Optimizing weight loss outcomes in bariatric surgery

OPTIMIZING WEIGHT LOSS OUTCOMES IN BARIATRIC SURGERY

Maria Marlena Romeijn

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CHAPTER 01

General introduction

Obesity has reached epidemic proportions globally and in recent years, it has resulted in the death of an estimated 2.8 million people each year [1]. Obesity is caused by an overaccumulation of adipose tissue, and is quantified by body mass index (BMI). A BMI of >30 kg/m^2 is classified as obesity, ≥40 kg/m^2 as morbid obesity and ≥50 kg/m^2 as super morbid obesity [2-3]. Obesity is a significant risk factor for multiple chronic diseases such as type 2 diabetes mellitus, cardiovascular disease, osteoarthritis and certain types of cancer [1,3]. Lifestyle modification strategies including diet, exercise and behavioral therapy generally result in a loss of 5-10% body weight [4,5]. It is however difficult to maintain this weight loss because the body tends to revert to its set point [4,5]. Moreover, 5-10% weight loss is unsatisfactory to many patients as their weight loss target based on a healthy BMI (19-25 kg/m^2) is frequently much higher.

Bariatric surgery is considered the most successful strategy for achieving weight loss in patients with morbid obesity [6-8]. On top of weight loss, bariatric surgery is known to reduce obesity-related morbidity and mortality [6-8]. In 2016, the total number of bariatric procedures performed worldwide was estimated at 685.874 patients [9]. According to the guidelines of the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO), bariatric surgery is offered to patients who had reasonable attempts of non-surgical weight loss in the past, and have a BMI of ≥35 kg/m^2 with obesity-related comorbidities, or a BMI of ≥40 kg/m^2 irrespective of comorbidities [8,10]. As stated in the Dutch and American guidelines, bariatric surgery may also be indicated in patients with a BMI of ≥30 kg/m^2 and uncontrollable type 2 diabetes mellitus [11,12]. In general, it is highly recommended the patient's eligibility for a bariatric procedure is assessed by a multidisciplinary team, including a bariatric surgeon, dietician, physical therapist and medical psychologist [13].

The search for the optimal bariatric procedure has started in the 1950s and has evolved in numerous procedures. Some of these procedures are nowadays commonly accepted. The mechanism behind the different bariatric procedures can be simplified into three categories and is explained below [14-16]:

1. Restriction: caloric intake is limited by reducing the gastric reservoir capacity. This can be achieved either by transecting the stomach and by creating a small gastric pouch, or by placing a gastric band. Examples of procedures utilizing these techniques are the sleeve gastrectomy (figure 1) and the adjustable gastric banding (figure 2). While the sleeve gastrectomy is a commonly accepted procedure, the gastric banding is used less frequently due to significant complications and disappointing long-term weight loss outcomes [15].
2. Malabsorption: nutrient absorption is decreased by shortening the absorption length of the gastrointestinal tract (i.e., bypassing absorption in the stomach, duodenum and the jejunum). An example of a malabsorptive procedure is the biliopancreatic diversion which, according to

Scopinaro, results in about 50 cm of common limb for resorption of food. This technique has significant metabolic complications including protein malnutrition and various vitamin- and mineral deficiencies. Yet in specific situations, the technique is still an option. Alternatives to this technique are the biliopancreatic diversion with duodenal switch and SADI [15].

3. A combination of restriction and malabsorption: caloric intake is limited through the creation of a small gastric pouch and furthermore, absorption is bypassed in the stomach, duodenum and proximal jejunum. Surgical procedures that apply this mechanism of action are the Roux-en-Y gastric bypass (RYGB, figure 3) and one- anastomosis gastric bypass. In addition to restriction and malabsorption (of micronutrients not of calories) these procedures also induce changes in the gut hormones, bile acids, gut microbiota and energy balance [14]. The exact mechanism is however not completely understood.

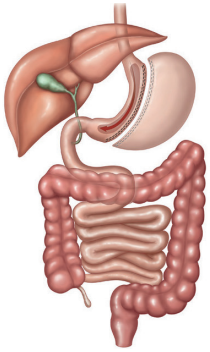

Figure 1. Sleeve gastrectomy

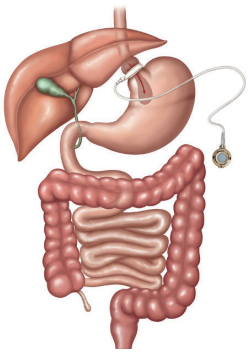

Figure 2. Laparoscopic adjustable gastric banding

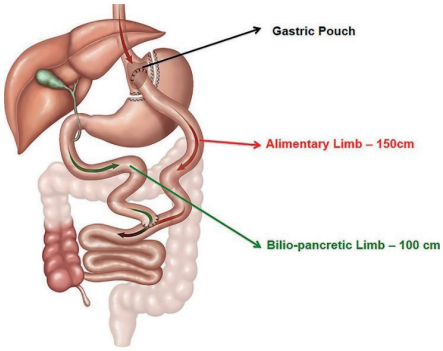

Figure 3. Roux-en-Y gastric bypass

Worldwide, the RYGB is performed approximately 200.000 times each year [9]. In the Netherlands, this number is estimated at 7400 covering roughly 60% of all bariatric procedures that are performed annually [17]. The RYGB is constructed in three phases [16]: 1) Creation of a gastric pouch with a volume of 15-30cc. 2) Creation of a gastrojejunal anastomosis resulting in the passage of food through an alimentary limb. This limb is often created with a length of 75-150cm. The anastomosis can be constructed by a hand-sewn or a stapled technique; the latter can be done with a circular or linear stapler. 3) Creation of a jejunojejunal anastomosis resulting in the addition of digestive juices from the biliopancreatic limb to the alimentary limb, together called the common limb. The biliopancreatic limb is often constructed with a length varying from 50-150cm.

Weight loss can be considered as one of the most important outcomes when examining the effects of bariatric surgery. Zooming in on weight loss after RYGB, the maximum loss is achieved approximately 1-2 years post-surgery (Figure 4) [18,19]. When expressed in %total

weight loss, the mean is 32% [6,7]; when expressed in %excess weight loss, the mean is 67% [18,19]. Frequently, this loss changes a patient's body composition. In detail, the mean loss after RYGB is caused by a relatively large reduction in fat mass (±52%) and a relatively smaller reduction in fat-free mass (±14%), and the latter represents skeletal muscle mass, organs and bones [20]. After two years, weight is often gradually regained resulting in an average of 27% total weight loss [6,7] and 52.5-55.4% excess weight loss 10-25 years post-surgery [18,19,21]. The weight that is regained is generally related to fat mass rather than fat-free mass [20].

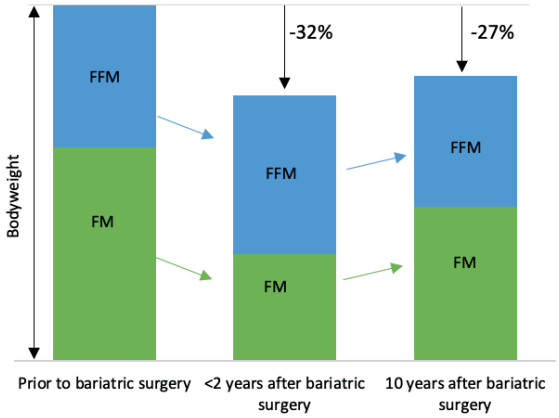

Figure 4. Weight loss pattern after Roux-en-Y gastric bypass. FFM represents fat-free mass, FM represents fat mass

The problem of non-response after bariatric surgery

Whilst the majority of patients follow the abovementioned weight loss pattern, there is a sizable group of patients (10-30%) that deviates from this. Terminology for describing this group greatly differs, yet our research group prefers using the term 'non-response' [19,22,23]. Non-response can be divided into a primary and secondary variant [24]. Primary non-response refers to patients that do not lose enough weight in the first place, for example less than 50% excess weight loss (EWL) or less than 20% total weight loss (TWL) [17,24,25]. In literature, this is also described as insufficient weight loss or weight loss failure. Secondary non-response refers to patients that regain excessive weight after initial successful weight loss, for example a regain of more than 15-25% of total body weight [23,24]. It is inevitable and well known that non-response negatively affects a patient's quality of life, and could lead to the reoccurrence of comorbidities like type 2 diabetes mellitus and hypertension which necessitate further treatment [23, 26]. Next to the medical impact, non-response has a large economic impact as for example, the costs of performing revisional surgery alone are estimated between $14,000 and 50,000 per patient [27].

The etiology of non-response is multifactorial and can be divided into patient-related factors and surgical-related factors. The first category covers the following causes [22,28,29]: 1) Nutritional non-compliance, e.g. an increased caloric intake, inadequate food choice and combining food with beverages; 2) Problematic eating behavior e.g. binge eating, emotional eating and grazing; 3) Physical inactivity, sedentary behavior and barriers to exercise; 4) Mental health issues for example mood disorders and substance abuse; 5) Hormonal imbalances e.g. high ghrelin levels, low peptide YY levels, low GLP-1 levels and reactive hypoglycemia; 6) Non-attendance at follow-up appointments. The second category entails surgical-related factors and covers anatomical alterations like gastro-gastric fistula, a dilated sleeve, a dilated gastroenterostomy and/or a dilated pouch [22,28,29].

Because the number of patients undergoing bariatric surgery is rising every year [9], the number of patients affected by non-response is also rising. Consequently, healthcare providers increasingly encounter patients with non-response wondering how to assess and treat these patients. As the etiology of non-response is multifactorial, it is important that a multidisciplinary team is involved in the assessment. It is advisable to closely examine a patient's nutritional intake, physical status and psychological well-being [22,30,31]. In addition to these examinations, the gastrointestinal anatomy can be examined by performing upper gastrointestinal contrast series, endoscopy or more advanced modalities such as 3D computed tomography [30,32,33]. The choice of treatment should be based on these examinations. Integral to any form of intervention is motivating the patient to optimize their lifestyle, as well as setting the correct weight loss goals and expectations.

In order to treat patients with non-response, multiple revisional procedures have been developed. Popular procedures comprise lengthening of biliopancreatic limb, placing a band or ring around the pouch and resizing the pouch and/or anastomosis [22,28,34]. Resizing is the most frequently performed procedure in the Dutch and Belgium centers followed by banding of the pouch [33]. A systemic review reported that the mean percent excess BMI loss one year after banding is 47.6%, and after revision of the pouch or anastomosis 43.3% [34]. It is important to note that these procedures may lead to major complications, occurring in 3.8% of the patients after banding, and in 3.5% after revision of the pouch or anastomosis [34]. In addition to surgical procedures, endoscopic procedures have gained interest for example by correcting the pouch and/or anastomosis through argon plasma coagulation or suturing [28,30]. Ongoing studies are necessary to provide evidence whether these procedures, both surgical and endoscopic, lead to successful long-term weight loss in patients with non-response.

Interplay between non-response and body composition

There is a strong need for identifying patient groups that are at risk of developing non-response. So far, known predictors of non-response are a male gender, older age, and the presence of comorbidities and/or binge eating [35-38]. In search of predictors, a patients' body composition (i.e., distribution of fat mass and fat-free mass) and its effect on metabolic processes seems understudied. A decrease in fat-free mass may negatively affect the resting metabolic rate, slow the rate of weight loss and predispose non-response [38]. Targeting the fat-free mass could perhaps play a role in the prevention of non-response. Against this background, there are three topics that need further consideration.

1. Preoperative dietary intake: (very) low calorie diets are frequently recommended prior to bariatric surgery because they are effective in reducing weight and liver volume [39-42]. This could improve surgical time, the amount of blood loss, length of hospital stay and decrease complications in 10% of the patients [39-42]. Nevertheless, the weight loss induced by these diets is associated with a significant reduction of fat-free mass [41].
2. Postoperative dietary intake: it is well known that dietary proteins contribute to the preservation of fat-free mass by stimulating muscle protein synthesis [43]. After RYGB, patients are advised to consume a minimum of 60 grams of proteins a day, otherwise stated as 1.5 gram/kg ideal weight per day [39,44]. It is however difficult for patients to adhere to this advice [39], as previous studies reported a protein intake of 46-58 g/day one year after RYGB [45,46].
3. Postoperative physical exercise: it is well known that resistance exercise contributes to the preservation of fat-free mass by stimulating muscle protein synthesis [43]. After bariatric surgery, guidelines recommended patients to perform both resistance and endurance training on moderate to vigorous intensity for 150-250 min/week (1200 to 2000 Kcal per week) to prevent weight regain [30,39]. A patient who remains sedentary may lose fat-free mass more rapidly [30].

Taken together, preoperative dieting and postoperative adherence to dietary and exercise recommendations could be prognostic factors for weight loss post-bariatric surgery. It is conceivable that a better understanding of the relation between dietary intake, physical exercise and fat-free mass may help delineate strategies to optimize weight loss outcomes.

Aims and outline of the thesis

This thesis aims to contribute to a better understanding of the growing problem of non-response following bariatric surgery. The studies presented in this thesis were conducted to answer the following questions:

1. What are predictors of non-response after bariatric surgery?
2. What are effective interventions that target non-response after bariatric surgery?
3. In what way do preoperative weight loss strategies affect fat-free mass loss and subsequent weight loss after bariatric surgery?

It is hypothesized that predictors and interventions of non-response can be identified and as a result weight loss outcomes could be improved. Moreover, weight loss strategies prior to bariatric surgery may also contribute.

Part I: Predictors of non-response in bariatric surgery

The first part aims to increase knowledge on pre-and postoperative predictors of non-response focusing on psychological, physiological, socioeconomic and surgical factors. In terms of psychological factors, **chapter 2** focusses on the role of emotional eating as predictor of non-response. Emotional eating is a maladaptive eating behaviour that is frequently reported in patients with obesity and may negatively affect postsurgical weight loss. **Chapter 3** assesses the predictive value of the 24-hour dietary recall and the 6-minute walk test because these tests are frequently used for the assessment of protein intake and physical function. The factors are related to a patient's body composition and are hypothetically associated with non-response. In **chapter 4**, a systematic review examines the differences in weight loss outcomes between employed and unemployed patients as employment status may be associated with non-response. **Chapter 5** assesses the role of two stapling techniques (circular versus linear) used during gastroenterostomy construction in RYGB surgery. It is hypothesized that the size of the gastroenterostomy varies between the two techniques and this could affect weight loss outcomes.

Part II: Interventions targeting non-response in bariatric surgery

The second part aims to increase knowledge on intraoperative and postoperative interventions targeting non-response. **Chapter 6** explores the ways in which a multidisciplinary evaluation impacts treatment strategy in patients with non-response after RYGB. Treatment strategies are divided into conservative and surgical approaches. **Chapter 7** elaborates on a conservative approach by focussing on the impact of additional protein intake of >60 g/day on fat-free mass preservation and weight loss outcomes in post-bariatric surgery patients. **Chapter 8** elaborates on a surgical approach by assessing the primary banded RYGB. Theoretically, the band may control pouch and stoma size thereby preventing dilatation and subsequent secondary non-response.

Part III: Optimizing weight loss prior to bariatric surgery

The third part aims to increase knowledge on weight loss strategies that are applied in the preoperative phase. These strategies are developed to reduce liver volume and intra-abdominal fat mass, but could unintentionally also reduce fat-free mass. **Chapter 9** assesses current weight loss goals set prior to bariatric surgery in the Dutch centers. In this chapter different strategies are explored including dietary prescriptions, supplementary prescriptions and recommendations regarding physical activity. In **chapter 10**, a systematic review highlights the advantages, but also the important disadvantage of fat-free mass loss in one of the most frequently prescribed preoperative diets (i.e., low calorie diet, 800-1500 kcal/day).

The main findings of the studies and their implications for the future are discussed in **chapter 11, 12 and 13.**

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PART I

Predictors of non-response in bariatric surgery

CHAPTER 02

Emotional eating as predictor of weight loss two years after Roux-en-Y gastric bypass

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Abstract

Introduction: there has been little agreement on the predictive value of emotional eating on weight loss outcomes after bariatric surgery. The aim of this study was to examine the predictive value of preoperative emotional eating, in response to clearly labelled emotions and diffuse emotions, on excess weight loss (EWL) and total weight loss (TWL) 2 years after Roux-en-Y gastric bypass (RYGB).

Methods: all participants included in this retrospective cohort study were screened for RYGB surgery by a multidisciplinary team. The level of emotional eating was derived from the Dutch Eating Behaviour Questionnaire (DEBQ); the level of psychological variables from the Symptom Checklist-90. Participants were clustered, based on their DEBQ score, in high and low emotional eaters. Multiple linear regression analyses were performed to examine the association between preoperative emotional eating and EWL, and TWL.

Results: there were no significant differences in EWL of the 172 included participants, defined as either high or low emotional eaters (EWL 82.7% ±18.2 versus 82.4% ±21.3, respectively). Based on the regression analysis, emotional eating was not significantly associated with EWL, nor with TWL. When corrected for psychological, demographic and biological variables, preoperative emotional eating in response to diffuse emotions negatively affected EWL ($\beta = -0.16$, $p = 0.048$), although this was not applicable for TWL.

Conclusion: preoperative emotional eating does not seem to influence EWL, nor TWL 2 years after RYGB. Since this study faced multiple limitations, further investigation is required regarding the predictive value of emotional eating.

Abbreviations: BMI, Body mass index; DEBQ, Dutch eating behaviour Questionnaire; EWL, Excess weight loss; RYGB, Roux-en-Y gastric bypass; SCL-90, symptom checklist-90; TWL, Total weight loss.

Introduction

Despite the impressive effects of bariatric surgery on weight loss and obesity related comorbidities, 25% to 35% of patients do not respond well to this intervention [1,2]. These patients may experience insufficient weight loss or regain a substantial amount of weight after initial adequate weight loss [3]. Insufficient weight loss is expressed as a primary non-response and is often defined as <50% excess weight loss (EWL) up to 2 years after bariatric surgery [4]. Given the high prevalence of the above, predictors of non-response after bariatric surgery have been an area of great interest.

Emotional eating is defined as a maladaptive coping strategy where emotional arousal leads to an excessive food intake [5]. An excessive food intake would hypothetically counteract postoperative weight loss and thereby induce a non-response. Emotional eating is reported in 38% to 59% of bariatric candidates and occurs in response to clearly labelled emotions (e.g. anger and fear) and diffuse emotions (e.g. boredom and restlessness) [6,7]. Compared to clearly labelled emotions, diffuse emotions are often more ambiguous, yet both types of emotional eating can be difficult for a patient to identify [5].

When reviewing literature, there are contradictory findings about the impact of emotional eating on weight loss outcomes [8-12]. Monpellier showed that a postoperative change in emotional eating was negatively related to the percentage of total weight loss (TWL) up to 4 years after Roux-en-Y gastric bypass (RYGB), but preoperative emotional eating did not predict a non-response [8]. On the contrary, Miller-Matero showed that preoperative emotional eating was associated with less TWL 1 year after surgery [9]. Similarly, Castellini showed that higher levels of preoperative emotional eating predicted lower excess body mass index (BMI) weight loss 1 year after surgery [10].

The primary aim of the current study was to investigate the predictive value of preoperative emotional eating on EWL and TWL 2 years after RYGB. The secondary aim of this study was to explore the differential impact of emotional eating in response to clearly labelled versus diffuse emotions on EWL and TWL. Based on the studies that found a negative association between emotional eating and postoperative weight loss, it was hypothesized that the level of preoperative emotional eating was negatively associated with EWL and TWL [9,10,12].

Methods

Study cohort

Data from participants that underwent a primary RYGB within our hospital between the 1st of January 2015 and the 31st of December 2015 were analysed in retrospect. All participants

were screened for surgery by a multidisciplinary team. To qualify for bariatric surgery, criteria of the 'International Federation for the Surgery of Obesity and Metabolic Disorders' were applied [13]. Participants were included if they completed the required psychosocial assessments preoperatively, and if they had been to the follow-up visits 2 years after RYGB. Participants who received psychological interventions pre- or postoperatively were not excluded from the study. Pregnancy during the follow-up period or missing anthropometric data 2 years after surgery were exclusion criteria. All procedures performed within this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Study procedure was approved by a local Medical Ethics Review Committee (N17.145, date of approval October 6, 2017).

Data collection

Sociodemographic and psychological information concerning gender, age, level of education, work status, marital status, medication use and/or mental healthcare treatment in the past were obtained by use of preoperative screening questionnaires, as well as additional information related to pre-or postoperative psychological interventions. The aim of these interventions were to implement small behavioural adjustments related to eating behaviour, diet and/or physical activity. The level of emotional eating was assessed prior to the start of a psychological intervention. Information about BMI and weight was obtained by using electronic patient files.

The Dutch Eating Behaviour Questionnaire

The Dutch Eating Behaviour Questionnaire (DEBQ) was used for assessment of emotional eating. The DEBQ is a validated 33-item self-report questionnaire that differentiates between emotional eating in response to clearly labelled and diffuse emotions, external eating and restrained eating [7]. Thirty-three statements are rated on a 5-point scale, with responses ranging from 1 (never) to 5 (very often). Total scores for the emotional eating scale range between 13 to 65, whereas for the external and restrained eating scale they range between 10 to 50. Higher scores indicate an eating behaviour which is more pathological. The Dutch version of the DEBQ is of high quality in terms of reliability and validity (α = 0.95- 0.96) [14]. Participants were clustered, based on their DEBQ score, in high and low emotional eaters. This classification was performed for the categories 'overall emotional eating', 'emotional eating in response to clearly labelled emotions' and 'emotional eating in response to diffuse emotions'. In order to make this classification, gender specific cut-off scores were applied based on normative data from a Dutch obese population [7,15,16].

Symptom Checklist-90

The Symptom Checklist-90 (SCL-90) was used for assessment of psychopathology including anxiety and depression. The SCL-90 is a self-report questionnaire that measures physical and psychological complaints [17]. The questionnaire contains eight subscales: agoraphobia, anxiety, depression, somatization, insufficient thinking or acting, distrust and interpersonal sensitivity, hostility and sleep problems. Ninety statements are rated on a 5-point scale with responses ranging from 1 (not at all) to 5 (extremely). Total SCL-90 scores are calculated as the sum of the subscale scores and range between 90 to 450. The subscale score for depression ranges between 16 and 80, while for anxiety this ranges between 10 and 50. The Dutch version of the SCL-90 is of moderate quality in terms of reliability and validity ($\alpha = 0.80$) [18].

Weight change

Weight loss was described as %EWL and was calculated as follows: (initial weight − final weight) / (initial weight − ideal body weight) × 100%. Initial weight was defined as the weight at the moment of preoperative screening. Ideal body weight was based on a BMI of 25 kg/m^2. Additionally, weight loss was expressed in %TWL and was calculated as follows: ([initial weight - final weight] / initial weight) × 100%. Participants were clustered, based on their %EWL, as primary responders and primary non-responders. An EWL of ≥50% 2 years after RYGB was considered as a primary response, while an EWL of <50% after 2 years was considered as a primary non-response [4].

Statistical analysis

Descriptive statistics were computed for sociodemographic and psychological characteristics. For each type of emotional eating, the associations between the level of emotional eating and covariates (i.e., gender, age, initial BMI, marital status, preoperative psychological intervention and the level of preoperative anxiety and depression) were analysed using (non-parametric) correlations. The internal consistency of the DEBQ and SCL-90 was assessed by measuring Cronbach's alpha. Independent sample t-tests were performed to examine differences between primary responders and primary non-responders in preoperative demographic and biological data. An independent sample t-test was performed to detect differences in %EWL in participants with either high or low scores of emotional eating.

A three-stage hierarchical multiple linear regression model was applied three times to examine the association between emotional eating (continuous, independent variable) and EWL (continuous, dependent variable), as well as to test whether these associations were independent of other predictors of EWL. In stage one, the primary predictor was entered which

was the total score on emotional eating in the first model, the score on emotional eating in response to clearly labelled emotions in the second model, and the score on emotional eating in response to diffuse emotions in the third model. In stage two, psychological covariates (preoperative anxiety and depression) were added. In stage three, demographic and biological covariates (gender, age, initial BMI, marital status, type 2 diabetes mellitus and preoperative psychological intervention) were added. For each model, the 95% confidence interval was calculated and the significance level was set at 5% ($p < 0.05$). The multiple linear regression model was repeated with TWL as dependent variable. All analyses were performed using the program Statistical Package for Social Sciences version number 22.0 (IBM SPSS 22.0).

Results

The sample set consisted of 302 participants. Two participants were excluded due to pregnancy during 2 year follow-up. An additional 128 participants were excluded due to missing data during 2 year follow-up, or due to an incomplete questionnaire that was required during preoperative screening (e.g. DEBQ). As a result, 172 participants were included in this study.

The sociodemographic characteristics of the cohort are shown in Table 1. Excluded participants did not differ significantly from the included patients in baseline characteristics for example gender, age and preoperative BMI (data not shown). The mean scores of emotional eating did not differ between the group of responders (32.3 ± 11.8) and non-responders (30.6 ± 10.1). Non-responders had a higher BMI ($p = 0.04$) and a higher use of mental healthcare in the past ($p = 0.02$) in comparison to responders. Between high and low emotional eaters, there were no significant differences in EWL with average overall scores of 82.7% ±18.2 and 82.4% ±21.3, respectively. The average score of the DEBQ within each category is illustrated in Table 2.

The regression model with overall emotional eating scores revealed that only initial BMI was a significant predictor for EWL ($\beta = -0.36$, 95% CI [−2.05, −0.84]) after adjusting for covariates (Table 3). Emotional eating in response to diffuse emotions showed, after adjusting for covariates, a negative association with EWL ($\beta = -0.16$, 95% CI [−1.57, −0.01]). The covariates accounted for 15.3%, 15.2% and 17.0% of the variance in EWL in the group of overall emotional eating, clearly labelled and diffuse emotions. Table 4 illustrates the regression model with overall emotional eating scores and TWL as the dependent variable. This analysis showed that only initial BMI was a significant predictor for TWL after adjusting for covariates ($\beta = 0.30$, 95% CI [0.24, 0.71]).

Table 1. Characteristics of the study population

	Total n=172	**Primary response[1] n= 161**	**Primary non-response[2] n= 11**	**P value[6]**
Gender, no. of females (%)	144 (83.7)	135 (83.9)	9 (81.8)	.86
Age, years mean ±SD	44.9 ± 10.2	44.6 ± 10.2	50.1 ± 9.7	.09
Initial weight (kg), mean ±SD	120.7 ± 19.3	120.2 ± 19.1	127.9 ± 22.7	.21
Initial BMI (kg/m^2), mean, ±SD	42.4 ± 5.0	42.2 ± 4.8	45.5 ± 7.1	.04*
EWL (%), mean, ±SD	82.4 ± 20.6	85.5 ± 18.5	44.0 ± 3.7	<.001*
TWL (%), mean, ±SD	32.7 ± 8.0	33.6 ± 7.4	19.2 ± 4.2	<.001*
Change in BMI (kg/m^2), mean, ±SD	13.9 ± 4.4	14.3 ± 4.2	8.9 ± 3.1	<.001*
Marital status, no. of married (%)	141 (82)	132 (81.9)	9 (81.8)	.99
Educational level[3] (%)				
< 6 years	14 (8.2)	14 (8.2)	0 (0)	.31
6-12 years	133 (77.3)	123 (71.5)	10 (91)	.27
More than 12 years	25 (14.5)	24 (14.9)	1 (9)	.60
Work status (%)				
Employed	112 (65.1)	107 (66.5)	5 (45.5)	.11
Unemployed	60 (34.9)	54 (33.5)	6 (54.5)	.11
Use of mental healthcare (%)	83 (48.3)	74 (46)	9 (81.8)	.02*
Preoperative psychological intervention (%)	62 (36)	59 (36.6)	3 (27.3)	.53
Preoperative use of antidepressants (%)	21 (12.2)	19 (11.8)	2 (18.2)	.53
Emotional eating[4], mean, ±SD	32.2 ± 11.7	32.3 ± 11.8	30.6 ± 10.1	.63
Clearly labelled, mean, ±SD	21.0 ± 8.4	21.2 ± 4.5	19.0 ± 6.8	.41
Diffuse, mean, ±SD	11.2 ± 4.1	11.2 ± 4.1	11.3 ± 3.8	.95
External eating[4], mean, ±SD	28.5 ± 5.7	28.6 ± 5.9	27. 5 ± 2.9	.54
Restrained eating[4], mean, ±SD	31.9 ± 6.5	32.1 ± 6.6	28.8 ± 5.1	.11
Psychoneuroticism[5], mean, ±SD	146.4 ± 39.7	145.9 ± 39.4	154.5 ± 44.3	.49
Depression, mean, ±SD	30.9 ± 29.4	30.9 ± 30.3	30.5 ± 11.0	.96
Anxiety, mean, ±SD	13.9 ± 4.6	13.9 ± 4.6	14.6 ± 3.9	.66

Abbreviations: BMI, Body Mass Index; EWL, Excess Weight Loss; TWL; Total Weight loss; SD, Standard Deviation, no, number

[1] Patients with ≥50% EWL 2 years after surgery.

[2] Patients with < 50% EWL 2 years after surgery.

[3] Six years of education (primary school). Six to 12 years of education (LTS, MAVO, (M)ULO, HAVO, VWO). More than 12 years of education (HBO, WO, post-HBO/master).

[4] Measured with the Dutch Eating Behaviour Questionnaire (DEBQ), Cronbach's alpha of 0.75.

[5] Measured with the Symptom Checklist-90 (SCL-90), Cronbach's alpha of 0.68.

[6] Based on independent samples t-test.

* $p \leq .05$

Table 2. Mean percentage of EWL and TWL in participants with high and low scores of emotional eating

	High score[1]			Low score[2]					
	DEBQ score, mean, ±SD	EWL (%), mean, ±SD	TWL (%), mean, ±SD	DEBQ score, mean, ±SD	EWL (%), mean, ±SD	TWL (%), mean, ±SD	P value[3]	95% CI[3]	Effect size (Cohen's *d*)[3]
Emotional eating overall	3.6 ±0.5	82.7 ±18.2	31.8 ±6.8	2.1 ±0.7	82.4 ±21.3	32.9 ±8.3	.92	-7.6 - 6.9	.02
Emotional eating clearly labelled	4.2 ±2.4	84.2 ±18.7	32.5 ±6.7	2.4 ±0.8	81.9 ±21.1	32.8 ±8.4	.53	-9.7 - 4.9	.12
Emotional eating diffuse	3.6 ±0.5	82.2 ±18.4	32.0 ±6.7	1.9 ±0.7	82.5 ±21.4	32.9 ±8.5	.94	-6.7 - 7.2	.01

Abbreviations: CI, confidence interval; DEBQ, Dutch Eating Behaviour Questionnaire; EWL, Excess Weight Loss; TWL; Total Weight loss; SD, Standard Deviation
[1] High score emotional eating "overall": man ≥2.6, females ≥3.3. High score emotional eating in response to clearly labelled emotions: man ≥2.5, females ≥3.1. High score emotional eating in response to diffuse emotions: man ≥2.7, females ≥3.7.
[2] Low score emotional eating overall: male <2.6, females <3.3. High score emotional eating in response to clearly labelled emotions: man <2.5, females <3.1. High score emotional eating in response to diffuse emotions: man <2.7, females <3.7.
[3] Based on independent samples t-test between EWL in participants with high and low scores of emotional eating.

Table 3. Multiple linear regression analysis for predictors of EWL two years after surgery

		Emotional eating overall		Emotional eating in response to clearly labelled emotions		Emotional eating in response to diffuse emotions	
		β	P value	β	P value	β	P value
Model 1[1]	Emotional eating	-.03	.71	-.02	.76	-.09	.24
Model 2[2]	Emotional eating	-.06	.49	-,05	.53	-.12	.15
	Anxiety	.00	1.00	.00	.99	.01	.90
	Depression	.12	.16	.11	.16	.12	.13
Model 3[3]	Emotional eating	-.06	.43	-.05	.51	-.16	.048*
	Anxiety	-.03	.66	-.04	.64	-.03	.74
	Depression	.07	.35	.07	.36	.08	.27
	Age	-.06	.44	-.06	.43	-.05	.52
	Gender	.06	.40	.06	.42	.07	.33
	Marital status	-.01	.92	-.01	.91	-.00	.96
	Diabetes mellitus type 2	-.08	.31	-.08	.32	-.11	.16
	Initial BMI	-.36	<.001*	-.35	<.001*	-.36	<.001*
	Preoperative psychological intervention	-.05	.50	-.05	.49	-.04	.62

Abbreviation: BMI, Body Mass Index. Dependent variable: %EWL 2-year after surgery.
Model 1: predictor emotional eating ("overall" or in response to clearly labelled, or diffuse emotions);
Model 2: predictor emotional eating ("overall" or in response to clearly labelled, or diffuse emotions), anxiety, and depression;
Model 3: predictor emotional eating ("overall" or in response to clearly labelled, or diffuse emotions), anxiety, depression, age, gender, marital status, diabetes mellitus type 2, BMI and preoperative psychological intervention.
* $p \leq .05$

Table 4. Multiple linear regression analysis for predictors of TWL two years after surgery

		Emotional eating "overall"		Emotional eating in response to clearly labelled emotions		Emotional eating in response to diffuse emotions	
		β	P value	β	P value	β	P value
Model 1[1]	Emotional eating	-.04	.65	-.03	.66	-.10	.18
Model 2[2]	Emotional eating	-.04	.65	-.04	0.64	-.11	.18
	Anxiety	-.05	.56	-.05	0.55	-.04	.65
	Depression	.05	.58	.05	0.58	.05	.49
Model 3[3]	Emotional eating	-.04	.65	-.04	.65	-.12	.15
	Anxiety	-.06	.43	-.06	.42	-.05	.48
	Depression	.07	.37	.07	.37	.08	.30
	Age	-.09	.24	-.09	.24	-.08	.29
	Gender	.03	.75	.03	.74	.03	.65
	Marital status	.02	.76	.02	.76	.03	.72
	Diabetes mellitus type 2	-.10	.19	-.10	.19	-.13	.11
	Initial BMI	.30	<.001*	.30	<.001*	.29	<.001*
	Preoperative psychological intervention	-.05	.49	-.05	.49	-.04	.59

Abbreviation: BMI, Body Mass Index. Dependent variable: %TWL 2-year after surgery.
Model 1: predictor emotional eating ("overall" or in response to clearly labelled, or diffuse emotions);
Model 2: predictor emotional eating ("overall" or in response to clearly labelled, or diffuse emotions), anxiety, and depression;
Model 3: predictor emotional eating ("overall" or in response to clearly labelled, or diffuse emotions), anxiety, depression, age, gender, marital status, diabetes mellitus type 2, BMI and preoperative psychological intervention.
* $p \leq .05$

Discussion

Earlier research shows that there has been little agreement on emotional eating as predictor of weight loss outcomes after bariatric surgery. The current study aimed to (1) investigate the association between emotional eating and EWL, and TWL; (2) explore the differential impact of emotional eating in response to clearly labelled and diffuse emotions on EWL and TWL because these are two distinguished types of emotional eating. With regard to the first aim of this study, our results showed no association between preoperative emotional eating and EWL/TWL 2 years after RYGB. In a separate analysis classifying high and low emotional eaters, there were no differences found between EWL and TWL. Regarding the second aim of this study our regression analysis showed that, when correcting for multiple covariates, emotional eating in response to diffuse emotions had a negative impact on EWL, although this was not applicable for TWL. It should be noted that the finding was borderline significant (p 0.048) and in presence of a confounder (initial BMI).

