improvement.

This article (The Extended Pouch trial) reports the results of a RCT looking specifically at pouch length. It is part of a series of three randomized controlled trials (RCTs) studying the possible gripping points to optimize the RYGB, the other two being: the Elegance trial (limb length)[15] and the Bandolera trial (banded bypass, not yet published). The aim of the present study was to compare the effect on weight loss, reduction of comorbidities and complications of an extended pouch gastric bypass (EP-GB) with our standard pouch gastric bypass (S-GB)(**Figure 1**).

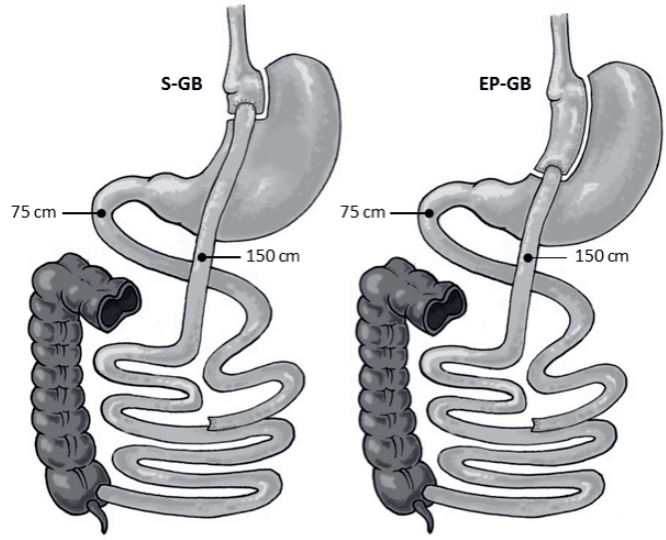

Figure 1. Surgical procedures
S-GB standard pouch Roux-en-Y gastric bypass, *EP-GB* extended pouch Roux-en-Y gastric bypass

Methods

This study (The Extended Pouch trial) was designed as single (high volume bariatric) center, single-blinded, randomized controlled trial. The study protocol is approved by the Central Medical Committee for Research in humans in Nijmegen and the local ethics committee in Arnhem and is registered at the clinical trials registry of clinicaltrials.gov (NCT02218957). This study was in accordance with the Declaration of Helsinki.

Patients

Patients eligible for primary gastric bypass surgery according the IFSO criteria (BMI > 40 kg/m^2 or >35 kg/m^2 with an obesity related comorbidity) who were referred to our center were approached by the surgeon for participation in the study. A history of bariatric surgery, any form of inflammatory bowel disease, renal dysfunction (GFS <30min) and therapy resistant reflux disease were additional exclusion criteria for this study. When interested, patients received additional information about the study, potential risks and benefits. Patients had two weeks to consider participation. To officially confirm participation in the study written informed consent was obtained from each patient in twofold.

Surgical procedures (S-GB and EP-GB)

Four experienced bariatric surgeons (>500 RYGB cases) performed all procedures. A standardized laparoscopic technique was used for this study. An antecolic antegastric RYGB

with a alimentary limb of 150 cm and a biliopancreatic limb of 75 cm was performed. To create the standard gastric pouch the first blue 60 mm lineal stapler (Echelon, Ethicon, Johnson & Johnson, New Brunswick, New Jersey, USA) was placed five cm below the angle of His at right angle to the minor curvature of the stomach. The small proximal pouch was finished using two 60 mm staplers placed against a 40 French stomach tube. The extended pouch was created firing the first stapler ten cm below the angle of His (four cm proximal of the pylorus) and was finished using three blue 60 mm staplers against a 40 French stomach tube. Oversewing of the staple line was not performed. Both the gastroenterostomy as well as the enteroenterostomy were created using a linear stapler (35mm (ETS, Ethicon, Johnson & Johnson, New Brunswick, New Jersey, USA) and 60mm respectively) and completed anteriorly using a barbed suture (V-loc™, Medtronic, Minneapolis, MN, USA). Staple lines were tested intraoperatively with an air leak test and mesenteric defects were closed with a double layer of hernia staples (EMS, Ethicon, Johnson & Johnson, New Brunswick, New Jersey, USA).

Outcomes (primary and secondary)

The primary outcome of this study was weight loss over a period of three years expressed as percentage total body weight loss (%TBWL) defined as weight loss divided by weight before surgery. It was anticipated that especially the difference in weight regain would make the significant difference. Weight loss was also calculated and expressed as percentage excess weight loss (%EWL) defined as weight loss divided by excess weight before surgery above a normal BMI of 25 kg/m^2.

Secondary outcomes were reduction of comorbidities (type 2 diabetes, hypertension and dyslipidemia), complaints of reflux disease, quality of life (QoL), nutritional deficiencies and complications after surgery. Type 2 diabetes (T2DM) was defined as the use of antidiabetic medication and/or a fasting glucose > 7 mmol/l and/or a HbA1c ≥ 6.5%. Remission was defined as discontinuation of antidiabetic medication for at least one year with normal laboratory values (HbA1c < 6.5%). Improvement was a reduction of antidiabetic medication and unchanged when no difference to the preoperative situation. Hypertension (HT) and dyslipidemia (DL) were defined, respectively, as the use of antihypertensive drug therapy and the use of lipid-lowering medication. Remission of these comorbidities were a discontinuation of the antihypertensive or lipid-lowering medication. Deficiencies in vitamins were defined as a value under the lower limit. Complaints of gastroesophageal reflux disease (GERD) were assessed using the GERD-Health Related Quality of Life (GERD-HRQL) which contains ten questions concerning reflux and dysphagia. A total score of zero is equal to no complaints and a score of 50 to very severe complaints[16]. In addition, the Bariatric Analysis and Reporting Outcome System (BAROS) and the RAND-36 were used to score QoL[17].

Pre and postoperative care

Preoperatively all patients underwent screening and counseling at the Dutch Obesity Clinic to prepare them for the lifestyle adjustment before and after surgery. During multiple sessions patients received dietary, physical and psychological counseling. During the preoperative consultation at the hospital patients were screened for nutritional deficiencies and if present they were corrected preoperatively.

In the postoperative phase the multidisciplinary sessions continue up till five years after surgery. During the regular annually medical control sessions questionnaires (BAROS, RAND-36 and GERD-HRQL) were taken and assessment of patient weight, BMI, medication use and blood values took place. Patients were advised specialized multivitamin supplements for RYGB patients (FitForMe Forte, Rotterdam, The Netherlands) and 20 mg of omeprazole for 7 months and calcium 1500 mg and 2400 IU vitamin D3 daily lifelong were prescribed.

Sample size, randomization and blinding

Sample size calculation was based on the assumption that the EP-GB leads to 5% more %TBWL after two years. Using a power of 80%, a sensitivity of 95%, a SD of 9.3% and taking into account a 10% drop out a minimum of 65 patient were required per group.

Randomization was performed by the hospital epidemiologist using Research Manager (Nova Business Software, Zwolle, The Netherlands). A 1:1 allocation ratio and concealed carrying permuted blocked size of two and four patients was used.

Patients were blinded during the complete duration of follow up (single blinded). Due to logistics researchers and surgeons could not be blinded for group allocation.

Statistical methods and monitoring

All parts of the study were monitored by an independent and trained monitor provided by the local ethical committee of the Rijnstate Hospital. Discrepancies or protocol violations, were reported to the national ethical board located in Nijmegen. All statistical analyses were performed by the coordinating investigator and an independent statistician from the Rijnstate Hospital. Per protocol analyses were performed to present primary and secondary outcomes. Protocol violations were excluded for these analyses.

Variables were analyzed using an independent Student t test for continuous data and a Fisher's exact test for categorical data. Additionally, the difference in weight loss between the groups was analyzed using a linear regression analysis to adjust for the baseline covariates, i.e. age, sex, preoperative BMI and preoperative diabetes. All tests were two-tailed and a p-value <0.05 was considered statistically significant.

Results

Between July 2014 and July 2015, 134 patients were included in the study. Sixty-five patients were randomized to S-GB and 69 to EP-GB. In both groups one patient withdrew from surgery. Both patients were excluded for all analyses. Baseline characteristics between the groups did not significantly differ (**Table 1**).

Table 1. Baseline patient characteristics

	S-GB	EP-GB
Number of patients	64	68
Female (%)	51 (80)	54 (79)
Age, years	47 ± 9	47 ± 10
Length, cm	170 ± 8	170 ± 8
Weight, kg	127 ± 17	126 ± 18
BMI, kg/m^2	44 ± 5	44 ± 5

S-GB standard pouch Roux-en-Y gastric bypass, *EP-GB* extended pouch Roux-en-Y gastric bypass, *BMI* body mass index, ± standard deviation

Despite our instant efforts, two patients were lost to follow-up after two years and an additional seven after three years. In total nine patients (7%) were lost to follow-up. Two patients in the EP-GB group withdrew participation, and in the S-GB group one patient became pregnant in the third year of follow up. Data of all these patients were used up until the point they were lost to follow-up, withdrew participation or became pregnant. A follow-up percentage of 98% after two years and 90% after three years was achieved (**Figure 2**).

Weight loss

During the first two years of follow-up no significant differences in terms of weight loss were seen between the groups. After 24 months the S-GB group achieved a %TBWL of 30% versus 32% in the EP-GB group (p=0.327). In the S-GB group patients regained three kg in the third year of follow-up. The %TBWL in the EP-GB remained stable. The %TBWL after 36 months in the EP-GB group was 31%, and in the S-GB group the value dropped to 27% (p=0.023). After adjustment for age, sex, preoperative BMI and preoperative T2DM the difference in %TBWL after 36 months between the EP-GB and the S-GB was 3.7% (p=0.043). Results of the weight parameters are shown in **Table 2**.

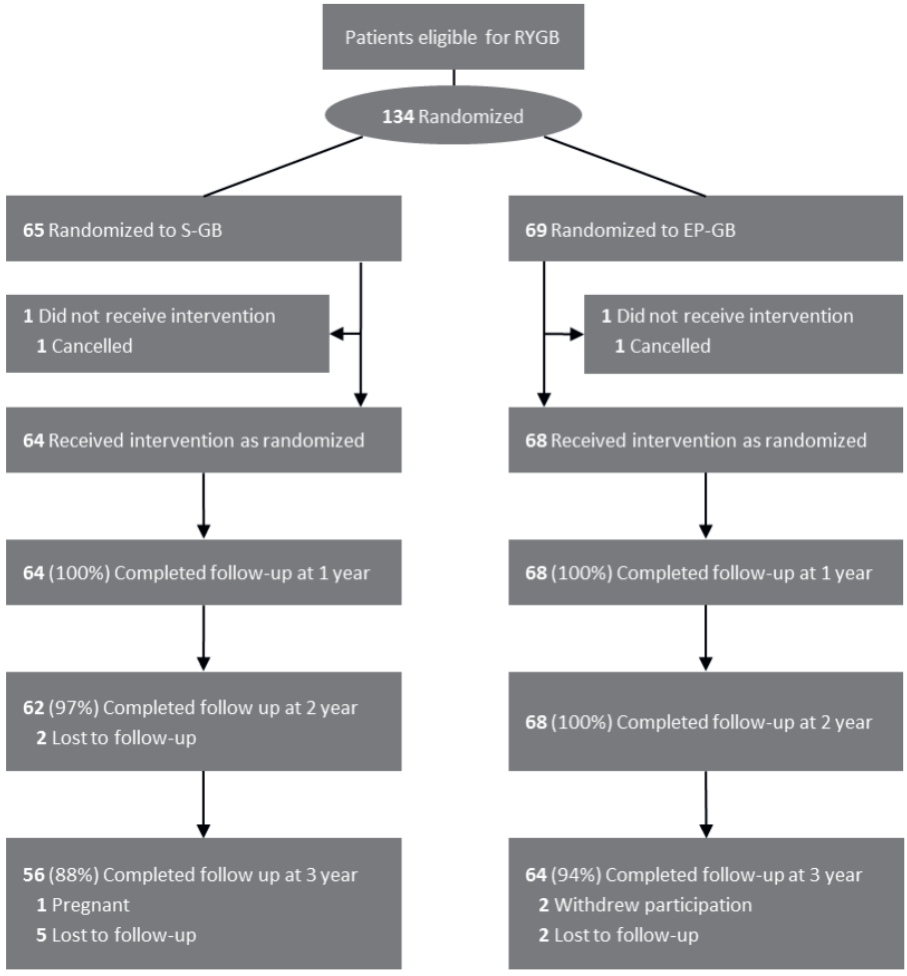

Figure 2. Flow diagram: number of patients during follow-up
RYGB Roux-en-Y gastric bypass, *S-GB* standard pouch Roux-en-Y gastric bypass, *EP-GB* extended pouch Roux-en-Y gastric bypass

Table 2. Weight loss parameters

		S-GB	EP-GB	*p* value
Weight, kg	12 months	88 ± 15	87 ± 16	0.687
	24 months	89 ± 17	86 ± 16	0.308
	36 months	92 ± 17	86 ± 17	0.061
BMI, kg/m^2	12 months	30 ± 4	30 ± 5	0.731
	24 months	30 ± 5	30 ± 5	0.344
	36 months	32 ± 5	30 ± 5	**0.035**
%EWL	12 months	74 ± 20	75 ± 20	0.696
	24 months	73 ± 24	77 ± 23	0.331
	36 months	65 ± 23	76 ± 25	**0.023**
%TBWL	12 months	31 ± 7	31 ± 8	0.728
	24 months	30 ± 10	32 ± 10	0.327
	36 months	27 ± 9	31 ± 11	**0.023**

S-GB standard pouch Roux-en-Y gastric bypass, *EP-GB* extended pouch Roux-en-Y gastric bypass, *EWL* excess weight loss, *TBWL* total body weight loss. Bold values indicate statistical significant outcomes.

Resolution of comorbidities

The number of patients that achieved remission of the most common obesity related comorbidities are listed in **Table 3**.

Type 2 diabetes

In total 54 (41%) patients were diagnosed with T2DM. Despite randomization more patients in S-GB group, 31 (48%), were diagnosed with T2DM compared to the EP-GB group, 23 (34%) (p=0.111). Both these groups included patients with glucose intolerance (a fasting glucose > 7 mmol/l and/or a HbA1c ≥ 6.5% without using antidiabetic medication), seven in the S-GB and two in the EP-GB group. In the S-GB group 61% achieved remission after two years and 71% after three years of follow-up compared to 70% and 57% in the EP-GB group. No significant differences between the groups were found.

Hypertension

In the S-GB group 25 (39%) and in the EP-group 28 (41%) suffered from hypertension. Remission rates increased during follow-up to 36% after 36 months in the S-GB and to 61% in the EP-GB group. The difference in remission rate between the groups was significant after two years and remained significant after three years in favor of the EP-GB group (p=0.043).

Dyslipidemia

At baseline 37 (28%) patients used lipid-lowering medication. In the S-GB group remission was achieved in ten (59%) patients after 24 and 36 months. In the EP-GB group the remission

rate dropped from 50% after 24 months to 30% after 36 months. The differences between the groups were not significant.

Table 3. Remission of obesity related comorbidities

		S-GB	EP-GB	*p* value
Type 2 diabetes (%)		31 (48)	23 (34)	0.111
24 months	Remission	19 (61)	16 (70)	0.612
	Improved	11 (36)	7 (30)	
	Unchanged	-	-	
	Unknown	1 (3)	-	
36 months	Remission	22 (71)	13 (57)	0.325
	Improved	8 (26)	7 (30)	
	Unchanged	-	-	
	Unknown	1 (3)	3 (13)	
Hypertension (%)		25 (39)	28 (41)	0.860
24 months	Remission	6 (24)	15 (54)	**0.043**
	No remission	19 (76)	12 (43)	
	Unknown	-	1 (4)	
36 months	Remission	9 (36)	17 (61)	**0.043**
	No remission	16 (64)	9 (32)	
	Unknown	-	2 (7)	
Dyslipidemia (%)		17 (27)	20 (29)	0.847
24 months	Remission	10 (59)	10 (50)	0.743
	No remission	7 (41)	10 (50)	
36 months	Remission	10 (59)	6 (30)	0.097
	No remission	7 (41)	11 (55)	
	Unknown	-	3 (15)	

S-GB standard pouch Roux-en-Y gastric bypass, *EP-GB* extended pouch Roux-en-Y gastric bypass. Bold values indicate statistical significant outcomes.

Complications

All short- and long term complications are listed in **Table 4**. A total number of eleven (8%) patients suffered a short term complication. Three patients in the S-GB group underwent a reoperation within 30 days. In two patients the enteroenterostomy was revised because of persistent dysphagia due to a stenosis at the anastomosis. One patient underwent relaparoscopy because of complaints of dysphagia due to adhesions already observed during the primary procedure.

A long term complication occurred in 25 (19%) patients. In total 21 reoperations were performed, most (11) of which were cholecystectomies because of symptomatic

gallstones. In the S-GB group one patient underwent surgery due to a perforation at the gastroenterostomy caused by a stomach ulcer in the third year of follow-up. No significant differences in short- and long-term complications between the groups were found.

Table 4. Short- and long term complications

	S-GB	EP-GB	*p* value
Short term (<30 days)			
Total number of patients (%)	6 (9)	5 (7)	0.759
Reoperation	3	0	
Revision enteroenterostomy	2	0	
Adhesion	1	0	
Conservative-treated bleeding	2	3	
Readmission	1	2	
Mortality	0	0	
Long term (>30 days)			
Total number of patients (%)	11 (17)	14 (21)	0.662
Reoperation	8	13	
Cholecystectomy	4	7	
Internal herniation	1	2	
Perforation gastroenterostomy	1	0	
Stenosis gastroenterostomy	0	1	
Diagnostic laparoscopy	2	3	
Incisional hernia (no surgery)	0	1	
Gastric ulcer	2	1	
Readmission	3	2	
Mortality	0	0	

S-GB standard pouch Roux-en-Y gastric bypass, *EP-GB* extended pouch Roux-en-Y gastric bypass.

Nutritional status

The number of patients with a deficiency preoperative or during follow-up are listed in **Table 5**. The number of patients that used specialized multivitamins as prescribed decreased from 79% after one year to 68% after three years of follow-up. Twelve months after surgery significantly more patients in the S-GB group developed a vitamin B_{12} deficiency and after two years more ferritin deficiencies were found in the EP-GB group.

Table 5. Nutritional and vitamin deficiencies

	S-GB				EP-GB			
	0 m (%)	**12 m (%)**	**24 m (%)**	**36 m (%)**	**0 m (%)**	**12 m (%)**	**24 m (%)**	**36 m (%)**
Anemia	3	5	7	10	6	10	17	20
Folic acid	0	2	2	2	0	0	3	2
Vitamin B_{12}	33	**16**	15	12	19	**5**	6	16
Ferritin	9	5	**9**	12	6	6	**23**	26
Vitamin D	63	5	9	8	76	3	8	16

S-GB standard pouch Roux-en-Y gastric bypass, *EP-GB* extended pouch Roux-en-Y gastric bypass, *0 m* baseline, *m* months. Bold values indicate that scores between the S-GB group and the EP-GB group are significantly different at this time point

Quality of life

Gastroesophageal reflux

The GERD-HRQL scores after 24 and 36 months in both groups were between 1.00 and 2.00 and did not significantly differ. After 36 months 22% in the EP-GB group was (still) using a proton pomp inhibitor (PPI) compared to 21% in the S-GB group (p=1.000).

BAROS

Two years after surgery 81% of the patients had a result of good or better with a mean score of 4.5 in the S-GB and 4.8 in the EP-GB group (p=0.435). Comparable results were found after three years of follow up.

RAND-36

Significant improvement in almost all domains was seen after 24 and 36 months in all patients compared to the preoperative values. Only in the role functioning/emotional domain a non-significant decrease of the score was seen after 36 months. There were no significant differences found between the groups.

Discussion

The growing number of patients with severe obesity is alarming and many patients and healthcare providers are looking for the most effective bariatric procedure with the least morbidity. But then the question remains which procedure will result in the best long term outcomes for a specific patient. Although promising new procedures are introduced, the sleeve gastrectomy and the RYGB are still the two most performed procedures.

The majority of operated patients are satisfied and reach a TBWL >25% or an EWL >50%. These levels are often used to define success, however additional weight loss above these thresholds is associated with the increase of remission of comorbidities and a better quality of life[18]. To improve results of the gastric bypass, the diameter of the gastroenterostomy, limb lengths and pouch size could be gripping points.

The EP-GB was designed based on the sleeve gastrectomy and the one anastomosis gastric bypass (OAGB) when it was introduced. These procedures share a relative long and narrow gastric reservoir that differs from gastric bypass design. It could well be that this pouch design plays an important role in the excellent weight loss results seen after these procedures. When added to the gastric bypass design it could potentially improve outcomes.

In the present study the effect of an extended pouch gastric bypass in the first three years after surgery was analyzed. After adjustment for age, sex, preoperative BMI and preoperative T2DM no differences in TBWL and EWL were found during the first two years of follow up, but after three years a difference in TBWL of 3.7% (p=0.043) in favor of the EP-GB was seen. This difference was mainly caused by the fact that no weight regain in the second and third year of follow-up was observed in the EP-GB group. In contrast, in the S-GB group TBWL dropped from a maximum of 31% after 12 months to 27% after 36 months due to regain of approximately three kg. This is an interesting finding at three years. As weight regain is observed in most metabolic surgery patients especially in year two to five post-surgery it would be interesting to see if this effect is even more pronounced in upcoming years.

Weight regain after bariatric surgery is seen in a subset of patients and several factors such as lifestyle, metabolic imbalance and technical aspects following bariatric surgery are thought to contribute to this phenomenon[19]. When taken into account Poiseuilles' Law, which states that flow rate is dependent on pipe length, and other physiological variables are ignored, patients with long pouches should have a longer pouch emptying time compared to patients with short pouches. Theoretically, a slower passage through the pouch, as a result of extending the pouch, could induce a more gradual and longer period of gut hormone secretion resulting in a more pronounced metabolic effect of the RYGB. This concept is supported by Deden et al. who found a slow gastric pouch passage of food in good responders after RYGB and a fast passage in bad responders[14].

Alternatively, the results in the EP-GB group could be explained by the fact that, according to Laplace's law, a longer and smaller pouch has less tendency to dilate compared to a short and wide pouch[6]. Since dilatation of the pouch is often suggested to contribute to weight regain on the long term, preventing it could improve results after RYGB. It is unclear whether both laws are applicable in the clinical setting. Also, other poorly understood variables such

as peristalsis, the diameter of the gastroenterostomy and vagal nerve stimulation are likely to play a significant role. In future research for the optimal design of the RYGB all these variables should be taken into account.

