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Bariatric Surgery versus Lifestyle Interventions for Morbid Obesity: 5-Year Changes in Body Weight, Risk Factors and Comorbidities

Master's Thesis in Clinical Health Science

Trondheim, June 2014.

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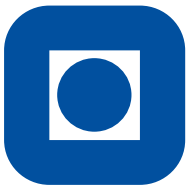

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Acknowledgments

Working on this thesis has been a roller-coaster ride. The hours spent on figuring out solutions to the problems I faced were challenging, and the inspiration from seeing progress in my work made it fun. It has been highly educational, and many have contributed and supported me in the process.

My heartfelt gratitude goes to my supervisor Catia Martins at the Norwegian University of Science and Technology (Trondheim, Norway). Her professional guidance, support, and devotion, is inspiring. I am extremely grateful. Additionally, my secondary supervisor Magnus Strømmen at the Obesity Clinic at St. Olavs Hospital (Trondheim, Norway) has given me great advice and feedback, which I truly appreciate. I would also like to thank Turid Follestad at the Norwegian University of Science and Technology for always answering my many questions; her assistance in statistics has been very valuable.

A special recognition must be given to the nurses Sissel Salater and Hege Tevik Bjøru at the Obesity Clinic at St. Olavs Hospital (Trondheim, Norway). They have each contributed in different ways and I am thankful for their help. I also want to thank several individuals who has helped me with information and shared their knowledge: Vegar Dahl and Kjersti Aas at Røros Rehabilitering (Røros, Norway), Randi Nossum and Siv Hege Forbord at Clinic of Clinical Services at St. Olavs Hospital, and Randi Pierre former nurse at the Obesity Clinic at St. Olavs Hospital. Additionally, I wish to thank the patients in the study, as well as all personnel involved in the recruitment, interventions, data collection and blood sampling. Thank you.

Last but not least, I would also like to thank my partner Thomas Olsen, my family and my friend Anne Lorentzen, for their encouragement, proofreading and enthusiastic support.

Trondheim, May 2014.

Bente Øvrebø

Abbreviations and acronyms

ANOVA - Analysis of variance

BCF - Baseline carried forward

BMI - Body mass index

BW - Body weight

DM2 - Diabetes mellitus type 2

HDL - High-density lipoprotein cholesterol

HUNT - Helseundersøkelsen i Nord-Trøndelag

ILI - Intensive lifestyle interventions

LDL - Low-density lipoprotein cholesterol

LMM - Linear mixed model

LOCF - Last observation carried forward

NHANES - National Health and Nutrition Examination Survey

PA - Physical activity

Q-Q plot - Quantil-quantile plot

RYGB - Roux-en-Y gastric bypass

SD - Standard deviation

SOS-study - Swedish Obese Subjects study

TG - Triglycerides

WL - Weight loss

$\Delta_{bl\text{-}y1}$ - 1-year change in body weight

Abstract

Background: Not all morbidly obese patients want, or are eligible for bariatric surgery, and therefore depend on effective lifestyle interventions. **Purpose:** This study aimed to compare changes in body weight (BW), risk factors and comorbidities 5 years after Roux-en-Y gastric bypass (RYGB) or three lifestyle interventions in morbidly obese patients. **Methods:** 209 (75.1% women) morbidly obese adult (mean (standard deviation (SD)): age 40.9 years (9.5), BW 133.4 kg (19.6), body mass index (BMI) of 45.4 kg/m^2 (5.6)) patients were non-randomly allocated to: A) laparoscopic RYGB (n = 58), B) weight loss (WL) camp (n = 30), C) residential intermittent program (n = 64), or D) hospital outpatient program (n = 57). BW, risk factors and comorbidities were assessed at baseline, 1 and 5 years. **Results:** 89.0% and 54.1% completed the 1- and 5-year follow-up, respectively. Analysis of 5-year completers yielded a general reduction in BW at year 1 (-25.9 kg, 95% CI [-30.3, -21.6], p<0.001), followed by a regain of 11.3 kg (95% CI [6.9, 15.6], p<0.001) from 1 to 5 years. An overall reduction in BW from baseline was observed at the 5-year follow-up (-14.7 kg, 95% CI [-19.1, -10.3], p<0.001). After 5 years the RYGB group had lost significantly more BW (-30.9kg, 95% CI [-35.9, -25.9]), compared to the lifestyle groups: B (-13.3kg, 95% CI [-24.5, -2.1]), C (-5.5kg, 95% CI [-10.8, -0.2]) and D (-4.1 kg, 95% CI [-10.0, 1.8]) (all p<0.001), with no significant differences observed between the three latter groups. RYGB, group B, and group C had significant within-group WL after 5 years (all p<0.05). Plasma glucose and high-density lipoprotein cholesterol (HDL) were significantly better in the RYGB group at 5 years compared with all lifestyle groups (all p<0.05). Furthermore, a higher proportion of patients in the RYGB group experienced remission of hypertension compared with the lifestyle groups merged into one group (p<0.05). **Conclusion:** At the 5-year follow-up the RYGB was associated with a greater WL, overall healthier glucose and blood lipids, and a larger remission of hypertension, compared with lifestyle interventions. However, a significant 5-year WL was observed with lifestyle interventions as well.

Keywords: Morbid obesity, Lifestyle intervention, Gastric bypass, Long-term follow-up, Weight, Risk factors, Comorbidities.

Relevance

With increasing prevalence of morbid obesity, the current study was meant to stimulate development of, and evaluate, non-surgical alternatives to bariatric surgery in the morbidly obese. This study may help understand lifestyle interventions in morbidly obese, and to measure the long-term effects of both RYGB and lifestyle interventions. Furthermore, observations from this study might yield results that future research should focus on.

1.0. Introduction

A common way of defining obesity is by use of BMI (1). With a BMI ≥30 kg/m^2 one is classified as obese, while morbid obesity is often defined with a BMI ≥40 kg/m^2 or ≥35 kg/m^2 with comorbidity (2-4). The prevalence of worldwide obesity has increased since 1980 (1, 5, 6) and the National Health and Nutrition Examination Survey (NHANES) in the US estimated the obesity rate at 35.5% in 2009-2010 (7). Although lower rates than in the US, Midthjell and colleagues (2013) reported an obesity prevalence of 22.6% amongst Norwegians in 2008 (8). Furthermore, research shows a dramatic increase in morbidly obese in the western countries (8-11) and the percentage of people with BMI ≥40 kg/m^2 in the US was 6.3% in 2009-2010 (7). HUNT-reports (Helseundersøkelsen i Nord-Trønderlag) from Norway revealed that the prevalence of people with BMI ≥40 kg/m^2 had increased from 0.4% in 1986 to 1.0% in 2008 (8). Other countries have reported similar obesity rates, and several studies predict an increase in the presence of obesity, especially morbid obesity (9-14).

Risk factors for metabolic syndrome, diabetes mellitus type 2 (DM2) and cardiovascular disease, such as glucose intolerance and dyslipidemia are often pronounced in the morbidly obese (15-18). Other, well-documented consequences of obesity are hypertension, non-alcoholic fatty liver disease, depression, anxiety, certain types of cancer, osteoarthritis, asthma, sleep apnea, polycystic ovary syndrome and cholelithiasis (15-20). Obesity may also affect hormonal status, infertility, mobility, quality of life, and lead to increased mortality (15, 19, 21-26). Morbidly obese have an even higher risk for obesity-related diseases which place a costly strain on the health care system (15, 16, 18, 19, 27), making treatment important for both health and economical reasons (28-30).

Bariatric surgery, lifestyle modification and pharmacotherapy are the main treatment strategies for WL. Of these, only bariatric surgery and lifestyle interventions are of relevance to this thesis, thus pharmacotherapy will not be discussed further.

There are mainly two bariatric surgical techniques used to achieve WL: restrictive (reducing the stomach volume) and malabsorption techniques (bypassing intestines), and the two may also be combined (31). Several surgical methods, with the use of these techniques, have been

developed to attain WL: gastric sleeve, biliopancreatic diversion, gastric bypass and gastric banding amongst others (31, 32). Most of these methods are now available laparoscopically (33-35). The RYGB, which combines malabsorption with a restrictive technique, is one of the most frequently used methods for surgical treatment of obesity (31, 33-35). Essentially, the RYGB results in smaller ingested meals and malabsorption due to bypassing the distal stomach and a length of the small intestine (31), but the exact mechanisms responsible for the large WL after RYGB remains unclear (36). Caloric restriction does not seem to be the only explanation, as gastrointestinal hormones and vagal innervation might play a significant role (36). WL after RYGB reported from the Swedish Obese Subject study (SOS-study) was 38% at year 1 and 25% at the 10-year follow-up, which seems to be sustained after 20 years (37-39). WL with RYGB like the ones found in the SOS-study has also been reported in additional studies, both short- and long-term (40-46). Research reveal that adverse events after laparoscopic RYGB may occur as well, like anastomotic leak, gastro-gastric fistula, internal herniation, small bowel obstruction and even death (31, 33). Furthermore, vitamin and mineral supplementation may be necessary following this method (47-49). Although complications might occur, RYGB has resulted in several positive outcomes such as lower overall mortality, remission of hypertension and DM2, better quality of life, improvements in hyperlipidemia, and a large long-term WL (31, 32, 38, 39, 42, 50-53).

