

Improving Procedure Selection and Surgical Technique in Bariatric Surgery

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I rörelse

Den mätta dagen, den är aldrig störst.

Den bästa dagen är en dag av törst.

Nog finns det mål och mening i vår färd -
men det är vägen, som är mödan värd.

Det bästa målet är en nattlång rast,
där elden tänds och brödet bryts i hast.

På ställen, där man sover blott en gång,
blir sömnen trygg och drömmen full av sång.

Bryt upp, bryt upp! Den nya dagen gryr.

Oändligt är vårt stora äventyr.

Karin Boye, Härdarna

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ABSTRACT

Bariatric surgery is currently the most effective treatment for obesity and its metabolic comorbidities. There are, however, unexplored differences between surgical methods regarding outcomes and suitability for the individual patient. There are also variations in surgical techniques, where the association between differences in outcomes are not fully explored. The overall aim of this thesis is to improve outcomes in bariatric surgery by optimizing procedure selection and refining surgical technique.

Paper I describes the design and rationale of the Bypass Equipoise Sleeve Trial (BEST), a large registry-based randomized multicenter trial comparing sleeve gastrectomy and Roux-en-Y gastric bypass (RYGB). In *Paper II*, the perioperative outcome of BEST is presented. *Paper III* is a retrospective study identifying, describing, and proposing a treatment option for postprandial symptoms due to a dysfunctional jejunojejunostomy after RYGB. *Paper IV* is a large observational registry study comparing surgical variations in the construction of the jejunojejunostomy regarding the association with post-operative small bowel obstruction.

In this thesis it is concluded that: 1) Sleeve gastrectomy and RYGB can both be performed safely and with low perioperative risk in adult patients undergoing primary bariatric surgery; 2) Many patients having postprandial pain, nausea, and/or vomiting after RYGB, improve or become symptom-free after surgical revision of the jejunojejunostomy; and 3) The risk of small bowel obstruction varies with the type of surgical technique used for the jejunojejunostomy, both in the short and long term.

Keywords: Bariatric Surgery, Roux-en-Y gastric bypass, Sleeve gastrectomy.

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SAMMANFATTNING PÅ SVENSKA

Fetmakirurgi är idag den mest effektiva behandlingen mot fetma och dess följsjukdomar. Det finns flera olika operationsmetoder, och skillnaderna mellan dessa, avseende såväl risker som vinster, är inte helt klarlagda. Dessutom finns det variationer i kirurgisk teknik inom samma operationsmetod, där man inte vet hur olika tekniska variationer är kopplade till risk för komplikationer, och hur man skall behandla komplikationerna när de väl uppstått.

Huvudsyftet med denna avhandling är förbättra fetmakirurgin genom att; 1. undersöka skillnader mellan olika kirurgiska metoder för att lättare kunna erbjuda rätt metod till rätt patient, samt; 2. att optimera den kirurgiska tekniken.

I *artikel I* beskrivs designen av, och motiven för att genomföra BEST-studien, där 1735 patienter vid 23 sjukhus randomiserats till operation med en av de två vanligaste operationsmetoderna: gastric sleeve och gastric bypass.

I *artikel II* rapporteras data om deltagarna i BEST före operationen, data angående operationernas genomförande samt komplikationer under de första 30 dagarna efter operationen.

I *artikel III* beskrivs en grupp patienter som fått sena problem efter gastric bypass. Vilka symptom som är vanliga, vad de tros bero på, och hur man eventuellt kan behandla dem.

I *artikel IV* användes data från det Skandinaviska Fetmakirurgiska registret, SOReg för att undersöka risken att få tarmvred i relation till vilken teknisk variant som använts vid operation med gastric bypass.

Avhandlingens slutsats är:

- Att både gastric sleeve och gastric bypass är säkra metoder med låg och likvärdig risk för tidiga operationskomplikationer.
- Att buksmärta efter måltid (ibland i kombination med illamående eller svåra blodsockerfall) hos patienter som tidigare opererats med gastric bypass kan bero på en dåligt fungerande nedre tarmkoppling; en situation som i många fall kan förbättras med en titthålsoperation.
- Att tekniska variationer i hur man konstruerar den nedre tarmkopplingen vid gastric bypass-kirurgi verkar vara relaterade till risken att för att drabbas av tarmvred.

