From the department of Clinical Sciences, KIDS
Karolinska Institutet, Stockholm, Sweden

GASTRIC BYPASS

POSITIVE AND NEGATIVE HEALTH EFFECTS

Olof Backman

Karolinska Institutet

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GASTRIC BYPASS-POSITIVE AND NEGATIVE HEALTH EFFECTS

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Olof Backman

Principal Supervisor:
Professor Erik Näslund
Karolinska Institutet
Department of Clinical Sciences (KIDS)

Co-supervisor(s):
Professor Finn Rasmussen
Lund University
Department of Health Sciences

M.D. Richard Marsk
Karolinska Institutet
Department of Clinical Sciences (KIDS)

Opponent:
Associate Professor Jan Dalenbäck
Sahlgrenska Academy at Gothenburg University
Institute of Clinical Sciences
Department of Gastrosurgical Research and Education

Examination Board:
Associate Professor Michael Fored
Karolinska Institutet
Department of Medicin (MedS)

Associate Professor Mats Lindblad
Karolinska Institutet
Department of Clinical Science, Intervention and Technology (CLINTEC)

Associate Professor Ville Wallenius
Sahlgrenska Academy at Gothenburg University
Institute of Clinical Sciences
Department of Gastrosurgical Research and Education

ABSTRACT

Obesity is a major health problem worldwide. It is preventable in theory, but in practice no country has been able to stop the development of increasing obesity. The only available treatment with sufficient long-term effect on weight loss and comorbid diseases is surgery. Bariatric surgery has increased over the last decades as several studies demonstrated long-term weight-loss, dramatic effect on diabetes and other comorbid diseases and an effect on mortality. The introduction of laparoscopic surgery and refinements of surgical procedures with an overall reduction of postoperative complications and morbidity has also helped to enhance public perception of bariatric surgery. The aim of this thesis was to evaluate the positive effect of bariatric surgery on diabetes, and other potentially negative effects of surgery.

As gastric bypass surgery became increasingly popular, several anecdotal reports suggested that these patients were overrepresented in alcohol treatment programs. In paper I we divided all patients who underwent bariatric surgery between 1980-2006 into two cohorts. One cohort consisted of patients that were operated with gastric bypass and the other consisted of patients operated with gastric banding or vertically banded gastroplasty, so called restrictive procedures. Data on inpatient diagnosis of depression, suicide attempt, alcohol and substance use disorders were retrieved from the National Patient Register. The main finding was that the risk for post-operative alcohol use disorders was elevated in the gastric bypass cohort compared to the restrictive cohort.

In paper II we compared patients operated with primary gastric bypass in Sweden between 2001-2010, with an age- and sex-matched control group that was sampled from the general population. The same outcome as in paper I was studied. In a subcohort we also analyzed the prescription pattern of antidepressants, benzodiazepines, hypnotics and sedatives and medication against alcohol dependence, before and after surgery. The main findings were that patients undergoing gastric bypass had a higher risk of preoperative diagnosis of depression, substance abuse and suicide attempts. After surgery the risk for all investigated diagnoses were elevated, including alcohol dependence. Prescriptions of benzodiazepines, hypnotics and sedatives, and medication against alcohol dependence increased after gastric bypass surgery.

In paper III we used the Scandinavian Obesity Surgery Registry and the Prescribed Drugs Register to investigate the effect of gastric bypass surgery on diabetes type 2 treatment. 67 % of patients with diabetes treatment before surgery were without diabetes treatment 2 years after surgery and 61% after 7 years. In patients with a short duration of diabetes treatment, the surgery was even more effective. Less than 2 % of patients with prediabetes before surgery were on diabetes treatment during 7-year follow up, which is lower than in a control group from the general population.

In 2010 we changed the surgical technique used for gastric bypass, from a technique where the mesentery was divided, to a technique where the mesentery was kept intact. In paper IV

we compared the 2 techniques retrospectively regarding postoperative complications, more specifically leakage during the first 30 days and ulceration/stenosis in the anastomosis during the first 6 months. Both leakage and ulceration/stenosis were significantly reduced after the change of technique.

In summary we demonstrate that gastric bypass surgery has a dramatic effect on diabetes, and also a diabetes preventive effect in non-diabetic patients. We show that the effect on diabetes is better if the surgery is performed early after diabetes onset. On the other hand, we found that patients seem to have a higher risk for postoperative alcohol abuse disorders after surgery. Finally, our last study on complications indicates that gastric bypass should be performed without division of the mesentery.

Gastric bypass is a safe surgical method with good long-term effects, but patients must be informed about potential negative effects and possibly, patients with previous alcohol abuse should be operated with another method.

LIST OF SCIENTIFIC PAPERS

This thesis is based on four papers, which will be referred to in the text by their Roman numerals (Papers I-IV)

I. Increased admission for alcohol dependence after gastric bypass surgery compared with restrictive bariatric surgery

Plecka Östlund M, **Backman O**, Marsk R, Stockeld D, Lagergren J, Rasmussen F, Näslund E.

JAMA Surgery. 2013; 148(4):374-377

II. Alcohol and substance abuse, depression and suicide attempts after Roux-en-Y gastric bypass surgery

Backman O, Stockeld D, Rasmussen F, Näslund E, Marsk R.

British Journal of Surgery 2016; 103:1336-1342

III. Gastric bypass surgery induces long-term pharmacological treatment remission of type 2 diabetes and reduces de novo cases to population levels

Backman O, Bruze G, Näslund I, Ottosson J, Marsk R, Neovius M, Näslund E.

Submitted manuscript.

IV. Laparoscopic Roux-en-Y gastric bypass without division of the mesentery reduces the risk of postoperative complications

Backman O, Freedman J, Marsk R, Nilsson H.

Submitted manuscript.

CONTENTS

LIST OF ABBREVIATIONS

ADH	Alcohol dehydrogenase
AGB	Adjustable gastric banding
BMI	Body mass index
BPD	Biliopancreatic diversion
CI	Confidence interval
DM-LRYGB	Divided mesentery laparoscopic Roux-en-Y gastric bypass
DS	Duodenal switch
EEA	Entero-entero anastomosis
EWL	Excess weight loss
GE	Gastro-entero anastomosis
GLP-1	Glucagon-like peptide
HbA1c	Glycated Hemoglobin
HR	Hazard ratio
IH	Internal herniation
IM-LRYGB	Intact mesentery laparoscopic Roux-en-Y gastric bypass
I.Q.R.	Interquartal range
IR	Incidence Ratio
IRR	Incidence rate ratio
JIB	Jejunoileal bypass
NBHW	National Bureau of Health and Welfare
NPR	National Patient Register
OR	Odds ratio
PDR	Prescribed Drugs Register
PYY	Peptide YY
RYGB	Roux-en-Y gastric bypass
SCB	Statistiska centralbyrån
SG	Sleeve gastrectomy
SOReg	Scandinavian Obesity Surgery Registry
SOS	Swedish obesity study
TWL	Total weight loss
VBG	Vertically banded gastroplasty
WHO	World Health Organisation

1 INTRODUCTION

1.1 DEFINITION AND EPIDEMIOLOGY OF OVERWEIGHT AND OBESITY

The standard classification of overweight and obesity is the Body Mass Index (BMI), which is calculated by taking the weight in kilograms divided to the height in meter squared (kg/m^2). This ratio is a better measure for obesity than weight alone, since the person's length is taken into consideration. BMI is not a perfect measure, as it does not directly assess body fat. A very muscular person could for instance have a high BMI without having excess body fat, but in most people it is a good indicator of the level of body fat. BMI is the classification used in most publications and research on this matter, even if other measurements are also available such as the waist-hip ratio and waist circumference. These measurements focus on abdominal obesity which is important since visceral fat is a predictor for obesity related comorbidity[1]. The disadvantage is that it is difficult to measure waist and hip circumference with precision, whereas BMI is easier to reproduce.

Table 1	BMI (kg/m^2)
Underweight	<18.5
Normal	18.5-24.9
Overweight	25-29.9
Obesity	>30
grade I	30-34.9
grade II	35-39.9
grade III	>40

Classification of overweight and obesity according to WHO guidelines

Obesity is a growing problem in the world and the problem is no longer restricted to developed countries. The average BMI has risen dramatically worldwide between 1980-2013, both in developed countries and developing countries[2]. The worldwide prevalence of overweight and obesity rose by 27.5% in adults and 47.1% in children during this period and it is estimated that the number of overweight and obese persons in the world is about 2.1 billion in 2013. In developed countries overweight seems to peak in men at the age of 55 years, when two of three men are overweight and one in four obese. These numbers are worldwide and the situation varies a lot in different countries. In the United States 60% of adult women and 70% of adult men are overweight, and about one of three is obese[2].

1.2 CAUSES OF OBESITY

The modern society is promoting the obesity epidemic by a general reduction in energy expenditure due to modern life-style[3] in combination with an overconsumption of energy. Changes in global food systems, with more processed, affordable and effectively marketed food leads to overconsumption of energy-rich food, which is probably the most important factor for the obesity epidemic[4-7]. Even if summation of the input and output of energy is the most obvious and important factor in the explanation of the obesity epidemic, the development of obesity is a more complex process involving socioeconomic[8,9], environmental[7] and genetical factors, as well as gut microbiome[10-12]. In high-income countries obesity follows a clear socioeconomic gradient, with greater prevalence in more disadvantaged population groups[9]. On an individual level certain genes have been linked to obesity[13], even if the exact mechanism are largely unknown. It also seems like some individuals have a gut microbial community more efficient at extracting energy from their diet and to deposit that energy in fat[11].

1.3 CONSEQUENCES OF OBESITY

Obesity increases the risk of developing hyperlipidemia, hypertension, diabetes and sleep apnea[14,15], all of which are independent risk factors for cardiovascular disease. Cardiovascular disease is one of the most common causes of disease related death worldwide and the risk factors are in a high degree related to lifestyle and therefore preventable[16]. Obesity is not only associated with cardiovascular risk factors[16], there is also evidence of an increased risk of certain cancers[17-19], pain from joints[20] and overall mortality[21] is higher among obese compared to normal weight persons. For example, one study estimate that white men between 20 and 30 years with a BMI >45 had a 22% reduction of remaining life-span[22]. Other studies reveals an increased risk of depression[23], and the Quality of Life is lower compared to non obese persons[24,25].

1.4 NON-SURGICAL TREATMENT OF OBESITY

Treatments of obesity include lifestyle interventions, diets, physical activity, behavioral therapy, pharmacological therapy and surgery. Studies on non-surgical obesity management are difficult to compare since treatments are not standardized. There are many different diets, intervention programs with different intensity and behavioral therapies, and methods are also often used in combinations. Changes in lifestyle are the logic treatment for obesity but even if certain individuals can achieve persistent weight-loss, the long-term results are discouraging. A large study with intensive lifestyle intervention in overweight and obese diabetes patients showed a moderate mean weight loss of 4.7% at 8 years[26] and this seems to be comparable to other studies[27]. Studies on non-surgical obesity management in patients with prediabetes have shown that diabetes to some degree can be prevented, or at least delayed[28,29]. However, trials of non-surgical weight loss in obese participants have failed to demonstrate a benefit in terms of reduced mortality or decreased cardiovascular disease event rates[29,30]. There are some randomized studies that compare surgical with nonsurgical methods[27,31-34] and all show that surgery is superior to non-surgical intensive interventions, this is also the conclusion in a recent review article showing that surgical treatments are significantly superior with more weight loss and greater effect on comorbid disease[35]. There are a few medical treatments for obesity, but many promising medical treatments have later been withdrawn because of adverse effects[36]. The treatments have modest effects on weight-loss[37], and some have side effects that are not well tolerated by patients which lead to discontinuation of treatment. In Sweden there are only a few listed medical treatments for obesity, orlistat, liraglutide and a newly registered combination therapy of naltrexone and bupropion (Mysimba). None of the drugs are frequently used in the clinical setting, since the treatments are expensive and not subventioned. Orlistat is an inhibitor of gastrointestinal lipase, which lead to excretion of 30% of ingested fat[37]. This treatment leads to a moderate weight-loss at the expense of diarrhea and other gastrointestinal side effects and only 10% of patients continue treatment more than 1 year, and less than 2% for 2 years[38]. Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor analogue that increases postprandial satiety and reduces energy intake. It is administered by daily subcutaneous injections and the treatment indication in Sweden is diabetes. In higher doses it can be used as a treatment for obesity, but this treatment is not subventioned in Sweden. A recent randomized study on patients with prediabetes show that liraglutide, in high doses, induces 4,3% weight loss difference when

compared to placebo[39]. The same study show that treatment could prevent or delay the development of diabetes in patients with prediabetes.

