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Bariatric Surgery

Outcomes after Gastric Bypass and Duodenal Switch

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Abstract

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Obesity is associated with increased morbidity and mortality. A BMI >40 kg/m^2 shortens life expectancy by about 10 years. The obesity related comorbidities diabetes, hypertension, dyslipidemia and sleep apnea contributes to the increased risk of cardiovascular events. There is also an increased risk of some forms of cancer (e.g. colon, breast, and prostate cancer) as well as mental illness (depression and low self-esteem). Bariatric surgery is indicated for those with a BMI >35 kg/m^2. Unfortunately, there are an increasing number of patients seeking bariatric surgery who are super obese (BMI >50 kg/m^2), a condition more difficult to treat because of insufficient weight loss with standard operations, like the Roux-en-Y Gastric Bypass (RYGB). Therefore some surgeons advocate the Duodenal Switch (DS) in super obese patients, because DS results in greater and more sustained weight loss. However, DS is a technically more challenging operation and is associated with an increased risk of malnutrition and surgical complications. There are also concerns about an excessive loss of fat-free mass during weight loss after RYGB and especially after DS.

This thesis focuses on weight-loss, effect on comorbidities, quality of life and complications after DS and RYGB, respectively, with comparisons between the two procedures in patients with super obesity.

DS resulted in a superior weight loss compared to RYGB (paper I, II and III) and body composition after weight loss did not differ compared with non-operated controls with the same BMI after surgery, for neither DS nor RYGB (paper I). Both DS and RYGB resulted in an improved metabolic control (paper II and III), but the effect on diabetes and hypertension was greater and maintained in the long-term after DS (paper III). Both DS and RYGB resulted in an improved physical quality of life, with greater improvements after DS (paper III). However, complications and long-term adverse effects were more common after DS (paper II and IV).

In conclusion, the superior weight loss and greater improvements in several obesity-related comorbidities after DS must be weighed against the increased risk of complications and long-term adverse effects compared to RYGB.

Keywords: Body composition, fat-free mass, resting metabolic rate, bariatric surgery, obesity, Roux-en-Y Gastric Bypass, Duodenal Switch, air-displacement plethysmography, Bod Pod, indirect calorimetry assessment, BAROS, quality of life, weight loss, diabetes, hypertension, dyslipidmia, depression, pain, antidepressants, opioids, complications, healthcare consumption, adverse events

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List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Skogar, M., Holmbäck, U., Hedberg, J., Risérus, U., Sundbom, M. (2016) Preserved Fat-Free Mass after Gastric Bypass and Duodenal Switch. *Obesity Surgery*, (2017) 27:1735–1740

II Skogar, M., Sundbom, M. (2017) Duodenal Switch Is Superior to Gastric Bypass in Patients with Super Obesity when Evaluated with the Bariatric Analysis and Reporting Outcome System (BAROS), *Obesity Surgery*, (2017) 27:2308–2316

III Skogar, M., Sundbom, M. (2019) Weight loss, Effect on Comorbidities and Quality of Life in the Long Term after Duodenal Switch and Gastric Bypass: A population-based cohort study. *Manuscript.*

IV Skogar, M., Sundbom, M. (2019) Complications, Adverse Events and Healthcare Consumption the First Ten Years after Duodenal Switch and Gastric Bypass in a Matched National Cohort. *Manuscript.*

Contents

Abbreviations

ADP	Air Displacement Plethysmograph
AGB	Adjustable Gastric Banding
BAROS	Bariatric Analysis and Reporting Outcome System
BIA	Bioelectric Impedance Analysis
BMI	Body Mass Index
BPD	Biliopancreatic Diversion
CCK	Cholecystokinin
CT	Computed Tomography
D_b	Body density
DS	Duodenal Switch
DXA	Dual energy X-ray Absorptiometry
FFM	Fat Free Mass
FM	Fat Mass
GLP-1	Glucagon-Like Peptide 1
JIB	Jejunoileal Bypass
MAQ	Moorehead-Ardelt quality of life Questionnaire
MCS	Mental Component Summary score (in SF-36)
MRI	Magnetic Resonance Imaging
NPR	National Patient Registry
PCS	Physical Component Summary score (in SF-36)
PYY	Peptide tyrosine tyrosine
QoL	Quality of Life
RMR	Resting Metabolic Rate
RYGB	Roux-en Y Gastric Bypass
SADI-S	Single Anastomosis Duodeno-Ileal Switch
SF-36	36-Item Short Form Survey
SG	Sleeve Gastrectomy
SOReg	Scandinavian Obesity Surgery Registry
SPDR	Swedish Prescribed Drug Register
TBW	Total Body Water
VBG	Vertical Banded Gastroplasty
WHO	World Health Organization

Introduction

Overweight (Body Mass Index [BMI] 25-30 kg/m^2) and obesity (BMI >30 kg/m^2) has increased dramatically world wide during the last decades, from 921 million in 1980 to 2.1 billion in 2013. The prevalence has increased by 28% for adults and 47% for children during this time period. [1] On a global perspective, obesity and its related diseases pose a greater threat to public health than malnourishment today. [2] The highest prevalence of obesity (>50%) is observed among men in Tonga and women in Kuwait, Kiribati, Micronesia, Libya, Qatar, Tonga and Samoa. In developed countries, men have the highest rates of overweight and obesity, while in developing countries, women exhibit higher rates. Obesity though, has higher prevalence in women overall. In Sweden 19% of men and 20% of women are obese. The US stands out for its high prevalence of obesity, with 32% of men and 34% of women being obese. [1]

Severe obesity (BMI >35 kg/m^2) is associated with increased morbidity and mortality. [3, 4] A BMI of 40-45 kg/m^2 shortens life expectancy by 8-10 years. [5] This is actually more than the effect of smoking, reducing life expectancy about 4 years. [6] The most important obesity-related comorbidities are diabetes, hypertension, hyperlipidemia and sleep apnea, all contributing to the increased risk for cardiovascular events. There is also an increased risk of some forms of cancer (e.g. colon, breast, and prostate cancer) as well as mental illness (depression and low self-esteem).

Diet and behavioral changes and increased physical activity are first line treatment for obesity. If these interventions have failed, surgery is indicated for those with severe obesity i.e. BMI >35 kg/m^2. Indications for surgery have largely been BMI-based since the 1991 consensus meeting. [7] These surgical procedures have been called bariatric, after *baros,* Greek for fat. The number of bariatric procedures has increased exponentially during recent decades, since surgery is the only available treatment with reliable and lasting result in these patients. [8, 9] Long-term results after bariatric surgery include sustained weight loss, high remission rates of diabetes, hypertension and dyslipidemia, and improved quality of life. [8, 10-12] Unfortunately, the prevalence of patients with very high BMI-levels has increased rapidly in recent years [13] and more than one quarter of the patients seeking bariatric surgery in the US have a BMI >50 kg/m^2, [14] a condition referred to as super obesity. The most common bariatric procedures, world wide and in Sweden, are the Roux-en Y Gastric Bypass (RYGB) and Sleeve Gastrectomy (SG). [15, 16] However, both RYGB and SG have an insufficient weight loss in patients with super obesity. More than half of the patients (50-78%) remain severely obese (BMI>35 kg/m^2) even after weight loss. [17-19] Therefore some surgeons advocate the Duodenal Switch (DS) in super obese patients, as it results in greater and more sustained weight loss. [20-22] However, DS is a technically more challenging operation and is associated with an increased risk of malnutrition and surgical complications. [23, 24]

The main focus of this thesis is on outcomes after DS and RYGB in patients with super obesity with comparisons between the two procedures.

Background

Etiology to obesity

It is well known that obesity develops from an imbalance between energy intake and energy expenditure. An imbalance of +100 kcal/day is enough to develop obesity over time. [25] A widespread view is that it is easy to deal with – “eat less and exercise more” – referring to the simple formula:

Energy stored = Energy intake – Energy expended.

However, even though the formula is true, the reason why some individuals develop obesity is complex and multifactorial.

Regulation of appetite

The regulation of appetite has a central role in the energy homeostasis. Many patients seeking help for severe obesity describes a lack of satiety after a meal and a constant feeling of being in need of something more. A dysfunction in their appetite regulation is thought to play a part in the development of severe obesity, however the exact mechanisms are largely unknown.

Hunger is influenced both by biological (e.g. hormones and signals from the gastrointestinal tract) and environmental factors (e.g. type of food and social context). The biological response to food intake is often referred to as “satiety signals” which are different depending on the characteristics of the nutrient ingested, i.e. taste, volume, energy density, osmolality and the proportions of macronutrients. The generated biological responses are depending on oral afferent stimulation, stomach distension, rate of gastric emptying, release of gastrointestinal hormones and plasma levels of glucose and other metabolites. Chemo- and mechanoreceptors in the gastrointestinal tract deliver information to the brain, mainly trough the vagal nerve. Metabolites also reach the circulation and induces endocrine responses in other organs, resulting in neurotransmitter synthesis in the brain which reflects the metabolic state [26], *figure 1*. Brain structures involved in the “hunger and satiety center” involve several nuclei in the hypothalamus (e.g. arcuate nucleus, nucleus tractus solitarius and paraventricular nucleus), nucleus accumbens (part of the brain rewarding circuit), as well as various structures of cerebral cortex (mainly frontal cortex). The interaction between hypothalamic structures and the rewarding system in the brain is mediated through cannabinoid receptors and some mutations in these receptors are connected to eating disorders and development of obesity in the early age. [27] Modulation of these receptors has also been a target for medical treatment of obesity (rimonabant [Accomplia®], a cannabinoid antagonist, now withdrawn due to psychiatric adverse effects like depression and suicide).

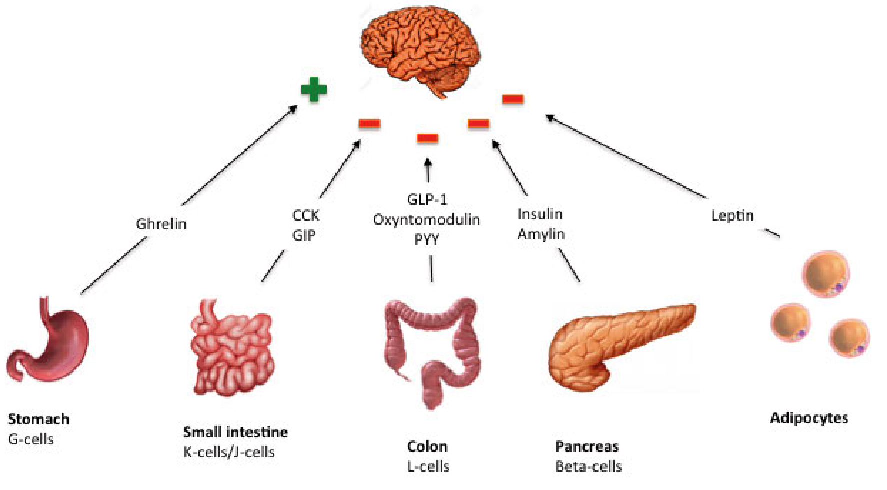


Figure 1. Model of gut hormones involved in the appetite regulation (modified from Wren and Bloom [28]).

The energy balance signals are usually divided into long and short acting. Long acting signals reflect the levels of energy stores and regulates body weight and the amount of energy stored as fat over the long term. These signals are mediated through **leptin** from adipocytes and **insulin** from the pancreas. Short acting signals are mediated through gut hormones and mechanical factors such as gastric distension, resulting in postprandial satiation and meal termination. This distinction between long and short acting signals is not absolute, since gut hormones like ghrelin and PYY (Peptide tyrosine tyrosine) are involved in both long and short-term regulation of energy balance. [28]

Ghrelin is the only known circulating hunger mediator. Endocrine cells synthetizing ghrelin (Ghrelin-cells) are found predominantly in the gastric fundus. There are several evidence that ghrelin regulates pre-prandial hunger and stimulates food intake. Levels of ghrelin increase on fasting and fall in proportion to the calories ingested. Weight loss by diet alone or by diet and exercise results in increased ghrelin levels, a physiological response counteracting weight loss. [28]

CCK (Cholecystokinin) is one of the most well studied gut hormones. The majority are synthetized in the duodenum and jejunum in response to nutrients in the gut and its main actions are delaying gastric emptying, stimulating pancreatic enzyme excretion, and stimulating gallbladder contraction. Activated CCK-receptors in the brain also have inhibitory effect on food intake. The half-life of CCK is only a few minutes and therefore a very short-time modulator of appetite. [28]

PYY is also a satiety hormone, released into circulation following a meal and suppressed by fasting. It is secreted from L-cells throughout the entire gastrointestinal tract, but particularly in the colon and rectum. Plateau levels are reached 1-2 hours after a meal and peak levels correspond to calories consumed. Its action involves increased absorption of fluid and electrolytes from the ileum, inhibit gastric and pancreatic secretions, gallbladder contraction and gastric emptying. Current data suggests that obese individuals have an impaired PYY release in response to food intake. [28]

GLP-1 (Glucagon-Like Peptide 1) and Oxyntomodulin are also released from intestinal L-cells in response to calorie intake. They appear to act both as short and long-term modulators of energy balance. GLP-1 is the most powerful incretin in humans and injection of GLP-1 analogues inhibits food intake. Obese individuals have a reduced secretion of GLP-1 and it is normalized after weight loss. Reduced GLP-1 secretion could therefore contribute to obesity and administration of GLP-1 analogues (Victoza®) has become a therapeutic target for obesity. A reduced calorie intake by 15% is seen if administered before a meal. Oxyntomodulin is also an effective anorectic hormone in humans but the importance in the development of obesity remains to be established. [28]

Environmental factors

Food shortage has been the norm during the human evolution. The homeostatic mechanisms evolved to allow the human race to survive famine are not well suited to the current situation.

Most countries in the world have experienced a shift of the dietary patterns during the last decades. There has been a large increase in animal food products (e.g. meat, eggs, diary products), added sugar to the diet, as well as more fats and oils and a decrease in total cereal and fiber intake. This has contributed to a more energy dense diet with more saturated fats and cholesterol and more calories consumed. Reasons for this shift has been, falling food prices, urbanization with spread of supermarkets and globalization with the emergence of large global food companies, which contributes to a constant food supply. The advantage in technology, which has led to a more sedentary lifestyle, is another contributing factor to the obesity epidemic. [29, 30]

These changes in diet and activity patterns are especially prominent in low-income populations. Obesity and its related conditions have an inverse association with socioeconomic status, since it is more common among adults with low income and low level of education. The lower level of health-related knowledge, greater difficulty to acquire healthier food (often more expensive), and fewer opportunities for recreational exercise, in combination with the easy access to energy dense food has been proposed as some of the factors, at least partly explaining, these health-inequities related to socioeconomic status. [31]

Genetic factors

The United States could be considered as a high-risk country for development of obesity, based on its high prevalence. Despite this, a large proportion of the population remains within normal weight range. [32] The question arises: Why is not everybody fat? This suggests that environmental factors are not the only reason for the growing obesity problem. Some individuals seem more susceptible to obesity, while others seem to be protected against weight gain, supporting the idea of genetic factors underlying the individual response. In a study from 1990 of identical twins grown up apart from each other, Stunkard et al. [33] concluded that the genetic influence on BMI were substantial, whereas the environment the child grew up in had little or no influence. In contrary, an American study found that genetic effects in males and females could explain 34% and 43% of variance in BMI changes, respectively, but environmental factors explained the majority of variance. [34] Children to obese parents have a 3 (one parent obese) to 15 (both obese) fold increased risk of being obese in adult life. Obesity during childhood and adolescence is also associated with the risk of obesity in adult life; with up to 22.3 fold increased risk for an obese child at the age of 10-14. [35] The search for genes, associated with an increased risk for obesity, started in the 1990's. Today, more than 50 genetic loci are identified to be associated with obesity. However, the effects of the identified loci are small and their ability to predict obesity is poor, not competitive with the predictive value of parental or childhood obesity. Personal genome profiling has been proposed to elucidate the increased risk in order to motivate people to adopt risk-reducing behaviors, but reports do not support this hypothesis and even suggest a feeling of loss of control and a "letting-go" of healthy life style. [35]

In summary, there is evidence supporting that people have different susceptibility being lean vs. obese, which interacts with environmental factors. [36]

Anthropometric measures and definitions

There are several different anthropometric methods to assess body composition and nutritional status. All methods vary in their validity, practicality and ability to identify obesity or malnutrition. Method of choice depends on the subject and the investigators ability to perform reliable measures and interpret the results appropriately. [37]

In the 19th century, the Belgian mathematician and physicist, Adolphe Quetelet, concluded that body mass in adults tends to vary with the square of height. [38] The Body Mass Index (BMI=weight/height^2 [kg/m^2]) originates from his observations and it has become the most common measure of body composition. However, BMI was originally developed as a risk indicator of obesity related diseases. BMI gained in popularity during the 1970s when researchers found it to be a good proxy for overweight and obesity related problems in epidemiological studies. The World Health Organization (WHO) has classified different BMI-categories, however, in the literature other definitions also occurs, see Table 1.