There are two remarkable findings when reviewing characteristics of the study population. First of all, there were only 11 participants defined as non-responders limiting further analysis of EWL in responders and non-responders. The low rate of non-response contradicts the rate of 25% to 35% reported in literature [1,2,8]. This finding could possibly be explained by the large set of excluded participants (43%) as these participants may have experienced more non-response. Non-response may have reduced motivation to attend follow-up appointments which could have contributed to missing data. Secondly, a large amount of participants (36%) received a psychological intervention preoperatively. This intervention may have altered levels of emotional eating postoperatively and consequently effected weight loss outcomes. However, participation in this intervention was not associated with EWL or TWL based on the regression analysis performed.

When considering all demographic and psychological variables tested in the regression analysis, initial BMI showed a negative association with EWL which is in line with other literature [19,20]. Initial BMI showed a positive association with TWL which is also supported by literature [21]. This difference can be explained by the fact that EWL is influenced by baseline BMI because it relies on an ideal body weight (i.e., BMI 25 kg/m^2), whereas TWL is less influenced by BMI [20]. There was no association between anxiety and EWL/TWL, nor between depression and EWL/TWL. These findings are not consistent across studies as some studies did find associations, yet the opposite has also been found [22-26].

Not finding an association between depression and EWL/TWL, and between anxiety and EWL/TWL could be explained by the use of the SCL-90. This is a self-report questionnaire that measured psychological symptoms and distress over the past week and was not designed to classify psychological or psychiatric disorders. Another explanation might be that the level of psychopathology in the cohort was not representative for the level of psychopathology in the population of individuals with obesity. Namely, bariatric candidates with high levels of preoperative psychopathology are more likely to be denied for surgery.

This study presents limitations that can be partly traced back to using the DEBQ emotional eating scale. Due to the DEBQ being a self-report questionnaire, response bias may have occurred. Participants may have underreported the level of emotional eating in order to be eligible for bariatric surgery. Alternatively, participants may have lacked insights into their own eating behaviour or emotions which may have influenced their questionnaire response. It is also important to note that the DEBQ assesses desire to eat in response to emotions as opposed to actual eating in response to emotions. It is possible that not assessing actual eating may have biased the results. Besides these limitations, it should be mentioned that this

study lacked examination of emotional eating postoperatively and it therefore unknown how emotional eating developed over time. Moreover, the follow-up time of 2 years may not have been long enough to detect non-response. Lastly, this study suffered from a poor response rate as 43% of the participants were excluded from the final analysis.

In order to develop a full picture of the relationship between emotional eating and postoperative weight loss, additional studies will be needed. Prospective studies in large cohorts (e.g. participants undergoing RYGB, as well as sleeve gastrectomy) should examine the effect of preoperative emotional eating on long-term weight loss outcomes including non-response. Longitudinal studies could gain insights in the development of emotional eating over time and how this may contribute to non-response. The yields of additional studies may result in a number of practical implications like improvement of preoperative evaluation and subsequent patient selection.

Conclusion

The current study found no association between preoperative emotional eating and EWL, nor between preoperative emotional eating and TWL 2 years after RYGB. When focusing on emotional eating specifically in response to diffuse emotions, it seemed that emotional eating had a negative impact on EWL although this was not applicable for TWL. This study faced multiple limitations such as response bias, underreporting bias and a poor response rate thereby hampering clinical guidance.

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CHAPTER 03

Can routine clinical tests for protein intake and physical function predict successful weight loss?

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Abstract

Introduction: protein intake and physical activity have a substantial impact on body composition and weight loss outcomes after bariatric surgery. The 24-h dietary recall and 6-min walk test (6mWT) are frequently used to monitor protein intake and physical activity, respectively. Despite its frequent use, it is unknown whether these tests can predict long-term weight loss.

Methods: this retrospective study included 85 patients who underwent laparoscopic Roux-en-Y gastric bypass. Protein intake was recorded using the 24-h dietary recall and physical function was measured using the 6mWT. Data about total weight loss (TWL) and non-response (i.e., insufficient weight loss and weight regain) were collected up to 5 years. Multiple regression analyses were performed to examine the predictive value of the 24-h dietary recall and 6mWT on weight loss outcomes.

Results: the mean protein intake 1 year postoperatively was 68.1 ± 15.0 g/day and the mean distance covered during the 6mWT was 591.7 ± 67.9 m. Both the 24-h dietary recall and 6mWT were not significantly associated with TWL and neither with non-response.

Conclusion: the 24-h dietary recall and 6mWT are poor predictors for long-term weight loss outcomes after gastric bypass. Despite the well-known advantages of these clinical tests, other monitoring tests are suggested for future research.

Abbreviations: 6mWT, 6-min walk test; 1RM, one repetition maximum; BMI, Body mass index; RYGB, Roux-en-Y gastric bypass; SRT, steep ramp test; TWL, Total weight loss.

Introduction

Bariatric surgery is considered the most effective treatment in patients with morbid obesity as it promotes significant long-term weight loss and reduces obesity-related comorbidities [1–3]. Despite its frequent success, 20–30% of patients do not respond well to bariatric surgery [4,5]. These patients may experience insufficient weight loss, defined as primary non-response, or regain an excessive amount of weight after sufficient weight loss, defined as secondary non-response [6]. In the etiology of non-response, studies provided evidence for surgical components like a dilated gastric pouch and/or anastomosis, as well as for physiological components like gender, preoperative body mass index (BMI), and preoperative age [7,8]. In addition to these components it is thought that nutritional noncompliance and physical inactivity may contribute to the development of non-response [9,10]. The mechanisms behind this are discussed below.

The recommended protein intake in patients following bariatric surgery is 60–120 g/day or 1.1–1.5 g/kg of ideal body weight [11–13]. An inadequate amount of protein intake could reduce the feelings of satiety and result in a loss of fat-free mass rather than fat mass [14–16]. This may, in turn, induce a decrease in the resting metabolic rate and negatively alter weight loss outcomes [14–16]. In terms of physical activity and bariatric surgery, guidelines recommend patients to perform both resistance and endurance training on moderate-to-vigorous intensity for 150–250 min/week to prevent weight regain and 300 min/week to maintain weight loss [12,14,17]. Low activity levels can only moderately contribute to the positive effects of physical activity, which are an increased total energy expenditure, preservation of fat-free mass and enhancement and/or maintenance of postsurgical weight loss [9,12,18].

In light of weight loss outcomes, it is of high clinical importance to thoroughly monitor protein intake and physical function. The 24-h dietary recall method is a well-known instrument for nutritional assessment [19], whereas the 6-min walk test (6mWT) is a commonly described instrument for assessment of a patients' functional capacity [20,21]. Both the 24-h dietary recall method and 6mWT are fast, inexpensive, and easy executable tests [19,20,22]. Because of these clinical advantages, it is presumed that the tests are frequently used in today's practice. Despite this, it is unknown how well these clinical tests can actually predict long-term weight loss after bariatric surgery. Therefore, this study aimed to determine the predictive value of the 24-h dietary recall and 6mWT on long-term weight loss outcomes.

Methods

Study population

Data of patients who underwent primary laparoscopic Roux-en-Y gastric bypass (RYGB) in a European bariatric center of excellence in 2014 were retrospectively analyzed. Patients were included if their body weight was noted 18 months after surgery and 2, 3, 4, or 5 years after surgery; and if their protein intake (24-h recall) and physical function (6-min walk test) were reported 1 year postoperatively. Patients who underwent a primary banded RYGB or one anastomosis gastric bypass were excluded for the sake of uniformity. Patients with a previous history of bariatric surgery such as laparoscopic adjustable gastric banding or Mason gastroplasty were excluded as well. At last, patients were excluded if they underwent revisional bariatric surgery due to non-response, as this interfered with weight loss outcomes. Ethics approval has been obtained from the Medical Ethics Committee of our center, reference number N20.045, date of approval 10-04-2020. For this type of study, formal consent from all individual participants was not required. The study was conducted according to the guidelines of the Declaration of Helsinki, and was approved by the Ethics Committee of the Máxima Medical Center (protocol code N20.045, date of approval 10-4-2020). Clinical Trial Registration is not applicable.

Standard pre- and postoperative care

All patients were screened for primary bariatric surgery in our center by a multidisciplinary team in accordance with the International Federation for the Surgery of Obesity and Metabolic Disorder guidelines [23]. An individual preoperative treatment with the dietician, physiotherapist, and/or medical psychologist was offered in addition to the regular program if the multidisciplinary team decided that this was necessary. The postoperative program included individual and group visits with a dietician and physical therapist with the aim to adopt a healthy lifestyle. Patients were advised to consume three meals and three healthy snacks per day, drink 1.5–2 L throughout the day, and add 30 g protein (whey) powder to their meals or drinks during the first 3 weeks after surgery. Furthermore, patients were advised to adhere to the Dutch Physical Activity Guidelines [24] and were, 4 weeks postoperatively, invited to participate in a training program at our center. Patients were offered two training sessions per week for 5–6 weeks, each session consisting of 30-min endurance training and 30-min resistance training. The intensity of the resistance training is calculated from one repetition maximum (1RM), starting from 50% to 60% of 1RM up to 70–80% of 1RM, while the intensity of the endurance training is calculated from steep ramp test (SRT) and 6mWT, aiming levels of Borg scale [13–15]. Patients were annually monitored for a period of 5 years with standard biochemical testing for vitamin deficiencies.

Twenty-four-hour dietary recall

The 24-h dietary recall method was routinely used 1 year postoperatively to estimate protein intake. During a 30-min assessment with a clinical dietician, patients were orally questioned about their diet from the past 24 h (from midnight to midnight) of, preferably, a weekday. Based on current guidelines, patients were categorized as ''adequate protein intake'' if their protein intake was ≥60 g/day, whereas patients were categorized as ''inadequate protein intake'' if their protein intake was <60 g/day [13,14].

Six-minute walk test

The 6mWT was routinely performed preoperatively and 1 year postoperatively to determine physical function. The test was executed according to a standardized protocol [25]. Patients were instructed to walk at their own pace as far as possible for 6 min by going back and forth in an at least 25-m long corridor. Outcomes were total distance covered in meters (m) and heart rate at rest and immediately after the test ended. The percentage of the predicted value of the distance covered was calculated as follows [26]: [(218 + 5.14 * height (cm) -5.32 * age (years) -1.8 * weight (kg) +51.31* sex (1– male, 0–female)]. Numbers of <82% were considered aberrant based on normative values of an obese population [27]. After the 6mWT, leg cramps and shortness of breath (dyspnea) were rated by the Borg scale. This is a 15-point scale ranging from 6 (''nothing at all'') to 20 (''very, very severe''). Patients were categorized as ''high physical function'' if the predicted percentage was ≥82%, whereas patients were categorized as ''low physical function'' if their predicted percentage was <82%.

Body weight and obesity-related comorbidities

Body weight was measured during preoperative screening and hospital consultation 12 and 18 months, and 2, 3, 4, and 5 years postoperative. The presence of obesity-related comorbidities (hypertension, diabetes, dyslipidemia, obstructive sleep apnea syndrome (OSAS), and osteoarthritis) was assessed as well. Weight loss was described as %total weight loss (%TWL), and was calculated as [(preoperative weight – postoperative weight)/preoperative weight] x 100%. The %TWL at 2 and 3 years after RYGB were averaged into %TWL at midterm, and %TWL at 4 and 5 years after RYGB were averaged into %TWL at long term. The percentage of weight regain was calculated as percentage kilogram (kg) gained after reaching the lowest postoperative weight (nadir weight). Non-response rates were defined as the following: primary non-response if the patients' %TWL was less than 15% within the first 18 months after surgery, and secondary non-response if the patients' %TWL was more than 15% plus a regain of more than 15% after 24 months, with respect to nadir weight following RYGB [28].

Statistical analyses

Descriptive statistics were computed for patient characteristics. Quantitative data are presented as mean with standard deviation (range) or median with interquartile range, and categorical data are expressed in numbers and percentages. Data were checked for normality using the Kolmogorov–Smirnov test. A paired t-test, or Wilcoxon signed-rank test in case of a non-normal distribution, was performed to compare pre- and post-measurements of physical function. A two-stage hierarchical multiple linear regression analysis was conducted to examine the contribution of protein intake (postoperatively assessed) and physical function (both preoperatively and postoperatively assessed) on %TWL at midterm and %TWL at long term. Both analyses were performed with protein intake and physical function as categorical and continuous variable. Furthermore, a two-stage hierarchical multiple logistic regression analysis was performed to examine the relation between protein intake and physical function on secondary non-response. To test whether associations were independent of other predictors, potential confounders were included as covariates (i.e., age, gender, preoperative BMI, preoperative individual treatment, and long-term complications). Statistical significance was set at $p \leq 0.05$. All analyses were performed using the program Statistical Package for Social Sciences version number 22.0 (IBM SPSS 22.0; Chicago, IL).

Results

Study population

A total of 227 patients were assessed. Four patients were excluded due to revisional surgery (2 patients underwent shortening of the common limb; 1 patient received a gastric ring; 1 patient underwent resizing of the stoma). Furthermore, 138 patients were excluded due to missing values in essential variables at various time points. In total 85 patients, of which 69 (81.2%) were female, were included in the study. Mean age was 45.8 ± 10.2 years and median BMI preoperatively was 42.0 kg/m^2 (interquartile range = 34.6). These and other patients' demographics are presented in Table 1.

Protein intake and physical function

Mean protein intake 1 year after surgery was 68.1 ± 15.0 g/day and the mean distance covered during the 6mWT was 591.7 ± 67.9 m. In total, 61.2% of the patients were grouped into ''adequate protein intake'' and 38.8% of the patients were grouped into ''inadequate protein intake''. Moreover, 37.6% of the patients were grouped into ''low physical function'', whereas 62.4% was grouped into ''high physical function'' (Table 2).

Weight outcomes

The follow-up rate was 96% at midterm and 85% at long term. The percentage of TWL was 34.7% ± 8.6% at 1.5 years, 33.3% ± 9.5% at 2–3 years, and 29.6% ± 10.4% at 4–5 years after surgery (Table 3). Based on the aforementioned criteria for non-response, no patients were classified as primary non-response, whereas 18 patients (21.2%) were classified as secondary non-response. Time to develop secondary non-response varied from 4 to 5 years.

Table 1. Baseline characteristics of the study population

	n=85
Gender, no. (%)	
Female	69 (81.2)
Male	16 (18.8)
Age# (years)[1]	45.8±10.2 (23-66)
Preoperative weight (kg)[2]	124.0 (104.3)
Preoperative BMI (kg/m²)[2]	42.0 (34.6)
Preoperative comorbidities, no. (%)	
Hypertension	37 (43.5)
Type II diabetes	11 (12.9)
Dyslipidaemia	18 (21.2)
OSAS	17 (20.0)
Osteoarthritis	8 (9.4)
No comorbidities	33 (39.0)
Preoperative individual treatment, no. (%)	
Intern	25 (29.4)
Dietician	7 (8.2)
Physiotherapist	0 (0.0)
Medical psychologist	20 (23.5)
Extern	1 (1.2)
Complications, no. (%)	
Short term <30 days	1 (1.2)
Long term >30 days	7 (8.2)

[1] Expressed in mean±SD (range): [2] Expressed in median (IQR 25-75). # Age at time of surgery. Abbreviations: OSAS = Obstructive Sleep Apnoea Syndrome, BMI = Body Mass Index, SD = Standard Deviation, IQR = Interquartile Range.

Table 2. Physical function at baseline and 1 year follow-up

		n	Baseline	n	1 year follow-up	p-value
SRT	Steep ramp test (Watt)[2]	85	160.0 (220.0)		N/A	
6mWT	Distance covered (meters)[1]	85	520.7±78.0 (300.0-688.0)	85	591.7±67.9 (432.0-778.0)	<0.001*
	Predicted percentage (%)[1]	85	81.7±9.9 (48.0-107.0)	85	83.4±8.0 (65.0-103.0)	0.068
	Heart rate at rest (beats/min)[1]	84	87.3±14.5 (55.0-139.0)	73	75.3±12.5 (51.0-102.0)	<0.001*
	Heart rate after effort (beats/min)[1]	85	126.5±18.8 (85.0-195.0)	71	107.5±19.3 (65.0-162.0)	<0.001*
	Borg score for dyspnea[2]	85	12.0 (13.0)	77	11.0 (3.0)	<0.001*
	Borg score for leg fatigue[2]	85	13.0 (12.0)	77	11.0 (11.0)	<0.001*
	Physical function#	85		85		0.162
	High physical function, no (%)		46 (54.1)		53 (62.4)	
	Low physical function, no. (%)		39 (45.9)		32 (37.6)	

[1] Expressed in mean±SD (range): [2] Expressed in median (IQR 25-75). * Paired t-test: significant difference compared to baseline, p≤0.05. # High physical function if predicted percentage is ≥82%; low physical function if predicted percentage is <82%. Abbreviations: SRT = Steep Ramp Test, 6mWT = 6-minute Walk Test, SD = Standard Deviation, IQR = Interquartile Range, N/A = Not Assessed.

Table 3. Weight loss and (non) response rates

	n	
%TWL		
1.5 years[1]	n=85	34.7±8.6 (18.4-55.9)
2-3 years (mid-term)[1]	n=82	33.3±9.5 (14.2-53.7)
4-5 years (long-term)[1]	n=72	29.6±10.4 (10.7-51.1)
Weight regain (%)[1]	n=80	10.5±5.8 (0.14-25.4)
Primary non-response, no. (%)	n=85	0 (0)
Secondary non-response, no. (%)*	n=85	18 (21.2)
Time to secondary non-response (years)[2]	n=85	5.0 (1.0)

[1] Expressed in mean±SD (range): [2] Expressed in median (IQR 25-75). * Secondary non-response is defined as a %TWL≥15% and a weight regain of ≥15% after 24 months. Abbreviations: TWL = Total Weight Loss, SD = Standard Deviation, IQR = Interquartile Range.

Predictors of weight loss and non-response

A stepwise multiple linear regression analysis revealed that both the 24-h dietary recall and 6mWT were not significantly associated with %TWL at midterm (p = 0.203 and p = 0.948) nor with %TWL at long term (p = 0.963 and p = 0.855) (Table 4). Being female (β = 0.34; p = 0.003) and having a greater preoperative BMI (β = 0.31; p = 0.006) resulted in a higher %TWL at midterm. Moreover, having a greater preoperative BMI (β = 0.35; p = 0.006) resulted in a higher %TWL at long term. Remarkably, multiple linear regression analysis showed similar results when including protein intake and physical function as continuous variables. When focusing on secondary non-response, a multiple logistic regression analysis revealed that protein intake and physical function were not significant predictors (Table 5). Due to the small group of patients with secondary non-response (n = 18), it was not possible to further assess predictors specifically in this subgroup.

Table 4. Multiple linear regression analysis for predictors of percentage of TWL at mid-term and long-term

		%TWL mid-term (n=82)		%TWL long-term (n=72)	
		β	p-value	β	p-value
Unadjusted model[a]	Protein intake (adequate vs. inadequate)[1]	-0.106	0.348	0.021	0.863
	Physical function (high vs. low)[2]	0.045	0.639	0.053	0.663
Adjusted model[b]	Protein intake (adequate vs. inadequate)[3]	-0.134	0.203	0.005	0.963
	Physical function (high vs. low)[4]	0.007	0.948	0.022	0.855
	Age	0.030	0.774	0.038	0.757
	Gender (female vs. male)	0.344	0.003*	0.180	0.156
	Preoperative BMI	0.308	0.006*	0.349	0.006*
	Preoperative individual treatment (yes vs. no)	-0.079	0.467	-0.003	0.978
	Long-term complication (yes vs. no)	0.034	0.743	-0.024	0.841

Abbreviations: TWL = Total Weight Loss, BMI = Body Mass Index. Dependent variables: %TWL mid-term and %TWL long-term. [a] Unadjusted model: protein intake and physical function. [b] Adjusted model: protein intake and physical function, age, gender, preoperative BMI, preoperative individual treatment and long-term complication.
[1] Protein intake (g/day) entered as a continuous variable: β=-0.061; p=0.594 and β=-0.147; p=0.223.
[2] Physical function (predicted percentage) entered as a continuous variable: β=0.061; p=0.594 and β=0.050; p=0.667.
[3] Protein intake (g/day) entered as a continuous variable: β=0.046; p=0.671 and β=-0.074; p=0.541.
[4] Physical function (predicted percentage) entered as a continuous variable: β=0.209; p=0.208 and β=0.214; p=0.253.
* p≤0.05

Table 5. Multiple logistic regression analysis for predictors of secondary non-response

		Secondary non-response (n=85)		
		Odds ratio	95% CI	p-value
Unadjusted model[a]	Protein intake (ref= inadequate)[1]	2.09	0.65-6.72	0.219
	Physical function (ref= low)[2]	0.36	0.12-1.07	0.066
Adjusted model[b]	Protein intake (ref= inadequate)[3]	2.68	0.72-9.97	0.142
	Physical function (ref= low)[4]	0.32	0.09-1.16	0.082
	Age	0.95	0.89-1.01	0.081
	Gender (ref= male)	2.87	0.49-16.48	0.237
	Preoperative BMI	0.89	0.77-1.02	0.101
	Preoperative individual treatment (ref= no)	3.85	1.04-14.2	0.043*
	Long-term complication (ref= no)	0.27	0.02-4.18	0.346

Abbreviations: BMI = Body Mass Index, CI = confidence interval, ref= reference. Dependent variable: secondary non-response, defined as a %TWL
≥15% and a weight regain of ≥15% after 24 months. [a] Unadjusted model: protein intake and physical function. [b] Adjusted model: protein intake and physical function, age, gender, preoperative BMI, preoperative individual treatment and long-term complication.
[1] Protein intake (g/day) entered as a continuous variable: OR=1.01; 95% CI 0.97-1.04, p=0.798.
[2] Physical function (predicted percentage) entered as a continuous variable: OR=0.93; 95% CI 0.87-1.00, p=0.053.
[3] Protein intake (g/day) entered as a continuous variable: OR=1.00; 95% CI 0.96-1.05, p=0.859.
[4] Physical function (predicted percentage) entered as a continuous variable: OR=0.92; 95% CI 0.85-1.01, p=0.073.
* p≤0.05

Discussion

Knowledge on strategies on how to maximize weight loss and reduce the rate of non-response after bariatric surgery is crucial. Protein intake and physical function are well-known factors that have a substantial impact on weight loss outcomes [9] and therefore, a routine assessment of these factors is advised [14,18]. The 24-h dietary recall and 6mWT are feasible tests in today's clinical practice to assess protein intake and physical function, although it is unknown what their predictive value is. The present study was designed to investigate this predictive value on TWL and non-response up to 5 years after RYGB.

In contrast to our initial hypothesis, it was found that protein intake as estimated by 24-h dietary recall was not predictive of TWL. There are three likely causes for this finding. First of all, in this study, the 24-h dietary recall has been used to estimate protein intake only, while there is evidence that a certain amount of carbohydrates along with protein is necessary to preserve fat-free mass [15,29]. It has also been suggested that energy restriction, rather than the protein diet's content, affects weight outcomes [30,31]. In detail, caloric intake is known to be reduced in the immediate postoperative phase, but in a subset of patients, energy intake gradually increases over time, which is thought to hinder weight loss and increase the risk on weight regain [32]. Lastly, when inquiring the diet of the last 24-h, there is a great demand on the short-term memory of the patients resulting in an under- or overestimation of the real protein intake. Taken together, presumably both protein and carbohydrate, as well as the energetic value of the diet are of important value when predicting weight loss outcomes.

Another important finding of this study was that physical function as estimated by 6mWT was not predictive of TWL. Yet again, there are several possible explanations for this result. The first explanation could be that this study exclusively focused on physical function, whereas physical activity participation was not taken into account. It is conceivable that the higher the physical activity, the higher the level of physical function; however, contrasting reports have been described focusing on this association [31,33]. A second explanation could be that physical function was measured only once postoperatively, which gives a limited amount of information about the patient's physical status. Third, there is a possible ceiling effect in the 6mWT for patients with normal or high exercise capacities pre-surgery, limiting the ability to detect performance improvements from pre- to postpositive. Lastly, there are many external factors (e.g. motivation, coaching effort) that could have influenced the outcomes of the 6mWT.

This retrospective study has multiple limitations that should be mentioned. Because of missing information, 63% of patients were excluded which may have influenced the generalizability of

the study population. Nevertheless, the sample size was calculated in retrospect and showed that the current sample size was sufficient (n = 84). Additionally, since we do not have analyzed data about excluded patients, the results might be prone to selection bias. Moreover, the 24-h dietary recall was measured only once postoperatively, which may have resulted in an unreliable measurement. On top of that, our study solely focused on the predictive effect of lifestyle factors (protein intake and physical function) on weight loss outcomes, whereas weight loss outcomes are suggested to have a multifactorial etiology with several patient (e.g. mental health) and surgery specific factors playing a role [9].

Hereafter, in the context of nutritional surveillance, the 24-h dietary recall should be performed at least twice to obtain a reliable estimation of habitual protein intake [34–36]. When looking for an alternative, multiple days of dietary records (e.g. 5 day food diary) optionally with pictures may be a valid choice as it will provide an optimal nutritional (protein) assessment [36]. In context of physical surveillance, an ergospirometry to measure peak oxygen uptake (VO2peak) should be preferred as it assesses exercise capacity more reliable without a ceiling effect [18]. For this study, these assessments were not available presumably because they are more time consuming, require more equipment, and are more expensive hampering their clinical use. In the assessment of physical status, it could be questioned whether it is sufficient to only perform this measurement before an exercise prescription, or it should be performed longitudinally. When performed postoperatively, the outcome can be used for further counseling as well as weight regain prevention.

Conclusion

There is emerging evidence that successful long-term weight loss is not maintained in a subset of patients after bariatric surgery. This study focused on the predictive value of protein intake and physical function, measured by the 24-h dietary recall and 6mWT, on long-term weight loss outcomes after RYGB. The results showed that neither the 24-h dietary recall, nor the 6mWT were significant predictors. These tests are therefore in common practice not feasible to predict successful long-term weight loss. Despite this, they are likely to be useful for their intended purposes, which are the examination of an eating pattern and the measurement of physical function. It is suggested to determine the clinical relevance of other monitoring tests, such as a 5-day food diary or ergospirometry, to predict and optimize weight loss after bariatric surgery.

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CHAPTER 04

Place Work on a Scale: What Do We Know About the Association Between Employment Status and Weight Loss Outcomes After Bariatric Surgery?

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Abstract

Introduction: despite the initial successful weight loss after bariatric surgery, a significant amount of patients experience weight loss failure and weight regain. Several factors are known to contribute to this, though the impact of employment status is unknown. The objective of this systematic review was to examine the impact of employment status on post-surgical weight loss outcomes.

Methods: an electronic literature search through MEDLINE, Web of Science and the Cochrane library was performed. Studies were included if they included patients who had undergone a malabsorptive bariatric procedure because of morbid obesity; if they noted employment status pre-surgery or post-surgery, and if they noted change in weight within two to ten years post-surgery. The primary outcome was the difference in weight loss, and subsequent weight regain, between employed and unemployed patients two to ten years after bariatric surgery.

Results: eight studies were included. The follow-up period ranged between two and ten years post-surgery. Employed patients seemed to present more weight loss (9.0–11.0% excess weight loss, 1.3–1.6% body mass index loss) compared to unemployed patients, but none of these numbers were statistically significant. Moreover, there were contrasting findings in terms of weight regain.

Conclusion: this review may highlight the importance of working status after bariatric surgery and warrants further investigation on this topic.

Abbreviations: BMI, Body mass index; EBMIL, Excess body mass index loss; EWL, Excess weight loss; Kg, Kilograms; RCT, Randomized controlled trials; RYGB, Roux-en-Y gastric bypass; SG, Sleeve gastrectomy; TWL, Total weight loss; QUIPS, Quality in Prognosis Studies.

Introduction

Bariatric surgery has a pivotal role in the treatment of morbid obesity as it effectively reduces weight and obesity related comorbidities [1,2]. It has a positive effect on physical functioning, psychological health and employment rate [3–6]. Based on a previous systematic review, employment rate has increased by 20% and 16–37% of unemployed patients succeed in finding a job post-surgery (re-employment rate) [5]. Bariatric surgery has also shown to decrease the rate of absenteeism and presenteeism which is the problem of employees being absent, and being present but not fully functioning because of a medical condition [5].

Non-response refers to the condition when a patient experiences insufficient weight loss, or regains a significant amount of weight [7]. The latter is seen in approximately 20–30% of patients and may result in the return of obesity related comorbidities and a decreased quality of life [8–10]. The etiology of non- response is multifactorial and includes factors like psychological health and compliance with dietary and exercise regimes [11]. In addition to these factors, it is known that pre-surgical BMI, age, type of surgery (e.g. adjustable gastric banding) and anatomical alterations (e.g. pouch and stoma size) are associated with non-response [9,11].

It is unknown if and how employment status contributes to the development of non-response. Despite this, it is well known that unemployment has a negative effect on both physical and mental health [12]. The underlying principle that may drive the relation between work and post-surgical weight loss can be found in the interaction between employment status and lifestyle behavior. Unemployed patients may experience more psychological stress and depression, potentially leading to decreased physical activity and increased caloric consumption [13–15]. Patients who work in shifts tend to have poorer sleep quality and poorer dietary patterns compared to non-shift workers [16]. Certain workstyle and lifestyle behavior may have predisposed the development of chronic illnesses like morbid obesity in the first place and hypothetically, it may counteract weight loss after bariatric surgery [16,17].

In order to maximize or maintain post-surgical weight loss, an understanding of the impact of factors like employment status on weight loss outcomes is essential. Up to now, articles primarily described the impact of bariatric surgery on post-surgical employment rate [5,6], while fewer articles described the predictive value of pre-surgical employment status on weight loss outcomes. Andersen et al. demonstrated that pre-surgical unemployment was a significant predictor for lower %excess body mass index loss (EBMIL) in women two years after sleeve gastrectomy (SG) [18]. Additionally, Cadena-Obando et al. found that lacking a fulltime job pre-surgery was a negative predictor for achieving successful weight loss (≥50% excess body weight

loss) one year after various bariatric procedures [19]. Only the study by Stenberg et al. reported long-term results and these results are in contrast to the abovementioned studies, as the authors found that pre-surgical employment as a professional or technician is independently associated with a lower %total weight loss (TWL) five years after Roux-en-Y gastric bypass (RYGB) [20]. A common observation is that an employed status is associated with better weight loss outcomes [18,19], though the opposite has also been described [20]. A systematic review comparing long-term outcomes in unemployed and employed patients is lacking and therefore, the objective of this study was to systematically review the literature available on employment status of patients that underwent revisional surgery and their weight loss outcomes.

Methods

This review complies with the recommendations of the Cochrane Handbook for Systematic Reviews and Interventions [21], and was recorded according to the PRISMA systematic review guidelines [22].

Eligibility Criteria

This review included observational studies and randomized controlled trials (RCTs). Studies were considered eligible if they included patients with a BodyMass Index (BMI) $\geq$35 kg/ m^2 who had undergone a malabsorptive bariatric procedure (RYGB, SG and biliopancreatic diversion); if they noted employment status pre-surgery or post-surgery, and if they noted change in weight within two to ten years post-surgery. The latter time points were chosen because weight loss reaches its maximum two years after surgery, and weight regain generally occurs in the subsequent years [23]. There were no restrictions regarding the expression of weight, such as change in kg, change in BMI or Excess Weight Loss (EWL). Due to assumed heterogeneity and a lack of information, it was not attempted to further define employment and unemployment. Studies were excluded in case of a restrictive bariatric procedure like adjustable gastric banding and vertical banded gastroplasty because these procedures are not recommended anymore and have little relevance to today's practice [24]. Besides this, studies were excluded in case of endoscopic procedures like gastric plication. Articles that were designed as animal studies, systematic reviews, letter to the editor and conference abstracts were excluded as well.

Systematic Literature Search Methodology

The systematic search was conducted on May, 2020. The search was conducted in three electronic databases: MEDLINE (new version 2020), EMBASE and The Cochrane Library.

There was no restriction regarding publication date. Keywords in the search strategy included [employment] and [bariatric surgery], and their synonyms. The full search strategies for all databases can be found in supplementary table 1 (supporting information). References within the included articles were screened to retrieve articles that might have been missed.

Study Selection

RefWorks software was used to manage references and support identification of duplicates. Titles and abstracts were screened on relevance. Full texts were obtained for clarification of eligibility criteria. Reasons for the exclusion of studies were recorded.

Data Extraction

Data extraction was performed in duplicate by two researchers (M.R. and D.H.) and was cross-checked by a third reviewer (L.J.). The following study characteristics were extracted from the included studies using predefined forms: authors' names, publication year, country, study design, sample size, type of procedure, gender, mean age, mean weight or BMI or EWL, and employment status. In case of missing data, the author of the article was contacted. It was noted whether the employment status was assessed before or after the assessment of weight loss.

Outcome Parameters

The primary outcome was the difference in weight loss, and subsequent weight regain, between employed and unemployed patients two to ten years after bariatric surgery. When describing these outcomes, the classification of employment status was preferably based on a pre-surgical assessment as this illustrates the direct impact of employment status on weight loss outcomes. If possible, weight loss outcomes were also described for students, retired and disabled patients. Mean differences in weight or BMI were calculated and if possible, standard deviations were extracted. If possible, the percentage of BMI was calculated and the delta (Δ) BMI was extracted. The formula for calculating Δ%BMI from presurgical to post-surgical was (pre-surgical BMI – postsurgical BMI)/ (pre-surgical BMI) ×100%. The following formula was furthermore used for the assessment of weight regain: (post-surgical highest BMI– post-surgical lowest BMI)/ (post-surgical highest BMI) ×100%. The advantage of this measurement is that it corrects for baseline differences in BMI, rather than measuring absolute BMI points. The secondary outcome was the difference in (un)employment rate two to ten years after bariatric surgery between pre-surgical employed and unemployed patients.

Quality Appraisal

In order to assess the methodological quality of the included studies, the Quality in Prognosis Studies (QUIPS) tool was used, as this tool was used. This tool was specifically designed to assess the relationship between the prognostic factor (employment status) and outcome (weight loss and regain) [25]. Two researchers (M.R. and D.H.) independently assessed the methodological quality of each study and if consensus could not be reached, inconsistencies were resolved by discussion with a third reviewer (L.J.). The following six domains were evaluated: study participations, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. Each of these domains were eventually rated as low, mediate or high risk of bias.

Results

The search retrieved 910 bibliographic references and a manual search retrieved two additional articles. A total of 680 articles remained when duplicates were removed. After screening titles and abstracts on relevance, 640 articles were excluded. Full text reading of the 40 remaining articles resulted in the selection of 8 eligible studies. Figure 1 provides a flow diagram of the screening process and inclusion of articles.