1.5 BARIATRIC SURGERY

Bariatric surgery increased rapidly in Sweden from the turn of the century, until the peak in 2011 (Fig 1). This was driven by the results from large studies presenting significant effect on overall mortality and effect on several obesity related comorbidities, especially diabetes[40-42]. Another important factor is the more widespread use of laparoscopic surgery, which lead to shorter hospital stay and less morbidity for the patient[43], and with experience also shorter operating times. The mean operating time of a gastric bypass in Sweden today is 60 min, 99% of the operations are performed laparoscopic and most patients leave hospital on the first or second postoperative day. Mortality is very low, with numbers around 0.05%[44]. The reason for decreasing volumes after 2011 is probably caused by a rebound effect after the rapid increase between 2007-2011.

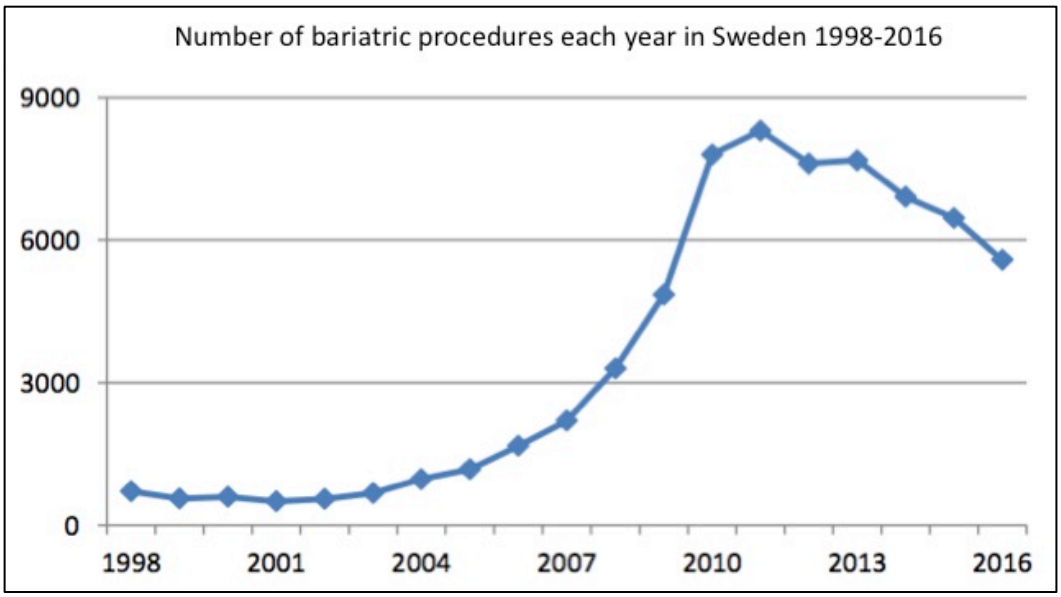


Fig 1. Number of bariatric procedures performed annually in Sweden 1998-2016. Figure from SOReg annual report 2016[44], reprinted with permission.

Bariatric surgery is not a single procedure, but rather a group of different operations that works by different mechanisms and have different effects on weight loss and comorbidity[45]. Unfortunately, they are sometimes evaluated as one group, which may underestimate the positive effect of surgery in the methods that have the best effects. This is also the reason that this type of surgery to some degree still struggle with its reputation since many of the older methods were associated with high complication rates and many needed revisional surgery[46]. For instance, the Swedish Obese Subject (SOS) trials which is the most important clinical trial comparing non-surgical treatment programs with surgical intervention is based on surgical methods that are not widely used today[45].

1.5.1 History of bariatric surgery

The idea of surgery as treatment for morbid obesity is not new; already in 1952 a surgical procedure to produce weight-loss by resection of a part of the small intestine is described.

Many different methods have been tried since, and some procedures have made more impact on the evolution of bariatric surgery (Fig 2). The most relevant procedures are jejunoileal bypass (JIB), Roux-en-Y gastric bypass (RYGB), vertical banded gastroplasty (VBG), biliopancreatic diversion (BPD)/ duodenal Switch (DS), adjustable gastric banding (AGB), and sleeve gastrectomy (SG). Today RYGB and SG are the most popular procedures, while JIB and VBG are abandoned.

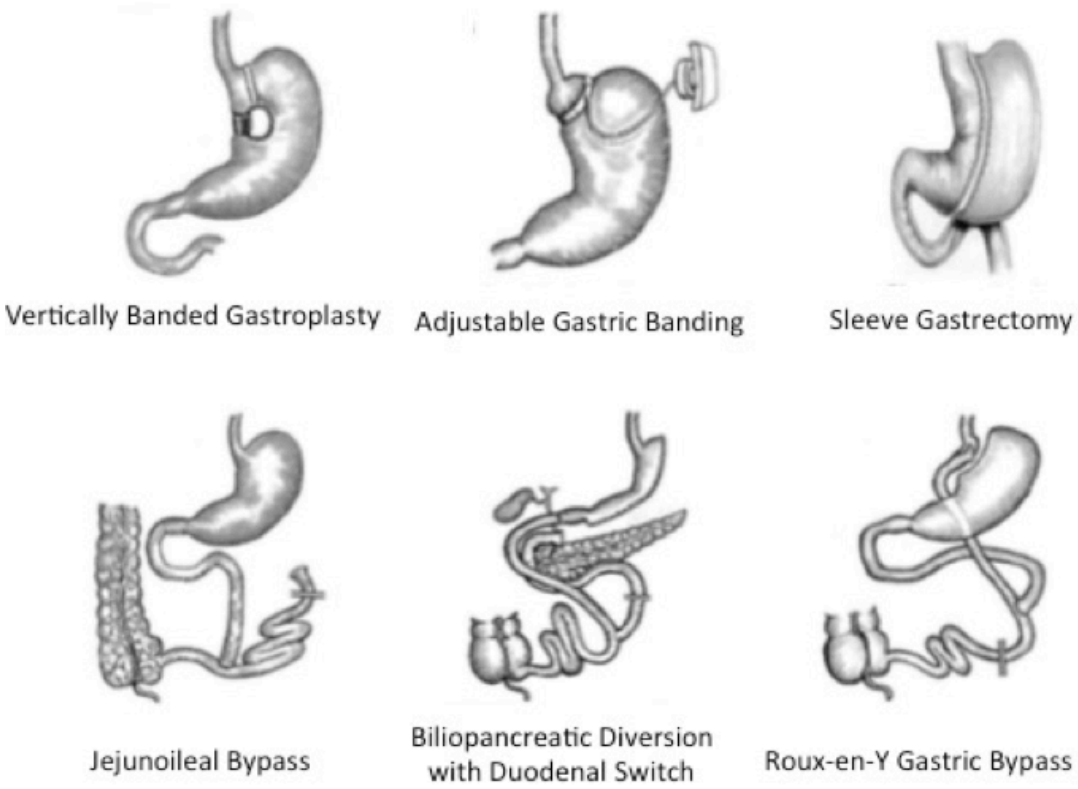


Fig 2. Bariatric surgery procedures. Illustrations from Karra et al. Mechanisms facilitating weight loss and resolution of type 2 diabetes following bariatric surgery[47]. Trends in Endocrinology and Metabolism 21 (2010) 337–344.

JIB

JIB, means that a large part of the small intestine is bypassed. It was performed widely in the 1970:ies and this procedure had good effect on weight loss but also many severe side effects, such as diarrhea, liver insufficiency, electrolyte deficiencies, urolitihiasis and osteoporosis. Because of these side effects, many patients had their shunt reversed with subsequent weight-gain[48,49]. This method is not in use today.

RYGB

The first version of the gastric bypass was published by Mason and Ito in 1967[50], inspired by the weight-loss seen after gastrectomy with the Billroth-II technique. The gastric bypass was further developed by others, and the first RYGB, similar to the procedure performed today, was published in 1977[51]. This procedure has been further refined, for example with a smaller gastric pouch, and it is still performed today.

AGB and VBG

The surgery changed in the 1980:ies, towards the principle of restrictive surgery were mechanical restriction was achieved by various gastroplasties. Several variations were tried, but in the end two popular techniques were widely used, AGB[52] and VBG[53]. These procedures produced weight loss and effect on diabetes and other comorbid diseases[54], and the more severe side effects that was seen with the earlier malabsorptive surgery were eliminated. VBG was the most popular procedure in Sweden in the 1980:ies and 1990:ies. It has now been abandoned due to poor weight loss, weight-regain and complications such as band erosion and vomiting, and many of those patients have later undergone revisional surgery[46,54]. GB is also abandoned in Sweden, because of long-term complications similar to those in the VBG and high revision-rates [55,56], but GB is still performed in some countries.

BPD/DS

The BPD/DS is the most potent operation against morbid obesity[57,58], but it also have more complications than RYGB and SG, thus limiting its use in clinical practice[57,59,60]. The complications and side effects are similar to, but not as severe as, the JIB. The advantage compared to the JIB is that no intestinal segment is left blind, thus preventing bacterial overgrowth. BPD/DS is mainly used in super obese patients, sometimes as a 2-step operation with the first procedure being a SG. This is a technically demanding procedure compared to RYGB and SG, and only 1-2% of bariatric procedures are performed with this technique.

SG

The SG is basically a gastroplasty where the stomach is divided longitudinally, forming a long narrow tube. It was originally described as a step in the DS, but is now being performed as a single procedure. This procedure is today the most popular procedure in the United States, and constitute about 50% of bariatric procedures from 2014[61]. SG produce good initial results on weight-loss and comorbid diseases, but long-term data are still lacking. It still remains unclear if this procedure will have the same problem as other gastroplasties with weight regain over time.

Current situation

RYGB has been the most common operation during the past 15 years. In 2010, 97.5% of bariatric surgery procedures in Sweden were performed with RYGB, while SG has become increasingly popular during recent years. 2016 approximately one third of the operations in Sweden was SG[44]. The same tendency is seen in other parts of the world and today the SG is the most commonly performed procedure internationally to achieve weight-loss[62], despite limited long term results (Fig 3).

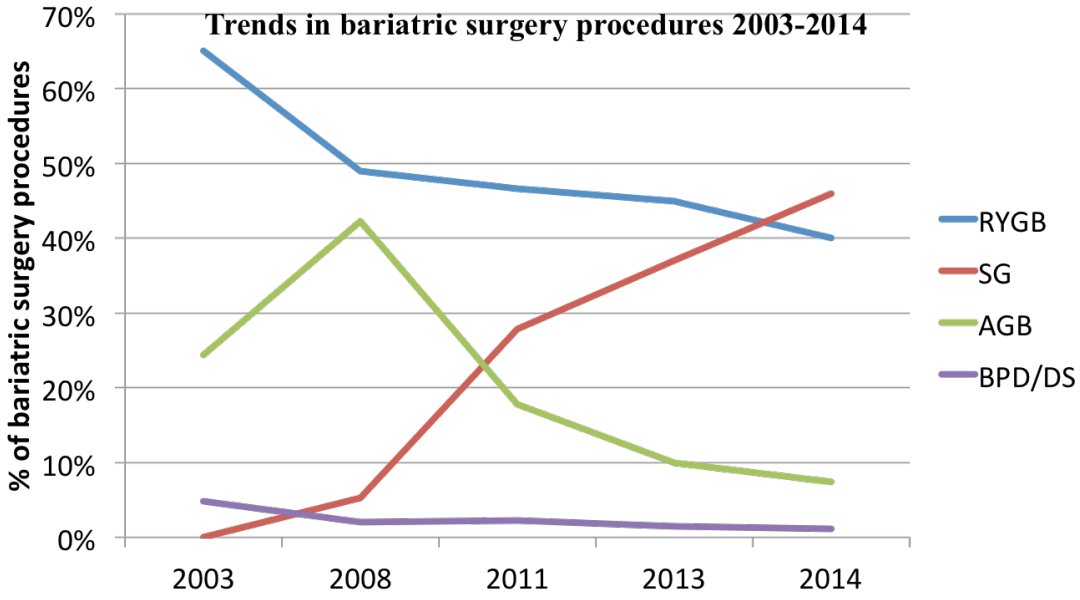


Fig 3. Trends in bariatric surgery procedures worldwide. Figure created using data from Angrisani et al Bariatric Surgery Worldwide 2013. Obes Surg 2013[63] *and Bariatric Surgery and Endoluminal Procedures: IFSO Worldwide Survey 2014. Obes Surg 2017*[64].