Lifestyle intervention treatment normally consists of a change in diet, physical activity (PA) and behavioral modification. A combination of a hypocaloric diet and increased PA creates energy deficit and is essential for lifestyle interventions to work. Several studies have found that increased PA correlates with WL and long-term maintenance of WL (54-59). Additionally, exercise has various benefits and improves health (54, 60, 61). A systematic review comparing WL in groups with either diet intervention alone or diet and exercise intervention concluded that both initial and 1-year WL was 20% higher when the intervention consisted of both diet and exercise (62). There seems to be agreement that a combination of the two interventions results in a better WL (54, 63, 64). Behavior modification usually comprise of different components like self-monitoring, goal setting, stimuli control, cognitive strategies, social support, and reinforcement (65). A Cochrane review by Shaw and colleagues (2005) concluded that behavioral therapy results in significantly higher WL compared to no behavioral therapy (66). Several studies in this review favored combining behavioral therapy with diet and/or exercise interventions, as it resulted in increased WL. Collectively, studies emphasize that a multidisciplinary approach targeting diet, PA and behavior seems more

effective in lifestyle interventions (54, 66-68).

Dropout and WL maintenance after lifestyle interventions in the morbidly obese are recurring problems (69, 70). Since bariatric surgery has been shown to produce good results and is associated with low risks, it has become increasingly popular (34, 35). As mentioned above, RYBG results in significant WL in morbidly obese patients (38, 44, 71). However, a substantial weight regain usually occur 1-2 years post-operative, which also lead to significant return of risk factors and comorbidities (37, 71). A randomized controlled trial from 2012 concluded that RYGB had a greater effect on WL and glucose control in patients with morbid obesity and DM2 compared with conventional treated patients after 2 years (72). Brolin (2002) emphasized that in the long-term control of morbid obesity, bariatric surgery seems to be the most effective regarding WL and recovery from comorbidities, as others have mentions as well (31, 38, 50, 73).

Despite the large improvements in BW and health outcomes after RYGB, not all morbidly obese patients are eligible for, or want bariatric surgery. Thus, this patient group is in demand of effective lifestyle interventions. Small, but sustained WL (of 5-10%) may improve the health and reduce medical costs in obese patients, but in morbidly obese a more profound WL might be necessary (1, 4, 74-77). Research shows that lifestyle interventions in morbidly obese can result in significant BW reduction - especially in the short term (45, 78-81). A randomized controlled trial showed that in morbidly obese patients a combination of diet and PA resulted in a significant WL and improvements in cardiometabolic risk factors after one year (78). Other similar studies in the morbidly obese have observed similar significant improvements (45, 70, 79, 82). However, clinical treatment of morbidly obese patients in the long term is difficult because of large dropout rates (69). Due to this there are only a few good long-term studies, with more than 1-2 year follow-up, looking at the impact of lifestyle interventions on WL in morbidly obese. There are, however, some studies that confirm a good response after lifestyle interventions in morbidly obese patients, with substantial WL maintained after several years (70, 83-85). Björvell and Rössner (1992) found that morbid obese patients who had participated in a 4-year lifestyle intervention treatment program maintained a lower BW after 10-12 years (85). Unfortunately, in this study the effects on risk factors and comorbidities were not measured. A newer study from 2007 concluded that intensive behavioral intervention could be very effective, with minimal risks for morbidly obese patients after a 5-year follow-up (70), but dropout rates increased after 2.5 years. They

also reported significant improvements in total cholesterol, low-density lipoprotein cholesterol (LDL), triglycerides (TG), blood pressure, and fasting plasma glucose after the treatment period, but no long-term risk factors were reported.

The SOS-study is a large currently ongoing study looking at the effect and safety of different bariatric methods (thereby RYGB) in morbidly obese (38). It is one of the largest and longest studies done on bariatric surgery, and the follow-up time has now reached 20 years. A matched control group, which received conservative treatment in the primary healthcare system, did not experience WL. The control group was offered treatment from their nearest health center, which varied from sophisticated lifestyle interventions to nothing at all (39). Because of the lack of standardization, this confounder makes the control group difficult to compare with others, undergoing structured lifestyle interventions. However, a study from 2012 compared RYGB with an intensive lifestyle intervention (ILI). This was a 1-year WL study on DM2 and cardiovascular risk factors in morbidly obese found that both the RYGB group and the ILI group had improvements in glucose metabolism, blood pressure, blood lipids and low-grade inflammation, however improvements in the RYGB group were larger (46). RYGB resulted in significantly higher WL, and higher remission rates of DM2 and hypertension, compared to the ILI group. However, the short time-span is a substantial limitation because participants might regain weight after the follow-up and the long-term results are unknown. In line with the previously mentioned study, Martins and colleagues (2011) reviewed 1-year data comparing three different lifestyle interventions with RYGB in morbidly obese, and found that RYGB resulted in a greater WL; however lifestyle interventions also produced significant 1-year WL (45). Blood lipids and glucose improved with RYGB, but also with lifestyle interventions. In terms of remission of comorbidities, only remission of hypertension was better after RYGB. Even with a smaller WL from lifestyle interventions, morbidly obese can have significant improvements in risk factors and comorbidities. However, the question is if these changes will be sustained in the long term. Therefore more long-term studies are needed comparing RYGB with structured lifestyle interventions, in regards to changes in BW, risk factors and comorbidities.

2.0. Aims and hypothesis

The aims of this study were to compare RYGB with three different lifestyle interventions in terms of changes in BW, risk factors and comorbidities in morbidly obese patients at the 5-year follow-up. We hypothesized that RYGB resulted in a higher WL, better improvements in risk factors and remission of comorbidities compared to lifestyle interventions after 5 years.

3.0. Methods

3.1. Design

This was a prospective, non-randomized intervention study with four different treatments for morbid obesity. Patients referred to bariatric surgery at St. Olavs Hospital in Trondheim (Norway) were invited to participate, and they were offered to choose either one of three lifestyle treatments of obesity or to await examination for bariatric surgery. The four treatment options included: A) laparoscopic Roux-en-Y Gastric Bypass (RYGB), B) Ebeltoft Kurcenter (WL camp), C) Røros Rehabilitering (residential intermittent program), D) St. Olavs Hospital (hospital outpatient program). The study was conducted and completed between 2005-2013.

3.2. Study sample

After giving informed consent, men and women aged between 18-65 years and with a BMI ≥40 kg/m² or BMI ≥35 kg/m² with comorbidity, were included in the study. Patients participating in other trials were not included. Other non-eligibility criteria were pregnancy, previous bariatric surgery, drug or alcohol abuse, severe psychiatric disorders and/or physical impairment that could interfere with the treatment. Additionally, only patients with less than one hour travelling distance to the treatment center were considered eligible for treatment option D (hospital outpatient program). For treatment option A (RYGB), in cases the surgeon for some reason converted the planned laparoscopic procedure into laparotomy, these were excluded from the study.

3.3. Ethics

This study was conducted according to the Declaration of Helsinki and was approved by the Regional Committee for Medical and Health Research Ethics in Central Norway (Ref.: 4.2005.33). All patients could withdraw at any time. Collected information was kept confidential.

3.4. Procedure

Treatment A: Laparoscopic Roux-en-Y gastric bypass (RYGB).

The surgical procedure involves the transformation of cardia into a gastric pouch (approximately 30 ml) and a Roux-en-Y gastrojejunostomy bypassing the distal stomach, the duodenum, as well as a variable length of proximal jejunum (about 20% of the small intestine). The RYGB was conducted by trained surgeons at St. Olavs Hospital (Trondheim, Norway) and performed laparoscopically. Post surgery patients were encouraged to visit their local doctor every third month and two times a year after that. A group meeting was held at St. Olavs Hospital 1-3 months post surgery. The meeting focused on education on body changes, nutrition and PA, and lasted one whole day. This was repeated approximately one year after surgery. The surgeon had follow-up consultations three and 12 months postoperative including blood tests and control for complications. Six months post surgery every patient had a personal meeting with a nutritionist. Two years after the RYGB the patients were screened for nutritional status, excess skin and weight stability. Additionally, three and five years post surgery the patients were called in for a check-up, either alone or in groups.

Treatment B: Weight loss camp at Ebeltoft Kurcenter in Denmark (hereon referred to as Ebeltoft).