When weight loss increases, the resolution of comorbidities improves. The remission rate of HT was significantly higher in the EP-GB group after 24 and 36 months, however this study fails to demonstrate a difference in remission of T2DM and DL. The most likely explanation is the lack of statistical power for these secondary outcomes. As mentioned before, despite randomization, more patients in the S-GB group were diagnosed with multiple comorbidities needing multidrug regimens. In those cases remission is harder to achieve.

In contrast to the results of this study other authors did not find a correlation between pouch size and weight loss. However, they did conclude that a smaller pouch reduces the risk of reflux symptoms and marginal ulcers[12]. In this study, in total, three (2%) patients had a gastric ulcer, which is low compared to literature[20]. Moreover, results of this study do not confirm the claim that smaller pouches reduce the occurrence of ulcers since more patients in the S-GB group (2) were diagnosed with a stomach ulcer compared to the EP-GB group (1). In fact, in the S-GB group one patient needed revisional surgery due to a perforation caused by a stomach ulcer. Additionally, after 36 months approximately 20% of patients in both groups still used a PPI. When compared to preoperative data, the number of users in the EP-GB group decreased and increased in the S-GB. Finally, GERD-HRQL scores of both groups did not significantly differ. Unfortunately, preoperative GERD-HRQL scores were not assessed. The number of patients with an ulcer in this study could be underestimated because not all patients with this complication experience symptoms or were referred to the hospital for a gastroscopy to confirm the diagnosis.

Extending the gastric pouch is a safe method to prevent weight regain after RYGB which is illustrated by comparable complication rates. A mean complication rate of 21% in the EP-GB group appears high compared to the literature. However, cholecystectomies were also scored as a complication. When this common phenomenon after bariatric surgery is not taken into account, complication rates drop to 10%, which is more in line with expectations.

More patients in the S-GB group suffered a vitamin B12 deficiency after 12 months, despite a comparable number of patients using multivitamins as prescribed preoperatively in both groups. Better vitamin B12 digestion and absorption could be the result of the longer pouch with slower gastric emptying. More patients in the EP-GB group developed a ferritin deficiency 24 months after surgery. At this specific time point more patients with an extended pouch were using a PPI compared with the patients of the S-GB group, which reduces the absorption of iron. This could be an important reason for the higher deficiency rate observed.

From a surgical perspective the EP-GB procedure has advantages compared to the S-GB procedure. When pulling up the alimentary limb to create the gastroenterostomy less traction is needed on the small intestine and the mesentery to reach the level of the pouch. Theoretically, less traction on the alimentary limb could also result in less (unexplained) postoperative pain. Unfortunately, postoperative pain was not assessed in a standardized manner. Secondly, an EP-GB makes revisional surgery of the pouch less difficult to perform, especially when there is an indication for shortening the pouch. A financial disadvantage of the EP-GB includes the fact that a longer pouch is more expensive to create since an additional stapler is needed.

Weight loss after bariatric surgery is associated with an improvement in QoL[21]. In line with literature improvement in all physical domains of the RAND-36 was observed, with no significant difference between the two surgical groups. The minor difference in weight loss we observed could have played a role.

Together with three other RCTs performed in our center this study looks into possible gripping points for improvement of the RYGB design. We acknowledge that the number of patients included in this this study has its limitations. Secondly, the follow-up period of three years to observe weight regain is questionable. It also remains a matter of debate if a difference of 3.7% TBWL, which equals approximately six kg, in favor of the EP-GB is of clinical relevance. However, to our knowledge this is the first RCT describing the effect of EP-GB. Together with other improvements such as optimizing limb lengths and placement of a non-adjustable ring around the pouch it could result in even more pronounced and perhaps lifelong sustainable weight loss after RYGB.

Conclusion

Extending the gastric pouch is a promising modification of RYGB design that seems to be a safe and effective technique which improves mid-term weight loss, potentially driven by a lower occurrence of weight regain.

Conflict of interest

ABB, MIC, EOA, TA, EJH and FJB declare to have no conflict of interest.

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CHAPTER 5

A non-adjustable ring in RYGB for preventing weight regain. Three year results of the randomized BANDOLERA trial

Abel Boerboom, Wendy Schijns, Edo Aarts, Bart Witteman, Eric Hazebroek, Frits Berends

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Abstract

Background

Although the Roux-en-Y gastric bypass (RYGB) is considered a standard procedure, many variations exist in the basic design. In order to achieve more pronounced and sustainable results after RYGB, factors such as diameter of the gastroenterostomy, limb length and pouch size are gripping points for improvement of design. Banding the pouch could improve results by altering food passage through the pouch.

Objective

The aim of this randomized controlled trial was to evaluate the effect of a banded pouch RYGB (B-GB) and standard pouch RYGB (S-GB).

Methods

In total, 130 patients were randomized in two groups: 65 patients received a B-GB using a non-adjustable silicone ring and 65 patients a S-GB. Subsequently, weight loss, remission of comorbidities, nutritional status, complications, quality of life and GERD-symptoms were assessed during a follow-up of three years.

Results

During the first two years of follow-up no significant differences in terms of weight loss were observed. In the third year of follow-up the TBWL in the B-GB group was 35% versus 32% in het S-GB group (p=0.048). Additionally, no differences in resolution of comorbidities, complications, quality of life and GERD-symptoms were found. In 5 (8%) patient the ring was removed during follow-up.

Conclusion

Banding a gastric bypass, by using a non-adjustable silicone ring, is a promising modification of the RYGB design. It could be effective technique to improve long-term results by preventing weight regain. Placement of the ring around the gastric pouch should not be too tight in order to prevent postoperative dysphagia.

Introduction

In the last decade a number of new bariatric procedures gained popularity. Even though, the Roux-en-Y gastric bypass (RYGB), still holds its ground as a prominent bariatric treatment. Especially when patients suffer from type 2 diabetes, the RYGB often remains the preferred procedure[1-6]. Remarkably, the basic design of the RYGB has not been changed much since its introduction in the sixties by Mason, et al[7,8]. Although the procedure is performed on a broad scale, no international standardized protocol on how to perform a RYGB exists and anatomical and technical aspects of the procedure are often based on local experience. In search for a standardized design its necessary to take a critical look at all aspect of the gastric bypass construction. One of the possible alterations that might lead to better outcomes is adding a band around the gastric pouch.

A banded RYGB using an adjustable gastric band is not recommended because of the high number of band related complications. Many surgeons do however believe that a primary banded RYGB using a non-adjustable band results in sustainable superior weight loss with acceptable complication rates[9]. Placing the ring proximal of the gastroenterostomy could prevent dilatation of the gastric pouch. Since enlargement of this structure is often associated with poorer weight loss and especially weight regain, prevention of this dilatation might improve long term results after RYGB surgery[10]. The majority of the bariatric surgeons however do not perform a banded bypass because they have concerns about long-term band related complications and postoperative dysphagia. Also, adding a band to the procedure does initially increase operation costs. There are numerous studies, including randomized controlled trials (RCTs), describing the positive effects of a primary banded RYGB[9-]. However, the vast majority are observational and descriptive studies. Larger RCTs with longer follow-up are necessary to further determine the role of the banded RYGB in the field of bariatric and metabolic surgery.

In search for an optimized, standardized design of the RYGB this article is part of series of four randomized controlled investigating possible gripping points for improvement of the design. The topic of the other studies are pouch configuration (EXTENDED POUCH trial)[11] and limb length (ELEGANCE and ELEGANCE REDO trials)[12,13]. This study (The BANDOLERA trial) reports the results of a RCT specifically looking at banding the gastric pouch. The aim of this RCT was to evaluate the effect of a primary banded RYGB (B-GB), using a non-adjustable silicone ring, and a non-banded standard RYGB (S-GB) on weight loss, remission of comorbidities and complication rates.

Methods

The protocol of the BANDOLERA trial was approved by the Central Medical Committee for Research in humans in Nijmegen and the local committee in Arnhem and registered at the clinical registry of clinicaltrials.gov (NCT02545647). The study was designed as a single center, randomized controlled trial and was in accordance with the Declaration of Helsinki.

Patients

All patients who were referred to our center for primary gastric bypass surgery and were eligible for the study were asked to participate. The IFSO criteria (BMI ≥ 35 kg/m^2 with an obesity related comorbidity or BMI ≥40 kg/m^2) were used to assess eligibility. Additional exclusion criteria for this study were a history of bariatric surgery, any form of inflammatory bowel disease, renal dysfunction (GFS <30min) and therapy resistant reflux disease. When interested, the surgeon discussed possible risks and benefits with the patient and afterwards were handed an information brochure. Patients had two weeks to consider participation. After these two weeks, written informed consent (twofold) was obtained from each patient to officially confirm participation.

Surgical procedures (S-GB and B-GB)

A standardized laparoscopic technique was used to create an antecolic antegastric RYGB. This technique was similar to the basic technique used in all four randomized trials to be able to compare outcomes. All procedures were performed by four experienced bariatric surgeons (>500 RYGB cases). A small gastric pouch of 40-50 ml was constructed using three blue 60 mm lineal staplers (Echelon, Ethicon, Johnson & Johnson, New Brunswick, New Jersey, USA) placed against a 40 French stomach tube. An alimentary limb of 150 cm and a biliopancreatic limb of 75 cm were created. The gastroenterostomy and the enteroenterostomy were performed using a 35 mm and 60 mm linear stapler (ETS, Ethicon, Johnson & Johnson, New Brunswick, New Jersey, USA) respectively combined with a barbed suture (V-loc™, Medtronic, Minneapolis, MN, USA). To test the integrity of the staple lines an air leak test was used. Mesenteric defects were closed with a double layer of hernia staples (EMS, Ethicon, Johnson & Johnson, New Brunswick, New Jersey, USA).

The B-GB was performed in exactly the same manner. After testing the staple lines, a perigastric tunnel was created through the omental burse from medial to lateral. The non-adjustable silicone ring (Minimizer™, Bariatric Solutions, Stein am Rhein Switzerland) (**Figure 1**) was passed through this tunnel from the lateral side. After insertion of a 40 French tube into the pouch, the ring was closed approximately two centimeters above the gastroenterostomy at one of the four closing positions enabling to close the ring at 6.5, 7.0, 7.5 or 8.0 cm circumference. An additional 5mm instrument should easily pass between the

pouch and the ring when closed. The soft needle at the tip of the ring was cut and removed after which the ring was fixated using two non-absorbable sutures.

Figure 1. Non-adjustable silicone ring

Primary and secondary outcomes

The primary outcome of this study was weight loss expressed as percentage total body weight loss (%TBWL) three years after bypass surgery. %TBWL was defined as weight loss divided by weight before surgery. Weight loss was also calculated and expressed as excess weight loss (%EWL) defined as weight loss divided by excess weight before surgery above a BMI of 25 kg/m2.

Secondary outcomes were resolution of the obesity related comorbidities type 2 diabetes mellitus (T2DM), hypertension (HT) and dyslipidemia (DL). Additionally, complications after surgery including complaints of reflux disease and nutritional deficiencies and quality of life (QoL) were assessed. Comorbidities were defined using the following criteria: for T2DM the use of antidiabetic and/or a fasting glucose > 7 mmol/l and/or a HbA1c ≥ 6.5%, for HT the use of antihypertensive drug therapy and for DL the use of lipid-lowering medication. Remission of T2DM was defined as discontinuation of antidiabetic medication for at least one year with normal laboratory values (HbA1c < 6.5%). Improvement was a reduction of antidiabetic medication and unchanged when no difference to the preoperative situation. Remission of HT and DL were defined as the discontinuation of the antihypertensive or lipid-lowering medication. Nutritional deficiencies were defined as serum levels falling below the lower normal limit. Complaints of reflux disease (GERD) were assessed using the GERD-Health Related Quality of Life (GERD-HRQL)[14]. The score of this questionnaire can vary from zero (no complaints) to 50 (very severe complaints). In addition, QoL was assed using the Bariatric Analysis and Reporting Outcome System (BAROS) and the RAND-36[15].

Perioperative care

Prior to surgery, all patients were screened and underwent extensive multidisciplinary educational lifestyle group sessions at the Dutch Obesity Clinic to prepare them for the lifestyle after surgery. These sessions intensified after surgery for at least two years. During preoperative consultation at the hospital, patients were screened for nutritional deficiencies and if present these deficiencies were corrected.

Patient were advised to take specialized multivitamin supplements for RYGB patients (FitForMe Forte, Rotterdam, The Netherlands). Additionally, 20 mg of omeprazole for six months, fraxiparin 5700IU for six weeks and calcium/vitamin D 500mg/880IU TID lifelong were prescribed. During the regular annual postoperatively medical sessions, which continue up till five years after surgery, the questionnaires (GERD-HRQL, BAROS and RAND-36) were filled in and patient weight, medications use and nutritional status were assessed.

Sample size, randomization and blinding

Based on the assumption that a B-GB would lead to a 5% higher %TBWL after three years, using a power of 80%, a sensitivity of 95%, a SD of 9.3% and taken into account a drop-out of 15%, a sample size of 65 patients per group was calculated.

Randomization was performed by the hospital epidemiologist by applying block randomization with a 1:1 allocation ratio and concealed carrying permuted blocked size of two and four patients. A web-based randomization module was used (Research Manager, Nova Business Software, Zwolle, The Netherlands).

Owing to the invasive nature of the intervention, patients, surgeons and researchers could, on these ethical grounds, not be blinded for group allocation.

Statistical methods and monitoring

An independent monitor provided by the local ethical committee of the hospital monitored the study on a regular basis. Deviations (Adverse and Serious Adverse Events) were reported to the Central Medical Committee for Research in humans in Nijmegen. Data analysis was performed by the coordinating researcher and the hospital statistician. Per protocol analyses was used for the primary and secondary outcomes. Protocol violations were excluded for these analyses. The Student t-test was used for continuous data and the Fisher's exact for categorical data. Additionally, to adjust for the baseline covariates age, sex, preoperative BMI and preoperative T2DM a linear regression analyses was performed. All tests were two-tailed and a p-value <0.05 was considered statistically significant.

Results

Between August 2015 and February 2016, all 130 patients required for this study were included in the study; 65 patients were enrolled in the S-GB group and 65 patients in the B-GB group. Baseline patient characteristics between the groups did not differ significantly (**Table 1**).

Despite all effort, there were a total of six (5%) patients lost to follow-up after three years. Two in the S-GB group and four in the B-GB group. One patient withdrew participation in the study in the third year of follow-up. In total, five rings were removed during three years of follow-up and in the S-GB group one patient received a ring to treat a severe dumping syndrome. The data of these patients was used up until the time they were lost to follow-up, withdrew participation, a ring was removed or placed. A follow-up percentage of 89% after three years was achieved (**Figure 2**).

Table 1. Baseline patient characteristics

	S-GB	B-GB
Number of patients	65	65
Female (%)	49 (75)	53 (82)
Age, years	45 ± 9	42 ± 9
Length, cm	170 ± 7	170 ± 9
Weight, kg	123 (116-139)	121 (112-137)
BMI, kg/m^2	42 (40-46)	42 (40-45)

S-GB standard pouch Roux-en-Y gastric bypass, *B-GB* banded Roux-en-Y gastric bypass, *BMI* body mass index, ± standard deviation. No significant differences between the S-GB group and the B-GB group.

Weight loss

No significant differences between the groups in terms of weight loss were seen during the first two years of follow-up. After 24 months both groups achieved their maximal %TBWL after surgery. The S-GB group achieved a %TBWL of 34% versus 36% in the B-GB group (p=0.219) after two years. After the third year of follow-up the B-GB group reached a %TBWL of 32% and the B-GB group 35 (p=0.048). After adjustment for the baseline covariates age, sex, preoperative BMI and preoperative T2DM the difference in %TBWL after 36 months between the S-GB group and the B-GB group was 2.6% (p=0.124). Weight loss results can be found in **Table 2**.

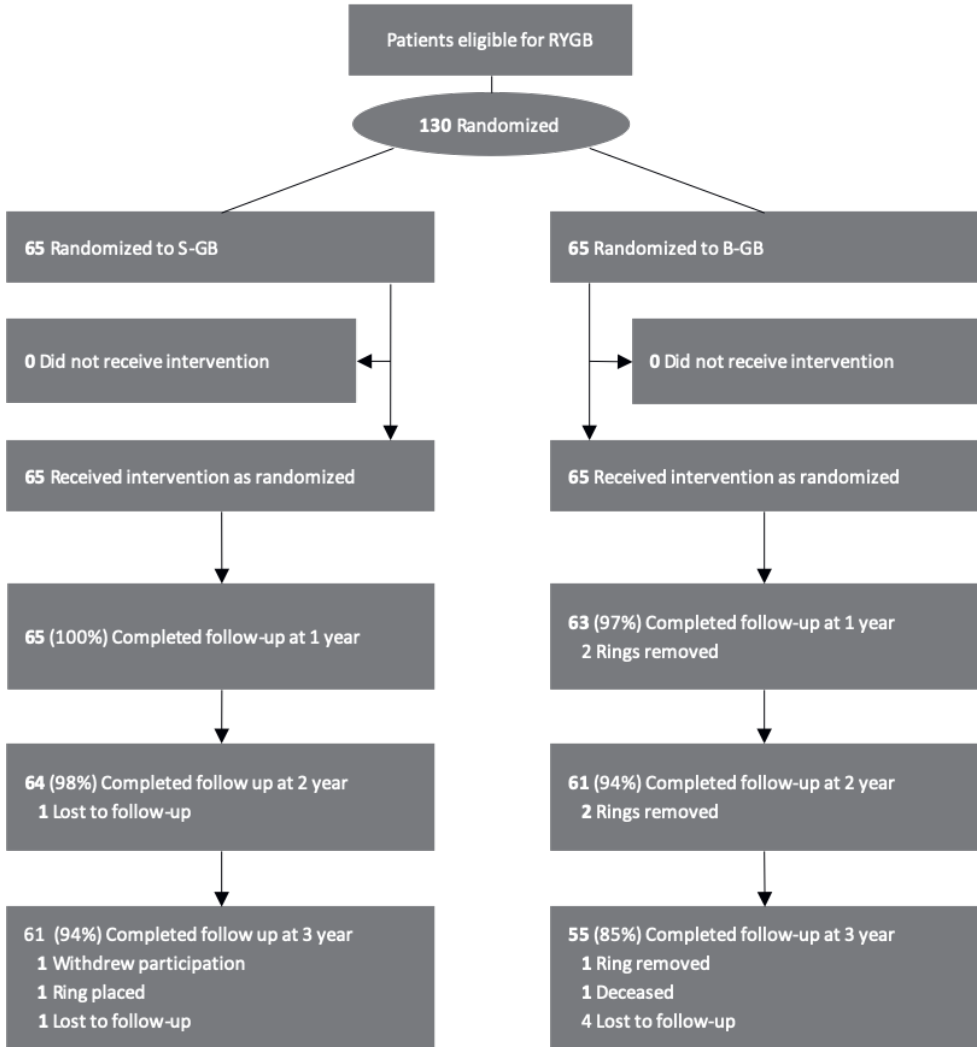

Figure 2. Flow diagram

Table 2. Weight loss parameters

		S-GB	B-GB	*p* value
Weight, kg	12 months	85 ± 15	82 ± 14	0.149
	24 months	84 ± 16	80 ± 16	0.223
	36 months	86 ± 17	82 ± 17	0.206
BMI, kg/m^2	12 months	29 ± 4	28 ± 4	0.133
	24 months	29 ± 5	28 ± 4	0.181
	36 months	30 ± 5	28 ± 5	0.118
%EWL	12 months	79 ± 20	84 ± 20	0.162
	24 months	81 ± 22	86 ± 23	0.216
	36 months	77 ± 24	85 ± 23	0.085
%TBWL	12 months	32 ± 7	34 ± 8	0.150
	24 months	34 ± 9	36 ± 9	0.219
	36 months	32 ± 9	35 ± 9	**0.048**

S-GB standard pouch Roux-en-Y gastric bypass, *B-GB* banded Roux-en-Y gastric bypass, *EWL* excess weight loss, *TBWL* total body weight loss, ± standard deviation. Bold values indicate statistical significant outcomes.

Resolution of comorbidities

An overview of the number of patient that achieved improvement and remission of the studied obesity related comorbidities can be found in **Table 3**.

Type 2 diabetes

At baseline 28 (22%) patients were diagnosed with T2DM, 17 (26%) in the S-GB group and 11 (17%) in the B-GB group. Patients with glucose intolerance (a fasting glucose > 7 mmol/l and/or a HbA1c ≥ 6.5% without using antidiabetic medication) were presents in both groups, one in the S-GB group and five in the B-GB group. At 24 months, when maximum weight loss was achieved 9 (53%) patients had a remission in the S-GB group versus 7 (64%) in the B-GB group. This number of patients increased in the third year of follow-up to 59% in the S-GB group and 73% in the B-GB group. No significant differences between the groups were found.

Hypertension

Despite randomization more patients in the S-GB group suffered from hypertension at baseline, 25 (38%) versus 13 (20%) in the B-GB group (p=0.051). In total 20 (53%) of all patients achieved remission after 36 months. Remission rates in both groups were comparable, no significant differences were found.

Dyslipidemia

The number of patients that were using lipid-lowering medication at baseline was 23 (18%), 16 (25%) in the S-GB group and 7 (11%) in the B-GB group. Three (43%) patients in the

B-GB group achieved remission after 36 months versus four (25%) in the B-GB group. No significant differences after 24 months and 36 months were found.

Table 3. Resolution of obesity related comorbidities

		S-GB	B-GB	*p* value
Type 2 diabetes (%)		17 (26)	11 (17)	0.292
24 months	Remission	9 (53)	7 (64)	0.489
	Improved	6 (35)	4 (36)	
	Unchanged	-	-	
	Unknown	2 (12)	-	
36 months	Remission	10 (59)	8 (73)	0.432
	Improved	5 (29)	1 (9)	
	Unchanged	-	-	
	Unknown	2 (12)	2 (18)	
Hypertension (%)		25 (38)	13 (20)	0.051
24 months	Remission	16 (64)	8 (62)	0.511
	No remission	7 (28)	5 (39)	
	Unknown	2 (8)	-	
36 months	Remission	15 (60)	5 (39)	0.324
	No remission	7 (28)	3 (23)	
	Unknown	3 (12)	5 (39)	
Dyslipidemia (%)		16 (25)	7 (11)	0.067
24 months	Remission	5 (31)	3 (43)	0.587
	No remission	9 (56)	4 (57)	
	Unknown	2 (13)	-	
36 months	Remission	4 (25)	3 (43)	0.471
	No remission	9 (56)	2 (29)	
	Unknown	3 (19)	2 (29)	

S-GB standard pouch Roux-en-Y gastric bypass, *B-GB* banded Roux-en-Y gastric bypass

Complications

All short- and long term complications are listed in **Table 4**. In total 14 (11%) patients suffered a short term complication after surgery. In the S-GB group two patients underwent a reoperation within 30 days. One patient needed surgery a second time because of a stenosis at the enteroenterostomy that resulted in a blow-out of the stomach remnant. In the B-GB group two rings were removed within two weeks after surgery. Both because of complaints of dysphagia. In one of these patients a gastroscopy showed a stenosis based on an ulcer at the gastroenterostomy and in the other patient a barium swallow imaging study showed slow passage at the gastroenterostomy. Both rings were removed. In both groups one patient required a cholecystectomy.