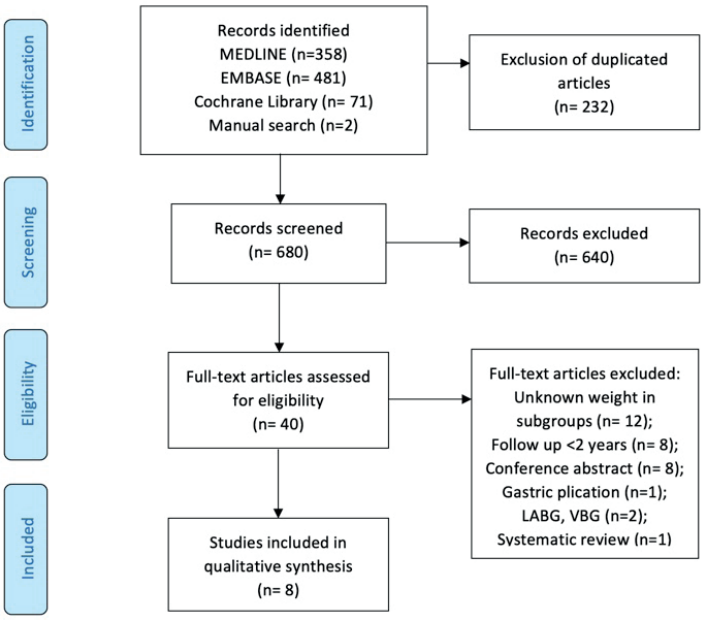

Figure 1. PRISMA flow diagram for study selection. Abbreviations: LABG= laparoscopic adjustable gastric banding, VBG= vertical banded gastroplasty

Study Characteristics

Table 1 provides an overview of the included studies. Among the eight included studies, four were retrospective cohort studies [26,27,29,32], three were prospective cohort studies [28,31,33] and one study contained baseline data from a randomized interventional study [30]. The studies add up to 2877 participants with a mean follow-up period of 4.6 years ±3.3. The percentage of females ranged between 70.7% and 87.8%. The study of Courtney et al. included patients with Roux-en-Y gastric bypass (RYGB), SG, one-anastomosis gastric bypass, as well as gastric banding [26]. The exact amount of patients undergoing each type of procedure is unknown. Two studies specifically mentioned that the procedure was done laparoscopy [28,29], while after contacting the corresponding authors four additional studies appeared to include laparoscopic procedures varying in a rate of 100–75% [26,27,29,30].

Table 1. Study characteristics

Author and year	Country	Study design	Number of subjects (female gender)	Age of subjects[1]	Surgical procedure	Follow-up (years)
Courtney et al, 2018 [26]	UK	Retrospective cohort	1011 (762)	47 (18-78)	Laparoscopic, multiple bariatric techniques[2]	2
Mancini et al, 2018 [27]	France	Retrospective cohort	238 (195)	40 (34-48)	Laparoscopic RYGB (64.7%) SG (35.3%)	2
Jambhekar et al, 2018 [28]	USA	Prospective cohort	713 (622)	41.7 ±11.2	Laparoscopic SG	2
Keith et al, 2018 [29]	USA	Retrospective cohort	586 (461)	43 (36-51)	Laparoscopic RYGB	9
Hanvold et al, 2015 [30]	Norway	Randomized lifestyle intervention study	165 (123)	44 ±8.6	Laparoscopic RYGB	2
Reid et al, 2018 [31]	Canada	Prospective cohort	48 (36)	50.7 ±9.4	Laparoscopic RYGB[3]	10
Velcu et al, 2005 [32]	USA	Retrospective cohort	41 (36)	32.4 ±3.6	Open RYGB	5
Diaz- Guerra et al, 2005 [33]	Spain	Prospective cohort	75 (53)	39	Open BPD of Larrad	5

Abbreviations: BMI= Body Mass Index, BPD= biliopancreatic diversion, RYGB= Roux-en-Y gastric bypass, SG= Sleeve Gastrectomy, UK= United Kingdom, USA= United States of America
[1]Expressed in mean with standard deviation or mean with range
[2]Included RYGB, SG, one-anastomosis gastric bypass and gastric banding
[3]Majority of patients were done laparoscopically (±75%)

As shown in Table 2, six studies noted employment status pre-surgery and five studies noted this post-surgery. From these six studies, five studies based their classification of employment status when describing weight loss outcomes, on the presurgical assessment [26–30]. In the other three included studies is it unknown whether the employment status used in the description of weight loss outcomes is assessed prior or after to the assessment of weight loss [31–33]. Four studies used self-report questionnaires for the evaluation of employment status [26,27,29,33], while patient files were also commonly used [26,28,29]. Three studies described the rate of retired and/or disabled patients separately [26,28,29]. Definitions of employment and unemployment were given in only two studies. Mancini et al. classified employed as full-time employed including students and maternity leave [27]; unemployed was classified as part-time employed, temporary impairment and job seeking. Reid et al. described employed and unemployed when this lasted for a minimum of one year. Additionally, unemployed also included retired and disabled participants [31].

Quality of the Studies (Risk of Bias)

Results for risk of bias were retrieved using the QUIPS tool as shown in Table 3. Overall, four studies were judged as "moderate" risk of bias [26,28,29,33] and four studies were judged as "low" risk of bias [27,30–32]. Due to a lost to follow-up of 39% after one year [28] and 50% after two years [29], two studies were judged as having a "moderate" risk of attrition bias. Furthermore, four studies were considered to have a "moderate" risk of bias concerning prognostic factor measurement, due to the lack of a questionnaire when evaluating employment status [26,28,29,33]. An important source of confounding was based on the finding that unemployed patients experienced more comorbidities [26] and used more psychopharmaceutical drugs [30].

Weight Loss Outcomes

Based on the studies that expressed weight loss in %EWL, employed patients lost 66.0% (pre-surgical assessed), 65.0% (post-surgical assessed) and 68.6% (post-surgical assessed) [26, 31]. Additionally, unemployed patients lost 55.0% (presurgical assessed), 70.8% (pre-surgical assessed), 56.0% (post-surgical assessed) and 78.9% (post-surgical assessed) [26,27,31]. This indicates a difference of 11.0% EWL in favor of pre-surgical employed [26], 9.0% EWL in favor of postsurgical employed [26] and 10.3% EWL in favor of postsurgical unemployed patients [31]. In addition, two studies used cut-off scores of 50% EWL to define success and failure [30,33]. These studies found that, in patients with successful weight loss, the rate of unemployment ranged between 33.6–42.4%; additionally, in patients with not successful weight loss, the rate unemployment ranged between 32.1–66.6% [30,33]. These rates were not described for employed patients.

Table 2. Changes in employment status and weight after bariatric surgery

Author	Employment status pre-surgery	Employment status post-surgery	BMI (kg/m²) pre-surgery	Weight loss post-surgery based on pre-surgical assessed employment status	Weight regain post-surgery
Courtney et al [26]	E: 444/746 (59.5%) U: 273/746 (36.6%) Retired: 29/746 (3.9%)	E: 707/1011 (69.9%)[1] U: 212/1011 (21.0%)[1] Retired: 92/1011 (9.1%)[1] 43% was documented <6 months, 60% 7-18 months, 41% 19-30 months post-surgery	E pre: 43 (30-68) U pre: 44 (28-72) Retired pre: 44 (34-54)	E pre: EWL 66% (6-169) U pre: EWL 55% (-159-122) E post: EWL 65% (-7-169)[2] U post: EWL 56% (-159-159)[2] Weight loss was measured 2 years post-surgery	Unknown
Mancini et al [27]	E: 158/238 (66.4%) Disabled and retired patients for 2 years were excluded.	E: 199/238 (83.6%)[3] Documented 2 years post-surgery	44.9^ (41-50)	U pre (n= 80): BMI 31.9 ±6.7 (= 28.9% ΔBMI), EWL 70.8% ± 28.2 Weight loss was measured 2 years post-surgery	Unknown
Jambhekar et al [28]	E: 300/713 (42.1%) U: 98/713 (13.7%) Retired: 16/713 (2.2%) Disabled: 34/713 (4.8%) Students: 23/713 (3.2%)	Unknown	E pre: 46.0 ±5.8 U pre: 45.7 ±6 Retired pre: 43.4 ±5.2 Disabled pre: 46.4 ±6.4 Students pre: 47.2 ±4.9	E pre: 32.4kg ±13.4 U pre: 33.5kg ±14.3 Retired pre: 19.7kg ±7.9 Disabled pre: 21.5kg ±6.7 Students pre: 49.0kg ±unknown Weight loss is based on lowest weight noted ≤2 years post-surgery	E pre: 3.8kg U pre: 5.4kg Retired pre: 7.9kg Disabled pre: 0.6kg Students pre: 3.5kg Weight noted 2 years post-surgery minus lowest weight
Keith et al [29]	E: 468/586 (80.0%) U: 43/586 (7.0%) Retired: 26/586 (4.4%), Disabled: 34/586 (5.8%), Student: 14/586 (2.3%)	Unknown	48.0 (44-54)	Unknown	Classified as >15% weight regain 1 year post-surgery E pre: 99/468 (21.2%) U pre: 11/43 (25.6%), Retired pre: 1/26 (3.9%) Disabled pre: 7/34 (20.6%) Student pre: 4/14 (28.6%)
Hanvold et al [30]	E or student: 101/162 (62.3%) U: 61/162 (37.7%)	E or student: 109/162 (66.7%) U: 54/162 (33.3%) Documented 2 years post-surgery	44.3 ±5.1	U pre: 9/28 (32.1%) <50% EWL, 45/134 (33.6%) ≥50% EWL U pre: 25/81 (31.3%) BMI ≥30, 29/84 (35.4%) BMI <30 Weight loss was measured 2 years post-surgery	Unknown

Table 2 (continued)

Author	Employment status pre-surgery	Employment status post-surgery	BMI pre-surgery	Weight loss post-surgery based on post-surgical or unknown assessed employment status	Weight regain post-surgery
Reid et al [31]	Unknown	E: 19/48 (39.6%) U: 29/48 (60.4%) Disabled: 5/29 (17.2%) Retired: 6/29 (20.7%) Timing of documentation is unknown	E post: 55.0 ±14.6 U post: 50.2 ±12.1	E post: nadir BMI 30.1 ±9.6 (= 45.3% ΔBMI), EWL 68.6% ±25.2 U post: nadir BMI 28.1 ±8.0 (= 44.0% ΔBMI), EWL 78.9% ±48.6 Timing of measurement weight loss is unknown	E post: BMI 36.3 ±10.9 (= 17.1% ΔBMI).Weight regain was measured 9 ±3 years post-surgery U post-op: BMI 33.2 ±9.5 (= 15.4% ΔBMI). Weight regain was measured 10 ±3 years post-surgery
Velcu et al [32]	E: 14/41 (34.1%) U: 27/41 (65.8%)	E: 16/41 (39.0%) 1 year post-surgery, 18/41 (43.9%) 5 years post-surgery U: 25/41 (60.9%) 1 year post-surgery, 23/41 (56.1%) 5 years post-surgery	E pre: 51.1 ±5.6 U pre: 55.7 ±8.3	E (pre or post is unknown): BMI 28.6 ±3.8 (= 44.0% ΔBMI) U (pre or post is unknown): BMI 32.1 ±5.9 (= 42.4% ΔBMI) Weight loss was measured 3 years post-surgery	E (pre or post is unknown): BMI 30.1 ±5.5 (= 5.0% ΔBMI). U (pre or post is unknown): BMI 32.5 ±5.5 (= 1.2% ΔBMI). Weight regain was measured 5 years post-surgery
Diaz-Guerra et al [33]	Unknown	Unknown	53.2 ±10	U or housewife (pre or post is unknown): 6/9 (66.6%) <50% EWL, 28/66 (42.4%) ≥50% EWL[4] Weight loss was measured 5 years post-surgery	Unknown

Abbreviations: E= employed, U= unemployed, BMI= Body Mass Index, EWL= excess weight loss, post= employment status is based on post-surgical assessment, pre= employment status is based on pre-surgical assessment

Data is expressed in mean, unless otherwise stated in median(^)

[1] Significant differences in rate of employment, unemployment and retirement between pre- and post-operative ($p<0.05$)

[2] Significant difference in %EWL between employed and unemployed patients post-op ($p<0.05$)

[3] Significant difference in rate of employment between pre- and post-operative ($p<0.0001$)

[4] Significant difference in the amount of unemployed patients with <50% EWL and ≥50% EWL ($p<0.01$)

Table 3. Assessment of risk of bias using the 'Quality Assessment in Prognostic Studies' (QUIPS) tool

Author	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting	Overall
Courtney et al, 2018 [26]	Moderate	Low	Moderate	Low	High	Moderate	Moderate
Mancini et al, 2018 [27]	Low	Low	Low	Low	Moderate	Low	Low
Jambhekar et al, 2018 [28]	Low	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Keith et al, 2018 [29]	Low	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Hanvold et al, 2015 [30]	Low	Low	Low	Low	Moderate	Low	Low
Reid et al, 2018 [31]	Low	Low	Low	Low	Low	Low	Low
Velcu et al, 2005 [32]	Low	Low	Low	Low	Moderate	Low	Low
Diaz- Guerra et al, 2005 [33]	Moderate	Low	Moderate	Low	Moderate	Moderate	Moderate

Low = low risk of bias, Moderate = moderate risk of bias, High = high risk of bias.
Level of risk of bias was determined by judgement of the prompting items belonging to each assessed domain.

Based on the studies that used BMI, employed patients lost 22.5 and 24.9 points, while the unemployed patients lost 13.0, 23.6 and 22.1 points [27,31,32]. Reid et al. reported a greater BMI loss by post-surgical employed patients (2.8 BMI points), while Velcu et al. reported a greater BMI loss by unemployed patients (1.1 BMI points) [31,32]. These findings were not statistically significant. When calculating %BMI loss, employed patients lost 1.3% (45.3% vs. 44.0%) and 1.6% (44.0% vs. 42.4%) more compared to unemployed patients [31,32].

Only one study expressed weight loss in kg which was a maximum of 32.4 kg in pre-surgical employed patients and 33.5 kg in pre-surgical unemployed patients [28]. The authors described that an employed status was almost uniformly associated with more weight loss up to two years post-surgery [28].

Weight Regain Outcomes

Looking at studies that assessed weight regain and %BMI was extracted, post-surgical employed patients gained 5.0% and 17.1%, while post-surgical unemployed patients gained 1.2% and 15.4% five and nine/ten years after surgery, respectively [31,32]. When expressed in absolute BMI points, this amounted a difference of 1.1 points between the groups and was not statistically significant. Jambhekar et al. found that presurgical unemployed patients gained slightly more weight compared to employed patients (5.4 kg versus 3.8 kg) two years after surgery [28]. Moreover, Keith et al. found that pre-surgical unemployed patients presented 4.4% more weight regain (>15% regain one year post-surgery) compared to employed patients [29]. Logistic regression analysis however, revealed that pre-surgical employment status was of no predictive value on weight regain (odds ratio 1.21, p value 0.482) [29].

Change in Employment Status

The amount of pre-surgical employed patients ranged between 34.1% and 80.0% [26–30, 32], and the amount of pre-surgical unemployed patients ranged between 7.0% and 65.8% [29,26,28,30,32]. The amount of post-surgical employed patients ranged between 39.6% and 83.6% [26,27,30–32], while for the post-surgical unemployed patients this was 21% and 60.9% [26,30–32]. Four studies assessed employment status pre- and post-surgery, thereby making it possible to detect changes. When focusing on the studies with a two year follow-up, employment rate increased by 4.4% [30], 10.4% [26] and 17.2% [27], while unemployment rate decreased by 15.6% 26]. Two studies found that the increase in employment rate was statistically significant [26,27], and also one study found that the decrease in unemployment rate was statistically significant [26]. Five years after surgery employment rate increased by

9.8% and the unemployment rate decreased by 9.7%. Nevertheless, this lacked statistical significance [32].

Discussion

Very little is known about the interplay of socioeconomic factors like employment status and their effect on weight loss after bariatric surgery, and how they interfere with the development of non-response. This systematic review aimed to investigate the impact of employment status on post-bariatric surgical weight loss outcomes. In summary, this study found that employed patients experienced more weight loss (9.0– 11.0% EWL [26], 1.3–1.6% BMI [31,32]) two to three years after surgery compared to unemployed patients; however, these findings are not consistent across the included studies and lacked statistical significance [28,31]. It can be debated whether these amounts of weight loss have sufficient clinical relevance. Nonetheless, it is well known that more weight loss is associated with better clinical outcomes such as an improved health related quality of life and physical fitness [34,35].

An obvious finding that emerges from this study is that various measurements were used when expressing weight loss (e.g. kg, %EWL, BMI), making a clear comparison between employed and unemployed patients difficult. The diversity in measurements used, as well as the accuracy of these measurements should be criticized. Lost BMI points and kg are highly dependent on their baseline measurement which may give an under- or overestimation of the actual weight loss. This may have been applicable when comparing weight loss reported by Reid et al. and Velcu et al. where there was a difference in baseline BMI [31,32]. In order to overcome this, we calculated the percentage of BMI which is a more commonly used measurement in articles describing post-surgical weight loss outcomes [36]. Besides the inaccuracy of absolute numbers, it is well known that %EWL is a suboptimal measurement as this is being influenced too much by common differences in baseline BMI [37,38]. Percentage TWL has been suggested as the most accurate measurement, though none of the included studies used this measurement.

There are four explanations for the finding that employed patients may experience more weight loss. Firstly, employed patients may be greater committed to health promoting behavior [13,14], thereby positively affecting eating habits, physical activities and subsequent weight loss. Reid et al. demonstrated that post-surgical employed patients performed 1591 more steps per day compared to unemployed patients [31]. Additionally, Courtney et al. showed greater improvements in functional status of pre-surgical employed patients than unemployed patients (35.7% vs. 29.2%) [26]. though the direction of causality between functional status/ physical activity and weight loss is uncertain, it does implicate the importance of employment

in post-bariatric patients. A second explanation is that unemployment is related to a lower socioeconomic status, and a lower socioeconomic status is associated with less post-bariatric weight loss [20,39]. In detail, inferior weight loss have been described in first-generation immigrants, residents in larger cities, patients with low income and patients who receive social security disability [20,28,39]. A third explanation for the aforementioned finding is that employed patients are more likely to be adherent to follow-up appointments after bariatric surgery, and attendance to these appointments is associated with better long-term weight loss outcomes [17,40,41]. A fourth explanation may be that employed patients experience more routineness in daily life. Because of this, it may take less effort to adjust a new lifestyle, for example learning new eating patterns. This explanation broadly supports the finding that being employed, either part-time or fulltime is associated with less frequent unhealthy eating compared to the unemployed [17]. The finding from Jambhekar et al. that students experienced more weight loss compared to retired patients may underline this theory as students attend school activities which gives them a certain routineness [28]. Employed patients may also show, as result of long working hours, irregular work schedules and thereby have less daily or weekly routineness [42].

Based on the studies that reported weight regain, employed patients gained 1.7–3.8% more BMI than unemployed patients five to ten years after surgery [31,32], though the opposite was also found (1.6 kg more regain by unemployed patients) [28]. These results lacked any statistical significance. It is difficult to explain why an employed patient would gain more weight and furthermore, a comparison with other studies is hard as these studies lack a sufficient follow-up period to detect weight regain. This warrants further research to obtain more information about the impact of employment status on losing and maintaining weight post-surgery. This study found that the employment rate increased by 4.4–17.2%, while the unemployment rate decreased by 15.6% after bariatric surgery. A note of caution is necessary as employment and unemployment rates showed large baseline variety and clarification lacked frequently (e.g. distinction between fulltime and part-time). The improvement in employment rate we found is in line with a previous systematic review which overlapped two studies [5,30,32]. The observed increase in employment might be explained in this way: weight loss caused by bariatric surgery results in patients becoming more healthy [34,35], and patients with a better health condition are more likely to find a job as opposed to jobseekers with a poorer health condition [12].

We acknowledge that this review has an important limitation due to its differences in the assessment of employment status at the moment of describing weight loss outcomes. As far as possible, we presented outcomes based on a pre-surgical assessment of employment status and indicated if this was not the case or uncertain. Despite this, it can be debated whether we

are looking at the direct impact of employment status on weight loss outcomes or a reverse relation (i.e., impact of weight loss on employment status). Within this relationship, other variables such as the type of job, type of insurance, level of education and neighborhood status may possible interfere. Unfortunately, these variables were very limitedly described in the included studies, highlighting the need for future studies to concentrate on these variables.

Other limitations of this study can be found in methodological issues. To start, the quality of the studies was limited with four studies being assessed as a moderate risk of bias. Selection bias may have been introduced in two studies as it seemed that highly motivated patients returned to follow-up appointments, thereby affecting the documentation of weight and employment status [26,28]. Furthermore, three studies lacked self-report questionnaires but referred to routinely collected documentation when evaluating employment status, thereby introducing information bias [26,28,29]. Multiple studies faced confounding as unemployed patients suffered from functional impairment, co-morbidities and mental health disorders, contributing to their unemployment [26,33]. None of the studies sufficiently accounted for potential confounders including age, gender, personality disorders, pre-surgical weight and physical activity, while these factors have consistently been associated with weight loss outcomes. Besides this, information lacked about the job type including shift work and a sedentary job, though both are related to obesity [16]. Lastly, it should be mentioned that different surgical procedures were used (laparoscopic versus open; restrictive versus malabsorptive) and it was not always clear how these procedures were distributed in the study cohort [26].

The question rises how the results of this review can be used in the daily practice. We should first be aware of the bidirectional interaction between employment status and post-bariatric weight loss outcomes. We should concentrate on identifying a patients' employment status in a pre-surgical setting, for example during screening for bariatric surgery, and subsequently in a postsurgical setting. All patients should be motivated and encouraged by healthcare professionals in bariatric centers to either become or stay employed. A collaboration with occupational health physicians could be beneficial for advising employed patients how they return to work, and for unemployed patients how they acquire a job. Further research should be done to see if the joint effort with the occupational health department is feasible.

Conclusion

This systematic review showed that an employed status could be beneficial for losing weight after bariatric surgery, though this finding is subjected to heterogeneity in included studies and a lack of statistical significance. The results may implicate that employed patients should

be encouraged by healthcare professionals to return to work and that unemployed patients should be supported to return to labor market. More knowledge is needed to fully understand the interplay between employment status, job type, socioeconomic factors and weight loss outcomes after bariatric surgery.

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CHAPTER 05

Comparison of Linear versus Circular-Stapled Gastroenterostomy in Roux-en-Y Gastric Bypass: A Nationwide Population-Based Cohort Study

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Abstract

Introduction: when performing a Roux-en-Y gastric bypass (RYGB), the gastroenterostomy can be constructed with a circular stapled or linear stapled technique. The size of the gastroenterostomy depends on the stapling method and this may affect weight loss outcomes. The aim of this study was to examine the impact of the stapling technique on weight loss outcomes after RYGB.

Methods: this is a nationwide population-based cohort study of patients that received a RYGB. Data were derived from the Dutch Audit of Treatment of Obesity. Primary outcome was the impact of stapling technique on the rate of non-response defined as significant weight regain (≥20% of a patients' lost weight) 2–4 years post-surgery, after initial successful weight loss (≥20% total weight loss, TWL). Secondary outcomes were the rate of response, defined as successful weight loss (≥20% TWL) within 1.5 years post-surgery, the incidence of complications and the progression of comorbidities.

Results: in a cohort of 12,468 patients, non-response was equally distributed between both groups (circular 18.0% vs. linear 17.6%). No differences in response rate (circular 97.0% vs. linear 96.5%) or %TWL were observed up to 4 years post-surgery. Patients in the circular stapled group experienced more complications, specifically major bleedings (2.4% vs. 1.2%; p=0.002) within 30 days postoperatively. No differences were found in deteriorated comorbidities, neither in de novo developed comorbidities.

Conclusion: when comparing stapling technique in RYGB, weight loss outcomes did not differ during a 4-year follow-up period. The linear stapled gastroenterostomy could pose an advantage due to its lower complication rate.

Abbreviations: AL, alimentary limb; BMI, body mass index; BP, biliopancreatic limb; CD, Clavien–Dindo; CSA, circular stapled anastomosis; DATO, Dutch Audit of Treatment of Obesity; DM, diabetes mellitus; GERD, gastroesophageal reflux disease; LSA, linear stapled anastomosis; OSAS, obstructive sleep apnea syndrome; RYGB, Roux-en-Y gastric bypass; TWL, total weight loss.

Introduction

Bariatric surgery is considered the best option for sustained weight loss in morbidly obese patients [1,2]. The laparoscopic Roux-en-Y gastric bypass (RYGB) is the most commonly performed primary bariatric procedure in the Netherlands [3]. Within the last 5 years, approximately 58,000 bariatric procedures have been performed including RYGB surgery in 59–75% [4]. During the creation of the RYGB, the gastroenterostomy can be constructed in three different ways: circular stapled, linear stapled, or completely hand-sewn. Worldwide, there is a large variety in applied techniques because to date, no surgical technique has been superior to the other [5]. Compared to the two stapling techniques, hand sewing is less frequently performed because it is technically demanding and not reproducible [5]. An important difference between the two stapling techniques is anastomotic size. Where the circular stapled anastomosis (CSA) usually has a diameter between 21 and 25mm depending on the device used, the diameter of the linear stapled anastomosis (LSA) is assumed to be wider with a diameter between 20 and 45mm[6,7]. Besides this, there is a financial difference as the circular stapling technique is more expensive.

It is known that 25–35% of patients after RYGB do not achieve adequate weight loss, or regain an excessive amount of weight after initial adequate weight loss [8–10]. This can be related to lifestyle, hormonal, and metabolic factors, but may also be explained by surgical factors like an enlarged pouch or gastroenterostomy [11–13]. A wide gastroenterostomy has been defined as exceeding 2 cm [11] and forms the basis of many currently used treatment strategies. These strategies aim to correct the size of the anastomosis through sclerotherapy, argon plasma coagulation, endoscopic plication, and endoscopic suturing [13,14].

As the size of the initial gastroenterostomy depends on the stapling technique (CSA versus LSA), one may reason that the stapling technique could influence weight loss outcome. Based on a nationwide study performed in Sweden, no differences in excess body mass index (BMI) loss nor total weight loss (TWL) were found 1 year after RYGB when comparing CSA with LSA [15]. Bohdjalian et al. found no differences in excess weight loss 1 and 2 years after RYGB when comparing the two techniques [6] and furthermore, Langer et al. found no differences in excess BMI loss up to 5 years after RYGB [16]. Both studies were designed as a matched-pair study and included only 150 patients.

To date, research has not yet described the impact of stapling technique on mid-term weight loss outcomes and importantly on weight regain in a high volume of patients. Therefore, the aim of this nationwide study was to assess the impact of stapling technique in RYGB on weight loss outcomes including weight regain (i.e., non-response) in a follow-up period of 4 years.

Methods

Study Population

This is a nationwide, population-based cohort study of patients that received a RYGB in the Netherlands. A pseudonymized dataset was obtained from the Dutch Audit of Treatment of Obesity (DATO), a registry covering all bariatric procedures performed within the Netherlands since 1 January 2015. Details on this registry and the recorded variables have been published before [3]. Patients were included if they underwent primary RYGB, between the age of 18 and 65 years, with a BMI ≥40.0 kg/m^2 or ≥35.0 kg/m^2, and suffering from an obesity-related comorbidity. The RYGB had taken place between 1 January 2015 and 31 December 2017. Eligibility for surgery was confirmed after evaluation by a multidisciplinary team and was in accordance with the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) guidelines [17]. Follow-up weights should be noted within 1.5 years and at 2 years for inclusion. Exclusion criteria were hand-sewn gastroenterostomy, a bariatric procedure other than RYGB (such as one-anastomosis gastric bypass or banded bypass), and revisional or secondary procedures.

Study Outcomes

The primary outcome of this study is the rate of non-response defined as significant weight regain (≥20% of a patients' lost weight) 2–4 years post-surgery, after initial successful weight loss (≥20% TWL). The threshold of 20% weight regain is based on the study by Uittenbogaart et al., whereas the threshold of 20% TWL is based on the DATO registry and previous publications [4,18,19]. Secondary outcomes include the rate of response defined as successful weight loss (≥20% TWL) within 1.5 years after RYGB, weight loss expressed in both TWL and change in BMI, the incidence of complications, and the progression of obesity-related comorbidities. The percentage of TWL was calculated as (preoperative weight – follow up weight)/(preoperative weight) × 100%. In addition, the change in BMI was calculated as (preoperative BMI − follow-up BMI).

Obesity-related comorbidities included type 2 diabetes mellitus (DM), hypertension, hyperlipidemia, gastroesophageal reflux disease (GERD), obstructive sleep apnea syndrome (OSAS), and osteoarthritis. The definition of these comorbidities is based on the ASMBS guideline by Brethauer et al. [3,4,20]. Comorbidities were recorded regardless of an active treatment. The comorbidities were categorized as resolved, improved, unchanged, deteriorated, and de novo. Because the status of the comorbidity at 3 and 4 years postoperatively was frequently missing, this outcome was assessed up to 2 years after surgery. Postoperative complications were registered both on short term (i.e., <30 days) and long term, and were categorized

according to the Clavien– Dindo Classification of Surgical Complications (CD) [21]. A severe complication was defined as CD grade IIIb (i.e., complication requiring intervention under general anesthesia) or higher. Mortality was recorded as CD grade V and included death from a postoperative complication.

Surgical Technique

The CSA was performed in a standardized fashion by four high-volume surgeons located in two centers. This stapling technique was previously described in detail by Dillemans et al. [22]. The technique involves introduction of a circular stapler of 25mm through a left lateral abdominal port site (2–3 cm). The anvil of the stapler is inserted into an opening in the gastric pouch and secured with a purse string suture. The biliopancreatic (BP) limb is then opened over a 2–3 cm length to introduce the stapler. After connecting the anvil with the stapler, the anastomosis is created. At the BP side of the anastomosis, the small intestine is closed and cut with a linear stapler to divide the limbs. The LSA was performed as standardized fashion by 15 surgeons located in 18 centers. This technique was published as an original technique in 2003 [23]. A small opening is made in the alimentary (AL) limb to introduce one side of the linear stapler, which is then inserted into a small opening in the gastric pouch with its other side. After firing and removing the stapler, the small opening through which the stapler was introduced is closed using a resolvable suture or with another stapler. At the BP side of the anastomosis, the small intestine is closed and cut with a linear stapler to divide the limbs. No intestine has to be excised with this technique. In both stapling techniques, the limb lengths were either estimated or measured prior to construction. Both techniques provide the option of closure of the mesenteric and Petersen's defects in order to limit the risk of internal hernias.

Statistical Analyses

Statistical analyses were performed using IBMSPSS statistics software, version 22.0. A p value of <0.05 was considered statistically significant. Continuous variables are presented as mean ± SD, while categorical variables are presented as absolute number (percentage). Categorical variables were compared with the $\chi 2$ test, and continuous variables with an independent t test. The association between non-response rates (outcome) and stapling technique (exposure) is analyzed using multivariate logistic regression. Within these analyses, corrections were made for known confounders based on literature (baseline BMI, age at surgery, gender [24]) and variables that may have a confounding effect based on univariate analysis (variables that are associated with the outcome with a p value <0.1 in a univariate analysis). Stratification was applied to explore effect modification by gender and age at surgery which was statistically tested by including an interaction variable into the regression model. Sensitivity analyses

were performed to test the robustness of the findings to missing data or possible variation in definitions and classifications.

Results

A total of 19,977 patients were registered during the study period (Fig. 1). A significant number of patients were excluded due to missing values in essential variables at various time points. In total, 12,468 patients were included in the study, 881 in the CSA group and 11,587 in the LSA group. In the CSA group, 881 patients (100.0%) completed ≤1.5 and 2 years of follow-up, 444 patients (50.4%) completed 3 years of follow-up, and 186 patients (21.1%) completed 4 years of follow-up. In the LSA group, 11,587 patients (100.0%) completed ≤1.5 and 2 years of follow-up, 6235 patients (53.8%) completed 3 years of follow-up, and 2694 patients (23.3%) completed 4 years of follow-up.

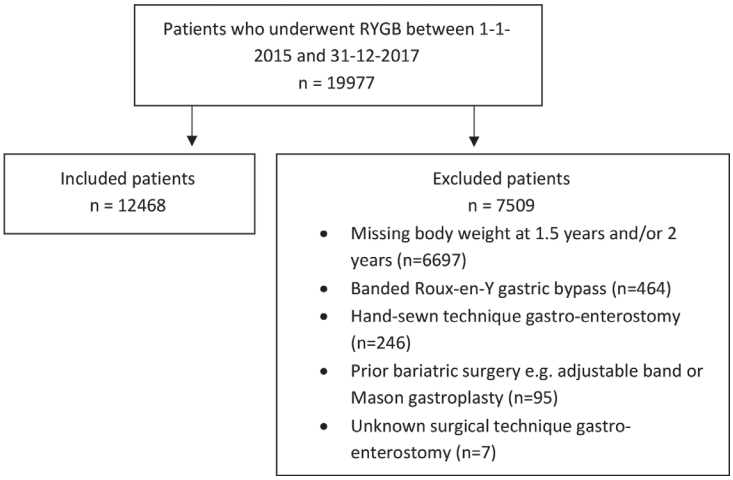

Figure 1. Flow diagram of inclusion and exclusion of patients

As shown in Table 1, preoperative BMI was equally distributed between the CSA and the LSA group (42.7 kg/m^2 vs. 42.8 kg/m^2, respectively). The CSA group had statistically significant lower numbers of preoperative type 2 DM, GERD, and osteoarthritis compared to the LSA group. Furthermore, the CSA group suffered from more short-term complications (CD grade I, CD grade II, CD grade IIIb, and CD grade IVa) than the LSA group (all p≤0.05). There were significantly more postoperative major bleedings in the CSA group (2.4% vs. 1.2%, p=0.002). In the long term, the CSA group suffered from more gallstones, incisional hernias, bowel obstructions, and internal hernias (Supplementary Table 1, supporting information). In the

CSA group, the most common length of the BP limb was 70 cm (57.0%) and 150 cm for the AL limb (80.2%). In the LSA group the length of the BP limb largely varied (65.6%, 50–80cm; 26.5%, 150 cm), while the most common length of the AL limb was 150 cm(60.8%).

When using ≥20% TWL as threshold for response (i.e., successful weight loss), there were no significant differences between the groups (Table 2). Based on the aforementioned criteria for non-response (i.e., weight regain after successful weight loss), there were also no significant differences. The percentage of TWL was similar in the CSA and LSA group, with a mean of 28.6% and 29.1% 4 years after surgery (p=0.533). Table 3 displays the results of the univariate and multivariate analyses indicating which variables are associated with non-response. Univariate analysis revealed that stapling technique was not associated with non-response (OR 1.03; 95% CI 0.86–1.23). Based on the multivariate analysis, a male gender and preoperative hypertension was associated with an increased risk of non-response (OR 1.29 and OR 1.16, respectively). Contrary, preoperative type 2 DM, preoperative GERD, a higher age and a longer BP limb were associated with a decreased risk of non-response (OR 0.78, OR 0.70, OR 0.99, and OR 0.99, respectively). When we included the interaction variables gender and age in the model, the ORs changed only slightly without affecting the abovementioned findings. Interestingly, the length of the AL limb and the other comorbidities (hyperlipidemia, OSAS, osteoarthritis) were not associated with non-response.