Patients had a stay at a private Danish health resort (Ebeltoft Kurcenter, Ebeltoft, Denmark) for 16 weeks. They followed an intensive intervention program involving a low-calorie diet, structured PA, and weekly cognitive therapy regimens. The treatment team consisted of nutritionists, physical therapists and psychotherapists. The patients were educated in techniques on how to maintain WL when they got home, but the main focus at Ebeltoft was PA consisting of at least 120 minutes of daily PA led by a physical therapist. For details see Christiansen et al. (86). Following the stay in Denmark, patients were offered optional monthly consultations by telephone or in person with a psychiatric nurse at the Obesity Center at St. Olavs Hospital (Trondheim, Norway).

Treatment C: Residential intermittent program at Røros Rehabilitering (hereon referred to as Røros).

This intervention took place at Røros Rehabilitering (Røros, Norway), where the patients first

stayed for eight to ten weeks, followed by eight weeks at home. Then the patients had another stay at Røros for four weeks, after this they had four to five months at home, followed by two weeks at Røros. After the first year the patients returned to Røros two weeks every six months until five years had passed. At Røros they consulted with a nutritionist, a physical therapist, a psychologist, a nurse, a medical doctor and a social worker. The patients attended monitored and structured PA with a physical therapist, both individually (one session/day) and in groups (two sessions/day). They were lectured on healthy eating, received nutritional education (principles of energy balance, nutritious food, healthy cooking, etc.) and ate six meals a day (four main meals and two snacks). Central to the treatment was group-based psychotherapy, focusing on how to use what they had learned when they got home and how to change their lifestyle.

Treatment D: Hospital outpatient program at St. Olavs Hospital in Trondheim (hereon referred to as St.Olavs).

This treatment consisted of a six-month WL program at Clinic of Clinical Services at St. Olavs Hospital (Trondheim, Norway), followed by a six-month maintenance phase. The intervention was based on cooperation between a physical therapist, an occupational therapist, a clinical nutritionist and a social worker. The multidisciplinary approach included nutritional guidance, principles of healthy cooking with practical tasks, exercise, PA education, coping strategies, and increasing awareness regarding motivation, habits and obesity-promoting circumstances. The main goal of the intervention was to improve behavior, diet and exercise. Further details about the intervention can be found in Nossum et al. (2009) (87). The intervention started with a two-day kickoff lifestyle course. It continued with six months of two or three weekly workouts (mainly endurance- and strength exercise) with a physical therapist and one weekly group meeting with the occupational therapist, the clinical nutritionist or the social worker. At some meetings, a psychologist was also present. The patients had to attend at least 80% of the meetings for the first six months. The WL program ended with a two-day course summarizing the intervention, the results, and introduction of the maintenance phase. In the maintenance phase the treatment team emphasized the necessity of continuing the process. There was group exercise once a week in the local community and a meeting with the multidisciplinary team every other month on how to sustain the motivation. The project was evaluated after 12 months, and the subjects were more or less 'left on their own', but summoned for measurements every year.

3.5. Data collection

The main outcome was change in BW. Blood results reflecting risk factors were secondary outcomes: plasma levels of glucose, total cholesterol, LDL, HDL and TG. Self-reported changes in any of the following comorbidities were reported as outcomes: asthma, arthritis, diabetes, coronary disease, hypertension, sleep apnea, cholelithiasis, eating disorder and mental disorder.

Data was collected at baseline, year 1 and year 5. Baseline BW was measured at the clinic. Further BW data was self-reported (questionnaire), measured at clinic, or found in hospital journals (at St. Olavs Hospital, Trondheim Norway). The risk factors were assessed through fasting blood samples, using Roche Modular P analysis instrument (at St. Olavs Hospital laboratory) and Friedewald equation when calculating LDL (88). Comorbidities were reported in questionnaire and/or in meetings with a study nurse at the Obesity Center at St. Olavs Hospital.

3.6. Statistical methods

Statistical analysis was performed with SPSS version 21.0 (SPSS IBM, New York, U.S.A.). All variables and/or residuals were checked for normal distribution with normality tests (Kolmogorov-Smirnov or Shapiro-Wilk tests), and visually with histogram or quantile-quantile (Q-Q) plots. Homogeneity of variance was assessed visually with residuals and predicted values in a scatterplot. Values were considered statistically significance when $p<0.05$, except when post hoc tests (Bonferroni) were performed. Bonferroni correction method was used to adjust for an increased risk of type 1 error as a result of multiple comparisons.

Since more patients in the Ebeltoft group were lost to follow-up or excluded at the 5-year follow-up, analyses were also performed by merging the three lifestyle groups into one combined lifestyle group (also called the latter), and comparing this to the RYGB group.

Differences in baseline characteristics between the groups were analyzed with one-way analysis of variance (ANOVA) or t-test (age, BW and BMI) and Chi-square test (gender). The continuous outcome variables were analyzed with Linear Mixed Model (LMM) because of unbalanced group size, repeated measurements, and missing values in the dataset. Subject was set as correlated random effect (because of repeated dependent measurements), and fixed effects were treatment group, time and the interaction treatment group*time. All variables were analyzed within and between groups, and Bonferroni post hoc tests was used if there

were overall significant effects of groups and/or time. The TG variable was reciprocal-transformed to get a normal distribution, and further analyzed with LMM. The exception of variables analyzed with LMM was the glucose variable, which was non-normal, so a non-parametric test was used. Kruskal-Wallis (four groups) or Mann-Whitney (two groups) tests were used to compare the groups at the different time-points, and Friedman's ANOVA was used to analyze changes over time within each treatment group. Thus, analysis of the interaction treatment group*time was not possible with the glucose variable.

Categorical variables (like comorbidities and percentage of WL in categories) were assessed with Chi-square test when assumptions were met, and Fisher's Exact when assumptions were not met. Z-test with adjusted p-values (Bonferroni method) was used to compare column proportions in the cross tabulation if either the Chi-square or the Fisher's Exact test was significant when the four groups were analyzed. This was to find which groups were significantly different from the others.

Multiple regression was used for prediction of WL from different parameters among the patients who completed the 5-year follow-up. The predictors were gender, age, baseline BMI and BW change the first year of the study. This analysis was performed with the whole sample (all 5-year completers) and with the completers split into two groups (RYGB and combined lifestyle). Assumptions were met with all completers, and when analyzing the two groups.

Because of large dropout rates intention-to-treat analysis with two different approaches were conducted. Last-observation carried forward (LOCF) and baseline carried forward (BCF) of the variable BW was completed with LMM. One-way ANOVA was used to analyze differences in mean follow-up time of the last observations between the four groups.

4.0. Results

The general structure of the study, as well as reasons for exclusion in analysis, is shown in Figure 1. Of the 209 patients who started the study, 186 (89.0%) completed the 1-year follow-up, and 113 (54.1%) the 5-year follow-up. Self-reported BW was submitted by 16 (14.2%) of the 113 5-year completers.