Visceral adipose tissue has a stronger association with diabetes than general fat, [39] and it also correlates to an increased risk of developing cardiovascular diseases. [40] Waist-to-hip ratio and waist circumference are proposed to better predict the visceral adipose tissue, than BMI, which measure general obesity. [41] However, all three anthropometric measures are highly correlated and appear to have the same ability to predict diabetes. [42]

Sagittal abdominal diameter is a measure of the anterior-posterior diameter in the L4-L5 region of the abdomen and is also proposed to better predict visceral adiposity and cardiovascular- and metabolic risks, but prognostic values in more diverse populations are not available. [37]

Skinfold calipers measures subcutaneous fat and allows an estimation of body fat. This procedure is also quick and requires noncomplex portable equipment, but this technique is more suitable for lean than obese individuals, since intra-abdominal fat cannot be assessed. [37]

Table 1. *Definitions of BMI-categories*

WHO classification	
<18.5	Underweight
18.5-24.9	Normal weight
25.0-29.9	Overweight
30-34.9	Obesity class 1
35-39.9	Obesity class 2
≥40	Obesity class 3
Other definitions	
≥35	Severe obesity
≥40	Morbid obesity
≥50	Super obesity

Measurement of body composition

As previously mentioned, BMI is the most common approximation of body composition. A major drawback of BMI is that body composition may vary among individuals with same BMI, as it does not quantify the relative amounts of various tissue masses in an individual. BMI is particularly inaccurate for people who are very athletic, since a high muscle mass can classify them in the overweight, or even obese, category. On the other hand, BMI is very easy to calculate.

To more accurately measure body composition, there are several different methods, each with its advantages and disadvantages. **Hydrostatic weighing** is considered "gold-standard", but it is time-consuming, often disliked by patients and impractical in most obese individuals. [43, 44] The hydrostatic weighing is an application of Archimedes' principle; a subject displaces its own volume of water and together with the weight of the subject, body density (mass/volume = D_b) is obtained. The residual volume of the lungs (RV) adds an error to the D_b, therefore it must also be calculated, either by an exact measurement with a gas dilution procedure or estimated based on a person's age and height. RV is then subtracted from the total displaced volume. Once D_b has been calculated, body composition can be estimated by mathematical methods. The most commonly used equations are those of Siri [45] and Brozek et al. [46], estimating the percent of body fat.

A more widely used method is **bioelectric impedance analysis (BIA)**. It is a quick, non-invasive and relative simple technology for estimation of body composition. It is used in many different settings like hospitals, outpatient clinics and gyms. A small, not experienced, current (I) of about 800µA are introduced with 50kHz, generating a voltage (V) between two electrodes and the impedance (in ohm [Ω] = V/I) is measured between two electrodes. Many equations are available to convert the measured impedance into an estimation of total body water (TBW) and fat-free mass (FFM) based on age, gender, weight and height. However, the estimation of body fat may vary as much as 10% of the total body weight because of different machines and methodologies used. [47]

Measurement of body composition in severely obese patients is difficult. Results from BIA must be interpreted with caution because the extracellular fluid volume is relatively greater in obese individuals. [47] **Computerized tomography (CT)** can be limited by patient's body size and has the drawback of radiation exposure. **Magnetic resonance imaging (MRI)** is also limited to a certain body size, associated with high costs, time-consuming and some patients experience claustrophobia. **Dual energy X-ray absorptiometry (DXA)** is commonly used among researchers since it is very precise. However, DXA is limited by the size of the scanning area and by the whole body-thickness in obese individuals. [48]

Bod Pod is a fast, non-invasive and reliable method to assess body composition in morbidly obese patients compared to the reference methods mentioned above. [43, 44, 49-52] A more general name for Bod Pod is Air Displacement Plethysmograph (ADP). An ADP is based on the Archimedes' principle, similar to hydrostatic weighing, but it measures the displaced volume of air instead of water, based on the physical relationship between pressure and volume. During measurement, very small volume changes are produced inside a chamber and the subsequent changes in pressure to these small volume changes are measured. The volume of air inside the chamber is calculated from the changes in pressure. By subtracting the volume of the empty chamber with the volume of air when a subject is inside the chamber, the volume of the subject is obtained. The Bod Pod calculates body density based on measured weight and body volume (mass/volume = D_b). Body density is then inserted into a standard formula for estimating percent fat mass (FM%) based on a two compartments model, e.g. the model of Siri (FM% = $495 / D_b - 450$) or Brozek (FM% = $457 / D_b - 414.2$).

Obesity related morbidity and mortality

Obese individuals have an increased risk of developing diabetes, hypertension, hypercholesterolemia, asthma, arthritis, obstructive sleep apnea, non-alcoholic liver disease and gallstone disease. [53-56] Both the degree and duration of obesity influence the risk of developing cardiovascular disease and cardiovascular death. [57] Cardiovascular specific death shortens the life expectancy with five years for individuals with BMI >40kg/m^2, according to American data. [58] Obesity and its related diseases, hypertension and diabetes, are together with smoking the top four global health threats today. [2] Severely obese individuals have an increased risk of premature death for all-cause mortality, compared with normal-weight adults. [4, 58] A large study from 2009 [5] of almost 900 000 adults, reported a reduced life expectancy of 2-4 years for BMI 30-35 kg/m^2 and 8-10 years for BMI 40-45 kg/m^2.

It is estimated that about 20% of all cancer incidence is related to overweight and obesity. Both genders have an increased risk of several forms of cancer. For males: cancer of the esophagus (adenocarcinoma), thyroid, colon, renal, liver, rectum, gallbladder, pancreas, prostate, malignant melanoma and myeloma. For females: cancer of the endometrium, gallbladder, esophagus (adenocarcinoma), renal, leukemia, thyroid, breast (postmenopausal), pancreas, colon and liver. [59] The mechanisms why these increased risks exists are in most cases not well understood, but it has been proposed that increased estradiol levels from fat tissue could be a factor in the development of breast and endometrial cancer in postmenopausal women. There is also evidence that hyperinsulinemia has a role in colon and pancreatic cancer. Reflux, which is increased in obese individuals, could be a mechanism for esophageal adenocarcinoma. The inflammatory processes induced by increased fat tissue, is also proposed to play an important role in the development of malignancies. [59]

Obesity is also associated with a reduced quality of life, defined as an individual's own assessment of well being both in physical and mental terms. [60] Obese individuals reports lower self-esteem, more anxiety and depression than normal-weight individuals. [61]

The Metabolic syndrome

As stated above, obese individuals has an increased risk of developing hypertension, hypercholesterolemia and diabetes, i.e. the metabolic syndrome. According to the American Heart Association and the International Diabetes Federation, the definition of metabolic syndrome is when three of the following five conditions occur simultaneously:

- Visceral obesity with a waist circumference of ≥ 94 cm in men and ≥80 cm in women.
- Hypertriglyceridemia of ≥150 mg/dl or on medication.
- Low levels of HDL cholesterol of <40 mg/dl for men and <50 mg/dl for women.
- Hypertension with a systolic blood pressure ≥130 mmHg and diastolic blood pressure ≥85 mmHg, or on antihypertensive medication.
- Elevated glucose levels with fasting glucose of ≥100 mg/dl or on medication.

Treatment of obesity

The first line treatment for obesity is diet and behavioral changes and increased physical activity. Numerous dieting methods are available on the market today; however, none with strong evidence of maintained weight loss over time. Low calorie diets (LCD, 800-1100 kcal/day) and very low calorie diets (VLCD, <800 kcal/day) are products designed to induce weight loss while preserving fat free mass. An American meta-analysis [62] of these diets showed good results in the short run with significant weight loss during the first months of up to about 40 kg. However, for most individuals the weight regain was almost as big as the initial weight loss after 5 years. The mean weight loss at 5 years was only 3 kg or 3.2% of their initial weight. The physical activity consistent with public health recommendations also promotes a very modest weight loss of about 2 kg. However, the weight loss on an individual level is very heterogeneous. [63] Unfortunately, no study has so far found a major, sustained weight loss by dieting. A reasonable physiological explanation could be that losing weight by dieting induces strong "starvation signals" from the gut and adipose tissue, all with the single aim of promoting hunger and storage of calories as fat.

Even though current evidence shows modest long-term effects with non-operative treatment of obesity on a population level, this should still be recommended as first line treatment because there are some individuals who succeed with a substantial weight loss and a few are able to maintain the weight loss over time, by these measures. The numerous health benefits from physical activity, even in the absence of weight loss, should also be emphasized. [63]

The pharmaceutical industry has been in search for a drug solving the global obesity epidemic for decades. There have been a number of antiobesity molecules developed throughout the years and there are constantly new one coming up, since the market for such a drug is enormous. [64] However, the only drug approved in Sweden and by FDA (Food and Drug Administration, US) for obesity, is Orlistat (Xenical® or Alli®). This drug inhibits lipase in the gut, preventing absorption of triglycerides and therefore facilitates weight loss. Comparing Orlistat vs. placebo, where both groups underwent lifestyle changes as well, showed that the Orlistat group lost 5.8 kg and the placebo group 3.0 kg after 4 years. [65] Even though the difference was statistically significant the clinical relevance of 2.8 kg is questionable.

Rimonabant (previously mentioned) is a cannabinoid receptor antagonist acting on the central nervous system in the brain's rewarding system. It had some effect on weight loss, but it was withdrawn due to psychiatric side effects like depression and suicides. Sibutramine (Reductil®), another weight loss drug, was withdrawn due to cardiovascular side effects.

Administration of individual gut hormones in high concentrations is associated with aversive behavior to food in rodents and nausea in humans. Low doses of PYY and GLP-1 have been shown to inhibit food intake additively. In the future, a smart cocktail of gut hormone-based drugs may perhaps prove a more effective obesity treatment than targeting a single system (in analogy with antihypertensive treatment). However, there is a major drawback with gut hormones as therapeutically drugs as they are short acting and needs intravenous or subcutaneous administration. [28] In Sweden today, the GLP-1 analogues (lixisenatid [Lyxumia®], exenatid [Byetta®, Bydureon®], liraglutide [Victoza®] and dulaglutid [Trulicity®]) are approved as adjunctive therapy with other glucose-lowering drugs when these provide insufficient glucose control in type 2 diabetes. However, the GLP-1 analogues also promote weight loss. In a recent RCT, [66] a weight loss of 7.8% for liraglutide and 13.8% for semaglutide, versus 2.3% for placebo, was reported for individuals with a BMI $\geq 30 kg/m^2$ after one year of subcutaneous injections once daily.

Bariatric Surgery

Surgical treatment is so far the most effective treatment for severe obesity as it results in greater, more sustained weight loss and has a better effect on obesity-related comorbidities compared to non-surgical treatment. [8, 10, 67-69]

According to national guidelines in Sweden [70] there is an indication for bariatric surgery in patients with age ≥18 years and BMI >35 kg/m^2, where conservative weight loss methods have failed. These criteria are similar in most international guidelines. However, the strict use of BMI as the only indicator for bariatric surgery is suboptimal and under discussion. There is evidence to support even lower BMI (30-35 kg/m^2) in patients with type-II diabetes, which has been adopted in some countries. [71, 72] Compared to Caucasian people, the Asian populations generally have a higher percentage of body fat and a higher risk of developing diabetes and cardiovascular disease at a certain BMI. [73] Therefore, bariatric surgery may be considered for Asians with metabolic syndrome or inadequately controlled type-II diabetes, with a BMI as low as ≥27.5 kg/m^2. [74]

History of bariatric surgery

The history of bariatric surgery started in the 1950's when intestinal bypasses were used to mimic short-bowel syndrome, which was a condition known to cause weight loss. Many different surgical procedures have been used throughout the years to treat obesity. The **jejunoileal bypass (JIB)** had its origin in 1953 at the University of Minnesota by Dr. Richard Varco. In the first cases most of the small bowel were bypassed with an end-to-end jejunoileostomy and a separate ileocecostomy of the bypassed bowel. The first cases were published in 1954. [75] The method were modified and standardized during the 1960's with an end-to-side jejunoileostomy, a 35 cm alimenatary limb and a 10 cm common channel, *figure 2B*. The JIB caused an excellent, maintained weight loss, however later on abandoned because of many early and late complications. The extensive intestinal bypass caused severe malabsorption and bacterial overgrowth in the bypassed bowel, resulting in severe diarrhea, electrolyte disturbances, vitamin and mineral deficiencies, kidney stones formation, steatohepatitis and progressive liver failure. Most patients previously operated with JIB have had their operation reversed with or without another bariatric procedure, however, there are a few patients with excellent weight loss result with no or minimal problem still living with their JIB operation. [76]

In 1966, Dr. Edward E. Mason published the first series of patients operated with **gastric bypass**. [77] These first operations were performed with a horizontal gastric division and a loop gastrojejunostomy. The operation was later modified with the construction of a small gastric pouch instead of horizontal gastric division. In 1977 the first gastric bypass with a Roux-en-Y gastrojejunostomy was presented, the classic RYGB, as we know it today, *figure 2C*. The RYGB rapidly grew in popularity and replaced the JIB because of fewer complications, and still with good weight-loss results. In 1994, the first laparoscopic RYGBs were presented by Alan C. Wittgrove et al. [76] Dr. Hans Lönroth (Sweden) refined the laparoscopic technique in 1996. [78]

The gastroplasty was introduced in 1973 where the original version consisted of a horizontal partial gastric division, leaving a 1.5 cm conduit along the greater curvature of the stomach. [79] During early 1980's, the gastric pouch was constructed with a vertical division instead and in 1982 Dr. Mason described the **vertical banded gastroplasty (VBG)**, where a mesh band was used to restrict the outlet in order to prevent enlargement of the pouch, *figure 2D*. The VBG procedure lost its popularity because of problems with weight regain due to staple line rupture and problem with reflux and vomiting in many patients due to the restrictive band. [76]

In the search of an operation with equally good weight results as the JIB, but without the severe complications, Dr. Nicola Scopinario presented the **biliopancreatic diversion (BPD)** in 1979. His theory was that there must be a continuous flow in the bypassed bowel to prevent bacterial overgrowth and the terminal ileum must be preserved to maintain fluid reabsorption. The BPD by Scopinario consist of a horizontal distal gastrectomy, a 250 cm alimentary limb and 50 cm common channel [80], *figure 2E*. The BPD operation was later modified by the Canadian surgeon Marceau and the American surgeon Hess, in the late 1990s. Instead of a distal gastrectomy a vertical sleeve gastrectomy with preservation of the pylorus was performed and the common channel was increased to 100 cm. [81] This is the duodenal switch procedure **(BPD/DS or DS)**, as we know it today, *figure 2F*.

Adjustable gastric banding (AGB) was a further development of the non-adjustable gastric band that was used in the 1970's and 1980's. A problem with gastric banding was its difficulties in getting it tight enough to promote weight loss and at the same time, loose enough to prevent reflux and vomiting. The AGB consists of an inflatable silicon balloon on a band that is placed around the upper part of the stomach, *figure 2G*. The balloon is connected to a subcutaneous injection port, allowing adjustment of the diameter of the band. Laparoscopically inserted AGB had its peak during the 1990's and early 2000's. [76] Some successful series have been reported, [82] but long-term weight regain and complications such as band slippage and band erosion into the stomach has given the procedure a bad reputation and it has been abandoned by most surgeons today.