A long term complications occurred in 24 (18%) patients. In total, twenty reoperations were performed, most of which (7) were cholecystectomies because of symptomatic gallstones. Seven patients were reoperated because of chronic abdominal pain, in four of these patients an internal hernia was found. In three patients the Minimizer was removed in the second and third year of follow-up. In all three patients because of a combination of abdominal pain and persistent dysphagia which could not be explained otherwise. One patient in the B-GB group (without abdominal complaints) committed suicide. No significant differences in short- and long-term complications between the groups were found.

Table 4. Short- and long term complications

	S-GB	B-GB
Short term (<30 days)		
Total number of patients (%)	6 (10)	8 (12)
Reoperation	2	4
Ring removal	-	2
Blow-out stomach remnant	1	-
Bleeding	-	1
Cholecystectomy	1	1
Conservative-treated bleeding	2	3
Pulmonary embolism	1	-
Readmission	1	-
Mortality	-	-
Long term (>30 days)		
Total number of patients (%)	10 (15)	14 (22)
Reoperation	8	12
Ring removal	-	3
Cholecystectomy	3	4
Internal herniation	3	1
Revision gastroenterostomy	1	-
Ring placed	1	-
Incarcerated umbilical hernia	-	1
Diagnostic laparoscopy	-	3
Gastric ulcer	1	-
Dysphagia	-	1
ACNES	1	-
Mortality	-	1

S-GB standard pouch Roux-en-Y gastric bypass, *B-GB* banded pouch Roux-en-Y gastric bypass

Nutritional status and compliance

The number of patients that were using the specialized multivitamin supplements for RYGB patients as advised dropped from 80% after two years to 58% after three years of follow-up. **Table 5** gives an overview of the percentage of patients with nutritional deficiencies during follow-up. The only notable difference that was found was a non-significant higher percentage of patients with a vitamin D deficiency after 36 months in the B-GB group.

Table 5. Nutritional and vitamin deficiencies

	S-GB				B-GB			
	Baseline (%)	12 months (%)	24 months (%)	36 months (%)	Baseline (%)	12 months (%)	24 months (%)	36 months (%)
Anemia	3	12	9	6	2	4	9	7
Folic acid	-	2	-	-	-	6	2	4
Vit B_{12}	22	9	4	6	18	9	11	9
Ferritin	5	5	14	13	2	4	13	17
Vit D	66	2	7	13	54	4	13	28

S-GB standard pouch Roux-en-Y gastric bypass, *B-GB* banded pouch Roux-en-Y gastric bypass, *Vit* vitamin. No significant differences between the S-GB group and the B-GB group.

Quality of Life

The results of all three questionnaires which were assessed during follow-up showed improvement of the quality of life in all domains. The GERD-HRQL scores decreased in both groups from 5.6 at baseline to 1.4 after 36 months in the S-GB group and from 3.0 to 2.5 in the B-GB group. In both groups approximately 21% of the patients was still using a proton pomp inhibitor (PPI) after three years. At the 'high point' of weight loss after two years 99% of all patients scored 'fair' or higher using the BAROS score. This result remained stable during the third year of follow-up. The results of the RAND-36 showed significant improvement of especially all physical domains during the complete follow-up. The only significant difference between groups in quality of life was seen after 24 months in the 'health change' domain in favor of the S-GB group that disappeared thereafter.

Discussion

Patients and healthcare providers are looking for the bariatric procedures with the most pronounced and sustainable results. Although promising new bariatric procedures emerged, the sleeve gastrectomy and the RYGB are still the two most performed bariatric procedures worldwide. The majority of all patients with obesity reach a TBWL >25% or EWL >50% after surgery. These thresholds are often used to define success. Additional

weight loss above these thresholds is associated with a higher patient satisfactory and an increased resolution of obesity related comorbidities[16]. Alterations in the basic RYGB design, for example adjusted limb lengths and pouch size, could potentially increase weight loss and therefore improve clinical outcomes. In the present study the effect of a banded RYGB, using a non-adjustable silicone ring, in the first three years after surgery was analyzed.

In the first two years of follow-up no differences in %TBWL and %EWL were found between the group. Both groups performed exceptionally well. At 24 months the S-GB group reached a %TBWL of 34% and the B-GB group 36% (P=0.202). After the third year of follow-up the S-GB reached a %TBWL of 32% and the B-GB group 35% (p=0.048). Although the difference between the groups was minor it was significant after 36 months. However, after adjustment for age, sex, preoperative BMI and preoperative T2DM the significant difference disappeared. Despite this, it still would be interesting to see if this trend toward a more pronounced effect in the B-GB group is observed in upcoming years, especially since weight regain is observed in most metabolic surgery patients in year two to five post-surgery. This idea is supported by studies that report on better weight loss in patients with a banded RYGB within two to five years after surgery[9,10].

Several factors such as lifestyle, metabolic imbalance and technical aspects are thought to have an effect on weight regain after bariatric surgery which is seen in a subset of patients[17]. Although hard evidence is lacking, enlargement of the gastric pouch and dilatation of the gastric pouch outlet has often been described[18,19]. It is suggested that placement of the non-adjustable silicone ring could counteract this dilatation of the pouch and could therefore prevent weight regain. The result of this study, in which a difference in weight loss is only seen after 36 months could support this statement, but further follow-up is necessary. It must be stressed that weight regain is a physical and psychological burden for patients that weighs heavily on quality of life. Any intervention that could help to prevent weight regain should be welcomed.

Since the ring is not placed tightly around the pouch it should not induce a primary restrictive effect which could affect initial weight loss. This idea is supported by the fact that the B-GB does not result in a more pronounced initial weight loss result after 12 and 24 months. However, the exceptionally good result in the first two years in both groups, but especially in the S-GB group, is worth mentioning. Compared to literature and to comparable RCTs conducted in our center in which the 'standard' gastric bypass was created in the same manner the S-GB group in this study performed better during the complete follow-up of the study[11,12]. We hypothesized that the non-blinded aspect of this study and the disappointment of patients when they were not enrolled in the B-GB group could had a positive effect on the motivation of these patients to adjust their lifestyle postoperatively and thus had an effect on weight loss outcomes.

The idea of preventing weight regain by preventing dilatation of the pouch is not new. Several adjustable and non-adjustable prosthesis, devices and materials to reinforce the gastric pouch and prevent enlargement were used and investigated[9]. Some resulted in a high number of band related complications and were abandoned and for numerous small and observational studies it proves hard to draw definitive conclusions. It is suggested that a silicone non-adjustable ring leads to less adhesions and a lower complication rate. This is confirmed in a study using a non-adjustable ring in 178 primarily operated patients in whom only 2.8% of the rings were removed during five years of follow-up[10]. The percentage of ring removal in this study was higher (8%) and is of concern. The high number of removals could be due to the fact that perigastric placement of a non-adjustable ring is challenging. Furthermore, a significant learning curve effect that was suggested in a multicenter cohort study investigating the effect of using the non-adjustable ring as revisional procedure. Both could explain the higher number of removals of this relatively new device in this study could contribute[20]. A strong conclusion about the risk-benefit ratio could follow after longer follow-up of this study in combination with a growing experience with the device.

Placement of a ring around the pouch may be associated with postoperative dysphagia. Therefore, when considering the use of a non-adjustable ring surgeons should keep in mind no to close the ring too tight. As advised by the manufacturer, a 40 French stomach tube inside the pouch and an additional 5mm instrument should easily pass between the pouch and the ring when closed. Disabling dysphagia resulted in ring removal in five patients in this study. Probably more patients will consider some degree of dysphagia as a desirable effect of the B-GB and adjust their eating patterns and will not report these complaints. This could have a good result in terms of weight loss, but this eating pattern could also be insufficient with a risk of developing nutritional deficiencies. In future studies dysphagia and its effect on eating behavior should be taken into account.

Although increasing weight loss after bariatric surgery is associated with improved resolution of comorbidities and a higher patient satisfactory this study fails to demonstrate a difference between the S-GB group and the B-GB group for these secondary outcomes. High remission rates of T2DM were achieved in both groups. These high percentages compared to literature could be explained by the fact that especially in the B-GB group patients with glucose-intolerance were present. In these patients, remission is easier to achieve. No differences in quality of life, including complaints of GERD, were observed during the complete follow-up. The minor difference in weight loss we observed could have played a role. Also, the lack of statistical power for these secondary outcomes could explain these findings.

Together with three other RCTs performed in our center this study looks into possible gripping points for improvement of the RYGB design. The number of patients included

in the study and the period of follow-up to observe weight regain has its limitations. Unfortunately, six patients were lost to follow-up. It is unclear how these drop-outs performed at 36 months. From experience with the adjustable gastric band, it has become clear that results of these patients may be disappointing. Furthermore, it is debatable if a difference in %TBWL of 3%, which equals four kilograms, is of clinical relevance. On the other hand, when combined with other improvements such as optimizing limb lengths and pouch size, addition of a ring could result in more pronounced weight loss after RYGB.

Conclusion

Banding a gastric bypass, by using a non-adjustable silicone ring, is a promising modification of the RYGB design. It could be effective technique to improve long-term results by preventing weight regain. Placement of the ring around the gastric pouch should not be too tight in order to prevent postoperative dysphagia.

Conflict of interest

ABB, WS, EOA, BW, EJH and FJB declare to have no conflict of interest.

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CHAPTER 6

Banding the pouch with a non-adjustable ring as revisional procedure in patients with insufficient results after Roux-en-Y gastric bypass: short-term outcomes of a multicenter cohort study

Abel Boerboom, Edo Aarts, Volker Lange, Andreas Plamper, Karl Rheinwalt, Katja Linke, Ralph Peterli, Frits Berends, Eric Hazebroek

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Abstract

Background

After laparoscopic Roux-en-Y gastric bypass (RYGB), approximately 10-35% of patients with morbid obesity regain weight after an initial good result or fail to achieve a sufficient amount of weight loss. Patients in which conservative measures are not successful may potentially benefit from revisional surgery.

Objective

To evaluate the effect of a non-adjustable ring placed around the gastric pouch in patients with insufficient weight loss or weight regain after RYGB.

Setting

Four specialized bariatric hospitals in The Netherlands, Germany and Switzerland

Methods

From 2011-2017, 79 patients underwent revisional surgery using a non-adjustable silicone ring because of insufficient results after RYGB. Data on weight loss and complications up to two years after revisional surgery was collected and analyzed retrospectively.

Results

A follow-up percentage of 86% after one year and 61% after two years was achieved. In 75% of patients further weight regain was prevented. Percentage total body weight loss improved by 7% to 26% one year after revisional surgery and remained stable during two years of follow-up. The additional weight loss effect of placing a non-adjustable ring was more pronounced in patients with an initial good result after primary RYGB. Eighteen (23%) rings were removed, most often due to dysphagia.

Conclusion

Especially for patients who experience weight regain after initial good weight loss, placing a non-adjustable silicone ring around the gastric pouch results in modest improvements in weight loss. To prevent the risk of ring removal due to dysphagia, surgeons should take notice not to place the ring too tight around the gastric pouch during revisional surgery.

Introduction

Since the introduction in 1966, the Roux-en-Y gastric bypass (RYGB) has proven itself in terms of weight loss and remission of comorbidities in patients with morbid obesity[1,2]. Unfortunately, 10-35% of patients regain weight after an initial good result or fail to achieve a sufficient amount of weight loss[3,4,5]. To get these patients back on track, additional counseling by a dietitian or a lifestyle coach is always the first line of treatment. The goals that patients with weight regain set themselves are often different from that of their healthcare providers and this often leads to disappointment on both sides. In patients in which conservative interventions do not improve results revisional surgery can be taken into consideration after multidisciplinary evaluation. With the increasing number of revisional bariatric procedures performed it is important to look further into the technical options and their outcomes.

Some revisional procedures, such as distalization of the gastric bypass, aim to induce hypoabsorption, whereas other aim at increasing restriction by adding an adjustable gastric band or resizing the pouch[6,7]. Unfortunately, there is a paucity of high quality studies on revisional surgery and results are often inconsistent in terms of weight loss and complication rates. Due to the lack of a standardized treatment protocol, revisional surgery after failed gastric bypass is mainly based on local experience. Therefore, there is a need for good clinical studies on this subject.

Another revisional option after insufficient weight loss or weight regain is banding of the gastric bypass[8]. This banded gastric bypass, using a non-adjustable ring (**figure 1**), is already performed as a primary procedure with promising results[9]. It is hypothesized that additional placement of a ring prevents long term weight regain due to dilatation of the gastric pouch. Therefore, it can be postulated that placement of a ring as a revisional procedure could counteract weight regain and improve weight loss results in patients with a Roux-en-Y gastric bypass[10,11]. In addition, the ring may delay food passage through the pouch, resulting in decreased food intake. As this revisional procedure is not frequently performed, a multicenter approach is necessary to collect reliable data. The aim of this study is to investigate the effect of a non-adjustable ring placed around the gastric pouch on weight loss in patients with insufficient weight loss or weight regain after RYGB two years after revisional surgery.

Figure 1. Non-adjustable silicone ring

Methods

Patient selection and data collection

All patients that underwent revisional surgery for either weight regain or insufficient weight loss after RYGB by means of a non-adjustable ring from 2011 to 2017 were included in this study. Patients that received a non-adjustable ring for dumping were not included in this study and are analyzed in a different retrospective study. The participating hospitals were: Rijnstate Hospital in Arnhem, the Netherlands (31 patients), St. Claraspital in Basel, Switzerland (33 patients), Helios Klinikum in Berlin, Germany (4 patients) and St. Franziskus Hospital in Köln, Germany (11 patients). Patients were divided into two subgroups based on the maximum weight loss result after the initial RYGB. Poor responders (insufficient weight loss) were defined as patients that achieved a total body weight loss (TBWL) <25% and good responders (weight regain) as patients that achieved TBWL>25%. The protocol of this retrospective study was approved by the local research committees of all four participating centers and this study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments. All patient data were collected retrospectively from medical records or from a prospective database by an investigator in the participating center after informed consent was obtained.

Surgical procedure and postoperative management

All included patients had a previous laparoscopic gastric bypass. All revisional procedures were performed laparoscopically. After introduction of the trocars and identification of the anatomic structures, adhesiolysis was performed. Approximately two centimeters proximal to the gastroenterostomy a perigastric tunnel was created through the omental bursa, dorsal of the gastric pouch from medial to lateral. The non-adjustable silicone ring (Minimizer™, Bariatric Solutions, Stein am Rhein Switzerland) was introduced into the abdomen, passed through this tunnel from the lateral side and locked at one of the four

closing positions enabling to close the ring at 6.5, 7.0, 7.5 or 8.0 cm circumference. Before locking a 36 French or 40 French gastric bougie was inserted into the pouch. The soft needle at the tip of the ring was cut and removed. The ring was fixed using one or two non-absorbable sutures. Postoperatively, thrombosis prophylaxis was prescribed according to local protocols. All patients were advised to take optimized multivitamins designed for bariatric patients.

Outcomes and statistical analysis

The primary endpoint of this study was the percentage total body weight loss (%TBWL) two years after revisional surgery. %TBWL was defined as weight loss in kilograms divided by total body weight measured before revisional surgery. To give an overview of the total body weight lost after bariatric surgery the %TBWL was also calculated using the weight before initial RYGB. To enable comparison with other studies percentage excess weight loss (%EWL) are also shown. Secondary endpoints included post-operative complications (general and ring-related) and band removal. Patients in whom the ring was removed were excluded from the complete analysis to avoid potential skewness. Statistical analysis was performed with IBM© SPSS© (version 21.0 Windows). All values are presented as mean ± standard deviation (SD), unless specified otherwise. Differences between the groups were analyzed by using Fisher's exact test for categorical data and student's *t* tests for continuous variable. To adjust for baseline covariates, i.e. age, sex, preoperative body mass index (BMI), adjustable gastric band (AGB) in history and preoperative type 2 diabetes mellitus (T2DM) a linear regression analysis was performed to calculate the difference in weight loss between the two groups. Tests were two-tailed and a *p*-value <0.05 was considered statistically significant.

Results

Seventy-nine patients, divided in 24 (30%) poor responders and 55 (70%) good responders after RYGB, underwent revisional surgery through surgical placement of a non-adjustable ring. The mean time between the primary RYGB and the placement of the ring was 56 months. The good responder group had a significantly higher body mass index (BMI) before RYGB and, as expected, the poor responder group had a significantly higher BMI before revisional surgery. In the poor responder group, there were more patients who had an adjustable gastric band in their history. All baseline characteristics are presented in **table 1**.

During follow-up, ten rings were removed during the first year of follow-up and an additional eight during the second year. In total, 24 patients were lost to follow-up despite persistent efforts. A follow-up percentage of 86% (59 patients) after one year and 61% (37 patients) after two years was achieved.

Table 1. Baseline patients characteristics

	Total (n=79)	**Poor responders** (n=24)	**Good responders** (n=55)	***p*-value**
Age, years	45±11	46±9	44±12	0.580
Female (%)	68 (86)	21 (88)	47 (86)	1.000
AGB in history (%)	15 (19)	11 (46)	4 (7)	**<0.001**
BMI, kg/m^2				
· Pre RYGB	45±7	43±6	46±8	**0.032**
· Minimal post RYGB	31±6	35±5	29±5	**<0.001**
· Pre revisional surgery	36±7	39±6	34±6	**0.003**
Months after RYGB	56±36	49±34	59±36	0.267
Length alimentary limb, cm	142±21	142±23	143±21	0.910
Length biliopancreatic limb, cm	60±23	61±25	60±22	0.877
Circumference ring (%)				
· 6.5 cm	20 (25)	6 (25)	14 (26)	
· 7.0 cm	27 (34)	7 (29)	20 (36)	
· 7.5 cm	18 (23)	4 (17)	14 (26)	0.409
· 8.0 cm	5 (6)	3 (13)	2 (4)	
· Unknown	9 (11)	4 (17)	5 (9)	

± standard deviation, AGB=adjustable gastric band, BMI=body mass index, RYGB=Roux-en-Y gastric bypass. Bold values indicate statistical significant outcomes (p<0.05)

Weight regain

The lowest weight and BMI obtained after the initial RYGB of the total group was 89.6±18.8 kg and 31±5 kg/m^2. Before revisional surgery, patients regained on average 14.6 kg resulting in a BMI of 36±7 kg/m^2. After revisional surgery, further weight regain was prevented in 75% of patients during the two year of follow up resulting in a BMI of 33±6 kg/m^2. A limited mean regain of 2.3 kg was seen in patients in whom revisional surgery did not prevent further weight regain.

Weight loss

An overview of the %TBWL over time, calculated with the weight prior to RYGB, is presented in **figure 2**. Approximately one third of patients reached a higher %TBWL one year after revisional surgery compared to the maximal %TBWL obtained after RYGB. One year after revisional surgery %TBWL improved by 6% in the poor responder group and 8% in the good responder group resulting in a %TBWL of 14±12% (weight 102±21 kg, BMI 36±6 kg/m^2) and 34±11% (weight 87±17 kg, BMI 30±4 kg/m^2) respectively one year after revisional surgery. These results remained stable up until two years after placing the non-adjustable ring. Two years after revisional surgery 13% of the patients in the poor responder group achieved a %TBWL > 25%, compared to 91% in the good responder group.

One year after revisional surgery a significant difference in %TBWL, calculated with the weight prior to revisional surgery, between the groups was found. After adjustment for age, sex, preoperative BMI, AGB in history and preoperative T2DM, the difference in %TBWL between the poor responder group and the good responder group was 6% ($p = 0.031$, n=52) after 12 months and 5% ($p = 0.204$, n=37) after 24 months in favor of the good responder group. In a subset analysis in which all the patients who had an AGB in the surgical history were removed from the analysis the difference in % TBWL between the good responder group and the poor responder group reduced to 4.4% after 12 months ($p = 0.128$).

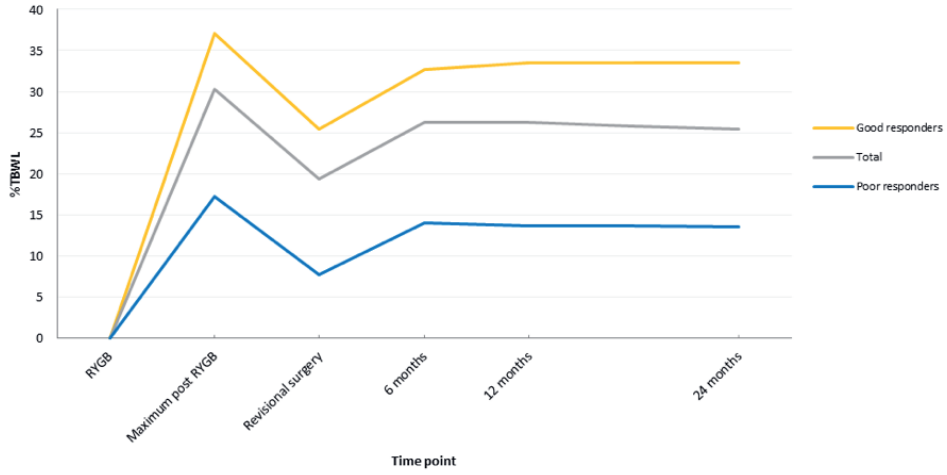

Figure 2. Total body weight loss after Roux-en-Y gastric bypass and revisional surgery
%TBWL=percentage total body weight loss, RYGB=Roux-en-Y gastric bypass

Complications

In total 27 (34%) patients suffered from complaints or a complication in the first two years following revisional surgery (**table 2**). The most common reason for readmission to the hospital was persistent dysphagia. Twenty-six (33%) patients underwent a reoperation. A total number of eighteen (23%) rings were removed after a mean follow-up of nine months and five (6%) were adjusted to a larger circumference. The main reason for band removal or adjustment was dysphagia (n=22). One ring was removed one day postoperative because of a perforation located just proximal to the ring. In one patient treatment of a gastric ulcer at the gastroesophageal junction necessitated removal of the silicone ring. Two patients were re-operated because of complications unrelated to the ring. Of the first 10 non-adjustable rings placed in each center 26% was removed. This percentage decreased to 17% when experience increased (>20 procedures) (**figure 3**).