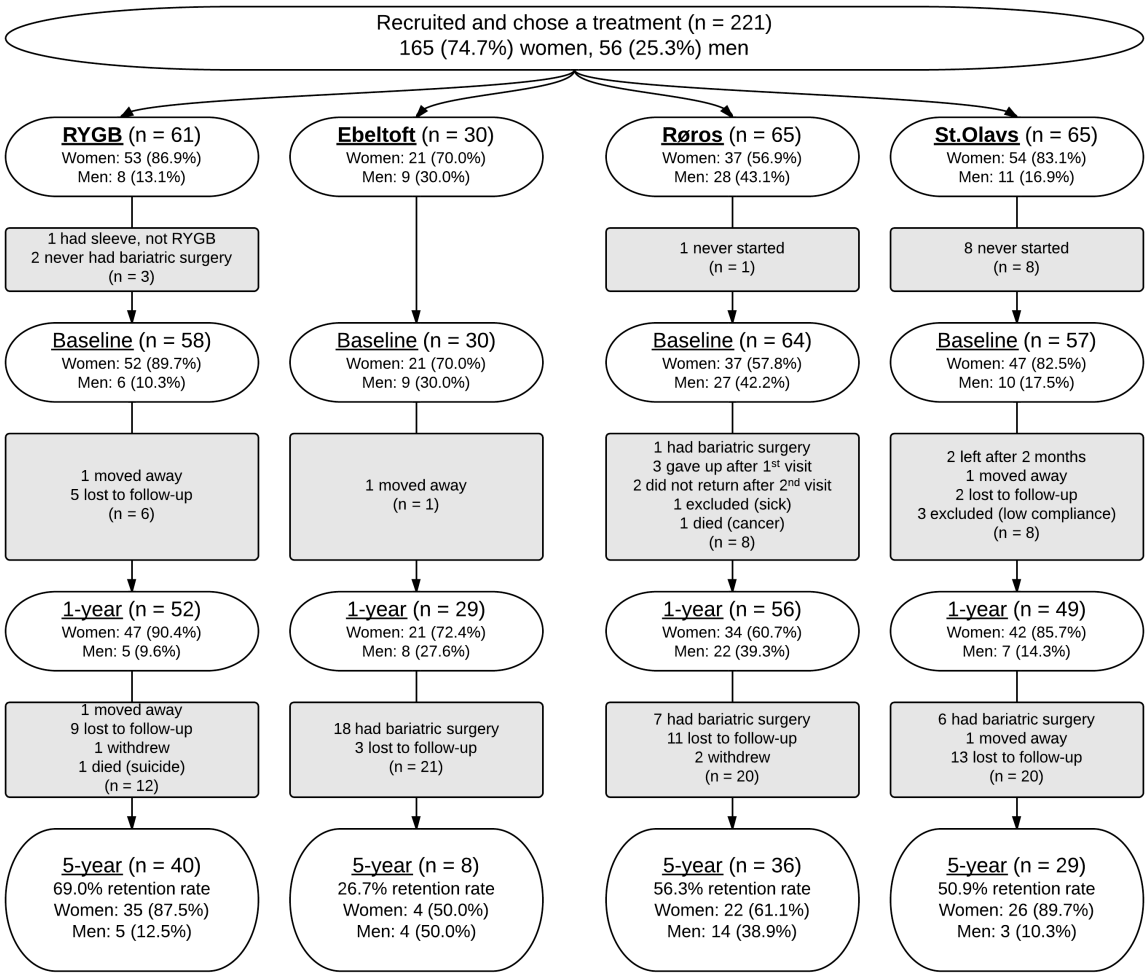


Figure 1. The flowchart displays an overview of the study with 5-year follow-up. The flowchart shows retention rates and reasons why patients were excluded from the current analysis. RYGB: Roux-en-Y gastric bypass.

4.1. Baseline characteristics

The baseline characteristics of the starting patients can be viewed in Table 1. A significant difference in BW ($p<0.001$), BMI ($p<0.01$) and gender distribution ($p<0.001$) was found between the four groups at baseline (see Table 1). Moreover, the RYGB had a larger proportion of women ($p<0.01$) than the combined lifestyle group.

Table 1. Baseline characteristics of starting patients (n = 209)

	RYGB (n = 58)	**Ebeltoft** (n = 30)	**Røros** (n = 64)	**St.Olavs** (n = 57)	**Combined lifestyle** (n = 151)	**Total** (n = 209)
Women (%)	52 (89.7%) [ab]	21 (70.0%)	37 (57.8%) [ac]	47 (82.5%) [c]	105 (69.5%) [b]	157 (75.1%)
Age (years)	40.2 ± 8.5	38.4 ± 10.1	42.0 ± 9.8	41.8 ± 9.9	41.2 ± 9.9	40.9 ± 9.5
BW (kg)	130.7 ± 18.1 [a]	144.2 ± 20.2 [ab]	137.1 ± 19.8 [c]	126.2 ± 17.2 [bc]	134.4 ± 20.1	133.4 ± 19.6
BMI (kg/m²)	45.0 ± 5.4	48.3 ± 6.6 [a]	45.3 ± 5.5	44.1 ± 4.9 [a]	45.5 ± 5.7	45.4 ± 5.6

Data is shown as mean ± SD. Numbers with similar superscript letters across columns are significantly different to one another ($p<0.05$). BMI: Body mass index. BW: Body weight. RYGB: Roux-en-Y gastric bypass.

4.2. Analysis of completers

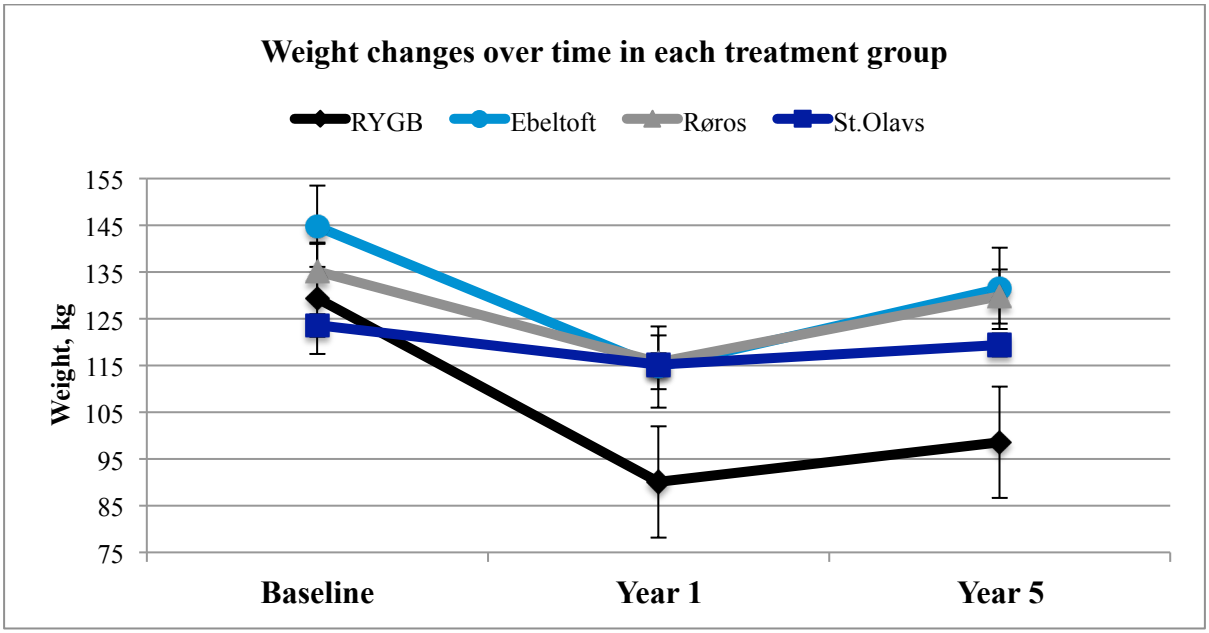
4.2.1. Change in body weight

LMM analysis found an overall significant relationship between BW and the following: treatment group ($p<0.001$), gender ($p<0.001$), time ($p<0.001$), and the interaction treatment group*time ($p<0.001$). This was found both when analyzing the completers in four and two groups.

Pairwise comparison of treatment groups revealed that the RYGB group had an overall lower BW compared to all other lifestyle groups (all $p<0.05$). Men had an overall 21.4 kg (95% CI [12.1, 30.6]) higher BW compared to women ($p<0.001$). A further look at time showed significant overall results; decrease in BW from baseline to year 1 (-25.9 kg, 95% CI [-30.3, -21.6], $p<0.001$), increase from year 1 to year 5 (11.3 kg, 95% CI [6.9, 15.6], $p<0.001$), but still a lower BW at year 5 compared to baseline (-14.7 kg, 95% CI [-19.1, -10.3], $p<0.001$). These overall results were identical when analyzing the completers in two groups.

Difference in BW between the RYGB group and the three lifestyle groups

Changes in BW over the 5 years in each treatment group are displayed in Figure 2. Post-hoc tests revealed no significant differences in BW between the groups at baseline. At year 1 the RYGB group had a significantly lower BW compared to all the lifestyle groups: Ebeltoft ($p<0.05$), Røros ($p<0.001$) and St.Olavs ($p<0.001$). After 5 years the mean BW in the RYGB group was still significantly lower compared to the lifestyle groups: Ebeltoft ($p<0.001$), Røros ($p<0.001$) and St.Olavs ($p<0.001$). There were no significant differences in BW at year 1 or at year 5 among the lifestyle groups.



RYGB	129.4 [123.1, 135.8] [12]	90.1 [83.7, 96.5] [abc13]	98.6 [92.2, 104.9] [abc23]
Ebeltoft	144.8 [130.6, 159.1] [12]	114.7 [100.5, 128.9] [a13]	131.5 [117.3, 145.7] [a23]
Røros	135.2 [128.5, 141.9] [12]	115.7 [109.0, 122.4] [b13]	129.8 [123.1, 136.5] [b23]
St.Olavs	123.6 [116.1, 131.0] [1]	115.2 [107.6, 122.7] [c1]	119.4 [112.0, 126.9] [c]

Figure 2. Changes in body weight over time in the four intervention groups. Lines are presented as means ± SEM. The mean weight in each group is presented in the table with CIs. Identical letters within columns represent significant differences between groups ($p<0.05$). Values with similar superscripts across columns represent significant within-group changes ($p<0.05$). RYGB: Roux-en-Y gastric bypass.

Differences in BW between the RYGB group and the combined lifestyle group

There were no significant differences at baseline between the two groups. The RYGB group had a significant lower BW compared to the lifestyle group both at the year 1 and 5-year follow-up (both $p<0.001$).

Changes in BW within each treatment group

Comparison of the time-points with post hoc tests within each group revealed a significant WL from baseline to year 1 in the RYGB group (-39.3 kg, 95% CI [-44.4, -34.2], p<0.001), followed by a significant increase from 1 to year 5 (8.4 kg, 95% CI [3.3, 13.6], p<0.001). Nevertheless, the BW at the 5-year follow-up was significantly lower than at baseline (-30.9 kg, 95% CI [-35.9, -25.9], p<0.001).