1.5.2 Mechanisms of bariatric surgery

Historically weight loss after bariatric surgery has been explained by two different mechanisms, restriction and malabsorption of calories. Some methods have been designated as restrictive procedures, for example different gastroplasties, and some methods malabsorptive procedure, for example JIB. RYGB has been viewed as a combined technique with the small gastric pouch as a restrictive component and the bypass of a part of the proximal small intestine as a malabsorptive component. Today we know that the mechanisms are more complex than this[65,66]. It is true that one of the mechanisms by which weight loss is achieved is of course a restriction of calorie intake[67]. The classic explanation has been that patients eat smaller volumes due to a small gastric pouch, and that the uptake of consumed calories is reduced when a part of the small intestine is bypassed. However, today we know that more complex mechanisms involve changes in gut peptide release[66,68-72], changes in gut microbiome[73,74] and changes in bile flow among other effects[75] (Fig 4).

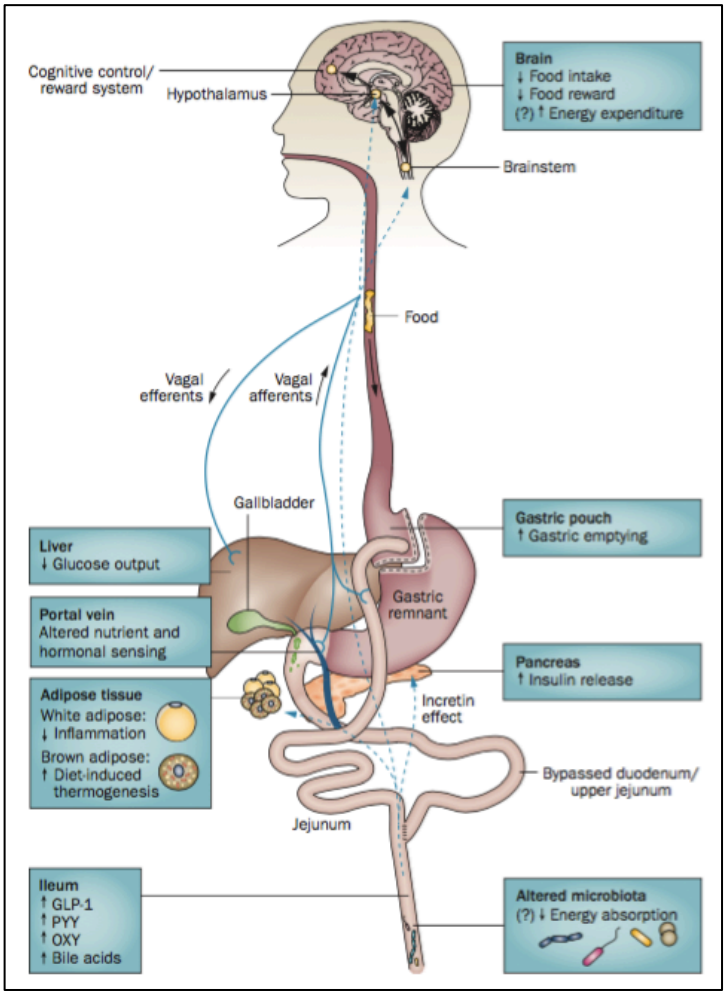


Fig 4. Schematic presentation of the physiological mechanisms that underlie weight loss and glycemic improvements after gastric bypass surgery. Figure from Miras et al.[65], reprinted with permission.

The effect on diabetes is remarkable and seen within days or weeks after surgery, before weight loss occurs. This effect is not yet exactly understood but theories involve the hindgut hypothesis and the foregut hypothesis. The hindgut hypothesis has been used to describe that the effects of some bariatric operations result from enhanced nutrient delivery to the distal intestine, accentuating secretion of anorexigenic and antidiabetic peptides. The foregut hypothesis suggests that surgical exclusion of nutrients from the proximal small intestine exerts antidiabetic and possibly weight-reducing effects[76].

The most investigated hormones are GLP-1, peptide YY (PYY) and ghrelin, which all have been suggested to play a role in weight-loss after RYGB[71,77,78]. GLP-1 and PYY is secreted by the L cells of the small bowel, with higher concentrations in the distal ileum. GLP-1 and PYY levels increases soon after RYGB and their gastrointestinal properties include delayed gastric emptying, reduction of hunger and increased sensation of satiety[79]. GLP-1 inhibits glucagon release and acts on the pancreas to secrete insulin. If these hormones are blocked, the appetite returns, indicating that they play an important role in the weight-loss after surgery[71,77].

Ghrelin is a peptide that stimulates appetite and was initially thought to be important in the weigh-loss after RYGB, since early studies showed a decrease in ghrelin levels after surgery.

Other studies have not been able to show the same results and the role of ghrelin remains unclear[80].

1.5.3 Bariatric surgery candidates

Standard criteria for bariatric surgery is BMI > 40, or BMI >35 with some comorbidity correlated to obesity. Other conservative methods should be tried before in most cases.

Characteristics of bariatric surgery candidates

Patients presenting for bariatric surgery differ from the general population on other measures than BMI. Generally the patients have lower education and socioeconomic status[81], they also have more obesity related diseases and more psychiatric morbidity. In Sweden, 14 % of the patients have preoperative treatment for diabetes, 25% for hypertension, 10% for hyperlipidemia and 10% for sleep apnea. Average BMI is 42 kg/m^2 in RYGB patients and slightly lower in SG patients[44].

Psychiatric morbidity in bariatric surgery candidates

Bariatric surgery candidates have higher rates of mood and anxiety disorders than the general population before surgery[82-84]. In an Italian study, almost 40% of the bariatric surgery candidates had a lifetime history of an Axis I disorder. About one fifth of the sample presented with a current Axis I disorder and the same percentage had a personality disorder[82]. Even higher rates of Axis I disorders were found in an American preoperative survey where patients reported a lifetime history of 66%, and 38% met diagnostic criteria at the preoperative evaluation[83]. These studies are small but results are confirmed in larger studies. In the longitudinal assessment of bariatric surgery (LABS) study, an American multicenter study including more than 2000 patients, about 30% of the patients reported at least mild depressive symptoms before surgery and 35% used antidepressant medication[84].

1.6 ROUX EN Y GASTRIC BYPASS

1.6.1 Surgical technique

RYGB is performed laparoscopically if there is no contraindication. The procedure is commonly performed by the initial creation of a small gastric pouch, followed by the creation of a Roux-limb. This is traditionally accomplished by transection of the proximal jejunum about 30 to 50 cm distal to the ligament of Treitz, followed by division of the jejunal mesentery. A gastro-entero anastomosis (GE) is constructed by approximation of the distal tip of the transected jejunum to the small gastric pouch, which is then anastomosed together. The Roux-en-Y reconstruction is completed by the creation of an entero-entero anastomosis (EEA) between the proximal, or biliary, end of the transected jejunum and the Roux-limb, typically about 100 cm distal to the GE[85]. This technique will be referred to as Divided Mesentery Laparoscopic RYGB (DM-LRYGB).

As with most procedures there are numerous variations of the basic RYGB technique, and those variances can of course affect the end result. For example, the Roux-limb can be

brought to the gastric pouch in both an antecolic and retrocolic fashion, the GE can be constructed with a circular or straight stapler, or even completely hand-sewn. Other things that might differ between different centers are the length of the roux limb, the size of the gastric pouch and if the mesenteric defects are closed or not and the perioperative routines.

A slight modification of RYGB, which today is standard in Sweden, creates an antecolic Roux-en-Y limb by first bringing a proximal jejunal loop up to the gastric pouch to create a side-to-side GE, without division of the mesentery. Subsequently, the EEA is created and the Roux-en-Y construction is completed by the division of the jejunal loop between the GE and the EEA[86]. This technique will be referred to as Intact Mesentery Laparoscopic RYGB (IM-LRYGB) (Fig 5).

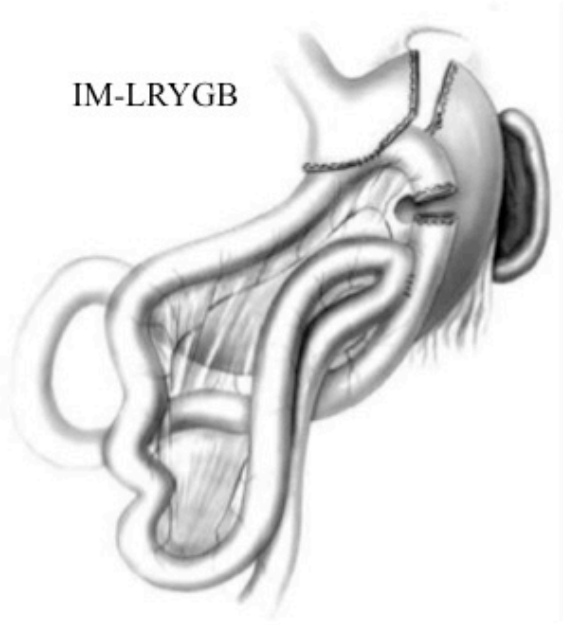


Fig 5. Illustration of the Laparoscopic Roux-en-Y Gastric Bypass technique with intact mesentery (IM-LRYGB). Illustration from Olbers, T et al. Laparoscopic gastric bypass: development of technique, respiratory function, and long-term outcome. Obesity Surg 2003. 13(3), 364–370. Reprinted with permission.

1.6.2 Positive effects of RYGB surgery

RYGB has many positive effects; one of the obvious is long-term weight loss. The weight loss itself is important, but even more important is the effect on comorbid diseases and the reduced mortality[40,42]. Non-surgical interventions to achieve weight-loss have so far been unable to show an effect on mortality, which in some way is the ultimate endpoint. Puzziferri et al[87] did a review of the literature and the average excess weight loss 2-years after RYGB was 65.7%, diabetes remission rates of 66.7% and remission of hypertension of 38.2%. RYGB also has an effect on hyperlipidaemia[41,87], sleep apnea[88], reduced pain from joints and positive effect on life quality[89].

Effect on weight loss

RYGB is a procedure that produces a rapid weight loss and most of the weight loss occurs in the first year after surgery[41]. Initial weight loss is about 25-35%[34,45] of total body weight or

up to 80% excess weight loss (EWL)[90]. Even if the patients gain some weight over time, long-term effects on weight is good with almost 30% persistent reduction of body weight after 5 years[27,45] and 60% EWL after more than 10 years[91]. This is not even comparable to other non-surgical means of weight-loss, where the most efficient studies report 5-10%[27,31,33,34] weight loss with a combination of medications and intensive lifestyle interventions. Other studies report no long-term weight loss at all[41]. The Swedish Obesity Study (SOS), which is one of the most cited studies in bariatric surgery, present a sustainable weight loss of about 30% of the total body weight[92]. The same study shows that the restrictive procedures, GB and VBG doesn´t result in the same weight loss as RYGB. The control group receiving conventional treatment (non-surgical) in the same study did not show any weight loss at all during follow-up. Data from SOReg show that the RYGB produce more weight loss than SG[44], which is also supported by published studies[90,93,94].

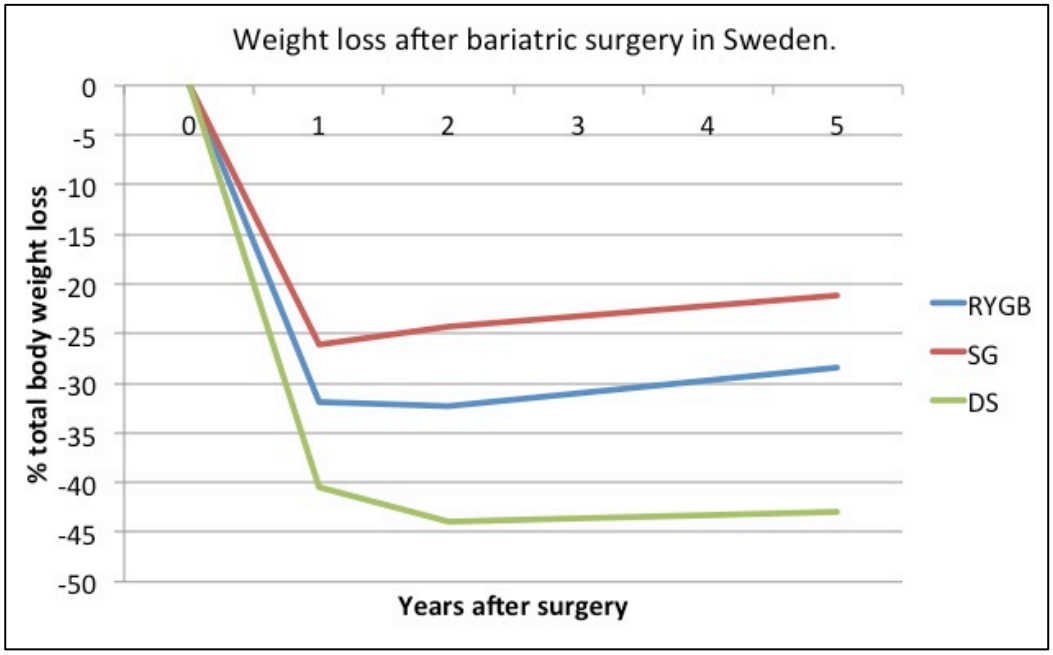


Fig 6. Weight loss after bariatric surgery in Sweden. Figure created with data from SOReg annual report 2016[44].