LIST OF PAPERS

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

- I. **Hedberg, S**, Olbers, T, Peltonen, M, Österberg, J, Wirén, M, Ottosson, J, Thorell, A. BEST: Bypass Equipoise Sleeve Trial; rationale and design of a randomized, registry-based, multicenter trial comparing Roux-en-Y gastric bypass with sleeve gastrectomy. *Contemporary Clinical Trials* 2019 Sept; 84: 105809.
- II. **Hedberg, S**, Thorell, A, Österberg, J, Peltonen, M, Andersson, E, Näslund, E, Hertel, JK, Svanevik, M, Stenberg, E, Neovius, M, Näslund, I, Wirén, M, Ottosson, J, Olbers, T. On behalf of the BEST study group. Perioperative Outcomes in Sleeve Gastrectomy and Roux-en-Y Gastric Bypass –a Randomized Clinical Trial in Sweden and Norway. In manuscript.
- III. **Hedberg, S**, Xiao, Y, Klasson, A, Maleckas, A, Wirén, M, Thorell, A, Laurenius, A, Engström, M, Olbers, T. The Jejunojejunostomy: an Achilles Heel of the Roux-en-Y Gastric Bypass Construction. *Obesity Surgery* 2021 Dec; 31(12): 5141–5147.
- IV. **Hedberg, S**, Thorell, A, Engström, M, Stenberg, E, Olbers, T. Surgical Technique in Constructing the Jejunojejunostomy and the Risk of Small Bowel Obstruction after Roux-en-Y Gastric Bypass. *Surgery for Obesity and Related Diseases* 2022 Sep; 18(9): 1151–1159.

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ABBREVIATIONS

ASMBS	American Society of Metabolic and Bariatric Surgery
BE	Barrett's Esophagus
BEST	Bypass Equipoise Sleeve Trial
BMI	Body Mass Index
CCK	Cholecystokinin
CI	Confidence Interval
CRF	Case Report Form
DVT	Deep Vein Thrombosis
GERD	Gastro-Esophageal Reflux Disease
GIP	Glucose-Dependent Insulinotropic Polypeptide
GJ	Gastro-jejunostomy
GLP-1	Glucagon-Like-Peptide-1
HR	Hazard Ratio
IFSO	International Federation for the Surgery of Obesity and Metabolic Disorders
IH	Internal Herniation
JJ	Jejuno-jejunostomy
NAFLD	Non-Alcoholic Fatty Liver Disease
OR	Odds Ratio
PAR	Swedish National Patient Registry
PE	Pulmonary Embolism

PTSD	Post-Traumatic Stress Disorder
PYY	Peptide YY
RCT	Randomized Controlled Trial
RYGB	Roux-en-Y Gastric Bypass
SAE	Serious Adverse Events
SFOK	Swedish Society for Metabolic and Obesity Surgery
SG	Sleeve Gastrectomy
SOReg	Scandinavian Obesity Surgery Registry
SOReg-N	Scandinavian Obesity Surgery Registry-Norway)
T2DM	Type 2 Diabetes Mellitus
WHO	World Health Organization

1 OBESITY

1.1 OBESITY - PREVALENCE AND SIGNIFICANCE

Obesity is a worldwide health challenge. Body mass index (BMI) is used to define overweight and obesity, both in research and in the clinic. BMI is calculated by dividing a person's weight in kilograms by the square of their height in meters (kg/m^2). The WHO defines overweight as a BMI greater than or equal to 25, and obesity as a BMI greater than or equal to 30¹.

Obesity is linked to a large number of co-morbidities², such as type 2 diabetes mellitus (T2DM)^{3,4}, cardiovascular disease⁵, obstructive sleep apnea⁶, polycystic ovarian syndrome⁷, non-alcoholic fatty liver disease (NAFLD)^{8,9}, gastro-esophageal reflux disease (GERD)¹⁰, osteoarthritis^{11,12}, gallbladder disease¹³, several types of cancer^{14,15}, overall mortality^{16,17}, and a reduced health-related quality of life¹⁸⁻²⁰.