Table 2. Complications

	Total	Poor responders	Good responders	*p*-value
Total number of patients (%)	27 (34)	6 (25)	21 (38)	0.309
Reoperation	26	5	21	
Ring removal	18	3	15	
Ring adjustment	5	-	5	
Internal herniation	1	1	-	
Hiatal hernia	1	-	1	
Cicatricial hernia	1	1	-	
Conservatively treated bleeding	1	1	-	
Stomach ulcer	1	-	1	

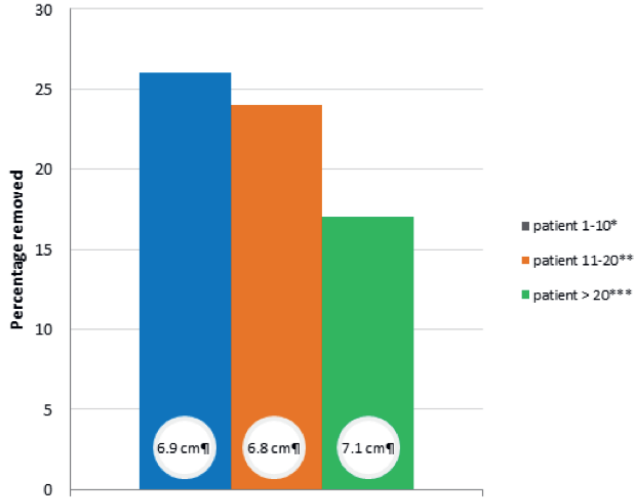

Figure 3. Percentage non-adjustable rings removed during 2 year follow up
*4 centers, **3 centers, ***2 centers
¶ mean circumference of removed rings

Discussion

Although gastric bypass surgery has been shown to induce long term weight loss, a subset of patients fails to achieve a sufficient amount of weight or regains weight after an initial good result[3,4,5]. Many factors, such as lifestyle, metabolic imbalance and technical aspects following surgery may contribute to insufficient weight loss after RYGB[12]. Additional counseling by a dietician and/or a lifestyle coach for weight loss treatment is preferred, however a substantial number of patients may require revisional surgery to improve results. Patients with failed weight loss surgery pose a challenge for healthcare providers, especially

when obesity related comorbidities recur. Despite the growing number of patients, there is no consensus in the literature and a standardized treatment protocol is not available. The present study investigated the effect of placing a non-adjustable silicone ring around the pouch as a revisional procedure in patients with insufficient results after RYGB.

In the literature, only Dapri et al. described their results after placing a non-adjustable silicon ring after failed RYGB surgery in six patients[8]. An average percentage excess weight loss of 70% was achieved one year after revisional surgery. However, it must be mentioned that these six patients had an average preoperative BMI of 29.5 kg/m^2.

In our study reporting on 79 patients, it is demonstrated that placing a non-adjustable ring prevented further weight regain in 75% of patients and limited weight regain in the remaining patients. In addition, the %TBWL based on the weight before primary surgery improved by 7% to a total of 26±15% one year after revisional surgery and remained stable until two years after the procedure. It can be debated if an overall 7% increase in TBWL corresponding with roughly 12 kg has enough clinical relevance[13]. However, more weight loss is associated with better clinical outcomes. Furthermore, it must be stressed that without revisional surgery it is very likely that the trend of weight regain would have led to even worse results of the earlier RYGB, which now could be prevented. From a patients' perspective weight regain is a significant physical and psychological burden that weighs heavily on self-image and quality of life. Any intervention that can help to turn around the progressive debilitating process of involuntary weight regain should be welcomed.

The additional weight loss effect of placing the non-adjustable ring was more pronounced in patients that had an initial good result after the RYGB compared to patients with insufficient weight loss after this procedure. This difference in %TBWL decreased when all the patients who had an AGB in the surgical history were removed from the analysis. Probably because of a type II error due to a smaller study group. The additional weight loss effect of the ring in the poor responder group did not contribute to an amount of weight loss that is defined as clinically successful (%TBWL > 25%). Only 13% of the patients in the poor responder group achieved this amount of weight loss. However, when preventing weight regain is the goal, placement of the ring could also be considered in this specific group of patients. To obtain a %TBWL > 25% in patients with insufficient weight loss after a RYGB other surgical interventions (e.g. distalization) may be necessary. However, these procedures often require adjustments of bowel configuration to induce malabsorption hence posing these patients at a higher risk of postoperative complications[6].

Weight regain due to enlargement of the gastric pouch and dilatation of the gastric pouch outlet has often been described[9,14]. Unfortunately, information about the aspect of the pouch during the revisional procedures in this study was not documented in detail in

operative charts and therefore could not be taken into account. Results of this study do suggest that placement of a ring around the pouch counteracts these pouch related problems causing weight regain. Although hard evidence is lacking, the non-adjustable ring could potentially prevent further weight regain by preventing further dilatation of the gastric pouch. Alternatively, restriction may play a role. But unlike the adjustable gastric band, the ring is not to be placed tightly around the pouch and therefore should not induce a primary restrictive effect. However, it could hamper the passage of a food bolus when eating large portions. Additional studies are needed to investigate these theories and are currently being performed at our institute.

Revisional surgery after RYGB is often associated with high perioperative morbidity[7]. Numerous studies on additional banding placement using adjustable and non-adjustable bands and rings are available but it proves hard to draw definite conclusions from them[7, 15,16]. It is suggested that a silicone non-adjustable ring leads to less adhesions and a lower complication rate[9]. This is confirmed in a study using a non-adjustable ring in 178 primarily operated patients in whom only 2.8% of the rings were removed and 3.4% were replaced due to a broken band during 5 years of follow-up[9]. The percentage of rings removed in our study (23%) is much higher and therefore of concern. This may suggest that placement of a non-adjustable ring is technically more demanding when performed as a secondary procedure. Compared to an adjustable band that is usually placed through the pars flaccida route, the perigastric placement of the non-adjustable ring is technically more challenging. Adhesion formation in the bursal sac induced by pouch formation during the gastric bypass can make tunneling behind the pouch more difficult at the time of revision. After analyzing the results in this study, it was shown that most of the rings in this study that had to be removed were placed in the start-up phase. Furthermore, most removed rings were constructed with a relatively small diameter. This suggests a significant learning curve effect in the first procedures per center. With increased experience and use of a larger circumference the number of removed rings decreased. Therefore, surgeons considering use of a non-adjustable ring during gastric bypass surgery should keep in mind not to close the ring too tight. As advised by the manufacturer, a 40 French tube inside the pouch and an additional 5mm instrument should easily pass between the pouch and the ring when closed. In addition, the ring should be placed perpendicularly in regard to the axis of the pouch to prevent tilting and sliding over the gastrojejunostomy.

Post-operative dysphagia associated with placement of a ring around the pouch is a matter of concern. Although the non-adjustable ring should not be placed tightly around the pouch, some patients have complaints of dysphagia which resulted in removal or adjustment in 22 patients in this study. In theory, the number of patients experiencing some degree of dysphagia may be even higher but many patients consider this a desired consequence of the procedure and therefore will not report these complaints. These

patients adapt their eating pattern which results in less complaints and often a good result in terms of weight loss[9]. However, when considering dietary intake and risk of nutritional deficiencies, these eating patterns may be insufficient and therefore should be monitored carefully. In future studies dysphagia and eating behavior and the effect on quality of life should be taken into account.

We acknowledge that this study has several limitations due to its retrospective design and important factors such as reduction of comorbidities and quality of life were not taken into account. Ring removal and loss to follow-up resulted in a reduced number of patients available for analysis. It is unclear how patients who dropped out performed at 24 months, but from our historical experience with adjustable banding it must be feared that results in that group could be disappointing. Furthermore, by creating two groups based on the %TBWL achieved after the primary RYGB it is possible that baseline differences may have affected overall outcome. Despite these limitations, this study is to our knowledge, the first multicenter study reporting on non-adjustable ring placement as a revisional procedure in a relatively high number of patients. Since there is no clear treatment algorithm for the management of patients with insufficient weight loss or weight regain after RYGB, this study could be the first step in creating an evidence-based treatment protocol for this specific group.

Conclusion

Patients who fail to counteract weight regain or insufficient weight loss following gastric bypass surgery with conservative measures could be considered candidates for revisional surgery. Placement of a non-adjustable ring around the gastric pouch is a technically feasible revisional bariatric procedure. Especially in patients who suffer from weight regain after initial good weight loss, modest improvements in weight loss were shown at mid-term follow-up. Placement of the ring around the gastric pouch should not be too tight in order to prevent the high number of patients with postoperative dysphagia in whom ring removal was necessary.

Conflict of interest

AB, EA, VL, AP, KR, KL, FB, EH and all other participating surgeons declare to have no conflict of interest. RP is a consultant to Ethicon Endosurgery, not related to this paper.

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CHAPTER 7

7

Weight Loss and malnutrition after conversion of the primary Roux-en-Y gastric bypass to distal gastric bypass in patients with morbid obesity

Yontha van der Burgh, Abel Boerboom, Hans de Boer, Bart Witteman, Frits Berends, Eric Hazebroek

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Background

After Roux-en-Y Gastric Bypass (RYGB), 15 to 35% of patients fail to lose sufficient weight. Distalization of the limbs of the RYGB (D-GB) with shortening of the common channel (CC), has been used to induce additional weight loss. However, this may increase the risk of malnutrition.

Objective

The aim of this study is to assess post-operative outcomes after D-GB with an alimentary limb of 250-300 cm and CC of 100 cm.

Setting

General hospital, specialized in bariatric surgery.

Methods

We retrospectively studied all patients who underwent revision of RYGB to D-GB between January 2014 and April 2018. Data were collected from medical records, including weight loss, nutritional deficiencies and comorbidities. Questionnaires on defecation pattern, quality of life and patient satisfaction were obtained.

Results

Forty-seven patients were included. Total body weight loss (%TBWL) increased significantly from 12% to 30% after D-RYGB. In 62% of patients %TBWL>25% was achieved. Patients with %TBWL<25% after primary RYGB, lost significantly more weight than initially reached after RYGB. Diabetes and hypertension remission occurred in 67% and 50%, respectively. Five patients (11%) needed subsequent lengthening of the CC to 250 cm due to protein malnutrition or debilitating defecation patterns. Nutritional deficiencies were present in 89% of patients after D-GB despite the prescription of specialized multivitamins.

Conclusion

Conversion of the primary RYGB to D-GB improves weight loss and comorbidities in patients with insufficient weight loss after primary RYGB. Following D-GB, nutritional complications and diarrhea are a risk. Based on this study, a modified D-GB with a longer CC of >200 cm will be considered.

Abstract

Introduction

Bariatric surgery is the most effective long-term strategy to reduce weight and maintain weight loss in patients with morbid obesity [1,2]. One of the most frequently performed bariatric procedures is the laparoscopic Roux-en-Y Gastric Bypass (RYGB), which provides substantial weight loss and resolution of obesity-related comorbidities in the majority of patients [2-4]. However, 10-35% of the patients fail to lose sufficient weight or regain weight after RYGB, sometimes with recurrence of comorbidities [5,6].

When conservative interventions, such as additional counselling by a dietitian or lifestyle coach fail to improve weight loss, revisional surgery may be considered. The surgical options for patients with weight loss failure after RYGB are limited [7]. One of the options is conversion of the primary RYGB to a distal RYGB (D-GB) by shortening of the common channel (CC), which increases the malabsorptive component of the RYGB. It has been shown that distalization can add significantly to weight loss but at the cost of developing severe diarrhea and multiple nutrient deficiencies [7-12].

Previous studies reported a CC of 50-300 cm by elongating the biliopancreatic limb (BPL, type 1 D-GB) or alimentary limb (AL, type 2 D-GB) [7-10]. However, there is no consensus on the length of the intestinal limbs of the D-GB in current literature. A systematic review by Tran *et al.* showed better weight loss with the type 1 D-GB, but less malnutrition with the type 2 D-GB [7].

In our hospital, we performed a combination of type 1 and 2 D-GB by creating a D-GB with a CC of 100 cm and a longer AL of 250-300 cm, with the aim to achieve sufficient weight loss with less severe malnutrition. The choice for these intestinal lengths was based on the study of Kalfarentzos *et al.* who showed good results with these intestinal lengths as a first step procedure in patients with a Body Mass Index (BMI) > 50 kg/m2 [13].

The aim of this study was to assess mid-term weight loss, nutritional status, defecation patterns and comorbidity remission up to 4 years after an adjusted D-GB, as a revisional procedure for insufficient weight loss or weight regain after RYGB in patients with morbid obesity.

Methods

Patient selection

All adult patients who underwent distalization after RYGB between January 2014 and April 2018 were included in this study. Patients were eligible for D-GB if they had no sufficient

weight result after RYGB, still met the International Federation for the Surgery of Obesity (IFSO) criteria, and conservative interventions had failed to improve weight loss [14]. If needed, gastrointestinal contrast studies were performed to evaluate the anatomy of the bypass. All cases were discussed in a multidisciplinary team to evaluate the appropriateness for D-GB.

The protocol of this retrospective study was reviewed and approved by the Local Ethical Committee. Data on weight loss, nutritional status, comorbidities and complications were collected retrospectively from medical records of regular follow-up visits. Patients were excluded from data-analysis if they did not have follow-up data after D-GB. All patients were contacted by phone and asked to fill out additional questionnaires about defecation pattern, quality of life (QoL) and patient satisfaction. Patients without scheduled follow-up visits were invited for follow-up at the outpatient department.

Surgical Procedure

All procedures were performed laparoscopically. First total intestinal limb length was measured to ensure that there was sufficient length to create a D-GB. The BPL and AL were divided at the site of the old junction using a linear stapler (Echelon, Ethicon, Johnson & Johnson, New Brunswick, NJ, USA). The AL was lengthened to 300 cm, cut and a new side-to-side enteroenterostomy 100 cm proximal of the ileocecal valve was created using a linear stapler combined with a running suture. The former BPL was re-anastomosed to the newly created proximal end of the small intestine, and thereby lengthened. The two newly formed mesentery defects were closed with a non-absorbable suture (**Figure 1**).

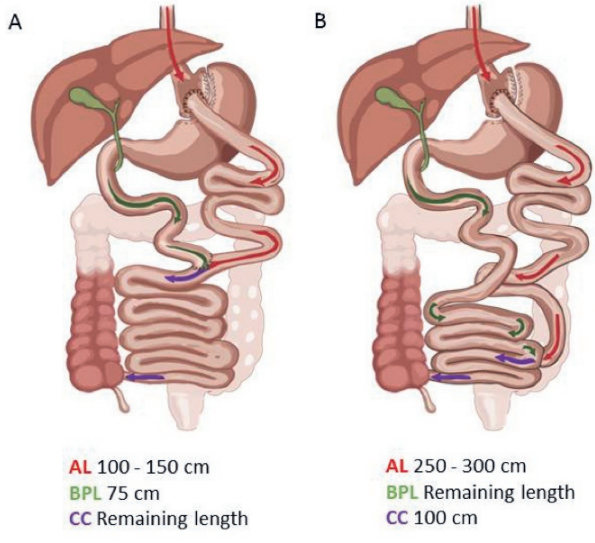

Figure 1. Intestinal lengths: A) Primary Roux-en-Y gastric bypass (RYGB) B) Distal RYGB
AL Alimentary limb, *BPL* Biliopancreatic limb, *CC* Common Channel

Postoperative management

After distalization, patients started with a clear liquid diet and switched to their normal diet at postoperative day two. All patients were advised to take a specific multivitamin developed for patients with more malabsorptive bariatric procedures, like Biliopancreatic diversion/Duodenal switch (FitForMe® FFM, Rotterdam, The Netherlands) and calcium carbonate/cholecalciferol 500mg/800IE three times daily. We also advised a minimal protein intake of 1.5 g/kg ideal body weight. A follow-up visit with the surgeon was scheduled at 4 weeks and 3, 6, 12 and 15 months postoperatively. After the first two years, patients were invited once a year for a complete check-up.

Outcomes

Primary outcome was weight loss, defined as percentage total body weight loss (%TBWL, weight loss at follow-up time point divided by preoperative weight) and percentage excess weight loss (%EWL, weight loss divided by preoperative excess weight based on ideal body weight at BMI 25 kg/m2). Sufficient weight loss was defined as a %TBWL > 25% [15]. Patients were categorized as a good responder if $\%TBWL_{max}$ after primary RYGB was > 25%, and as poor responders if $\%TBWL_{max}$ was < 25% TBWL.

Secondary outcomes were nutritional status, defecation pattern, occurrence of comorbidities, complications, QoL and patient satisfaction after D-GB. Vitamin and mineral deficiencies were defined as serum levels below the lower normal limit (LNL) of our hospital reference values (reference values are shown in tables). Severe protein malnutrition was defined as a serum albumin level < 25 g/L that is not explained by either hepatic failure or renal or gastrointestinal protein loss [12]. Severe protein malnutrition was treated with nasogastric tube feeding, that contains small peptides and medium chain triglycerides that are easily absorbed (Perative®), in combination with pancreatic enzyme supplementation [(16)]. Defecation pattern was assessed and overall QoL was measured using the Fecal Score and BODY-Q questionnaire respectively [17,18]. Patient satisfaction was rated on a five-point scale, ranging from very unsatisfied to very satisfied.

The prevalence of comorbidities, including Type 2 Diabetes Mellitus (T2DM), dyslipidemia and hypertension was retrieved from medical records. Resolution of T2DM was defined as glycosylated hemoglobin (A1C) within the normal range and no need for diabetic medication. Reduction of dyslipidemia (DL) was defined as triglycerides and total cholesterol within the normal range without need for medication [19]. A physiologic blood pressure was defined as patients with a blood pressure between 140/90 and 100/60 mmHg and no need for antihypertensive medication [20].

Data analysis

Patients were excluded from data analysis if they did not have follow-up data or had a known genetic mutation that causes obesity. After proximalization surgery (elongation of the CC to 250 cm), patients were also excluded from data-analysis.

Descriptive statistics were performed and reported as means ± standard deviation (SD), counts and percentages. Statistical analysis to assess differences over time was performed using Linear Mixed Models with covariance type autoregression 1 and time as fixed effect, and reported as mean ± standard error of the mean. Results with $P < 0.05$ were considered statistically significant. Data was analyzed using SPSS Statistics (version 22.0 for Windows).

Results

Forty-seven patients with obesity underwent distalization of the RYGB between June 2014 and April 2018. Three patients were excluded from data analysis: one because of a known Melanocortin 4 receptor (MC4R) mutation, one because of death within 30 days postoperatively due to a blow-out of the stomach remnant probably due to internal herniation, and one because of loss to follow-up directly after the operation. In total, 44 patients had postoperative follow-up data, with a mean follow-up time of 34 months (range 12-58) after D-GB. Baseline characteristics are shown in **Table 1**. Twenty-four patients (55%) filled out the questionnaires.

Table 1. Baseline characteristics at the time of D-RYGB surgery

	Total (n=44)	**Poor responders** (n=13)	**Good responders** (n=31)	***p*-value**
Age (years)	44 ± 11	52 ± 11	41 ± 9	**0.001**
Female (%)	33 (75%)	8 (62%)	24 (77%)	0.291
BMI (kg/m^2)				
· Pre RYGB	49 ± 7	44 ± 6	51 ± 6	**0.001**
· Max effect of RYGB	35 ± 5	38 ± 4	34 ± 5	**0.014**
· Pre D-RYGB	43 ± 4	43 ± 4	43 ± 4	0.856
Interval between RYGB and D-RYGB (months)	76 ± 32	62 ± 25	81 ± 31	**0.040**
Duration of D-RYGB surgery (minutes)	77 ± 28	87 ± 37	72 ± 21	0.093
Hospital stay (days)	1 ± 1	1 ± 0	1 ± 1	0.934
Limb Lengths after D-RYGB (cm)				
· AL length	295 ± 39	292 ± 38	296 ± 38	0.799
· BPL length	217 ± 102	200 ± 90	222 ± 102	0.652
· Common channel length	103 ± 9	105 ± 10	102 ± 107	0.214
· Total intestinal limb length	615 ± 110	595 ± 110	616 ± 107	0.934

Mean ± standard deviation, *RYGB* Roux-en-Y Gastric Bypass, *D-RYGB* Distal RYGB, *AL* Alimentary limb, *BPL* Biliopancreatic limb

Weight loss

Mean %TBWL after primary RYGB, at the time of distalization was 12% (95% CI 9-15%). D-GB significantly improved %TBWL at 12, 24 and 36 months to 28%, 30% and 26%, respectively ($P < 0.001$) (**Figure 2**, **Table 2**). Adequate weight loss was achieved in 24 of 39 patients (62%) (with exclusion of the 5 patients that needed elongation of the common channel) after sequential RYGB and D-GB surgery at the mean follow-up of 34 months.

Thirteen patients had a poor response after primary RYGB (%TBWL<25%), whereas 31 patients initially had a good response after primary RYGB (%TBWL>25%) but later regained weight. Poor responders had a significantly lower pre-RYGB BMI compared to good responders (P=0.001). There was no difference in BMI at the time of D-GB (P=0.856). Patients with a poor response after primary RYGB lost significantly more weight at 12 and 24 months after D-GB than they ever had reached after primary RYGB (P=0.042, P=0.024). Patients with an initial good response after primary RYGB showed similar weight loss after D-GB as had occurred after RYGB (p=0.673) (**Figure 2**). After D-GB, poor and good responders had similar %TBWL over time (p=0.488), but good responders had better overall results.