Table 4 displays the effect of stapling technique on the progression of obesity-related comorbidities. There was no significant difference in deterioration of comorbidities in the CSA compared to the LSA group, neither in de novo developed comorbidities. In the CSA group, there was a better resolution of hypertension and OSAS (65.1% vs. 52.8%; 76.3% vs. 64.3%). Instead in the LSA group, these comorbidities were more often merely improved (25.6% vs. 13.0%; 19.4% vs. 7.5%). Moreover, in the LSA group there was a better resolution of GERD and osteoarthritis than in the CSA group (75.2% vs. 62.3%; 43.8% vs. 36.8%).

Table 1. Baseline characteristics of the study population

	CSA, n= 881	LSA, n= 11587	p-value
Gender, no. (%)			
Female	713 (80.9)	9541 (82.3)	.291
Age (years)	45.2 ±10.5	45.1±10.6	.885
Preoperative comorbidities, no. (%)			
Hypertension	333 (37.8)	4269 (36.8)	.571
Type II diabetes mellitus	143 (16.2)	2595 (22.4)	<.001*
Hyperlipidaemia	169 (19.2)	2523 (21.8)	.071
Gastroesophageal reflux disease	89 (10.1)	1667 (14.4)	<.001*
OSAS	265 (30.1)	2231 (19.3)	<.001*
Osteoarthritis	344 (39.0)	5699 (49.2)	<.001*
Preoperative weight (kg, ±SD)	122.7±18.6	122.7±17.9	.994
Preoperative BMI (kg/m^2 ±SD)	42.7±4.9	42.8±4.7	.265
Laparoscopic, no. (%)	879 (99.8)	11573 (99.9)	.396
Length of biliopancreatic limb (cm ±SD)	72.9±15.3	90.5±38.6	<.001*
Length of alimentary limb (cm ±SD)	145.8±9.7	133.6±33.7	<.001*
Length of hospital stay (days ±SD)	2.3±1.7	1.5±2.7	<.001*
Number of readmission (<30 days), no. (%)	25 (2.8)	283 (2.4)	.466
Postoperative complication <30 days, no. (%)			
CD grade I	19 (2.2)	89 (.8)	<.001*
CD grade II	25 (2.8)	99 (.9)	<.001*
CD grade IIIa	3 (.3)	29 (.3)	.610
CD grade IIIb	41 (4.7)	382 (3.3)	.032*
CD grade IVa	4 (.5)	15 (.1)	.017*
CD grade IVb	-	9 (.1)	.408
CD grade V	-	1 (.0)	.783
Type of complication, no. (%)			
Major bleeding	21 (2.4)	136 (1.2)	.002*
Anastomotic leakage	1 (.1)	43 (.4)	.214
Intra-abdominal abscess	2 (.2)	13 (.1)	.343
Wound infection	1 (.1)	14 (.1)	.952
Intestinal obstruction	1 (.1)	28 (.2)	.447
Anastomotic stricture	0 (.0)	1 (.0)	.783

Data is presented as number (%) or mean (standard deviation). *p value is below the threshold of <.05. Abbreviations: CD= clavien dindo classification, CSA= circular-stapled anastomosis, LSA= linear-stapled anastomosis, OSAS= obstructive sleep apnea syndrome, BMI= body mass index. IIIa is a complication requiring intervention under local anesthesia; IIIb is a complication requiring general anaesthesia; IVa is a complication resulting in single organ failure; IVb is a complication resulting in multiple organ failure; V is a complication resulting in death

Table 2. Weight loss outcomes comparing circular- and linear stapled anastomosis of the gastroenterostomy

	CSA		**LSA**		
	no. in analysis[3]	no. (%)	no. in analysis[3]	no. (%)	p-value
Response rate[1]	881	855 (97.0)	11587	11177 (96.5)	.360
Non-response rate[2]	881	159 (18.0)	11587	2045 (17.6)	.765
	no.	% ±SD	no.	% ±SD	p-value
TWL based on lowest weight within 1.5 years	881	33.9 ±7.5	11587	33.4 ±7.6	.046*
TWL 1.5 years	655	33.5 ±7.9	6812	33.7 ±8.0	.416
TWL 2 years	881	32.9 ±8.3	11587	32.7 ±8.5	.613
TWL 3 years	444	30.9 ±8.2	6235	31.0 ±9.0	.884
TWL 4 years	186	28.6 ±8.7	2694	29.1 ±10.1	.533
	no.	% ±SD	no.	% ±SD	p-value
ΔChange in BMI based on lowest weight within 1.5 years	881	14.6 ±4.0	11587	14.4 ±3.8	.142
ΔChange in BMI 1.5 year	655	14.4 ±4.2	6812	14.5 ±4.0	.386
ΔChange in BMI 2 years	881	14.2 ±4.4	11587	14.1 ±4.2	.781
ΔChange in BMI 3 years	444	13.4 ±4.6	6235	13.4 ±4.4	.909
ΔChange in BMI 4 years	186	12.4 ±4.9	2694	12.6 ±4.7	.629

1. Defined as successful weight loss (≥20 %total body weight loss) within 1.5 years after surgery.
2. Defined as significant weight regain (≥20% of a patients' lost weight) after initial successful weight loss (≥20 %total body weight loss) 2 years after surgery.
3. The total amount of patients included in the CSA group was 881 patients. The total amount of patients included in the LSA group was 11587 patients.
Data presented as number (%) or mean (standard deviation). *p value is below the threshold of <.05.
Abbreviations: CSA= circular-stapled anastomosis, LSA= linear-stapled anastomosis, TWL = total weight loss, SD = standard deviation

Table 3. Results of univariate (unadjusted OR) and multivariate (adjusted OR) logistic regression of variables associated with non-response after RYGB

	Unadjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Stapling technique (circular)	1.03	.86-1.23	0.765	.93	.78-1.12	.439
Gender (male)	1.34	1.20-1.50	<.001#	1.29	1.14-1.47	<.001*
Age at surgery (years)	0.99	.99-1.00	.001#	0.99	.98-.99	<.001*
Preoperative BMI (kg/m^2)	0.99	.98-1.00	0.253			
Preoperative hypertension (yes)	1.11	1.01-1.21	0.032#	1.16	1.03-1.29	.014*
Preoperative type 2 DM (yes)	0.97	.95-.98	<.001#	0.78	.69-.89	<.001*
Preoperative hyperlipidemie (yes)	1.01	.91-1.13	0.830			
Preoperative GERD (yes)	0.68	.58-.78	<.001#	0.70	.60-.82	<.001*
Preoperative OSAS (yes)	1.12	1.00-1.25	0.044#	1.01	.88-1.15	.868
Preoperative osteoarthritis (yes)	0.91	.83-.99	0.035#	0.92	.83-1.02	.105
Length of biliopancreatic limb (cm)	0.99	.99-1.00	<.001#	0.99	.99-1.00	<.001*
Length of alimentary limb (cm)	1.00	1.00-1.00	<.001#	1.00	1.00-1.00	.306
Length of hospital stay (days)	1.01	1.00-1.02	0.156			
Complication by clavien dindo classification (yes)	1.09	.95-1.27	.204			

Dependent variable:% non-response. #p value is below the threshold of <0.1, therefore this variable is included in the multivariate analysis. *p value is below the threshold of <.05. Abbreviations: CI= confidence interval, DM= diabetes mellitus, GERD= gastroesophageal reflux disease, OSAS= obstructive sleep apnea syndrome, OR= odds ratio.

Table 4. Progression of obesity-related comorbidities between circular- and linear stapled anastomosis of the gastroenterostomy

	CSA 1.5-2 years follow-up						LSA 1.5-2 years follow-up					
	no.[1]	Resolved no. (%)[2]	Improved no. (%)[2]	Unchanged no. (%)[2]	Deteriorated no. (%)[2]	De novo no. (%)[3]	no.[1]	Resolved no. (%)[2]	Improved no. (%)[2]	Unchanged no. (%)[2]	Deteriorated no. (%)[2]	De novo no. (%)[3]
Hypertension	324/ 333	65.1**	13.0**	21.6	0.3	7.1	3258/ 4269	52.8**	25.6**	20.3	1,1	2.0
Type 2 DM	133/ 143	69.2	26.3	3.8	0.8	0.0	1706/ 2595	69.9	21.5	7.6	0.9	0.0
Hyperlipidaemia	76/ 169	51.3	13.2	35.5	0.0	0.0	1399/ 2523	55.8	16.2	27.4	0.6	3.6
OSAS	253/ 265	76.3**	7.5**	16.2	0.0	0.0	1394/ 2231	64.3**	19.4**	15.7	0.5	5.8
GERD	53/ 89	62.3*	17.0	20.8	0.0	0.7	499/ 1667	75.2*	11.0	12.6	0.8	3.1
Osteoarthritis	280/ 344	36.8*	32.9*	28.2	2.1	1.9	2458/ 5699	43.8*	26.7*	24.3	4.5	2.2

[1.] Number of patients from which comorbidity status is known at 1.5-2 years follow-up/ number of patients with preoperative comorbidity.
[2.] Based on the number of patients with preoperative comorbidity and known status at 1.5-2 years follow-up (numerator in 'no.' column).
[3.] Based on the number of patients without preoperative comorbidity and known status at 1.5-2 years follow-up.
*p value is below the threshold of .05, ** p value is below the threshold of .01. Abbreviations: CSA= circular-stapled anastomosis, DM= diabetes mellitus, GERD= gastroesophageal reflux disease, OSAS= obstructive sleep apnea syndrome, LSA= linear-stapled anastomosis.

Discussion

Preoperative knowledge on factors related to insufficient weight loss and weight regain after bariatric surgery is crucial. Within this topic, lifestyle, hormonal, and surgical factors have been an area of great interest [8,9,13]. It was hypothesized that the stapling technique used in RYGB construction may contribute to non-response, as it affects the size of the gastroenterostomy and an enlarged anastomosis size is associated with weight regain [11–13]. In this study reporting on 12,468 patients, it was shown that surgical technique (CSA vs. LSA) does not affect non-response rate nor TWL up to 4 years after RYGB. The results regarding TWL were similar to those reported by other authors [25,26].

As no difference in weight loss outcomes was found, it can be suggested that the diameter of the gastroenterostomy may not be of influence. Caution must be applied here, as it can only be speculated what the actual diameter of the anastomosis was and how this varied between the two stapling techniques. Technical information about the anastomotic diameter is not available and controversy is still present regarding which measurement gives the most reliable assessment. Besides this, if we would assume that a larger anastomotic diameter allows more passage of food and less satiety, there must be another explanation. For instance, a larger anastomotic diameter could more easily cause dumping and this may, in turn, have a restraining effect as patients want to prevent these dumpings. This explanation could play a role in the balance between anastomotic diameter and caloric intake.

The number of patients in the CSA group that experienced a short-term complication, specifically CD grades I, II, IIIb, and IVa, was higher than expected. Based on previous reports, the rate of these complications is estimated at 0.5–1.5%, 0.2– 1.3%, 1.9%, and 0.7% for CD grades I, II, IIIb, and IVa, respectively [4]. The patients in the CSA group experienced more postoperative major bleedings with an average of 2.4%, being nearly twice as high as the national average [27]. Yet, this finding is in line with prior literature [15,28–30]. The origin (i.e., intraperitoneal or intraluminal) of bleedings reported in this study as well as the need for interventions were unfortunately unknown. Nevertheless, it is likely that these bleedings accounted for the CD grade IIIb–IVa complications and thus resulted in relaparoscopy with general anesthesia and/or single-organ dysfunction [21]. Possible explanations for finding more bleedings in the CSA group are differences in stapler height, the number of stapler rows, and reinforcement of the staple line [15,28–30]. This could also be influenced by local differences in routine drain placement, hemoglobin testing, and thromboembolic prophylaxis.

Continued efforts are needed to lower the incidence of bleedings in particular when performing a circular stapled RYGB. In order to identify patients that are at risk of developing

nonresponse, multiple factors have been investigated and so far, a pattern of an older age, a higher preoperative BMI, the presence of comorbidities, and behavioral and psychosocial factors have been shown to predict non-response [8,24,31–33]. The current study showed male gender and preoperative hypertension increased the risk of non-response. This finding supports the work of other studies [32,33], although conflicting results were also found [24]. One remarkable finding was that preoperative type 2 DM and GERD lowered the risk of non-response. This is in contrast to the study by Stenberg et al. who found that preoperative DM was associated with a reduced %TWL after 5 years, although GERD was not associated with less %TWL [32]. There is no clear explanation for this controversy although hypothetically, patients with type 2 DM might be better motivated to keep their weight off in order to prevent recurrence of their disease and resumption of therapy. The insights gained from this study may contribute to a broader understanding of the characteristics of patients that develop non-response.

The current study showed that hypertension and OSAS had a better resolution in the CSA group. The resolution of hypertension is consistent with other studies, while the resolution of OSAS was strikingly high [34]. Notably, a high percentage of OSAS was observed preoperatively in the CSA group (CSA 30.1% vs. LSA 19.3%). The reason why the circular stapled technique was superior in the resolution of this comorbidity cannot easily be explained and is not in line with (limited) available literature [35]. A hypothesis may be that resolution or improvement of comorbidities has been assessed, interpreted, and registered differently in the centers. Another hypothesis is that the sample size was too low, resulting in a type II error. These factors may have led to erroneous conclusions and may be responsible for the contrasting findings of this study.

There are other aspects that should be considered when comparing the LSA with the CSA. Previous studies showed that the LSA reduces costs (£824 for materials per patient reported by Fehervari et al.; 250USD for used staplers per patient reported by Major et al.), operation time, as well as length of hospital stay [15,29,36,37]. However, there are no studies that have assessed whether the LSA results in less postoperative pain and thus earlier mobilization. The rationale behind this could be that the larger left lateral incision, to allow access of the circular stapler, causes more pain due to more muscle/nerve damage during dissection. As a next step, comparative studies should be designed focusing on pain and mobilization, but also on broader clinical outcomes like quality of life and treatment satisfaction.

This study presents three limitations. First, as data from multiple centers were included in this study, there may have been differences in protocols that influenced weight loss outcomes. The

total duration, frequency, and adherence to follow-up appointments within the Dutch centers varies greatly, possibly effecting the development and signaling of weight regain [38]. Second, the average lost to follow-up 4 years after primary surgery in the Dutch centers is approximately 52% and this may be an important source of selection bias, as weight regain could be a reason for not showing up [39]. Third, the retrospective nature of this study may have accounted for errors in data entry, miscoding, and interpretation. Despite these limitations, this study is the first nationwide cohort study reporting mid-term weight loss outcomes and in particular non-response rates in LSA and CSA. Taking the incidence of complications, weight loss outcomes and reported costs into account, the LSA presents an advantage and could be favored.

Conclusion

In this comparative study reporting on 12,468 patients, it is demonstrated that the surgical technique used during gastroenterostomy construction (circular vs. linear) in RYGB does not affect weight loss, nor does it affect the risk of weight regain. The percentage of postoperative complications, particularly major bleedings within 30 days, was significantly higher in the circular stapled technique (2.4% vs. 1.2%). Based on this, the linear stapled technique could be favored. No differences were found in deteriorated comorbidities and neither in de novo developed comorbidities between the two techniques. One unanticipated finding was that the circular stapling technique resulted in a better resolution of hypertension and OSAS, although these results should be interpreted with caution as it can be debated whether this study had sufficient power to assess these outcomes. A further study should be designed, preferably a randomized controlled trial, with extensive follow-up rate to definitively demonstrate superiority of one of these stapling techniques.

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PART II

Interventions targeting non-response in bariatric surgery

CHAPTER 06

A Multidisciplinary Approach for Non-responders Following Bariatric Surgery: What Is the Value?

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Abstract

Introduction: approximately 25% of patients after bariatric surgery either do not lose enough weight or regain a considerable amount of weight, both are referred to as non-response. This study aimed to describe the added value of a multidisciplinary approach on treatment strategies in patients with non-response.

Methods: the primary outcome of this retrospective cohort study was the initiated treatment by the multidisciplinary team (MDT). Outcomes were described separately for patients with primary (i.e., <50% excess weight loss [EWL]) and secondary non-response (i.e., ≥50% EWL followed by >5% regain).

Results: of the 83 included patients, 10 patients underwent revisional surgery. A total of 73 patients received a conservative treatment as they either had not been able to change their lifestyle or due to certain behavioral factors. Conservatively treated patients stabilized in weight after 2 years (-0.9 kg ±5.8, n = 27), while surgically treated patients did lose weight (-12.1 kg ±16.9, n = 7). One patient suffered from an ulcerative stenosis at the gastroenterostomy after limb length alteration.

Conclusion: a conservative treatment was the most frequently advocated treatment by the MDT. A surgical treatment resulted in successful weight loss, although only a few patients were selected for this by the MDT. A multidisciplinary approach can be beneficial for the identification of lifestyle and behavioral factors.

Abbreviations: BMI, body mass index; BPD/DS, biliopancreatic diversion/ duodenal switch; EWL, excess weight loss; MDT, multidisciplinary team; OAGB/MGB, one anastomosis gastric bypass/mini gastric bypass; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; TWL, total weight loss.

Introduction

Bariatric surgery has proven to be the most effective treatment for obesity to achieve long-term substantial weight loss [1,2]. However, ±25% of patients do not respond well as they lose an insufficient amount of weight, or regain weight after sufficient weight loss [3,4]. These phenomena can be described as primary non-response and secondary non-response. One can distinguish between these two types of non-response by applying a cutoff score. Frequently used cutoff scores are the amount of excess weight loss (EWL) and the amount of total weight loss (TWL) reported 1 to 2 years postsurgery [5–7]. The etiology for non-response can be lifestyle related, but can also be explained by anatomical alterations like a dilated pouch, dilated sleeve, dilated gastroenterostomy, or fistula formation such as gastrogastric fistula [8,9].

Revisional bariatric surgery constitutes a popular solution for patients with non- response [10]. Commonly offered procedures are conversion from sleeve gastrectomy (SG) to Roux-en-Y gastric bypass (RYGB), one anastomosis gastric bypass/mini gastric bypass (OAGB/MGB), lengthening of biliopancreatic limb, band, or ring placement, revision of the gastric pouch and/or stoma, and a biliopancreatic diversion/ duodenal switch (BPD/DS) [7-13]. To date, the long-term efficacy and safety of these procedures is difficult to predict. Lengthening of the biliopancreatic limb may result in severe malnutrition leading to the need for reoperation, whereas ring placement may result in reoperation due to dysphagia and/or ring migration [8,13].

In 1991, the National Institutes of Health Consensus Statement advocated that a multidisciplinary team (MDT) is required to optimize bariatric patient care [14]. This resulted in the formation of dedicated teams consisting of bariatric surgeons, obesity physicians, dieticians, physical therapists, and medical psychologists. The beneficial effect of MDTs on surgical outcomes has extensively been described in the field of surgical oncology [15–17]; however, the effect of a MDT on non-response after bariatric surgery is relatively poorly understood. It was Srivastava and Buffington who demonstrated that an intensive multidisciplinary lifestyle intervention combined with medication could improve early weight loss in patients with non-response [18]. This suggests that the role of a MDT needs further expansion in the management of non-responders after bariatric surgery and triggers the need for a more extensive analysis. The aim of this study was to describe the added value of a multidisciplinary approach, in a bariatric tertiary referral center, on treatment strategy in non-responders after bariatric surgery.

Methods

Study population

Data about non-responders after RYGB and SG was collected in our center from the first of January 2016 till the first of December 2020. Patients were included if they regained ≥5% weight with respect to the lowest postoperative weight after RYGB or SG (i.e., nadir weight). At the moment of inclusion, ≥5% regain was a commonly used cutoff score [6]. Patients were excluded in case of a banded RYGB and OAGB/MGB because these were less frequently performed procedures and this would have introduced heterogeneity otherwise. A history of laparoscopic adjustable gastric banding or Mason gastroplasty before the RYGB or SG was no criteria for exclusion. Ethical approval was obtained from the Medical Ethics Committee of our center, reference number: N19.054 (L19.065). For this type of study, formal consent from all individual participants was not required.

The primary procedure could have taken place in our center or elsewhere. In our center, all patients were screened for primary bariatric surgery by a MDT, and IFSO criteria were used for qualification [19]. Patients were monitored in the outpatient clinic by members of the MDT for a period of 5 years. Patients were categorized as primary non-responders if the EWL was <50% after primary surgery; patients were categorized as secondary non-responders if the EWL exceeded the 50% EWL threshold and a regain of >5% was reported as per nadir weight. The below section elaborates on the process and approach taken before and during the multidisciplinary assessment.

Assessment before MDT meeting

Initial assessment of the patient was done by a bariatric surgeon. Subsequently, the patient was referred to a dietician and physical therapist for assessment of nutritional habits and physical activity. The dietician focused on food intake, food choices, feelings of satiety, and hunger and signs of emotional eating. The physical therapist focused on activity habits. If indicated, consultation by a medical psychologist was offered.

MDT meeting

Following individual consultation by all team members, the treatment strategy was discussed in a joint multidisciplinary meeting with weekly occurrence. At least one member of the following fields of expertise attended this meeting: bariatric surgeon (chair), nurse practitioner, dietician, physical therapist, and medical psychologist. Notably, under certain circumstances, the patient was discussed in the meeting despite that this patient was not seen by all team members (e.g. persistent lack of attendance at one of the appointments).

Treatment strategy

After evaluation by the MDT, a decision was taken whether the patient needed a lifestyle and/or behavioral intervention or whether the patient was qualified for revisional surgery. For the purpose of this study, treatment options were divided into conservative and surgical treatment (Figure 1). A conservative treatment consisted of a nutritional and/or physical intervention, summarized as ''lifestyle.'' A nutritional intervention was indicated, for example, in case of unhealthy food choices and detrimental eating patterns, whereas a physical intervention was indicated in case of a sedentary lifestyle with the goal to increase activity habits. Moreover, a behavioral intervention was indicated if there were signs of emotional eating and problems in impulse control. If there were signs indicating an eating disorder, patients were referred to a psychiatric clinic specialized in treatment of such disorders.

The indication for revisional surgery was not based on the degree of weight loss or regain, so no cutoff scores were applied by any surgeon. The type of procedure depended on the index procedure, perioperative findings, and expert opinion. Preoperative upper gastrointestinal series and upper endoscopy were performed in patients who were offered revisional surgery.

Study outcomes

The primary outcome was the initiated treatment by the MDT, either conservatively or surgically. Secondary outcomes were weight loss achieved in a period of 4 years after start of the treatment and complications after surgical treatment. Weight loss was described as %EWL, which can be calculated as follows: (preoperative weight - nadir weight)/ (preoperative weight - ideal body weight) x 100%. Ideal body weight was based on a body mass index (BMI) of 25 kg/m^2; initial body weight was the weight at the moment of screening. Weight loss was also expressed in %TWL, which can be calculated as follows: (preoperative weight - nadir weight)/preoperative weight) x 100%, or (postoperative highest weight - postoperative lowest weight achieved after treatment of non-response)/postoperative highest weight x 100%. The percentage of regain was calculated as percentage kg gained after reaching the lowest postoperative weight (nadir).

Statistical analyses

Quantitative data are presented as mean with standard deviation (range) or median with interquartile range; categorical data are expressed in numbers and percentages. A paired t-test was performed to compare the weight before and after the treatment of non-response initiated by the MDT. All analyses were performed using the program Statistical Package for Social Sciences version number 22.0 (IBM SPSS 22.0; Chicago, IL).

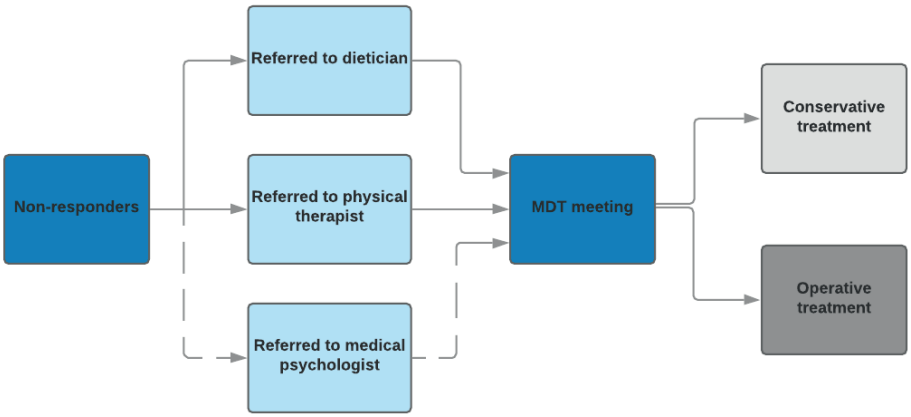

Figure 1. Flowchart of multidisciplinary management in patients with non-response after bariatric surgery. MDT, multidisciplinary team

Description of the population

A total of 119 patients were initially included in the study. Fifteen patients were excluded due to either having a banded RYGB (n=9), an OAGB/MGB (n=2) or because they did not receive RYGB or SG but a different procedure (i.e. Laparoscopic Adjustable Gastric Banding n=3, BPD n=1). Of the 104 remaining patients, 21 patients did not attend their appointment with the dietician, physical therapist and/or medical psychologist. Therefore, no optimal treatment could be advised and consequently these patients were excluded from further analysis. All 83 remaining patients were referred, prior to the multidisciplinary meeting, to a dietician and a physical therapist. Twenty-six patients (31.3%) were referred to a medical psychologist as well.

The baseline characteristics of the 83 included patients are demonstrated in Table 1. The group of conservatively treated patients consisted of 73 patients (88%), whereas the group of surgically treated patients consisted of 10 patients (12%). There were no significant differences in terms of gender, preoperative BMI and percentage of regain between the two groups. Based on the aforementioned definitions, 14 patients (16.9%) were defined as primary non-responders which all received a conservative treatment. The remaining 69 patients (83.1%) were defined as secondary non-responders and within this group, 59 patients received a conservative treatment and 10 patients a surgical treatment.

Table 1. Baseline characteristics of the study population

	Total, n=83	**Conservative treatment, n=73**	**Surgical treatment, n=10**
Gender, no. (%)			
Female	75 (90.4)	66 (90.4)	9 (90.0)
Age at the time of MDT meeting (years)	43.7±9.8 (41.6, 45.8)	44.0±9.9 (41.7, 46.3)	41.4±9.2 (34.9, 47.9)
Preoperative comorbidities, no. (%)			
Hypertension	17 (20.5)	14 (19.2)	3 (30.0)
Type II diabetes	7 (8.4)	5 (6.8)	2 (20.0)
Dyslipidaemia	4 (4.8)	4 (5.5)	-
OSAS	7 (8.4)	7 (9.6)	-
Osteoarthritis	5 (6.0)	5 (6.8)	-
History of bariatric surgery, no. (%)			
LAGB	17 (17.5)	14 (19.2)	3 (30.3)
Mason	6 (7.2)	6 (8.5)	-
SG	5 (6.0)	5 (6.8)	-
Index procedure, no. (%)			
RYGB	73 (88.0)	65 (89.0)	8 (80.0)
SG	10 (12.0)	8 (11.0)	2 (20.0)
Laparoscopy	79 (95.2)	69 (94.5)	10 (100.0)
Complications, no. (%)			
No complications	73 (88.0)	63 (86.3)	10 (100.0)
Clavien-Dindo grade I	1 (1.2)	1 (1.4)	-
Clavien-Dindo grade II	2 (2.4)	2 (2.7)	-
Clavien-Dindo grade III	7 (8.4)	7 (9.6)	-
Preoperative weight (kg)	127.6±20.7 (123.0, 132.1)	126.2±20.3 (123.0, 132.1)	137.5±21.6 (122.1, 152.9)
Preoperative BMI (kg/m^2)	44.7±7.0 (43.2, 46.2)	44.7±7.4 (43.1, 46.2)	44.9±3.5 (42.4, 47.5)
Maximal EWL (%)	77.9±23.7 (72.8, 83.2)	78.6±25.0 (72.8, 83.2)	73.7±10.1 (66.4, 80.9)
Maximal TWL (%)	32.9±9.7 (30.8, 35.0)	32.9±10.2 (30.8, 35.0)	32.2±3.6 (29.7, 34.8)
Amount of primary non-response (%)	14 (16.9)	14 (19.2)	-
Amount of secondary non-response (%)	69 (83.1)	59 (80.8)	10 (100.0)
Weight regain (%)	24.9±15.1 (21.6, 28.2)	25.5±15.7 (21.6, 28.2)	20.9±9.1 (14.4, 27.5)
Interval to presentation (years)	4.1±2.2 (3.6, 4.6)	4.0±2.2 (3.6, 4.6)	5.0±1.8 (3.7, 6.3)
Analysis of non-response			
Upper gastrointestinal series (%)	28 (33.7)	18 (24.7)	10 (100.0)
Endoscopy (%)	5 (6.0)	3 (4.1)	2 (20.0)

Data presented as number (%), mean with standard deviation and 95% confidence interval. Primary non-response is defined as <50% excess weight loss. Secondary non-response is defined as ≥50% and a regain of ≥5% with respect to nadir weight. List of abbreviations: MDT= multidisciplinary team, OSAS= Obstructive Sleep Apnoea Syndrome, BMI= Body Mass Index, LAGB= Laparoscopic Adjustable Gastric Banding, RYGB= Roux-en-Y Gastric bypass, SG= Sleeve Gastrectomy, EWL= Excess Weight Loss, TWL= Total Weight Loss.

When focusing on the conservative treatment, 63 patients (86%) received a nutritional intervention, 46 patients (63%) a physical intervention and 18 patients (25%) a behavioral intervention. When focusing on the surgical treatment, four different procedures were performed as described in table 2. The index procedure was RYGB in 8 patients and SG in 2 patients. In particular, 2 patients with prior SG underwent conversion to RYGB; 3 patients with perioperative common limb lengths between 440-600cm underwent shortening of the common limb to 200-380cm; 4 patients with a perioperative large pouch and/or stoma underwent resizing; 1 patient received a gastric ring (Minimizer).

Table 2. Overview of given treatment for non-response, initiated by the multidisciplinary team

Total, n=83	
Conservative treatment n=73, no. (%)	
Nutritional intervention	63 (86.3)
Physical intervention	46 (63.0)
Behavioral intervention	18 (24.7)
Referred to psychiatric institution	4 (5.5)
Surgical treatment n=10, no. (%)	
Alternation of the limb length	3 (30.0)
Revision of the gastric pouch and/or stoma	4 (40.0)
Roux-en-Y Gastric bypass	2 (20.0)
Ring placement	1 (10.0)

Data presented as number (%).

Weight loss outcomes

Table 3 displays the effect of the treatment, initiated by the MDT up to 4 years after start of the treatment. As result of a conservative treatment, patients lost on average 0.9kg within 2 years (SD=5.8) and gained 0.2kg within 4 years (SD=9.4). Recalculated in %TWL, the weight loss was 1.2% (SD=5.5), 0.7% (SD=6.3), 2.7% (SD=10.5) and 0% (SD=9.3) within respectively 1, 2, 3 and 4 years. Additional analysis showed that 4 years after start of the conservative treatment (n=17) 47% lost weight, while 53% gained weight. As result of a surgical treatment, patients lost on average 12.1kg within 2 years (SD=16.9) and even more within 3 and 4 years; however, only a small number of patients was assessed at these time points. The weight loss 1, 2 and 3 years after revisional surgery was statistically significant ($p \leq 0.01$). Recalculated in %TWL, the weight loss was 12.1% (SD=12.0), 11.6% (SD=15.8), 26.9% (SD=0.6) and 23.9% (n=1) within respectively 1, 2, 3 and 4 years.

Complications after surgical treatment

One postoperative complication occurred in a patient with a history of gastric banding, followed by RYGB and subsequent alteration of the limb length. This patient developed an ulcerative stenosis at the gastroenterostomy one year after alteration, presumably due to nonsteroidal anti-

inflammatory drugs use and the presence of Helicobacter pylori. The patient was successfully treated with endoscopic dilatation and received eradication therapy for this Helicobacter pylori.

Lost to follow up

After 2 years, 49 patients (59.1%) were lost to follow-up and after 4 years this number increased to 65 patients (78.3%). The reason of lost to follow-up is unknown. The baseline characteristics were analyzed comparing missing patients with non-missing patients 2 years after the start of the treatment. This analysis showed that the percentage of regain was significantly higher in the group of missing patients (28.3% versus 20.3%, p= 0.02). On the contrary, the prevalence of preoperative hypertension and type 2 diabetes was lower in the group of missing patients (10.4% versus 34.3%, p= 0.01 and 2.1% versus 17.1%, p= 0.02, respectively). Other baseline characteristics did not differ between the two groups.

Table 3. Effect of a conservative and surgical treatment on weight in non-responders following bariatric surgery

Conservative treatment									
	Total			**Primary non-response**			**Secondary non-response**		
Weight at start of treatment (kg)	104.8±20.9 (99.9, 109.7)	n=73		123.0±24.3 (109.0, 137.1)	n=14		100.5±17.6 (95.9, 105.0)	n=59	
ΔWeight (kg's) ≤ 1 year	-1.7±6.1 (-3.7, +0.3)	n=39	p 0.09	-0.9±2.9 (-3.3, -1.5)	n=8	p 0.39	-1.9±6.8 (-4.3, +0.6)	n=31	p 0.13
ΔWeight (kg's) ≤ 2 years	-0.9±5.8 (-3.2, +1.4)	n=27	p 0.44	-3.9±4.7 (-11.5, +3.4)	n=4	p 0.19	-0.3±5.9 (-2.9, +2.2)	n=23	p 0.79
ΔWeight (kg's) ≤ 3 years	-3.4±10.8 (-8.0, +1.2)	n=24	p 0.14	-5.2±11.9 (-19.9, +9.5)	n=5	p 0.38	-2.9±10.9 (-8.2, +2.3)	n=19	p 0.25
ΔWeight (kg's) ≤ 4 years	+0.2±9.4 (-4.7, +5.0)	n=17	p 0.92	-0.04±.7.6 (-9.5, +9.4)	n=5	p 0.99	+0.4±10.3 (-6.2, +6.9)	n=12	p 0.91
Surgical treatment									
	Total			**Primary non-response**			**Secondary non-response**		
Weight at start of treatment (kg)	115.6±17.9 (102.8, 128.4)	n=10		x			115.6±17.9 (102.8, 128.4)	n=10	
ΔWeight (kg's) ≤ 1 year	-13.0±12.1 (-22.3, -3.7)	n=9	p 0.001*	x			-13.0±12.1 (-22.3, -3.7)	n=9	p 0.001*
ΔWeight (kg's) ≤ 2 years	-12.1±16.9 (-27.7, +3.5)	n=7	p 0.003*	x			-12.1±16.9 (-27.7, +3.5)	n=7	p 0.003*
ΔWeight (kg's) ≤ 3 years	-26.3±0.4 (-29.4, -23.1)	n=2	P 0.000*	x			-26.3±0.4 (-29.4, -23.1)	n=2	p 0.000*
ΔWeight (kg's) ≤ 4 years	-27.0	n=1	x	x			-27.0	n=1	x

Data presented as mean with standard deviation and 95% confidence interval.
* Paired t-test: significant difference compared to the weight at the start of the treatment, p≤0.05.

Discussion

There is no standardized approach in the treatment of non-responders following bariatric surgery. While ongoing studies about the efficiency of revisional surgery are being reported in literature [8,9,11–13] studies about the effect of a multidisciplinary approach fall behind. Although it is proposed that a multidisciplinary approach is useful in the analysis of patients with non-response [7,9,13,20] this study is the first in describing the added value of such a multidisciplinary approach.