BW in the Ebeltoft group significantly decreased from baseline to year 1 (-30.2 kg, 95% CI [-41.4, -18.9], p<0.001), and increased from year 1 to year 5 (16.8 kg, 95% CI [5.6, 28.1], p<0.001). However, the BW at year 5 was still significantly lower than at baseline (-13.3 kg, 95% CI [-24.5, -2.1], p<0.05).

BW in the Røros group was significantly reduced from baseline to year 1 (-19.5 kg, 95% CI [-24.8, -14.2], p<0.001), but increased between year 1 and 5 (14.0 kg, 95% CI [8.7, 19.3], p<0.001). Still, at the 5-year follow-up the BW was significantly lower compared to baseline (-5.5 kg, 95% CI [-10.8, -0.2], p<0.05).

In the St.Olavs group there was a significant decrease in BW from baseline to year 1 (-8.4 kg, 95% CI [-14.5, -2.3], p<0.01), but it non-significantly increased (with 4.3 kg, 95% CI [-1.9, 10.4]) to year 5. The 5-year BW was not significantly different from baseline (-4.1 kg, 95% CI [-10.0, 1.8]).

Analysis with the combined lifestyle group yielded a significant WL from baseline to year 1 (-16.5 kg, 95% CI [-20.5, -12.6], p<0.001). There was an increase in BW of 10.7 kg, 95% CI [6.8, 14.6], from year 1 to year 5 (p<0.001), but even so the BW was significantly lower at the 5-year follow-up compared to baseline (-5.8 kg, 95% CI [-9.7, -1.9], p<0.001).

Percentage of WL

The percentage of patients within each group experiencing weight gain or at least a 5, 10, 15, or 20% WL at the 5-year follow-up in the different treatment groups are presented in Table 2. Analysis revealed that a significantly larger number of patients from the RYGB group had lost a higher percentage of BW (in all percentage WL categories), and a lower proportion of patients who had gained weight, compared with both the Røros and the St.Olavs group (all p<0.001). This was also found when comparing RYGB with the combined lifestyle group (all p<0.001). The Ebeltoft group was not significantly different from the RYGB in any of the weight change categories. The only significant difference in weight change between the lifestyle groups was the significantly higher proportion of patients with a WL ≥10% in the

Ebeltoft group, compared to the Røros group (see Table 2).

Table 2. Percentage of patients' weight change after 5 years in each treatment group

Weight change (%)	RYGB	Ebeltoft	Røros	St.Olavs	p-value (4 gr)	Lifestyle combined	p-value (2 gr)
Weight gain	0.0% (0) [abc]	12.5% (1)	38.9% (14) [a]	37.9% (11) [b]	<0.001	35.6% (26) [c]	<0.001
≥5% WL	92.5% (37) [abc]	62.5% (5)	44.4% (16) [a]	37.9% (11) [b]	<0.001	43.8% (32) [c]	<0.001
≥10% WL	82.5% (33) [abc]	62.5% (5) [d]	16.7% (6) [ad]	24.1% (7) [b]	<0.001	24.7% (18) [c]	<0.001
≥15% WL	75.0% (30) [abc]	37.5% (3)	11.1% (4) [a]	6.9% (2) [b]	<0.001	12.3% (9) [c]	<0.001
≥20% WL	57.5% (23) [abc]	12.5% (1)	8.3% (3) [a]	6.9% (2) [b]	<0.001	8.2% (6) [c]	<0.001

Data is presented as percentage in each group (n). Values with identical superscript letters across columns denote significant differences between groups (p<0.05). RYGB: Roux-en-Y gastric bypass. WL: Weight loss.

4.2.2. Changes in risk factors

Changes in glucose plasma levels

Changes in all risk factors over time for all groups are shown in Table 3. Results from analyzing blood glucose between the groups at the different times, yielded only significant differences at the 5-year follow-up (p<0.001), where the RYGB group had a significantly lower glucose level compared to all other lifestyle groups: Ebeltoft (p<0.05), Røros (p<0.05), and St.Olavs (p<0.001) (see Table 3). There were no significant changes over time in glucose within the RYGB group. Significant glucose changes within each group were only found in the Røros group (p<0.01), where a significant increase from year 1 to year 5 (p<0.01) was observed (see Table 3).

Analysis with RYGB versus combined lifestyle group showed a lower glucose level in the RYGB group at the 1- and 5-year follow-up (p<0.05 and p<0.001, respectively). Changes within the lifestyle group were significant (p<0.001) and a further look revealed a significant increase in glucose from year 1 to year 5 (p<0.001).

Table 3. Changes in risk factors over time in the different treatment groups

	RYGB			Ebeltoft			Røros			St.Olavs			Lifestyle combined		
	BL	**Y1**	**Y5**	**BL**	**Y1**	**Y5**	**BL**	**Y1**	**Y5**	**BL**	**Y1**	**Y5**	**BL**	**Y1**	**Y5**
Glucose (mmol/L)	5.33 [4.66, 6.00]	5.22 [a] [4.58, 5.86]	5.07 [bcde] [4.45, 5.68]	6.68 [5.44, 7.91]	5.23 [3.99, 6.46]	6.73 [b] [5.36, 8.10]	5.99 [5.40, 6.57]	5.25 [1] [4.58, 5.91]	6.11 [c1] [5.45, 6.76]	5.52 [4.88, 6.17]	5.46 [4.48, 6.45]	6.36 [d] [5.69, 7.04]	5.88 [5.47, 6.29]	5.25 [a1] [4.75, 5.74]	6.29 [e1] [5.85, 6.74]
Total cholesterol (mmol/L)	4.26 [3.95, 4.57]	4.10 [3.80, 4.40]	4.71 [4.43, 4.99]	5.13 [4.54, 5.72]	5.09 [4.50, 5.68]	5.21 [4.59, 5.82]	4.74 [4.47, 5.02]	4.65 [4.34, 4.97]	4.93 [4.64, 5.23]	5.23 [4.92, 5.54]	4.85 [4.41, 5.30]	5.26 [4.94, 5.57]	4.98 [4.78, 5.18]	4.81 [4.58, 5.04]	5.09 [4.89, 5.30]
HDL (mmol/L)	1.11 [12] [1.01, 1.22]	1.41 [13] [1.31, 1.51]	1.64 [abcd23] [1.55, 1.74]	1.37 [4] [1.17, 1.57]	1.61 [ef45] [1.41, 1.81]	1.33 [a5] [1.12, 1.54]	1.14 [1.05, 1.24]	1.24 [e] [1.13, 1.34]	1.12 [b] [1.02, 1.22]	1.28 [1.18, 1.39]	1.19 [f] [1.05, 1.34]	1.29 [c] [1.18, 1.39]	1.22 [1.15, 1.29]	1.30 [1.22, 1.38]	1.21 [d] [1.14, 1.28]
LDL (mmol/L)	2.46 [2.18, 2.73]	2.25 [1.99, 2.52]	2.54 [2.29, 2.79]	3.15 [2.62, 3.67]	3.01 [2.49, 3.54]	3.28 [2.73, 3.82]	2.85 [2.61, 3.10]	2.83 [2.55, 3.11]	3.10 [2.84, 3.37]	3.25 [2.97, 3.52]	3.08 [2.69, 3.48]	3.32 [3.04, 3.60]	3.04 [2.87, 3.22]	2.95 [2.74, 3.15]	3.21 [3.03, 3.39]
TG (mmol/L)	1.53 [1.29, 1.77]	0.98 [0.75, 1.21]	1.17 [0.95, 1.38]	1.36 [0.90, 1.82]	1.04 [0.58, 1.50]	1.32 [0.84, 1.80]	1.67 [1.45, 1.89]	1.30 [1.06, 1.55]	1.58 [1.36, 1.81]	1.55 [1.31, 1.79]	1.28 [0.92, 1.63]	1.44 [1.19, 1.69]	1.59 [1.44, 1.74]	1.25 [1.07, 1.43]	1.50 [1.34, 1.65]

The table displays mean group values [CI]. Values with similar superscripts across columns are significantly different to one another ($p<0.05$). Letters represent significant differences between groups. Numbers represent significant differences within groups. BL: Baseline. Y1: Year 1. Y5: Year 5. RYGB: Roux-en-Y gastric bypass. HDL: High-density lipoprotein. LDL: Low-density lipoprotein. TG: Triglycerides.

Changes in total cholesterol plasma levels

Analysis showed that total cholesterol was significantly associated with treatment group ($p<0.001$) and time ($p<0.001$), but not with the interaction treatment group*time. Post hoc tests revealed that the RYGB group had the overall lowest total cholesterol compared to the lifestyle groups (Ebeltoft ($p<0.05$), and St.Olavs ($p<0.001$)). Comparison of time-points yielded a significant overall increase in total cholesterol from baseline to year 5 ($p<0.05$) and from year 1 to year 5 ($p<0.001$).