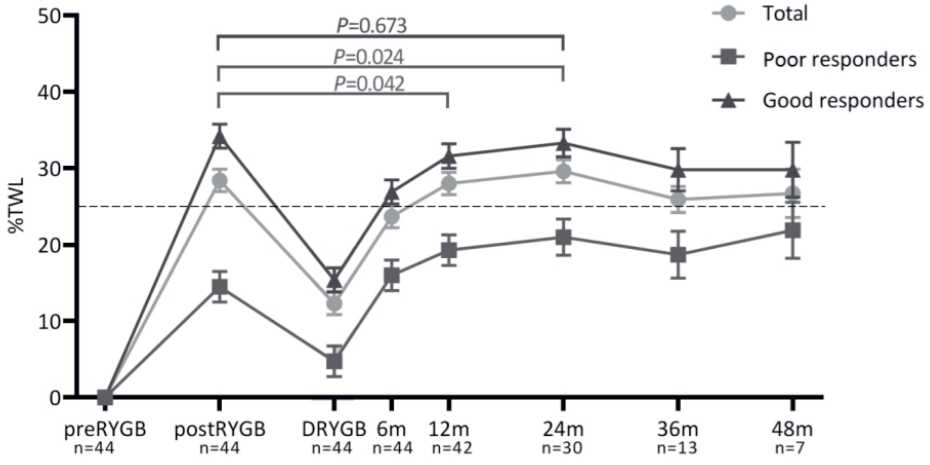

Figure 2. Postoperative Total Weight Loss (%TBWL), including maximum %TWL after primary Roux-en-Y Gastric Bypass (RYGB) and %TBWL after Distal RYGB (D-GB) with a maximum follow-up of 48 months.
Mean ± SEM (Standard Error of the Mean)

Table 2. Postoperative weight outcomes after primary Roux-en-Y Gastric Bypass (RYGB) and Distal RYGB (D-GB) with a maximum follow-up of 48 months

	Before RYGB	Max effect of RYGB	At the time of D-GB	After D-GB				
				6 m	12 m	24 m	36 m	48 m
	n = 44	n = 44	n = 44	n = 44	n=42	n=30	n=13[a]	n=7[a]
Weight (kg)	147 ± 3 (141-154)	104 ± 3 (98-111)	128 ± 3 (121-135)	111 ± 3 (104-118)	105 ± 3 (98-112)	103 ± 4 (96-110)	106 ± 5 (96-115)	104 ± 6 (92-116)
BMI (kg/m^2)	49 ± 1 (48-51)	35 ± 1 (33-36)	43 ± 1 (41-44)	37 ± 1 (35-39)	35 ± 1 (33-37)	34 ± 1 (33-36)	35 ± 1 (33-38)	35 ± 2 (31-38)
%EWL from D-GB	NA	NA	NA	33 ± 2 (28-37)	45 ± 2 (40-49)	48 ± 3 (43-54)	42 ± 4 (35-50)	49 ± 5 (39-59)
%TBWL from D-GB	NA	NA	NA	13 ± 1 (11-15)	18 ± 1 (16-20)	19 ± 1 (18-22)	16 ± 1 (13-19)	18 ± 2 (14-22)

Mean ± Standard Error of the Mean, 95% Confidence Interval. *RYGB* Roux-en-Y Gastric Bypass, *D-GB* Distal RYGB, *BMI* Body Mass Index, *EWL* excess weight loss, *TBWL* total body weight loss. [a] Excluding patients with proximalization of the D-GB

Nutritional deficiencies

Nutritional deficiencies were present in 40 of 44 patients (89%) after D-GB, despite the use of multivitamins, calcium carbonate and additional cholecalciferol. The most common nutritional deficiencies were calcium, vitamin A, vitamin D, selenium, zinc, and protein (as reflected by a serum albumin < 32 g/L) (**Table 3**). Additional supplementation was needed in 64% of the patients and 45% of the patients needed intensified follow-up at the Internal Medicine department for treatment of their nutritional deficiencies. Vitamin D deficiencies led to hyperparathyroidism in 16 patients. Four patients with a vitamin D deficiency did not respond to 100.000 IE oral vitamin D per week and needed Cholecalciferol injections to achieve sufficient vitamin D levels. Excess vitamin B6 levels were present in 69% of the patients. Six patients (14%) developed severe protein malnutrition with albumin levels < 25 g/L. Five of those patients needed supplementary nasogastric tube feeding (Perative□) combined with pancreatic enzyme supplementation to increase albumin levels. In two patients, the CC was lengthened from 100 cm to 250 cm. The three other patients refused proximalization, because of fear of weight regain. They managed to maintain their albumin levels > 30 g/L with oral protein supplements and pancreatic enzyme supplementation.

Table 3. Nutritional deficiencies

	n	n deficient (%)	Range	LNL	
Hemoglobin	44	29 (66%)	F: 5.5 - 7.3 M: 5.6 - 8.2	F: 7.4 M: 8.4	mmol/L
Ferritin	42	10 (24%)	5 - 21	22	µg/L
Vitamin B12	43	11 (26%)	76 - 186	200	pmol/L
Vitamin B11	43	1 (2%)	3.8	5.0	nmol/L
Albumin	42	18 (43%)	12 - 41	32	g/L
Calcium	43	26 (60%)	1.94 - 2.19	2.20	mmol/L
Phosphate	34	4 (12%)	0.5 - 0.7	0.8	mmol/L
Magnesium	34	3 (9%)	0.64 - 0.65	0.66	mmol/L
Selenium	16	13 (81%)	0.32 - 0.57	0.63	µmol/L
Zinc	30	19 (63%)	5.7 - 9.0	9.2	µmol/L
Copper	5	0 (0%)	> 9.1	8.8	µmol/L
Vitamin A	32	16 (50%)	< 0.35 - 1.02	1.05	µmol/L
Vitamin B6	32	0 (0%)	> 63	25	nmol/L
Vitamin B1	32	0 (0%)	> 96	95	nmol/L
Vitamin D	42	21 (50%)	< 8 - 47	50	nmol/L
HPT	40	16 (40%)	1.3 - 6.6	6.8*	pmol/L
Vitamin E	9	2 (22%)	10.0 - 10.2	12.8	µmol/L
Vitamin K	5	4 (80%)	<0.16 - 0.16	0.22	nmol/L
Prolonged PTT	26	11 (42%)	16 - 27	15*	sec.

LNL lower normal limit, *F* female, *M* male, *HPT* Hyperparathyroidism, *PTT* prothrombin time, * *UNL* Upper normal limit

Defecation

Defecation frequency was on average six times per day (range 0-20). Seven patients (16%) reported fecal incontinence. Pancreatic enzyme replacement therapy was needed in 18 of 44 patients (41%), either for debilitating defecation patterns or as treatment for protein malnutrition. Three patients needed lengthening of the CC from 100 cm to 250 cm due to self-reported debilitating defecation patterns with severe diarrhea >10 times per day. Twenty-four patients (55%) filled out the questionnaires on Fecal Score. Reduced QoL due to defecation pattern was reported by 22 patients (92%), of which 15 patients (63%) reported daily reduced QoL due to their defecation pattern.

Comorbidities

Sixteen of the 44 patients (36%) had a persistent comorbidity at the time of D-GB, in the form of T2DM, hypertension or dyslipidemia (**Table 4**). After D-GB, T2D was resolved in 67% and hypertension was resolved in 50% of the patients.

Table 4 Resolution of comorbidities

	Pre-distalization	Post-distalization remission
Type 2 Diabetes Mellitus	6 (14%)	4/6 (67%)
Hypertension	10 (23%)	5/10 (50%)
Dyslipdemia	1 (2%)	1/1 (100%)

Re-operation

In total, ten patients (23%) needed reoperation after D-GB of which proximalization was most commonly performed (**Table 5**). Proximalization of the common channel to 250 cm was needed in five patients (11%) due to severe protein deficiency (n=2) or debilitating defecation patterns (n=3) two years after D-GB. Protein deficiency resolved after proximalization and defecation frequency decreased from 7-20 times to 1-6 times daily. However, vitamin and mineral deficiencies were persistent in three out of five patients despite proximalization. Weight regain was common after proximalization, %TBWL was 16-28% after distalization and decreased to 12-16% after proximalization. All patients who needed proximalization were good responders to the initial RYGB.

Table 5. Reasons for short- and long-term reoperation

Reoperation short-term and long-term		n
< 30 Days	Death (blow-out stomach remnant)	1
	Reoperation	
	BPL dilatation	1
> 30 Days	Reoperation, total	10
	Proximalization	5
	Cholecystectomy	4
	Diagnostic laparoscopy for abdominal pain	3
	Hernia cicatricalis	1
	Internal herniation	1

short-term < 30 days; long term > 30 days, *BPL* biliopancreatic limb

Quality of Life and patient satisfaction

Overall QoL was determined with the BODY-Q questionnaire in 24 patients, on a scale from 0 to 100, with 100 as the best possible score. Body image and sexual well-being were scored low, 32 ± 24 and 35 ± 28 respectively. Psychological wellbeing was scored 52 ± 23, physical activity was scored 58 ± 23 and social well-being was scored 65 ± 26.

After D-GB, 9 of 24 (38%) patients were satisfied with the outcome and 10 of 24 (42%) patients were unsatisfied with the outcome. The remaining patients were neutral.

Discussion

The present study demonstrates that D-GB, based on a combination of the type 1 and 2 D-GB by creating a CC of 100 cm and an AL of 250-300 cm, is effective in achieving additional weight loss in patients with weight loss failure after primary RYGB. A %TBWL > 25%, was achieved in 62% of the patients. This decreased to 56% when the five patients who underwent proximalization surgery (elongating the CC to 250 cm) were included. Weight loss after D-GB was achieved at the expense of persistent malnutrition, debilitating defecation patterns and reoperations in a substantial number of patients.

The %EWL in our study was 60%, which is slightly lower compared to studies that performed a type 1 D-GB (short AL of 100-150 cm and a CC varying from 100-300 cm) and showed an %EWL ranging from 66 to 85% [5, 8-11, 21-24]. Brolin *et al.* performed a type 2 D-GB, with a very long AL, and reported an %EWL of 48% [25]. This implicates that the AL is still able to absorb macronutrients, resulting in less weight loss.

Revision of RYGB to D-GB was effective in patients with a poor response to RYGB as well as in those with weight regain after an initially good response to primary RYGB. Patients with a poor response after primary RYGB (%TBWL < 25%) had significantly more weight loss after D-GB than they ever reached after RYGB and none of them needed proximalization surgery. This suggests that D-GB might be a suitable strategy for this difficult patient group. However, our sample size per group was too small at three and four-year follow-up to draw firm conclusions.

Protein malnutrition after D-GB is thoroughly reported in the literature since this causes severe problems in D-GB patients. In our study, 14% of the patients had severe protein malnutrition, which is low compared to other studies, but still significant. Sugerman *et al.* created a CC of 50 cm, which led to protein malnutrition in all five patients and subsequent death in two patients [10]. Other studies showed severe protein malnutrition in 7-31% of the patients, with higher prevalence in patients with a CC of 100-150 cm and an AL of 100-150 cm [5, 8-11, 21-25]. Shin *et al.,* reported a CC of 200 cm and AL of 100-150 cm with a prevalence of severe protein malnutrition similar to our study, 14% of their patients needed proximalization surgery due to severe protein malnutrition [8]. After the type 2 D-GB, severe protein malnutrition occurred in 7% of the patients and 4% needed proximalization surgery [25]. With a common channel of 300 cm, severe protein malnutrition did not occur [9]. These results imply that a longer CC (200-300 cm) and a longer AL both lead to a lower risk of severe protein malnutrition.

Micronutrient deficiencies were found in 89% of the patients, despite the prescription of multivitamins specifically developed for patients after more malabsorptive bariatric

procedures [26]. Most common nutritional deficiencies in our study were selenium, zinc, calcium, vitamin A and vitamin D, for which additional supplementation was needed in 64% of the patients. Only a few studies reported nutritional deficiencies after D-GB, from which vitamin D (25-77%), vitamin A (20-100%), iron (6-36%), vitamin B12 (6-32%) and calcium (14-23%) are most commonly reported [5, 8-10, 22]. These findings are comparable to our study results. In our study zinc and selenium were the most common nutritional deficiencies. Although these specific deficiencies are scarcely reported in literature, our data suggest that these minerals should be included in the standard nutritional blood screen for D-GB patients. Concordant with previous studies, our study underlines that close monitoring of nutritional deficiencies in D-GB patients is essential and that a wide spectrum of vitamins and minerals should be screened during follow-up [8, 12].

D-GB had a significant adverse impact on defection patterns, which negatively influenced QoL and patient satisfaction. In our patient group, defecation frequency increased on average to six times per day (range 0-20) and diarrhea (often due to steatorrhea) was present in 33%, which was directly correlated with impaired QoL in 89% of the patients. Moreover, debilitating defecation patterns did lead to proximalization surgery in two patients. Four other studies with similar CC length and shorter AL mentioned defecation patterns, in which diarrhea was present in 13-79% of the patients [(5, 8, 9, 22)]. In the study of Ghiassi *et al.,* diarrhea was not present in patients with a CC of 300 cm. This illustrates that a longer CC decreases the prevalence of diarrhea. We hypothesize that most patients have diarrhea due to steatorrhea, which occurs less in patients with a longer CC due to increased fat absorption. Especially since 41% of our patients needed pancreas enzyme replacement therapy, which increases fat digestion and improved the defecation pattern in most patients.

Overall QoL after D-GB showed similar results, when compared to the bariatric patients in the validation study of Klassen *et al.* [18]. Therefore, D-GB did not seem to impair quality of life more than other bariatric procedures. Only physical activity and psychological wellbeing scored slightly lower after D-GB. Moreover, there was a wide variation between patients. This can be expected, as the D-GB has a higher complication rate, more nutritional deficiencies and a higher prevalence of debilitating defecation patterns compared to other types of bariatric surgery [7]. Unfortunately, no QoL data pre-distalization was available and therefore no firm conclusions can be drawn.

Limitations of this study include the small size of the population and the retrospective design. By separation of groups based on %TBWL after primary RYGB we created two small groups that differ on several issues at baseline, including age and initial BMI, and this may have had an effect on the results. Due to the retrospective design, we could not evaluate dietary intake before D-GB. This may have affected the degree of weight loss after D-GB

and the risk for nutritional deficiencies. Furthermore, although we aimed to create an AL of 250-300 cm and CC of 100 cm in all patients, minor differences in AL and CC length were found when reoperation was needed. This was attributed to the lack of a standardized way to measure intestinal length, and inter- and intraoperator differences may have occurred [27]. Although we were able to reach 93% of patients, only half of the patients were willing to complete the questionnaires and this may have reduced the strength of conclusions. The high nutrient deficiency rates may have been prevented if patients had been more compliant with follow-up visits.

The results of our study imply that a longer common channel (200-300 cm) might be a better option for weight loss with less malnutrition and diarrhoea to reach the best quality of life in these patients. More studies regarding the lengths of the AL, BPL and CC for revisional surgery, as well as longer follow-up are warranted.

Conclusion

Conversion of the primary RYGB to D-GB with a common channel of 100 cm and an alimentary limb of 250 cm improves weight loss and remission of comorbidities. However, this comes at the expense of persistent vitamin deficiencies, protein malnutrition, debilitating defecation patterns and reoperations in some patients. In the subset of patients with insufficient weight loss after primary RYGB, distalization shows promising mid-term results. When still considering D-GB as a revisional procedure, adequate pre-operative counselling and close patient monitoring are mandatory. Based on this study, more research towards a modified D-GB with a longer CC of >200 cm is needed

Conflict of interest

YB, AB, HB, BW, FB, EJH declare to have no conflict of interest.

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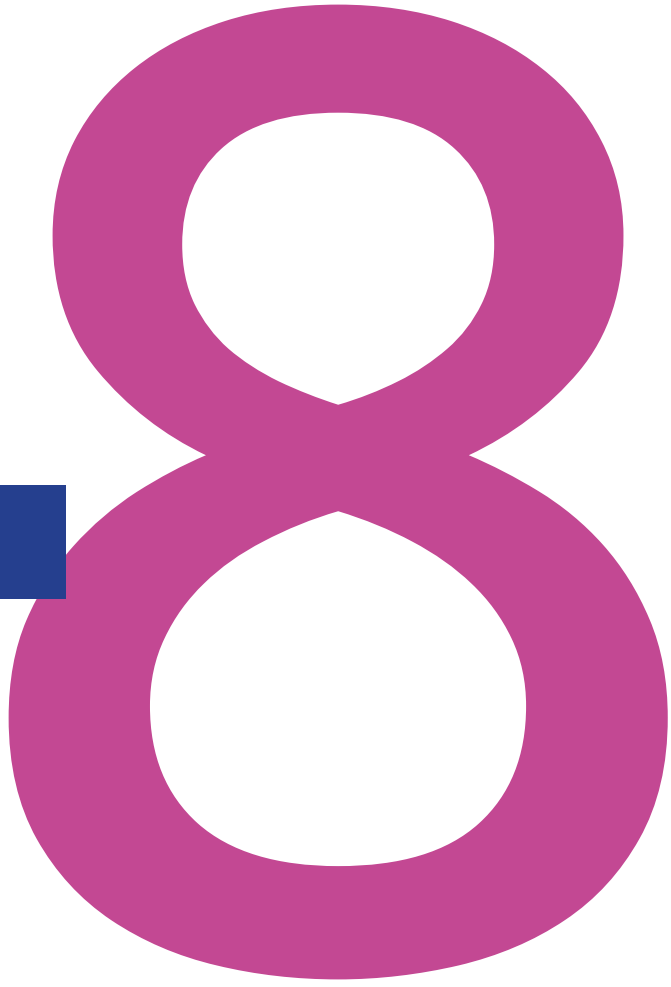
CHAPTER 8



Failed sleeve gastrectomy: Single Anastomosis Duodenoileal Bypass or Roux-en-Y gastric bypass? A multicenter cohort study

Philip Dijkhorst, Abel Boerboom, Ignace Janssen, Dingeman Swank, René Wiezer, Eric Hazebroek, Frits Berends, Edo Aarts

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Abstract

Background

Sleeve gastrectomy (SG) has become the most performed bariatric procedure to induce weight loss worldwide. Unfortunately, a significant portion of patients show insufficient weight loss or weight regain after a few years.

Objective

To investigate the effectiveness of the Single Anastomosis Duodenoileal Bypass (SADI) versus the Roux-en-Y Gastric Bypass (RYGB) on health outcomes in morbid obese patients who had undergone SG previously, with up to two-year of follow-up.

Methods

From 2007 to 2017, 140 patients received revisional laparoscopic surgery after SG in four specialized Dutch bariatric hospitals. Data was analyzed retrospectively and included comparisons for indication of surgery, vitamin/mineral deficiencies, and complications; divided into short-, medium-term. To compare weight loss, linear regression and linear mixed models were used.

Results

Conversion of a SG to SADI was performed in 66 patients and to RYGB in 74 patients. For patients in which additional weight loss was the main indication for surgery, SADI achieved 8.7%, 12.4% and 19.4% more total body weight loss at 6, 12 and 24 months compared to RYGB (all $p < .001$). When a RYGB was indicated in case of gastroesophageal reflux or dysphagia, it greatly reduced complaints almost directly after surgery. Furthermore, a similar amount of complications and nutritional deficiencies was observed for both groups. There was no intra- or post-operative mortality.

Conclusion

Conversion into a SADI resulted in significantly more weight loss while complications rates and nutritional deficiencies were similar and may therefore be considered the recommended operation for patients in which only additional weight loss is required.

Introduction

The sleeve gastrectomy (SG), as derived from the first step of the duodenal switch procedure, has recently become the most performed bariatric procedure worldwide. It has especially gained popularity during the past decade because of its relative simplicity compared to for example the Roux-en-Y gastric bypass. In the short-term, the SG yields good results for weight-loss and comorbidity resolution[1]. However, if weight loss is inadequate or patients experience weight regain, they are advised to undergo revisional surgery. This is especially apparent in those with a higher initial BMI before the SG [2]. Other patients have satisfactory weight loss but suffer from functional complications such as severe gastroesophageal reflux disease (GERD) or dysphagia due to a stenosis. Perhaps more concerning are recent reports of patients developing Barrett esophagus as soon as five years post SG, which theoretically increases the risk of esophageal carcinoma[3-6]. To compound matters, these patients do not benefit enough from the SG as a stand-alone procedure and are advised to undergo revisional surgery.

As the duodenal switch is technically demanding and associated with a high rate of perioperative morbidity[7, 8], other procedures for revisional surgery are needed. The question still remains which bariatric procedure should be performed as revisional surgery after a SG. Two available options include the single anastomosis duodenoileal bypass (SADI) and RYGB. The SADI has been introduced by Sanchez-Pernaute, A et al. (2007) as a simplification of the biliopancreatic diversion and duodenal switch[9]. It is suggested that weight loss results are similar to those obtained after the duodenal switch, but complications rates and nutritional deficiencies might be less frequent[10-12]. However, data available upon this matter are scarce, especially for revisional surgery. A second option is the RYGB, which has been used regularly for many years and has proven its effect in bariatric surgery as a safe and effective primary as well as revisional procedure[13-16]. A major advantage for GERD patients is that in a RYGB, the restrictive function of the pylorus is bypassed, which is why this operation is the best option to reverse GERD symptoms[17]. However, questions have been raised regarding failure rates following RYGB[18, 19].

To date, studies on SADI following SG reported on only small sample sizes. Furthermore, a comparison with the RYGB as a second step has never been made. The aim of this study is to investigate the effectiveness of the SADI versus the RYGB on health outcomes in morbid obese patients who have undergone SG with up to two-year follow-up.

Methods

Patient selection and data collection

Patients who underwent revisional bariatric surgery after SG to SADI or RYGB at one of four Dutch bariatric hospitals (of the five performing SADI in the Netherlands) from 2007 to 2017 were included in this study. These hospitals include the Haaglanden Medical center in The Hague, Groene Hart in Gouda, Rijnstate in Arnhem and St. Antonius in Nieuwegein. The institutional review board approved this retrospective study prior to data collection. The patients included in the study, were divided into two groups. The first group consisted of patients that were operated on in order to improve weight loss after either weight regain or insufficient weight loss. The second group consisted of patients that were operated on because of a functional problem with the SG (e.a. stenosis, reflux or fistula). This group was analyzed separately. These indications were determined after a multidisciplinary consultation. Inclusion criteria consisted of: a prior SG, age 18-65 years, BMI of >35kg/m^2 and all other criteria described in the European guidelines for bariatric surgery by Fried, M.[20]. Exclusion criteria were known malignancies, pregnancy or conditions associated with poor compliance (psychiatric illness).

Data were collected retrospectively from medical records, supplemented with data and laboratory results collected during the lifestyle program that is provided by the Dutch Obesity Clinic.

Surgical procedures

All surgical procedures were started laparoscopically, however, three had to be converted to an open laparotomy, of which two were a SADI and one a RYGB.

*SG***:** The SG was performed as a primary operation[21-23]. First, the greater curvature and angle of His were dissected to staple the gastric fundus and greater curvature parallel to a 40 French gastric bougie, which is inserted in the stomach through the esophagus. Stapling is started from a distance of 3-5cm from the pylorus on the side of greater curvature side toward the angle of His. This results in a tube-like stomach with a volume of approximately 100cc made from the lesser curvature only. Respectively, a black, a green, a gold and up to three additional blue cartridges are used without buttressing material.

*SADI***:** The SADI was exclusively performed as a secondary procedure after a SG. Following an evaluation of the abdominal cavity, the stomach was held upwards to identify the pylorus and dissect the duodenum three cm distal of the pylorus. From the ileocecal junction, the surgeon measured 250cm counting with five cm intervals to mark the point for anastomosis. This part was pulled cranially to be anastomosed with the proximal duodenal stump using a stapler and/or V-loc sutures. Two of the participating centers recently changed the common

channel measurement to 300cm, leading to four SADI patients with a common channel of 300cm.