Effect on diabetes

RYGB has a dramatic effect on diabetes [32,45,81,87,95-99]. Many studies present an initial diabetes type 2 remission of up to 70%[41,98], depending on which criteria's that are used to define remission. There are many studies with short follow-up, a recent study however present 5 year data with a diabetes remission rate of 54%[97]. The SOS study presents 10 year data with diabetes remission of 36%[41]. It is important to notice that most of the patients in the SOS-study were treated with VBG and GB, procedures we know have an inferior effect on diabetes[87]. Studies including only RYGB patients demonstrate long-term remission in up to 60%[91,98]. Remission of diabetes with conservative treatment on the other hand is very low and all studies comparing surgery with intensive lifestyle interventions combined with medical therapy shows that RYGB has superior effect[27,31-34,96,98,100].

Except for the extreme effects on diabetes, RYGB also seems to prevent against the development of diabetes in obese patients[95,101].

Because of the remarkable effects of RYGB surgery on diabetes, it is discussed whether surgery should be considered in patients with diabetes even with BMI <35, or even <30 in drug-refractory diabetes. Several studies have been performed with good effect on diabetes in non-obese patients, even if the effect is not as obvious as in obese patients[102,103]. So far, metabolic surgery is not performed routinely in non-obese patients with diabetes type 2, but it is performed in many countries on patients with BMI 30-35 with diabetes. .

Effect on other cardiovascular risk factors and disease

Although the effect on weight and on diabetes is the most eye-catching, RYGB also have an effect on other cardiovascular risk factors such as sleep apnea[88], hypertension[41,87,98] and hyperlipidaemia[41,87]. As expected, bariatric surgery doesn´t only reduce risk factors for cardiovascular diseases, it also has proven effects on actual cardiovascular diseases such as myocardial infarction and stroke[81,92], and is also effective in reducing cardiovascular deaths[42,92].

Effect on cancer

Obesity is a risk factor for certain cancers, such as colon, breast (in postmenopausal women), endometrium, kidney, esophagus (adenocarcinoma), gastric cardia, pancreas and gallbladder[18,19,104-107]. Before obesity surgery arrived there were no studies proving that weight loss would reduce the risk for cancer, simply because it was too hard to reach significant weight loss. With obesity surgery we can now study the cancer preventive effects on patients with significant and persistent weight loss. The SOS study has shown that bariatric surgery reduces cancer incidence in obese women, but could not show the same effect in men[108]. Other large studies show a significant reduction in both cancer incidence and cancer mortality after bariatric surgery[109,110]. These changes are probably related to the weight loss and not to the surgery itself.

Effect on mortality

The SOS study has shown that bariatric surgery reduces overall mortality compared to obese control subjects[40], this important finding is supported by other studies[42,111]. In a recent review article the authors concluded that bariatric surgery patients had significantly reduced long-term all-cause mortality when compared to severely obese non-bariatric surgical control groups[111]. They also had reduced cardiovascular-, stroke-, and cancer-caused mortality when compared to severely obese non-operated controls.

On the contrary, non-disease related mortality such as accidents and suicides seems to be elevated amongst the patients that have surgery[42,111,112].

Effect on Health Related Quality of Life and depression

Obesity is typically associated with poorer Health Related Quality of Life (HRQoL)[113]. The HRQoL is improved after surgery[57,89,90,114-116], and seems to be correlated to weight-loss, with the highest scores 1-year after surgery when maximum weigh-loss has occurred. In the weight-regain period there seems to be a slight deterioration even if long-term effects persist[116]. The Quality of Life seems to improve most in physical aspects, whereas some studies have been unable to show improvement in the psychosocial aspect of Quality of

Life[117]. The reported effects on mood and anxiety disorders after RYGB are a bit conflicting. Thirtysix percent of the patients in a mixed bariatric surgery cohort presented with depressive symptoms before surgery, and after an initial improvement, the same amount of patients had depressive symptoms 7 years after surgery[118]. Another study presented improvement of Axis I disorders from 30.2% preoperatively to 18.4% at three-year follow up. Other studies also show an improvement after surgery, even if there seems to be deterioration in improvement after the first postoperative year[84].

1.6.3 Negative effects of RYGB surgery

Patients undergoing RYGB often have preoperative risk factors for complications, such as severe obesity, diabetes and other comorbid diseases. As after all surgical procedures there is a risk for general complications such as deep vein thrombosis, pulmonary embolus, urinary tract infection, pneumonia and complications related to anesthesia. Complications more correlated to the procedure itself is leakage in the anastomosis, ulceration and stenosis in the anastomosis, small bowel obstruction, internal herniation, ventral hernias, abdominal pain, dumping and anemia. Generally, the complications after RYGB have decreased with time and the perioperative mortality is very low.

Leakage

The most feared surgical complication after RYGB is leakage, usually occurring in the GE. Leakage is usually obvious in the first postoperative days and early symptoms include epigastric pain and tachycardia. Historically leakage occurs in 0,6-4,4%[119] of patients, but large later studies present leakage rates closer to 1%[120] which is similar to leakage rates presented in SOReg[44]. Leakage is most often treated with surgical exploration, drainage and sometimes, endoscopic stenting[121].

Stenosis and ulceration in the anastomosis

Symptoms of stenosis include dysphagia, nausea and vomiting. Reported rates of stenosis after RYGB vary greatly in the literature, variations might depend on different surgical technique, length of follow-up and definition of stenosis for example. Stenosis is much more usual after circular stapling of the anastomosis[122,123]and maybe also with an antecolic roux-limb[124]. Linear stapling is the most common technique and many studies report stenosis rates of about 5-10% with linear stapling [125-128]. Stenosis is treated with endoscopic dilation, sometimes repeated, and surgical intervention is seldom required.[125,127,128] Dilation is generally safe, but perforation is a potential threat. Ulceration at the anastomosis is another usual complication. Incidence of symptomatic ulceration differs between studies and a review of the literature found an average incidence of ulceration of 4.6%, with a variation between 0.6% and 25%[129]. Stenosis might actually be the result of an ulcer healing with stricture. One study performed routine endoscopy 1-month after surgery and found ulceration in 12% of patients, and in 40% of those with ulceration there was also some degree of stenosis[130]. Reasons for ulceration are probably multifactorial. Helicobacter Pylori, smoking and diabetes are risk factors[131,132], and Proton Pump Inhibitors have a prophylactic effect[133-135]. Tension

and ischemia at the anastomotic site are other factors that could increase the risk for ulceration. Most ulcers heal with PPI treatment and surgical revision is unusual [134].

Internal herniation

Internal herniation (IH) is a common complication after RYGB. In general it is seen after a substantial weight has been lost, usually at least 1 year after surgery. It can occur several years after surgery. IH can cause bowel obstruction and symptoms include intermittent abdominal pain, vomiting and abdominal swelling. Sometimes the patients present with acute symptoms, and other times they present with more chronic intermittent symptoms. In severe cases IH can cause strangulation of the small bowel with subsequent bowel gangrene [136]. Since follow-up after surgery generally decreases after the first few years, late complications can be underestimated. Some studies with longer follow-up report IH in 10-16% of patients[137-139]. Internal herniation can occur in the Petersen defect, located in the mesenteric defect under the roux limb or in the mesenteric defect at the EEA site. If the roux limb is brought up to the gastric pouch in a retrocolic way there is also the possibility of herniation in the mesenteric defect of the colon[140].

IH rates have been proposed to be lower when performing IM-LRYGB, possibly by reducing the size of Petersen´s defect. A retrospective study of 1400 patients found IH in only 0.2 % after IM-LRYGB even if the mesenteric defects were left open [141]. This seem very low and the follow-up time was short, other case series also show higher rates of IH at a later time point [137]. A retrospective comparison of DM-LRYGB with IM-LRYGB, show a decrease in IH in favor for the IM-LRYGB, but these results must also be interpreted with caution since the mesenteric defects was closed in the IM-LRYGB and not in the DM-LRYGB[142]. A recent randomized study found IH in 10% of patients operated with IM-LRYGB[143] without closure of the mesenteric defects. There has been a discussion whether or not the mesenteric defects should be closed or not, and even if most surgeons have advocated closure of the defects evidence have been lacking. However, the same randomized study, show that internal herniation can be reduced from about 10% to 5% if the mesenteric defects are closed[143].

Dumping

Dumping syndrome, a common complication of RYGB, can be divided into early and late dumping symptoms. Early dumping occurs within 1 h after a meal, when the rapid emptying of undigested food into the small intestine triggers fluid shifts into the intestinal lumen and release of gastrointestinal hormones. Common symptoms include abdominal pain, nausea, diarrhea, and vasomotor symptoms such as fatigue, flushing, palpitations, perspiration, tachycardia and hypotension[144] (Fig 7).

Late dumping occurs 1 to 3h after intake of carbohydrates, caused by a hyperinsulinemic response resulting in hypoglycemia. Typical symptoms of hypoglycemia are fatigue, weakness, confusion, perspiration, palpitations, tremor and irritability[144].

Dumping symptoms after RYGB vary from mild to severe, and since the spectrum of symptoms and severity is broad, the reported prevalence after RYGB varies between

different studies[144-146]. A recent study report that 93,4% of patients have no or mild symptoms, and only 1,4% have severe symptoms after RYGB [145]. Dumping syndrome can be troublesome, but most of the times symptoms can be reduced by avoiding carbohydrate dense meals and soda, not drinking at the same time as eating and to eat slowly[144].

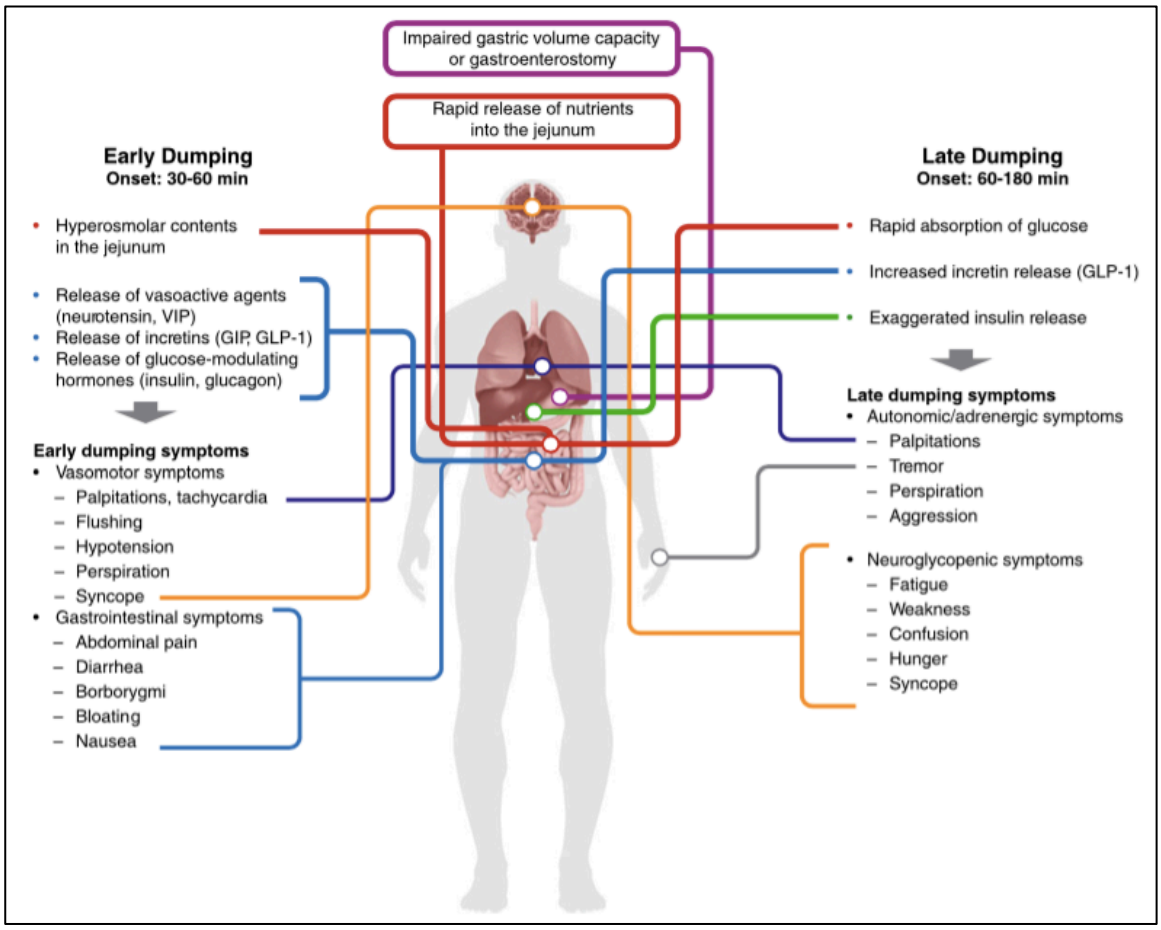


Fig 7. Physiology and symptoms of dumping syndrome. Figure from Van Beek et al. Obes Rev. 2017[144].