In 2016 the World Health Organization (WHO) declared that more than 650 million adults worldwide had obesity. In the global adult population, the prevalence of obesity is 13%, and it is estimated that 4 million deaths annually can be linked to overweight and obesity, surpassing those linked to underweight^{1,2}. There is also an increasing global prevalence of overweight and obesity, not in the least among children (5-19 years), from 4% in 1975 to 18% in 2016¹. This used to be considered only a challenge of the high-income countries but obesity is now dramatically increasing also in low- or middle-income countries, and the rate of increase of obesity among children is 30% higher in developing countries¹. The prevalence of adult obesity in Sweden was 16% in 2021 according to the Public Health Agency of Sweden²¹ and has been increasing over the past decades²².

Apart from the physical health consequences of obesity, there is also the added psychological burden of stigma. Western societies in particular are abound with messages about thinness and that obesity is somehow immoral. This message, deeply ingrained in our society, affects the person with obesity both in how they perceive themselves and how others look upon and treat them, and gives real repercussions on both psychological and physical health²³.

During most of mankind's evolution, starvation has been a more serious threat to continued existence than obesity, thus making it an evolutionary asset to

collect and preserve energy. Today this is no longer the case in large parts of the world.

On the face of it, it seems as if decreasing energy intake and increasing energy expenditure should solve the problem, but humans are not machines with a clear linear combustion curve, and thus other means are needed to reach the goal of reduced obesity.

How all aspects of genetics, hunger, satiety, taste, exercise, age, pregnancy, menopause, socio-economics, gut microbiota, etc. influence body weight is well beyond the scope of this thesis²⁴. However, a short glance at gut hormones is warranted.

The complex interplay of central and peripheral hormone signaling involves both short- (from the stomach and intestines) and more long-term signals (from adipocytes and the pancreas) of both satiety and hunger. Satiety signals lead to termination of the meal, by among other pathways, slowing the motility in the gastrointestinal tract. Peripheral satiety signals include the incretins: glucagon-like-peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), as well as cholecystokinin (CCK), peptide YY (PYY), amylin, and oleoylethanolamide. Ghrelin is a peripheral hunger hormone, produced predominantly in the stomach. In the longer-term interplay of hormones, insulin from β -cells in the pancreas as well as leptin and adiponectin from adipocytes have central roles²⁵.

1.2 NON-SURGICAL OBESITY TREATMENT AT A GLANCE

Non-surgical obesity treatments include lifestyle interventions. A combination of dietary advice, exercise, and psychological support are usually employed. With the exception of a limited number of individuals responding very favorably, the best results show 5-10% weight loss in the first year, with a gradual weight regain over time²⁶. These programs usually consist of intense initial contact between the patient and caregivers (at least once a week for 6 months), and a close long-term follow up. Programs with less intensity often show lower efficacy at start and a more rapid weight regain compared to more intensive programs. In a recent review and meta-analysis by the Swedish National Board of Health and Welfare, it was concluded that while it is uncertain whether lifestyle interventions have any long-term benefits in terms

of weight loss (compared to controls), there is no apparent (physical) harm and they may be beneficial for some patients²⁷.

Pharmacological treatments for obesity²⁸ currently available in Sweden include:

Orlistat, an inhibitor of gastrointestinal lipases, reduces fat uptake in the gastrointestinal tract. Treatment with orlistat in combination with a low-fat diet leads to a modest weight loss²⁹. In a double-blind randomized controlled trial (RCT), Torgerson *et al.* showed that the orlistat group had lost 5.8 kg as compared to 3.0 kg in the placebo group at 4-year follow-up³⁰.

GLP-1 receptor agonists (such as liraglutide, semaglutide) increase GLP-1 signaling and thus the perceived satiety, leading to a decreased meal size. In addition to reducing body weight, GLP-1 receptor agonists improve glycemic control in patients with T2DM. Studies show a mean weight loss of 7%-16% after 1 year³¹.

Tirzepatide is a combined GLP-1 and GIP receptor agonist showing promising results in the treatment of T2DM and obesity in short-term studies, up to a mean of 21% weight loss at 1-year follow-up³².