*RYGB***:** After SG, the RYGB was performed by creating a 30-50ml pouch using a linear stapler by transecting the sleeve at the level of the cardia. A Roux limb with a length of 100cm was attached to the gastric pouch using a linear stapler with a running suture. The biliopancreatic limb was on average 150 cm in length, measured with a hand-over-hand technique along the mesenteric border.

Post-operative management

After revisional surgery, patients started with clear liquids and ambulation on the day of operation. A thrombosis prophylaxis (Fraxiparine ®5700 IU [GlaxoSmithKline Inc., Mississauga, Ontario, Can) was administered once a day for 28 days. Multivitamins from Fit For Me (FFM, Rotterdam, The Netherlands) were advised to all patients after revisional surgery; SADI patients received FFM maximum and RYGB patients received FFM forte.

Outcomes

The primary outcome was weight loss following revisional surgery, defined as percentage total body weight loss (%TBWL, weight loss in kg at a follow-up time point divided by weight in kg measured at secondary operation or at the time of SG). Weight was measured with light clothes on only and to compensate one kilogram was deducted of the measured weight in kilograms. For the second operation, weight was measured on the day of revisional surgery. Follow-up weight was measured at 1.5, 3, 6, 12, 18, and 24 months following revisional surgery and yearly thereafter. These measurements were performed by doctors or specialized bariatric nurses in one of the hospitals or at the Dutch Obesity Clinic.

Secondary outcomes were complications following revisional surgery and change in vitamin or mineral status. Complications were divided into short-term (<30 days), medium-term (>1, <12 months) and long-term (>12 months). Within these times frames, the complications included readmission to the hospital and reoperation.

Blood tests were performed before the second operation, multiple times during the first year after secondary surgery, and then annually. Patients were diagnosed with a deficiency if a specific value for the mineral or vitamin was under a lower limit. The lower limits used are those reported by the American Society for Metabolic and Bariatric Surgery Integrated Health Nutritional Guidelines (2016)[24]. The percentage of patients that were deficient was calculated by dividing the number of patients with a deficiency by the total number of patients that were available. If patients did not show up at follow-up for serum level analyses they were excluded from this analysis from that time on.

Statistical Analysis

All collected data were analyzed retrospectively. Normally distributed values were presented as mean ± standard deviation and non-normally distributed as median with range.

Chi-square tests were used to compare complication rates and the presence of vitamin and mineral deficiencies. Weight loss was only compared for patients with weight improvement as a main indication for surgery. Linear regression analysis was performed to compare %TBWL at 6, 12 and 24 months post-surgery for the SADI and RYGB. Missing data for weight loss at these time points was solved with linear interpolation imputation by taking the average of the value before and after the missing time point. Furthermore, linear mixed models was used to analyze the progression of %TBWL. As potential confounders that might be associated with both weight loss and the type of surgery performed, an analysis with the following variables was performed: gender, age at secondary surgery (date of secondary surgery - date of birth, center, pre-operative weight (measured the day of surgery or the day before) and minimum weight post-SG (lowest weight obtained before secondary surgery). On a theoretical basis, no variables were considered to be potential effect modifiers. P-values of <0.05 will be considered as statistically significant. All statistical analyses were run with the IBM SPSS Statistics version 24.0 for windows.

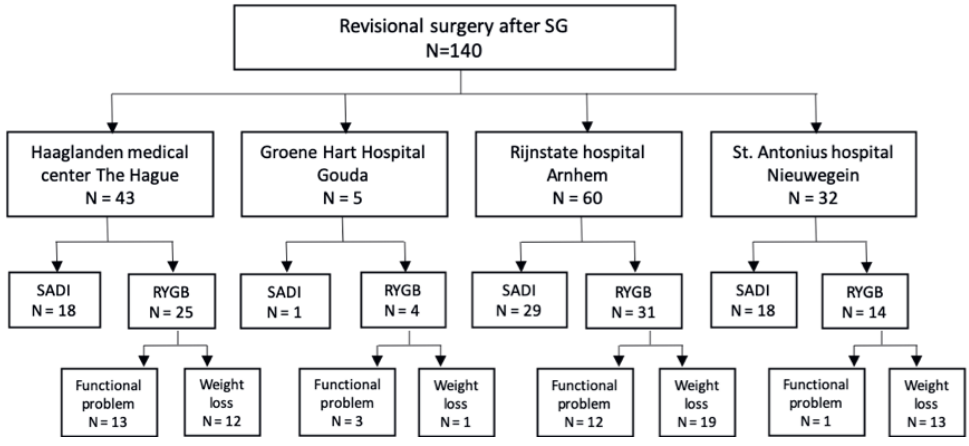

Figure 1. Number of patients included per clinic and division for type of surgery
SADI single anastomosis duodenoileal bypass, *RYGB* Roux-en-Y gastric bypass, *SG* sleeve gastrectomy

Table 1. Baseline characteristics and operation related variables

	SG N=140		SADI N=66		RYGB N=74		P-value
Age in years	41.3	(±11.1)	43.3	(±11.0)	45.1	(±10.9)	.344
Sex ratio (F:M)	114:26		55:10		59:16		.367
Weight, kg	154.4	(±30.6)	130.3	(±22.0)	113.1	(±25.3)	<.001
BMI, kg/m2	53.9	(±10.3)	45.6	(±6.9)	39.3	(±7.9)	<.001
Minimum weight post-sleeve, kg			124.8	(±24.5)	97.1	(±22.3)	<.001
Years after sleeve			3.1	(1.0-14.9)	2.1	(0.3-6.8)	.001
Operative time, minutes	71.6	(±23.6)	84	(40-199)	78	(39-212)	.869
Hospital stay after surgery, days			1	(1-8)	2	(1-25)	.002
Comorbidities (%)							
Hypertension			46.7%		49.3%		.814
Diabetes mellitus			20.0%		32.4%		.238
Dyslipidemia			21.4%		37.8%		.282
OSAS*			20.6%		11.6%		.167

P-values indicate differences between SADI and RYGB. *SD* Standard deviation, *BMI* body mass index, *SG* sleeve gastrectomy, *SADI* single anastomosis duodenoileal bypass, *RYGB* Roux-en-Y gastric bypass; *OSAS* obstructive sleep apnea syndrome. Outcomes given in number with standard deviation or median with range

Results

140 morbidly obese patients underwent revisional surgery after primary SG. A SADI was performed on 66 patients and 74 patients were converted to a RYGB. All of the SADI patients were operated on to improve weight loss. Indications for revision to a RYGB for insufficient weight loss in 39 (52.7%) patients, SG related functional problems or reflux in 29 patients (39.1%), or a combination of both in 6 patients (8.1%). An overview of the baseline characteristics is given in **Table 1**. The SADI group had a higher average pre-operative BMI, was younger, had a shorter hospital stay and underwent surgery later after a SG compared to the RYGB group.

Confounders

The following possible confounding parameters were analyzed using mixed models: gender, age at secondary surgery, center, pre-operative weight and minimum weight post-SG. Of these variables, none managed to change the difference in %TBWL between RYGB and SADI with more than 10%. Therefore, no confounding factor was apparent in this study.

Weight loss

Weight loss was analyzed for patients with insufficient weight loss or weight regain as a main indication for surgery. Before revisional surgery, mean BMI was 45.6(±6.9) kg/m^2 in the SADI group and 42.5(±6.0) kg/m^{2}in the RYGB group. Mean BMI two years after secondary surgery was 32.7(±7.0) kg/m^2 for the SADI group and 39.5(±5.5) kg/m^2 for the RYGB group. To adjust for the difference in weight between the groups at baseline, the %TBWL was calculated. Firstly, the progression of %TBWL after revisional surgery is shown in **Table 2**, with corresponding p-values for the differences between SADI and RYGB. An overview of the %TBWL over time is given in **Figure 2**, calculated with the weight prior to SG as baseline. Secondly, the average %TBWL was calculated with mixed models. It was found that the RYGB had an average %TBWL of 6.3% and SADI of 16.5% over time, leading to a difference of 10.2% in favor of SADI patients (p<.001). Weight loss results at two years following revisional surgery were available for 47% (9/21) of SADI patients and 52% (22/42) of RYGB patients.

Table 2. Percentage total body weight loss (%TBWL) following secondary surgery

	%TBWL at 3 months	%TBWL at 6 months	%TBWL at 12 months	%TBWL at 24 months
SADI	11.3%(±4.1)	16.5%(±5.8)	21.5%(±8.1)	26.4%(±10.4)
RYGB	5.9%(±5.3)	7.8%(±6.8)	8.9%(±8.7)	6.9%(±11.3)
P-value	<.001	<.001	<.001	<.001

SADI = single anastomosis duodenoileal bypass; RYGB = Roux en-Y gastric bypass; ± = standard deviation in percentage

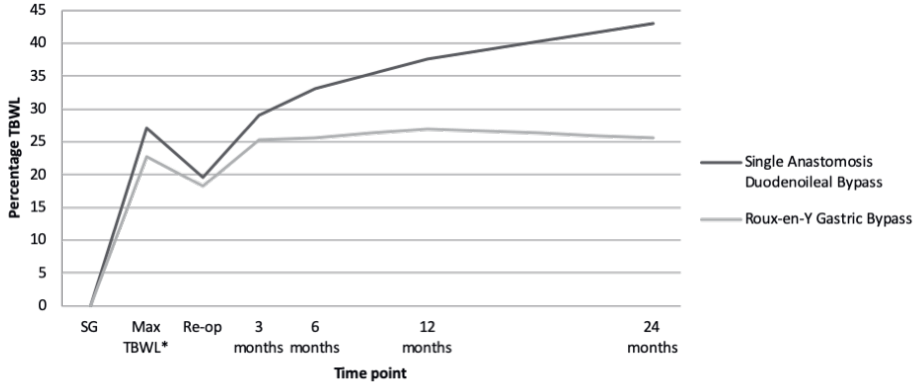

Figure 2.: Average percentage total body weight loss after sleeve gastrectomy (SG) and revision to single anastomosis duodenoileal (SADI) bypass or Roux-en-Y gastric bypass (RYGB)
SG sleeve gastrectomy, *Maximum %TBWL obtained after sleeve gastrectomy and before revisional surgery

Complications

An overview of complications is given in **Table 3**. Reasons for readmission to the hospital were abdominal pain, high fever or persistent nausea. No peri- or postoperative mortality was observed in both groups. Within the first year of surgery, eleven (16.7%) complications were observed after a SADI and thirteen (17.6%) after a RYGB (p=.888). Choledocholithiasis for which a laparoscopic cholecystectomy was performed (n=7) was not counted as a complication. This occurred in two patients following SADI and five after RYGB. Furthermore, two of the medium-term complications in the SADI group included reoperation in the form of a re-sleeve because of insufficient weight loss. One patient presented with severe chronic diarrhea after SADI and underwent a subsequent duodenojejunostomy at 150cm from the ligament of Treitz for enteral feeding.

Table 3. Short-term (<30 days) and medium-term (>1 month and <12 months) complications

	SADI N = 66 (%)	**RYGB** N = 74 (%)	**Total** N = 140 (%)	**p value**
Short-term complication (<30days)	4 (6.1%)	6 (8.1%)	10 (7.1%)	.639
Readmission	3	4	7	
Reoperation	1	2	3	
Abscess	1			
Anastomotic leakage		1		
No focus		1		
Med-term complication (>1 and <12 months)	7 (10.6%)	7 (9.5%)	14 (10%)	.821
Readmission	1	3	4	
Reoperation	6	4	10	
Internal herniation		2		
Incisional hernia	1			
Anastomotic leakage	1			
Revisional surgery*	1			
Re-sleeve	2			
Stenosis		1		
No focus	1	1		

SADI single anastomosis duodenoileal bypass, *RYGB* Roux-en-Y gastric bypass, *= duodenojejunostomy at 150cm from the ligament of Treitz for enternal feeding

Nutritional status

Although patients were advised to use specialized multivitamins, a deficiency was found in 30 (64%) SADI patients and in 28 (62%) RYGB patients (p =.705), during the two-year follow-up. The absolute number of deficiencies with corresponding percentages can be found in **Table 4**.

Table 4. Post-operative nutritional deficiencies within the first two years after revisional SADI and RYGB

	Post-SADI N = 20-47*	**Post-RYGB** N = 29-42*	
	Number of deficiencies (%)	**Number of deficiencies** (%)	**p-value**
Anemia	16 (34%)	11 (26%)	.421
Ferritin	6 (14%)	11 (31%)	.071
Folate	10 (31%)	5 (12%)	.066
Vitamin B12	0	13 (33%)	<.001
Vitamin D	13 (28%)	9 (23%)	.587
Parathyroid hormone	3 (7%)	3 (8%)	.875
Calcium	3 (7%)	2 (5%)	.705
Albumin	5 (12%)	5 (17%)	.525
Vitamin B1	1 (5%)	0	N.A.
Vitamin B6	0	0	N.A.

SADI = single anastomosis duodenoileal bypass; RYGB = Roux en-Y gastric bypass, *Dependent on nutritional value

Functional problems and GERD after SG

Thirty-five patients presented with functional problems after SG. Eight patients were diagnosed with therapy resistant GERD, 20 patients experienced dysphagia (for example due to a stenosis), five patients had persistent complaints of nausea and vomiting, and one presented with a fistula. A conversion to RYGB was performed in all of these patients. Cases of dysphagia or fistulas were all solved after revisional surgery to a RYGB. For patients with GERD, complaints remarkably improved for all patients. However, two out of eight patients still had GERD related symptoms occasionally.

Discussion

The present study investigated the effectiveness of the Single Anastomosis Duodenoileal (SADI) bypass versus the Roux-en-Y Gastric Bypass (RYGB) on health outcomes as a revisional procedure after a failed sleeve gastrectomy (SG). To our knowledge, this study, which included 66 SADI and 74 RYGB patients, is the first to compare the SADI and RYGB as a second step operation for insufficient weight loss or weight regain.

The main results of the current study demonstrate good definitive weight loss results following SADI, with a %TBWL of 26% and mean BMI of 33 kg/m2 at 24 months following revisional surgery. Compared to the RYGB, the SADI resulted in significantly better weight loss (p=<.001). Moreover, 72% of RYGB patients regained a part of their lost weight two years

after revisional surgery; opposed to SADI patients, who seem to progressively lose weight during the two-year follow-up period. Another important finding was the comparable rate of complications following SADI and RYGB in the first year following surgery. Furthermore, a similar amount of deficiencies was observed between the two procedures.

Two previous studies evaluated weight loss after a SADI procedure with a prior SG and found excellent results, with a percentage excess weight loss of 70-80% after 24 months[10, 12]. These findings are similar to our results, where a percentage excess weight loss of 78% was found, and adds evidence to the notion that a SADI after SG provides consistent weight loss, even in different populations. When the RYGB after SG is compared to the existing literature, there seems to be agreement on a peak in weight loss after twelve months, and a decline in weight loss or even regain after this period[25, 26]. The overall level of %TBWL reported in these papers seems to be slightly higher than those obtained in our study but does not exceed 20%. Another proposed procedure to improve weight loss after a prior SG is the revisional sleeve gastrectomy (Re-SG), which is particularly promising when the original sleeve has dilated. It is found that the overall percentage of excess weight loss following the Re-SG can reach up to 57% at 12 months and up to 60% at 20 months follow-up[27, 28]. These percentages seem to exceed weight loss reported for RYGB in the current study, however, contrary to these outcomes Alsabah et al. found more weight loss following revisional RYGB than after a Re-SG[28]. Still, they are not as high as those obtained after a SADI.

A second outcome evaluated in the present study was the rate of complications after revisional surgery. The SADI was originally developed as a modification of the biliopancreatic diversion with duodenal switch (BPD-DS). A reduction to just one anastomosis in SADI might be the reason why there are less complications when compared to the BPD-DS. Few studies compared the BPD-DS with RYGB after SG and found a generally higher amount of complications following BPD-DS, however, not significant[29, 30]. The present study found a similar complication rate, however, it can only be speculated on whether the SADI is an actual improvement for complication rates due to scarcity of this topic in the existing literature.

In studies comparing nutritional deficiencies after SADI, generally a higher percentage of deficiencies is described than observed in our patients[10, 12]. A difference in common channel length might have played a role in this, as previous studies included some cases with a common channel length of 200cm; whereas the length was 250cm for all but four of our patients. The authors mentioned that patients with a shorter common channel length were also more likely to develop deficiencies. Homan, J. et al. (2015) compared nutritional values for RYGB and BPD-DS after SG and found more deficiencies after BPD-DS (82% vs. 57%), however, not significant due to a small sample size[29]. The observation of a similar amount of

nutritional deficiencies found in our sample provides some support for the hypothesis that deficiencies are less common after a SADI than after the traditionally performed BPD-DS.

The underlying mechanism for the difference in weight loss between the SADI and RYGB after SG might be explained by the difference in common channel and biliopancreatic limb length. It is assumed that a common channel length of 250cm (with the exception of four common channels of 300cm) in combination with a longer biliopancreatic limb length in SADI increases the malabsorptive component when compared to the RYGB leading to far better weight loss. Besides, a decline in weight loss or stabilization in weight one year after RYGB surgery, is shared by several studies and can be considered as a failure of the procedure[31, 32]. Therefore, it may be questioned whether the RYGB should still be considered as an option for patients seeking to improve their weight loss after SG. Yet, many surgeons and patients are reluctant to choose a more invasive malabsorptive procedure such as the duodenal switch or SADI because of the disadvantages in terms of complications and deficiencies. It is argued that these disadvantages outweigh the benefits of more weight loss following these procedures when compared to the RYGB[7]. Perhaps these arguments might have led to a form of selection bias, in which patients with a higher pre-operative BMI are more likely to undergo a SADI, as can be seen in our data by the difference in baseline BMI before revisional surgery. However, after evaluation of the current results, it is reasonable to conclude that the disadvantages have been overemphasized, as was also mentioned previously by Sánchez-Pernaute et al.[10]. In addition, identical operative times were observed and SADI patients experienced a shorter hospital stay after surgery. However, it should be noted that patients who presented with a functional problem are advised to undergo a RYGB. These patients were perhaps more prone to complications, leading to a higher rate of complications and a longer hospital stay following a RYGB.

Another concern associated with bariatric procedures that have larger malabsorptive characteristics, such as a SADI, is an increase in the occurrence of nutritional deficiencies. In the present study, the similarity of post-operative deficiencies found in both groups is likely related to sufficient supplementation, as every patient is advised to take specialized multivitamins to meet their daily requisite of vitamins after surgery and to prevent nutritional deficiencies from occurring. Moreover, patients are under strict guidance to meet their daily protein intake and multiple laboratory check-ups in the first year and yearly after that should ensure early detection of deficiencies and suitable treatment. As such, compliance to a strict vitamin regime is mandatory. It has been previously addressed that the super-morbid obese population is characterized for their extreme non-compliance[33], which might negatively impact the issue. This finding emphasizes the importance of regular follow-up for blood tests and a strict program by the clinic in which patients are treated.

A RYGB can be performed as revisional surgery if patients present with functional problems after a SG, such as dysphagia due to a stenosis or GERD. A narrow sleeve can be the cause of both of these problems, therefore, a SADI will most likely not solve the problem as the sleeve is left untouched. When a SG is converted into a RYGB, the sleeve is dissected to form a gastric pouch with a Roux-en-Y construction. As a result, problems attributed to a previous sleeve should resolve by bypassing the pylorus and promoting gastric emptying. In the present study, all patients but two were free of complaints after RYGB as a revisional procedure.

We acknowledge that our study has several limitations. Firstly, this includes the retrospective nature of our study, despite of the prospectively collected data in medical records. Secondly, an important factor after bariatric surgery which was not taken into account in the present study because of missing data is quality of life. Even though the SADI group did lose more weight, this does not necessarily lead to a better quality of life. Finally, as mentioned before, the super-morbid obese patients are known for their non-compliance. This was noticeable in our data by the significant amount of missing data. However, because of the frequent follow-up protocol, longitudinal data was mostly available. Points that contributed to the strength of our study were the relatively high number of patients included when compared to previous research. Furthermore, the present study combined results of multiple centers, which improves external validity of the results. Additionally, the SADI procedure as a second step has not been around for long and is still viewed as experimental, therefore, results that yield up to and including two-year follow-up are warranted[34].

Conclusion

In conclusion, revisional surgery following SG into RYGB or SADI are both feasible options, with a similar risk for complications and nutritional deficiencies. For cases of GERD or functional problems after SG a conversion to RYGB is preferred. However, conversion into a SADI offers significantly more weight loss without increased short- and long-term morbidity and may therefore be considered the recommended operation for patients seeking weight improvement.

Disclosures

The authors declared that they have no associations that might be a conflict of interest.

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CHAPTER 9

Discussion and future perspectives

The amount of people suffering from obesity worldwide has nearly tripled in the last four decades. Due to this growing prevalence, obesity has become a major public health risk and came with rapidly increasing health care costs in almost every region in the world. Obesity is regarded a pandemic, leading to over 4 million related deaths each year[1].

Various reasons for a rise in obesity

Despite significant advances in our knowledge on the development of obesity, our understanding of its etiology and pathophysiology is still incomplete. The simplified fundamental cause of obesity and overweight is an energy imbalance between calories consumed and calories expended. This imbalance is caused by a complex interplay of multiple genetic, metabolic, behavioral and environmental factors. A better understanding of all these factors is necessary to diagnose and treat obesity, and perhaps more important, to prevent it.

Although many people suffering from obesity regard genetics to be a major cause of obesity, only a small proportion can be directly related to a genetic mutation[2]. However, multiple suspected genes have been identified and are further investigated in clinical studies to investigate if they influence eating behavior, food preference and weight gain.

Beside genetics, it is thought that complex impaired brain circuits and neuroendocrine feedback are associated with pathological overeating and physical inactivity and therefore lead to obesity[3].

When asked, many people know that for example 10,000 steps a day is regarded a healthy amount, but only a minority of overweight people reach that amount on a daily basis and often overestimate their own physical activity. Multiple behavioral factors are associated with overweight. For example, sleep deprivation is linked to increased body weight[4-6]. A negative correlation between hours of sleep and BMI has been demonstrated, and sleep restriction has shown to increase hunger and appetite. Several pathways could link sleep deprivation to weight gain and obesity, including increased food intake, decreased energy expenditure, and changes in levels of appetite-regulating hormones such as leptin and ghrelin. Factors that have a strong link to short sleep times, for example shift-work, long working hours and increased time commuting to and from work have also been hypothesized to favor overweight[7].