Excess skin

Massive weight-loss leads to excess skin in almost all patients. In a questionnaire study 84% of RYGB patients reported problems with surplus skin [147].The abdomen, upper arms, medial thigh and breast were the sites where most patients had problems. In the same study 46% of patients reported that the excess skin cause eczema, fungal infections and lesions below the abdomen, the breast or in the groin [147].

Abdominal pain

Chronic abdominal pain after RYGB is a complication that is not unusual[148], 5-years after surgery about one third of patients report some form of chronic abdominal pain. Some of those patients had symptoms that could be related to a specific complication, but in most patients no obvious reason was detected[149]. Thorough examination of these patients to exclude treatable conditions such as cholelithiasis, ulcerations or internal herniations is vital, but sometimes no diagnose can be found.

Suicide

Even though some studies suggests an improvement in depression and HRQoL after surgery, for some reason surgery increases the risk of suicide and death by accidents[42,111,112,150]. The reason for this is not established but one theory is that bariatric surgery, and especially RYGB could lead to alcohol and substance abuse[151-155].

Alcohol abuse disorders

Patients undergoing RYGB surgery seem to be more prone to develop alcohol use disorders than those undergoing restrictive procedures[151,152,156], which might be due to the altered uptake and metabolism of alcohol seen after RYGB[157-159].

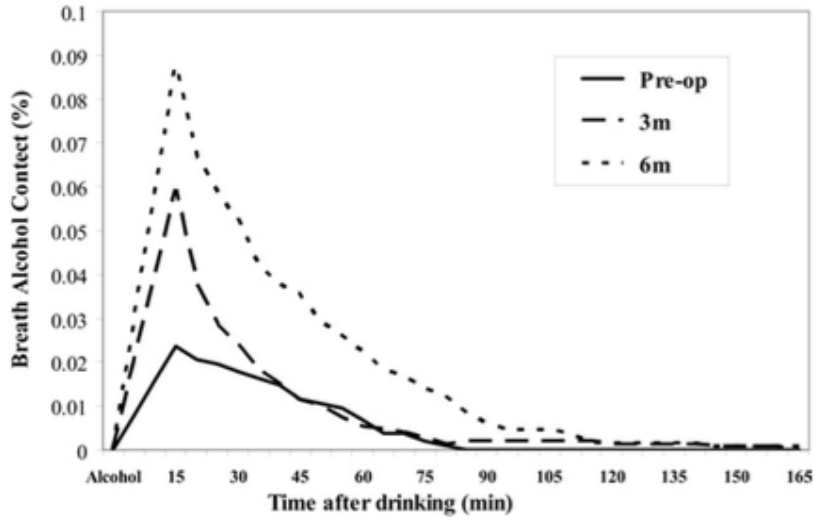


Fig 8. Peak alcohol concentration before and after gastric bypass surgery. Figure from Woodard et al. J Am Coll Surg 2011[159].

It is known that the time of gastric emptying affects the absorption of alcohol[160]. Ethanol undergoes a first pass metabolism in the stomach and liver. Gastric first pass metabolism of ethanol primarily depends on the activity of gastric alcohol dehydrogenase (ADH). In addition, the speed of gastric emptying may modulate both gastric and hepatic first pass metabolism of ethanol[160]. The small gastric pouch with rapid emptying to the small intestine after RYGB is likely to reduce the first pass metabolism exerted by gastric ADH. One study gave the same amount of alcohol to RYGB patients, before and after surgery, and there was a higher and more rapid peak alcohol concentration after surgery[159]. This means that the patients more easily get drunk from small amounts of alcohol after surgery, possibly triggering alcohol abuse. When the same test was performed on GB patients there was no such difference[161]. It has also been shown that RYGB patients have higher risk of being admitted for alcohol abuse than patients operated by restrictive methods[151]. One study from the United States showed that 16% of patients seeking bariatric surgery were problem drinkers[162], and a large multicenter study from the US reported significantly higher prevalence of hazardous alcohol use, symptoms of alcohol abuse/dependence, and fulfilled

criteria for alcohol abuse/dependence at 2-year follow-up after RYGB surgery, compared to the first postoperative year and prior to surgery[156].

Most studies regarding alcohol and substance abuse are based on interviews and questionnaires[156,163-165], and some have problem with low participation rate, small sample size and retrospective collection of data[163,165]. There is also a reason to consider that those with ongoing abuse could have a lower participation rate, leading to biased results.

2 AIM

2.1 GENERAL AIM

Our general aim was to characterize positive and negative aspects of gastric bypass surgery.

2.2 SPECIFIC AIMS PAPER I-IV

Paper I

The aim in paper I was to investigate if the risk for psychiatric disorders including alcohol and substance abuse is increased after RYGB surgery. Further to investigate if there is a difference between RYGB and other restrictive surgery methods.

Paper II

The aim in paper II was to investigate if the risk for psychiatric disorders including alcohol and substance abuse is higher in RYGB patients compared with general population comparators, before and after RYGB.

Paper III

The aim in paper III was to determine remission rates of diabetes treatment after RYGB surgery in diabetic patients, and to determine if surgery protects against future diabetes treatment in non-diabetic patients.

Paper IV

The aim was to determine if there was a difference in anastomotic complications between 2 different techniques of RYGB, where the mesentery was either divided or kept intact. More specifically the aim was to determine if ulceration and stenosis in the anastomosis during the first 6months, and anastomotic leakage during the first 30 days, were reduced after changing the technique.

3 PATIENTS AND METHODS

3.1 INFORMATION SOURCES

All Swedish citizens have a personal identification number (PIN) that allows linkage between different registers and this makes it possible to get information about large nationwide cohorts of patients.

In Sweden there are a number of different registers that contains information about education, health care diagnosis, death cause, data on prescribed drugs etc., below is a description of the main registries that have been used in this thesis project.

3.1.1 Register of the Total Population

This register contains information on all Swedish residents and it is held by Statistics Sweden (SCB). It includes a number of variables, for example PIN, sex, age, name, address, marital status, citizenship, immigration, emigration and date of death[166]. Data from this register is used in paper I-III

3.1.2 The Cause of Death Register

The National Board of health and welfare (NBHW) holds this register and it contains dates of all deaths among Swedish citizens from 1961 and cause of death in almost all cases. About 1% have no cause of death registered[167]. Data from this register is used in paper I-III.

3.1.3 Prescribed Drugs Register

The nationwide Swedish Prescribed Drug Register (PDR)[168] was established in 2005 and includes all dispensed prescription drugs classified according to the World Health Organization Anatomical Therapeutic Chemical (ATC) classification system. The register does not include medications administered in hospital. Data from this register for example include patients' age, sex, personal identification number, date of prescription and dispensing, the practice that has prescribed the drug and the profession of the prescriber.

Data from this register is used in paper II and III.

3.1.4 The National Patient Register

The National Patient Register (NPR), is a nationwide register held by NBHW, to which all hospitals are obliged to report. It contains dates of admission and discharge as well as ICD-codes for diagnoses and surgical procedures from 1964. The inpatient part of NPR attained national coverage in 1987 and since then covers nearly 100 per cent of all hospital admissions. From 2001 NPR also contains information about outpatient visits in specialized health care, with a coverage rate of about 75% during the first years and around 96% today. [169] Data from this Register was used in paper I-III.

3.1.5 The Scandinavian Obesity Surgery Registry

The Scandinavian Obesity Surgery Registry (SOReg) is a nationwide, prospective quality registry of bariatric surgery started in 2007. The register has been estimated to cover about 99% of all bariatric surgery procedures in Sweden, but the numbers are lower at follow-up (listed below in parentheses). Data in SOReg include information about type of procedure, weight, complications, medications and blood-chemistry. Data is registered before surgery and then 6 weeks (94,8%), 1 year (82%), 2 year (59%) and 5 year (49%) after surgery. 43 surgical units report to SOReg[44] .

Data from SOReg has been used in paper III.

3.1.6 Internal Quality Registry held at Danderyd Hospital

Data on all bariatric procedures have been held at Danderyd Hospital since 1995 for quality assurances. The Internal Quality Registry (IQR) includes information about date of surgery, type of procedure, surgeon, complications as well as weight data. Data from this registry was used in paper IV.

3.2 COHORTS

All studies are retrospective studies using data from the different registries. In paper I and II we used the NPR to identify obesity surgery patients, by using the Swedish version of the Classification of Surgical Procedures (NOMESKO) codes related to bariatric surgery (4751, 4753, JDF00, JDF01, JDF10, JDF11, JDF20, or JDF21) with a confirmatory code of obesity from the ICD classification system (277.99, 259X, 278A, E66.0, E66.1, E66.8, or E66.9). In paper III we used SOReg data to gather our cohort of gastric bypass surgery patients. In paper IV we used data from the internal quality registry (IQR) at Danderyd Hospital to identify our study cohort.

Table 2	**Paper I**		**Paper II**	**Paper III**	**Paper IV**	
Surgery method	RYGB	Restrictive (VBG/GB)	RYGB	RYGB	DM-LRYGB	IM-LRYGB
Patients	4161	6954	16755	22047	1016	1404
Controls	NA		167550 matched controls from the general population	175138 matched controls from the general population	NA	
Main Data sources	NPR		NPR, PDR	SOReg, PDR, NPR	IQR	
Study period	1980-2006		2001-2010	2007-2012	2006-2015	
Outcome measure	Psychiatric comorbidities		Psychiatric comorbidities, Prescriptions	Diabetes medication	Complications	

NPR = National Patient Register; PDR = Prescribed Drugs Register; SOReg = Scandinavian Obesity Surgery Registry; IQR = Internal Quality Register

3.3 STUDY DESIGN AND STATISTICS

3.3.1 Paper I

In this retrospective cohort study the RYGB cohort was compared to the restrictive cohort (VBG/GB), regarding inpatient diagnosis of depression, substance abuse, alcohol abuse and suicide attempts before and after surgery.

The number of hospitalizations before and after surgery, according to the *ICD-8*, *ICD-9*, or *ICD-10*, for the following diagnoses was gathered from the NPR: depression (*ICD-8* and *ICD-9*: 300 and 790.2; *ICD-10*: F32-F39), substance abuse (excluding alcohol abuse) (*ICD-8* and *ICD-9*: 304; *ICD-10*: F11- F16), attempted suicide (*ICD-8* and *ICD-9*: E95 and E98; *ICD- 10*: X60-X84 and Y10-Y34), and alcohol abuse (*ICD-8* and *ICD-9*: 303; *ICD-10*: F10).

Incidence Rate Ratios (IRR) were calculated preoperatively. The person was considered as having an event if the diagnosis in question was detected in the NPR from the age of 18 years to the date of surgery.

In the analysis of postoperative morbidity, a person was considered to have an event the first time the person was diagnosed in the NPR after surgery. Person-time at risk was calculated. Patients were followed until death, emigration or the end of the study (31dec 2006). In Cox proportional hazards regression analysis, the postsurgical hazard ratio (HR) was adjusted for age at surgery, preoperative occurrence of the same diagnosis, socioeconomic position, and education level.

3.3.2 Paper II

In this retrospective cohort study, the surgery cohort consisting of only primary RYGB patients >18 years of age, was compared with a matched control group from the general population regarding the same inpatient diagnosis as in study 1.

Each RYGB patient was matched to ten age- and sex-matched controls, selected randomly from the general population. Each member of the reference group was assigned a pseudo-surgery date corresponding to that of the case participant, resulting in the same before and after observation periods for the matched individuals.

Preoperative and postoperative incidence rate ratios (IRR) were calculated. The preoperative person-time at risk was calculated from the age of 18 years to the date of surgery/pseudo-surgery or until the person had an event for the first time. The person was considered to have an event when the diagnosis in question was detected in the NPR.

In the analysis of postoperative morbidity, the patient was considered to have an event the first time the diagnosis was detected in the NPR; person-time at risk was calculated accordingly. The follow-up time was from date of surgery/pseudo-surgery until date of death, emigration or the end of the study, whichever came first. Post-surgery HR was calculated with the Cox regression model, adjusting for age, sex, preoperative diagnosis (alcohol use disorder, substance use disorder, depression, suicide attempt), socioeconomic

status and educational level.