With two-group analysis, the significant overall associations were the same as the ones found in the four-group analysis. There was an increase in total cholesterol both from baseline to year 5 ($p<0.05$) and from year 1 to year 5 ($p<0.001$). The RYGB had an overall significantly lower total cholesterol compared to the combined lifestyle group ($p<0.001$).

Changes in HDL plasma levels

Treatment group ($p<0.01$), gender ($p<0.01$), time ($p<0.05$), and the interaction treatment group*time ($p<0.001$) was overall significantly associated with plasma HDL. Post hoc test of treatment group revealed that overall HDL was higher in the Ebeltoft group compared to the Røros group ($p<0.05$). Pairwise comparison of time showed a significant overall increase in HDL from baseline to year 1 ($p<0.05$). Women had in general a higher HDL level compared to men (+0.187 mmol/L, 95% CI [0.050, 0.324] $p<0.01$). Comparisons of treatment group at each time-point (see Table 3), showed a significant difference at year 1, where the Ebeltoft group had a significantly higher HDL than Røros ($p<0.01$) and St.Olavs ($p<0.01$). At the 5-year follow-up the RYGB group had a significantly higher mean HDL than the other lifestyle groups: Ebeltoft, Røros and St.Olavs ($p<0.05$, $p<0.001$, $p<0.001$, respectively).

Inspection of within-group changes revealed no significant changes over time in neither the Røros nor the St.Olavs group. In the Ebeltoft group there was a significant increase in HDL from baseline to year 1 ($p<0.05$), and a reduction from year 1 to year 5 ($p<0.01$) (see Table 3). In the RYGB group there was a significantly increase from both baseline to year 1 ($p<0.001$), and from year 1 to year 5 ($p<0.001$). Hence, the HDL level was significantly greater at the 5-year follow-up in this group ($p<0.001$).

Two-group analysis did not reveal a significant relationship between HDL and gender, but treatment group, time, and the interaction treatment group*time was significantly associated with HDL (all $p<0.01$). Overall the RYGB had a significantly higher HDL than the combined lifestyle group ($p<0.05$). Post hoc test revealed a general increase in HDL from

baseline to year 1 ($p<0.001$) and from baseline to year 5 ($p<0.001$). At the 5-year follow-up the RYGB had a significantly higher HDL level when compared with the combined lifestyle group ($p<0.001$). There were no significant changes of HDL within the lifestyle group.

Changes in LDL plasma levels

The LMM analysis showed an overall significant relationship between LDL and time ($p<0.01$), and LDL and treatment group ($p<0.001$). There was no significant association between LDL and the interaction treatment group*time. Pairwise comparisons of treatment groups revealed that the RYGB group had an overall significantly lower mean LDL compared to Ebeltoft ($p<0.05$), Røros ($p<0.01$) and St.Olavs ($p<0.001$). In general there was a significant increase in LDL from year 1 to year 5 ($p<0.01$).

Two-group analysis yielded the same significant overall relationships as what was found in analysis with the four groups (both $p<0.01$). The RYGB group had an overall lower LDL compared to the combined lifestyle group ($p<0.001$), and overall LDL increased from year 1 to year 5 ($p<0.01$).

Changes in TG plasma levels

LMM revealed an overall significant association between TG and treatment group ($p<0.05$) and TG and time ($p<0.001$). Further inspection of treatment groups with Bonferroni correction showed that the RYGB had an overall significantly lower TG level compared to the Røros group ($p<0.05$). Post hoc test of time yielded an overall significant decrease in TG from baseline to year 1 ($p<0.001$), an increase from year 1 to year 5 ($p<0.001$), but at the 5 year follow-up the general TG level remained significantly lower than at baseline ($p<0.01$).

Analysis with the RYGB group versus the combined lifestyle showed the same overall significant results (both $p<0.01$). Pairwise comparison of time found the same significant effects as in the four-group analysis. Overall, the RYGB group had a significantly lower TG level ($p<0.01$).

4.2.3. Changes in comorbidities

5-year changes in comorbidities in the different treatment groups are displayed in Table 4. Changes in comorbidities among the groups, either diagnoses or remission from a condition,

were only significantly observed with hypertension (see Table 4). Both when analyzing the completers in two and four groups, the RYGB had a significant larger proportion of patients with reversal of hypertension (both p<0.001).

Table 4. Change in comorbidities at the 5-year follow-up in each treatment group

	RYGB	Ebeltoft	Røros	St.Olavs	p-value (4 gr)	Lifestyle combined	p-value (2 gr)
Asthma							
Resolved	53.8% (7)	0% (0)	25% (1)	50% (3)	p=0.427	30.8% (4)	p=0.428
Diagnosis	0% (0)	20% (1)	6.9% (2)	0% (0)	p=0.139	5.8% (3)	p=0.550
Arthritis							
Resolved	25% (2)	50% (1)	20% (1)	20% (1)	p=1.000	25.0% (3)	p=1.000
Diagnosis	7.7% (2)	0% (0)	16.0% (4)	15.8% (3)	p=0.787	14.3% (7)	p=0.484
DM2							
Resolved	40.0% (2)	0% (0)	33.3% (2)	33.3% (1)	p=1.000	27.3% (3)	p=1.000
Diagnosis	0.0% (0)	16.7% (1)	7.4% (2)	4.8% (1)	p=0.179	7.4% (4)	p=0.292
Coronary disease							
Resolved	0% (0)	0% (0)	0% (0)	0% (0)		0% (0)	
Diagnosis	2.9% (1)	12.5% (1)	0.0% (0)	4.2 % (1)	p=0.258	3.2% (2)	p=1.000
Hypertension							
Resolved	78.6% (11) [abc]	40.0% (2)	17.6% (3) [a]	12.5% (2) [b]	p<0.001	18.4% (7) [c]	P<0.001
Diagnosis	4.8% (1) [a]	66.7% (2) [a]	11.8% (2)	11.1% (1)	p=0.060	17.2% (5)	p=0.380
Sleep apnea							
Resolved	81.8% (9) [a]	50.0% (1)	40.0% (2)	0.0% (0)	p=0.168	37.5% (3) [a]	p=0.074
Diagnosis	8.3% (2)	0.0% (0)	18.5% (5)	13.0% (3)	p=0.636	14.3% (8)	p=0.715
Cholelithiasis							
Resolved	100.0% (3)	50.0% (1)	50.0% (2)	100.0% (3)	p=0.373	66.7% (6)	p=0.509
Diagnosis	6.3% (2)	0.0% (0)	0.0% (0)	0.0% (0)	p=0.415	0.0% (0)	p=0.139
Eating disorder							
Resolved	33.3% (2)	12.5% (1)	50.0% (2)	50.0% (3)	p=0.901	54.5% (6)	p=0.620
Diagnosis	6.9% (2)	16.7% (1)	13.8% (4)	5.6% (1)	p=0.587	11.3% (6)	p=0.706
Mental disorder							
Resolved	27.3% (3)	100.0% (2)	50.0% (6)	36.4% (4)	p=0.298	48.0% (12)	p=0.295
Diagnosis	29.2% (7)	20.0% (1)	9.5% (2)	16.7% (2)	p=0.353	13.2% (5)	p=0.186

Data is shown as percentage (n). Resolved: Patients who had comorbidity at baseline, but had remission within the 5-year follow-up. Diagnosis: Did not have the comorbidity at baseline, but developed it within the 5 years. Numbers with similar superscripts across columns are significantly different to one another (p<0.05). DM2: Diabetes Mellitus type 2. RYGB: Roux-en-Y gastric bypass.

78.6% of patients in the RYGB group with baseline hypertension had reversed it at the 5-year follow-up, compared to 18.4% in the combined lifestyle group, and 17.6% and 12.5% in the

Røros and St.Olavs group, respectively. Ebeltoft did not differ significantly from the RYGB group when analyzing with four groups. There was a tendency (p=0.074) that a larger proportion of patients in the RYGB group had a remission of sleep apnea compared to the combined lifestyle group (81.8% vs. 37.5%).

4.2.4. Predicting 5-year body weight change

Predicting 5-year BW change from all completers

Using multiple regression to predict 5-year change in BW with 1-year change in BW (heron symbolized with $\Delta_{bl\text{-}y1}$) yielded a significant regression model ($p<0.001$). Both when all predictors (age, sex, baseline BMI and $\Delta_{bl\text{-}y1}$) were entered together, and when $\Delta_{bl\text{-}y1}$ was the only predictor, a significant regression model was found. A closer look revealed significant result with $\Delta_{bl\text{-}y1}$ as a predictor in both analyses ($p<0.001$). In both analyses with all predictors and with only $\Delta_{bl\text{-}y1}$ as a predictor approximately 59.0% ($R^2 = 0.590$) of the variation in the outcome was accounted for by $\Delta_{bl\text{-}y1}$. When $\Delta_{bl\text{-}y1}$ was the only predictor the regression equation became: 5-year BW change: $6.70 + 0.87(\Delta_{bl\text{-}y1})$. The other variables did not significantly predict 5-year change in BW.