Naltrexone/bupropion is a compound medication with naltrexone (an opioid receptor antagonist) and bupropion (a dopamine and norepinephrine reuptake inhibitor). The combination of these two centrally acting substances leads to a decreased food intake and increased energy expenditure. Mean weight loss at 1 year has been reported to be 6.4% (placebo 1.2%)³³.

2 BARIATRIC SURGERY

Obesity surgery, bariatric surgery, metabolic surgery – the name has changed and evolved over time, as have the procedures the concept encompasses. But at the heart of the matter is a surgical intervention that aims to reduce the degree of obesity and the comorbidities associated with obesity, with as few and as inconsequential adverse events as possible.

Compared to non-surgical treatment of obesity³⁴⁻³⁶, bariatric surgery usually induces marked and sustained long-term weight loss. Studies have shown improvement of obesity-related morbidities³⁷⁻⁴⁰ such as T2DM⁴¹⁻⁴⁴, hypertension⁴⁵, cardiovascular disease^{46,47} as well as reduced mortality^{39,48,49}. Improvements in quality of life⁵⁰ have also been shown, especially regarding health-related quality of life⁵¹⁻⁵⁴.

The National Institute of Health (USA) published a consensus statement in 1991⁵⁵ based on the available data at that time. These recommendations have been slightly amended through the years, but the recommendation of bariatric surgery for patients with a BMI > 40, or a BMI > 35 together with at least one significant comorbidity, has guided clinical practice since then. These are also the recommendations under which the majority of the participants in this thesis were operated. In December 2022, the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) and the American Society of Metabolic and Bariatric Surgery (ASMBS) published a joint updated indication document for bariatric and metabolic surgery based on current amassed knowledge. Among other changes they now recommend bariatric surgery for patients with a BMI >35 irrespective of comorbidities, and for patients with T2DM and BMI >30. Moreover, bariatric surgery should be considered for patients with BMI >30 in combination with either comorbidities or failure at prior non-surgical treatment⁵⁶. In 2016 there was a joint statement by most international diabetes organizations placing bariatric surgery in the treatment algorithms for T2DM⁵⁷.

Although there are many surgical procedures in use, the most common are Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG).

While the mechanisms of action are not fully understood, the traditional explanation of “restriction and malabsorption” has mainly been dispelled for RYGB and SG. In RYGB the food bypasses the disconnected main part of the stomach, duodenum, and proximal jejunum, rapidly passing the pouch to the distal jejunum and onward. In SG, food is present in all remaining parts of the

gastrointestinal tract; the stomach volume is greatly reduced, resulting in a rapid transit to the duodenum and onward which appears to partially result in a surprisingly similar gut hormone response as in RYGB. Although such changes have been vastly characterized it remains to be demonstrated which changes are crucial for weight loss and weight loss maintenance, or if the combination of changes are important. CCK is increased as a response to a meal in RYGB and even more so in SG⁵⁸. Ghrelin levels stay at the same non-fed level after RYGB but may be deacylated more rapidly after a meal, while there is a sustained decrease in ghrelin levels in SG⁵⁹. PYY and GLP-1 are greatly increased after a meal in both RYGB and SG^{60,61}. Strong evidence suggests that GLP-1 is important in glucose homeostasis^{60,62}. There are also indications that post-operative changes in bile acids may influence glucose homeostasis⁶². There are also studies indicating differences in gut microbiome between persons with and without obesity, but the significance of this remains unclear^{62,63}.

The following pages will introduce RYGB and SG regarding the surgical construction, technical variations, and complications.

2.1 A GLIMPSE AT HISTORY

While you will not be regaled with a detailed history of bariatric surgery, it does seem appropriate to note that the first mention of an operation performed with the intention to create weight loss was by Viktor Henrikson in Gothenburg, in 1952^{64,65}. He had noted the often unwanted weight loss in patients after small bowel resection and aimed at using this effect as an obesity treatment. While his treatment (a 105 cm resection of the small intestine) was ultimately of little help for his patient, it demonstrates a model of thinking that has been of use in the development of bariatric surgery at several timepoints, namely realizing that a complication in one setting could in fact be a benefit in another.

A very important observation was when Edward Mason noted that a Billroth II reconstruction often left patients struggling with substantial and maintained weight loss. This observation led him on to a series of experimental surgeries on dogs and eventually to the first gastric bypass in a human in 1966⁶⁶.