In a subgroup of patients, prescribed drug dispensation data were collected from the PDR for the following ATC group of drugs: alcohol dependence (N07BB), benzodiazepines (N05BA), hypnotics and sedatives (N05C), and antidepressants (N06A). This subgroup included all patients from the main cohort who had surgery between July 2006 and March 2008. This cohort was used to determine drug use before and after surgery and the time period was chosen because we wanted to have prescription data from the PDR for these patients at least 1 year before surgery and 4 years after surgery.

In the analysis of drug prescriptions, the percentage of persons who had at least one prescription filled per year was calculated for each drug. A Poisson regression with generalized estimating equations to account for within-individual correlation due to repeated measurements to estimate relative risks (proportions), confidence intervals and *P* values was performed. Wald χ^2 tests were used for analysis.

3.3.3 Paper III

In this retrospective cohort study, we linked SOReg data with the NPR and the PDR. Patients without baseline HbA1c were excluded as well as patients with a diagnosis of diabetes type 1, without a diagnosis of diabetes type 2, in the NPR.

From these patients we created 2 different cohorts, called the remission cohort and the incidence cohort based upon diabetes treatment status in the last year before surgery.

The remission cohort consists of patients with at least one prescription of diabetes drugs the year before surgery. This cohort was used to study remission of diabetes drug treatment after surgery.

The incidence cohort consists of patients without any history of diabetes drug treatment in the PDR or diabetes diagnosis in the NPR. From this group, we also excluded patients with a preoperative HbA1c levels indicating diabetes. This cohort was used to study incidence of diabetes treatment after surgery in patients without diabetes at baseline.

The annual proportion of diabetes drug treatment in the remission cohort was calculated for up to 5 years preoperatively and up to 7 years postoperatively.

For patients in the incidence cohort the prevalence of diabetes drug treatment, for each 1-year interval from the date of surgery up to 7 years after surgery, was calculated for the total surgery group as well as for the subgroups with euglycemia and prediabetes.

For the incidence cohort, incident use of pharmacological diabetes treatment was also analyzed using survival analysis. Adjusted hazard ratios were estimated using conditional Cox regression (conditioned on the matching set with each set containing 1 surgery patient and up to 10 general population comparators). Robust confidence intervals were estimated and the proportional hazard assumption was evaluated by interacting time and treatment.

3.3.4 Paper IV

In this study, we retrospectively compared LRYGB patients operated at Danderyd Hospital with two different surgical methods (DM-LRYGB vs. IM-LRYGB), regarding postoperative anastomotic complications. The outcomes studied were leakage in the first 30 days and ulceration/stenosis in the anastomosis during the first 6 months. The data used in this study was gathered from the internal quality registry held at Danderyd Hospital.

Differences in characteristics between the 2 groups were analyzed using the two-sample t-test or Pearson Chi^2 test as appropriate. Failure curves were calculated using Kaplan-Meier estimates. Independent predictors of complications were identified and odds ratios (OR) calculated using multivariate logistic regression. The threshold for statistical significance was set to $\alpha<0.05$

STATA software was used for data management and all statistical calculation in paper I, II and IV. In study III some statistical analyses were performed using SAS (version 9.4).

4 RESULTS

4.1 PAPER I

A total of 11115 patients underwent a primary bariatric surgery with RYGB (37%) or a restrictive method (63%) during the study period 1980-2006. Restrictive methods included were VBG and GB surgery. The 2 groups had similar patient characteristics at baseline. The mean (SD) follow-up time was 3.8 (4.5) years for the RYGB cohort and 11.5 (6.0) years for the restrictive cohort.

Tab 3. Preoperative IRR, and postoperative HRs of depression, substance abuse, suicide attempts and alcohol abuse for the RYGB cohort compared with the restrictive surgery cohort. Full table is found in paper I.

Diagnosis	Preoperative IRR (95% CI)	Postoperative HR (95% CI)
Alcohol abuse	1.1(0.8-1.4)	2.3 (1.7-3.2)
Substance abuse	1.7 (1.2-2.5)	2.6 (1.7-5.0)
Depression	1.1 (1.0-1.3)	1.3 (1.0-1.7)
Suicide attempt	1.1 (1.0-1.4)	1.9 (1.4-2.5)

IRR = Incidence Rate Ratio; HR = Hazard Ratio; RYGB = Roux-en-Y Gastric Bypass; CI = Confidence Interval

Preoperatively the patients in the gastric bypass cohort were more likely to have been diagnosed with substance abuse compared to the restrictive cohort. Postoperatively the risk for substance abuse, suicide attempt as well as alcohol abuse were significantly higher in the gastric bypass cohort.

4.2 PAPER II

A total of 16755 patients > 18 years old who underwent a primary RYGB surgery between 1th Jan 2001 and 31 Dec 2010 were included in the analysis. The median follow-up time was 1.9 (i.q.r. 0.83 – 3.76) years. Patients in the control group from the general population had higher education and higher socioeconomic status than patients in the RYGB surgery cohort.

The RYGB cohort had a higher risk of diagnosis of substance abuse, depression and suicide attempt before surgery compared to the reference cohort from the general population. After surgery, this risk was higher in all groups, including alcohol abuse.

Tab 4. Preoperative IRR and postoperative HR of depression, substance abuse, suicide attempts and alcohol abuse for the RYGB cohort compared with the reference cohort. Full table is found in paper II.

Diagnosis	Preoperative IRR (95% CI)	Postoperative HR (95% CI)
Alcohol abuse	1.13 (1.00-1.27)	2.73 (2.36-3.15)
Substance abuse	1.80 (1.56-2.06)	3.17 (2.52-3.99)
Depression	2.41 (2.25-2.58)	3.20 (2.81-3.65)
Suicide attempt	2.00 (1.84-2.16)	2.85 (2.40-3.39)

IRR = Incidence Rate Ratio; HR = Hazard Ratio; RYGB = Roux-en-Y Gastric Bypass

The prescription cohort is a subcohort that is comprised of 3139 RYGB patients from the main cohort. The cohort was selected so that all patients had 1-year preoperative data and 4-year postoperative data from the PDR, the general characteristics in this cohort was similar to the main cohort.

We found that patients in the RYGB cohort had more prescriptions of antidepressive medication, benzodiazepines and hypnotics before surgery. After surgery, the prescription of medication against alcohol dependence, benzodiazepines and hypnotics also increased in the surgery group, but not in the control group. The medication with antidepressants remained stable after surgery (Fig 9).

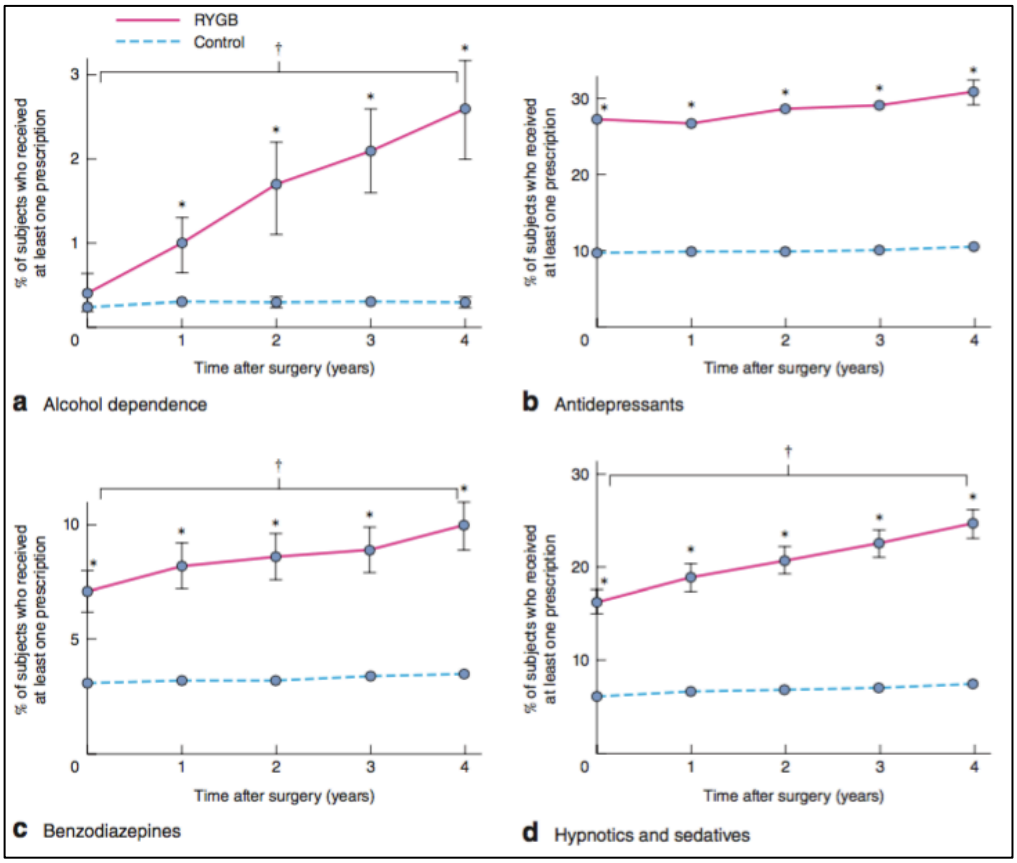
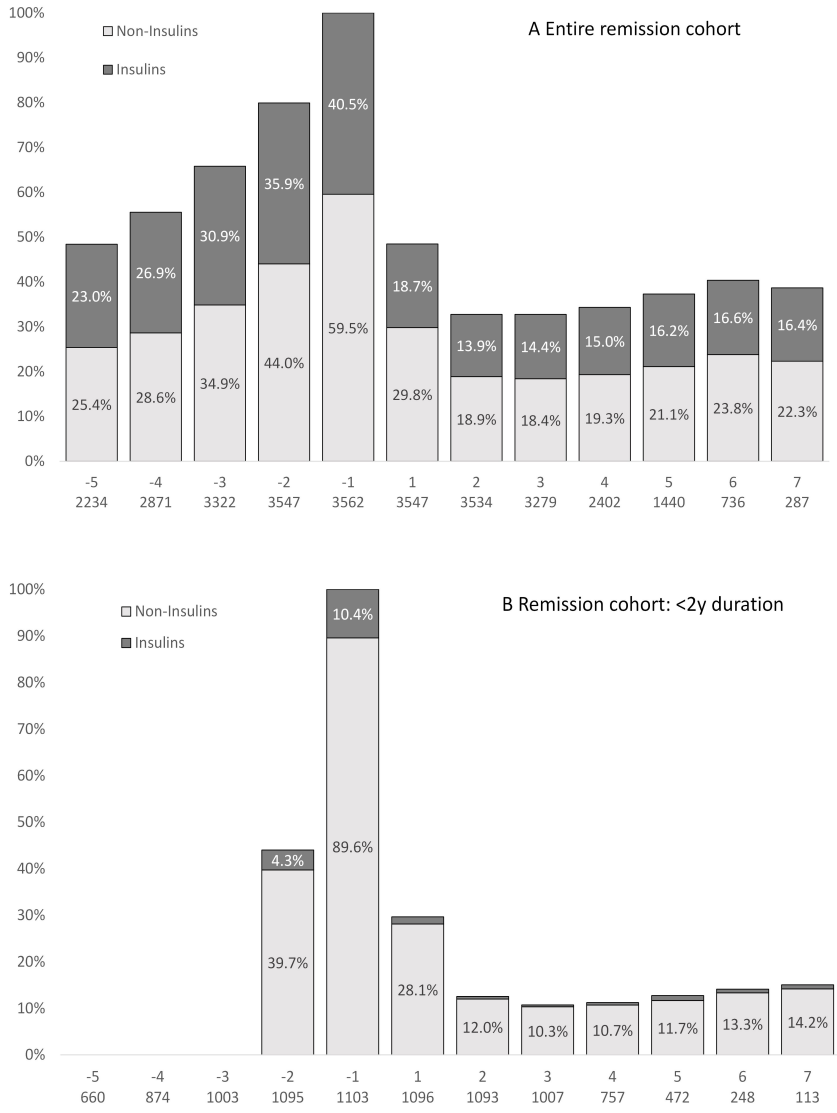


*Fig 9. Percentage of patients operated with Roux-en-Y gastric bypass (RYGB) surgery and control subjects who received at least one prescription each year for **a** alcohol dependence, **b** antidepressants, **c** benzodiazepines, and **d** hypnotic and sedatives in the year before surgery (year 0) and during a 4-year follow-up interval after surgery. *P < 0.050 versus control group, †P<0.05 before versus after RYGB (Wald χ^2 test).*

4.3 PAPER III

Diabetes treatment remission

A total of 3629 patients with pharmacological treatment of type 2 diabetes in the year before surgery were included for analysis (mean age 49 years; 60.7% women; mean preoperative BMI 42.2) of remission.