The **sleeve gastrectomy (SG)**, *figure 2H*, is the most recent bariatric procedure that has gained an enormous popularity, especially in the US. [83] It was first described in 2003 [84] as a first-step procedure in super obese patients, in whom a second-stage bowel bypass was planned. Dr. M Gagner popularized SG as a stand-alone procedure, and during 2013-2014 SG became the most rapidly growing bariatric procedure. [76]

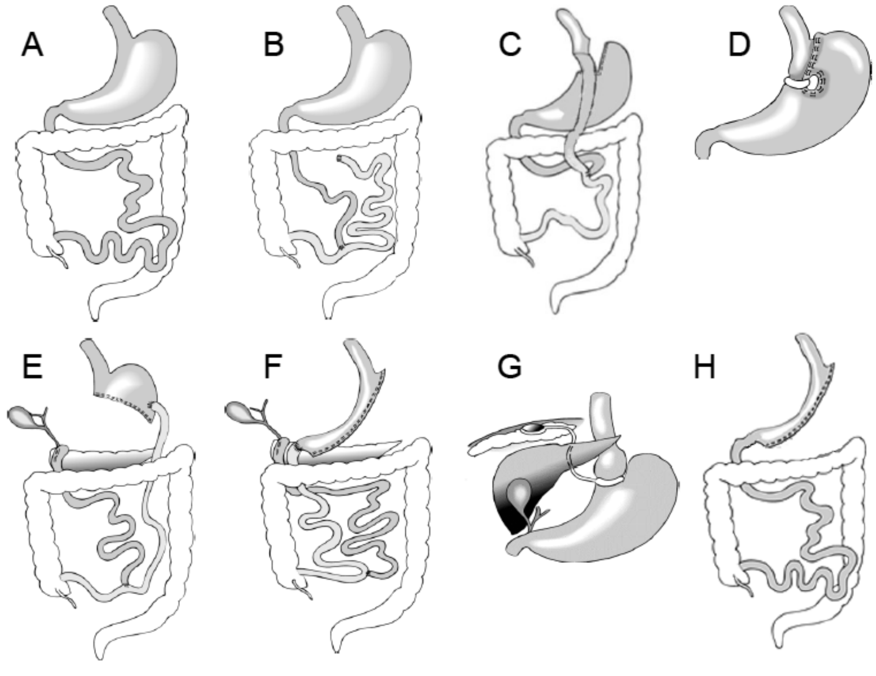


Figure 2. Schematic anatomical descriptions of: **A** Normal anatomy **B** Jejunoileal bypass (JIB) **C** Roux-en Y Gastric bypass (RYGB) **D** Vertical banded gastroplasty (VBG) **E** Biliopancreatic diversion (BPD) **F** Duodenal switch (DS) **G** Adjustable gastric banding (AGB) **H** Sleeve gastrectomy (SG)

Mechanism of action for bariatric surgery

All bariatric procedures involve restriction (e.g. gastric sleeve) or malabsorption or both (e.g. gastric bypass and duodenal switch). The restrictive part results in lower energy intake and the malabsorptive part results in lower energy uptake. To what extent restriction and malabsorption correlates with degree of weight loss is not fully understood. Since the nutrients are absorbed in the common channel after a gastric bypass, it has been thought that the length of the alimentary (Roux) limb and the biliopancreatic limb affects the degree of malabsorption. However, according to a review in the field [85], it appears as if the length of the alimentary limb and biliopancreatic limb has a very small, if any, impact on the final weight result. Evidence suggests that the length of the common channel is the most important factor for degree of malabsorption. The lengths of alimentary and biliopancreatic limbs routinely used in a gastric bypass (mean 110 cm [range 35-250 cm] and 48 cm [range 10-250 cm], respectively) [86] has small impact on the remaining length of the common channel since the total length of the small bowel is very long. When measured in 100 obese patients, it was on average 671 cm (range 434-990 cm). [87] For practical reasons the common channel is not routinely measured during a gastric bypass. The method focuses on the length of the Roux and biliopancreatic limb. In a duodenal switch, however, the common channel is measured to 100 cm and becomes the malapsorptive component.

As previously described, the regulation of appetite and the homeostatic mechanisms for energy balance are complex. Bariatric surgery influences a number of different neurohormonal systems in the body that promotes weight loss and improvements of metabolic disorders. There is evidence of a weight-loss independent effect on obesity related comorbidities after bariatric surgery, like diabetes, hypertension and dyslipidemia. [69, 88, 89] Therefore it is also called metabolic surgery. As research in the field has evolved, we now understand more, but certainly not all, about the mechanisms of action. The change in gut-hormone profile is one important mechanism. For example, a gastric bypass results in a significant increase in PYY, GLP-1 and oxyntomodulin (satiety mediators), while ghrelin (hunger mediator) either falls or fails to rise, despite significant weight loss. [90] During a SG about ¾ of the stomach is removed, including the fundus, where most of the ghrelin is synthetized. Interestingly, patients often report dramatically reduced hunger after bariatric surgery long before the weight loss has occurred. This supports the idea of modulations in the satiety signaling system after bariatric surgery.

Bariatric surgery today

Today, sleeve gastrectomy (*figure 2H*) is the most common surgical procedure worldwide (54%), followed by Roux-en-Y Gastric Bypass (*figure 2C*, 30%). [15] SG has gained in popularity since it does not require any bowel manipulations or anastomosis. In addition, short-term data shows good results on weight loss, obesity related comorbidities and the complication profile is acceptable when compared with RYGB. [91] There are two recent randomized clinical trials with 5-year data comparing RYGB and SG; one reporting greater weight loss and higher remission of hypertension after RYGB compared to SG, [92] and one reporting a similar weight loss, but more reflux after SG compared to RYGB. [93]

In Sweden, RYGB has been the most common bariatric procedure since the late 1990's, with its peak in 2011-2012 when about 97% were RYGB. Although SG has gained in popularity also in Sweden (6% in 2013 to 34% in 2016), RYGB still represents 64% of all bariatric procedures. DS is a less common operation (<1%), mostly offered in patients with super obesity (BMI >50 kg/m^2). DS is only performed routinely at two centers in Sweden

(Uppsala and Torsby). Overall, 99% of all bariatric procedures are performed laparoscopically in Sweden. [16]

Bariatric surgery in super obese patients

Unfortunately, the prevalence of super obesity is increasing and in the US more than one quarter of the patients seeking bariatric are surgery super obese. [14, 94] The super obese patients are a challenge, not only because of their medical comorbidities and technically difficulties during bariatric surgery, but also because there is no consensus of which procedure is the best in practice for this group of patients. RYGB is a safe and effective bariatric procedure, [10] however, due to insufficient weight loss and/or weight regain more than 50% of the super obese patients are still severely obese (BMI >35 kg/m^2) even after surgery. [19, 88] The advantage with DS is a greater and more sustained weight loss, [20, 22, 95] and its superior effect on the obesity-related comorbidities compared to RYGB. [89, 96] However, in the only RCT comparing the two procedures in super obese patients (31 RYGB, 29 DS) with long-term data (5 years), an increased risk for nutritional, surgical and gastrointestinal adverse events was reported after DS compared to RYGB. [23] DS also requires a compliant patient, who closely follows the nutritional advices and attends regular checkups to minimize the risk of malnutrition. A Canadian high volume center reports, however, excellent long-term results after DS in super obese patients, with complication rates similar to other bariatric procedures. [21, 97] This could reflect a learning curve both for the operation and the nutritional support.

Complications and adverse events after bariatric surgery

In the systematic review and meta-analysis by Chang et al. [98] from 2014 of more than 160 000 patients from 164 worldwide studies, they found an overall complication rate of 10-17%, a reoperation rate of about 7% and a 30-day mortality of 0.08%. According to Swedish data from the 2016 report from Scandinavian Obesity Surgery Register (SOReg), the 30-day complication rate is 6.7%, whereof 2.5% suffers a severe complication (Clavien-Dindo ≥3B). Since the start of SOReg in 2007, the overall complication rate has been reduced by about 50%. It is now uncommon with major complications such as anastomotic leak (0.9%), bleeding (1.1%), abdominal abscess (0.6%) and bowel obstruction (0.6%). The mortality rate (<90 days) is as low as 0.02%, [16] actually lower than after cholecystectomy (0.15%). [99]

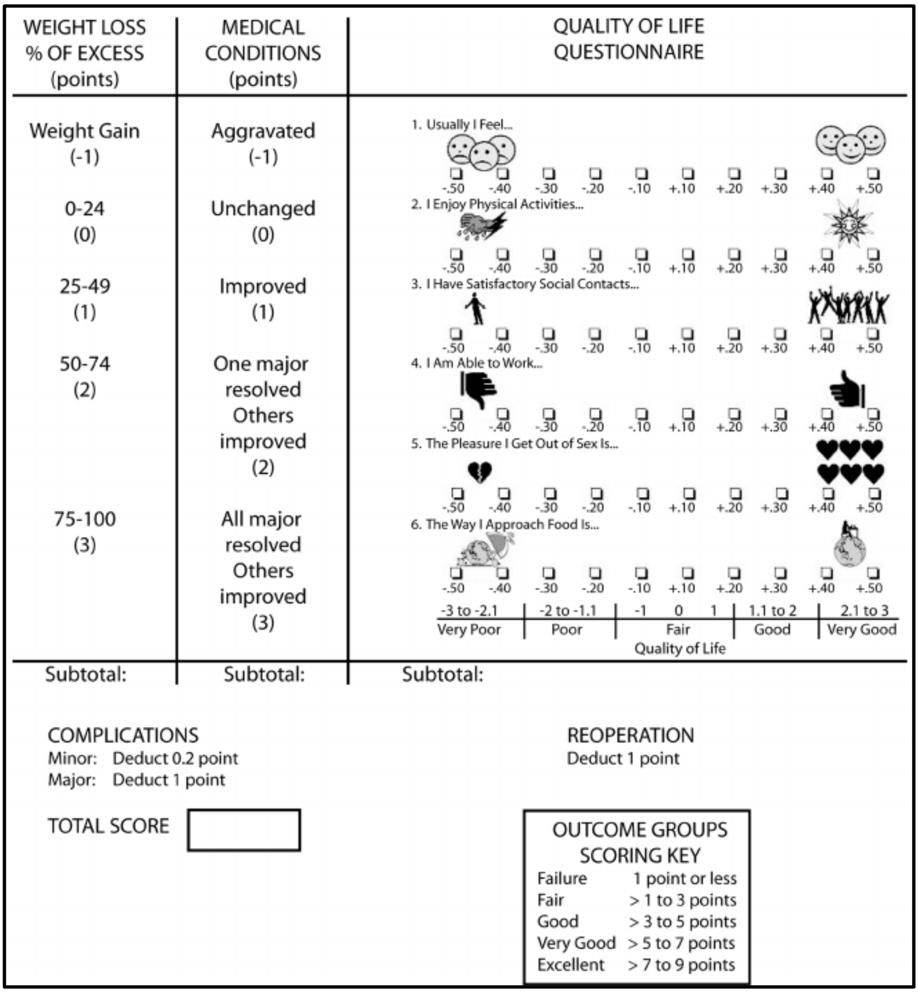
Long-term adverse events/effects after bariatric surgery includes both physiological aspects with nutritional deficiencies [100] and gastrointestinal symptoms, [101] and psychological aspects with an increased risk of alcohol abuse (9.6% vs. 7.6% prior to surgery) [102] and a four times higher risk of completed suicide compare to general population (4 vs. 1/10 000) [103].

Body composition after bariatric surgery

During weight loss there is a reduction in both fat mass (FM) and fat-free mass (FFM). [104-108] The FFM is responsible for maintaining the body's functional capacity and its maintenance requires energy also in resting state, i.e. the resting metabolic rate (RMR), [109] which constitutes about 70% of the total daily energy expenditure. [110] A maintained FFM is therefore of great importance for sustained weight loss. During weight loss the proportion of weight loss as loss of FFM is about 25%. [111] However, this is only an approximation since proportion of FFM loss varies over time during weight loss. It also depends on degree of baseline adiposity, gender, level of physical activity, amount of energy intake and diet composition. [111-114] Concerns for the possibility of malnutrition and an excessive loss of FFM after RYGB, and especially after DS, have been raised and the safety in regard to nutrition and body composition are considered potentially problematic according to a systematic review by Chaston et al. [115]

The Bariatric Analysis and Reporting Outcome System - BAROS

The desired outcome after bariatric surgery is an improvement in patients' health both physically and mentally. It is therefore of importance to study changes in comorbidities and quality of life (QoL), in addition to weight loss, when evaluating the outcome after bariatric surgery. For evaluation of these three domains (weight loss, comorbidities and QoL), Oria et al. presented the Bariatric And Reporting Outcome System (BAROS) in 1998 [116]. In BAROS, QoL is evaluated with the Moorhead-Ardelt Quality of Life Questionnaire (MAQ). It was designed especially for the bariatric patients and it correlates well with other, more widely used QoL instruments like SF-36. [117] The refined version of MAQ [117] was included in BAROS in 2008. [118] The maximum score in each domain in BAROS is three points, thus nine in total. In addition, occurrence of a complication and/or reoperation deducts points. The final score classifies the results into 5 outcome groups, from failure (1 point or less) to excellent (>7-9 points), *figure 3*.



WEIGHT LOSS % OF EXCESS (points)	MEDICAL CONDITIONS (points)	QUALITY OF LIFE QUESTIONNAIRE
Weight Gain (-1)	Aggravated (-1)	1. Usually I Feel... -.50 -.40 -.30 -.20 -.10 +.10 +.20 +.30 +.40 +.50
0-24 (0)	Unchanged (0)	2. I Enjoy Physical Activities... -.50 -.40 -.30 -.20 -.10 +.10 +.20 +.30 +.40 +.50
25-49 (1)	Improved (1)	3. I Have Satisfactory Social Contacts... -.50 -.40 -.30 -.20 -.10 +.10 +.20 +.30 +.40 +.50
50-74 (2)	One major resolved Others improved (2)	4. I Am Able to Work... -.50 -.40 -.30 -.20 -.10 +.10 +.20 +.30 +.40 +.50
		5. The Pleasure I Get Out of Sex Is... -.50 -.40 -.30 -.20 -.10 +.10 +.20 +.30 +.40 +.50
75-100 (3)	All major resolved Others improved (3)	6. The Way I Approach Food Is... -.50 -.40 -.30 -.20 -.10 +.10 +.20 +.30 +.40 +.50
		-3 to -2.1 Very Poor; -2 to -1.1 Poor; -1 0 1 Fair; 1.1 to 2 Good; 2.1 to 3 Very Good — Quality of Life
Subtotal:	Subtotal:	Subtotal:

COMPLICATIONS
Minor: Deduct 0.2 point
Major: Deduct 1 point

REOPERATION
Deduct 1 point

TOTAL SCORE

OUTCOME GROUPS SCORING KEY	
Failure	1 point or less
Fair	> 1 to 3 points
Good	> 3 to 5 points
Very Good	> 5 to 7 points
Excellent	> 7 to 9 points

Figure 3. The Bariatric Analysis and Reporting Outcome System (BAROS)

Aims

The aim of this thesis is to compare postoperative outcomes in super obese patients after DS and RYGB, respectively.

The specific aims are:

I To examine body composition and RMR in weight-stable patients after DS and RYGB, and compare these two bariatric groups with non-operated controls within the same age and BMI interval.

II To compare outcome after DS and RYGB using BAROS in a regional Uppsala-cohort of super obese patients. A secondary aim is to investigate possible differences of gastrointestinal symptoms after the two operations.

III To compare long-term weight loss, effect on comorbidities and quality of life after DS and RYGB in a nation-wide registry-based cohort of super obese patients.

IV To compare early complications, healthcare consumption, long-term adverse events and mortality in a registry-based cohort of super obese patients up until 10 years after primary DS and RYGB, respectively

Material and Methods

A summary of the included studies is provided in Table 2, at the end of the Material and Methods section.

Paper I

Body composition and RMR were measured with Bod Pod and indirect calorimetry, respectively, at least 2 years after RYGB (n=15) and DS (n=12). Results were compared with non-operated controls (n=17) from a previous study, [119] matched for age and BMI. All participants were 30-55 years old and had a BMI of 28-35 kg/m^2. All participants were in fasting state since midnight and the measurements were performed in the morning at room temperature. During the measurements with the Bod Pod, participants were dressed in underwear and used a swim cap to tuck in their hair.

Data of fat mass (FM), fat-free mass (FFM), percent fat mass (FM%) and percent fat-free mass (FFM%) was obtained from the Bod Pod. In addition the Bod Pod estimated RMR (in kcal/24h) based on the relationship between FM and FFM, by the Nelson Prediction Equation (RMR (kcal/24h) = 25.80 x Fat-free mass (kg) + 4.04 x Fat mass (kg)).

Statistics

Analysis of variance (ANOVA) was used for comparison of parametric data between the three groups and tukey's method was used for simultaneous post-hoc comparison of means. Unpaired t-test was used when comparing two groups. Chi2-test was used for comparison of independent proportions. A p-value of <0.05 was considered statistically significant.

Paper II

This was a retrospective study of 211 super obese patients operated with either RYGB or DS in Uppsala during 2003 to 2012. The patients were contacted by mail, and if they accepted to participate they were asked to fill in the quality of life questionnaire (MAQ) in BAROS and our local questionnaire about gastrointestinal symptoms, additional operations, rehospitalization, comorbidities, current weight and general perception of their operation. Medical records were used for baseline characteristics and information about possible adverse events.