In addition, several commonly used medications including psychotropic medication, antihypertensives, steroid hormones and contraceptives and antihistamines are identified in contributing to the obesity epidemic[8,9]. For example, atypical antipsychotic drugs and

antidepressants cause weight gain that cannot be explained solely by improvement in depressive symptoms. The pharmacological mechanisms underlying weight gain are still poorly understood. It is hypothesized that specific types of medication interfere with central nervous functions regulating energy balance. Patients using psychotropic medication report increased appetite for sweet and fatty food and when appetite is reduced when using antipsychotic or antidepressant drugs it is thought an altered resting metabolic rate could explain weight gain[10].

Environmental factors are thought to be the main cause of the increased prevalence of overweight in the last four decades. The increase is associated with the lack of supportive policies in sectors such as health, agriculture, transport, urban planning, environment, food processing, distribution, marketing and education. Our modern way of life has shifted in ways that promote overeating. In our obesogenic environment, highly palatable foods, rich in calories and fat have become widely available in large portions and are easily accessible at a relatively low cost[1,9].

Lifestyle and behavior change

Although challenging, it is important to counteract and decrease the number of patients with obesity. The logical first step of treatment for all people with obesity is to provide support for behavioral change. Overweight patients, regardless of BMI, can benefit from lifestyle interventions. A well-balanced eating pattern and regular physical activity is advised. In the Netherlands for example, combined lifestyle intervention therapy (Dutch abbreviation: GLI) is offered to patients with overweight and obesity as a first line of treatment. When choosing an adapted lifestyle, it is important to take into account the patients' individual preference, social circumstances and the outcome of previous treatment. Weight loss as main goal is favored by most patients, however realistic targets for outcomes other than weight loss, such as increased physical activity and healthier eating are advised. The biggest challenge is that many patients with overweight and obesity do not start with attempts to lose weight, although they realize in many cases that it would be better for their health[11].

Large clinical randomized studies on the effect of lifestyle intervention in patient with obesity show weight loss of more than 5% in selected patients with obesity[12-14]. In most studies, patients were only selected when they were highly motivated. The results of these studies have ensured that intensive lifestyle treatment became part of the reimbursed care in the Netherlands. Although this primary care lifestyle treatment is more accessible and affordable then all clinical intensive treatment interventions it results in less weight loss and the health advantages are limited. Three clinical studies (1 Randomized controlled trial

(RCT) and 2 observational studies) on the effect of three GLI programs in the Netherlands showed a weight loss of only 2-3% after a maximum follow-up of 18 months[15-17]. Only in one GLI program 20% of the participants reached a weight loss of 5% and more[16]. It could be debated that not the result in weight loss, but the relatively low cost of approximately 800 euros per patient to participate in the program resulted in inclusion of package of reimbursed care in the Netherlands. It is questionable if the current results of GLI programs will lead to much enthusiasm among patients and health care professionals in the long term. However, GLI could still become an important part of obesity treatment, especially when combined with an additional type of treatment (medication or surgery) which most people with severe obesity require.

Pharmacological treatment

When a combined approach on achieving a healthy diet and increased physical activity level have not resulted in sufficient weight loss or weight loss has reached a plateau another option is to add pharmacological treatment. Before the start of a pharmacological agent, it is important to discuss potential benefits and limitations, including the mode of action, adverse effects and the potential impact on the patients' motivation[11]. Current available pharmacological options for improving or maintaining weight loss are limited. In the past a number of treatments were available, but most were withdrawn because of severe side effects.

In the Netherlands, Orlistat is registered for prescription to adult patients with obesity. Orlistat inhibits pancreatic lipases to do its work which is to break down dietary fat to absorbable free fatty acids. It prevents the absorption of up to 32% of ingested fats which are excreted in the feces[18,19]. A meta-analysis of 33 RCTs showed an additional weight loss of 2.12 kg when Orlistat is prescribed in addition to lifestyle intervention[20]. The duration of the therapy varied from 2 months to 3 years. In addition to the weight loss Orlistat resulted in 37% risk reduction of type 2 diabetes mellitus (T2DM) in a double blinded RCT with a follow-up of 4 years[21]. Gastrointestinal side-effects are common and use of the medication could lead to an oily stool, fecal urgency or incontinence. Another challenge is that it only binds fatty acids, while many people get the majority of their calories in the form of carbohydrates. For these people Orlistat will only have a limited effect.

A pharmacological therapy investigated frequently in the past few years for improving weight loss is Liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist. In response to the ingestion of food or glucose GLP-1 is released from the gastrointestinal tract. This incretin hormone acts centrally by suppression of appetite and peripherally by decreasing gastrointestinal transit and altering the glucose homeostasis[22,23]. Several trials demonstrated

the efficacy of Liraglutide in patients with obesity and in overweight patients with T2DM. A weight loss of 6% after one year of follow-up was seen in patients who used 3 mg Liraglutide daily versus 2% in the placebo group[24]. In addition to the weight loss GLP-1 therapy led to improvement in glycemic control. An average reduction of 1% of HbA1c was observed in a large systematic review and meta-analysis[25]. Other obesity-related comorbidities such as hypertension and dyslipidemia also improved using this relatively new pharmacological agent[26]. A disadvantage of a GLP-1 receptor agonist is that is has to be administered once daily subcutaneously by injection. One could wonder whether the additional weight loss of 4% is worth injecting yourself on a daily basis. Especially in the already poorly motivated overweight patients this could impair treatment adherence. Gastrointestinal side effects of Liraglutide are often mild, but cases of severe pancreatitis have been described in literature[27]. Perhaps some of the downsides will be resolved with the next generation GLP-1 agonists. Semaglutide has the advantage to have a much longer half-life which results in a once a week dose which will theoretically increase compliance. Also, average weight loss seems to increase as well[28].

Although promising, the results of pharmacotherapy in addition to lifestyle intervention are limited by their results in terms of weight loss and long-term results are lacking. Therefore, prescribing pharmacological agents to improve weight loss should be only limited to clinics specialized in obesity treatment.

Endoscopic treatment

In search of a minimal-invasive treatment for obesity, several endoscopic treatments have been introduced. Among these endoscopic therapies used and investigated, there are space-occupying devices, bypass liners and aspiration devices. Intragastric balloons can be placed endoscopically, filled with fluid and thus occupy space in the stomach to limit food intake[29]. Besides mechanical effects, the working mechanism actually might be more incretin driven. Ghrelin levels rise slower after a balloon is placed and it appears that GLP-1 levels change due to slower passage of food from the stomach to the small intestine[30]. Currently, there is also a swallowable gastric balloon on the market that does no longer require endoscopy for placement and removal. This innovation makes balloon treatment much more popular. Average weight loss is 12.1% after 4 months[31], but as with every endoscopic procedure weight gain is seen in a subset of patients[32]. It requires lifelong habitual changes to remain successful, so combining a gastric balloon with a lifestyle intervention program is eminent.

A duodenal-jejunal bypass liner is a device that is implanted in the duodenal bulb and extends 60 cm into the small bowel. This liner allows food to bypass the duodenum and

proximal jejunum, without food coming into contact with the mucosa of the duodenum[33,34]. So far, mainly T2DM patients have been treated with this device and it results in a weight loss of 10% upon removal of the device[35]. The device needs to be removed after 6 to 12 months and medium-term results show that the effect on T2DM and weight in a large portion of patients diminishes. This requires a different strategy with multiple placements after another. One study investigating the effect of a duodenal-jejunal bypass liner was prematurely terminated due to a high number of hepatic abscessed observed in the study group[36].

When using aspiration therapy a gastrotomy tube is surgically placed through the abdominal wall into the stomach and approximately one third of each meal is aspired a few minutes after consumption. This is done by flushing a saline solution through the catheter into the stomach and after a period of time let the fluid and gastric content partially flow out again. In literature only one two studies describe the effect of this therapy. A weight loss of 15% after 6 months of usage is seen. The biggest downside is of course the gastrostomy tube, which is always visible and has the same challenges as any transcutaneous tube, such as local irritations and infection[37].

An endoscopic restrictive procedure is the primary obesity endoluminal (POSE). An endoscopic technique that involves placement of gastric transmural plications in the fundus and pre-antral area to trigger earlier physiological feedback of fullness and less hunger. In a study investigating this technique an EWL of 49% with very few complications one year after the procedure was seen[38].

Besides the gastric balloon, most of these wide-ranging offerings of endoscopic treatments are in the early or mid-stage of development and show promising results in the short-term. However, long-term results are lacking and complication rates of some endoscopic devices are high. It is therefore questionable if current available endoscopic bariatric techniques will prove to be successful over a prolonged period of time.

Metabolic surgery

Since conservative, medical and/or endoscopic treatment is currently not sufficient to achieve significant long-term weight loss in the majority of patients with severe obesity, (bariatric or) metabolic surgery is, to date, the most effective treatment for weight loss with good results in the long-term. Metabolic surgery has proven to result in sustainable weight loss and reduced obesity-related comorbidities like T2DM, cardiovascular diseases and improves the psychological burden of patients with overweight[39,40]. Due to all these benefits the number of procedures has increased significantly in recent decades[41]. Although

several new surgical procedures have been introduced in recent years, the RYGB is still one of the most prevalent surgical procedures in Europe. The complex anatomical design of the RYGB suggests that there are a number of gripping points for improvement of its original design, ranging from a variety in pouch designs to variations in limb lengths.

Limb length

The effect of the length of the alimentary limb (AL) on weight loss has been studied extensively. For many years the AL was considered to be responsible for weight loss after RYGB. Although some non-randomized studies report exceptional weight loss in patients who had a RYGB with a long biliopancreatic limb (BPL), the effect of the BPL on weight loss has been studied to a much lesser extent[42]. In this thesis the long BP limb was investigated in patients undergoing a RYGB procedure (**chapter 2 and 3**). After four years of follow-up, weight loss was higher in the long BP limb group in both RCTs.

The underlying mechanism behind these better results in both long BP limb RYGB groups remains partially unclear. It is hypothesized that lengthening the BP limb results in an increased postprandial glucagon-like protein-1 response which reduces appetite and gastrointestinal motility. Additionally, it is thought that a longer BP limb results in increased plasma levels of bile acid resulting from an increased uptake of bile acids due to a lack of ingested food in the BP limb. In contrast to the traditional view, bile does not function simply as a fat solubilizer, but also influences cholesterol and glucose metabolism by acting on nuclear receptors. Bile has also been shown to modulate energy expenditure by stimulating brown adipose tissue and skeletal muscle. Therefore, it is plausible that the altered bile acid metabolism contributes to the improved metabolic changes seen after a long BP limb RYGB[43].

Together with the question if an even longer BP limb leads to even greater results after RYGB, it should be kept in mind that at some point the total length of excluded intestine could lead to malabsorptive problems. Although this complication was not encountered in patients with a long BP limb of 150 cm RYGB in our trials, this has been described in a trial describing the effect of lengthening the BP limb in a variant of the RYGB, the one anastomosis gastric bypass (OAGB). In this study, a trend with more pronounced deficiencies in procedures with a BPL of 200-250 cm was seen[44].

Pouch size

Numerous studies have investigated the effect of pouch size, mainly focusing on decreasing pouch size. The majority are only descriptive and observational studies that do not demonstrate a correlation between pouch size and weight loss[45-47]. Some studies do report a reduced risk of marginal ulcers in patients with a small pouch, theoretically attributed to the scarcity of parietal cells proximal in the stomach[48,49]. In this thesis a longer, narrow

pouch design was investigated (**chapter 4**). Better mid-term weight loss, driven by a lower occurrence of weight regain, was seen in patients with a longer, narrow pouch desging. Theoretically, taking into account Poiseuille's Law, ingested food passes a longer pouch more slowly compared to a smaller pouch and could therefore induce a longer period of hormone secretion improving the metabolic effect of the RYGB. Furthermore, a longer and smaller pouch has less tendency to dilate compared to a short and wide pouch[50]. Since dilatation of the pouch is often suggested to contribute to weight regain in the long term, preventing it could improve results after RYGB. The concerns about increased gastro-oesophageal reflux and a higher prevalence of marginal ulcers when creating an longer, narrow pouch where not supported by the results of this trial.

Primary banded bypass

The combination of placing an adjustable gastric band around the pouch when constructing a RYGB is not routinely performed. This is mainly due to the high number of complications seen after placement of a laparoscopic adjustable gastric band when performed as a stand-alone procedure[51]. However, there are studies that suggest that placing a (non-adjustable) ring around the pouch could prevent dilatation of the pouch and therefore may reduce weight regain over time[52,53]. Still, most bariatric surgeons do not perform a RYGB with an additional ring around the pouch due to concerns of long-term band related complications such as stenosis, erosion and postoperative dysphagia. In this thesis the effect placement of a silicone non-adjustable ring around the pouch in RYGB surgery was studied (**chapter 5**). After three years, the difference in weight loss between the groups was minor but significant in favor of the banded group. It would be interesting to see if this trend toward a more pronounced effect in the banded group is observed after a longer period of follow-up. The number of rings removed in this study was high which is of concern. The fact that perigastric positioning of the silicone ring can be challenging and is associated with a significant learning curve could explain the high number of removals of this new device. Especially placing the ring too tight seems to lead to most of the removals due to dysphagia. When experience with the non-adjustable silicone ring grows it is important to make a solid risk-benefit ratio.

Secondary surgery: banded bypass

In the majority of patients a RYGB provides substantial weight loss and resolution of obesity-related comorbidities. However, 10-35% of patients fail to lose sufficient weight or regain part of their weight after an initial good result, sometimes with recurrence of comorbidities[54-56]. From the patient's perspective, weight regain is a significant physical and psychological burden that weighs heavily on self-image and quality of life. Any intervention that could improve results should be welcomed. To get these patients back on track conservative intervention is always the first line of treatment. Therefore, patients are advised additional counseling by a dietician or lifestyle coach. Behavioral adjustments

that were self-evident directly after surgery may have become less important in the patients' point of view. When conservative interventions fail to improve results, revisional or secondary surgery can be considered. Due to a lack of standardized protocols for weight regain following bariatric surgery and limited surgical options, secondary surgery after a failed RYGB is mainly based on local or national experience. In this thesis the effect of placement of a non-adjustable ring placed around the gastric pouch in RYGB patients with insufficient weight loss or weight regain was investigated. Especially in patients who suffer from weight regain after an initial good result, modest improvement in weight loss was demonstrated after two years of follow-up. Furthermore, no additional weight regain occurred in these patients. Unfortunately, the number of removed rings in this study was high. Analysis showed that most ring removals was associated with placement in the early phase of the study and also when a smaller diameter was used. This suggest that to prevent postoperative dysphagia and the risk of ring removal, placement of the ring should not be too tight. Also, surgeons should be aware of the learning curve of perigastric placement of this device.

Secondary surgery: distalization

Another surgical option for patients with weight loss failure after RYGB is conversion of the primary RYGB to a distal RYGB (D-GB). By shortening the common channel, the malabsorptive component of the RYGB increases[57-62]. In this thesis the effect on weight loss and nutritional status of the D-GB is described (**chapter 7**). Conversion to a D-GB improved weight loss but came at the expense of persistent vitamin deficiencies, protein malnutrition, debilitating defecation patterns and reoperations. In a subset of patient with insufficient weight loss after primary RYGB, distalization showed promising mid-term results. Based on this study a modified D-GB with a common channel of at least 200 cm is advised.

It is important to offer adequate preoperative counseling when considering revisional surgery. Every patient should undergo multidisciplinary evaluation to determine the weight loss goals in light of the potential drawbacks of the treatment. This implies that patients should be well informed about any potential complications and side-effects to make a balanced decision. In addition, close postoperative patient monitoring to detect postoperative complications at an early stage is mandatory.

Secondary surgery: Sleeve to RYGB

The sleeve gastrectomy (SG) gained popularity the past decade because of its relative simplicity in design compared to the RYGB and is currently the most performed bariatric procedure worldwide. After a SG, RYGB can be performed as a revisional procedure in patients with insufficient weight loss results or functional complications such as severe gastroesophageal reflux disease (GERD). In recent years, the single anastomosis duodenoileal bypass (SADI) procedure has shown good results as a second step after SG[63-65].

In this thesis the effect of the SADI and RYGB on health outcomes in patients who had previously undergone SG is investigated (**chapter 8**). In all patients who underwent revisional RYGB surgery for functional problems after SG, these symptoms resolved, and complaints of GERD improved. For patients who seek weight improvement after SG, SADI offers more weight loss in short- and long-term compared to the RYGB.

Limitations

All modifications in the basic RYGB design showed significant or at least promising results in terms of weight loss. Besides the strengths of each study, there are also limitations to discuss.

First, we encountered some discrepancies with the available literature. There are several studies that have reported a higher resolution of obesity-related comorbidities and better quality of life in cases of weight regain following bariatric surgery. The RCTs in this thesis failed to demonstrate these effects, which can be partly attributed to lack of statistical power.

Secondly, every new design has technical disadvantages. Sometimes a long BP limb RYGB is harder to perform because in some patients with a relatively short mesentery it could prove to be more difficult to pull up the longer BP limb up to the level of the gastric pouch. The EP-GB takes a little more time to perform and is also more expensive to create because an additional stapler is needed to create a longer pouch. Finally, when creating a B-GB the ring should not be placed too tight to prevent dysphagia resulting in ring removal. When bariatric surgeons start using the ring to create a B RYGB they must first gain experience in the challenging perigastric placement of the device to prevent a high number of removals.

Third, to observe weight loss and especially weight regain a follow-up period of three or four years may have been too short. It is often seen that patients stabilize in weight or regain some weight two to five years after surgery. Therefore, longer follow-up is necessary to assess if weight loss sustains. Especially because the frustration in advocating for universal policies and mandating insurance coverage for the treatment of patients with obesity is fueled by the lack of high-quality long-term data.

Fourth, it remains a matter of debate if the difference in weight loss between the modified RYGB procedures and the standard RYGB is of clinical relevance. The modifications to the design resulted in an additional weight loss of 3 to 5%, which equals 3 to 6 kilograms. It is therefore questionable if this weight loss advantage is worth the abovementioned disadvantages and also if patients are willing to undergo a relatively new procedure with unknown long-term follow-up data.

Fifth and final, the retrospective design and the relatively small number of patients in the studies on revisional surgery after a failed bariatric procedure offer several limitations. Due to the retrospective design important factors such as the rate of dysphagia, eating behavior and quality of life could not be assessed. In these studies, several patients were lost to follow-up and therefore it remains unclear how these patients performed. From our historical experience with adjustable gastric banding, it must be feared that results in these patients are disappointing and could alter the perspective on secondary surgery.

Future perspectives

Obesity has became a hot topic in recent years, since the WHO in 2004 called upon all stakeholders to take action at global, regional and local levels to improve diets and physical activity patterns at the population level to counteract the disturbing rising level of people with overweight and obesity [66]. It is likely that the recent COVID-19 pandemic makes the pandemic of obesity worse as vast populations across the globe currently live in (partial) lockdown conditions. The inability to go to work and exercise, emotional stress and financial hardship will provide the perfect environment for the obesity pandemic to rage even faster. All governments have the difficult task to promote a healthier lifestyle and to prevent further increase of people with overweight and obesity. It seems however, together with all governments, we are failing. But how do we prevent obesity in the obesogenic environment we have shifted towards?

An important part of the increase in obesity is the ever-growing influence of the food industry in our society. Together we created an environment in which marketing of the food industry is promoting consumption. In addition, it is easier to obtain food with a junk-food outlet opportunity in every street in town. A preventive action could be cutting down on the selling of caloric rich food and make healthier food more accessible. This 'fat tax' looks like a simple solution but it does not fit the main goal of the food industry which is to make as much profit as possible. Furthermore, the government and its subsidiaries need financial resources and subsidizing healthier food and making it more accessible could interfere.

The countries Sweden, Denmark, Finland, Norway and Iceland all have highly regulated societies with a focus on obesity prevention and even in these Nordic countries the prevalence of overweight and obesity increased over the last decade[67]. One common ambition stated in the Nordic Plan of Action in 2006 was the continuous monitoring of diet, physical activity and body weight among adults and children. All Nordic countries implemented similar obesity prevention initiatives. For example, national guidelines for health professionals with a focus on prevention are developed, free nutritious lunch in primary school and at political level a 'health in all policies' approach is adopted. Despite all initiatives the obesity epidemic among adults in these highly regulated welfare states is also not leveling off. This shows again the difficulty and complexity of obesity prevention.

Healthy behavior and prevention of overweight should be promoted throughout the entire life cycle because at every stage in life there are determinants that influence the risk of becoming overweight. It should be started in childhood. Children who have parents with obesity develop obesity more often compared to children with parents without obesity[68]. Further in life, for example recently retired people could be at risk of developing overweight partially due to less physical activity.

As long as bariatric surgery is the most effective treatment for weight loss in patient with obesity with good results in the long-term it is important to develop new or further optimize existing bariatric procedures and improving the pre- and postoperative follow up.

A relatively new bariatric procedure introduced in 1997 is the One Anastomosis Gastric Bypass, also known as the mini gastric bypass[69]. The pouch is somewhat similar to the pouch of the SG but the biggest difference is that the pylorus is excluded from the equation. A wide gastro-jejunal anastomosis is created to a loop of jejunum 150cm distal to the ligament of Treitz. An advantage of the OAGB is that it has only one anastomosis, resulting in a lower risk profile for internal herniation, bleeding and leakage. Although weight loss results are excellent and a reduction of obesity-related comorbidities was seen, controversy remains regarding the theoretical risk of biliary reflux and its possible complications, such as gastric stump cancer[70-72]. The latter is however not proven and based on old assumptions of gastric resections from the past in which for example proton pump inhibitors were not available. When (biliary) reflux occurs, the OAGB is easily transformed in a RYGB[73]. While the benefits outweigh the risks, since a few years it is recognized as a proven effective primary bariatric procedure by international organizations such as IFSO and ASMBS.

Although some newly developed bariatric procedures have been introduced, the SG and the RYGB are still the two most prevalent procedures. Especially when type 2 diabetes mellitus is present the RYGB still holds its place as prominent bariatric procedure. In this thesis several options for optimizing the procedure are investigated. Lengthening the BP limb results in better weight loss and creating an extended pouch or placing a non-adjustable ring around the pouch both result in better mid-term weight loss, potentially driven by a lower occurrence of weight regain. Still, longer follow up to assess if the induced weight loss is sustainable is necessary. One can speculate that a RYGB using the combination of a long BP limb and a banded extended pouch could result in even more weight loss and less weight regain. To investigate this theory, our study group initiated an RCT in which the effect of a combination of an extended pouch combined with a ring will be assessed (UPGRADE trial, NL62168.091.17).