67% of the RYGB patients with diabetes treatment preoperatively were in remission of diabetes treatment 2 years after surgery, and after 7 years of follow-up 61% were without pharmacological diabetes treatment.

Patients with a short duration (<2years) of diabetes treatment had a better chance of persistent treatment remission than patients with a longer duration of diabetes treatment (>2 years) during 7 years of follow-up.

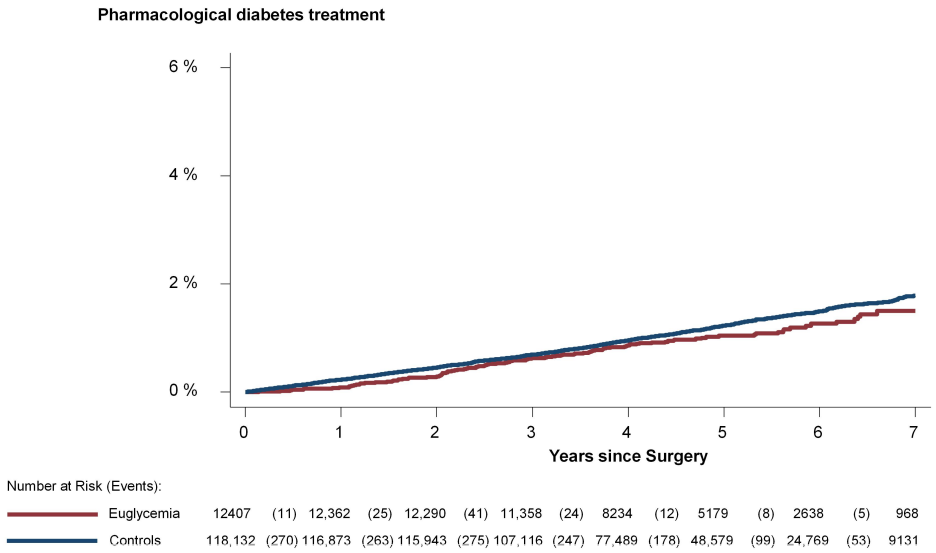
Fig 10. Diabetes treatment before and after gastric bypass in patients with diabetes treatment the year before surgery in the (A) entire cohort and in (B) patients with < 2 years duration of diabetes treatment preoperative.

Diabetes treatment incidence

A total of 18 418 patients without previous diabetes diagnosis, HbA1c<6.5% at baseline and no history of pharmacological treatment of type 2 diabetes were included for analysis (mean age 39 years; 78.8% women; mean preoperative BMI 42.7) of diabetes incidence. The group with comparators (matched for age and sex) from the general population were on average higher educated and had less medication for hyperlipidemia and hypertension.

During a median follow-up of 4.6 years, there were 189 incident cases of pharmacological diabetes treatment in the total incidence cohort and 2319 in the matched general population comparators (21.4 vs. 27.9 cases per 10 000 person-years; adjusted hazard ratio 0.77 (95%CI 0.67-0.89; P<0.001).

For the subgroups that were compared with their own matched cohort from the general population the adjusted hazard ratios were 0.87 (95%CI 0.73-1.03; P=0.11) for patients with euglycemia and 0.62 (95%CI 0.48-0.80; P<0.001) for prediabetes.



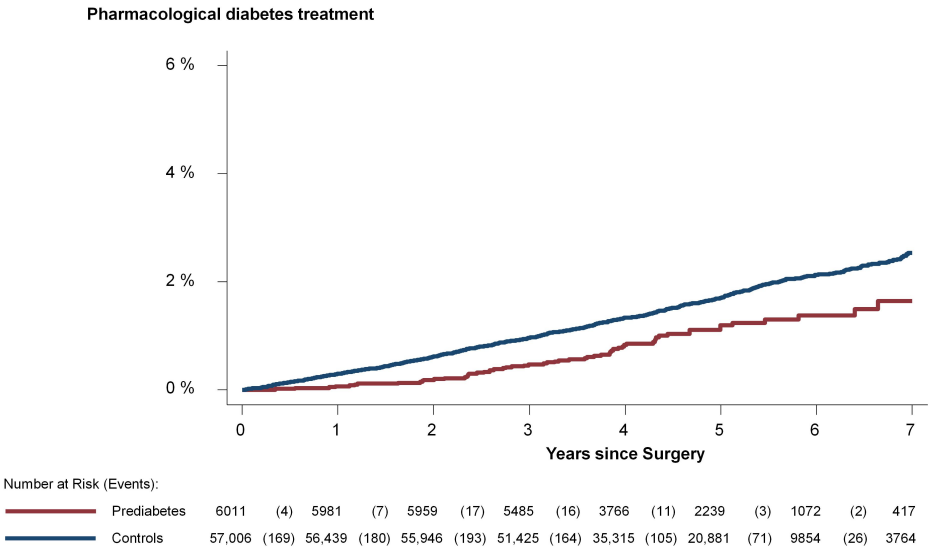


Fig 11. Cumulative incidence of diabetes treatment after gastric bypass, in patients without diabetes before surgery. Patients are divided by glycemic status at baseline and comparators are from the general population.

4.4 PAPER IV

All patients treated with a primary antecolic Laparoscopic RYGB (LRYGB) at Danderyd Hospital from 2006 to June 30th 2015 were identified in the internal quality registry (n=2949). To minimize the effect of learning curve bias 329 patients operated by surgeons with less than 100 LRYGB procedures during this period were excluded from the analysis. 1116 of the patients had surgery between December 2006 and September 2010 with DM-LRYGB and 1504 patients had surgery between November 2010 and June 2015 with the IM-LRYGB method. To further minimize the effect of learning curve bias the first 100 patients operated with each technique were also excluded prior to analysis, leaving 2420 patients included in the data analysis. 1016 of the included patients had surgery with DM-LRYGB and 1404 patients had surgery with the IM-LRYGB method.

Patients in the DM-LRYGB group were slightly older and had somewhat higher BMI, other baseline characteristics were similar (Table 5).

The rate of GE leakage was reduced after the change of surgical technique, from 2.6% in the DM-LRYGB group to 1.1% in the IM-LRYGB group ($p<0.05$). The rate of stenosis or ulceration was significantly improved, from 5.6% in the DM-LRYGB group to 0.1% in the IM-LRYGB group ($p<0.05$). Adjusted Odds Ratio for leakage in the IM-LRYGB cohort compared to the DM-LRYGB cohort was 0.46 (95% CI 0.24-0.87), and for stenosis or ulceration the odds ratio was 0.01 (95% CI 0.002-0.09)

Table 5. Results paper IV			
	DM-LRYGB (n=1016)	**IM-LRYGB (n=1404)**	**P**
Leakage in the first 30 days (%)	2.6	1.1	P<0.05
Odds Ratio Leakage (95% CI) IM-LRYGB vs. DM-LRYGB		0.46 (0.24-0.87)	
Ulceration/Stenosis first 6 months (%)	5.6	0.1	P<0.05
Odds Ratio Ulceration/Stenosis (95% CI) IM-LRYGB vs. DM-LRYGB		0.01 (0.002-0.09)	
General characteristics at baseline			
Women (%)	74.3	74.6	
Age (years); (mean (SD))	43.0 (11.4)	41.7 (11.6)	
BMI (kg/m2); (mean (SD))	42.1 (6.0)	39.4 (5.3)	
Operation time (minutes); (mean (SD))	71.6 (25.2)	58.2 (20.0)	
Completed laparoscopic surgery (%)	98.2	99.3	

DM-LRYGB = Divided Mesentery Laparoscopic Roux-en-Y Gastric Bypass; IM-LRYGB = Intact Mesentery Laparoscopic Roux-en-Y Gastric Bypass; BMI = Body Mass Index; CI = Confidence Intervals; SD = Standard Deviations

5 DISCUSSION

5.1 GENERAL ASPECTS

Obesity is a major health problem in the world, involving also developing countries[2]. Modern society is driven by consumption of cheap processed food, fast food, soda, and candy that is marketed by companies. This, in conjunction with the fact that people perform less manual labor, results in an imbalance with increased calorie intake and reduced energy expenditure. Since obesity is mainly caused by modern life-style throughout the world, it is very hard to prevent, in fact there are almost no examples of preventive programs in any countries that has proven to be efficient. Life-style treatment programs and medical treatment lack long-term effect in most patients, and surgery has evolved as the most effective treatment in morbidly obese patients[31,35]. Historically bariatric surgery has been hampered by unacceptable rates of complications, but in the last decades with increased volumes of surgery, the surgical technique has been refined with laparoscopic surgery and some methods have been abandoned. Today the most common bariatric procedures are SG and RYGB, even if AGB is still performed in certain countries[62]. BPS/DS seems to be an alternative in some super obese patients[57,60,170]. The procedures have been refined and complications and perioperative mortality is today low[44].

Positive effects of surgery are well established, and the effects on weight loss, diabetes and other comorbid diseases are way superior compared to other available treatments. Most people, even bariatric surgeons, probably realize that treating conditions that really are caused by life-style problems in society with surgery is not the ideal long-term solution. Ideally, we would need to prevent the epidemic of obesity by radical changes in physical activity from school age and by promoting healthy diets, possibly by applying special taxes on unhealthy food or other drastic measures. This is for obvious reasons not easily done. Effective life-style treatment programs in obese patients would also be an attractive option, but even if some studies can show some effect on long-term weight-loss, results are disappointing when compared to surgery[34]. Those intensive treatment programs also require significant resources to be successful with continuous contacts over several years. In patients where life-style intervention programs are not effective, pharmacological treatment would also be an attractive option. However, the pharmacological treatments available today all have inferior effect on weight loss compared to bariatric surgery, and the side effects of the medications are sometimes problematic[37]. Effective pharmacological treatment against obesity would be a gold mine for pharmacological companies, and lots of resources are likely to be invested in this research in the future. Bariatric surgery might play a role in the development of new pharmacological treatments as we today know that the weight loss and effect on diabetes seen after gastric bypass is more complex than just a reduction of calorie intake and uptake. In fact, we still don´t know the exact mechanisms. With further progress in research on the physiological alterations after RYGB, new pharmacological treatments might evolve.

Until we can manage to prevent obesity or treat obesity with effective non-surgical treatments, bariatric surgery will continue to play an important role in the global war against the obesity epidemic. It is today undisputed that bariatric surgery is very effective, what we need to know more about is which procedures produces the best long-term results, in combination with low complication rates. The procedures in use can also be refined to even

further reduce complications. Another important issue is to know more about which patients are suitable, and not suitable, for surgery and when surgery should be considered.

The focus of this thesis was to investigate not only the positive effects of gastric bypass surgery but also at some possible negative health effects of surgery, and to add information valuable for the selection of patients for surgery. The more specific topics in this thesis will be further discussed in the next sections.

5.2 DIABETES

In paper III we linked SOReg data with the PDR to get full information on prescribed drugs in patients operated with RYGB between 2007 and 2012. We show that 67% of patients with diabetes treatment before surgery were in remission of diabetes treatment after 2 years, and that 61% of patients were still in remission at 7 years follow-up. These are remission rates in line with earlier studies, but this study add strength to the existing literature in the way that it is a nationwide study with almost complete follow-up of up to 7-years, since all prescribed drugs in Sweden are found in the PDR. Another strength is that only RYGB patients are included in this study, compared to some other studies that have a mix of surgical treatments. We also show that in patients with a short duration (< 2 years) of diabetes treatment the effects were even more remarkable with remission of diabetes treatment of 88 % at 2 years and 86 % at 7 years follow-up. RYGB is not only effective in the treatment of diabetes, it also seems to prevent against new cases of diabetes in obese patients. Previous studies have compared bariatric surgery patients without diabetes to an obese control group and demonstrated that that surgery is preventive against new cases of diabetes in obese patients[95,171]. In fact, we show in paper III that even patients with prediabetes at baseline have lower risk for diabetes treatment after surgery, compared to a control group from the general population. The control group in our study was not matched for weight or glycemic status since it was not available. The results from this study indicate that patients with diabetes have an effective long-term result on their diabetes. It also demonstrates that patients should be considered for surgery early after their diabetes debut, or even already when prediabetes is present. Even in cases with persistent diabetes treatment after surgery we demonstrate that more than 50% of patients with insulin treatment preoperative manage without insulin at least 7 years after surgery.

RYGB has a positive effect on diabetes even in patients with mild obesity[32]. A joint statement from international diabetes organizations in 2016 stated that surgery was *recommended* to treat type 2 diabetes in patients with obesity grade III (BMI>40), and in those with grade II obesity (BMI 35.0–39.9) when diabetes is inadequately controlled by lifestyle and optimal medical therapy. The same statement also declared that surgery should be *considered* for patients with type 2 diabetes and BMI 30.0–34.9 if hyperglycemia is inadequately controlled despite optimal treatment with either oral or injectable medications [172].