The main finding of this study was that the MDT advocated a conservative treatment more frequently than a surgical treatment (88% vs. 12%). The majority of patients were considered not to be eligible for revisional surgery as they either had not been able to change their lifestyle or due to certain behavioral factors. Based on previous research in our center between 2012 and 2015, it has been identified that before the introduction of a MDT, 68% of the non-responders underwent surgery after failed RYGB [11]. That study included 65 patients with weight loss failure and weight regain who were consulted by a bariatric surgeon. Consultation by a dietician and physical therapist and/or medical psychologist was not scheduled on a routine basis. Furthermore, no joint meeting by the MDT took place. The result of this study (68% revisional surgery) is in sharp contrast with the result of the current study (12% revisional surgery). One can argue that the MDT may have underselected appropriate candidates for revisional surgery or alternatively may have optimized the selection of candidates. The small sample size and heterogeneity in revisional procedures in the current study restricts making firm statements about this.

When reviewing weight loss outcomes, the weight loss achieved by revisional surgery was superior to the weight loss achieved by a conservative treatment. Notably, one could also argue that the weight was sustained as result of a conservative treatment, indicating that it may prevent patients from gaining more weight in the future. The question arises why a conservative treatment should be advocated as this resulted in less weight loss. In the context of revisional surgery it is worth noting that a patient is exposed to the risks of major complications and the risk of unsustainable weight loss in the long term [8,21]. A reason for this can be that surgery does not resolve the lifestyle and/or behavioral problems that may have contributed to non-response in the first place [20,22,23].

The observed complication rate within our study is in line with other literature. Complication rate after pouch/ anastomosis revision is estimated at 3.5% and after limb alteration at 12% [8]. Revision of the gastric pouch and/or stoma was most frequently performed in this study. The four patients who underwent this procedure did not suffer from any complications. From the

three patients who underwent limb alternation, one patient suffered from an ulcerative stenosis at the gastroenterostomy, which is a frequently reported complication in literature [24,25].

This study distinguished outcomes between primary and secondary non-responders. Previous studies did not report treatment outcomes using this classification, although it is proposed as standardized terminology [6,10]. This study supports this classification as it was found that patients with secondary non-response rather than primary non-response were treated surgically. This may indicate the need for a different treatment strategy in patients with primary and secondary non-response. A note of caution might be appropriate as there were demographical differences between the two groups. Speculatively, primary non-response might be a manifestation of insufficiently treated or even untreated eating behaviors and/or psychological problems, whereas secondary non-response might indicate anatomical problems. This theory warrants further research to obtain more information about the etiology and treatment strategy that is most efficient per non-response type.

This retrospective study has several limitations that should be considered. Not all patients received their primary surgery in our center and therefore information about preoperative screening and treatment could have been missed. It is questionable whether certain lifestyle and/or behavioral factors were present before primary surgery and whether the patients' adjustments met the standards used in our center. Another limitation could be that the MDT experienced a learning curve as the multidisciplinary evaluation of non-responders was introduced in 2016 in our center. It is possible that the different team members experienced a change in their evaluation and subsequent treatment. Moreover, pharmacological therapy was not used, while this has shown beneficial results in the treatment of non-response [26]. It should also be mentioned that results regarding weight loss and complication rates are limited due to the small selected group of patients who underwent revisional surgery. Furthermore, the 20% of patients who were excluded from the analysis due to no-show may have introduced selection bias, as well as the patients who did not attend their follow-up appointments after the treatment was set. The latter may be explained by further weight regain or by a loss of confidence in the MDT [27]. Notwithstanding these limitations, the study offers insights into the treatment of non-responders after bariatric surgery. For further practices, a checklist of relevant factors was made proposing a conservative or surgical treatment in non-responders (Table 4).

Conclusion

This study demonstrated that when patients with non-response after bariatric surgery are evaluated by a MDT, a conservative treatment is more often applied than a surgical treatment.

The MDT identified patient-specific factors presumably contributing to the non-response and these factors constituted the framework for a conservative treatment. At present, the question that remains unanswered is whether a multidisciplinary approach set the right treatment as perhaps the selection of candidates for revisional surgery was incorrect. More studies are required to position the multidisciplinary approach in the treatment of non-response, as well as determine what kind of revisional procedure should be preferred.

Table 4. Checklist of factors that can be used during the assessment of a patient with non-response advocating a conservative, or surgical treatment

Factors in favor of conservative treatment	Factors in favor of surgical treatment
Excessive dietary intake	Signs of surgical failure, e.g. pouch or stoma dilatation, gastro-gastric fistula
Inappropriate food choices	Dietary compliance
Lack of satiety	No signs of maladaptive eating habits
Constant hunger sensation	Physically active
Emotional eating	No signs of mental health disorder
Binge eating	No signs of alcohol or drug use
Sweet eating	
Grazing behavior	
Physically inactive	
Mental health disorder, e.g. depression, anxiety, personality disorders	
Alcohol or drug use	

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CHAPTER 07

The effect of additional protein on lean body mass preservation in post-bariatric surgery patients: a systematic review

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Abstract

Introduction: as result of bariatric surgery, patients are susceptible to protein deficiency which can result in undesirable lean body mass (LBM) loss. Consumption of high-protein diets or supplements could counteract this, but evidence about the effect is scarce. This paper systematically reviewed the literature to determine the effect of additional protein intake (≥60 g/day) on LBM preservation in post-bariatric patients.

Methods: an electronic search of PubMed, EMBASE and the Cochrane Library was conducted. Studies were included if patients received a high-protein diet or protein supplements for at least one month, and LBM was assessed. The primary outcome was difference in mean LBM loss between the experimental (protein) and control group. Secondary outcomes were differences in body fat mass, total body water, body mass index and resting metabolic rate.

Results: two of the five included studies (n= 223) showed that consumption of proteins resulted in significant LBM preservation. Only one study reported a significant difference in the reduction of body fat mass and resting metabolic rate in favor of a high-protein diet, but none of the studies showed a significant difference in total body water loss or body mass index change between the two groups.

Conclusion: this paper showed inconclusive evidence for LBM preservation due to protein supplementation or a high-protein diet in post-bariatric patients. This outcome might be subjected to certain limitations, including a lack of blinding and a low compliance rate reported in the included studies. More specific and personalized recommendations regarding protein intake may need to be established by high quality research. Studies investigating the quantity (g/day) and quality (whey, casein or soy) of proteins are also needed.

Abbreviations: BIA: Bioelectrical impedance analysis; BFM: Body fat mass; BMI: Body mass index; BS: Bariatric surgery; DXA: Dual-energy X-ray absorptiometry; IBW: Ideal body weight; LBM: Lean body mass; MRI: Magnetic resonance imaging; RCT: Randomized controlled trial; RMR: Resting metabolic rate; SG: Sleeve gastrectomy; RYGB: Roux-en-Y gastric bypass; TBW: Total body water.

Introduction

Bariatric surgery (BS) is considered the most effective treatment for severe obesity [1–3]. Despite the successful weight loss, patients are prone to develop nutrient deficiencies due to energy restriction, malabsorption and food intolerances [4,5]. Current guidelines recommend patients to consume 60-80 g proteins a day or 1.2 g/kg of the ideal body weight (IBW) [6–8], but adherence to these guidelines is known to be problematic in 45% of BS patients [4]. There is a substantial prevalence of excessive lean body mass (LBM) loss in BS patients. Within the first year after laparoscopic Roux-en-Y gastric bypass (RYGB), patients lose about 22% of their LBM [9,10]. LBM plays an important role in resting energy expenditure, functional capacity, muscle strength and cardiovascular health [11–13]. In post-bariatric surgery patients, an excessive loss of LBM can be detrimental as it may slow down weight loss or even trigger weight regain [14–16]. Mechanisms behind this are a reduced resting metabolic rate (RMR) and a direct change in appetite [14,16–18]. Moreover, an inadequate protein intake (≤60 g/day) potentially results in decreased feelings of satiation and decreased diet-induced thermogenesis, which may hinder weight loss [19]. For these reasons, an adequate protein intake and preservation of LBM in BS patients is of significant importance in long term weight management.

There is a paucity of data that shows the correlation between protein intake and LBM loss after BS. In 2017, a systematic review concluded that two of the four studies with an adequate protein intake (≥60 g/day) was associated with significantly less LBM loss one year after RYGB [17–19]. A major criticism of this review is that the protein intake in eight studies was relatively inadequate (<60 g/day) generating insufficient evidence. Currently, no systematic review has investigated the effect of an adequate protein intake (≥60 g/day) achieved by high protein diets or protein supplements on LBM preservation, while multiple randomized controlled trials (RCTs) have been performed. Therefore, the aim of this systematic review was to evaluate the effect of protein supplementation or a high-protein diet (≥1 month) on LBM preservation in post-bariatric surgery patients, compared to patients following standard treatment.

Methods

This review complies with the recommendations of the Cochrane Handbook for Systematic Reviews and Interventions [20] and was recorded according to the PRISMA systematic review guidelines [21]. The systematic review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42020176839.

Search strategy

The systematic search was performed in February 2020 and was conducted in three electronic databases: MEDLINE (PubMed Legacy), EMBASE (Ovid) and The Cochrane Library. The search included only human studies that were published in English or Dutch, and was not restricted by publication date. Keywords in the search strategy included [dietary protein], [protein supplementation] and [bariatric surgery], and their synonyms. The full search strategies for all databases can be found in supplementary Table 1 (supporting information). References of relevant reviews and included studies were hand searched for potential eligible studies that have been missed.

Eligibility criteria

Studies were considered eligible if they included: 1) patients in the age of 18–65 years with a body mass index (BMI) of ≥35 kg/m^2 who underwent RYGB or sleeve gastrectomy (SG), 2) daily protein supplementation or a high-protein diet for ≥1 month (≥60 g/day), started within 2 weeks after surgery, compared to standard treatment (control), 3) body composition as outcome measurement determined by either air displacement plethysmography, bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DXA) or magnetic resonance imaging (MRI), 4) a follow-up of ≥2 months, and 5) an experimental or observational study design including a control group. Exclusion criteria were 1) inclusion of pregnant women, 2) protein supplementation or a high-protein diet combined with ≥2 times supervised strength training per week, without data about the effect of proteins only, 3) no data about primary outcome (LBM), or 4) reviews, letters, case series, case reports, conference abstracts and editorials.

Study selection

Initial records were screened for relevance on titles and abstract. Full-texts of relevant articles were obtained for checking final inclusion. Endnote X9 software was used to manage all references, including removal of duplicates.

Data extraction

The following data was extracted by one researcher (D.H.) using a standardized study form: authors' names, publication year, study design, follow-up period, sample size, gender, mean age, mean BMI, baseline LBM, surgery type, intervention protocol, protein intake prior to surgery, actual protein intake, compliance and study outcomes (LBM, body fat mass (BFM), total body water (TBW), BMI and RMR. A second author (M.R.) crosschecked the information.

Study outcomes

The primary outcome was difference in mean LBM loss between the experimental (protein) and control group. Secondary outcomes were differences in BFM, TBW, BMI and RMR. If no score (in kg or %) of the predefined outcome was provided, a score was calculated based on the available data (pre- and post-surgery). Effect sizes of the individual studies were calculated using Cohen's d. An effect size of ≤0.2 was considered trivial, 0.2–0.49 was considered small, 0.5–0.79 was considered moderate and ≥0.8 was considered high [22].

Quality assessment

Study quality was assessed by the Cochrane Collaboration's Risk of Bias Tool [23]. The Cochrane Collaboration's Risk of Bias tool subdivides studies into "low", "unclear" or "high" risk for various biases (selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias). Two reviewers (D.H., M.R.) judged the quality of each individual study based on a set criteria. Any disagreements were solved by a third reviewer (L.J.).

Results

Study selection

In total, 881 articles were identified in three electronic databases and one article was identified in a reference list. After duplicate removal, 743 articles remained. After screening of titles and abstracts, 23 potentially relevant articles were selected for full-text reading. At the end, five studies met the inclusion criteria and were considered eligible for this systematic review [24–28] (Fig. 1).

Study characteristics

The sample sizes of the included studies varied from 20 [28] to 60 [25,27] patients (Table 1). The follow-up periods ranged from 8weeks [24] to 6months [25,26,28] and 12months [27]. Two studies included only SG patients [25,27], two studies included only RYGB patients [24,26] and one study included both types of BS [28]. Three of the five studies used protein supplements [25,26,28], one study used amino acid supplements [24] and one study used a protein-enriched diet to increase daily protein intake [27]. The dose of protein supplements or protein content in high-protein diets varied from 15 g/day [28] to 2.0g/kg IBW/day [27]. Two of the included studies reported a high level of patients' compliance [27,28], whereas two studies reported a low level [25,26] and one study did not asses compliance [24]. Some authors reported reasoning for the low compliance, proposing that this can be improved by

closer follow-up and face-to-face interviews [25]. Three of the five studies assessed body composition by BIA [25,27,28], whereas the other two studies assessed body composition using DXA [24,26].

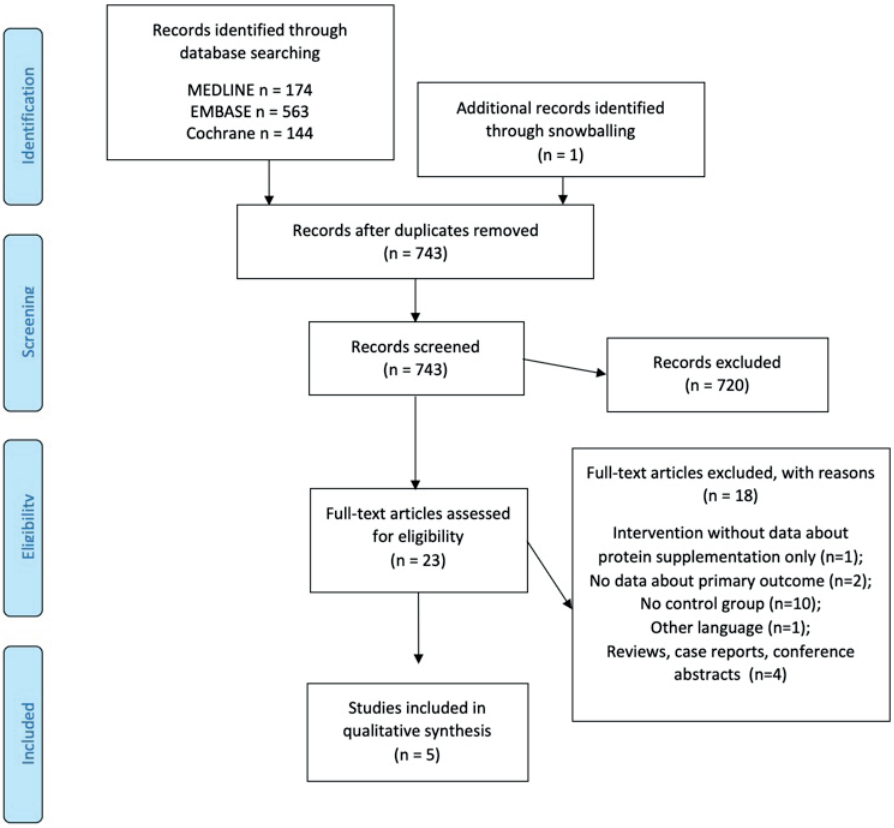

Figure 1. PRISMA flow diagram showing selection of articles

Table 1. Study characteristics of the included studies

Author, year	Study design, follow-up	Sample size Gender	Age (yr) BMI (kg/m²) LBM (kg)		Surgery type	Intervention	Pre-surgery protein intake (g/day)	Actual protein intake (g/day)	Compliance	Protein intake analyzed	Outcomes analyzed
			CON	PRO							
Clements et al., 2011 [24]	Unblinded randomized control pilot study, 8 weeks	30 M (n=1) F (n=29)	46.0 ± 7.5 43.6 ± 4.2 54.0 ± 8.1	47.9 ± 9.6 42.9 ± 4.1 52.4 ± 6.9	RYGB (n=30)	CON: usual care, no use of protein supplements. PRO: oral supplement containing 24g leucine metabolite, glutamine and arginine twice daily for 8 weeks.	*NA*	*NA*	*NA*	Log sheets	TBW, BMI Body composition using DXA (BFM, LBM) RMR
Günes et al., 2019 [25]	Randomized controlled trial, 6 months	60 M (n=9) F (n=51)	43.5 ± 8.4 45.9 ± 6.5 61.7 ± 13.3	40.3 ± 11.4 46.2 ± 5.0 47.5 ± 13.5	SG (n=60)	CON: standard diet for 1 month, no use of protein supplements. PRO: standard diet + 1,2 g/kg IBW/ day protein (±80g) whey powder for 1 month.	*NA*	CON: *NA* PRO: 51	38%*	*NA*	TBW, BMI Body composition using BIA (BFM, LBM)
Oppert et al., 2018 [26]	Randomized controlled trial, 6 months	53 F (n=53)	43.9 ± 10,7 43.6 ± 6.2 55.6 ± 8.4	42.5 ±8.7 43.3 ± 6.0 55.9 ± 6.1	RYGB (n=53)	CON: usual care with general dietary and physical activity counselling. PRO: oral supplement containing whey-protein-enriched powder (24g) twice daily for 6 months.	CON: 80 PRO: 82	CON: 60 PRO: 82	55%	Dietary history method. Return of empty cans of protein powder	TBW, BMI Body composition using DXA (BFM, LBM)

Table 1 (Continued)

Author, year	Study design, follow-up	Sample size Gender	Age (yr) BMI (kg/m²) LBM (kg)		Surgery type	Intervention	Pre-surgery protein intake (g/day)	Actual protein intake (g/day)	Compliance	Protein intake analyzed	Outcomes analyzed
Schiavo et al., 2017 [27]	Randomized comparative study, 12 months	60 M (n=60)	41.0 ± 6.2 40.7 ± 5.3 75.0 ± 11.9	43.0 ± 5.5 42.1 ± 6.2 76.3 ± 7.0	SG (n=60)	NPD (normal protein diet): 1.0 g/kg IBW/day protein (23.3%), 15% fat and 61.7% carbohydrates for 12 months. PED (protein-enriched diet): 2.0 g/kg ideal IBW/day protein (±160g)(47.7%), 15% fat and 37.7% carbohydrates for 12 months.	*NA*	CON: 67 PRO: 143	Very high	Questionnaires, 3 day dietary record, 72h-recall	TBW, BMI Body composition using BIA (BFM, LBM) RMR
Schollenberger et al., 2016 [28]	Randomized controlled double-blind pilot study, 6 months	20 M (n=3) F (n=17)	47.0 ± 11.9 49.0 ± 5.1 68.9 ± 13.4	43.4 ± 13.3 52.0 ± 7.6 65.2 ± 14.2	RYGB (n=5) SG (n=15)	CON: pure maltodextrin powder, 15 g/day first month, 30-35 g/day second-sixth month. PRO: milk protein powder, 15 g/day first month, 30-35 g/day second-sixth month.	CON: 93 PRO: 97	CON: 53 PRO: 67	86%	4 day dietary record, interviews	TBW, BMI Body composition using BIA (BFM, LBM)

Values are expressed as mean ± SD. List of abbreviations: CON = control group; PRO = protein group; RGYB = Roux-en-Y gastric bypass; SG = sleeve gastrectomy; IBW = ideal body weight; NA = not assessed; TBW = total body weight; BMI = body mass index; BFM = body fat mass; LBM = lean body mass; RMR = resting metabolic rate; DXA = dual-energy X-ray absorptiometry; BIA = bioelectrical impedance analysis.

* indicates the percentage of patients adhering to the guideline regarding protein intake (≥60 g/day).

Quality of individual studies

Four studies were free from a high risk of bias in all domains [25–28]. One study contained a high risk of bias based on funding [24]. In addition, in four of the five studies [24–27] the risk of bias was unclear concerning blinding. A summary of the risk of bias for the individual studies can be found in Table 2.

Lean body mass

All studies reported that LBM (kg) decreased significantly from pre-surgery to 8 weeks [24], 6 months [25,26, 28] and 12 months [27] post-surgery. Two studies showed that protein supplementation [25] and a high protein diet [27] resulted in significantly more preservation of LBM compared to control, respectively 8% vs. -12% and − 12% vs. -19% (Table 3). The other three studies demonstrated no differences towards LBM preservation following protein supplementation [24,26,28]. The studies that showed a significant difference in the decrease of LBM had an effect size of 0.31 [25] and 0.61 [27], which is considered small and moderate, respectively.

Table 2. Assessment of risk of bias

Author, year	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	
Clements et al., 2011 [24]	+	?	?	+	+	+	− *
Günes et al., 2019 [25]	+	+	?	+	?	+	?
Oppert et al., 2018 [26]	+	?	?	+	+	+	?
Schiavo et al., 2017 [27]	+	?	?	+	?	+	?
Schollenberger et al., 2016 [28]	+	+	+	+	+	+	?

*indicating bias regarding funding

− = high risk of bias

\+ = low risk on bias

? = unclear risk bias

Table 3. Results of the individual studies

Author, year	LBM change (kg)(change%)	Effect size (d)	BFM change (kg) (change%)	TBW change (kg) (change%)	BMI change (kg/m²) (change%)	RMR change (kcal/day)
Clements et al., 2011 [24] [1]	CON: -7.9 ± 4.5 (14.6%)* PRO: -7.7 ± 3.5 (14.7%)*	0.23 (-0.48 to 0.95)	CON: -8.0 ± 3.5 (14.3%)* PRO: -9.2 ± 3.2 (15.7%)*	CON: -15.7 ± 2.5 (13.8%)* PRO: -15.8 ± 2.6 (13.9%)*	CON: -6.1 ± 1.1 (14%)* PRO: -5.9 ± 0.9 (13.8%)*	CON: -294.1 ± 207.2 (15.9%)* PRO: -286.6 ± 271.1 (15.9%)*
Günes et al., 2019 [25] [2]	CON: -7.2 (12%)* PRO: 3.8 (8%)*^	0.31 (-0.24 to 0.78)	CON: -25.1 (41%)* PRO: -36.7 (49.5%)*	CON: -33.0 (26.9%)* PRO: -33.1 (27.2%)*	CON: -12.6 (27.4%)* PRO: -12.2 (26.5%)*	*NA*
Oppert et al., 2018 [26] [3]	CON: -8.8 (-10.1 to -7.5)* (16%) PRO: -8.2 (-9.3 to -7.1)* (15%)	*NA*	CON: -19.7 (-21.5 to -17.9)* PRO: -19.8 (-21.3 to -18.2)*	CON: -28 (-30.6 to -25.4)* PRO: -27.2 (-29.4 to -25.1)*	CON:-10.5 (-11.4 to -9.6)* PRO: -10.2 (-11.0 to -9.4)*	*NA*
Schiavo et al., 2017 [27] [1]	CON: -14.5 (19%)* PRO: -8.8 (12%)*^	0.61 (0.07 to 1.15)	CON: -23.7 (50%)* PRO: -43.2 (84%)*^	CON: -38.8 (31%)* PRO: -46.7 (36%)*	*NA*	CON: -645.16 (29%)*^ PRO: -380.18 (17%)*^
Schollenberger et al., 2016 [28] [1]	CON: -7.8 (11.3%)* PRO: -7.6 (11.7%)*	0.3 (-0.59 to 1.18)	CON: -21.0 (30.8%)* PRO: -29.1 (37.2%)*	CON: -28.7(20.9%)* PRO: -36.4 (25%)*	CON: -10.3 (21%)* PRO: -13.0 (25%)*	*NA*

[1] expressed as mean ± SD (change%); [2] expressed as mean (change%); [3] expressed as mean (CI) (change%). *denotes significant difference from baseline. ^denotes significant difference from control

Abbreviations: CON = control group; PRO = protein group; NA = not applicable or not assessed; LBM = lean body mass; BFM = body fat mass, TBW = total body weight; BMI = body mass index; RMR = resting metabolic rate.

Discussion

As result of bariatric surgery, patients are susceptible to protein deficiency which can result in an undesirable LBM loss. Evidence about the effect of protein supplementation or a high-protein diet (≥60 g/day) on LBM preservation is scarce. Therefore, this systematic review was conducted to evaluate these effects. Two of the five studies supported the hypothesis that protein supplementation or a high-protein diet resulted in significant LBM preservation [25,27], whereas the other three studies did not support the hypothesis [24,26,28]. This discrepancy can be attributed to differences in protein intake, type of surgery and measurement tools which are discussed below.

The first explanation for why three studies failed to detect a significant LBM preservation is that the actual daily protein intake of these patients may have been too low. The studies that failed to demonstrate significant LBM preservation following protein supplementation reported an actual daily protein intake of 67 and 82 g/day [26,28], though this amount is considered as adequate according to literature [6–8]. The actual daily protein intake in one of the studies that observed a significant LBM preservation was much higher, namely 143 g/day [27]. The other study that showed a significant LBM preservation reported a daily protein intake of just 51 g/day, while the protein intake of the control group was unknown [25]. The amount of 51 g/day should be criticized as protein intake was measured the first month after surgery and it is plausible that patients increased their protein intake hereafter, resulting in a higher protein intake at the time of measuring LBM (3 and 6 months). Based on the abovementioned findings (143 g/day resulting in significant LBM preservation [27]; 67 g/day to 82 g/day not resulting in LBS preservation [26,28]), it could be questioned whether 60–80 g/day is sufficient to maintain LBM.

A lack of compliance might explain the relatively low actual protein intake within the first months after surgery. In the study of Oppert et al. this may have attributed to insignificant outcomes [26]. Unfortunately, none of the included studies reported clear causes for poor compliance. We speculate that this could be attributed to the occurrence of side effects, food intolerances and a lack of understanding regarding the need of adequate proteins [29,30]. Protein intake and subsequent absorption may have been influenced by the type of surgery as both restrictive and malabsorptive procedures were included in this study. The two studies that found a significant effect included patients who underwent a restrictive procedure(SG) [25,27], in contrast to the studies that included RYGB patients where no effect was found [24,26,28]. It is interesting to note that Schollenberger et al. reported, in a separate analysis of only SG patients, that protein supplementation led to significant LBM preservation [28]. An

explanation for these findings may be that protein digestion and absorption is higher after restrictive surgery. This proposes that the additional protein intake is less effective in RYGB patients, but results in more pronounced LBM preservation in SG patients.

A third explanation may be the usage of different tools for measuring body composition (BIA versus DXA), both presenting important limitations. The two studies that detected a significant LBM preservation used BIA [25,27]. However, BIA is known for overestimating LBM in bariatric patients and the validity of BIA is influenced by fatness [31–33]. As a result, the two significant outcomes are potentially more pronounced. Additionally, DXA is limited by the fact that the fat free mass compartment is measured rather than directly muscle mass [32]. Future research is recommended to measure body composition with a four-compartment model to overcome this limitation.

It is conceivable that physical activity might have influenced study outcomes as it is known from the field of sports physiology that physical activity plays an important role in LBM preservation [34–36]. Four of the five studies did not report anything about physical activity of the patients, implying uncertainty on whether and how physical activity influenced LBM preservation. The study that did report about physical activity (i.e., supervised strength training for 18 weeks plus additional protein intake), failed to show a significant preservation in LBM [26]. Contrarily, Muschitz et al. approved the synergistic effect of physical activity on protein supplementation as they observed significant LBM preservation [37]. The discrepancy in this outcome may be explained by the difference in study length, 18 weeks vs. 24 months respectively [26,37]. Further studies investigating the synergistic effect of physical activity and protein supplementation in bariatric patients are limited, which implies that it is difficult to draw conclusions based on these two studies.

There are some methodological limitations in this systematic review which should be mentioned. Four of the five studies lacked (double) blinding, which could have influenced the study outcomes. Furthermore, only two of the five studies reported high compliance to protein intake and because of this, outcomes are potentially less pronounced than expected. Moreover, the number of the included studies in this systematic review is small, potentially resulting in a relative low power of this systematic review. A further comparison of the included studies was complicated due to heterogeneity of the study protocols (e.g. supplementation type, dose and timing) and the measurement tools. New studies investigating the most effective dose of supplements to preserve LBM in post-bariatric surgery patients are warranted as perhaps the dose of 60–80 g/day is insufficient to maintain muscle mass. In addition, it is advised to conduct studies examining the most effective composition of protein supplements (e.g. whey

vs. casein vs. soy) in order to enable interstudy comparison. Special attention needs to be paid to the effect of leucine on LBM preservation, given its key role in muscle protein synthesis. On top of that, studies focusing on the synergistic effect of physical activity and protein intake on LBM preservation are warranted.

Conclusion

Although the preservation of LBM in post-bariatric surgery patients is of extreme importance, our systematic review resulted in the inclusion of only five studies. These studies showed inconclusive evidence for LBM preservation due to protein supplementation or a high-protein diet. Notwithstanding, this work offers awareness to current healthcare providers who should prompt an adequate protein intake in post-bariatric surgery patients. More specific and personalized recommendations regarding protein intake may need to be established by high quality research. New studies investigating the quantity (g/day) and quality (whey, casein or soy) of protein supplements or high protein diets, possibly in combination with resistance training, in larger study populations are needed.

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CHAPTER 08

A comparative analysis between primary banded and non-banded Roux-en-Y gastric bypass: a retrospective series of almost 13.000 patients

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Under review

Abstract

Introduction: banding of a Roux-en-Y gastric bypass (RYGB) has been proposed to optimize weight loss outcomes. The aim of this retrospective study was to compare weight loss outcomes, specifically (non) response rates and total weight loss (TWL), in primary banded RYGB and non-banded RYGB patients.

Methods: a nationwide population-based cohort study was conducted. Data were derived from the Dutch Audit of Treatment of Obesity. The primary outcome was the rate of non-response, defined as significant weight regain (≥20% of a patients' lost weight) 2-4 years postoperatively, after initial successful weight loss (≥20% TWL). Secondary outcomes were the rate of response, defined as successful weight loss (≥20% TWL) within 1.5 years postoperatively, the incidence of complications (i.e. general and band-related), and the progression of obesity related comorbidities.

Results: A total of 12.982 patients were included in this study (banded RYGB n=351; non-banded RYGB n= 12.631). The rate of non-response was lower in the banded RYGB group (12.5% vs. 17.1%, p= 0.012), whereas the rate of response was higher in this group (99.4% vs. 96.3%, p= 0.002). In the banded RYGB group, 126 patients (35.9%) completed 3 years follow-up and 37 patients (10.5%) completed 4 years follow-up. Whereas in the non-banded RYGB group, 6773 patients (53.6%) completed 3 years follow-up and 2923 patients (23.1%) completed 4 years follow-up. Mean %TWL in the banded RYGB group was higher up to 3 years postoperatively. The incidence of severe general complications was equally distributed between the two groups. The incidence of band-related complications was 0.6% (n=2). The non-banded RYGB group presented higher rates of resolved comorbidities. The results of this study could be influenced by a poor follow-up rate and inadequacies in data registry.

Conclusion: A banded RYGB, in comparison to a non-banded RYGB, significantly reduced the rates of non-response, yet improved the rate of response as well as %TWL up to 3 years postoperatively.

Abbreviations: BMI, body mass index; CD, clavien-dindo; DATO, Dutch Audit of Treatment of Obesity; EWL, excess weight loss; GERD, gastroesophageal reflux disease; OR, odds ratio; OSAS, obstructive sleep apnea syndrome; RYGB, Roux-en-Y gastric bypass; SD, standard deviation; TWL, total weight loss; T2D, Type 2 Diabetes.

Introduction

Since the mid 1990's, the banded Roux-en-Y gastric bypass (RYGB) as described by Fobi and Capella [1-2] gained popularity in patients suffering from severe obesity and obesity related comorbidities. In addition to the construction of a RYGB, a marlex mesh, ring, or a (non) adjustable band was fitted to the gastric pouch. This technique has been suggested to improve weight loss outcomes [3]. Improvement of these outcomes is necessary as approximately 25% of post-bariatric patients experiences inadequate weight loss or regain a significant amount of weight, so-called non-response [4-5]. Regaining weight is invariably related to an increased energy intake, changes in energy expenditure and decreased physical activity, but is also related to changes in the size and shape of the gastric pouch and gastroenterostomy [5-7]. Intake restriction after RYGB is achieved through a small pouch combined with a narrow gastroenterostomy. Importantly, when this enlarges restriction is lost and subsequent weight regain may occur. A banded RYGB may overcome this problem as it prevents enlargement of the gastric pouch and gastroenterostomy [8].

A growing body of literature is showing that weight loss achieved by a primary banded RYGB is greater than that of a standard non-banded RYGB. Ten year weight loss outcomes after banded RYGB, as reported in reviews between 2006 and 2014, demonstrated that the excess weight loss (EWL) was 9.0- 19.4% greater [1,9-10]. It is important to bear in mind that these reviews included open procedures and techniques that are nowadays considered old fashioned (e.g. transected silastic ring vertical gastric bypass). In the subsequent years, cohort studies with a maximum of 432 patients were published, demonstrating that the banded RYGB increased EWL by 7.1% after two years [2] and 8.8% after five years [3]. Despite these studies, there is a reluctance in practice to shift from non-banded RYGB to banded RYGB. This might be due to a lack of large cohort studies or randomized controlled trials, using updated weight loss outcomes (e.g. %total weight loss (TWL) instead of %EWL) and focusing on the progression of comorbidities [11-13]. The aim of this nationwide study was to compare weight loss outcomes, specifically (non) response rates and %TWL, in primary banded RYGB and non-banded RYGB patients.

Methods

Study population

This is a nationwide population-based cohort study using pseudonymized data that originates from the Dutch Audit of Treatment of Obesity (DATO). Reporting to the DATO is mandatory in the Netherlands and it serves as nationwide clinical audit. The registry started in January 2015 and covers all bariatric procedures that has been performed since then. The registry includes data on patient characteristics, obesity-related diseases, surgical technique, perioperative complications, reinterventions, readmissions, mortality and weight loss outcomes [14]. Records

were obtained from patients who underwent a primary banded RYGB or a non-banded RYGB between 1 January 2015 and 31 December 2017. Patients were eligible for surgery if they were between 18 and 65 years old and had a body mass index (BMI) of more than 40 kg/m^2 or a BMI of more than 35 kg/m^2 combined with an obesity related comorbidity [15]. Follow-up weights at 2 years postoperatively were required for inclusion, otherwise the rates of non-response could not be determined. Patients were excluded if they had prior bariatric surgery for example an adjustable band, sleeve gastrectomy or Mason gastroplasty.

Study outcomes

The primary outcome is the rate of non-response defined as significant weight regain (≥20% of a patients' lost weight) 2-4 years postoperatively, after initial successful weight loss (≥20% TWL). The threshold of 20% weight regain is based on the study by Uittenbogaart et al. [16], whereas the threshold of 20% TWL is based on the DATO registry and previous publications [11,14]. Secondary outcomes include the rate of response defined as successful weight loss (≥20% TWL) within 1.5 years postoperatively, total weight loss (%TWL), general and band-related complications, and the progression of obesity related comorbidities.

Obesity related comorbidities included type 2 diabetes (T2D), hypertension, hyperlipidaemia, gastroesophageal reflux disease (GERD), obstructive sleep apnea syndrome (OSAS) and osteoarthritis. The definition of these comorbidities is based on the ASMBS guideline by Brethauer et al. [14,17]. Comorbidities were recorded regardless of an active treatment (e.g. no use of painkillers in a patient with osteoarthritis). The evolution of comorbidities was assessed at four time-points (1.5, 2, 3 and 4 years) and was classified as resolved, improved, unchanged, deteriorated and de novo.