For each patient a BAROS score was calculated according to the updated version of BAROS, [118] where we defined the presence of a comorbidity by the use of medication and remission defined as cessation of all medication for the specific disease.

Statistics

Statistical methods used for comparison between the two groups were Mann-Whitney test for non-parametric data and unpaired t-test for parametric data. When analyzing gender distribution, comorbidities and complication rates, Chi2-test, or when applicable, Fischer's exact test was used.

Paper III and IV

These were retrospective cohort studies, with outcomes after DS and RYGB in super obese patients, on a nationwide level. Cross-matched data from SOReg, the National Patient Register (NPR, öppen- och slutenvårdsregistret), the Swedish Prescribed Drug Register (SPDR, läkemedelsregistret), Statistics Sweden (SCB) and the Swedish Cause of Death Register was used. Eligible patients were those with a BMI≥48 kg/m^2 on the day of surgery. All primary open and laparoscopic procedures were included, while revisional procedures were excluded. In total 429 DS and 7432 RYGB were found in SOReg.

Data extracted from the registries

SOReg: Baseline characteristics (age, gender, year of operation, height, weight, BMI), perioperative results (operating time, length of stay), early complications (<30 days), reoperations (<30 days), readmissions (<30 days), change in BMI (up until 5 years), change in QoL (SF-36 score, up until 5 years) and data of subsequent revisional procedures.

NPR: All inpatient care and visits at specialized outpatient clinics (i.e. hospital based clinics and emergency departments) up until 31st of December 2016. All subsequent provided health care was analyzed by primary diagnosis and classified according to the chapters in ICD-10. Specific long-term adverse events analyzed were in-hospital care due to protein-malnutrition/malabsorption (E40-E64, K90-K91), additional diagnostic/therapeutic upper endoscopy (UJD02, UJD05) and additional abdominal operations (any type, JA-JX), with the subgrouping: cholecystectomy

(JKA20-21), incisional hernia repair (JAD) and operation due to bowel obstruction (JAS, JFK, JFL).

SPDR: Data of all prescribed drugs up until 31st of December 2017. The prescribed drugs were identified via the Anatomical Therapeutic Chemical Classification system (ATC), and used as a proxy for the presence of a specific obesity-related condition. The analyzed comorbidities were: diabetes (A10A, A10B), hypertension and/or cardiovascular disease (C01, C02, C03, C07, C08, C09), dyslipidemia (C10), depression (N06A), pain treated with NSAID and/or acetaminophen (M01, N02B) and pain treated with opioids (N02A), reflux and/or dyspepsia (A02), diarrhea (A07D), iron deficiency (B03A) and B12- Folic acid deficiency (B03B). Comparisons between DS and RYGB were made at four time-points, baseline (12-0 months prior to surgery), 2nd year (12-24 months), 6th year (60-72 months) and 10th year (108-120 months). Remission was defined as complete cessation of all drugs for the specific condition.

SCB: Education level, used as a baseline variable for the propensity score

Cause of Death Register: Mortality and all cause of death.

Statistics

Propensity score matching was performed to minimize the effect of possible confounding variables. Baseline characteristics used to model the likelihood of receiving DS were age, gender, BMI, year of operation, education level (extracted from Statistics Sweden), and the following comorbidities (based on medication at baseline): diabetes (insulin/anti-diabetics except insulin/combination therapy), hypertension, dyslipidemia, depression, pain (NSAID and acetaminophen/opioids), gastrointestinal symptoms (reflux/diarrhea) and deficiencies (iron/B12- and folic acid deficiency). A 1:4 matching was performed. The matching algorithm used was nearest neighbor matching without replacement within a specified caliper distance. Standardized difference in means was used for assessment of covariate balance in the matched groups, *figure 4*.

Parametric data was analyzed with independent sample t-test for comparison between groups or paired sample t-test for comparison within groups and reported as mean ±SD. Mann-Whitney U test was used for independent non-parametric data and Wilcoxon signed rank test for dependent non-parametric data and reported as median ±interquartile range. Fisher's exact test was used for comparison of independent proportions, while McNemar test was used for comparison of dependent proportions. A p-value <0.05 was considered statistical significant.

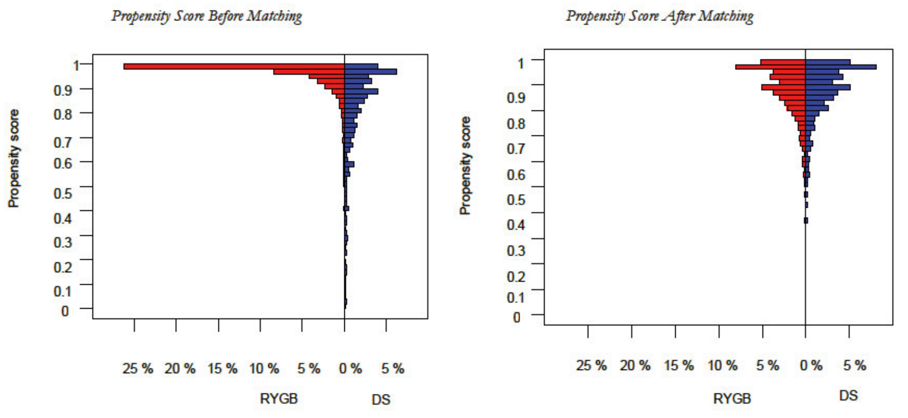


Figure 4. Propensity score before (429 DS, 7432 RYGB) and after matching 1:4 (333 DS, 1332 RYGB).

Ethics

The Regional Ethical Board at Uppsala University approved all four studies.

- Paper I: Dnr: 2008/154, all subjects signed an informed consent form.
- Paper II: Dnr: 2008/373
- Paper III and IV: Dnr: 2015/091/1

Table 2. *Overview of the included studies*

Paper	**I**	**II**	**III**	**IV**
Objective	Examine body composition and RMR after DS and RYGB	Compare BAROS score and GI-symptoms after DS and RYGB	Compare weight loss, comorbidities and quality of life after DS and RYGB, long-term	Compare early complications, healthcare consumption, long-term adverse events and mortality after DS and RYGB
Design	Cross-sectional, clinical study	Retrospective study, including mail survey and medical records	Population-based, retrospective, cohort study with cross-matched data from four national registries	Population-based, retrospective, cohort study with cross-matched data from five national registries
Setting	Measurements were performed at the metabolic laboratory at the Akademiska University Hospital	Akademiska University Hospital, Uppsala	Swedish national registers with nation-wide coverage	Swedish national registers with nation-wide coverage
Participants	Weight stable patients operated >2 years ago with DS or RYGB. Matched, non-operated controls	Super obese patients operated 2003-2012 with DS or RYGB, at the Akademiska University Hospital	Patients with a BMI≥48 kg/m^2 operated 2007-2017 with primary DS or RYGB in Sweden	Patients with a BMI≥48 kg/m^2 operated 2007-2017 with primary DS or RYGB in Sweden
Sample size	12 DS, 15 RYGB and 17 Controls	113 DS and 98 RYGB	333 DS and 1332 RYGB	333 DS and 1332 RYGB
Outcome measures	Weight, FFM, FM, FFM/FM, FFM%, FM%, RMR, RMR/FFM	BAROS-score (weight loss, comorbidities, complications and QoL) and GI-symptoms	Weight loss, medication for obesity related conditions and QoL	Early complications, healthcare consumption, long-term adverse events, mortality
Statistical methods	ANOVA with post hoc test, unpaired t-test and chi2-test	Mann-Whitney U test, unpaired t-test and chi2-test	Propensity score matching. Unpaired t-test, Mann-Whitney U test, Wilcoxon signed rank test, Fischer's exact test and McNemar test	Propensity score matching. Unpaired t-test and Fischer's exact test

Results

Paper I

Preoperative BMI was higher in DS compared to RYGB (52.2 and 45.1 kg/m^2, respectively). The individuals in the DS and RYGB group were examined on average 6.4 and 4.1 years after surgery, respectively. DS had resulted in a BMI-loss of 21.0 ±5.1 kg/m^2 and RYGB 11.8 ±2.5 kg/m^2 ($p<0.01$) and total body weight loss was 39.9 ±6.4% for DS and 26.2 ±4.1% for RYGB ($p<0.01$). The groups had a similar male/female ratio, age, height, weight and BMI at examination. Table 3.

The FFM (kg) and FM (kg) were similar in DS, RYGB and controls, *figure 5*. The mean FFM% was 61%, 58% and 58% for DS, RYGB and controls, respectively, *figure 6*. Overall, both DS and RYGB resulted in a body composition similar to that of the controls and no difference in body composition between groups was detected when comparing men and women separately either.

Table 3. *Characteristics at examination*

	DS (n=12)	**RYGB (n=15)**	**Controls (n=17)**
Gender, male/female	5/7	3/12	3/14
Age ±SD (years)	44.5 ±7.3	45.9 ±5.8	45.7 ±8.4
Height ±SD (cm)	171 ±0.10	169 ±0.10	170 ±0.08
Weight ±SD (kg)	91.8 ±12.8	93.8 ±12.9	89.4 ±10.9
BMI ±SD (kg/m^2)	31.2 ±2.1	32.7 ±1.7	31.0 ±2.5

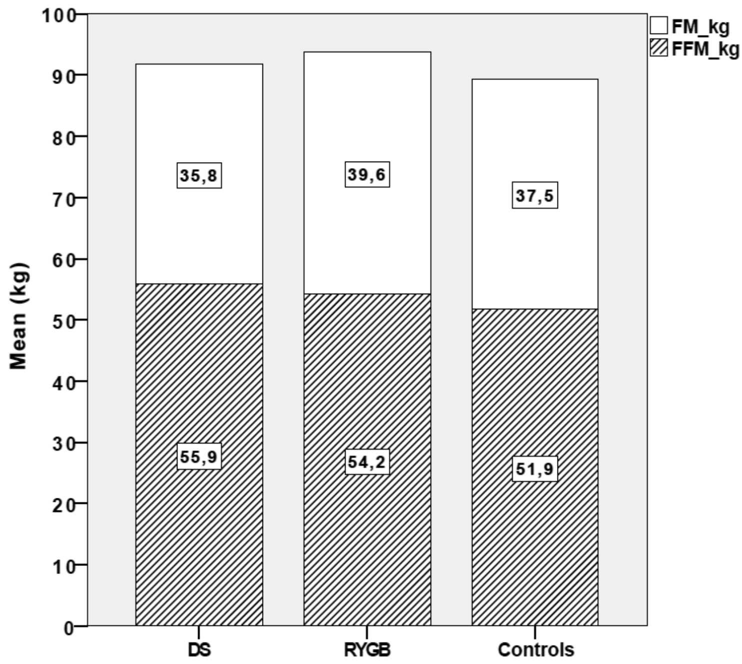


Figure 5. Total body weight (kg) divided into fat mass (FM) and fat-free mass (FFM).

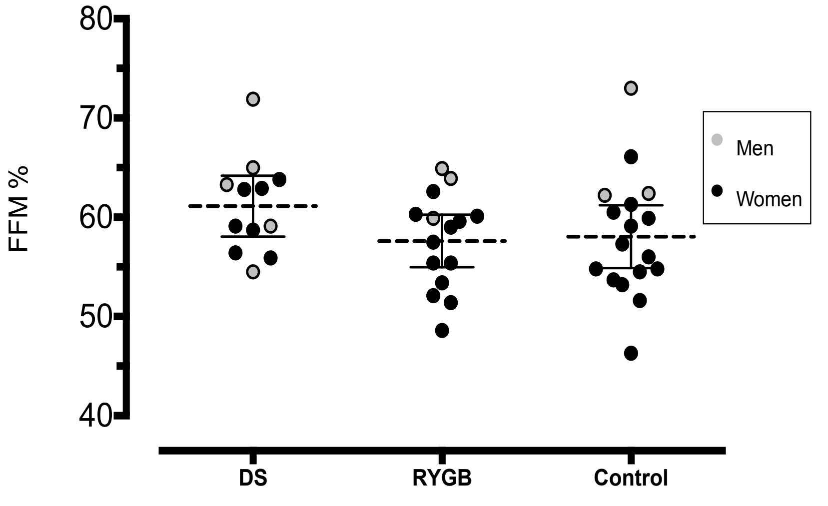


Figure 6. Body composition, presented as mean percent fat-free mass (FFM%) with 95% CI.

Mean RMR (kcal/24h) was similar between groups, *figure 7*, and no difference in RMR/FFM (kcal/24h/kg) was observed between DS, RYGB and controls, 28, 29 and 29 kcal/24h/kg, respectively.

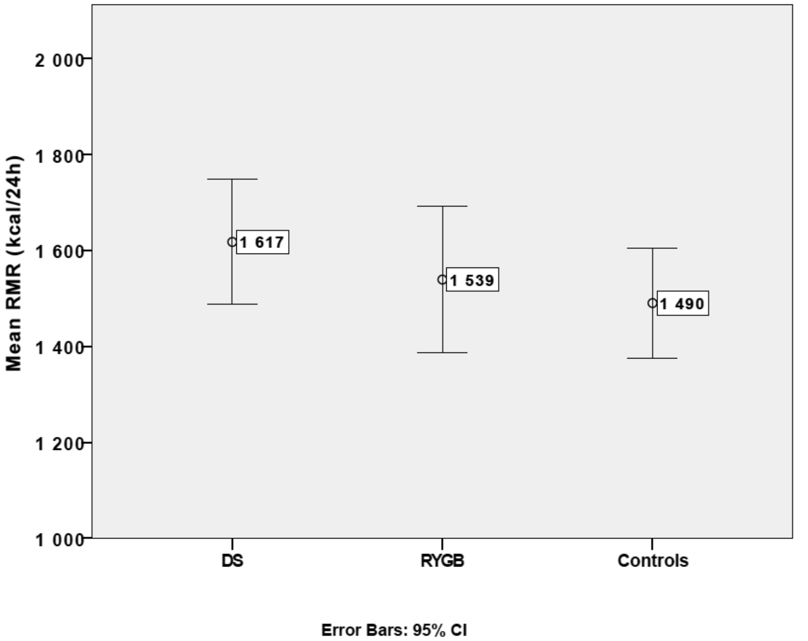


Figure 7. Mean resting metabolic rate (RMR) with 95% CI.

Paper II

Of the patients operated during 2003 to 2012, 63% were included in the study. The analysis comprised of 211 previously super obese patients (113 DS and 98 RYGB), with a mean follow-up time of 4 years. Gender distribution, age and comorbidities were similar between groups, while the preoperative BMI was higher in the DS group. Table 4.

Table 4. *Baseline characteristics*

	DS (n=113)	**RYGB (n=98)**	***p*-value**
Female No. (%)	66 (58)	68 (69)	0.12
Age (years)	40±9.9	40±10	0.96
BMI (kg/m^2)	56±6.7	52±4.0	<0.01
Any comorbidity No. (%)	66 (58)	61 (62)	0.58
Diabetes No. (%)	27 (25)	14 (15)	0.08
Hypertension No. (%)	40 (37)	35 (38)	1.00
Cardiovascular Disease No. (%)	1 (1)	3 (3)	0.34
Sleep apnea No. (%)	25 (23)	18 (20)	0.61
Dyslipidemia No. (%)	18 (17)	14 (15)	0.85

A sensitivity analysis was possible for 112 of the 121 non-responders from SOReg data. Concerning RYGB, there were more men in the non-responding RYGB group (53 vs. 31%, p<0.01). The non-responding DS group were slightly younger (36 vs. 40 years, p<0.05) and had a lower prevalence of diabetes (7 vs. 25%, p<0.01) compared to the responding DS group. Otherwise the non-responders were similar concerning baseline characteristics.

BAROS score

Overall, DS resulted in a higher BAROS score. Table 5. More DS-patients had an "Excellent" outcome and fewer patients were classified as "Fair" or "Failure", compared to the patients operated with RYGB (p=0.036), *figure 8*.