In fact, several studies have been performed with good effect on diabetes also in non-obese patients (BMI <30), even if the effect is not as obvious as in obese patients[103,173]. Today this surgery is only performed within research projects and the consensus is that further evidence is needed before recommending it to non-obese patients. However, based on present knowledge, it is possible that RYGB, SG or some further developed method of surgery, will be a recommended treatment option in non-obese patients with drug refractory diabetes type

2, when more long-term data exists.

Prediabetes is a condition that untreated will lead to diabetes in most patients. In a 45-year old patient with prediabetes, the lifetime risk of developing diabetes has been estimated to be 74% [174]. In patients with BMI<40 and prediabetes it is reasonable to start with lifestyle interventions. Studies on patients with prediabetes have shown that development of diabetes can be successfully intervened, or at least delayed, even with moderate weight-loss[28,175]. Liraglutide could also be an option in some of those patients, in addition to dietary change and physical activity. Liraglutide has proven effects on prediabetes and weight-loss, even if the effects are moderate especially regarding weight-loss and the treatment is expensive and requires daily injections [39]. Patients with prediabetes should be closely monitored, and if conservative interventions fail to produce weight-loss, or if the patients develop diabetes, surgery should be recommended early as demonstrated by the results in paper III in this thesis. In severely obese patients with prediabetes, my opinion is that bariatric surgery should be recommended.

5.3 PSYCHIATRY, ALCOHOL AND SUBSTANCE ABUSE

Some early reports indicated that there might be an increased risk for alcohol abuse after gastric bypass surgery, otherwise not much was known on this topic at the start of this thesis project. Studies had also shown that the risk for suicide and attempted suicide was elevated in bariatric surgery patients after surgery[112]. In papers I and II we used the Swedish NPR to examine if gastric bypass surgery patients have more inpatient care diagnosis of alcohol abuse, substance abuse, depression or suicide attempts, before and after surgery, compared to restrictive surgery patients (paper I) and general population controls (paper II). In paper I we compared patients operated with RYGB, with patients operated by restrictive procedures, more exactly VBG or GB. We found that RYGB patients had higher postoperative risk for diagnosis of alcohol abuse and attempted suicides compared with restrictive surgery patients. This might be caused by the altered metabolism of alcohol seen after RYGB[158,159,176], but not after restrictive procedures, leading to higher ethanol concentrations in the blood. Alcohol is degraded partly in the gastric mucosa by alcohol dehydrogenase and after RYGB a large proportion of the gastric mucosa is bypassed and also the emptying of the gastric pouch is quicker after RYGB[160]. This leads to higher peak alcohol concentrations, which could be one factor that stimulates alcohol related problems. Another finding in paper II suggesting that alcohol related problems are more common after RYGB surgery is that the prescription of medication against alcohol abuse increases significantly after surgery. Prescriptions of benzodiazepines, sedatives and hypnotics also increase after surgery. There are no indications that patients have more anxiety or sleeping disorders after surgery, thus increased prescriptions could indicate a substance abuse problem. Since we don´t know the exact reasons for the prescriptions we cannot draw any conclusions, but the findings indicate that this should be investigated further. There are other studies that present increased substance abuse after surgery[153,177]. Papers I and II provide an important addition to previously existing literature because of the large cohort with good follow up, whereas some previous studies were small and had problems with incomplete follow-up. Today we can say that the existing literature shows that alcohol related problems, accidents, as well as suicide and suicide attempts increases after RYGB surgery[150,178]. There might be an association of these factors since alcohol abuse increases the risk for accidents and suicide.

Patients need to be educated of this problem before surgery. Patients with suspected ongoing alcohol or substance abuse should not undergo RYGB surgery, not only because the alcohol abuse can be worsened, but also as patients must adhere to given instructions for food and vitamin intake after surgery. In worst case Wernicke's encephalopathy has been described[179]. In patients with a history of problematic alcohol use, other bariatric surgery methods than RYGB should be considered to reduce the risk of postoperative alcohol abuse. These patients also require closer monitoring and counseling in the postoperative period.

In paper II we demonstrate that there is no reduction in prescriptions of antidepressants or inpatient care diagnosis of depression after surgery. About 30% of patients are on anti-depressive treatment preoperative, and some patients expect surgery to be the solution to all their psychological problems. Even if overall HRQoL is improved after surgery, it is mostly in the physical aspect, whereas long-term benefits in psychosocial QoL remain uncertain [117] . This must be communicated to the patients before surgery, to avoid unrealistic expectations.

5.4 COMPLICATIONS

As mentioned in the introduction, the most common complications after surgery are bleeding, internal hernias, small bowel obstruction, leakage, ulceration and stenosis in the anastomosis. There are also general complications such as urinal infections, deep vein thrombosis, and infections as in all larger surgical procedure. Other negative effects of surgery that can´t be related to a specific complication are for example problem with dumping, chronic abdominal pain and extreme skin excess. Complications and postoperative morbidity have been reduced with the introduction of laparoscopic technique and improved perioperative care. Increased surgical volumes has probably also helped to reduce complications.

Technical refinements can reduce complications after RYGB, for example linear stapling reduces the risk for stenosis [123,180], closure of mesenteric defects reduces the risk for IH [143], laparoscopic surgery decreases the risk for wound complications and use of PPI reduces the risk for marginal ulcer [133]. Further refinements will continue to evolve. In paper IV we compare two different techniques of RYGB, regarding postoperative complications. At Danderyd hospital, we changed our technique in 2010 from the classic RYGB with divided mesentery, to a technique where the mesentery is left intact. This was done since we had high complication rates compared to other centers in Sweden, already using the intact mesentery method, according to SOReg. In paper IV we present a significant reduction of leakage and ulceration/stenosis in the anastomosis at our clinic, after alteration of the technique. Our theory behind this is that the circulation to the anastomosis is compromised when the mesentery is divided, leading to ischemic ulceration and stenosis. This is not farfetched, since mucosal stapling itself leads to mucosal ischemia[181]. Division of the mesentery, which supplies blood to the intestine, might very well enhance this ischemia. Ulceration and stenosis is investigated as one entity in our study, because we think that they are correlated and caused partly by the same mechanisms. When routine endoscopy is performed in patients after RYGB, 12% have marginal ulceration after 1 month, and in patients with marginal ulcer 40% have some grade of stenosis at the same time[130]. This could indicate that stenosis is the result of an ulcer, healing with fibrosis. Even if our study has some obvious weaknesses, discussed

in the limitation section, we think that our study strongly indicates that RYGB should be performed without division of the mesentery to reduce complications. However, a randomized study is needed to definitely prove this.

Surgeons performing RYGB surgery, and other bariatric surgery, need to stay curious and updated on new techniques and follow their patients regarding postoperative complications. The ambition must be to further evolve existing and new techniques to reduce complications for the benefit of the patients.

5.5 LIMITATIONS

5.5.1 General limitations

All studies in this thesis are of retrospective character, based on data from different registries. Swedish registries are generally of good quality, but data is not stored for the intention of specific research projects. Even if they have a completion rate of almost 100% for every hospital stay or visit in the outpatient clinic, the diagnosis stored is not always the correct one, or some secondary diagnosis might be missed. If data is not stored correctly the results of the studies will be affected. This might differ between different diagnoses; for example, diabetes is probably more correctly diagnosed than alcohol and substance abuse. The data from the registries will not in any way be exactly correct, but in a comparison with a control group it is probably valid since misdiagnosing will be performed equally in the study group and in the control group.

5.5.2 Limitations Papers I and II

Except for the general limitations of registry studies, there are some other limitations of these studies. In paper I we compare patients operated with different methods, popular during different periods. Patients operated with restrictive procedures are generally operated earlier than patients operated with RYGB, thus leading to longer follow-up in the patients operated with restrictive procedures. Even if the Cox regression model should deal with this, it might affect the result to some degree. We also know that postoperative complications have been reduced over the years, even if this hardly affects the results of this study in any significant way.

In both studies, we only analyze inpatient diagnosis of depression, suicide attempt, alcohol and substance abuse, meaning that patients diagnosed only in the outpatient clinic is not detected. For depression, alcohol abuse and substance abuse we can assume that a significant number of patients are missed because of this, but the comparison between the groups regarding inpatient diagnosis are still valid since this will affect both groups equally.

There is also a potential of follow-up bias since patients undergoing surgery is more likely to be in contact with healthcare during routine follow-up or because of complications. If patients are in contact with healthcare, other problems are more likely to be diagnosed as well.

5.5.3 Limitations paper III

In the study of diabetes remission, we lack glycemic status during follow-up in both the surgery and population control group, thus relying only on diabetes treatment as an indication of patients' diabetes status. Some patients probably go with untreated diabetes, even if we can assume that patients with previous diabetes have some kind of long-term follow-up.

In the study of diabetes incidence, we also lack glycemic status and weight in the general population controls. This means that some individuals in the general population probably will have undiagnosed diabetes or prediabetes at baseline, whereas in the surgery cohort the patients are screened and no patients have diabetes at baseline.

5.5.4 Limitations paper IV

There are several limitations in paper IV. Firstly, the retrospective character of the study with patients operated during different time frames makes the groups somewhat hard to compare since we know that complications are generally decreasing after bariatric surgery. There is an issue with potential learning curve bias, even if we tried to reduce this by eliminating the first 100 patients in both groups, as well as patients operated by a surgeon with less than 100 total procedures. Unfortunately, we also extended our postoperative PPI treatment from 1-month to 3-months at the same time as we changed surgical technique and this probably also affect the results on ulceration/stenosis.

Another issue is that we only use data from our internal quality registry at Danderyd. If a patient was treated elsewhere for complications it would not be detected in our registry. In Stockholm, there is consensus that each clinic takes care of its own complications, reducing the risk for this. However, some of the patients are patients from other regions in Sweden and they are more likely to be treated at their regional hospital, especially for ulceration/stenosis, which is most often diagnosed after patients leave hospital. Ulceration and stenosis is to a higher degree treated by endoscopic interventions and medicine, which might be taken care of at a regional hospital.

5.6 FUTURE OF BARIATRIC SURGERY

Bariatric surgery will probably continue to be the most effective treatment for morbid obesity in the near future. SG has lately become an alternative to the RYGB, but long-term effects are still not evaluated. We know that patients operated with SG have slightly inferior effect on weight-loss and comorbidities, but also slightly fewer complications than RYGB patients[90,93,182-187]. Based on the experience from earlier gastroplasties, they tend to have a good initial effect but regain weight in the long-term. Some studies are starting to report 5-year follow up after SG and the tendency with weight-regain is seen also in the SG patients[188]. Patients, wishing for a simpler operation, largely drive the trend to more SG procedures. Short-term results after SG are comparable to RYGB and this brings a good reputation among patients. The BEST study is an ongoing randomized multicenter study in Sweden, randomizing patients between RYGB and SG. Long-term data from this study will hopefully help us, and our patients, to choose the most suitable procedure in the future.

Based on current knowledge it is possible that bariatric surgery will be used to treat diabetes type 2 also in non-obese patients in cases of drug refractory diabetes, when more long-term

data from studies exist. New surgical methods with even lower complication rates would also lower the threshold for surgery in patients with diabetes.

We will need better tools to decide which procedure is best for the individual patient. Patients with different behavior patterns, e.g. drinking and eating behaviors, could be better suited for different surgical procedures. Patients must also be informed about potential negative health effects and patients with a history of problematic alcohol use should be advised to have other bariatric surgery than RYGB.

From what we know today RYGB should probably be the first choice procedure for most patients, because of well-known long-term effect and reasonably low complication rates. Recent studies favor closure of the mesenteric defects to reduce internal hernias even if early complications slightly increase[143]. RYGB should also be performed without division of the mesentery to reduce complications, as shown in paper III, and prolonged PPI treatment for 3months is also advisable. SG seem to be the alternative, at least in patients with a BMI <40 without comorbidities, with the advantages of a simpler operation and no risk for internal hernias, but long-term effects need to be evaluated further.

6 CONCLUSIONS

RYGB is a safe operation with remarkable effects on diabetes type 2 treatment in obese patients. Treatment with RYGB should be considered in an early stage of diabetes to get the best effect. It also prevents future treatment of diabetes in obese patients with prediabetes.

RYGB increases the risk for diagnosis of alcohol use disorders and suicide attempts, patients have increased prescriptions of benzodiazepines, hypnotics and drugs against alcohol abuse after surgery. RYGB does not lead to a reduction of inpatient diagnosis of depression or reduced antidepressive treatment.

RYGB should be performed with the intact mesentery technique to reduce complications in the anastomosis.

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