Early postoperative complications (<30 days) were registered and categorized according to the Clavien-Dindo Classification of Surgical Complications (CD) [18]. The percentage of TWL was calculated as (preoperative weight – follow-up weight)/(preoperative weight) ×100%. In order to compare our data with prior literature, weight loss was also described in change in BMI, with the calculation of (preoperative BMI – follow-up BMI) and in %EWL using the formula (preoperative weight − follow-up weight) / (preoperative weight − ideal body weight) ×100%. Ideal body weight is defined as a BMI of 25kg/m^2.

Surgical technique

The surgical technique depended on the surgeon's preference and centre. The RYGB was generally constructed with a vertical pouch of 5-7cm and a volume of 30-50ml. The gastroenterostomy was constructed by using a stapler technique (i.e. linear or circular) or a hand-sewn technique [19,20]. The lengths of the limbs, as well as closure of mesenteric and Petersen's defects followed

local protocols. For the construction of a banded RYGB, two techniques were generally applied as described by previous studies [12-13]. These techniques included the placement of a silicon tube (8-Fr) [12] and a silicon ring (MiniMizer) [13]. The devices were applied according to manufactures protocol, meaning that they were placed 1-2cm proximal of the gastroenterostomy, resulted in a circumference of 6.5-8.0cm and were checked on tightness [12-13].

Statistical Analyses

Statistical analyses were performed using IBM SPSS statistic software, version 22.0. A p value of <0.05 was considered statistically significant. Continuous variables are presented as mean ± standard deviation (SD), while categorical variables are presented as an absolute number (percentage). Categorical variables were compared with the $\chi 2$ test, and continuous variables with an independent t test. The association between non-response rates (outcome) and surgical technique (exposure) was analyzed using multivariate logistic regression. Within these analyses, corrections were made for known confounders based on literature (baseline BMI, age at surgery, gender [21] and variables that may have a confounding effect based on univariate analysis (variables that are associated with the outcome with a p-value <0.1 in a univariate analysis). Stratification was applied to explore effect modification by gender and age at surgery which was statistically tested by including an interaction variable into the regression model. In presence of effect modification, additional analyses were performed. Sensitivity analyses were furthermore performed to test the robustness of the findings to missing data (e.g. patient characteristics) and variation in outcome definition (i.e. 15% TWL instead of 20%). Separate analyses were performed for patients with a BMI below and above 50 kg/m^2.

Results

A total of 20.286 patients were registered during the study period. One hundred two patients were excluded due to previous bariatric surgery and an additional 7202 patients were excluded due to missing weight registered within 1.5 and/or at 2 years after surgery. In total, 12.982 patients were included in this study with 351 patients in the banded RYGB group and 12.631 in the non-banded RYGB group. In the banded RYGB group, 126 patients (35.9%) completed 3 years follow-up and 37 patients (10.5%) completed 4 years follow-up. Whereas in the non-banded RYGB group, 6773 patients (53.6%) completed 3 years follow-up and 2923 patients (23.1%) completed 4 years follow-up.

The non-banded RYGB was performed in a standardized fashion by 29 surgeons located in 18 bariatric centers. In addition, the banded RYGB was performed by 7 surgeons located in 4 bariatric centers with the vast majority (98.8%) of procedures being performed in 1 center. Baseline characteristics are presented in Table 1, showing that the number of females was significantly lower in the banded RYGB group (75% vs. 82%, p= <0.001). In the banded RYGB

group, 76.1% of the patients received in a MiniMizer ring, while for other 23.9% the type of banding was not documented. Next to this, the circumference of the ring was unknown.

Table 1. Baseline characteristics of the study population

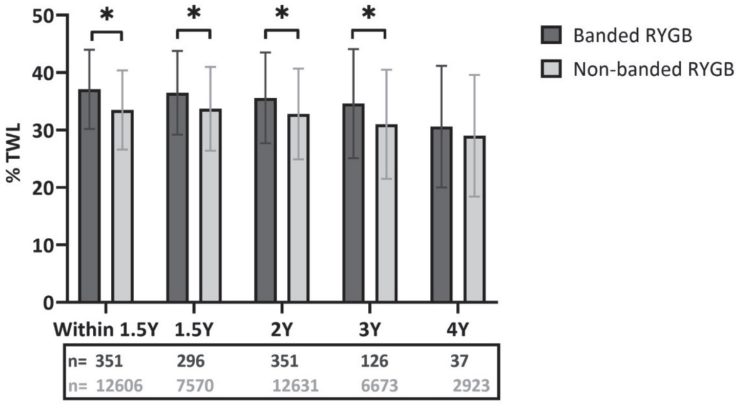
	Banded RYGB n= 351	**Non-banded RYGB n= 12631**	**p-value**
Gender, no. (%)			
Males/ Females	88/263 (25/75)	2247/10384 (18/82)	<.001*
Age at surgery, no. (%)			.991
18-35 years	68 (20)	2516 (20)	
36-45 years	99 (28)	3484 (28)	
46-55 years	124 (35)	4453 (35)	
56-65 years	60 (17)	2178 (17)	
Preoperative comorbidities, no. (%)			
Hypertension	133 (38)	4647 (37)	.673
Type 2 diabetes	67 (19)	2771 (22)	.203
Hyperlipidemia	70 (20)	2720 (22)	.474
Gastroesophageal reflux disease	37 (11)	1765 (14)	.067
OSAS	60 (17)	2523 (20)	.182
Osteoarthritis	234 (67)	6126 (49)	<.001*
Preoperative weight (kg, ±SD)	123.7±18.6	122.6±17.9	.278
Preoperative BMI, no. (%)			.095
<40 kg/m^2	64 (18)	2479 (20)	
40-49 kg/m^2	238 (68)	8839 (70)	
≥50 kg/m^2	49 (14)	1313 (10)	
Laparoscopic, no. (%)	351 (100.0)	12613 (99.9)	.479
Length of biliopancreatic limb, no. (%) [1]			<.001*
≤60 cm	145 (94)	3293 (30)	
61-75 cm	9 (6)	2887 (26)	
76-100 cm	1 (0)	2153 (19)	
≥101 cm	0 (0)	2797 (25)	
Length of alimentary limb, no. (%)[2]			<.001*
≤120 cm	153 (99)	3680 (32)	
121-150 cm	1 (.5)	7606 (65)	
≥151 cm	1 (.5)	315 (3)	
Length of hospital stay, no. (%)			<.001*
0-1 days	314 (90)	8025 (63)	
2 days	26 (7)	3777 (30)	
≥3 days	11 (3)	829 (7)	

Data presented as number (%), mean (standard deviation). *p <.05
[1] Due to missing values, banded RYGB group n= 11130, non-banded RYGB group n= 155.
[2] Due to missing values, banded RYGB group n= 11601, non-banded RYGB group n= 155.
List of abbreviations: BMI= Body Mass Index; OSAS= Obstructive Sleep Apnea Syndrome; RYGB, Roux-en-Y Gastric Bypass; SD = Standard Deviation.

The rate of non-response was significantly lower in the banded RYGB group (12.5% vs. 17.7%, p= 0.012). In addition, the rate of response was significantly higher in this group (99.4% vs. 96.3%, p= 0.002). A change in cutoff in TWL meaning 15% instead of 20% revealed similar results (non-response 12.5% vs. 18.6%; response 100.0% vs. 99.1%) suggesting robustness of

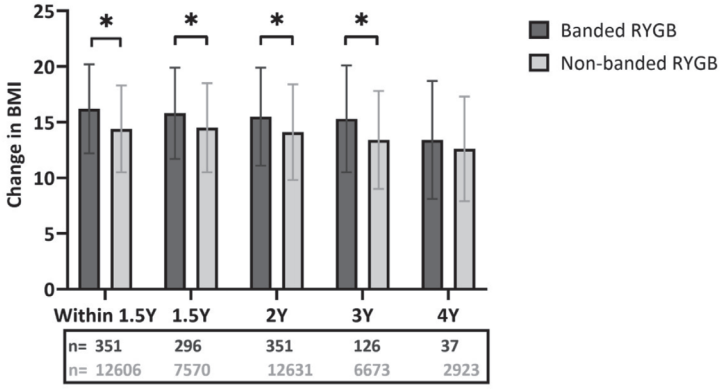
this data. Statistical significant differences in %TWL and change in BMI, in favor of the banded RYGB group, were found up to 3 years after surgery (Figure 1 and Additional File 1). When expressed in %EWL, comparable results were found (Additional File 2). Subgroup analysis demonstrated that in patients with a BMI over ≥50 kg/m^2 (n= 1039, banded RYGB group n= 33; non-banded RYGB group n= 1006) the incidence of non-response tended to be lower in the banded RYGB group, although this lacked statistical significance (6.1% vs 15.7%, p= 0.131).

Figure 1. Total weight loss (%) in banded RYGB and non-banded RYGB



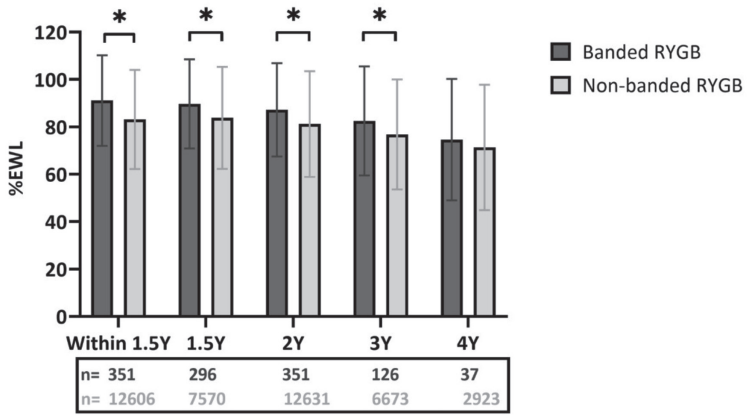
Abbreviations: TWL, total weight loss; RYGB, Roux-en-Y gastric bypass; Y, years. n is amount of patients included in the analysis.*p <.001

Additional file 1. Change in BMI (kg/m^2) in banded RYGB and non-banded RYGB



Abbreviations: BMI, body mass index; RYGB, Roux-en-Y gastric bypass; Y, years. n is amount of patients included in the analysis.*p <.001

Additional file 2. Excess weight loss (%) in banded RYGB and non-banded RYGB



Abbreviations: EWL, excess weight loss; RYGB, Roux-en-Y gastric bypass; Y, years. n is amount of patients included in the analysis.*p <.05

The results of the univariate and multivariate analyses are displayed in Table 2. Univariate analysis showed that the surgical technique (i.e. banding versus non banding) was significantly associated with non-response (OR 0.67; 95% CI 0.49-0.92). In the multivariate analysis, the banded RYGB was associated with a decreased risk of non-response (OR 0.26; 95% CI 0.12-0.54), while male gender, having preoperative hypertension or T2D, and a longer alimentary limb were associated with an increased risk of non-response (OR 1.33, OR 1.18, OR 1.29 and OR 1.86, respectively). On the contrary, having preoperative GERD, a higher age, and a longer biliopancreatic limb were associated with a decreased risk of non-response (OR 0.70, OR 0.69 and OR 0.78, respectively). When we included the interaction variables age and gender in the model, there was a significant interaction between age and surgical technique (OR 0.14-0.32). Additional analysis showed however, that non-response was not significantly affected by surgical technique in the different age groups (OR 0.25-0.55).

Table 2. Results of univariate and multivariate logistic regression of variables associated with non-response after RYGB

	Unadjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Surgical technique (ref= non-banded RYGB)	.67	.49-.92	.013#	.26	.12-.54	<.001*
Gender (ref= female)	1.37	1.22-1.52	<.001#	1.33	1.17-1.51	<.001*
Age at surgery (years)						
18-35 (ref)						
36-45	1.02	.89-1.17	.711	1.01	.87-1.17	.906
46-55	.95	.84-1.08	.401	.84	.73-.98	.026*
56-65	.81	.69-.94	.006#	.69	.57-.83	<.001*
Preoperative BMI (kg/m^2)						
<40 (ref)						
40-49	1.01	.90-1.13	.861			
≥50	.88	.74-1.05	.162			
Preoperative hypertension (ref= no)	1.13	1.03-1.24	.012#	1.18	1.05-1.32	.005*
Preoperative type 2 diabetes (ref= no)	1.32	1.19-1.46	<.001#	1.29	1.14-1.46	<.001*
Preoperative hyperlipidaemia (ref= no)	1.02	.91-1.13	.784			
Preoperative GERD (ref= no)	.67	.58-.77	<.001#	.70	.60-.82	<.001*
Preoperative OSAS (ref=no)	1.14	1.02-1.27	.021#	1.02	.89-1.17	.767
Preoperative osteoarthritis (ref= no)	.89	.82-.98	.015#	.95	.85-1.05	.292
Length of biliopancreatic limb (cm)						
≤60 (ref)						
61-75	.99	.88-1.12	.902	.94	.82-1.07	.346
76-100	.62	.53-.72	<.001#	.57	.49-.67	<.001*
≥101	.65	.57-.75	<.001#	.78	.64-.96	.017*
Length of alimentary limb (cm)						
≤120 (ref)						
121-150	1.39	1.25-1.54	<.001#	1.26	1.05-1.52	.012*
≥151	1.53	1.15-2.03	.003#	1.86	1.34-2.62	<.001*
Length of hospital stay (days)						
0-1 (ref)						
2	1.14	1.03-1.26	.009#	1.02	.91-1.15	.692
≥3	1.15	.96-1.38	.125	1.01	.82-1.23	.955
Complication by clavien dindo classification (yes)	1.13	.98-1.29	.104			

Dependent variable:% non-response. #p value is below the threshold of <0.1, therefore this variable is included in the multivariate analysis. *p value is below the threshold of <.05. Abbreviations: CI= confidence interval, GERD= gastroesophageal reflux disease, OSAS= obstructive sleep apnea syndrome, OR= odds ratio, ref= reference.

Postoperative complications are shown in Table 3. A total of 325 patients (2.5%) were readmitted within 30 days after surgery and this number did not statistically differ between the groups (banded RYGB 4.0% vs. RYGB 2.5%. p= 0.071). The most common short-term complications were classified CD grade III and were equally distributed (2.0% vs. 1.6%, p= 0.536). Aside from vomiting, there were no significant differences in the type of complication (e.g. major bleeding and anastomotic leakages) between both groups. The number of patients with a band-related complication was 0.6% (n=2), including one patient with an infection and one with an erosion. Unfortunately, it is unknown in which exact time period these complications occurred and what the type of treatment was.

Table 4 displays the effect of banded RYGB and non-banded RYGB on the progression of obesity related comorbidities. Because the status of comorbidity at 3 and 4 years was frequently missing, this outcome was expressed 1.5-2 years after surgery. In the non-banded RYGB group, there was a significant better resolution of hypertension, GERD and osteoarthritis. There were no significant differences in deteriorated and de novo developed comorbidities between the two groups.

Table 3. Complications after banded RYGB and non-banded RYGB

	Banded RYGB n= 351	**Non-banded RYGB n= 12631**	**p-value**
Number of readmission (<30 days), no. (%)	14 (4.0)	311 (2.5)	.071
Postoperative complications <30 days, no. (%)			
CD grade I	-	60 (.5)	.196
CD grade II	-	46 (.4)	.257
CD grade III	7 (2.0)	199 (1.6)	.536
CD grade IV	1 (.3)	72 (.6)	.481
Type of complications <30 days, no. (%)			
Major bleed	2 (.6)	163 (1.3)	.234
Anastomotic leakage	3 (.9)	53 (.4)	.220
Intra-abdominal abscess	1 (.3)	18 (.1)	.491
Wound infection	1 (.3)	13 (.1)	.306
Stoma ulceration	-	3 (.0)	.773
Vomiting	2 (.6)	19 (.2)	.054
Postoperative complications ≥30 days , no. (%)			
Marginal ulcer	1 (.3)	23 (.2)	.658
Anastomotic stricture	1 (.3)	14 (.1)	.344
Early dumping syndrome	-	3 (.0)	.773
Late dumping syndrome	-	17 (.1)	.492
Bowel obstruction	-	22 (.2)	.434
Gall stone formation	1 (.3)	197 (1.6)	.055
Internal herniation	5 (1.4)	371 (2.9)	.096
Band erosion	1 (.3)	na	na
Band infection	1 (.3)	na	na
Band slippage	-	na	na

List of abbreviations: CD, Clavien-Dindo; NA, not applicable; RYGB, Roux-en-Y Gastric Bypass. *p <.05

Table 4. Progression of obesity-related comorbidities between banded RYGB and non-banded RYGB

	Banded RYGB 1.5-2 years follow-up						Non-banded RYGB 1.5-2 years follow-up					
	no.[1]	Resolved no. (%)[2]	Improved no. (%)[2]	Unchanged no. (%)[2]	Deteriorated no. (%)[2]	De novo no. (%)[3]	no.[1]	Resolved no. (%)[2]	Improved no. (%)[2]	Unchanged no. (%)[2]	Deteriorated no. (%)[2]	De novo no. (%)[3]
Hypertension	117/133	41.0**	19.7	38.5**	0.9	0.0	3629/4647	54.0**	24.4	20.4**	1.0	2.2
Type 2 diabetes	58/67	72.4	20.7	5.2	1.7	0.0	1871/2771	70.0	21.8	7.3	0.9	6.9
Hyperlipidaemia	58/70	48.3	12.1	37.9	0.0	0.0	1953/2720	56.4	13.7	29.5	0.4	3.8
OSAS	48/60	64.6	22.9	12.5	0.0	0.0	1669/2523	66.3	17.4	15.9	0.4	1.1
GERD	8/37	37.5**	50.0**	12.5	0.0	0.0	699/1765	73.2**	11.7**	13.9	1.0	5.4
Osteoarthritis	162/234	11.7**	50.6**	29.6	7.4	0.0	2797/6126	43.3**	27.4**	24.5	4.3	2.1

[1.] Number of patients from which comorbidity status is known at 1.5-2 years follow-up/ number of patients with preoperative comorbidity.
[2.] Based on the number of patients with preoperative comorbidity and known status at 1.5-2 years follow-up (numerator in 'no.' column).
[3.] Based on the number of patients without preoperative comorbidity and known status at 1.5-2 years follow-up.
*p value is below the threshold of .05, ** p value is below the threshold of .01. Abbreviations: GERD= gastroesophageal reflux disease, OSAS= obstructive sleep apnea syndrome.

Discussion

The results of this study show that a banded RYGB, in comparison to a non-banded RYGB, significantly improved the rates of non-response, as well as %TWL up to 3 years postoperatively. After correction for possible confounders, the odds of non-response were 0.26 times lower in the banded RYGB group. When expressing weight loss in %TWL, the finding that the banded RYGB group experienced 34.6-36.5% TWL 1.5-3 years postoperatively corroborates previous findings [12, 22]. When focusing on %EWL and change in BMI, an increase was found of 5.8-6.0 %EWL and 1.4-1.9 BMI points in the banded RYGB group versus the non-banded RYGB group 1.5-3 years postoperatively, which is also supported by previous literature [1,3,10,23]. Despite the seemingly small impact of these numbers, literature has shown that this additional weight loss may contribute to improvement in a patients' physical capacities and comorbidity status [24,25].

How banding of the RYGB leads to superior weight loss is still up for debate. Immediately after surgery, it is thought that the band controls the size of the pouch and gastroenterostomy, potentially resulting in a restrictive effect [2-3]. Furthermore, the band may increase satiety and might minimize dumping as it delays emptying of the pouch into the jejunum [26-27]. This theory is somewhat contradicted by the finding that there was no difference in dumping between the banded RYGB and non-banded RYGB group in this study cohort. Over time, it is thought that the band prevents enlargement of the pouch and stoma, thereby counteracting weight regain. At our latest follow-up, a non-significant difference in weight was found which does not strengthen this mechanism of action. Previous studies described conflicting results as Lemmens et al. found significant less weight regain in the banded RYGB group, but Zarate et al. did not [3,28]. Altogether, this highlights the need for additional studies to examine the mechanism of action of the banded RYGB more thoroughly.

The safety profile of the banded RYGB is a point of debate, in particular band-related complications. According to the two most recently published systematic reviews the incidence of general postoperative complications is not different between the banded and the non-banded RYGB [23,29]. This is confirmed by the results of this study. With respect to band-related complications, this study described no patients with slippage, one patient with an infection (0.3%) and one patient with an erosion (0.3%). The incidence of erosion is in accordance with the previously reported range of 0-7.7% [3,23,29] and furthermore, the incidence of slippage matches the numbers reported by Lemmens et al. and Shoar et al. [3,23]. The low band-related complication rate and earlier reports showing a band-removal rate of 0-2.8% within 5 years postoperatively, implicate that banding is a safe procedure [1,3,23,29].

Frequently mentioned disadvantages of the banded RYGB are food intolerance, vomiting and dysphagia [23,26]. This study only assessed vomiting and found an incidence of 0.6% in the banded RYGB group and 0.2% the non-banded RYGB group (p= 0.05). Overall, this incidence is much lower than the reported rates of 12.5-26.8% in the banded and 5.9-11.6% in the non-banded group [30-31]. This could perhaps be explained by different study designs. When comparing the two groups, systematic reviews found both higher [23] and similar rates [29] of vomiting in the banded RYGB group. This indicates that care should be given to this topic, as banding may results in more patients suffering from vomiting.

Aside from weight loss and postoperative complications, the progression of comorbidities is an important outcome in bariatric surgery. This study showed that in the banded RYGB group the resolution rate of T2D was 72.4%, for hypertension 41.0%, for OSAS 64.6% and for hyperlipidemia 48.3%. This data is similar with the remission rates described by Galal et al. and Buchwald et al. who reported rates of 74.5-84.2% for T2D, 40.8-58.0% for hypertension, 50.0-91.4% for OSAS and 39.8-59.4% for hyperlipidemia [3,12]. This study described better resolution rates of hypertension, GERD and osteoarthritis in the non-banded RYGB group. This is a remarkable finding that is counterintuitive to the difference found in weight loss. Furthermore, this finding contradicts previous studies that reported no difference in remission rate of all five comorbidities [23,29,31]. It should be noted that our findings could be influenced by a small sample size (i.e. banded RYGB group), as well as heterogeneity in the assessment of comorbidities across centers. Furthermore, when looking at previous literature, different terminology (e.g. resolution vs. remission) and time points are used, which interferes with a proper comparison between studies. Future comparative studies should focus on the progression of comorbidities and should seek to express these outcomes as accurately as possible.

There are several limitations to this study. Firstly, there is a lack of information about band circumference, band-related re-interventions, food intolerance and dysphagia. This limits the possibility to make firm conclusions about the superiority of the banded RYGB as these factors may negatively influence outcome and a patients' quality of life. Secondly, there is a low follow-up rate after 2 years. Not finding a difference in %TWL at 4 years could be due to under powering of the banded RYGB group. In addition to this, there was a sizable amount of patients (35.5%) excluded from analysis because of missing data regarding weight loss. Thirdly, the follow-up period of this study was only 4 years while preferably, when evaluating weight regain this is 5 to 10 years. Fourthly, one center contributed to 98.8% of the banded bypass cases which may have influenced the results. Lastly, it should be acknowledged that there are limitations associated with the use of a nationwide database as it depends on others for accurate recordkeeping (e.g. comorbidity resolution and band-related complication).

Conclusion

To our knowledge, this is the first population-based study that compared weight loss outcomes, as well as comorbidities, in banded and non-banded RYGB patients. The primary banded RYGB improved weight loss outcomes up to 3 years post-surgery. Because the usage of a nationwide database entails certain limitations, it remains uncertain whether the banded RYGB should be routinely performed instead of the non-banded RYGB. It is desired to perform prospective randomized studies preferably looking at weight loss outcomes, progression of comorbidities, food intolerances and quality of life.

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PART III

Optimizing weight loss prior to bariatric surgery

CHAPTER 09

Current preoperative strategies applied in the Dutch bariatric centers: A national survey

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Abstract

Introduction: there is no consensus about the optimal management of patients undergoing bariatric surgery. This study aimed to identify current weight loss goals prior to bariatric surgery, as well as aimed to explore preoperative strategies related to diet, nutritional supplements and physical activity.

Methods: an online survey was distributed among bariatric surgeons and dietitians in all 18 Dutch bariatric centers. This survey included the following four domains: weight loss, diet, nutritional supplements and physical activity. For the analyses one answer per center was used, either the most common answer or the answer given by the most expert responder.

Results: all 18 centers reported at least one response. Preoperative weight loss was requested in 28% of the centers, whereas 61% desired a stable weight or weight loss, and 11% had no requests. A preoperative diet was routinely recommended in 78% of the centers and on indication (i.e., depending on baseline weight and/or comorbidity status) in 22%. The most frequently prescribed diet was a low-energy diet (800-1500 kcal/day) in 44% of the centers. Nutritional supplements were recommended in 78% of the centers. Physical activity with low intensity was recommended in 83% of the centers, while physical exercise training with mid- to high-intensity was recommended in 72%. Inconsistent responses within centers were observed in 56% of the questions.

Conclusion: the current bariatric practice within the Netherlands shows high variability and inconsistencies in preoperative management. Consensus-building and standardization of strategies should be promoted in the future.

Abbreviations: ASMBS, American Society for Metabolic and Bariatric Surgery; DSMBS, Dutch Society of Metabolic and Bariatric Surgery; LED, low-energy diet; NDBC, Netwerk Diëtisten Bariatrische Chirurgie (in English: Society of Dietitians in Bariatric Surgery); VLED, very low-energy diet.

Introduction

Bariatric surgery is considered the most effective treatment for severe Obesity [1,2]. Over the past years, approximately 11 500 bariatric procedures have been performed annually in the Netherlands [3]. These procedures are considered safe as only 2.8% of the patients develops a major complication within 30 days after primary surgery [4]. Due to an altered anatomy in patients with morbid obesity, bariatric surgery can be technically challenging. These challenges are related to abdominal wall thickness, increased visceral adiposity and the presence of an enlarged liver reducing intra-abdominal space [4,5]. This may increase the difficulty of the surgical procedure. In order to overcome these challenges, it is conducive that a patients' liver volume and weight are preoperatively lowered [5-7].

Key aspects of preoperative strategies can be listed into energy restricted diets and physical activity. In terms of energy-restricted diets, both very low-energy diets (VLED, <800 kcal/day) and low energy diets (LED, 800-1500 kcal/day) are considered to be effective [5-7] Systematic reviews reported a reduction in liver size (5%-20% VLED; 12-27% LED) [5,7,8] intrahepatic fat (43% VLED; 40%-51% LED) [7,9,10] and body weight (2.8-14.8 kg VLED; 5.4-23.6 kg LED) [5,7,8]. Regardless of the selected dietary strategy it is recommended to assess and, if necessary, supplement micronutrients (e.g., iron, zinc, calcium, folic acid, vitamin D and B12) as this may improve overall health [11]. In terms of physical activity, a variety of exercise programs have shown to be beneficial in the preoperative phase. These programs last 1 to 24 weeks and consist of at least partially supervised trainings, with an intensity of 65% VO2 max and 55% to 85% peak heart rate [12]. These exercise programs reduce weight (4.1-5.0 kg) with possible maintenance of lean body mass, as well as improve cardiometabolic risk factors and physical fitness [11,12]. The exact effect of these exercise programs on liver volume is unknown, nonetheless it has shown to be effective in improving fatty liver disease [13].

According to the American Society for Metabolic and Bariatric Surgery (ASMBS) in 2016, there is no level A evidence about the most optimal type of preoperative weight loss program (i.e., dietary or exercise strategies) and neither about the content and duration of this program [14]. A high variability in preoperative work up has since then been described in multiple countries [15-17], yet it is unknown if and how this applies in the Dutch bariatric centers. The primary aim of this study was to identify variations in current weight loss goals prior to bariatric surgery.

Methods

Study population

In the Netherlands, bariatric surgery is performed in 18 centers and these centers can only be certified if at least 200 bariatric procedures are performed each year [4]. Centers performing bariatric surgery can be described as non-academic teaching hospitals and non-academic nonteaching hospitals. A survey study was performed among professionals in all Dutch bariatric centers. Bariatric surgeons, surgical residents, physician assistants and nurse practitioners of the Dutch Society of Metabolic and Bariatric Surgery (DSMBS) were invited to participate in an online survey. Dietitians specialized in bariatric care affiliated with the Society of Dietitians in Bariatric Surgery (Network Dietitians Bariatric Surgery, NDBC) were invited as well. Both societies contacted their members by email in April/May 2020. In this email, the content of the study and a weblink to the survey were provided. Centers with no dietitians associated to the NDBC were contacted separately by email. Only surveys that were completed for >80% were included in this study. We aimed to include at least one respondent, either a bariatric surgeon or a dietitian, per center.

Study parameters

The primary study outcome was the variability in preoperative strategies related to weight loss goals in the 18 Dutch bariatric centers. The secondary outcome was the applied strategies in terms of diet, nutritional supplements and physical activity. Dietary advice was listed into composition-, duration- and consistency of the diet, as well as the number of eating moments per day and fluid intake. Nutritional supplements were listed into multivitamin, calcium and vitamin D, protein and probiotics. Physical activity was classified into low-intense activity and moderate- to high-intense activity (i.e., exercise training). If possible, information about the type, frequency, duration and facilitated supervision of physical activity was collected. Other outcomes involved substantiation and experience with the preoperative strategy, as well as the level of inconsistency in responses within a center.

Survey

A web-based survey was designed by two researchers (A.K., M.R.), one bariatric surgeon (F.D.) and one dietitian specialized in bariatric care. The survey was developed based on prior studies [15-17] and was administered using Qualtrics electronic survey software [18]. Survey replies were registered anonymously; however, the type of center and profession were asked. The survey consisted of 60 questions, but the actual survey length could vary between 9 and 60 questions since display and skip logic was included to benefit survey flow. The survey contained

the following four domains: preoperative weight loss (2-3 questions), diet (1-21 questions), supplement use (1-24 questions) and physical activity (2-9 questions). Questions were mainly designed as multiple-choice (28 questions). Open questions or text entry boxes were inserted to obtain additional information (29 open questions, 8 text entry boxes). Other question designs included a slider (2 questions) and "pick and rank" order question (2 questions). The survey was conducted in Dutch. In order to increase international understanding of this article, the survey was translated to English (supporting information).

Data analysis

The Statistical Package for the Social Sciences for Windows (version 22.0; IBM SPSS Inc, Chicago, Illinois) was used for descriptive data analysis [19]. Categorical data were expressed in numbers and percentages. Continuous data were expressed in mean (SD, range) or median (range) depending on data distribution. Names of the centers were removed and substituted by a random code between 1 and [18,20]. To obtain one protocol per center, answers from different respondents within the same center were combined by two researchers (A.K., D.H.) and crosschecked by a third researcher (M.R.). In case of nominal variables (yes/no/I do not know), the answer "I do not know" was neglected and the most frequent response was used for the combined protocol. In case of continuous variables, a mean was calculated and used as a final result. In case of ordinal variables, one ranking was made based on the most chosen answer at the most frequent position. When considering multiple-choice questions, the answers that were provided by at least half of the respondents were used for the combined protocol. By equal responses, the bariatric surgeon's answer was leading in weight goal questions and the dietitian's answer in diet and nutritional supplements questions. The level of inconsistency was identified for all four domains and an overall score was calculated. If at least one response was different compared to other responses within a center, this was classified as inconsistent. A median of inconsistency was calculated by expressing the amount of different responses as a percentage to the total amount of responses.

Results

Within an eight-week inclusion period, bariatric surgeons and dietitians from all 18 bariatric centers in the Netherlands responded to the survey. There was one center with a response from a bariatric surgeon that did not reach the 80% completion rate, therefore this response was excluded. Yet, this center was included in the analysis because the dietitian responded adequately. From the 78 responses, 59 responses were included in the analysis (Figure 1). Main reasons for exclusion were respondents working in a setting other than in a bariatric center

(n = 5), respondents working in a field other than bariatric surgery (n = 2) and respondents who were currently unemployed (n = 1). In 11 centers the overall preoperative protocol was implemented for over 5 years, in 4 centers more than 3 years, in 2 centers 1 year and in 1 center less than 1 year.

Weight loss goal

Preoperative weight loss was requested in 5 (28%) centers, while patients had to remain stable on their weight or lose weight in 11 (61%) centers. Two (11%) centers did not set any weight loss goals (Table 1). In case centers requested a specific weight loss (44%, n = 8), it was usually between 3 to 10 kg and/or 5% to 10% of total weight loss. In 7 (39%) centers, surgery would be cancelled or postponed if the desired weight was not obtained (Figure 2).

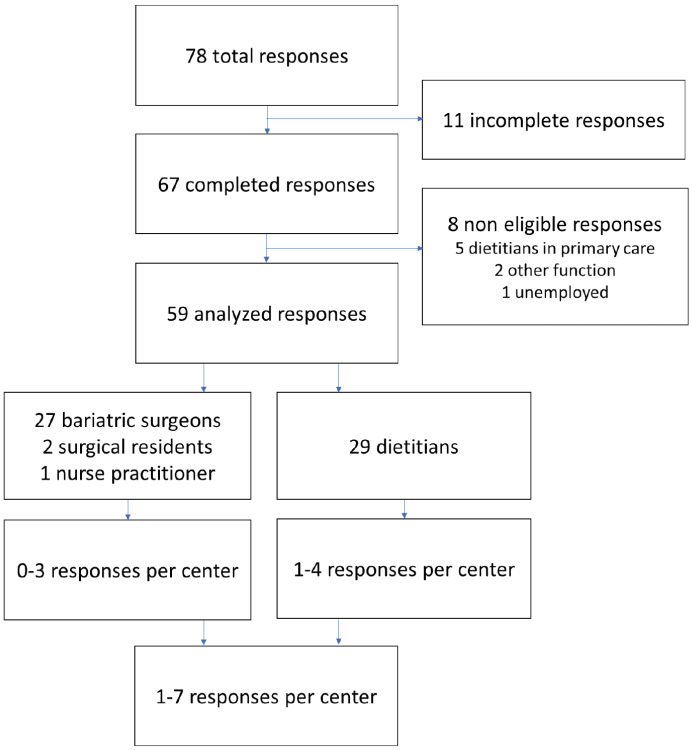

Figure 1. Flowchart of the study inclusion

Table 1. Overview of preoperative recommendations given by 18 bariatric centers

Overview of preoperative recommendations	Number of centers	Percentage
Weight loss		
Lose weight	5	28%
Remain stable or lose weight	11	61%
Weight does not matter, may even gain weight	2	11%
Dietary prescription		
Yes	14	78%
No	0	0%
On indication	4	22%
Use of nutritional supplements		
Yes	14	78%
No	3	17%
Unknown	1	6%
Increase of physical activity		
Yes	15	83%
No	3	17%
Unknown	0	0%

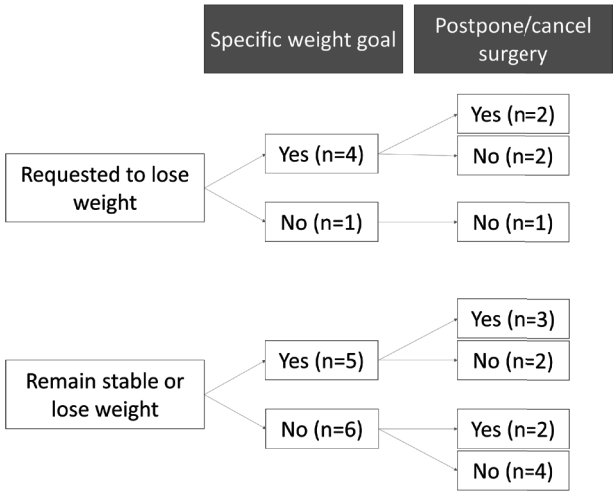

Figure 2. Flowchart of weight loss goals and postponement of surgery in 16 bariatric centers

Dietary recommendations

A specific diet was routinely recommended in 14 (78%) centers, while in 4 (22%) centers this was done only on indication (Table 1). The recommended diet contained between 500 and 1500 kcal per day in 12 centers, with 8 (44%) of the centers recommending an LED and 4 (22%) a VLED (Figure 3). In 4 centers, the amount of kcal/day was unknown, while in 2 centers the energy intake of the corresponding diet was tailored to the individual patient. The duration of the diet ranged between 1.5 and 7.5 weeks, with a median of 2 weeks. In 2 centers, the duration of the diet depended on baseline body mass index. The most important goal of the recommended diet was liver volume reduction (60%, n = 11), followed by reduction of complications (17%, n = 3) and preparation of patients for post-surgery eating habits (11%, n = 2; Supplementary Figure 1, supporting information).