Table 5. *BAROS score*

	Possible outcome	**DS (n=113)**	**RYGB (n=98)**	***p*-value**
Weight loss	-1 to 3	2.6±0.6	1.9±0.8	<0.01
Change in comorbidities	-1 to 3	1.1±1.2	1.0±1.2	0.67
Quality of Life	-3 to 3	1.2±1.2	1.1±1.1	0.51
Complications	-1 to 0	-0.2±0.4	-0.1±0.2	<0.05
Total	-6 to 9	4.7±2.0	4.0±2.1	<0.05

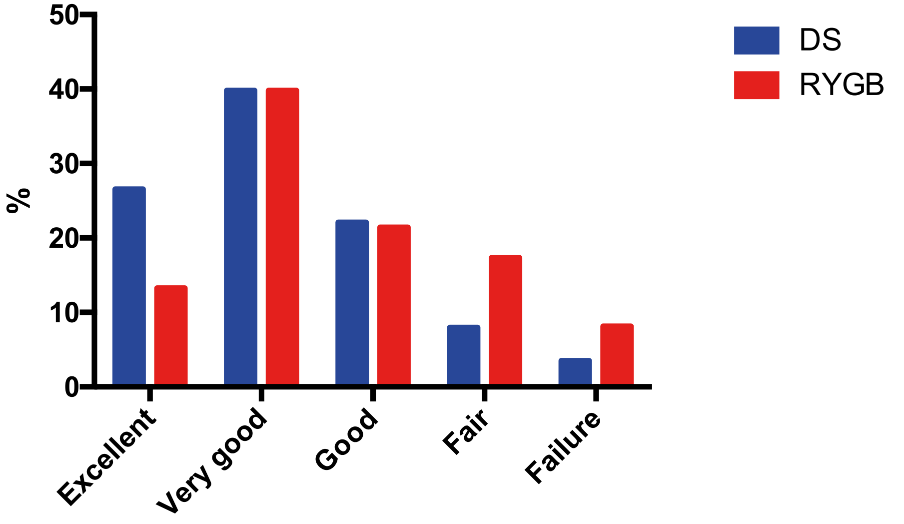


Figure 8. The proportions of patients in the five outcome categories

Weight loss: Despite a higher initial BMI in the DS group (56 vs. 52 kg/m^2, $p<0.01$), the superior weight loss after DS resulted in a significantly lower postoperative BMI for this group (31 vs. 36 kg/m^2, $p<0.01$). Total body weight loss was 43.4 ±9.3% for DS and 31.8 ±11.5% for RYGB ($p<0.01$).

Change in comorbidities: Both groups had a significant reduction in diabetes and sleep apnea, while the reduction in dyslipidemia was significant only for the DS group. The reduction of hypertension failed to reach statistical significance for both groups. The effect on diabetes was even more pronounced after DS (93% vs. 79% remission, $p<0.05$); otherwise both operations had similar effects.

Quality of life: No difference in MAQ-score was found between groups.

A multiple ordinal regression (MAQ-score set as dependent variable and gender, type of operation, age, complication [no, minor, major], GI-symptoms [yes/no] and %Excess BMI loss set as independent variables) showed that %Excess BMI loss had a significant positive influence on QoL ($p<0.001$), while nausea/vomiting and fecal incontinence had a significant negative impact on QoL (both $p<0.05$).

Complications: Complications were more common after DS, 27% had one or more complications during the follow-up period, compared to 14% in the RYGB group ($p=0.03$).

Gastrointestinal symptoms: A larger proportion of patients in the DS group reported problems with diarrhea (59% vs. 20%), gases (80% vs. 41%), gastroesophageal reflux (12% vs. 8%) and fecal incontinence (8% vs. 2%), while dumping was more common in RYGB (13% vs. 2%). No differences were observed for nausea/vomiting and abdominal pain (4 vs. 1% and 11 vs. 8%, respectively). *Figure 9.*

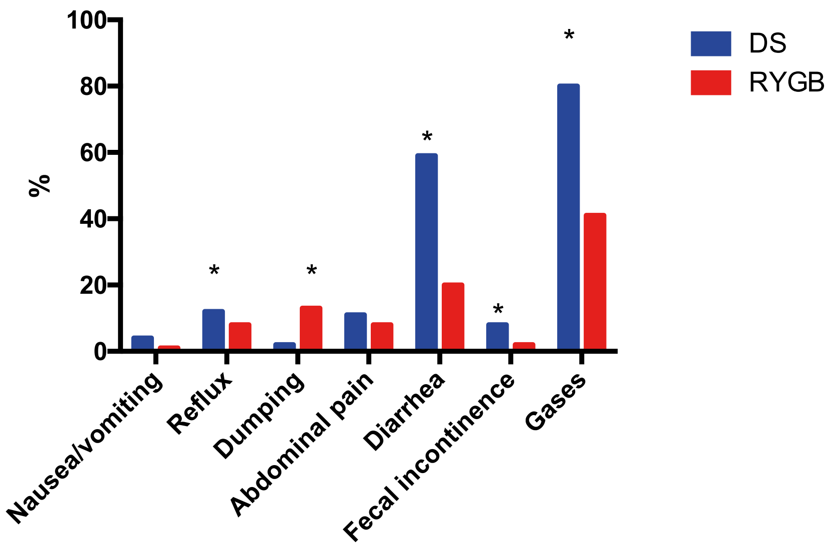


Figure 9. The proportions of patients reporting gastrointestinal symptoms occurring weekly or more often (* $p<0.05$).

Paper III and IV

After propensity score matching of 1 DS to 4 RYGB, the study population consisted of 333 DS and 1332 RYGB. Both groups consisted of 61% females, aged 38.5 years, baseline BMI of 55 kg/m^2 and mean elapsed time since surgery was 5.1 years. Diabetes was more common (20.1% vs. 14.5%, $p=0.014$), while reflux was less common (13.2% vs. 24.6%, $p<0.01$) in the DS group. Otherwise, comorbidities were similar. Laparoscopic approach was used in 25.2% of the DS (no conversions to open surgery) and 92.6% of the RYGB (2% conversions). Operating time and length of stay was longer for DS (150.9 vs. 87.3 minutes and 5.9 vs. 2.2 days, respectively, both $p<0.01$). Baseline characteristics are shown in Table 6.

Table 6. *Baseline characteristics*

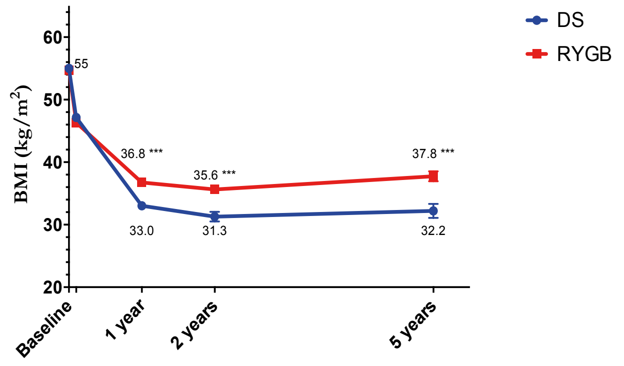
		DS (n=333)	**RYGB (n=1332)**	**Total (n=1665)**
Gender				
Female	No. (%)	202 (60.7)	809 (60.7)	1011 (60.7)
Male	No. (%)	131 (39.3)	523 (39.3)	654 (39.3)
Age at Surgery				
	Mean (SD)	38.8 (10.9)	38.4 (11.1)	38.5 (11.0)
	Median	39	38	38
	Range	18 to 67	16 to 68	16 to 68
Height (cm)				
	Mean (SD)	172.4 (10.0)	170.6 (9.6)	170.9 (9.7)
	Median	172	170	170
	Range	150 to 200	140 to 203	140 to 203
Weight (kg)				
	Mean (SD)	164.0 (23.1)	159.6 (23.6)	160.5 (23.6)
	Median	162	156.5	157
	Range	120 to 235	109 to 262	109 to 262
BMI (kg/m^2)				
	Mean (SD)	55.0 (4.5)	54.7 (5.4)	54.8 (5.2)
	Median	54.0	53.3	53.5
	Range	48.1 to 73.1	48.0 to 78.9	48.0 to 78.9
Comorbidities				
Diabetes	No. (%)	67 (20.1)	193 (14.5)	260 (15.6)
Hypertension	No. (%)	127 (38.1)	479 (36.0)	606 (36.4)
Dyslipidemia	No. (%)	40 (12.0)	155 (11.6)	195 (11.7)
Depression	No. (%)	69 (20.7)	267 (20.0)	336 (20.2)
Pain [a]	No. (%)	124 (37.2)	534 (40.1)	658 (39.5)
Severe pain [b]	No. (%)	72 (21.6)	285 (21.4)	357 (21.4)
Reflux	No. (%)	44 (13.2)	328 (24.6)	372 (22.3)
Diarrhea	No. (%)	3 (0.9)	17 (1.3)	20 (1.2)
Iron deficiency	No. (%)	24 (7.2)	113 (8.5)	137 (8.2)
B12-/Folic acid deficiency	No. (%)	62 (18.6)	236 (17.7)	298 (17.9)
Operating time (min)				
	Mean (SD)	150.9 (36.2)	87.3 (44.7)	100.0 (50.1)
	Median	145	77	89
	Range	70 to 438	25 to 413	25 to 438
Length of stay (days)				
	Mean (SD)	5.9 (9.3)	2.2 (2.8)	2.9 (5.0)
	Median	5	2	2
	Range	1 to 109	0 to 60	0 to 109

[a] Use of NSAID and/or acetaminophen

[b] Use of opioid analgesics

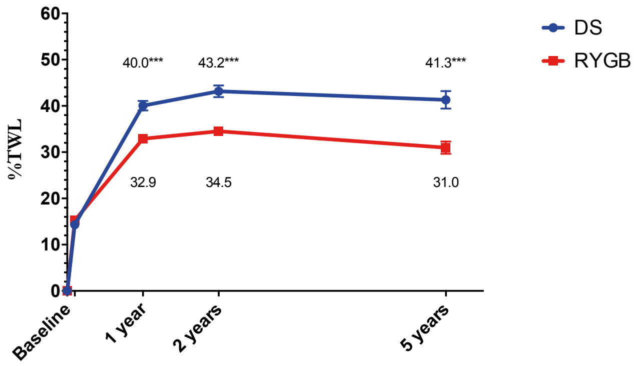
Weight loss

BMI at baseline was 55.0 kg/m^2 for DS and 54.7 kg/m^2 for RYGB. DS resulted in a lower BMI compared to RYGB at 1 year (33.0±5.6 vs. 36.8±5.8, $p<0.001$), 2 years (31.3±5.8 vs. 35.6±6.3, $p<0.001$) and 5 years (32.2±5.5 vs. 37.8±7.3, $p<0.001$), *figure 10*. The reduction in BMI from baseline to 5 years was significant for both groups, however, 27% (26/95) of DS and 64% (200/314) of RYGB had a BMI ≥35 kg/m^2 at 5 years. Total body weight loss was 41.3% for DS and 31.0% for RYGB at 5 years ($p<0.001$), *figure 11*.



	Baseline	1 year	2years	5 years
DS (n)	333	266	211	95
RYGB (n)	1332	1119	764	314

Figure 10. Mean BMI (with 95% CI) at baseline, 1, 2, and 5 years after DS and RYGB, respectively (***=p<0.001).



	Baseline	1 year	2years	5 years
DS (n)	333	266	211	95
RYGB (n)	1332	1119	764	314

Figure 11. Mean total body weight loss (%TWL, with 95% CI) at baseline, 1, 2, and 5 years after DS and RYGB, respectively (***=p<0.001).

Medication for obesity-related conditions

Diabetes

Despite a higher prevalence of diabetes at baseline for DS compared to RYGB (20.1% vs. 14.5%, p=0.01), the prevalence was lower at the 6th year (1.1% vs. 5.2%, p=0.02). At the 10th year, no DS-patients had diabetes, while the anti-diabetic effect had been lost in RYGB (7.8% compared to 14.5% at baseline, p=0.27), *figure 12.*

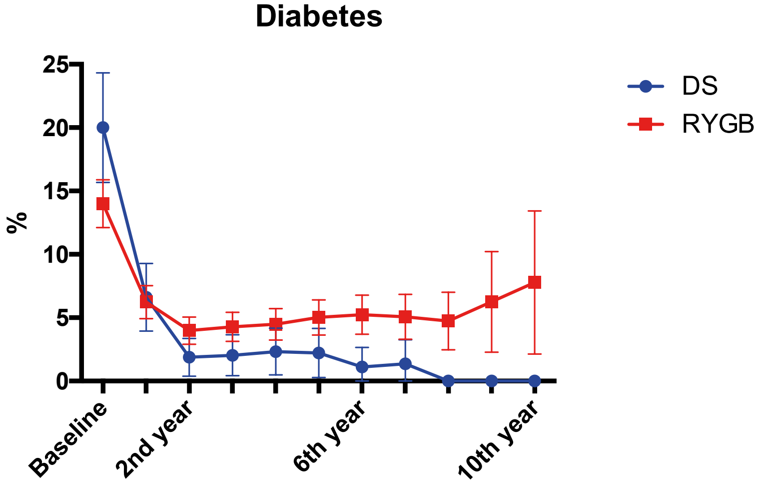


Figure 12. The proportions of patients using insulin and/or other antidiabetics (ATC-codes: A10A, A10B).

Hypertension and/or cardiovascular disease

No differences between DS and RYGB were seen from baseline to the 6th year. Because of the subsequent annual increase in hypertension and/or CVD for RYGB, DS provided a better outcome at the 10th year (15.6% vs. 37.8%, p=0.03), *figure 13.*

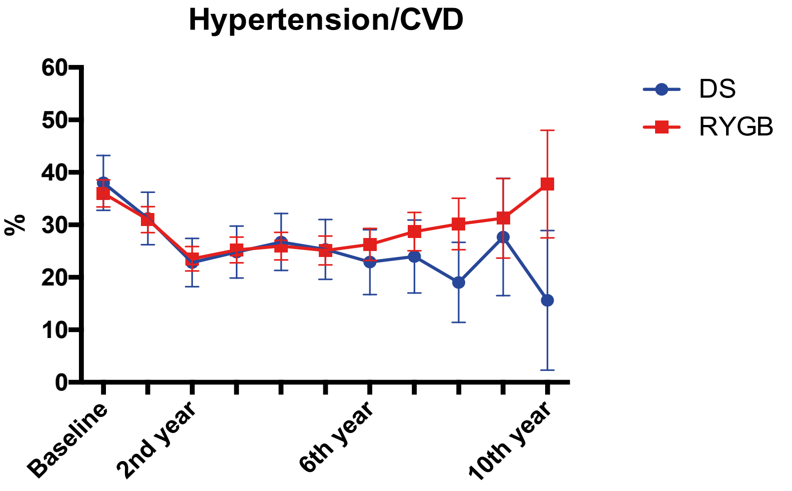


Figure 13. The proportions of patients using drugs for hypertension and/or cardio-vascular disease (ATC-codes: C01, C02, C03, C07, C08, C09)

Dyslipidemia

No differences between DS and RYGB were observed from baseline to the 10th year. At the 10th year, no DS-patient had any medication for dyslipidemia, while the incidence remained stable in the RYGB group, *figure 14*.