Predicting 5-year BW change in the RYGB group and the combined lifestyle group

Predicting BW change after 5 years with multiple regression resulted in a significant regression model when all predictors were entered together, both in the RYGB and the combined lifestyle group (both $p<0.001$).

In the RYGB group $\Delta_{bl\text{-}y1}$ as a predictor was significant both when it was the only predictor, and with all predictors together. When baseline BMI was the only predictor it yielded a significant regression model ($p<0.05$), accounting for 12.4% of the variation. When baseline BMI and $\Delta_{bl\text{-}y1}$ were entered together as predictors, only $\Delta_{bl\text{-}y1}$ as a predictor was significant. With $\Delta_{bl\text{-}y1}$ as a predictor for 5-year BW change 42.4% ($R^2=0.424$) of the variation was accounted for by this predictor. The regression equation for 5-year BW change: $0.71 + 0.82(\Delta_{bl\text{-}y1})$.

In the combined lifestyle group, only the $\Delta_{bl\text{-}y1}$ was a significant predictor, both when entering all predictors together and when entering $\Delta_{bl\text{-}y1}$ as a predictor alone. With only $\Delta_{bl\text{-}y1}$ as a predictor approximately 29.8% ($R^2=0.298$) of the variation in 5-year BW change was

accounted for by this predictor. The regression equation: 5-year BW change: 3.98 + 0.58($\Delta_{bl\text{-}y1}$).

4.3. Intention-to-treat analysis

Analyses of 5-year BW change done with completers and the two intention-to-treat are shown in Table 5.

Table 5. 5-year weight change in each treatment group with different analysis

	RYGB	Ebeltoft	Røros	St.Olavs	Lifestyle combined
Completers (n = 113)	-30.9 kg * [-35.9, 25.9]	-13.3 kg § [-24.5, -2.1]	-5.5 kg § [-10.8, -0.2]	-4.1 kg [-10.0, 1.8]	-5.8 kg * [-9.7, -1.9]
LOCF (n = 163)	-35.0 kg * [-39.3, -30.8]	-13.4 kg § [-22.6, -4.3]	-6.0 kg * [-10.6, -1.5]	-3.7 kg [-8.4, 1.0]	-5.9 kg * [-9.1, -2.7]
BCF (n = 163)	-22.1 kg * [-26.7, -17.4]	-8.9 kg [-18.8, 1.1]	-4.0 kg [-8.9, 0.9]	-2.6 kg [-7.8, 2.5]	-4.0 kg § [-7.4, -0.5]

Data is presented as mean change [CI]. Values with § ($p<0.05$) or * ($p<0.01$) represent significant 5-year changes from baseline weight within each treatment group. BCF: Baseline carried forward. LOCF: Last observation carried forward. RYGB: Roux-en-Y gastric bypass.

4.3.1. Last observation carried forward analysis

For the 163 patients included in the LOCF mean follow-up time was 47.4 months (SD = 19.5), close to 4 years. Mean follow-up time in each treatment group was: RYGB: 47.0 months ± 20.6 (3.9 years), Ebeltoft: 48.0 months ± 18.1 (4 years), Røros: 51.2 months ± 15.6 (4.3 years), and St.Olavs: 43.7 months ± 22.0 (3.6 years). There were no significant differences in mean follow-up time between the four groups.

LOCF analysis done with both two and four groups, showed the same overall significant results of time, treatment group, gender and the interaction treatment group*time (all $p<0.05$) on BW, as what was found with completers. Pairwise comparison of the treatment groups at each time-point also resulted in the same significant results (but slightly different p-values), the only exception being that in the analysis with four groups, the St.Olavs group had a significantly lower BW at baseline compared to the Ebeltoft group and the Røros group ($p<0.05$ for both). Two-group analysis found the same significant results as

with completers. Within-group changes were the same as found in completers.

4.3.2. Baseline carried forward analysis

Findings from BCF analysis with both two and four groups, revealed the same overall significant associations between BW and the following: time, treatment group, gender, and the interaction treatment group*time (all $p<0.05$), as found with completers. Comparison of the treatment groups at each time-point also yielded exactly the same significant results (but slightly different p-values), the only exception being that in the four-group analysis, the St.Olavs group had a significantly lower BW at baseline compared to the Ebeltoft group and the Røros group (both $p<0.05$). Two-group analysis resulted in the same significant results as with completers. Analysis found the same significant changes within the St.Olavs and the RYGB group as analysis of completers. Changes from baseline to year 1, and year 1 to year 5 were the same as with completers in the Ebeltoft and Røros group. In the two latter groups the BW at year 5 was no longer significantly lower than baseline BW, which was found in analysis of completers. BCF analysis with the combined lifestyle group showed the same results as with completers.

5.0. Discussion

This study aimed at comparing RYGB with three different lifestyle interventions in morbidly obese patients after 5 years. It was found that RYGB was associated with the best outcomes in terms of WL; risk factors; and remission of hypertension and sleep apnea, compared to the lifestyle intervention groups, which supports the hypothesis set prior to the study. However, lifestyle interventions produced significant WL as well.

As expected, RYGB resulted in a larger 5-year WL (30.9 kg) compared to the lifestyle groups, and with similar WL reported in previous studies on RYGB (38, 40, 43, 44, 53, 89-91). However, the Ebeltoft and the Røros groups did have a significant 5-year WL (-13.3 kg and -5.5 kg, respectively). The St.Olavs intervention did not result in any significant WL after 5 years (-4.1 kg). A possible explanation may be the absence of follow-up sessions from trained personnel after the first year. In contrast, the two other lifestyle intervention groups had optional regular follow-up sessions, and both groups had a significant WL. This might suggest that regular or scheduled follow-up sessions are important for WL maintenance. A 4-year follow-up study with a combined behavior treatment program reported that booster sessions positively correlated with WL in morbidly obese (83). Long-term follow-up sessions might result in WL success (85, 92, 93). Moreover, a possible reason why the Ebeltoft group had a significant WL at the 5-year follow-up may be due to the magnitude of WL the first year. Among the lifestyle groups, Ebeltoft had the highest WL the first year (-30.2 kg, vs. -19.5 kg in Røros and -8.4 kg in St.Olavs). This WL was not significantly higher compared to the other lifestyle groups, probably due to the smaller sample size. Multiple regression in the present study revealed that 1-year WL was associated with 5-year WL. This is in line with findings of Anderson et al. (2007) who reported that morbidly obese individuals with a mean WL of 61 kg in 44 weeks maintained a WL of 30 kg at 5 years (70). Additional studies have indicated that greater initial WL is associated with a higher long-term WL success (58, 86, 94-99).

The present study reported a 4.4% average WL in the combined lifestyle group at 5 years, and that 24.7% achieved a ≥10% WL. This is similar to observations from a study with an ILI on morbidly obese patients with DM2 including long-term follow-up sessions (92). However, studies with WL camps or shorter WL programs in morbidly obese also report

similar 4-5 year WL (86, 100). As previously mentioned, this might be because of the large initial WL. But, the fact that shorter WL interventions with little or no follow-up sessions can produce similar WL as more ILI in the long term, suggests that this could be an alternative to residential intermittent programs. This, especially for people who are unable to be away from work or family for longer periods over several years.

The present study reported a 5.8 kg WL in the combined lifestyle group after 5 years. Some studies report significant sustained WL in (morbidly) obese (70, 85, 99-102), while others have yielded less favorable long-term results following lifestyle interventions with weight regain as a normal outcome (64, 86, 100, 103-105). Björvell & Rössner (1985) showed that behavioral modification, exercise, nutritional advice and readmission at relapse, yielded WL of 11.7 kg after 4 years, and 10.6 kg was the mean WL at the 10-12 year follow-up (83, 85). These results are considerably larger compared with findings from the current study, which might be due to a lack of very intensive interventions with a large focus on relapse treatment (as in Björvell & Rössner study). Nevertheless, even though a very large WL was not found with lifestyle interventions in the present study, the intervention might still have prevented some patients from gaining additional BW or having a stable BW (37, 44, 106). Furthermore, other benefits that were not evaluated in this thesis might also have occurred, such as improved body composition and quality of life; lower medication use; healthier food intake; and increased PA, as other studies have reported after lifestyle interventions (102, 107, 108).

BCF analysis revealed that even with the worst possible outcome (back to baseline BW) in the lost to follow-up patients the WL in RYGB and the combined lifestyle group was still significant, which suggests that a significant part of the patients benefited from these interventions.

The RYGB group had significant improvements in HDL and had an overall better risk factor profile compared to all lifestyle groups, however additional improvements within the RYGB might have been expected because of the large WL (109).

No significant 5-year improvements of risk factors were found within the RYGB or the lifestyle groups, with the exception of HDL in the RYGB group. Small sample sizes and missing values decreases statistical power, which may have affected the results. Furthermore, many of the patients in all groups had risk factors within the reference range both at baseline and after 5 years (data not shown). A study from 2007 found that morbidly obese with abnormal baseline LDL-levels had greater reductions after the WL phase (of average 44

weeks) (70). This suggests that improvements are more prevalent in patients with abnormal risk factor values at baseline. Additionally, risk factors are affected by other parameters as well. Diet and PA may have affected changes in risk factors both positively and negatively in all treatment groups in the present study, but this was not accounted for.