The initial gastric bypass anastomosed a jejunal loop to a small gastric pouch. This was eventually abandoned in favor of the Roux-construction, to minimize both tension of the anastomosis, which might increase the risk of leakage and bile reflux. The initial gastric pouches were mainly horizontal, and rather large, with the anastomosis created along the greater curve of the fundus. In an

attempt to increase weight loss, Torres introduced the smaller vertical pouch, approximately 50 ml along the lesser curvature⁶⁷. There have also been varying lengths of the intestinal limbs over time, from the initial 40 cm Roux-limb and 10 cm biliopancreatic limb, to Torres 150 cm common limb and 90 cm alimentary limb and a long biliopancreatic limb. The technical, surgical advances over time eventually lead to the development of the laparoscopic RYGB⁶⁸. There are, however, still uncertainties concerning the best construction method. Part of the aim of this thesis has been to tweak and improve the antegastric/antecolic Gothenburg method, pioneered by Hans Lönroth in the late 1990s^{69,70}.

In the first decade of the 2000s, the laparoscopic RYGB became the gold standard for bariatric surgery in Sweden. The superior long-term results led to a switch from the previously dominating banded procedures (vertical banded gastroplasty, gastric banding)⁷¹⁻⁷³, and for several years the RYGB was the totally dominating procedure in Sweden.

In the late 1990s surgeons were also considering whether a vertical gastric resection could lead to sufficient weight loss. The first laparoscopic gastric sleeve procedure was performed by Michael J. McMahon in 2000 in Leeds⁷⁴. Simultaneously in New York, Michel Gagner serendipitously noted that the laparoscopic gastric sleeve sometimes was efficacious enough to stand alone when used as the first step of a two-step duodenal switch procedure, making the second step of the procedure superfluous^{68,75}.

The laparoscopic sleeve gastrectomy (SG) rapidly gained popularity during the early 2010s. It appears that in the United States, the long-term issues with the laparoscopic gastric banding were increasingly acknowledged at that point and SG appeared to be a technically less demanding operation than RYGB, but with better results than the laparoscopic band.

Simultaneously, in Swedish and Scandinavian bariatric surgery there was an increase in the number of patients with abdominal pain after RYGB that was likely, at least partly, driving a rather rapid shift towards SG, and in 2019 it surpassed RYGB as the most common bariatric procedure in Sweden⁷⁶. As can be seen in figure 1, the lines have crossed again, and it is fair to say that RYGB and SG amount to approximately 50% each of current primary bariatric surgery in Sweden.

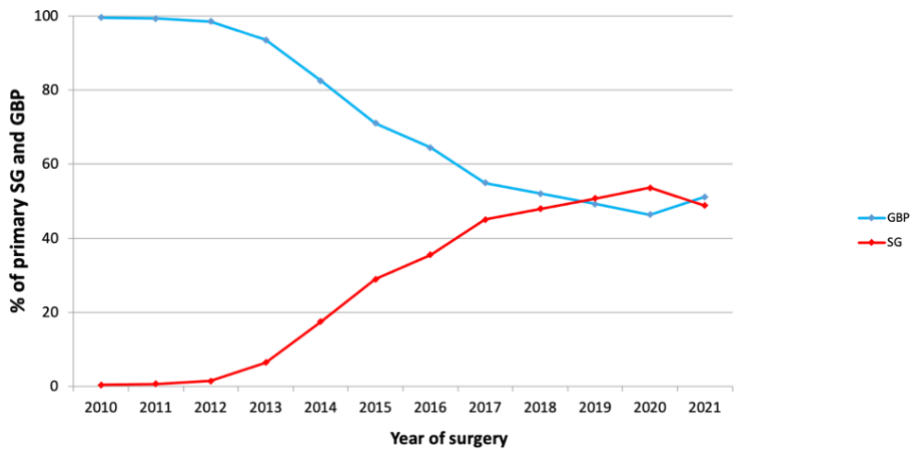


Figure 1. Percentage laparoscopic gastric bypass (GBP) and laparoscopic sleeve gastrectomy (SG) of all primary procedures in Sweden 2010–2021. *Scandinavian Obesity Surgery Registry annual report 2021, part 1*⁷⁶.