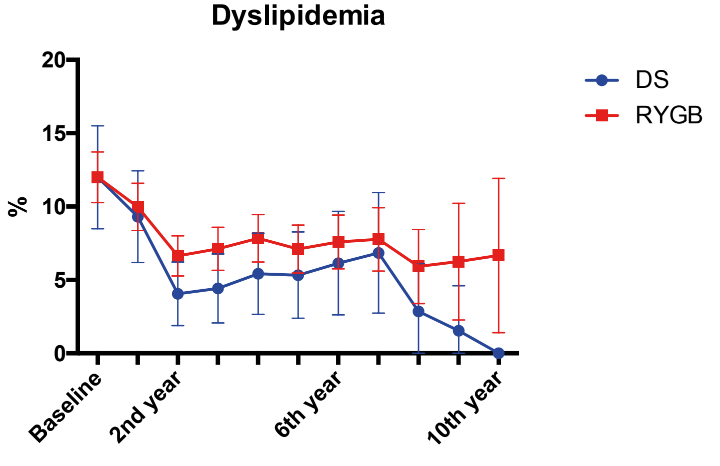


Figure 14. The proportions of patients using lipid-lowering drugs (ATC-code: C10)

Depression

The use of anti-depressants was similar between DS and RYGB at all time points. Both groups had an increased use of anti-depressants over time, however, significant only at 6th year for both groups, *figure 15.*

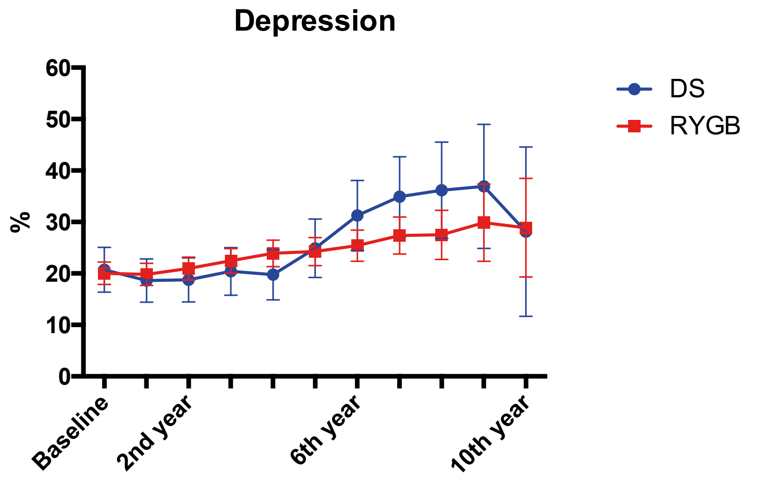
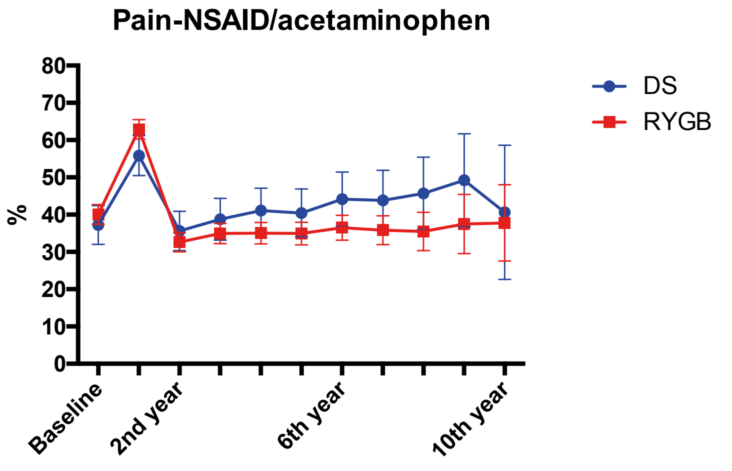


Figure 15. The proportions of patients using antidepressants (ATC-code: N06A)

Pain

The use of NSAID and/or acetaminophen was similar between DS and RYGB at all time points. Use of opioids was similar between DS and RYGB at baseline, but more common in DS at the 2nd (27.8% vs. 18.5%, p<0.001) and 6th year (30.7% vs. 19.3%, p=0.001), *figure 16.*



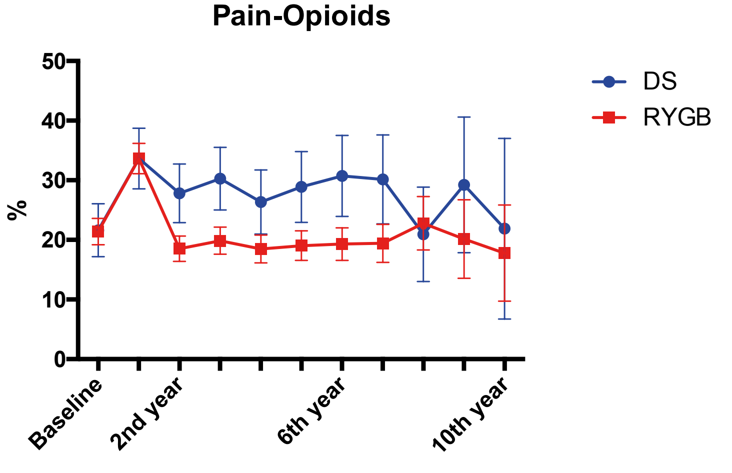


Figure 16. The proportions of patients with pain treated with NSAID and/or acetaminophen (ATC-codes: M01, N02B) and severe pain treated with opioids (ATC-code: N02A)

Reflux and/or dyspepsia

Prevalence was lower for DS at baseline (13.2% vs. 24.6%, $p<0.001$). However, higher prevalence was observed for DS at the 2nd and 6th year. No difference was observed at the 10th year. Overall, DS had an increase over time; while RYGB had an initial decrease was followed by a return to baseline levels at the 10th year, *figure 17.*

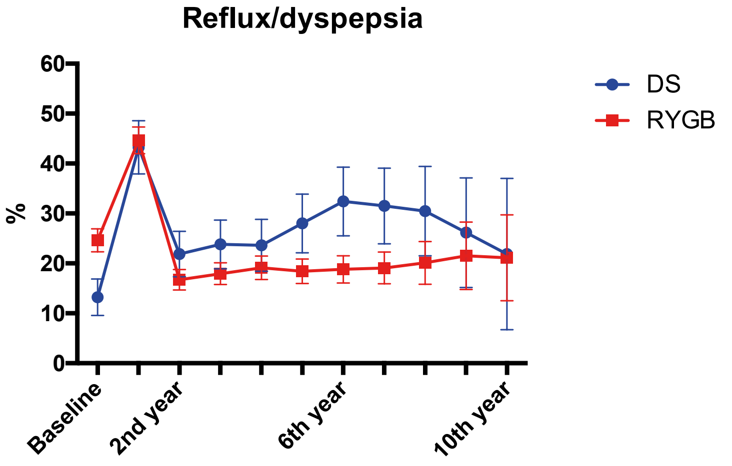


Figure 17. The proportions of patients using PPI and other antacids (ATC-code: A02)

Diarrhea

Use of antidiarrheal drugs was similar between DS and RYGB at baseline, but more common in the DS group at the 2nd year (4.1% vs. 1.1%, p=0.001). No differences were observed at the 6th or 10th year, probably because of the low prevalence for both groups, *figure 18*.

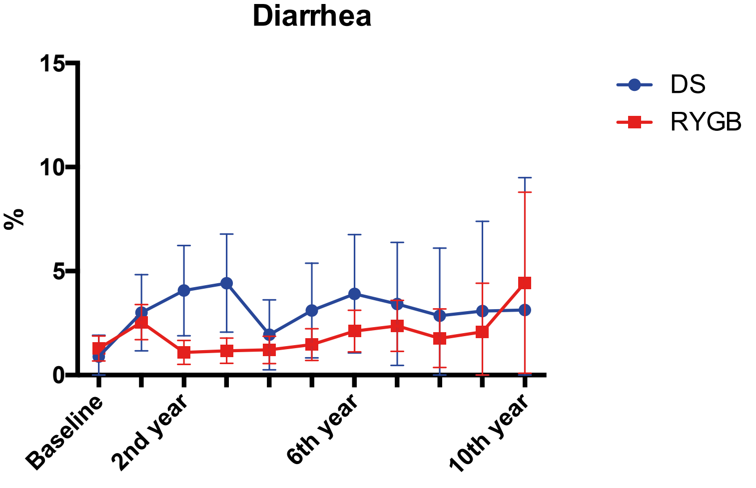


Figure 18. The proportions of patients using drugs for diarrhea (ATC-code: A07D)

Quality of Life

Both groups had an improvement in the physical component summary (PCS) from baseline to five years (DS: 34.6±16.8 to 53.0±11.0, $p<0.001$ and RYGB: 38.7±16.2 to 49.7±14.1, $p<0.001$), with greater improvement for DS (15.1±16.7 vs. 9.6±12.2, $p<0.001$). No difference was observed in the mental component summary (MCS) at five years (DS: 49.2±15.6 to 52.5±25.0, $p=0.26$ and RYGB: 51.7±16.9 to 50.2±19.1, $p=0.06$), *figure 19.*

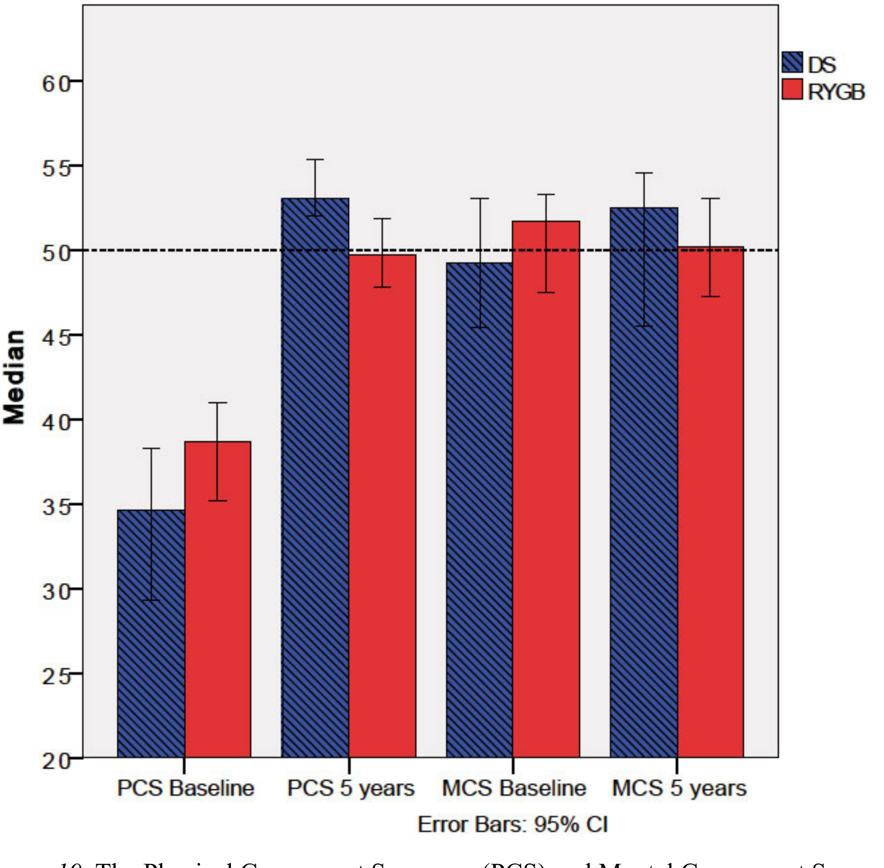


Figure 19. The Physical Component Summary (PCS) and Mental Component Summary (MCS) of SF-36 at baseline (n=284 DS, 947 RYGB) and at 5 years (n=65 DS, 183 RYGB). The values of PCS and MCS in SF-36 have been standardized against a reference population with the same age and gender distribution. The average of this reference population has been set to 50, i.e. lower values than 50 show lower quality of life in physical and mental terms, in comparison with the reference population.

Early complications (≤30 days)

Overall, 9.5% of the patients suffered from one or more complications within 30 days of the operation. A higher overall rate was observed for DS (15.3% vs. 8.1%), while reoperations due to an early complication were similar between groups. The 30-day readmission rate was 11.7% for DS and 8.2% for RYGB (p=0.052). Table 7.

Table 7. *Early complications and reoperations. One patient could have more than one complication/reoperation.*

		DS (n=333)	**RYGB (n=1332)**	p-value
Early complications	**No. (%)**	**51 (15.3)**	**108 (8.1)**	**<0.01**
Leak	No. (%)	6 (1.8)	19 (1.4)	0.62
Bleeding	No. (%)	6 (1.8)	23 (1.7)	1.00
Abscess	No. (%)	5 (1.5)	19 (1.4)	1.00
Wound dehiscence	No. (%)	3 (0.9)	4 (0.3)	0.15
Surgical site infection	No. (%)	26 (7.8)	20 (1.5)	<0.01
Bowel obstruction	No. (%)	0 (0)	9 (0.7)	0.22
Stomal ulcer	No. (%)	1 (0.3)	7 (0.5)	1.00
Cardiovascular event	No. (%)	2 (0.6)	4 (0.3)	0.35
DVT/PE	No. (%)	1 (0.3)	1 (0.1)	0.36
Pulmonary complication	No. (%)	3 (0.9)	13 (1.0)	1.00
Urinary tract infection	No. (%)	5 (1.5)	3 (0.2)	0.01
Other	No. (%)	5 (1.5)	33 (2.5)	0.41
Early reoperations	**No. (%)**	**8 (2.4)**	**17 (1.3)**	**0.30**
30-day readmission	**No (%)**	**39 (11.7)**	**109 (8.2)**	**0.05**

Healthcare use in the long-term

The National Patient Register included data from 1st January 1997 to 31st December 2016, which made it possible to analyze long-term healthcare consumption of 326 DS and 1239 RYGB up until 10.6 years after surgery.

Total number of hospital admissions after surgery was 435 for DS and 1404 for RYGB. The causes for hospital admissions differed between the groups, as shown in *figure 20.* Mean number of hospital admissions after surgery was similar between DS and RYGB (1.3 and 1.1, p=0.30), as well as additional in-hospital days (6.6 and 7.2, p=0.81).

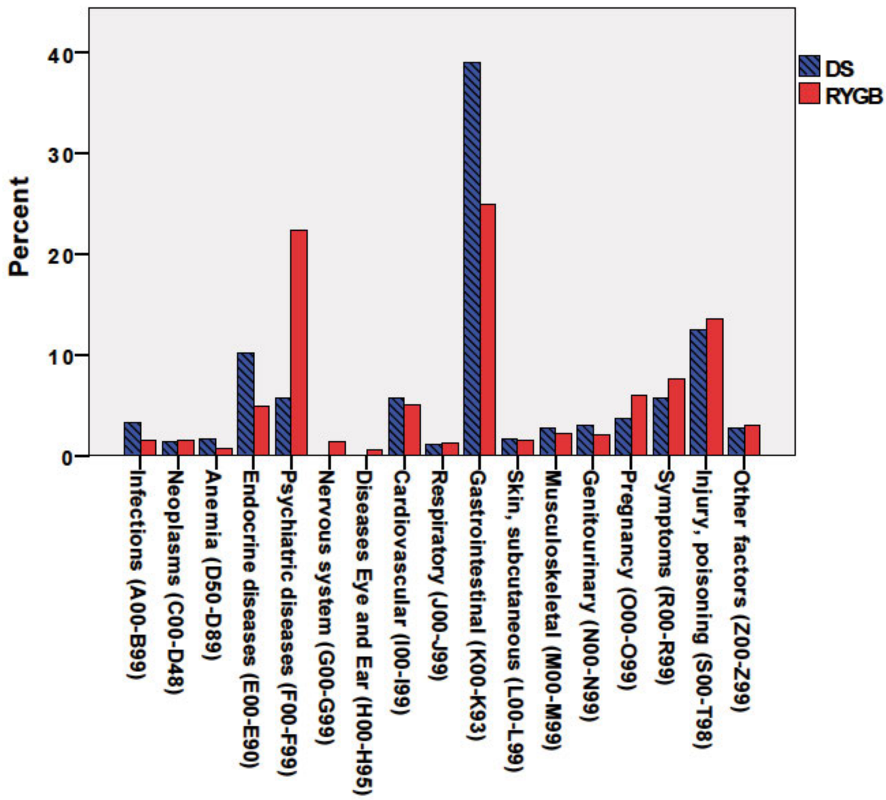


Figure 20. All hospital admissions grouped by primary diagnosis and classified according to the chapters in ICD-10. In total, 435 for DS and 1404 for RYGB.

Visits to specialized outpatient clinics were more frequent after DS than RYGB (mean 7.2 and 4.3 visits, p<0.01). The causes for outpatient care differed between groups, as shown in *figure 21*. One third (33.5%) of the visits to specialized outpatient clinics were related to checkups (Z00-Z13) for the DS group (7.0% for RYGB). If checkups were omitted, no difference in outpatient care was observed (4.8 vs. 4.0, p=0.14).

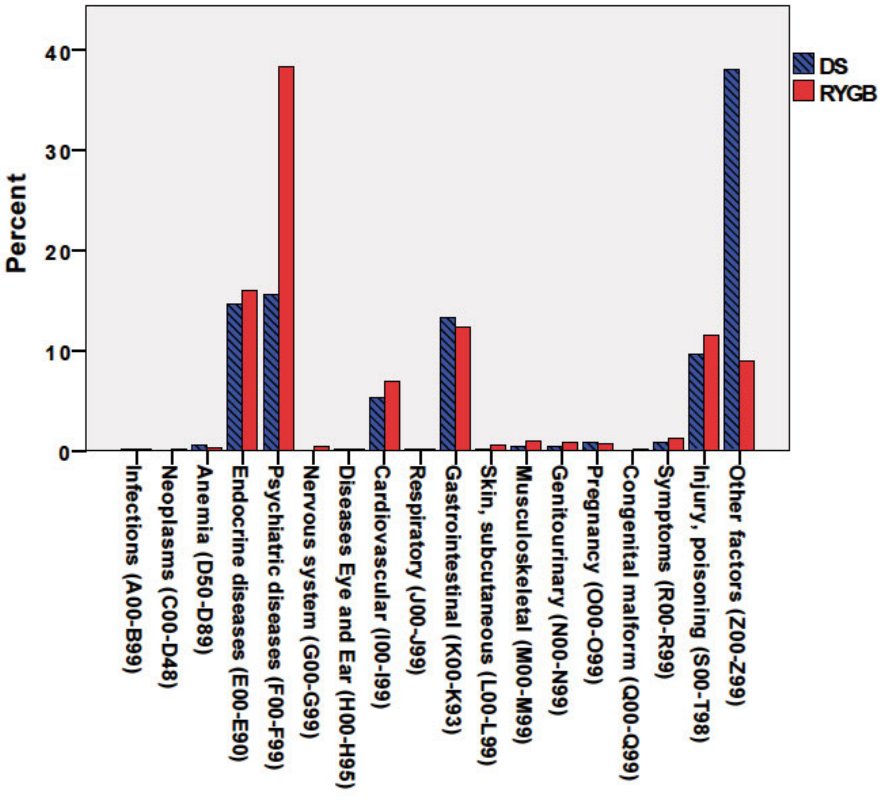


Figure 21. All visits to specialized outpatient clinics grouped by primary diagnosis and classified according to the chapters in ICD-10. In total, 2345 for DS and 5342 for RYGB.