As previously noted, RYGB in the present study was associated with an overall better risk factor profile. This is in line with a study from 2012 that revealed significantly better 6-year improvements in the RYGB group in all risk factors (glucose, total cholesterol, HDL, LDL and TG) compared to the two non-intervened control groups in the study (44). Furthermore the SOS-study reported lower 2- and 10-year glucose levels in the surgically treated group while it had increased in the control group (no standardized treatment). Moreover, HDL and TG were more favorable in the surgical group compared to the control group (37). Subgroup analysis of the surgical group in the SOS-study revealed that gastric bypass had the best improvements in risk factors. However, the two previously mentioned studies only compare findings to control groups. They suggest that RYGB is better compared to little, or no treatment, while the current study suggests that RYGB is better than lifestyle interventions as well.

Although no improvements were observed at the 5-year follow-up in the lifestyle intervention groups some studies in the morbidly obese report improvements in risk factors in the longer term. A study in obese (average BMI 36 ± 5.9 kg/m^2) comparing an ILI with a control group (receiving diabetes support and education only), found that the ILI had greater improvements in glucose and HDL compared to the control group, at the 4-year follow-up (102). The ILI group had a 4.7% WL, while the control group had 1.1%. Although this was a significant difference in WL, it might suggest that a greater WL is necessary to achieve long-term improvements in risk factors with lifestyle interventions, as no significant improvements were observed in total cholesterol, LDL or TG. Additionally, reports from the same study show that morbidly obese who lost ≥10% of their BW with an ILI were more likely to achieve the American Diabetes Association's risk factor goals at the 4-year follow-up compared to the morbidly obese who were weight stable (92). However, another study reported only significant healthier blood glucose after 5 years in the group who had lost more BW after the initial 6-week intervention, and that this was significantly worse in participants who had gained weight (103). This study suggests that further WL after initial WL might result in improvements of risk factors, while weight gain may worsen them. So although there were no significant 5-year improvements in risk factors in the lifestyle groups in the present study, the small WL and/or the interventions might have prevented a worsening (except glucose in the

combined lifestyle group). A review from 2011 mentions that to sustain improved lipid levels over a longer period (3 years or more) a higher WL might be needed, and that additional lifestyle changes needs maintaining as well. Since this was concluded from BMI <35 kg/m^2 population, it might suggest that it is even more important in the morbidly obese.

With a WL of 4.4% in the combined lifestyle group this might explain no improvements in risk factors. This is supported by the SOS-study, which reported that a WL (from both surgical and non-surgical treatment) between 9-38% resulted in improvements in several risk factors after a 10-year follow-up in severely obese subjects (109). A WL of 5% was not enough to improve risk factors. When surgical and conventional treatment was analyzed separately, they found similar improvements in risk factors when a similar weight was lost. The exception was glucose where surgery was more favorable

Weight gain might worsen risk factors (103). Overall, weight gain was not observed in the present study at 5 years, but with no adjustments for medications it is not certain that no risk factors were worsened. As several studies have suggested (80, 92, 109) a large WL in the long-term is needed in the morbidly obese to see any improvements in risk factors. Hence, there is a need to develop lifestyle interventions that can achieve a greater WL in the long term.

The current study reports significant remission of hypertension in the RYGB group (78.6%) compared to the combined lifestyle group (18.4%). Adams et al. (2012) and the SOS-study (2004) both report significant remission of hypertension after RYGB compared to control groups, which was either non-intervened or had no standardized intervention (37, 44). Unexpectedly, the remission rate in the lifestyle group was similar to the control groups in the two previously studies. This suggests that the effect from lifestyle interventions on hypertension in the current study was not present. There might be several reasons for this, where one might be because comorbidities (thereby hypertension) were self-reported.

There was also a tendency for the proportion of patients with remission of sleep apnea to be larger in the in the RYGB group (81.8%) compared with the combined lifestyle group (37.5%). This is in accordance with findings from Fredheim et al. (2013), who also mentions that the improvements in sleep apnea might be connected to the WL, not the RYGB itself (110). This might indicate that a larger WL from lifestyle interventions might improve sleep apnea as others have reported (111, 112).

Although the present study did not yield significant remission rates of DM2 in the RYGB group (40%) compared to the lifestyle groups, that may be due to the fact that only a

few of the completers had DM2 at baseline. In fact, numerous of studies have reported great effects of RYGB on DM2 both in the short and long term (37, 40, 43). Adams et al. (2012) found significant remission of diabetes (62%) in the RYGB group treated at the 6-year follow-up (44).

Although there was only a significant remission of hypertension and a tendency of sleep apnea being in remission in the RYGB compared to the lifestyle group in the current study, several studies have shown that RYGB can lead to remission of comorbidities (38, 40, 44, 113). However, it needs to be emphasized that in the present study some patients in the lifestyle group did resolve their comorbidities, even though their proportions were much lower than the RYGB group. Although RYGB may result in a higher remission of comorbidities, long-term research on the effects of lifestyle interventions in morbidly obese with comorbidities is lacking. Nonetheless, lifestyle intervention might prevent new cases of comorbidities, as they often promote increased PA and healthy food.

5.1. Strengths and limitations

This study has several strengths. First, the long-term follow-up was probably the most important. Secondly, very few studies have compared RYGB with three different lifestyle interventions in the morbidly obese. Third, the whole study sample was from a bariatric waiting list, which makes them more comparable. An additional strength is the use of LMM that accounts for each patient's random effect and missing values.

However, there are also several limitations in this study. The two main limitations: non-randomization and lack of non-intervened control group. Randomizing patients would be unethical, especially with risks associated with surgery. Additionally, morbidly obese are entitled to treatment in Norway, and giving them the option they want might increase the probability for success. Another limitation in this study was no power calculation of the study sample. This was because the study started as an initiative from the Central Norway Regional Health Authority (Helse Midt-Norge) to find an alternative to surgery, and therefore the sample size was based primarily on treatment capacity and increasing the numbers in each treatment group would delay the study. Ideally in a prospective study like this, measurements of the variables should have been done more frequently, but lack of resources prevented this. Another possible limitation was that patients may have changed or dis-followed their interventions and not mentioned this, which may have influenced the results (both in a

positive and negative way). Although patients should have reported use of other interventions, this might have been omitted. A limitation to the generalizability of the study was that the study population was mostly women with Caucasian ethnicity. Although the inclusion criteria were quite broad, the study participation was only offered to people awaiting bariatric surgery that were already seeking and wanting help for their obesity. From this, arguments can be made that the results can only be generalized to individuals seeking obesity treatment. Another limitation is the generalizability of the results regarding the comorbidities. Comorbidities were self-reported, and it is unknown if these diseases were diagnosed by a physician. Some diseases like mental- or eating disorders are taboo, and might therefore be underreported. Additionally, mental disorders can range from 'normal' depression to severe disorders that disrupt and limit a normal life, which makes the category unspecific and very broad. Furthermore, a yes/no answer to a presence of a disease does not show improvements. This might have occurred in for example asthma and hypertension where the usage of medications can have been reduced. The reliability of how the comorbidities were reported and the uncertainty regarding specifics makes the validity of the results questionable. Moreover, findings might also be generalized to completers only, as they were the basis of the main analyses. Although the 5-year retention rates were 54.1%, loss-to-follow-up is a limitation. Even though intention-to-treat analyses were included, these analyses are based on speculations. Other limitations were not controlling for known and unknown cofounders like medication use or for different diets, as this might affect BW and blood lipids. A limitation in the lifestyle groups is that it is unclear which part of the treatment gave the significant WL; if it was diet, PA or behavior modifications.

5.2. Future research

Finding effective lifestyle interventions tailored to the treatment of morbidly obese are important, as an alternative to bariatric surgery should exist. As it would seem that a WL higher than 5% is needed to produce improvements in risk factors and comorbidities, future research should focus on how to attain a larger WL in the longer term. For interventions to be cost-effective future studies should, possibly with subgroup analysis, try to identify who would benefit from different interventions in the long term (in example rapid WL vs. long-term follow-up). Furthermore, a goal should be to early distinguish the individuals who do not meet their WL goals to develop and implement new individual and adapted interventions.

6.0. Conclusions

In the treatment of morbidly obese, RYGB is associated with a higher WL, overall better risk factors and larger remission rates of hypertension at the 5-year follow-up, compared to patients treated with lifestyle interventions. Notably, patients in the lifestyle intervention groups did have a significant 5-year WL, which might have prevented weight gain and a worsening of several risk factors, in addition to affecting health positively. Future research should focus on how to achieve a larger WL with lifestyle interventions tailored for the morbidly obese in the long term.

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