2.2 SOREG AND THE CURRENT STATE OF BARIATRIC SURGERY IN SWEDEN

The Scandinavian Obesity Surgery Registry (SOReg) is a national quality registry that started in 2007 and has captured data on virtually all bariatric surgery in Sweden since 2013⁷⁷. The registry operates with an “opt-out model” where patients are informed preoperatively of the registry and that they can opt out of participation at any time point. The registry has a high acquisition rate (97.4%) and a demonstrated high internal validity⁷⁸.

The SOReg registration starts with a baseline assessment capturing data on variables such as anthropometry, comorbidities, and quality of life. The intraoperative registration includes details regarding the surgical intervention. At registration 6 weeks after surgery the 30-day complication data is captured. The treatment efficacy is assessed with a similar template for registration as at baseline, along with information about possible complications and side effects at 1, 2, 5, 10, and 15 years after surgery. SOReg is also routinely cross-matched

with the Swedish Total Population Registry⁷⁹ (for death and emigration) and the Cause of Death Registry, providing a 100% follow-up on mortality.

SOReg-Norway (SOReg-N) was established in 2014, and since 2019 it covers all public and the majority of the private hospitals performing bariatric surgery in Norway. The variables in SOReg and SOReg-N are identical, and any major changes must be agreed upon bilaterally.

Bariatric surgery in Sweden was performed laparoscopically in 99.8% of procedures in 2021 with a 0.05% conversion rate⁷⁶. The all-cause complication rate in 2021 was 5.3%, and the rate of serious complications (Clavien-Dindo > IIIb) was 2.1%⁷⁶. The all-cause mortality rate is 0.031% at 30 days, 0.055% at 90 days, and 0.19% at 1 year after surgery⁸⁰.

Rates of complications may vary with patient selection (i.e., BMI, comorbidities), operating time, and preventive measures. Post-operative complications include deep vein thrombosis (DVT), pulmonary embolism (PE)^{81,82}, other pulmonary complications, urinary tract infections, port site infections, etc. Among the surgical perioperative complications, both bleeding and anastomotic leaks are noted, although their location and seriousness may vary by procedure.

As seen in figure 1, RYGB and SG together constitute the majority of primary bariatric surgery in Sweden. The annual number of procedures has varied over time (figure 2). After a steep increase between 2007 and 2011, there was a drop until 2019 whereafter the Covid-19 pandemic reduced the numbers additionally. On a national level there seems to be a return to about 5000 procedures yearly in Sweden, but there are large regional differences and several hospitals have not yet returned to the pre-pandemic situation.

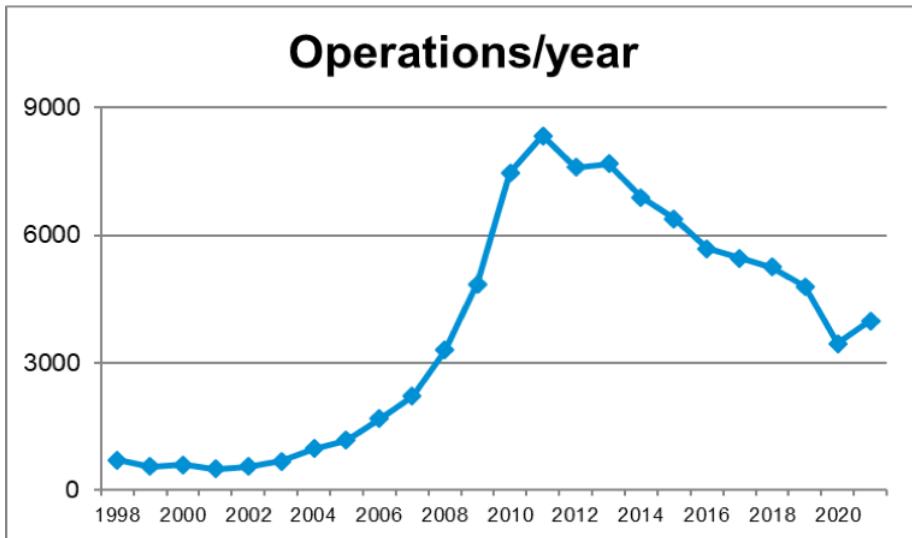


Figure 2. Bariatric operations per year in Sweden (data from Swedish National Board of Health and Welfare, 1998-2007, and the Scandinavian Obesity Surgery Registry, 2008-2021)⁷⁶.