Long-term adverse events and additional surgical procedures

Individuals in the DS group were more likely to require in-hospital care because of protein-malnutrition/malabsorption (OR 11.7 [3.1-43.5]) and to have an additional abdominal operation (any type) (OR 1.9 [1.4-2.6]), where incisional hernia repair and cholecystectomies were more frequent after DS than RYGB (8.3% vs. 2.6% and 12% vs. 5.2%, respectively, both $p<0.01$). The proportions of patients having had a cholecystectomy before the bariatric procedure were similar between DS and RYGB (6.4% vs. 8.3%, $p=0.30$). The need for upper endoscopy and operation for bowel obstruction were similar between groups. Four patients in each group had revisions of their bariatric operation, in DS due to malnutrition or severe reflux/vomiting and all four RYGBs due to insufficient weight loss or weight recidivism.

Mortality

The overall mortality rate was 2.1% (n=7) for DS and 1.7% (n=23) for RYGB ($p=0.64$). Table 8. Two patients died within 30 days after surgery, one DS due to pulmonary emboli and one RYGB who had a postoperative bleeding and secondary heart failure. Of the 7 cases with unknown cause of death, all but one died during 2017 and cause of death was not available in the registry yet.

Table 8. *Causes of death*

		DS (n=333)	RYGB (n=1332)	Total
Unknown cause	n	3	4	7
Cardiovascular event	n	0	7	7
Accident/suicide	n	1	5	6
Malignancy	n	0	4	4
Gastrointestinal perforation	n	0	1	1
Infection	n	0	1	1
Gastrointestinal bleeding	n	0	1	1
Liver failure	n	1	0	1
Pulmonary emboli	n	1	0	1
Other	n	1	0	1
Total	n	7	23	30

Discussion

The ultimate goal with bariatric surgery is an improvement in patients' health both physically and mentally. To achieve that, it is of great importance with maintained weight loss, improvement of comorbidities and quality of life over time, while the risks of complications and long-term adverse events must be minimal. In our studies, these outcome-parameters have been explored in super obese patients after DS and RYGB, respectively.

In short, DS resulted in superior weight loss compared to RYGB (paper I, II and III). Body composition after the massive weight loss did not differ from non-operated controls with the same BMI, for neither DS nor RYGB (paper I). Both DS and RYGB resulted in an improved metabolic control (paper II and III), but the effect on diabetes and hypertension was greater and was maintained to a greater extent in the long-term after DS compared to RYGB (paper III). Both DS and RYGB resulted in an improved physical quality of life, with greater improvements after DS (paper III). However, complications and long-term adverse events/effects were more common after DS (paper II and IV).

Weight loss

In paper I, II and III, DS resulted in a greater total body weight loss compared with RYGB (40% vs. 26%; 43% vs. 32% and 41% vs. 31%). These results are in line with the only RCT of super obese patients (29 DS and 31 RYGB, BMI 50-60) with long-term data, by Risstad et al. [23], reporting a total body weight loss of 40.3% for DS and 26.4% for RYGB at 5 years. Prachand et al. [20] reported in their 3-year study of 350 super obese patients, a BMI reduction from 58.8 to 33.6 kg/m^2 for DS and 56.4 to 37.2 kg/m^2 for RYGB. In paper III, we found a similar result 5 years after surgery, 55.0 to 32.2 kg/m^2 for DS and 54.7 to 37.8 kg/m^2 for RYGB.

The insufficient weight loss and weight regain in super obese patients after RYGB is a concern. In paper II, 49% of the RYGB-patients were still severely obese (BMI >35kg/m^2) at follow-up (mean 4.1 years). In paper III, 64% of the RYGB-patients had a BMI>35 kg/m^2 at 5 years and thus still fulfilling the indication for bariatric surgery. These findings are consistent with previous studies with long-term data of RYGB in super obese patients

[19, 88]. The weight loss after DS, on the other hand, is maintained even in the long run. Strain et al. [22] reported in their 9-year follow up of more than 200 patients operated with DS, a BMI reduction from 53.4 to 31.5 kg/m^2.

Body composition and RMR after weight loss

In paper I we examined long-term effects on body composition and RMR after DS and RYGB. The most important finding was that body composition did not differ from that of the non-operated controls with the same BMI (28-35 kg/m^2), despite the large weight loss after DS and RYGB (40% and 27% total body weight loss, respectively). A study from 2000 [120] found significantly higher FFM and RMR in 14 patients 30 months after DS compared to 14 controls (matched for age, gender and height). This favorable difference for the DS-group was probably because of higher body weight, since the groups were not matched for weight or BMI. A study from 2003 [121] of 101 female DS-patients and 53 weight-matched, non-operated controls, reported similar results to ours, with a body composition close to physiological values. In a review from 2007 [115], RYGB and DS were found to cause greater percentage of FFM loss compared with restrictive bariatric surgery (laparoscopic adjustable gastric banding). The safety in regard to nutrition and body composition after RYGB, and especially DS, were considered potentially problematic. However, the included studies in this review are difficult to compare in several aspects; initial BMI varied, more women in restrictive bariatric surgery groups, restrictive surgery resulted in less total body weight loss, follow up time was very diverse and statistical comparisons were made without weighting by the number of patients (n) included in each study. A study published in 2018 [122], reported a maintained FFM, 1 to 5 years after RYGB.

Preservation of a high RMR is important since it accounts for about 70% of the total daily energy expenditure and therefore counteracts weight regain. [110, 123] Whether bariatric surgery also promotes weight loss through effects on RMR is uncertain. Schmidt et al. [124] found a decrease in RMR after RYGB; while others [125] have concluded that the increased postprandial RMR could be one possible mechanism that contributes to weight loss after RYGB. Our study suggests that both RYGB and DS result in a RMR and RMR/FFM similar to that of non-operated controls with the same BMI (28-35 kg/m^2).

Comorbidities

The effect on comorbidities was studied in paper II and III. In both studies, the presence of a comorbid disease was determined by the use of medication, and remission was defined as cessation of all medication for the specific condition (CPAP for sleep apnea in paper II).

In paper II, the effect on diabetes was greater after DS compared to RYGB (93% vs. 71% remission), while the reduction in hypertension, dyslipidemia and sleep apnea were similar between groups after 4 years.

In paper III, all prescribed drugs were analyzed in the SPDR up until 10 years after surgery. At 5 years, both DS and RYGB provided a significant reduction in diabetes, but thereafter an increase was observed for RYGB while a 100% remission at the 10th year was observed for DS. At the 10th year, the use of anti-hypertensive drugs was significantly lower for DS compared to RYGB, while the reduction in dyslipidemia was similar between groups over time.

Two previous retrospective studies [89, 96], comparing DS and RYGB in super obese patients, have reported a greater resolution of diabetes, hypertension and dyslipidemia for DS after 3-4 years. Prachand et al. [89] also found a weight-loss-independent improvement of comorbidities after both DS and RYGB. The latter probably reflecting the neurohormonal changes that occur after bariatric surgery, counteracting the metabolic syndrome. In the previously mentioned RCT [23] (29 DS and 31 RYGB), DS provided a significantly lower $HbA1_c$ and serum lipids, but no difference in blood pressure was found between groups at 5 years.

In paper III, the use of anti-depressants increased for both groups after surgery, a somewhat surprising finding, since improvement of depressive symptoms are reported after bariatric surgery in 11 of 12 studies (including 2 RCTs) in a meta-analysis from 2016. [126] However, we studied the use of anti-depressants, not depressive symptoms. The use of opioid analgesics was also remarkably high, about 21% for both groups at baseline, and it was more common after DS at the 2nd (25.2% vs. 18.0%) and 6th year (31.4% vs. 19.9%). The massive weight loss, especially in DS, ought to reduce the patients' musculoskeletal pain, why this finding probably reflects something else. In recent years there has been a concern about opioid analgesic use among bariatric patients. Two recent studies, one from the US [127] and one from Sweden [128], reports an overall increased use of opioids after bariatric surgery.

Quality of Life

In paper II, the Moorhead-Ardelt quality of life Questionnaire (MAQ) was used for comparison of QoL between the 113 DS and 98 RYGB postoperatively. It is well known that a higher weight loss is associated with a higher QoL. [12, 129] Despite the superior weight loss for DS in that study, no difference in MAQ-score was observed between groups (1.2 vs. 1.1). The higher complication rate after DS was thought to be a possible explanation, but no significant difference was found in MAQ-score between patients who had had a complication compared to those who had not. A possible explanation was that most of the patients had recovered from their complication at follow up. To analyze this further, we did a multiple ordinal regression model (after publication of the manuscript). According to this regression model the %Excess BMI loss had a significant positive influence on QoL ($p<0.001$), while nausea/vomiting and fecal incontinence had a significant negative impact on QoL (both $p<0.05$). The other GI-symptoms (except gases) were also associated with lower QoL, however not significant. This suggests that the more pronounced gastrointestinal symptoms after DS, at least partly, could explain why their QoL was not better despite better weight loss.

In paper III, the mental and physical summary scores (MCS and PCS) in SF-36 were analyzed at baseline and at 5 years in SOReg. This allowed comparisons between groups and changes within groups from baseline. The PCS scores were equally poor for DS and RYGB at baseline (33.4 and 34.9). After 5 years both groups had significant physical improvements, with scores similar to a reference population with the same gender and age composition. The greater PCS-score for DS at 5 years (53.0 vs. 49.7) was likely explained by the greater weight loss after DS. For both DS and RYGB, MCS-scores were similar to reference values at baseline and at 5 years and no difference was observed between or within groups at 5 years.

Complications and adverse events

Despite the superior weight results, a broad adoption of DS has never occurred. The increased risk of surgical complications and malnutrition [23, 24] has brought disrepute to the operation. Due to the complexity and the more malabsorptive features of DS, it is not surprising that we also found more complications, gastrointestinal symptoms and long-term adverse events after DS compared with RYGB. However, the higher complication risks in revisional bariatric surgery [130] must also be taken into account in RYGB since more than 50% of the super obese patients remain severely obese and unsatisfied with the weight loss.

In paper II, we found an overall complication rate of 27% for DS and 14% for RYGB and the patients reported more gastrointestinal symptoms after DS (especially diarrhea). A greater use of medication for reflux and diarrhea and an increased use of opioid analgesics were seen for DS compared to RYGB in paper III. In paper IV, the 30-day complication rate was 15.3% for DS and 8.1% for RYGB and the 30-day readmission rate was 11.7% for DS and 8.2% for RYGB. Long-term, DS was associated with an increased risk of protein-malnutrition/malabsorption requiring in-hospital care and a higher need of additional abdominal operations. The higher complication rate seen in DS was, however, biased by the surgical approach since laparoscopy was less common (25% vs. 90% of RYGB), a factor that probably explains why surgical site infections and incisional hernias were more common. The long-term health care consumption was similar between groups concerning number of additional hospital admissions and days in hospital, while DS consumed more health care at specialized outpatient clinics, however, as expected due to on the more rigorous follow-up program.

Reports on complications are heterogenic in the literature and therefore difficult to compare. Dorman et al. [96] concluded that DS and RYGB had similar complication rate, with the exception of more emergency department visits for DS patients, and in the study by Marceau et al. [21] where outcomes 5 to 20 years after DS was studied, they found a complication rate similar to that of other bariatric procedures. Since DS is a more technically difficult operation, it is probably beneficial if the treatment with DS is centralized to a few surgeons at a center with an adequate follow-up program.

According to SOReg, the 30-day complication rate for bariatric surgery in general in Sweden is 6.7% (2.5% severe complications i.e. Clavien-Dindo ≥3B). The complication rate seen in paper II (DS 27% and RYGB 14%) where of all complications with a mean follow-up time of 4 years and the definition of a complication was different from that used in SOReg. In paper IV (SOReg data), the 30-day complication rate was 9.5% (DS 15.3%, RYGB 8.1%) and 30-day reoperation rate was 1.5% (DS 2.4%, RYGB 1.3%). Since the study was of super obese patients only, a slightly higher complication rate was expected. However, the 30-day reoperation rate was low.

Strengths and limitations

Paper I

The strength of the study was the analysis of body composition and RMR in weight stable RYGB and DS patients with a representative postoperative BMI of 28-35 kg/m^2 and the comparison to a non-operated control group, with the same BMI. Concerning the characteristics of the cohorts in this study, a BMI 28-35 kg/m^2 and age 30-55 years was considered representative, since the average BMI is 31 and 32 kg/m^2 five years after RYGB and DS, respectively, and the average age of a bariatric patient is about 40 years. [131] Another reason for the chosen age interval was that FFM is maintained up to 60 years of age and decreases by age thereafter. [132]

However, there are some limitations in the study that needs consideration. Firstly, our initial aim was to examine whether RYGB and DS results in an excessive loss of FFM, but there is no generally accepted definition of “excessive loss of FFM” and we did not have any measurements of body composition before surgery. Instead we compared the operated patients with a non-operated control group. Therefore, we were only able to conclude that the operated patients had a similar body composition as the non-operated controls, with the risk of type-II error due to the small sample size. Secondly, there were more men in the DS group (approximately 40% vs. 20% in RYGB and controls), which could have affected the results. However, we could not find a difference in FFM or FFM% between groups when comparing men and women separately either (with the obvious risk of type-II error). Thirdly, since the majority of weight loss is loss of FM, a previous higher BMI, as in the two bariatric groups, might result in higher remaining FFM% after weight loss. Fourthly, we were not able to draw any conclusions about possible differences in exercise patterns since this data were not available.

Paper II

This study included a broad analysis of weight loss, changes in comorbidities, QoL, complications and gastrointestinal symptoms, on average 4 years postoperatively, a relatively long follow-up time. Another strength of the study was the detailed analysis of medical records, which provided more detailed information about complications than registry data (e.g. SOReg).

The retrospective non-matched design together with a response rate of 63% is a limitation. However, a sensitivity analysis of 93% of the non-responders did not reveal any major differences concerning baseline characteristics. The presence of a comorbid disease was determined by the use of drugs and remission was defined as complete cessation of all drugs for the specific condition. Therefore improvement in the specific condition was not possible to detect. A more accurate way would have been to analyze blood samples before and after surgery to measure glycemic control, blood lipids etc. Most of the patients (200 of 211) were operated with open surgery, which is associated with a higher risk for complications such as incisional hernia compared to laparoscopic surgery, which is standard today. The questionnaire regarding gastrointestinal symptoms has not been validated, nevertheless, our results were in line with the literature. [23, 96, 133]

Paper III and IV

The strengths of these studies were the registry-based design, allowing cross matching of five national registries, the high coverage of these registries, the long follow-up time and the use of propensity score matching.