Due to the increasing number of patients who are candidates for metabolic surgery, expansion of the number of procedures per year is needed. The risks of surgery have degraded very fast for metabolic surgery due to increased experience and professionalization. Centralization and more clinics and centers specializing in metabolic surgery will be necessary to keep up with the demand. In every center a multidisciplinary team and infrastructure adapted to the needs of the patient is mandatory to provide the best care for the patient. One of the biggest challenges to increase the number of metabolic procedures is limited availability hospital resources and medical personnel. To keep up

with the demand and to lowering the costs one could argue if metabolic surgery could be performed in careful selected patients on a day-case basis as suggested by some studies[74].

It can be questioned to what extent further adjustments in the design of the RYGB lead to significant better results and if other factors such as lifestyle modification are gripping points for improvement. To make results after bariatric surgery more sustainable patients must follow an intensive multidisciplinary educational program. All patients follow sessions counseling them on nutrition, physical activity, and motivation, because a new lifestyle must be adopted postoperatively. The sessions are often on a regular basis during the first two years after surgery and thereafter on an annual basis. It is often seen that patients stabilize in weight or regain some weight two to five years after surgery and loosen their new adopted lifestyle. To keep patients on track in this critical phase and prevent weight regain one could suggest that a more intensified postoperative lifestyle program may also be useful after the first two years post-surgery.

General conclusion

In conclusion, optimizing the RYGB by lengthening the BP limb could result in more weight loss, reduction of obesity-related comorbidities and improvement in quality of life. By creating an extended pouch or a banded pouch using a non-adjustable ring weight loss could further improve by preventing weight regain. When results after RYGB are insufficient and conservative interventions do not result in sufficient weight loss, revisional surgery by placement of a non-adjustable ring around the pouch or creating a 'distalized' RYGB shows promising results in selected patients.

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CHAPTER 10

10

Summary

The amount of people suffering from obesity worldwide has nearly tripled in the last four decades. Due to this growing prevalence, obesity has become a major public health risk and came with rapidly increasing health care costs in almost every region in the world. Obesity is regarded a pandemic, leading to over 4 million related deaths each year[1].

Metabolic surgery

Since conservative, medical and/or endoscopic treatment is currently not sufficient to achieve significant long-term weight loss in the majority of patients with severe obesity, (bariatric or) metabolic surgery is, to date, the most effective treatment for weight loss with good results in the long-term. Metabolic surgery has proven to result in sustainable weight loss and reduced obesity-related comorbidities like T2DM, cardiovascular diseases and improves the psychological burden of patients with overweight[2,3]. Due to all these benefits the number of procedures has increased significantly in recent decades[4]. Although several new surgical procedures have been introduced in recent years, the RYGB is still one of the most prevalent surgical procedures in Europe. The complex anatomical design of the RYGB suggests that there are a number of gripping points for improvement of its original design, ranging from a variety in pouch designs to variations in limb lengths.

Limb length

The effect of the length of the alimentary limb (AL) on weight loss has been studied extensively. For many years the AL was considered to be responsible for weight loss after RYGB. Although some non-randomized studies report exceptional weight loss in patients who had a RYGB with a long biliopancreatic limb (BPL), the effect of the BPL on weight loss has been studied to a much lesser extent[5]. In **chapter 2** and **3,** results from the ELEGANCE trials are presented. In these RCTs, the effect of two types of BPL lengths on weight loss and reduction of obesity-related comorbidities were compared. In the first ELEGANCE trial, the long BP limb was investigated in patients undergoing a primary RYGB procedure (**chapter 2**) and in the second trial as a revisional procedure in patients who in an earlier stage had received a laparoscopic adjustable gastric band (**chapter 3**). In both studies, 146 patients were randomized between a short BP limb of 75 cm and a long BP limb of 150 cm. After four years of follow-up, weight loss was higher in the long BP limb group in both RCTs. In the primary operated long BP group, the remission rate of dyslipidemia after 48 months and quality of life after 24 months were also significantly better in the long BP RYGB.

Pouch size

Numerous studies have investigated the effect of pouch size, mainly focusing on decreasing pouch size. The majority are only descriptive and observational studies that do not demonstrate a correlation between pouch size and weight loss[6-8]. Some studies do report a reduced risk of marginal ulcers in patients with a small pouch, theoretically attributed to the scarcity of parietal cells proximal in the stomach[9,10]. To investigate the effect of a longer,

narrow pouch design the Extended pouch trial was conducted. The results are described in **chapter 4**. In this RCT, 134 patients were included and randomized into two groups. Patients received a standard RYGB (S-GB) with a pouch length of 5 cm or an extended pouch RYGB (EP-GB) with a pouch length of 10 cm, stapled alongside a 40 French stomach tube to prevent dilatation, and were followed for three years. Better mid-term weight loss, driven by a lower occurrence of weight regain, was seen in the EP-GB group.

Primary banded bypass

The combination of placing an adjustable gastric band around the pouch when constructing a RYGB is not routinely performed. This is mainly due to the high number of complications seen after placement of a laparoscopic adjustable gastric band when performed as a stand-alone procedure[11]. However, there are studies that suggest that placing a (non-adjustable) ring around the pouch could prevent dilatation of the pouch and therefore may reduce weight regain over time[12,13]. Still, most bariatric surgeons do not perform a RYGB with an additional ring around the pouch due to concerns of long-term band related complications such as stenosis, erosion and postoperative dysphagia. In **chapter 5** the effect placement of a silicone non-adjustable ring around the pouch in RYGB surgery was studied. In the BANDOLERA trial, 130 patients undergoing RYGB were randomized into two groups. 65 patients received a banded RYGB (B-GB) and the others received a S-GB. After three years, the difference in weight loss between the groups was minor but significant in favor of the B-GB group.

Secondary surgery: banded bypass

Due to a lack of standardized protocols for weight regain following bariatric surgery and limited surgical options, secondary surgery after a failed RYGB is mainly based on local or national experience. **Chapter 6** describes the effect of placement of a non-adjustable ring placed around the gastric pouch in RYGB patients with insufficient weight loss or weight regain. In this international multicenter cohort study, the effect of ring placement was investigated in 97 patients. Especially in patients who suffer from weight regain after an initial good result, modest improvement in weight loss was demonstrated after two years of follow-up.

Secondary surgery: distalization

Another surgical option for patients with weight loss failure after RYGB is conversion of the primary RYGB to a distal RYGB (D-GB). By shortening the common channel, the malabsorptive component of the RYGB increases[14-19]. In **chapter 7** the effect on weight loss and nutritional status of the D-GB is described. In this study, 47 patients who underwent distalization to a common channel of 100 cm were analyzed. Conversion to a D-GB improved weight loss but came at the expense of persistent vitamin deficiencies, protein malnutrition,

debilitating defecation patterns and reoperations. In a subset of patient with insufficient weight loss after primary RYGB, distalization showed promising mid-term results.

Secondary surgery: Sleeve to RYGB

After a sleeve gastrectomy (SG), RYGB can be performed as a revisional procedure in patients with insufficient weight loss results or functional complications such as severe gastroesophageal reflux disease (GERD). In recent years, the single anastomosis duodenoileal bypass (SADI) procedure has shown good results as a second step after SG[20-22].

Chapter 8 describes SADI versus RYGB on health outcomes in patients who had previously undergone SG. In all patients who underwent revisional RYGB surgery for functional problems after SG, these symptoms resolved, and complaints of GERD improved. For patients who seek weight improvement after SG, SADI offers more weight loss in short- and long-term compared to the RYGB.

In conclusion, optimizing the RYGB by lengthening the BP limb could result in more weight loss, reduction of obesity-related comorbidities and improvement in quality of life. By creating an extended pouch or a banded pouch using a non-adjustable ring weight loss could further improve by preventing weight regain. When results after RYGB are insufficient and conservative interventions do not result in sufficient weight loss, revisional surgery by placement of a non-adjustable ring around the pouch or creating a 'distalized' RYGB shows promising results in selected patients.

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CHAPTER 11

11

Dutch summary

De afgelopen 40 jaar is wereldwijd het aantal mensen met obesitas verviervoudigd. In Nederland heeft 51% van de volwassen last van overgewicht en bij 14% is er sprake van obesitas. Obesitas is een groot risico voor de volksgezondheid en leidt jaarlijks tot meer dan 4 miljoen sterfgevallen. Daarnaast gaat de toegenomen prevalentie van overgewicht gepaard met stijgende kosten van de gezondheidszorg.

Onze kennis van de etiologie en pathofysiologie van obesitas is nog steeds onvolledig. In de basis is er sprake van een disbalans tussen geconsumeerde en verbruikte calorieën. Deze wordt veroorzaakt door een complex samenspel van genetische, metabole, gedrags- en omgevingsfactoren. Een beter begrip van al deze factoren is nodig bij de preventie, diagnose en behandeling van obesitas.

De preventie en behandeling van obesitas is complex. Vanwege de 'obesogene' omgeving waarin we leven, met onder andere marketing vanuit de voedselindustrie en economische systemen die consumptie bevorderen in plaats van de reduceren, is de preventie van overgewicht een uitdaging. De huidige stijging van de prevalentie van obesitas hangt samen met het gebrek aan ondersteunend beleid in sectoren als de gezondheidszorg, landbouw, transport, voedselverwerking en -distributie, marketing en onderwijs.

De conservatieve behandeling van obesitas, door verandering van eetgedrag en leefstijl, leidt op de korte termijn tot gewichtsverlies. De uitdaging zit echter met name in het handhaven van de leefstijl die noodzakelijk is om opnieuw gewichtstoename op de lange termijn te voorkomen. Het grootste deel van de mensen met obesitas die afgevallen is, met behulp van het aanpassen van de leefstijl, komt na verloop van tijd weer aan in gewicht.

Verschillende onderzoeken hebben een positief effect aangetoond van medicatie, zoals een GLP-1 receptor agonist als aanvulling op leefstijlaanpassingen, bij de behandeling van obesitas. Daarnaast zijn er meerdere endoscopische behandelingen, bijvoorbeeld een maagballon, die vaak gebruikt worden als een tijdelijke behandeling van obesitas. De korte termijn resultaten van al deze, relatief nieuwe behandelingen van obesitas, zijn veelbelovend. Lange termijn resultaten vallen echter tegen of ontbreken.

Wanneer de conservatieve en de medicamenteuze behandeling van obesitas niet volstaan om bij patiënten met obesitas gewichtsverlies op de lange termijn te bewerkstelligen, is de volgende stap bariatrische chirurgie. De behandeling van obesitas met behulp van bariatrische chirurgie leidt tot significant gewichtsverlies op de korte- en lange termijn en resulteert in vermindering van aan obesitas gerelateerde comorbiditeiten, zoals diabetes mellitus type 2 en hypertensie. Vanwege deze voordelen is het aantal bariatrische procedures dat elk jaar wereldwijd wordt uitgevoerd de afgelopen tien jaar gestegen tot een half miljoen per jaar.

Om in aanmerking te komen voor metabole chirurgie moeten patiënten voldoen aan de criteria die zijn vastgesteld door de National Institutes of Health (NIH). Alle patiënten met klasse drie obesitas (BMI ≥40 kg/m^2) of met klasse twee obesitas (BMI ≥35 kg/m^2) met één of meer aan obesitas gerelateerde comorbiditeiten, zijn kandidaten om bariatrische chirurgie te ondergaan.

Er zijn meerdere bariatrische procedures die uitgevoerd kunnen worden voor de behandeling van obesitas. De keuze van de procedure hangt af van vele factoren, waaronder BMI en specifieke kenmerken van de patiënt. Eén van de meest uitgevoerde bariatrische procedure is de Roux-en-Y Gastric Bypass (RYGB), tevens de focus van dit proefschrift. Bij de RYGB wordt er een maagpouch van 30-45cc gecreëerd en worden delen van de dunne darm verlegd. Voedsel komt na de pouch in de voedingslis van de dunne darm en komt op een later moment in aanraking met de verteringenzymen die vervoerd worden door de biliopancreatische lis (BPL). Deze verteringsenzymen worden gemaakt door de restmaag, lever en alvleesklier.

Sinds de introductie van de RYGB in 1966 zijn er slechts een paar veranderingen geweest in het ontwerp. De toevoeging van de Roux-Y configuratie was waarschijnlijk de meest radicale verandering. Het complexe anatomische ontwerp van de RYGB suggereert echter dat er meerdere aanwijzingen zijn voor verbetering van het oorspronkelijke ontwerp, variërend van de pouch tot de lengte van de verschillende delen van de dunne darm.

Het doel van dit proefschrift is te onderzoeken hoe het resultaat na een bariatrische ingreep, met de focus op de RYGB, kan worden verbeterd door het optimaliseren van de procedure. Tevens werd er gekeken naar chirurgische opties wanneer een primaire bariatrische ingreep faalt.

Er is weinig onderzoek gedaan naar het effect van de lengte van de BPL na een RYGB. In hoofdstuk 2 en 3 worden de resultaten van de ELEGANCE trials gepresenteerd. In deze gerandomiseerde gecontroleerde trials (RCT) werd het effect van verschillende lengtes van de BPL, op onder andere gewichtsverlies, vergeleken. In de eerste ELEGANCE studie werd de lange BPL RYGB onderzocht bij patiënten die een primaire RYGB ondergingen (**hoofdstuk 2**). In de tweede studie werd de lange BPL RYGB onderzocht als een revisie procedure bij patiënten met in de voorgeschiedenis een laparoscopische verstelbare maagband (**hoofdstuk 3**). In beide studies werden 146 patiënten gerandomiseerd tussen een korte BPL van 75 cm en een lange BPL van 150 cm. Na vier jaar follow-up was het gewichtsverlies in beide RCT's groter in de groep met de lange BPL. Daarnaast was het aantal patiënten met complete remissie van dyslipidemie na 4 jaar en de kwaliteit van leven na 2 jaar, beter in de primair geopereerde lange BPL groep.

Veel studies hebben onderzoek gedaan na het effect van de grootte van de pouch bij een RYGB. In het merendeel van de studies werd er gekeken naar het effect van een kleinere pouch. Om het effect van een langere, smallere pouch te onderzoeken werd de Extended pouch trial uitgevoerd. De resultaten worden beschreven in **hoofdstuk 4**. In deze RCT werden 134 patiënten geïncludeerd en gerandomiseerd in twee groepen. Patiënten kregen een standaard pouch RYGB met een pouch lengte van 5 cm of een extended pouch RYGB (EP-GB) met een pouch lengte van 10 cm. In de EP-GB-groep werd een beter gewichtsverlies op middellange termijn gezien, met name doordat in de EP-GB-groep minder gewichtstoename op de middellange termijn werd gezien.

Een aantal studies suggereert dat het plaatsen van een (niet-verstelbare) ring rond de pouch, verwijding van de pouch zou kunnen voorkomen en daardoor gewichtstoename na verloop van tijd zou kunnen verminderen. In **hoofdstuk 5** werd het effect van het plaatsen van een siliconen, niet-verstelbare ring, rond de pouch bij een RYGB bestudeerd. In de BANDOLERA trial werden 130 patiënten die een RYGB ondergingen gerandomiseerd in twee groepen. Vijfenzestig patiënten kregen een RYGB met een ring om de pouch, de anderen kregen een standaard RYGB. Na drie jaar was het verschil in gewichtsverlies tussen de groepen klein, maar significant in het voordeel van de groep van patiënten met een ring om de pouch.

Bij de meerderheid van de patiënten resulteert een RYGB in aanzienlijk gewichtsverlies en het verdwijnen van comorbiditeiten. Bij 10-35% van de patiënten lukt het echter niet om voldoende gewicht te verliezen of komt een deel van het verloren gewicht terug na een in eerste instantie goed resultaat. Het (opnieuw) aanpassen van de leefstijl is voor deze groep de eerste stap in de behandeling. Wanneer conservatieve interventies de resultaten niet verbeteren, kan een revisie- of secundaire operatie worden overwogen. Door een gebrek aan gestandaardiseerde protocollen, voor gewichtstoename na bariatrische chirurgie en de beperkte chirurgische opties, is secundaire chirurgie na een mislukte RYGB voornamelijk gebaseerd op lokale ervaringen.

Hoofdstuk 6 beschrijft het effect van het plaatsen van een niet-verstelbare ring rond de pouch, bij patiënten met een RYGB met onvoldoende gewichtsverlies of gewichtstoename op de lange termijn. In deze internationale multicenter cohort studie werd het effect van de ring onderzocht bij 97 patiënten. Vooral bij patiënten met gewichtstoename na een initieel goed resultaat, werd een bescheiden verbetering van het gewichtsverlies aangetoond na twee jaar follow-up. Bovendien trad bij deze patiënten geen extra gewichtstoename op. Helaas was het aantal verwijderde ringen in deze studie hoog. Analyse toonde aan dat het verwijderen van de ring gerelateerd was aan plaatsing in de vroege fase van de studie en er een kleinere diameter van de ring werd gebruikt.

Een andere chirurgische optie voor patiënten met onvoldoende gewichtsverlies na een RYGB, is conversie van de primaire RYGB naar een distale RYGB (D-GB) waarbij de malabsorptieve component van de RYGB toeneemt. In **hoofdstuk 7** wordt het effect van de D-GB op het gewichtsverlies en voedingstoestand van 47 patiënten beschreven. Het omzetten naar een D-GB verbeterde het gewichtsverlies, maar ging wel gepaard met aanhoudende vitaminen- en eiwittekorten, invaliderende defecatiepatronen en operaties in verband met complicaties. In een subgroep van de patiënten met onvoldoende gewichtsverlies na een primaire RYGB, toonde distalisatie veelbelovende resultaten op middellange termijn.

Bij patiënten met onvoldoende gewichtsverlies of functionele complicaties, zoals ernstige refluxziekte na een sleeve gastrectomie (SG), kan de SG omgezet worden in een RYGB. **Hoofdstuk 8** beschrijft het effect van een RYGB bij patiënten die eerder een SG hebben ondergaan. Bij alle patiënten waarbij de SG werd omgezet naar een RYGB, in verband met functionele problemen na een SG, verbeterde de refluxklachten.

APPENDICES

A

Appendices

List of abbreviations
Research Data Management Summary
List of publications and presentations
Curriculum vitae
Word of gratitude

List of abbreviations

25-OHD	25-Hydroxyvitamin D
%EWL	Percentage excess weight loss
%TBWL	Percentage total body weight loss
A	
AGB	Adjustable gastric band
AL	Alimentary limb
ASMBS	American Society for Metabolic and Bariatric Surgery
B	
BAROS	Bariatric Analysis and Reporting Outcome System
B-GB	Banded pouch Roux-en-Y gastric bypass
BMI	Body Mass Index
BP	Biliopancreatic
BPD-DS	Biliopancreatic diversion with duodenal switch
BPL	Biliopancreatic limb
C	
CC	Common channel
CMO	Central Medical Committee for Research in Humans
D	
DL	Dyslipidemia
D-GB	Distal Roux-en-Y gastric bypass
E	
EP-GB	Extended pouch Roux-en-Y gastric bypass
EWL	Excess weight loss
G	
GERD	Gastroesophageal reflux disease
GERD-HRQL	Gastroesophageal reflux disease-Health related quality of life
GFS	Glomerular filtration rate
GLI	Combined lifestyle therapy
GLP-1	Glucagon-like peptide-1
H	
HPT	Hyperparathyroidism
HT	Hypertension
I	
IBD	Inflammatory bowel disease
IFSO	International Federation for the Surgery of Obesity and Metabolic Disorders

L

LABG	Laparoscopic adjustable gastric band
LBP-GB	Long biliopancreatic limb Roux-en-Y gastric bypass
LNL	Lower normal limit

M

MC4R	Melanocortin 4 receptor
MVS	Multi vitamin supplement

N

NIH	National Institutes of Health

O

OAGB	One anastomosis gastric bypass
OSAS	Obstructive Sleep Apnea Syndrome

P

POSE	Primary obesity endoluminal
PPI	Proton pomp inhibitor
PTH	Parathyroid hormone
PTT	Prothrombin time

Q

QoL	Quality of life

U

UNL	Upper normal limit

R

RAND-36	Research and Development-36
RCT	Randomized controlled trial
RDA	Recommended daily allowance
RYGB	Roux-en-Y gastric bypass

S

SADI	Single Anastomosis Duodenoileal bypass
SD	Standard deviation
SG	Sleeve gastrectomy
S-GB	Standard Roux-en-Y gastric bypass

T

TBWL	Total body weight loss
T2DM	Type 2 Diabetes Mellitus

W

WHO	World Health Organization

Research Data Management Summary

The medical and ethical review board Committee on Research Involving Human Subject Region Arnhem Nijmegen, Nijmegen, the Netherlands has given approval to conduct the prospective studies. These studies were also registered at clinicaltrials.gov. All participants gave written informed consent to participate in the studies. Retrospective studies were approved by the Local Ethical Committee of the Rijnstate Hospital.

Research date presented in this thesis and obtained during this PhD trajectory at the Vitalys Obesity Clinics at the Rijnstate Hospital were archived to the Findable, Accessible, Interoperable and Reusable (FAIR) priniciples[1].

Data were captured and processed in Microsoft Office Excel and IBM SPSS Statistics. All files were stored on a local server at the department of Surgery of the Rijnstate Hospital. A daily backup of these local servers was performed. The files were only accessible for scientific members of our research group and locked with a password.

Vitalys Obesity Clinic at the Rijnstate Hospital was responsible for trial design, trial set-up, trial management and all statistical aspects of the trial.

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IFSO World Congress 2018 (Dubai). Band and Extend? Results of 2 randomized controlled trials on RYGB improvement.

IFSO World Congress 2018 (Dubai). The failed Roux-en-Y gastric bypass: band or distalization?

IFSO European Chapter Congress 2018 (Athens). Band and Extend? Results of 2 randomized controlled trials on RYGB improvement.

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DSMBS Congres 2018 (Veenendaal). Band en Extend? Resultaten van 2 randomized controlled trials.

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Curriculum vitae

Abel Boerboom was born on the November 2nd, 1988 in Zevenaar, the Netherlands. After graduating from Liemers College in Zevenaar (VWO), he started medical school in 2007 at the Utrecht University. After obtaining his medical degree in 2014, he started as a medical doctor at the department of surgery in the Hospital Gelderse Vallei in Ede. In 2016 he started working as a fulltime researcher with his own PhD-traject in the Rijnstate Hospital in Arnhem under supervision of dr. F.J. Berends, dr. E.O. Aarts en prof. dr. E. Hazebroek. This research has led to a variety of publications and presentations at national and international congresses. The years of research have also been important in making a conscious choice for further education. In 2019 he started as a general practitioner in training at the Radboudumc in Nijmegen. In his spare time, he continued to work on his PhD traject in which he hopes to be able to complement a translation of this thesis into general practice.

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