2.3 ROUX-EN-Y GASTRIC BYPASS

The laparoscopic RYGB is a well-established bariatric procedure with well-known outcomes in terms of weight loss and improvement or resolution of comorbidities. Data from SOReg shows that patients lose approximately 75% of their excess weight until 2 years after surgery, followed by a slight increase in weight, but relative weight stability in the longer term⁸³ (figure 3).

For improvement in obesity-related comorbidities^{34,84}, Sundbom *et al.* showed that the prevalence of T2DM was reduced from 15.5% at surgery to 5.9% at 5 years post-surgery⁸⁵. Significant improvements were also seen regarding the prevalence of hypertension (29.7% - 19.5%), dyslipidemia (14.0% - 6.8%), and sleep apnea (9.6% - 2.6%).

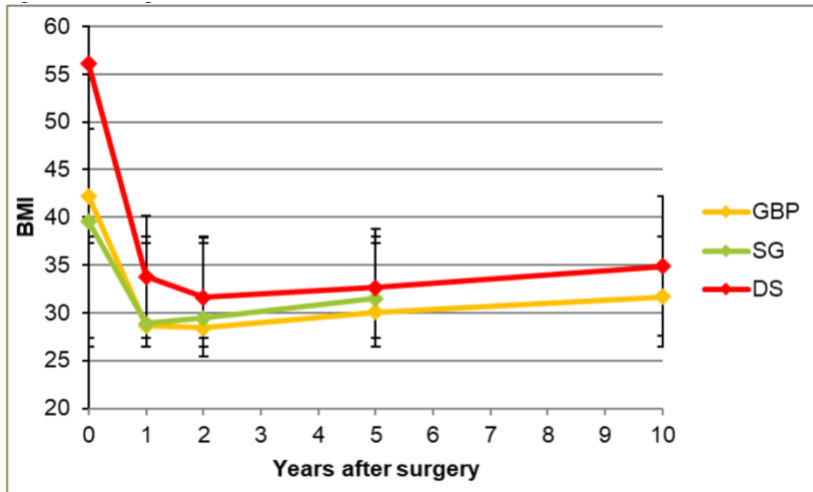


Figure 3. Body mass index (BMI) loss over time after primary bariatric surgery. (GBP Roux-en-Y gastric bypass; SG sleeve gastrectomy; DS duodenal switch). Data from SOReg.

2.3.1 RYGB TECHNIQUE

In Scandinavia and northern Europe, the dominating version of the gastric bypass is the laparoscopic RYGB developed by Lönroth and colleagues in the late 1990s⁶⁹. This antegastric, antecolic procedure (figure 4) is performed by creating a small (10-30 ml) gastric pouch, using 2–4, 45mm linear staples. The ligament of Treitz is identified and an omega loop is brought up without tension to the gastric pouch. The gastro-jejunostomy (GJ) is created by inserting one fork of a linear stapler in the small bowel and the other in the gastric pouch, thus creating a stapled posterior anastomosis, and closing the remaining open defect with a handsewn running suture. The Roux-limb is measured to the desired length (80-160 cm), and a jejunojejunostomy (JJ) is created with the same technique as the GJ, immediately distal to the GJ on the afferent side to form an “omega-loop”. Finally, the bowel is transected between

the GJ and the JJ, and the mesenteric defects at the JJ and Petersen's space are closed with either metal clips or a running non-resorbable suture^{86,87}.

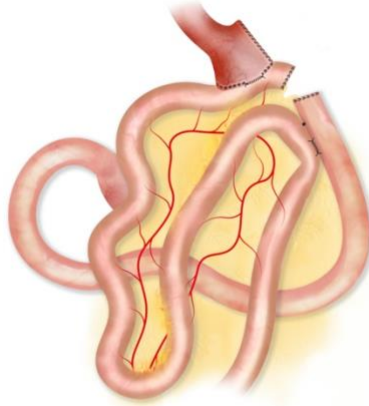


Figure 4. Classic Roux-en-Y gastric bypass (unidirectional jejunojejunostomy, short/no mesenteric division). Illustration by Jan Funke.