All 11 centers that recommended full or partial liquid meal replacements allowed patients to consume regular products next to the recommended diet. These products included raw vegetables in 11 (100%) centers, clear soups in 10 (91%) centers, steamed/boiled vegetables in 6 (55%) centers and dairy products in 5 (46%) centers. Eight centers (44%) recommended a protein intake between 51 and 95 g per day, carbohydrate intake between 30 and 127 g per day and fat intake between 3 and 28 g per day; of the other centers, macronutrient composition of the diet was unknown. Recommendations regarding fluid intake were given in 16 centers and ranged between 1.5 and 4.0 liters per day, with most of the centers recommending patients to consume 1.5 to 2.0 liters per day. The number of eating moments ranged between four and six times per day. Compliance with the recommended diet was estimated between 75% and 100% by 13 centers. The dietary protocol was based on clinical experience in 16 (89%) centers, on scientific evidence in 10 (56%) centers and on guidelines in 9 (50%) centers.

Nutritional supplement recommendations

Nutritional supplements were recommended in 14 (78%) centers, while 3 (17%) centers did not recommend these supplements (Table 1). Multivitamin supplements were routinely recommended in 10 (59%) centers, while 2 (12%) centers recommended multivitamin supplements only on indication (e.g., deficiency). The multivitamin supplementation was generally recommended between 2 and 4 weeks before surgery and the type and dose depended on the type of surgery. As shown in Table 2, calcium and vitamin D supplementation was recommended routinely by 2 (12%) centers and most of the centers (82%, n = 14) did not recommend protein supplementation.

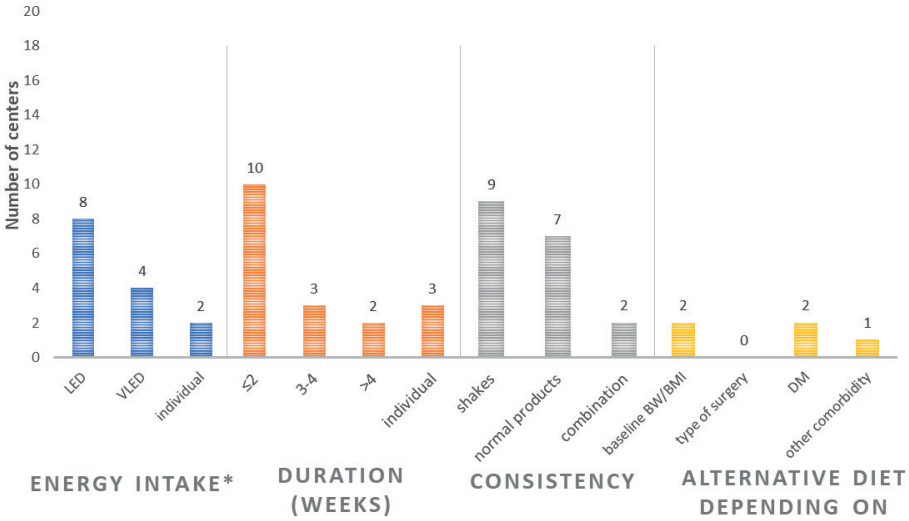

Figure 3. Characteristics of the diets, recommended in the preoperative phase by 18 bariatric centers
Abbreviations: LED = low energy diet, VLED = very low energy diet, BW = body weight, BMI = body mass index, DM = diabetes mellitus. *In 4 centers, the amount of kcal/day was unknown.

Table 2. Overview of nutritional supplements recommended in preoperative phase by 17 bariatric centers

Overview of nutritional supplements	Number of centers	Percentage
Multivitamin		
Yes	10	59%
No	5	29%
On indication	2	12%
Calcium and Vitamin D		
Yes	2	12%
No	5	29%
On indication	10	59%
Proteins		
Yes	0	0%
No	14	82%
On indication	3	18%
Probiotics		
Yes	0	0%
No	16	94%
On indication	1	6%

Physical activity recommendations

Any form of physical activity (i.e. low intensity) was recommended in 15 (83%) centers (Table 1), while actual physical exercise training (moderate- to high-intensity) was recommended in 13 (72%) centers. Three centers (17%) facilitated supervised physical exercise training to all patients, while 2 centers (11%) facilitated this only on indication (e.g. patients with low aerobic fitness). Four centers recommended patients to adhere to the Dutch Physical Activity Guidelines [21]. The type, frequency and duration of physical activity being recommended was frequently unknown. The main goals of the centers that recommended physical activity were behavioural change (63%, n = 10) and improving overall physical fitness (38%, n = 6).

Inconsistencies within centers

Over half of the questions (56%), reflecting the four domains, were answered inconsistently by respondents within the same center. The greatest inconsistency was found in the domain of nutritional supplements (65%) followed by weight loss goals (59%) and physical activity (59%) (Figure 4). Respondents of only 1 center provided no inconsistent answers, while in 12 (71%) centers the respondents answered 50% to 100% of the questions inconsistent. The median of inconsistent answers within a center was 25%.

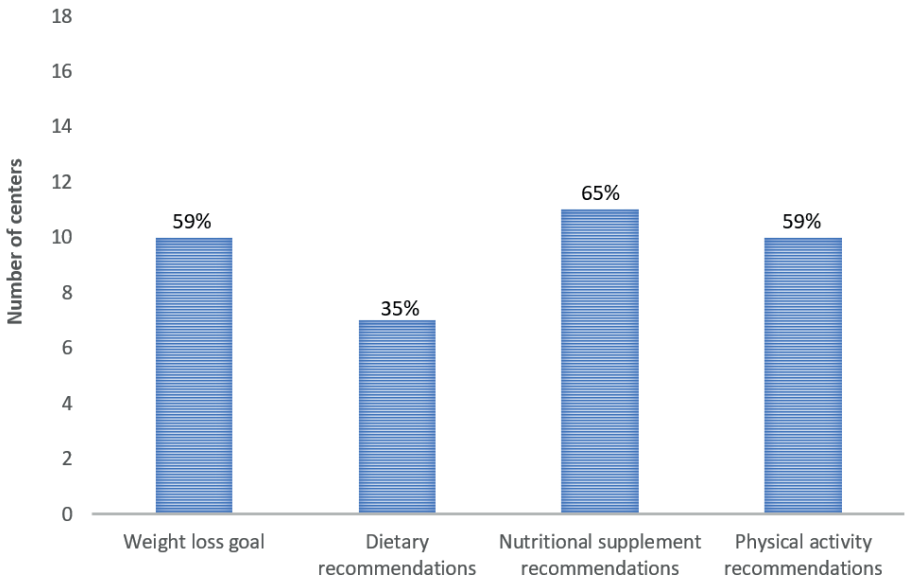

Figure 4. Overview of inconsistent answers from respondents based on the four domains

Discussion

This study aimed to identify current weight loss goals prior to bariatric surgery in the Dutch bariatric practices, as well as to explore current preoperative strategies related to diet, nutritional supplement and physical activity. The most obvious finding that emerged from this study was the large variation in applied strategies and inconsistencies in responses within centers. These inconsistencies were described in 56% of all questions and covered all domains. This implicates that centers need to collaborate in multidisciplinary teams in order to align their preoperative protocols.

With respect to preoperative weight loss, the majority (72%) of the centers did not request weight loss. The absolute necessity for preoperative weight loss is arguable and based on recently updated Dutch guidelines, surgery should be performed irrespective of preoperative weight loss [22]. Preoperative weight loss has been associated with a decreased liver volume and a decreased surgical complexity, but inconsistent data has been found for short-term outcomes like complication rate and hospital stay [14,23]. Furthermore, there is no evidence that long-term outcomes are improved by better preoperative weight loss [14]. These findings likely explain the variety found in weight loss goals.

Preoperative dietary regimes greatly differ per country [15-17]. This study identified that particularly in the Netherlands, an LED was the most commonly prescribed diet while for example, Australia seemed to prefer VLEDs [17]. Both diets have shown to be effective in reducing liver volume [5,7]; however, an LED might be advantageous as it avoids unnecessary energy restriction and may improve dietary compliance. This study identified that the median duration of the diet was 2 weeks. This duration seems to be sufficient as researchers found that 80% to 100% of liver volume reduction occurred within the first 2 weeks of dieting [9,24].

Centers reported limited and diverse recommendations regarding nutritional supplements, whilst there is a proven high prevalence of micronutrient deficiencies in bariatric candidates [25,26]. These deficiencies negatively affect the patient's health as it may result in anaemia, peripheral neuropathy, osteoporosis and bleeding disorders [25,26]. Despite these risks, this study as well as prior studies reported that nutritional supplementation is frequently omitted in the preoperative phase [15,16]. In this study, calcium and vitamin D supplementation was not recommended in five centers (29%). This does not entirely match the position of the ASMBS recommending to perform a nutritional assessment in all patients prior to bariatric surgery, and to anticipate on any deficiencies [27]. The Dutch guideline has not taken a position on this point [22] making it plausible that preoperative nutritional assessments and subsequent regimes have varied across centers.

It is well known that physical activity is beneficial for improving overall fitness and health. In the field of bariatric surgery, structured preoperative physical exercise training including aerobic and strength training for 3 times a week for 12 weeks, is associated with a greater decrease in body mass index postoperatively, and is effective in increasing physical fitness 1 year after surgery [28]. The current survey showed that 83% of the centers recommended patients to increase their low-intense physical activities, while only 72% recommended patients to increase their moderate- to high-intense activities. An implication of these findings is that more centers recognize the advantages of moderate- to high-intense activities preoperatively and recommend patients to perform these activities.

Since this survey used a non-validated questionnaire, the questions could be interpreted slightly different by the respondents than anticipated by the researchers. Moreover, the assessment of physical activity was limited since physical therapists were not invited as respondents. Notwithstanding these limitations, the study had a response from every Dutch bariatric center and offers valuable insights into the commonly used preoperative strategies. It would be interesting to understand the impact of the different preoperative strategies on clinical outcomes like complications, weight loss and comorbidity resolution. This information was not available in this study, but would be recommended in future research.

Conclusion

This study indicates that there is a high variability in preoperative care in the Dutch bariatric centers and reveals large inconsistencies between respondents within the same center. Alignment of local protocols should be a priority for multidisciplinary teams. Well-designed studies are warranted as they can contribute to the development of (intern)national guidelines and may build upon consensus about the best preoperative strategy.

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CHAPTER 10

Effectiveness of a Low-Calorie Diet for Liver Volume Reduction Prior to Bariatric Surgery: a Systematic Review

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Abstract

Introduction: an energy-restricted diet is often prescribed before bariatric surgery to reduce weight and liver volume. While very low- calorie diets (VLCDs, 450–800 kcal per day) have shown to be effective, the effectiveness of low-calorie diets (LCDs, 800–1500 kcal per day) is less obvious. The objective of this systematic review was to elucidate the effectiveness of LCD on liver volume reduction in patients awaiting bariatric surgery.

Methods: an electronic search of PubMed, EMBASE and the Cochrane Library was conducted. Studies were included if an LCD of 800 up to 1500 kcal/day was prescribed in patients selected for bariatric surgery, and liver volume was assessed. The primary outcome was reduction in liver volume and secondary outcomes were differences in weight and body composition, tolerance and acceptability of the diet, surgical complexity, complications and biochemical- and clinical parameters.

Results: eight studies (n=251) were included describing nine different diets (800-1200 kcal/day, 2-8 weeks). All studies demonstrated that an LCD was effective in liver volume reduction (12-27%) and weight loss (4-17%). The largest decrease in liver volume was observed when the diet lasted for two to four weeks. From the overall weight loss, the lean body mass accounted for 23%-60%. An LCD showed a high compliance rate (80-89%) and seemed well tolerated by patients.

Conclusion: this study shows that an LCD is effective in liver volume reduction, particularly during the first weeks. An LCD should be the preferred diet instead of a VLCD because unnecessary excessive dietary restriction and subsequent downsides may be countered.

Abbreviations: BMI, Body mass index; LBM, Lean body mass; LCD, Low-calorie diet; NAFLD, Nonalcoholic fatty liver disease; RCT, Randomized controlled trial; TWL, Total weight loss; VLCD, Very-low-calorie diet.

Introduction

Bariatric surgery is considered the most effective treatment for severe obesity as it promotes long-term weight loss and reduces or controls obesity-related comorbidities [1]. The incidence of short-term life-threatening complications is considered relatively low (1–5% for anastomotic leakage and bleeding) [2,3] but depends on the patients' comorbidities and technical difficulties that are encountered during surgery. In obese patients, technical difficulties are related to increased abdominal wall thickness, increased visceral adiposity and the presence of an enlarged liver. All these factors may contribute to reduced intra-abdominal space, reduced freedom of surgical movement and limited exposure of the gastric cardia, making the surgery technically more challenging and potentially resulting in complications [4,5]. Up to 90% of candidates for bariatric surgery have nonalcoholic fatty liver disease (NAFLD) characterized by an enlarged and fatty liver [6]. An enlarged left liver lobe complicates the approach to the gastroesophageal junction and results in an increased risk of bleeding upon surgical manipulation since the NAFLD liver is more vulnerable [5].

For these reasons, it is imperative that a patient lowers weight and liver volume prior to bariatric surgery. In order to do so, an energy-restricted diet is routinely prescribed. There is however a lack of consensus regarding the optimal composition of this diet. A very-low-calorie diet (VLCD) and a low-calorie diet (LCD) are both popular hypocaloric diets that are widely advised [5,7,8]. A VLCD is generally defined as an intake of 450– 800 kcal per day, while an LCD implies 800– 1500 kcal per day [9,10]. The duration of very-low calorie diets (VLCDs) varies between 10 and 63 days, and the consistency varies between exclusively liquid meal replacements or a combination of liquid meal replacement and food meals [4,5,10]. In 2017, a systematic review showed that a VLCD was effective in liver volume reduction (5–20%, mean 14%) [10]. Several studies indicate that an LCD may also be effective [10–12], but a similar systematic review has not been performed yet.

When prescribing a VLCD and LCD, there are potential risks that need to be considered. One of the two prevailing risks is that the diet may turn the body into a catabolic state leading to lean body mass (LBM) loss [13]. A decreased LBM could negatively impact energy balance, functional capacity and cardiovascular health [14,15], which may impede recovery after bariatric surgery [16]. Secondly, the patient may experience symptoms related to the catabolic state like fatigue, headache and nausea compromising the compliance and acceptability of the diet [17]. How these risks relate to the level of dietary restriction is unclear, but it is intuitive that the risks are larger in a higher degree of caloric restriction. This leads to a substantial doubt as to whether a VLCD should be the preferable diet.

The purpose of this systematic review was to evaluate the literature on the effect of an LCD on liver volume reduction in patients awaiting bariatric surgery. If an LCD would result in sufficient liver volume reduction, this diet could be a preferable alternative for the commonly prescribed VLCD [7].

Methods

This review complies with the recommendations of the Cochrane Handbook for Systematic Reviews and Interventions [18] and was recorded according to the PRISMA systematic review guidelines [19]. The review was registered at PROSPERO as registration number CRD42020176838.

Systematic Literature Search

The systematic search was conducted on February 13, 2020, and was performed in three online databases: MEDLINE (PubMed Legacy), EMBASE (Ovid), and The Cochrane Library. The search was restricted to articles published in English and Dutch. There was no restriction regarding the date of publication. Keywords in the search strategy included [low calorie diet] and [bariatric surgery] and their synonyms. The full search strategies for all databases can be found in Supplementary Table 1 (supporting information). Reference lists of identified articles were manually screened to retrieve articles that might have been missed. The authors were contacted by email if no full text was available online.

Eligibility Criteria

This review included randomized controlled trials (RCTs) and observational studies. Inclusion criteria were (1) prescription of low-calorie diets (LCDs) containing 800 to 1500 kcal/day with a duration of at least 5 days and up to 3 months, (2) patients with a BMI $\geq$35 kg/m^2 and selected for bariatric surgery, (3) assessment of liver volume by magnetic resonance imaging (MRI), computed tomography (CT) or ultrasound, and (4) caloric intake obtained from standardized meals or more than 75% from prescribed meals with dietary compliance controlled by urinary ketone. Food-based self-selection or energy prediction based on food recalls was excluded. Articles were excluded if they were designed as animal studies or as reviews, letters to the editor and conference abstracts.

Study Selection

Database searches were imported into Endnote X9 to manage references and support identification of duplicates. Titles and abstracts were screened on relevance. Full texts were obtained for clarification of eligibility criteria. Excluded studies and the reason for exclusion were recorded.

Data Extraction

Data abstraction was performed by two reviewers (A.K., M.R.) who used pre-defined forms for the following study characteristics: authors' names, publication year, country, study design, sample size, gender, mean age, mean BMI, kcal/day, duration and composition of the diet. Additionally, information about liver volume, weight, body composition, tolerance and acceptability of the diet, surgical complexity, complications and biochemical- and clinical parameters was extracted.

Outcome Parameters

The primary outcome was liver volume reduction (total or left liver lobe) by LCD prior to bariatric surgery. Secondary outcomes were differences in weight and body composition, represented in means. Additional outcomes were tolerance and acceptability of the diet, surgical complexity, complications and biochemical- and clinical parameters. Standard deviations were extracted if available. If only pre- and post-data was provided, a percentage was calculated from these data points.

Quality Appraisal

The methodological quality of the included studies was assessed using the Cochrane risk of bias tool [20] for randomized controlled trials (RCT) and a modified Methodological Quality Checklist as described by Downs and Black [21] for non-RCTs. For the Cochrane risk of bias tool, studies were classified as "high" risk of bias if two or more indications of "high" risk of bias were classified. Furthermore, studies with three or more indications of "unclear" risk of bias were classified as "moderate" risk of bias, while studies were classified as "low" risk of bias if they had four or more indications of "low" risk of bias. Downs and Black's checklist was modified to increase suitability as no control group was included in the non-RCTs. An overview can be found in Supplementary Table 2. A score of 25–27 points was considered excellent, 19–24 was considered good, 14–18 was considered fair and ≤13 was classified as poor study quality. Two reviewers (A.K., M.R.) critically assessed the quality of the studies independently. Forthcoming discrepancies were resolved in accordance with both reviewers.

Results

The search retrieved a total of 2067 records. An additional manual check of reference lists resulted in the addition of one study. After removing duplicates, 1688 studies remained. After screening the titles and abstracts on relevance, 1616 of the 1688 articles were excluded. Full-text reading of the remaining 72 articles resulted in the inclusion of eight eligible studies (Figure 1).

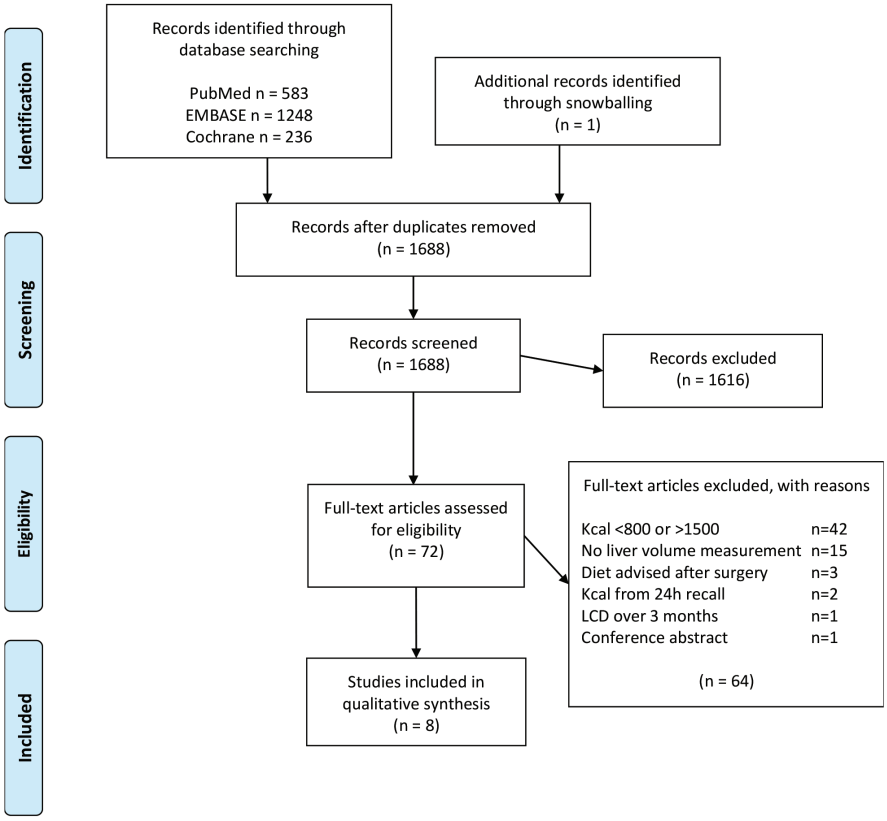

Figure 1. PRISMA flow diagram showing selection of articles

Study Characteristics

Of the eight included studies, three studies were RCTs [12,22,23] and five were observational studies [4,11,24,25,26]. One study described two LCDs; both were included in this review [12]. A total of 251 patients, with an age of 34–46 years, were included. A control group to assess liver volume was included in three studies, with two studies receiving no dietary intervention [22,24] and in one study omega 3 supplementation on top of a 2000 kcal diet [23]. Six studies assessed total liver volume [4,11,12,23,25,26], while only two studies exclusively assessed left liver lobe volume [22,24] (Table 1). Nine LCDs were included with varying dietary characteristics among eight studies. Energy intake ranged from 800 to 1200 kcal daily with heterogeneity in diet composition and consistency (Table 1). The duration of the diet ranged from two to eight weeks with a median duration of four weeks.

Quality of the Studies

Two RCT studies [22-23] scored a low risk of bias and one RCT study [12] scored a moderate risk of bias on the Cochrane risk of bias tool. All of the observational studies [4,11,24,25,26] scored a fair study quality on the Modified Methodological Quality Checklist as described by Downs and Black. Blinding of both participants and personnel, as well as external validity of subjects, lacked in most of the observational studies [4,11,24,25,26]. Blinding also lacked in one of the RCTs [12]. None of the observational studies [4,11,24,25,26] performed a power calculation based on liver volume reduction. Quality assessment of the included studies is presented in Supplementary Figure 1 (for RCTs) and Supplementary Table 2 (for observational studies) (both supporting information).

Liver Volume Reduction

Left liver lobe volume showed a decrease of 11–29% [22,23,24,25] and total liver volume showed a decrease of 12–27% with a mean of 16% [4,11,12,23,25,26]. Studies with a diet ranging between 2 and 4 weeks [11,12,22,24,26] showed a liver volume decrease of 11–23% (Table 2).

Weight Loss

Six of the eight studies reported the pre and post LCD weight [11,12,22,24,25,26]. The weight loss ranged from 5.4 to 23.6 kg, corresponding with a percentage original body weight loss ranging from 4.2 to 16.7% with a median of 6.0% (Table 2). In the diets with a duration of 2 and 4 weeks, a body weight loss of 4.2–6.5% was observed [11,12,22,24,26].

Body Composition

Four studies [12,22,25,26] assessed body composition. Three studies [12,25,26] measured body composition by bioimpedance, while one study used dual-energy X-ray absorptiometry (DEXA) [22]. LBM accounted for 22.9–59.7% of the weight loss with a median of 50.9%. This implies that 40.3–77.1% of the weight loss was fat mass.

Table 1. Summary of the study characteristics of the included studies

Year	Author	Country	Study design	Sample size (female gender)	Initial BMI (kg/m²)	Kcal per day Diet type	LCD duration (weeks)	Diet composition	Measurement Left lobe and/or total liver
2019	Bakker et al. [23]	The Netherlands	Randomized controlled trial	26 (26)	41.4 (6)	800 Modifast + food	2	unknown	MRI Left lobe & total liver
2019	Chakravartty et al. [22]	United Kingdom	Randomized controlled trial	10 (10)	53.4 (45.1-61.7)	800 Cambridge milk diet	4	82g CHO 61g PRO 30g FAT	Ultrasound Left lobe
2018	Contreras et al.* [12]	Spain	Randomized clinical trial	43 (29)	47.3 ± 5.3	800 Optifast	3	107g CHO 73g PRO 8g FAT	CT Total liver
2018	Contreras et al.* [12]	Spain	Randomized clinical trial	41 (34)	47.2 ± 5.0	1200 Food + Optifast	3	166 gr CHO 109 g PRO 12g FAT	CT Total liver
2011	Edholm et al. [11]	Sweden	Prospective observational	15 (15)	42.9 ± 3.0	800-1100 Modifast	4	124g CHO 59g PRO 22g FAT	MRI Total liver
2015	Edholm et al. [26]	Sweden	Prospective observational	10 (10)	41.7 ± 2.6	800-1100 Modifast	4	124g CHO 59g PRO 22g FAT	MRI Total liver
2020	Ekici et al. [24]	Turkey	Retrospective observational	49 (32)	45.1 ± 4.4	1000 Unknown	4	Unknown High PRO	Ultrasound Left lobe
2013	González-Pérez et al. [4]	Mexico	Prospective observational	20 (17)	46.0 ± 5.3	800 Food	6	40g CHO 68g PRO 41g FAT	CT Total liver
2015	Schiavo et al. [25]	Italy	Prospective cohort study	37 (0)	45.2 ± 4.9	1200 food	8	141g CHO 80g PRO 35g FAT	Ultrasound Left lobe & total liver

* = study included two low calorie diets. Abbreviations: LCD = low calorie diet, BMI = body mass index, MRI = magnetic resonance imaging, CT = computed tomography, CHO = carbohydrates, PRO = protein, FAT = fat, Left lobe = left liver lobe volume, Total liver = total liver volume.
Values are expressed as mean, mean ± SD or mean (CI) or mean (range-range).

Table 2. Results of liver volume reduction and changes in body weight

Author	Change in liver volume	Change in weight	Additional liver measurements
Bakker et al. [23]	Total: -12.7% LL: -11.1%	BMI: -4.6%	Surgeon scored 31% of the patients with enlarged liver and 39% had a liver that was fatty with yellow discoloration
Chakravartty et al. [22]	LL: -23% Control: -2%	TWL: -5.4% FM: 40.3% LBM: 59.7%	No change in fibrosis, shown by ARFI and APRI No difference on size left liver lobe, sharpness of liver edge, exposure of hiatus and diaphragm from control
Contreras et al. [12] 800 kcal	Total: -15.6 ± 11.2%	TWL: -5.8% FM: 53.8% LBM: 46.2%	Liver enzymes: increase in AST and ALT, and unaffected GGT
Contreras et al. [12] 1200 kcal	Total: -12.3 ± 10.6%	TWL: -4.2% FM: 49.1% LBM: 50.9%	Liver enzymes: unaffected AST and ALT, and decreased GGT
Edholm et al. [11]	Total: -12%	TWL: -6.1%	Intrahepatic fat decreased by 40% from 9.41 ± 6.17% to 5.53 ± 4.11% Surgeon's perception: decreased left lobe size and better sharpness of liver edge and exposure of hiatal region compared to controls
Edholm et al. [26]	Total: -18 ± 4%	TWL: -6.5% FM: 71.2% LBM: 28.8%	Intrahepatic fat decreased by 51 ± 16% Liver volume reduction within the first two weeks, no further change afterwards Liver enzymes: unaffected AST and ALT
Ekici et al. [24]	LL: -11.2% Control: 0.7%	TWL: -4.4%	Not assessed
González-Pérez et al. [4]	Total: -20.3%	EWL: 14.4± 5.9%	Liver volume reduction Week 0-2: -22%; Week 2-4: -13%; Week 4-6: +17%
Schiavo et al. [25]	Total: -26.9% LL: -29.1%	TWL: -16.7% FM: 77% LBM: 23%	Liver enzymes: decreased GOT and GPT, and unaffected GGT

Abbreviations: ARFI = acoustic-radiation force-impulse imaging, APRI = aspartate aminotransferase to platelet ratio index, AST = Aspartate Aminotransferase, ALT = Alanine Transaminase, BMI = body mass index, EWL = excess weight loss, FM = fat mass, GGT = Gamma glutamyl transferase, GOT =glutamic oxaloacetic transaminase, GPT = Glutamic-Pyruvic Transaminase, LBM = lean body mass, LL = left liver lobe volume, TWL = total weight loss.

Compliance and Tolerance of LCD

Six studies [4,12,23,24,25,26] recorded compliance and tolerance of the LCD. Compliance was measured in four different ways: (1) presence of ketonuria [24,26], (2) the combination of presence of ketonuria with weight loss [4,25], (3) formula sachets returned [12], and (4) unblinded patient interviews [23]. The studies reported a generally high compliance of 80–89% [4, 12, 24]. Tolerance was measured in three different ways: (1) questionnaires [4,25,26], (2) unblinded patient interviews [23], and (3) unknown assessment technique [12]. In general, the LCD was well tolerated, but some studies reported side effects like hunger, nausea, the feeling of wanting to chew, headache, diarrhea or constipation, and dizziness [4,12,23,26].

Surgical Outcomes and Complications

Mixed results on surgical complexity ratings were found. One study reported improvement of surgical complexity after LCD [11], while another study reported no change in surgical complexity [22]. Surgical duration decreased in one study [24], while two studies found no difference [11, 22]. No difference in incidence of complications was observed [12,22,23,24] (Supplementary Table 3, supporting information).

Discussion

A VLCD is known to be effective in liver volume reduction (5–20%, mean 14%) according to a previously published systematic review including 140 patients [10]. However, it also results in negative side effects due to this extreme energy restriction. This systematic review identified eight studies with nine LCDs ranging from 800 to 1200 kcal. All studies demonstrated that an LCD was effective in reducing liver volume (12–27%, mean 16%).

The largest decrease in liver volume was observed when an LCD lasted for two to four weeks. Previously, Edholm et al. demonstrated that liver volume decreased during the first two weeks with 18 ± 6.2% and no further change afterwards [11]. Moreover, Gonzales-Perez et al. measured a decrease of 32% between baseline and week four after an LCD and a much smaller decrease (17%) between week four and six [4]. These findings are confirmed by Colles et al. who demonstrated that 80% of total liver volume reduction occurred in the first two weeks [27]. This overlapping data indicates that a dietary duration of two to four weeks is sufficient to induce liver volume reduction and should be preferred in clinical practice.

In order to assess whether a VLCD should be substituted by an LCD, it is important to evaluate the downsides including LBM loss. This study found that 51% of the weight loss was contributed

to LBM loss rather than fat mass loss. When comparing this finding with a VLCD, previous research showed that this resulted in an even larger LBM loss (62%) [28]. This indicates that an LCD leads to less LBM loss, but there are some notes of caution hampering firm conclusions. This review reported a high variety in results with two studies that showed a LBM loss of 23–29% [25, 26] and three studies that showed a LBM loss of 46–60% [12,22]. Moreover, three studies [12,25,26] measured body composition by bioelectrical impedance analysis which is prone to error [29]. In future research, it is important to realize that LBM preservation not only relies on dietary composition but also on physical activity [30]. Up to now, exercise has shown promising results in LBM preservation in patients awaiting bariatric surgery [31], though the effect on liver volume is unknown.

When evaluating the side effects, this study found that an LCD was well tolerated and that patients were highly compliant (80–89% compliance rate). Yet again, this data must be interpreted with caution because some studies determined compliance using subjective methods such as counting the returned empty formula sachets and interviewing patients in an unblinded manner. Additionally, the high compliance rate and few side effects might be explained by the relatively short period of energy restriction.

This study observed that perceived surgical complexity, duration of surgery and hospital stay were improved or remained the same, and that complication rate was unchanged. Previously, van Nieuwenhove et al. demonstrated that, in a single-blinded RCT, a two weeks lasting LCD reduced perceived surgical difficulty and 30-day complications, without affecting the duration of surgery [32]. Additionally, a Scandinavian study including over 22,000 patients showed that a weight loss of about 5% reduced the risk of overall postoperative complications in the range of 13–18% [33]. The inconsistencies between these findings and the findings of this review might be attributable to insufficient power, lack of blinding by the surgeon and different dietary approaches. Further RCTs are necessary to clarify the controversy of the effect of an LCD on surgical complexity and complications.

There are several limitations that should be considered when interpreting this systematic review. First, there was a large heterogeneity in terms of diet composition, diet duration and liver volume measurement. Second, different surgical techniques were used which may represent different populations. Third, the quality of the studies was limited with five observational studies being included. Fourth, a control group and blinding of assessor lacked in almost all of the studies which may have caused detection bias. Lastly, secondary outcomes were underpowered thereby possibly failing to detect differences.

In the future, it could be questioned if all patients will actually benefit from a universal LCD. Perhaps preoperative diets would be better in a personalized way, depending on what goals are being set by a multidisciplinary team. These goals could vary between patients with different BMI's or comorbidities, for example reduction in liver volume or stabilization of glucose levels. It is warranted to perform new studies investigating the effect of LCDs in different study populations.

Conclusion

This study demonstrates that an LCD is effective in reducing liver volume and weight. It is recommended that an LCD provides 800–1200 kcal per day and that it lasts for 2 to 4 weeks. Based on prior literature involving a VLCD, it appears that an LCD is even effective in liver volume reduction. Hence, an LCD should be preferred because, in this way, unnecessary excessive dietary restriction and subsequent downsides (e.g. LBM loss, side effects) can be countered. Further research should explore personalization of preoperative diets and focus on the effects of exercise on liver volume and LBM preservation in bariatric candidates.

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CHAPTER 11

Summary and general discussion

Bariatric surgery is considered the best solution for sustained weight loss in patients suffering from severe obesity. However, approximately 25% of patients do not lose enough weight on the long term [1-2]. This so-called non-response is the main focus of this thesis. Non-response refers to the condition where a patient either does not lose enough weight in the first place, or regains a significant amount of weight after initial adequate weight loss. In order to prevent patients from developing non-response in the future, it is imperative to gain a better understanding of this problem. This thesis aimed to (1) identify patients at risk of non-response; (2) investigate interventions targeting non-response; (3) investigate preoperative weight loss strategies because these interventions are in a way related to the preservation of fat-free mass which might influence weight loss outcomes.