Propensity score

Propensity-score matching was used to minimize the effect of possible confounding variables. Propensity score is defined as the probability of treatment assignment (0 to 1) based on observed baseline characteristics. [134] It could also be considered as a balancing score, where the distribution of included baseline variables will be similar between treated and controls after matching on propensity score. In this way a non-randomized study mimics a randomized controlled trial after propensity-score matching. However, propensity score cannot account for any unmeasured confounders, leaving some residual confounding possible. A logistic regression model estimated the propensity score, where treatment was regressed on observed baseline characteristics. This is the most common way to estimate a propensity score. [134] A propensity score could be used in different ways to reduce confounding. However, matching on propensity score is one of the most commonly used methods. [135]

Regression adjustment has been more commonly used historically than propensity score, for estimating treatment effect. There are however several advantages with propensity score methods versus regression adjustments. Firstly, it is more transparent, i.e. easier for the reader to determine whether the propensity score model has been adequately specified, just by looking at the groups' differences in baseline characteristics, than it is to determine whether a regression model has been adequately specified. Secondly, propensity score matching separates the design of the study from the analysis of the study, similar to a RCT, where effect of treatment is estimated first after completion of the inclusion in the study. In propensity score matching an acceptable balance in baseline covariates must be reached before proceeding to analysis of treatment effect. When using regression models, the outcome is always in sight, and the researcher could be tempted to adjust the model until the desired association has been achieved. Thirdly, it is easier to examine the degree of overlap of baseline covariates between groups with propensity score matching. If there are substantial differences in baseline covariates between treated and untreated subjects, this will be evident by the small number of matched subjects. It is more difficult to assess the overlap in a regression model, with the risk of not being aware that the two groups differ systematically, and the fitted regression model can lead to biased estimates of treatment effect.

Since there were more controls (RYGB) than treated (DS) available in our data set, groups were matched 1:4, which was a tradeoff between having two well-matched groups, while maintaining as many patients in each group as possible. The most common matching is 1:1, but matching >1:1 has the advantage with improved bias reduction and less excluded subjects from the original data set, i.e. improved generalizability. The matching algorithm we used was nearest neighbor matching without replacement within a specified caliper distance. Nearest neighbor matching means that one DS were matched with four RYGBs, whose propensity score was the closest to the selected DS. The caliper distance defined the maximum allowed difference in propensity score. The caliper distance used was 0.2 SD of the logit (inverse logistic function) of the propensity score, which is the recommended and most commonly used. [134, 135] Without replacement means that, once an untreated subject is matched to a treated subject, that subject is no longer available as a potential match to subsequent treated subjects. With replacement is commonly used if there is less untreated than treated subjects, where one untreated could be included in more than one matched set. Standardized difference in means was used for assessment of covariate balance in the matched groups, which is described in more detail in the paper by Austin [134] and Deb et al. [135].

Which statistical methods to use when analyzing the treatment effect in a propensity score matched sample is a matter of debate in the literature. [136] Some authors argue that dependent statistical methods should be used [134] (e.g. paired sample t-test, McNemar's test) because the groups are not independent of each other after propensity score matching, while other suggests that independent methods should be used [137] (e.g. independent sample t-test, chi2-test). After consultation with two independent statisticians, both recommending the regular independent tests, we proceeded with that.

Limitations of paper III included the small sample size at the 10th year, providing limited statistical power for assessing differences of comorbidities at this time point. Similar to paper II, the outcome for each individual was binary (no medication vs. one or more medications) and improvements without total cessation of all drugs for the specific condition could therefore not be registered. Another limiting factor was the lack of long-term data in SOReg. The inclusion rate is very good in SOReg (99%), but five-year data is only reported to the register in about half of the patients. This, in combination with an average elapsed time since surgery of 5.1 years, explains why only about one quarter of the patients were possible to include in the analysis of weight loss at 5 years. The response rate of SF-36 from eligible patients at 5-years was less than 50%, limiting the interpretation of the results and was also the reason why only the summary scores (PCS, MCS) were reported in this study.

Paper IV was limited by the possible underdiagnosis of several clinically important long-term adverse events/effects (e.g. anemia, hypocalcaemia and other nutritional deficiencies). It was also difficult to determine whether the additional abdominal operation was related to a complication/adverse event. Since DS patients are actively entered into follow-up programs at specialized outpatient clinics, while RYGB are mainly followed up in primary care (not included in the register), the use of diagnoses from specialized outpatient clinics were of limited scientific value. We decided to analyze the presence of malnutrition/malbsorption since it is often emphasized as a major risk after DS, however, only based on primary diagnosis for in-hospital care since no blood samples were available and therefore less severe malnutrition was not detectable.

Conclusion

When considering a DS or RYGB for a super obese patient, the superior weight loss and greater improvements in several obesity-related comorbidities after DS must be weighed against the increased risk of complications and long-term adverse effects compared to RYGB. We therefore believe that the choice of bariatric procedure must be made in close agreement between the surgeon and a well-informed patient, where the compliance to an adequate follow-up program is of great importance to minimize the risk of long-term adverse effects after DS.

Paper I

Weight stable patients with BMI 28-35 kg/m^2 after RYGB and DS have a body composition and RMR similar to that of non-operated individuals within the same BMI interval. Moreover, the results support the notion that RYGB and DS do not yield excessive loss of fat-free mass.

Paper II

Patients with super obesity have superior weight reduction and a better effect on diabetes with DS. This occurs at the cost of more adverse events and gastrointestinal symptoms, but with similar QoL, compared to patients operated with RYGB. Overall, DS resulted in higher BAROS score compared to RYGB.

Paper III

DS provided a superior weight loss at 5 years and lower prevalence of diabetes and hypertension compared to RYGB during the 10-year follow-up. Both groups had an improvement in physical quality of life, with superior improvement in DS at 5 years.

Paper IV

DS was associated with more early complications and an increased risk for protein-malnutrition/malabsorption requiring in-hospital care and more additional abdominal surgeries, however, the overall mortality and long-term need of in-hospital care were similar to RYGB. As expected, the more rigorous follow-up program after DS resulted in more outpatient care at specialized clinics

Future perspectives

To date, there is a deficient knowledge about body composition after bariatric surgery, and also diverging conclusions about the importance of RMR as a weight-loss promoting mechanism, affected by bariatric surgery. Most of the studies on body composition after bariatric surgery do not extend beyond the initial weight loss phase (1-2 years). Additionally, several studies rely on methods for assessment of body composition that have not been sufficiently validated in severely obese patients (e.g. BIA). Key assumptions such as tissue hydration may differ significantly compared to normal-weight controls and may yield invalid results in severely obese individuals.

As previously mentioned, our study of body composition and RMR (paper I) was also limited by several factors, especially the lack of longitudinal data during weight loss and the small sample size with limited statistical power to detect differences. The optimal control group would have been individuals who had reached BMI 28-35 kg/m^2 without surgery, with a previous BMI similar to that of the bariatric groups preoperative BMI. However, such control group is very hard to find since achieving that amount of weight loss and maintain it over time is very rare with only life style interventions. To clarify the issue of body composition after bariatric surgery, future studies should focus on the use of reliable methods for severely obese patients in longitudinal trials with repeated measures of body composition and include data of physical activity and RMR.

Which bariatric procedure that is to prefer for a super obese patient is still under debate and the choice is in most cases based on what bariatric procedures that is performed at the center where the patient is referred to. In Sweden most of the DS have been performed in Uppsala (70%) and Torsby (20%), while other Swedish centers most commonly perform RYGB or SG in these patients. Globally there are some centers in the US, Canada and Europe who advocates the DS, otherwise RYGB or SG is more common. There is also an emerging interest in the Single Anastomosis Duodeno-Ileal Switch (SADI-S) both as a primary bariatric procedure and as revisonal surgery for weight regain. This procedure is designed to reduce the technical complexity with standard DS (one bowel anastomosis instead of two) and possibly reduce the risk of malnutrition by using a longer common channel. However, no evidence exists in favor of SADI-S compared to DS, despite a possible trend of less malabsorption after SADI-S according to a review in the field. [138]

There is basically unity in the literature concerning the superior weight loss and greater effect on obesity related comorbidities, at the price of more complications in DS compared to RYGB. Level of evidence is based mainly on retrospective studies and the two small RCTs, one by Sovik and Risstad et al. (29 DS, 31 RYGB), with 1-year results [139], 2-year results [140] and 5-year results [23], and one by Hedberg and Sundbom [141] (24 DS, 23 RYGB) with 3-year results. A larger RCT is lacking and studies comparing the two methods beyond 5 years are very scarce in the literature and ought to be the focus for future studies.

The remarkably high prevalence of patients using opioid analgesics, both before (20%) and after surgery (20-30%), as well as the increased use of antidepressants after bariatric surgery (paper III), needs further studies to clarify causality.

Populärvetenskaplig sammanfattning på svenska

Mycket svår fetma (Body Mass Index [BMI] >50 kg/m^2) är ett livshotande tillstånd som tyvärr blir allt mer vanligt förekommande. I denna avhandling har två operationsmetoder jämförts med syftet att undersöka vilken operation som ger bäst resultat för dessa individer. Vi fann i våra studier att den mindre vanliga operationen duodenal switch gav en betydligt större viktnedgång och bättre effekt på fetmarelaterade följdsjukdomar, till priset av något ökade komplikationsrisker och långsiktiga biverkningar, jämfört med gastric bypass, som är den vanligaste operationsmetoden i Sverige.

En normalviktig individ har ett BMI mellan 18,5 och 25. Sedan 1980-talet har förekomsten av övervikt (BMI >25) och fetma (BMI >30) ökat med ca 30 % hos vuxna och ca 50 % hos barn globalt sett. Det har också skett en kraftig ökning av antalet individer med mycket höga BMI-nivåer. Under åren 2000-2010 ökade antalet individer med BMI >40 med 70 % i USA och antalet med BMI >50 fördubblades. Fetma och dess följdsjukdomar, diabetes och högt blodtryck, utgör tillsammans med rökning, de 4 största globala hälsoproblemen i dagsläget. Fetma är också kopplat till höga blodfetter, sömnapné (nattliga andningsuppehåll), hjärtsjukdomar, psykisk ohälsa och en ökad risk för ett flertal cancerformer. Man räknar med att en individ med ett BMI >40 har en förväntad livslängd som är 8-10 år kortare jämfört med en normalviktig individ, vilket är en större negativ påverkan på livslängden än effekten av rökning.

Behandlingen av fetma är i första hand kost- och livsstilsförändringar. Det finns även ett fåtal läkemedel som har visat sig ge en viss viktnedgång, men det rör sig i regel om ett fåtal kilon. Kirurgisk behandling är indicerat för individer med svår fetma (BMI >35) som försökt gå ner i vikt utan att lyckas. Det är bara kirurgi som har vetenskapligt stöd för en betydande och bestående viktnedgång vid svår fetma. Viktreducerande operationer brukar benämnas bariatrisk kirurgi efter det grekiska ordet för fett, *baros*. De vanligaste operationsmetoderna globalt och i Sverige är gastric bypass och sleeve gastrektomi. Dessa operationer har dock visat sig ge en otillräcklig viktnedgång hos individer med mycket svår fetma, s.k. superobesitas (BMI >50). I mer än hälften av fallen har dessa individer en bestående svår fetma (BMI

>35) även efter operation. Individer med BMI >50 är den snabbast växande gruppen som söker bariatrisk kirurgi. Idag utgör dessa individer en dryg fjärdedel av patienterna som genomgår överviktskirurgi i USA (ca 9 % i Sverige). Duodenal switch är den mest kraftfulla operationen och kan enkelt beskrivas som en kombination av gastric bypass och sleeve gastrektomi, men då en betydligt större del av tunntarmen förbikopplas minskar näringsupptaget ytterligare. Duodenal switch har i flera studier visat sig ge en större och mer bestående viktnedgång och i vissa studier också bättre effekt på de fetmarelaterade följdsjukdomarna. Dock är duodenal switch associerat med en ökad risk för biverkningar från magtarmkanalen (diarré, uppblåsthetskänsla och i svåra fall avföringsinkontinens) och en ökad risk för malnutrition (näringsbrist) på längre sikt. Detta, i kombination med att duodenal switch är en tekniskt svårare operation att utföra, har gjort att den hamnat i vanrykte hos många kirurger. Idag utgör duodenal switch mindre än 1 % av alla överviktsoperationer globalt och i Sverige. Kliniker i bl.a. USA och Kanada som specialiserat sig på duodenal switch för individer med superobesitas redovisar dock utmärkta långtidsresultat efter denna operation med komplikationsfrekvenser i nivå med andra överviktsoperationer, trots större viktnedgång och bättre effekt på följdsjukdomar. Möjligen förtjänar därför duodenal switch mer uppmärksamhet som förstahandsval till denna växande patientkategori.

Vid viktnedgång är det önskvärt att en betydande del av fettmassan minskar medan muskulaturen bibehålls i så stor utsträckning som möjligt. Muskulaturen har stor betydelse för kroppens funktion och den basala ämnesomsättningen. Den basala ämnesomsättningen utgör ca 70 % av den totala dagliga energiförbrukningen och har därmed stor betydelse för att motverka framtida viktuppgång. Det finns en tumregel som säger att vid viktminskning utgörs den totala viktnedgången av ca ¾ fettmassa och ca ¼ fettfri massa (mestadels muskulatur). Det finns en oro att överviktskirurgi, framförallt gastric bypass och duodenal switch, leder till malnutrition och därmed en oproportionerligt stor förlust av muskelmassa i samband den kraftfulla viktnedgången efter operationen. Detta studerades i delarbete I, där kroppsammansättningen och basal ämnesomsättning mättes hos 12 individer opererade med duodenal switch och 15 individer opererade med gastric bypass, som alla nått ett BMI på 28-35. När dessa båda grupper jämfördes med en icke-opererad kontrollgrupp bestående av 17 individer med samma BMI- och åldersintervall, kunde ingen skillnad ses i kroppsammansättningen eller basal ämnesomsättng mellan de opererade patienterna och kontrollgruppen. Detta trots en total viktnedgång på 40 % efter duodenal switch och 26 % efter gastric bypass.

Viktnedgång är ofta det primära utfallsmåttet efter överviktskirurgi. Dock saknas en tydlig definition av hur stor viktnedgången ska vara för att resultatet ska anses som lyckat. Överviktskirurgi leder, utöver viktnedgång, också till stora förbättringar vad gäller de fetmarelaterade följdsjukdomarna (bl.a. diabetes, högt blodtryck och höga blodfetter) och en förbättrad livskvalitet. Därför bör även dessa utfallsmått tas med när man värderar resultat efter överviktskirurgi. Det validerade instrument BAROS (Bariatric Analysis and Reporting Outcome System) klassificerar resultatet efter överviktskirurgi i 5 kategorier (från ”failure” till ”excellent”) utifrån viktnedgång, förbättringar av följdsjukdomar och livskvalitet. I delarbete II användes BAROS tillsammans med ett formulär om magtarmsymptom för att jämföra 113 patienter opererade med duodenal switch och 98 patienter opererade med gastric bypass. Operationerna var utförda i Uppsala i genomsnitt 4 år tidigare. Totalt sett resulterade duodenal switch i högre BAROS-poäng, då den gav en större total viktnedgång (43 % mot 32 % för gastric bypass). En högre andel av patienterna blev också av med sin diabetes efter duodenal switch (93 % mot 79 %), medan båda grupperna hade liknande förbättringar avseende högt blodtryck, höga blodfetter och sömnapné syndrom. Inga skillnad i livskvalitet sågs mellan grupperna, detta trots att komplikationsfrekvensen var högre efter duodenal switch (27 % mot 14 %). Patienterna opererade med duodenal switch hade också mer besvär från magtarmkanalen, framförallt diarré och besvärande gasbildning, men även halsbränna och några fall av avföringsinkontinens.

I delarbete III och IV jämfördes 333 patienter opererade med duodenal switch och 1332 patienter opererade med gastric bypass. I dessa studier undersöktes viktnedgång, effekt på följdsjukdomar, komplikationer, långsiktiga biverkningar och total sjukvårdskonsumtion under en 10-årsperiod genom utdrag ur 5 nationella register. Patienterna i de båda grupperna var matchade med s.k. propensity score, en statistisk metod för att få så jämförbara grupper som möjligt. Även här sågs en större total viktnedgång 5 år efter duodenal switch (41 % mot 31 %). Båda operationerna gav en minskning av diabetes, högt blodtryck och höga blodfetter. Duodenal switch hade dock bättre effekt på diabetes och högt blodtryck 10 år efter operation. Båda operationerna resulterade i en förbättrad livskvalitet efter 5 år, men större förbättringar sågs efter duodenal switch. Duodenal switch resulterade dock i fler komplikationer inom 30 dagar (15 % mot 8 %) och malnutrition och ytterligare bukoperationer var vanligare på lång sikt jämfört med gastric bypass. Behovet av inneliggande sjukhusvård skiljde sig dock inte mellan grupperna (i genomsnitt drygt ett ytterligare slutenvårdstillfälle för båda grupperna).

Sammanfattningsvis anser vi att valet av operationsmetod är något som måste göras i samförstånd med en välinformerad patient. Den större viktnedgången och bättre effekten på fetmarelaterade följdsjukdomar efter duodenal switch måste vägas mot den något högre risken för komplikationer och långsiktiga biverkningar jämfört med gastric bypass.

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