Part I: Predictors of non-response in bariatric surgery

Predictors of non-response encompass patient-related and surgical-related factors, and these factors apply in different perioperative phases. In the preoperative phase, mental health disorders like depression, substance use and food urges are previously identified as predictors for regaining weight [1,2]. In **Chapter 2,** this topic is further discussed by describing a retrospective study that assessed the predictive value of preoperative emotional eating. In a cohort of 172 patients, it was demonstrated that emotional eating does not affect excess weight loss, nor total weight loss two years after RYGB. When corrected for psychological, demographic and biological variables, emotional eating in response to particularly diffuse emotions (e.g. boredom and restlessness) did negatively affect excess weight loss. However, no association was found between emotional eating and total weight loss. This study calls for more research on this association, preferably by performing prospective studies in larger cohorts with longitudinal assessments of emotional eating.

In the postoperative phase, there are reasons to assume that protein deficiency and physical inactivity are associated with non-response. Both proteins and physical exercise contribute to fat-free mass preservation which play an important role in several metabolic mechanisms, such as the resting energy expenditure, bone remodeling and functional capacity [2-5]. As described in **Chapter 3**, a study was performed assessing the predictive value of both the 24-hour dietary recall for assessment of protein intake, as well as the 6-minute walk test for assessment of physical function on weight loss outcomes. It was hypothesized that an inadequate protein intake (i.e., <60 g/day [3,4]) and a low physical function (i.e., <82% of the predictive value of the distance covered during the test) contributed to non-response. In a cohort of 85 patients, this study shows that both tests are poor predictors of total weight loss five years after RYGB. These tests are therefore in common practice not feasible to predict

successful weight loss. This study calls to determine the predictive value of other assessments, for example the 5 day food diary and ergospirometry.

Prior studies identified that the group of patients prone to non-response is characterized by low income status [6], first-generation immigrants [7] and residents of large cities [7]. In addition to these characteristics, a systemic review evaluated the effect of employment status on weight loss outcomes. In **Chapter 4** this review is reported showing that employed patients, in comparison to unemployed patients, experience more weight loss (9-11% excess, 1.3-1.6% BMI loss) two to three years after bariatric surgery. In terms of weight regain, the study reported contrasting findings. It is worth mentioning that the individual studies were heterogeneous, of poor quality (i.e., moderate risk of bias) and of small sample size (3 studies $n<100$). Nonetheless, this review highlights the importance of an employed status after bariatric surgery and warrants further investigation on this topic.

During RYGB surgery, the dimension of the gastric pouch and gastroenterostomy (i.e., length and width) is the key to restriction and thus losing weight [1,2,8,9]. As the diameter of the gastroenterostomy is defined by the stapling technique used during RYGB (i.e., circular versus linear), the stapling technique may affect weight loss outcomes. This concept was studied by comparing the two stapling techniques as reported in **Chapter 5**. For this study, data was derived from a nationwide registry called the Dutch Audit for Treatment of Obesity (DATO). In a cohort of 12.468 patients, the rate of non-response was equal for the two techniques. Yet importantly, the circular stapling technique was associated with more short-term complications, specifically major bleedings (2.4% vs. 1.2%, p=0.002). This result is in line with prior literature [10,11] and suggests that using the linear stapling technique should be preferred.

Throughout this thesis, multiple predictors have been investigated demonstrating different effects on weight loss outcomes. Table 1 presents a summary of the findings and is interesting in two ways. First, the predictive value of a higher baseline BMI largely varied (i.e., more total weight loss, less excess weight loss, no effect on non-response). This range of variation is supported by previous studies [1,2,7,12-15] and can be explained by the fact that the association depends on the assessed outcome, and this acquires a different calculation. Second, the largest cluster of unfavorable weight loss outcomes was found for a male gender followed by the presence of preoperative hypertension. Given the fact that this finding is consistent throughout literature [2,7,12], it underlines which patients are at risk of developing non-response.

Table 1. Overview on the effects of patient-related predictors on weight loss outcomes following bariatric surgery

	Increase	No effect	Decrease
Employment status (employed versus unemployed)	**Chapter 4**: increased EWL and BMI loss 2-10 years after various bariatric procedures in employed patients	**Chapter 2**: no effect on </≥ 50% EWL 2 years after RYGB	
Higher preoperative BMI (versus lower)	**Chapter 2, 3**: increased TWL 2-5 years after RYGB	**Chapter 5, 8**: no effect on non-response ≥2 years after RYGB*	**Chapter 2**: decreased EWL 2 years after RYGB
Gender (male versus female)		**Chapter 2**: no effect on EWL and TWL 2 years after RYGB	**Chapter 3, 5, 8**: decreased TWL 2-3 years after RYGB for male gender; increased non-response ≥2 years after RYGB for male gender
Older age (versus younger)		**Chapter 2, 3**: no effect on EWL and TWL 2 years after RYGB; TWL 2-3 years after RYGB	**Chapter 5, 8**: decreased non-response ≥2 years after RYGB
Preoperative hypertension (yes versus no)	**Chapter 5, 8**: increased non-response ≥2 years after RYGB		
Preoperative type 2 DM (yes versus no)	**Chapter 8**: increased non-response ≥2 years after RYGB	**Chapter 2**: no effect on EWL and TWL 2 years after RYGB	**Chapter 5**: decreased non-response ≥2 years after RYGB
Emotional eating (yes versus no)		**Chapter 2**: no effect on EWL and TWL years after RYGB	
Protein intake (adequate versus inadequate)		**Chapter 3**: no effect on TWL 2-3 years after RYGB	
Physical function (high versus low)		**Chapter 3**: no effect on TWL 2-3 years after RYGB	

Abbreviations: BMI, body mass index; DM, diabetes mellitus; EWL, excess weight loss; RYGB, Roux-en-Y gastric bypass; TWL, total weight loss.
* Non-response is defined as significant weight regain (≥20% of a patients lost weight) after ≥20% TWL [16].

Part II: Interventions targeting non-response in bariatric surgery

Assessment by a multidisciplinary team could contribute to knowledge on the etiology of non-response and this is essential for setting an accurate treatment. The assessment should focus on dietary patterns (e.g. protein intake), psychological disorders (e.g. emotional eating) and levels of physical activity [1,2,9]. **Chapter 6** expands on this topic by reporting a study that compared treatment strategies (surgical versus conservative) that were advised by a multidisciplinary team in patients with non-response. On the one hand, a conservative treatment was predominantly advised by the team (88%) and resulted in a stabilization of weight after four years. A surgical treatment on the other hand resulted in more weight loss,

but also in the occurrence of one severe complication (n=10). Another interesting aspect was that on average four years (±2.2) had passed before a patient reported non-response, which is roughly in line with the five years (±1.0) reported in chapter 3. These results could be used by the multidisciplinary team during patient counseling and during subsequent follow-up.

Proteins influence the feeling of satiety and fat-free mass by metabolic mechanisms. One may question whether a higher protein intake (>60 g/day) prevents patients from developing non-response [3,17,18]. In **Chapter 7** a systematic review of five studies is presented describing the effect of a high-protein intake or supplements on fat-free mass (i.e., lean body mass) preservation and weight loss outcomes. In terms of lean body mass preservation, only two studies (n=120) reported a positive effect and in terms of total body weight loss, no effect was found. Because the power of the included studies is relatively low, it is advised to perform new high-quality studies. These studies should focus on the optimal dose and content of proteins for fat-free mass preservation and weight optimization following bariatric surgery.

The concept of combining a RYGB with a non-adjustable band or ring that attached to the gastric pouch ('banded RYGB') was studied. It may be postulated that the band hampers a large food bolus to widen the gastric pouch and/or gastroenterostomy over time, thereby possibly preventing weight regain [19,20]. As described in **Chapter 8**, a study was conducted with data from the DATO resulting in an inclusion of almost 13.000 patients. A striking observation was that the banded RYGB lowered the rates of non-response compared to the non-banded RYGB (12.5% vs. 17.1%, p= 0.012). Furthermore, the banded RYGB showed higher rates of total weight loss up to three years after surgery. The incidence of general complications was low in both groups and the incidence of band-related complications was acceptable (0.6%). Altogether, this study encourages surgeons to perform the banded RYGB.

Part III: Optimizing weight loss prior to bariatric surgery

Our personal experience was that many bariatric centers recommend patients to lose weight prior to surgery, yet it was unknown what the exact recommendations and subsequent interventions were. To address this paucity, a survey study was set out including dieticians and bariatric surgeons from all 18 Dutch bariatric centers. As described in **Chapter 9**, it was found that 28% (n=5) of all centers requested preoperative weight loss and that 61% (n=11) desired a stable weight or weight loss. To lose weight, 78% (n=14) of the centers routinely prescribed a diet. This diet contained 800-1500 kcal/day (i.e., low-caloric diet) in 8 centers and less than 800 kcal/day (i.e., very-low calorie diet) in 4 centers. Furthermore, in 2 centers the recommendation depended on baseline BMI or body weight. The diversity adds to the question whether one diet is superior to the other, and whether there is a role for personalization of a diet.

Chapter 10 expands on the aforementioned reasoning by describing a systematic review available on low-calorie diets. The review demonstrates that a low-calorie diet is effective in reducing weight (4-17%) and liver volume (12-27%). Importantly, this comes at the expense of 23-60% lean body mass loss. These results were subjected to a large heterogeneity in prescribed diets, a low quality in study measurement (e.g. use of bioelectrical impedance analysis), and small sample sizes ($n<50$ in all 8 studies). Yet, when comparing our outcomes with literature that focuses on a very-low calorie diet, the low-caloric diet seems to present less lean body mass loss. Therefore the low-caloric diet should be preferred when pursuing fat-free mass preservation.

Future perspectives

It could be questioned whether predictors could guide the selection of a pre- or intraoperative intervention in patients who need to undergo a bariatric procedure. Table 2 presents an overview of possible interventions, bearing in mind the patient characteristics as presented in table 1 including baseline BMI, comorbidity status, employment status, protein intake and physical activity. In terms of baseline BMI, patients with a BMI of $\geq$50 kg/m^2 could benefit from a primary banded RYGB or a stricter preoperative weight loss regime. In order to examine this, a clinical trial on the effects of a banded RYGB on weight loss outcomes is currently ongoing in our center (NL8093). In terms of employment status, patients could be supported by healthcare professionals to maintain employed, or return to the labor market if they are unemployed. In order to gain insights into the re-integration of patients and the interplay with occupational health physicians, a qualitative study is currently being performed.

Table 2. Overview of possible interventions, taking into account the previously identified predictors for optimizing weight loss outcomes after bariatric surgery.

Characteristics addressed in this thesis	Rationale	Possible interventions
Preoperative higher preoperative BMI	Associated with more weight regain [1,2,12,13]	Preoperative diet containing less kcal/day, e.g. very-low calorie diet, or a longer duration. Primary banded RYGB
Preoperative type 2 DM or hypertension	Associated with more non-response [chapter 5,8], potential risk of reoccurrence of disease	Preoperative diet containing less kcal/ day, e.g. very-low calorie diet, or a longer duration. Primary banded RYGB
(Pre/ postoperative) unemployment	Associated with less weight loss compared to employed patients [chapter 4]	Support by healthcare professionals to either maintain, or return to labor market
Postoperative protein deficiency	Contributes to a greater fat-free mass loss, potential risk of non-response [2-5]	Fat-free mass preservation by protein-enriched diet, preferably combined with resistance training
Postoperative physical inactivity	Contributes to a greater fat-free mass loss, potential risk of non-response [3,4]	Fat-free mass preservation by protein-enriched diet, preferably combined with resistance training

There is a role for fat-free mass preservation when aiming to optimize weight loss outcomes. As discussed throughout this thesis, fat-free mass could be targeted by *preoperative* dietary intake, *postoperative* dietary intake and *postoperative* physical exercise. The preoperative dietary regime may be adapted by enhancing the amount of kcal/day (low-calorie diet rather than very-low calorie diet), or by protein enrichment (i.e., ketogenic diet [22]). In light of this, a research proposal has been written by our group describing a randomized controlled trial examining a ketogenic diet with a (very) low-caloric diet. The postoperative dietary regime may be adapted by protein enrichment (>60 g/day) and in addition, postoperative physical exercise may be promoted. Nonetheless, what is lacking in the aforementioned list and has been covered too little in this thesis, is *preoperative* physical exercise. Promoting exercise preoperatively is a cornerstone of prehabilitation programs and has presented multiple health benefits. Aside from the physical effects (increased cardiorespiratory fitness, increased muscular strength), it may accelerate postoperative recovery and return to work, as well as improve weight loss outcomes [23,24]. In light of this, we previously conducted the BONUS study (Bariatric care Optimization through combined Nutrition and Sports medicine in pre- and postoperative setting) in our hospital. Continuing efforts are needed to further develop this.

Conclusions

The major conclusions of this thesis are summarized as follows:

- Patients at risk of developing non-response after bariatric surgery are characterized by a male gender, the presence of preoperative hypertension and unemployment.
- The stapling technique used during the construction of the gastro-enterostomy in gastric bypass surgery does not affect weight loss; however, it does affect postoperative bleedings (linear < circular).
- The most frequently proposed intervention of non-response by a multidisciplinary team entails a non-surgical approach.
- A primary banded gastric bypass improves weight loss outcomes.
- Diets that are prescribed in the preoperative phase negatively affect fat-free mass; the amount of fat-free mass loss is presumably lower for a low-caloric diet than for a very low-caloric diet.
- Fat-free mass preservation is pre-eminently an area that should be future explored when attempting to optimize weight loss outcomes after bariatric surgery.

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CHAPTER 12

Reflection on the scientific impact

Scientific impact

Bariatric surgery has emerged as the most successful treatment for patients suffering from morbid obesity and its associated comorbidities. Despite the frequent success of bariatric surgery, 20-30% of patients do not respond well as these patients may experience insufficient weight loss or may regain an excessive amount of weight after sufficient weight loss. This condition can be described as non-response. This thesis contributes to a deeper understanding of non-response.

In the first part of this thesis, patients at risk of developing non-response are identified. A cluster of male gender, preoperative hypertension and unemployment was found (**chapter 3, 4, 5, 8**). In the second part of this thesis, the most frequently proposed intervention of non-response is described. According to a multidisciplinary team, this intervention consisted of a non-surgical approach (**chapter 6**). When focusing on a surgical approach, the usage of primary banded gastric bypass reduced the rate of non-response (**chapter 8**). In the third part, this thesis identified commonly used preoperative weight loss regimes i.e., (very) low-caloric diets and explored how they contribute to a loss in fat-free mass (**chapter 9, 10**). As fat-free mass influences metabolic processes and subsequently weight loss outcomes, this thesis encourages other researchers to focus on these aspects.

Social relevance

Non-response affects a large group of patients and, as a result, many healthcare professionals encounter patients with this problem. Importantly, the number of patients suffering from non-response is expected to rise due to an increasing number of patients undergoing bariatric surgery worldwide [1]. Therefore, there is an urgent need for preventive care, early detection and long-term treatment of non-response. This thesis contributes to this need in various ways. Reports were provided in scientific journals and on (inter)national congresses thereby targeting health care professionals. Moreover, reports were translated in such a way that it is understandable for patients. As an example, the reports of **chapter 4 and 9** were shared via the patient platform ‘Bariatrie Groep Nederland’ and in our local hospital.

Aside from the large patient population, non-response has multiple negative social consequences. It could impair a patients’ quality of life, lead to feelings of worthless, guilt, shame and social isolation [2]. Patients may consequently deprive themselves from getting professional support. Awareness of non-response is facilitated by this thesis which is essential for lowering the wide range of potential negative social consequences.

Economic relevance

Non-response strongly increases healthcare costs because it could lead to recurrence of obesity-related comorbidities and necessitates further treatment. One of the treatment options includes revisional surgery. It important to note that the safety profile of revisional surgery differs from primary surgery due to a higher complication rate. This may lead to extreme health care costs [3,4]. Against this background, a non-surgical treatment of non-response is appealing. In this thesis the effect of two non-surgical treatments are described demonstrating a limited effect on weight loss (multidisciplinary approach in **chapter 6**; protein supplementation in **chapter 7**).

An example of how this thesis directly influences healthcare costs can be found in chapter 5. When focusing on the incidence of bleedings in primary surgery, the linear stapling technique should be preferred rather than the circular stapling technique. A shift towards using the linear stapling technique could greatly affect daily surgical expenses which are estimated at €938 per procedure.

Target population

The results of this thesis carry relevance for patients, as well as for healthcare professionals that are involved in the field of bariatric surgery. The latter includes clinicians, dieticians, psychologists, physical therapists, general physicians and occupational health physicians. By educating healthcare professionals on non-response, patient counseling could be improved. In order to educate healthcare professionals, an overview of non-response was published via the Dutch Journal of Medicine (‘Nederlands Tijdschrift voor Geneeskunde’) [5].

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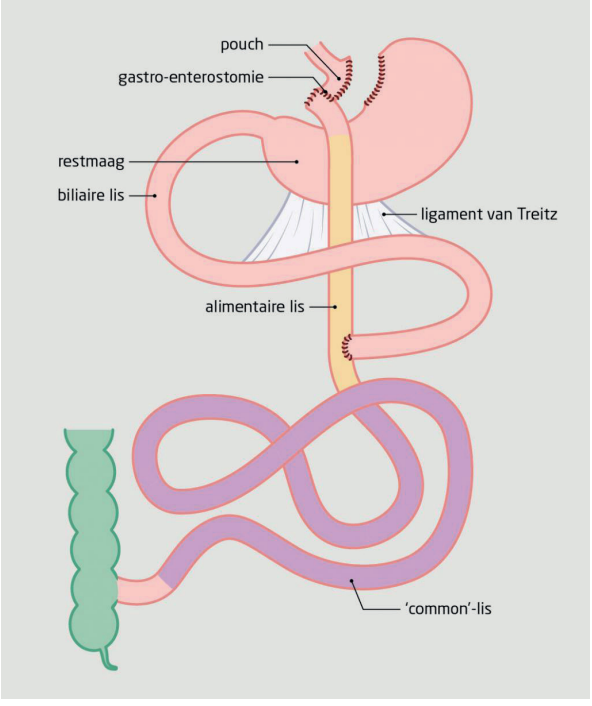
CHAPTER 13

Nederlandse samenvatting

Obesitas en bijkomende aandoeningen zoals diabetes type 2, slaapapneu en hart- en vaatziekten komen wereldwijd steeds vaker voor [1]. Er wordt gesproken van obesitas indien de Body Mass Index (BMI) gelijk aan of hoger is dan 30 kg/m^2. Voor personen met een BMI gelijk aan of hoger dan 40 kg/m^2, of een BMI gelijk aan of hoger dan 35 kg/m^2 met een bijkomende aandoening, is bariatrische chirurgie de meest effectieve behandeling [2]. Deze behandeling heeft als doel een langdurige en aanzienlijke gewichtsreductie te bewerkstelligen en eventueel bijkomende aandoeningen te verminderen. Hierdoor zal de kwaliteit van leven verbeteren en de levensverwachting toenemen.

Met 7400 ingrepen per jaar is de laparoscopische maagomleiding (Roux-en-Y Gastric Bypass, RYGB) de meest uitgevoerde bariatrische operatie in Nederland [3]. De anatomie van het maagdarmstelsel na een RYGB is weergegeven in Figuur 1. Op de lange termijn zorgt deze operatie voor een totale gewichtsreductie van circa 25% en in een ruime meerderheid van de gevallen zullen bijkomende aandoeningen verdwijnen of in ieder geval sterk verbeteren [4-5]. De gewichtsreductie is terug te voeren op een verlies aan vetmassa, maar ook op een ongewenst verlies aan vetvrije massa (=spieren en organen).



Figuur 1. Anatomie van het maag-darmkanaal na een Roux-en-Y-gastric bypass [6]

Een aanzienlijk deel van patiënten weet de 25% gewichtsreductie niet te bereiken door initieel onvoldoende gewichtsverlies of gewichtstoename in de loop van de jaren. Wanneer dit probleem zich voordoet, spreken we van 'non-respons' [6]. Omdat richtlijnen over de diagnostiek en de behandeling van non-respons ontbreken, is het een complex probleem voor zowel de patiënt als het behandelteam. Vervelend genoeg wordt dit probleem steeds groter omdat het aantal patiënten dat een bariatrische operatie ondergaat alleen maar meer wordt.

Dit proefschrift heeft de kennis rondom non-respons na bariatrische chirurgie getracht te vergroten. Het proefschrift is opgesplitst in drie delen, zoals beschreven in **hoofdstuk 1**. Het eerste deel had als doel om te identificeren welke patiënten risico lopen op het ontwikkelen van non-respons. Het tweede deel had als doel om behandelingen van non-respons te identificeren. Het derde deel beschrijft verschillende manieren van gewichtsverlies voorafgaand aan een bariatrische operatie. Een belangrijke schakel hierin is de invloed van vetvrije massa op het gewichtsbeloop na een bariatrische operatie.

Deel 1: risicofactoren van non-respons na bariatrische chirurgie

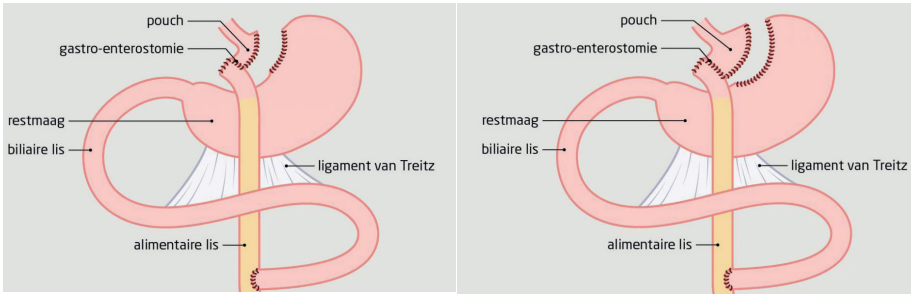
De afgelopen decennia is het in toenemende mate duidelijk geworden dat het gewichtsbeloop na bariatrische chirurgie afhankelijk is van psychologische, fysiologische, socio-economische en anatomische factoren. **Hoofdstuk 2** is erop gericht om het effect van één van de psychologische factoren, genaamd emotie eten, te beschrijven. In deze retrospectieve studie werd onderzocht of gewichtsverlies 2 jaar na een RYGB werd beïnvloed door de aanwezigheid van emotie-eten voorafgaand aan de operatie. Gewichtsverlies werd uitgedrukt in procent totaal gewichtsverlies (total weight loss, TWL) en in procent overgewichtsverlies (excess weight loss, EWL). De mate van gewichtsverlies bleek niet geassocieerd te zijn met emotie-eten. Echter, wanneer er onderscheid werd gemaakt tussen twee vormen van emotie-eten, zogeheten uitgesproken emoties en diffuse emoties bleek er wel een associatie te zijn. Hoe meer emotie-eten als reactie op diffuse emoties, hoe lager het percentage EWL. Meer onderzoek met grotere patiëntengroepen is nodig om hier meer duidelijkheid in te verkrijgen.

Na een bariatrische operatie zijn er redenen om aan te nemen dat het innemen van onvoldoende eiwitten en fysiek inactief zijn, kunnen bijdragen aan het ontstaan van non-respons. Eiwitten en fysieke activiteit zijn belangrijk voor het behoud van vetvrije massa (lees: spiermassa). Zij behouden namelijk het rustmetabolisme wat leidt tot een juiste energiebalans. Door een afname van het rustmetabolisme raakt de energiebalans verstoord en neemt de kans op gewichtstoename toe [7-8]. Er is dus voldoende spiermassa nodig om het rustmetabolisme op peil te houden en het gewicht laag. In **Hoofdstuk 3** wordt beschreven of het gewichtsverlies 5

jaar na een RYGB wordt beïnvloed door de inname van eiwitten en de fysieke functie gemeten 1 jaar na de operatie. Eiwitinname werd gemeten met behulp van een 24 uurs voedingsnavraag en fysieke functie met behulp van een 6 minuten wandeltest. Eiwitinname en fysieke functie bleken in deze studie niet geassocieerd te zijn met het percentage TWL. Echter, het uitblijven van een associatie zou mogelijk kunnen worden verklaard door beperkingen van de gebruikte meetinstrumenten. Het advies zou zijn om bij een toekomstige studie de associatie met andere meetinstrumenten te onderzoeken, zoals het vijfdaagse voedingsdagboek en de ergospirometrie.

Naast de hierboven genoemde psychologische en fysiologische factoren zijn er ook socio-economische factoren die het gewichtsbeloop na een bariatrische operatie kunnen beïnvloeden. **Hoofdstuk 4** beschrijft de invloed van werkstatus op gewichtsverlies met de onderliggende gedachte dat werkstatus mogelijk effect heeft op iemand zijn eet- en beweeggedrag. De bestaande literatuur werd systematisch onderzocht om het gewichtsbeloop tussen werkende (parttime of fulltime) en werkloze patiënten te kunnen vergelijken. De werkende patiënten verloren 2 tot 3 jaar na de operatie ongeveer 10%% meer EWL dan de werkloze patiënten. Echter, er werden geen duidelijke verschillen gevonden in gewichtstoename tussen de twee groepen tot 10 jaar na de operatie. Mogelijk ligt hier een kans voor zorgprofessionals om bewuster om te gaan met de werkstatus van een patiënt, en wellicht zelfs om de patiënt aan te sporen om te gaan werken.

Tenslotte kan de oorzaak van non-respons zijn gelegen in anatomische factoren, waaronder een vergroting van de pouch (Figuur 2), een verwijding van de gastro-enterostomie en fistelvorming van de pouch naar de restmaag [6,9]. De diameter van de gastro-enterostomie is afhankelijk van de chirurgische techniek die gebruikt wordt tijdens het aanleggen van de zogeheten anastomose. Wereldwijd zijn de circulaire stapler en de lineaire stapler de twee meest gebruikte chirurgische technieken. Naar verwachting verschillen deze twee technieken in diameter. In **Hoofdstuk 5** wordt beschreven of deze twee technieken eventueel leiden tot een verschillend gewichtsbeloop tot 4 jaar na een RYGB. Voor dit onderzoek werd data verkregen van een landelijk registratiesysteem, genaamd de ‘Dutch Audit for Treatment of Obesity (DATO)’. In een cohort van totaal 12.468 patiënten werd geen verschil in non-respons aangetroffen tussen de twee technieken. Het onderzoek laat echter wel duidelijk zien dat er meer korte termijncomplicaties optraden, met name nabloedingen, bij de techniek met de circulaire stapler (2.4% versus 1.2%, p=0.002). Gebaseerd op deze resultaten wordt geadviseerd om te kiezen voor de lineaire stapler techniek tijdens het aanleggen van de gastro-enterostomie.



Figuur 2. Normale versus vergrootte pouch als oorzaak van non-respons na een Roux-en-Y-gastric bypass [6]

Deel 2: behandelingen van non-respons na bariatrische chirurgie

Patiënten bij wie non-respons optreedt dienen geëvalueerd te worden in een multidisciplinair team bestaande uit een bariatrisch chirurg, verpleegkundige, diëtist, medisch psycholoog en fysiotherapeut [6,9,10]. Het team kan achterhalen wat de non-respons heeft veroorzaakt, en kan beoordelen welke behandeling – conservatief of operatief – de voorkeur heeft. In **Hoofdstuk 6** wordt een overzicht gegeven van de behandelingen die in het verleden zijn ingezet door het team en hoe succesvol deze behandelingen vervolgens waren. In een cohort van 83 patiënten werd een conservatieve behandeling veel vaker ingezet dan een operatieve behandeling (88% versus 12%). Het gewicht van de patiënten die conservatief behandeld waren stabiliseerde tot 4 jaar na de behandeling. Het gewicht van patiënten die operatief behandeld waren daalde significant, echter trad er ook één ernstige complicatie op. De uitkomsten van het onderzoek zouden gebruikt kunnen worden door zorgprofessionals tijdens het counselen van een patiënt op het moment dat non-respons zich voordoet.

Zoals eerder beschreven zouden eiwitten het gewichtsbeloop na een bariatrische ingreep kunnen beïnvloeden vanwege hun effect op de vetvrije massa (spiermassa) en het rustmetabolisme. Daarnaast hebben eiwitten een zeer sterk verzadigende werking wat gunstig zou kunnen zijn voor het gewichtsbeloop. Gemiddeld genomen heeft een patiënt die een RYGB heeft ondergaan minimaal 60 gram eiwit per dag nodig [7]. **Hoofdstuk 7** richt zicht op de hypothese dat wanneer je meer dan 60 gram eiwit per dag inneemt, dit een beschermende werking zou hebben op het verlies aan vetvrije massa en op het ontstaan van non-respons. De bestaande literatuur werd systematisch onderzocht om deze hypothese te onderzoeken. Uit slechts twee studies bleek dat een hogere eiwitinname het verlies aan vetvrije massa vermindert. Geen enkele studie rapporteerde significant meer gewichtsverlies bij inname van een hogere dosis aan eiwitten. Echter was de methodologische kwaliteit van deze studies

beperkt. Er wordt geadviseerd om nieuwe methodologisch goede studies uit te voeren om een uitspraak te kunnen doen over de juiste dosering en samenstelling van eiwitten.

Hoofdstuk 8 beschrijft het effect van het plaatsen van een bandje rondom de pouch bij de RYGB, de zogeheten 'banded RYGB'. Voor dit onderzoek werd opnieuw gebruikt gemaakt van data van het landelijke registratiesysteem, de DATO. In een cohort van bijna 13.000 patiënten bleek dat het risico op non-respons lager was bij patiënten die de banded RYGB hebben ondergaan dan bij patiënten die de standaard RYGB hebben ondergaan (12,5% vs. 17,1%, p= 0,012). Bovendien was het percentage TWL tot 3 jaar na de operatie significant hoger in de patiënten met de banded RYGB. Ernstige korte termijncomplicaties deden zich in beide patiëntengroepen nagenoeg evenveel voor. De resultaten van dit onderzoek suggereren dat de banded RYGB een groot voordeel heeft op het gewichtsbeloop. In de toekomst dient te worden onderzocht wat het effect van deze operatie op de lange termijn is ten aanzien van het gewichtsbeloop, bijkomende aandoeningen en de kwaliteit van leven.

Deel 3: gewichtsverlies voorafgaand aan bariatrische chirurgie

Gewichtsverlies voorafgaand aan een bariatrische operatie heeft een gunstig effect op het levervolume wat de technische moeilijkheid van de operatie kan verminderen. Echter kan preoperatief gewichtsverlies ook leiden tot een katabole toestand met vermindering van de vetvrije massa. Welke strategie het beste is om tot gewichtsverlies te komen, is onbekend. In **Hoofdstuk 9** wordt beschreven welke adviezen er momenteel gegeven worden vanuit de verschillende centra, aan patiënten die een bariatrische operatie ondergaan. Voor dit onderzoek werd er een enquête verspreid onder bariatrisch chirurgen en diëtisten in de 18 bariatrische centra in Nederland. Het onderzoek laat zien dat er veel verschillen zijn tussen deze centra. Een kwart van de centra (n=5, 28%) adviseert om af te vallen, waarbij het gewichtsverlies varieert tussen de 3 - 10 kg, en tussen de 5 - 10% TWL. Kijkend naar strategieën om gewicht te verliezen, zagen wij dat circa driekwart (n=14, 78%) van de centra altijd een dieet voorschrijft. Hierbij is het meest voorgeschreven dieet een laag calorisch dieet (800-1500 kcal/dag) in 8 van de centra gevolgd door een zeer laag calorisch dieet (<800 kcal/dag) in 4 van de centra.

Voortbordurend op de bovenstaande resultaten richt **Hoofdstuk 10** zich op de voor-en nadelen van een laag calorisch dieet (800-1500 kcal/dag). Een zoekactie in de literatuur leverde drie gerandomiseerde studies en vijf observationele studies op. Deze studies tonen aan dat een laag calorisch dieet effectief is in het reduceren van gewicht (4-17%) en levervolume (12-27%). Een belangrijke bevinding is dat deze reductie ten koste gaat van 23-60% verlies aan vetvrije massa.

Het viel op dat de diëten die werden voorgeschreven heterogeen waren en dat de omvang van de studiepopulaties klein was. Wanneer de resultaten worden vergeleken met die van een zeer laag calorisch dieet (<800 kcal/dag), kan worden opgemerkt dat het verlies aan vetvrije massa daar nog groter is. Om het verlies aan vetvrije massa te beperken kan een laag calorisch ketogeen dieet worden overwogen, hoewel de literatuur daaromtrent nog beperkt is.

Samenvattend heeft dit proefschrift aangetoond dat:

- De afwezigheid van werk, het mannelijk geslacht en een hoge bloeddruk voorafgaand aan de operatie een negatieve invloed kunnen hebben op gewichtsverlies na bariatrische chirurgie .
- De stapler techniek (circulair versus lineair) niet verschilt in de mate van het gewichtsverlies/ non-respons na een bariatrische operatie, maar wel verschilt in complicaties en dat ten nadele van de circulaire techniek.
- Een multidisciplinair team vaak de voorkeur gaf aan een conservatieve behandeling van non-respons.
- Het plaatsen van een bandje rondom de pouch ('banded RYGB') van toegevoegde waarde is gebleken om de kans op non-respons te doen verkleinen.
- Gewichtsverlies in de preoperatieve fase door middel van diëten een nadelig effect heeft op de vetvrije massa, waarbij in deze fase de voorkeur uitgaat naar het laag calorische dieet in plaats van een zeer laag calorisch dieet.
- Er beter moet worden gekeken naar het behoud van vetvrije massa om het gewichtsbeloop na een bariatrische operatie te verbeteren.

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APPENDICES

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Non-scientific publications

1. “Een maag zo groot als een kiwi bespaart een hoop ellende”. Interview Trouw. 19 sep 2020.
2. “Maak kennis met”. Interview Nederlands Tijdschrift voor Geneeskunde. 6 nov 2020.

Achievements

1. Member of the JUMPstart Training Program initiated by Frenisius Kabi. Jan 2021- July 2021.

Curriculum Vitae

Marleen Romeijn was born on September 13th, 1991 in Gorinchem (Zuid-Holland), the Netherlands. She grew up in Noordeloos in a family of 3 children. After graduating from high school (VWO at Lyceum Oudehoven, Gorinchem) in 2009, she studied Biomedical Sciences at the University of Amsterdam. She performed her first research internship at the surgery department of the Leiden University Medical Centre. After obtaining her bachelor degree, she started a medicine program with research profile (ZIGMA program) at the VUmc School of Medical Sciences in Amsterdam. After 4 years, she obtained her master degree and started working as a resident (ANIOS) at the surgery department. First, in the Slotervaart Hospital in Amsterdam, followed by the Noordwest Hospital in Alkmaar. In december 2018, she started working as a PhD candidate in het Máxima Medical Center in Veldhoven under the supervision of dr. F.M.H. van Dielen, dr. W.K.G. Leclercq and prof dr. J.W.M. Greve. She combined clinical projects on institutional data with research projects on nationwide data (from the Dutch Audit for Treatment of Obesity) and systematic reviews. In July 2021, she took a new challenge as she started her surgical residency (AIOS) at the Máxima Medical Center in Veldhoven and the Maastricht University Medical Center. Marleen lives in Eindhoven with her partner Stefan. In her free time, she enjoys spending time with her family as “Tante Leen” and friends.