2.3.2 RYGB COMPLICATIONS

The general perioperative complications are briefly mentioned in section 2.2. In the following paragraphs, the more specific RYGB complications are reviewed.

Leakage from anastomoses are generally feared among gastrointestinal surgeons; leaks at the GJ present a particular challenge since this poses a high risk of not only peritonitis but also mediastinitis. Early detection and drainage are of utmost importance to avoid general inflammation, organ failure and, in the worst cases, mortality^{88,89}.

Leaks⁹⁰, kinks, or intraluminal blood clots at the JJ also constitute risks. Apart from peritonitis, there is also the risk of blow-out of the remnant stomach if the JJ is obstructed, especially in the perioperative phase. A blow-out with leak and dissemination of gastric content in the abdomen results in a situation with systemic inflammation and peritonitis which can be lethal. Secondary prevention of this very precarious situation has often been to place a gastrostomy tube in the remnant stomach, in particular when the situation is due to small bowel obstruction and kinking of the JJ.

Bleeding is also a potentially serious complication. Bleeding can be intraabdominal or intraluminal and depending on the volume and location, some bleedings require re-operation while others may be self-limiting and can be handled by supportive care. Intraluminal bleedings may result in transient obstruction of blood clots resulting in small bowel obstruction or gastric outlet obstruction.

Before closure of mesenteric defects at primary surgery was routinely performed, the most common long-term complication of RYGB was internal herniation (IH), where the small bowel herniates through the open mesenteric defects at Petersen's space or at the JJ. When mesenteric defects are not closed, this complication has a reported incidence of up to 16% over 10 years⁹¹. It was suggested that closing of the mesenteric defects at primary surgery could decrease the incidence. However, there were also concerns that complications, such as bleeding at primary surgery, would outweigh the potential benefits. Therefore, the benefit of closing the mesenteric defects was addressed in a registry-based RCT in SOReg and clearly demonstrated that the incidence of IH at 3 years decreased (hazard ratio, HR, 0.56, 95% confidence interval, CI, 0.41–0.76, $P = 0.0002$). Although there was an increase in the 30-day complication rates, mainly due to kinking at the JJ (OR 1.55, 95% CI 1.01–2.39, $P = 0.044$)⁸⁶, the overall rates of small bowel obstruction at 5-years post-surgery was reduced from 6 to 2.5%⁸³. The 10-year incidence of IH is currently in the range of 2.5% in Sweden⁸³.

Among the common side effects of RYGB is the dumping syndrome. Within an hour of a meal, especially after a meal with a high content of sugar and/or fat, patients can experience gastrointestinal symptoms (abdominal discomfort and pain, bloating, nausea, and diarrhea) and vasomotor symptoms (flushing, palpitations, hypotension, tachycardia, perspiration, fatigue, and a need to lie down). It is believed that these symptoms occur as a response to an osmotic effect in the small bowel because of a high concentration of nutrients, and the related gut hormone signaling^{92,93}. The dumping syndrome after RYGB can usually be successfully handled by eating smaller meals more often and by reducing the content of fat and refined carbohydrates. The dumping syndrome is viewed by some as a positive consequence of surgery, as it “forces” patients to make healthier choices.

Occasional postprandial hyperinsulinemic hypoglycemia (previously labelled “late dumping”, also known as “reactive” or “postprandial” hypoglycemia) can be regarded as a physiological effect of RYGB. However, so-called complex hypoglycemia is a long-term complication that can cause the patient significant suffering. Changes in carbohydrate uptake and insulin secretion related to gut

hormone signaling after RYGB are suggested to cause postprandial hypoglycemia^{42,94}. Symptoms occur 1–3 hours after meals with mainly classic hypoglycemia symptoms (palpitations, tremor, fatigue, perspiration, weakness, and hunger), which can be reversed by ingesting carbohydrates.

The dumping syndrome and postprandial hypoglycemia can usually be managed by dietary interventions. For a very limited number of patients this is not sufficient and pharmaceutical treatment or eventually reversal of RYGB may be necessary in severe cases. An interesting observation in our research group is that complex postprandial hypoglycemia can be associated with postprandial abdominal pain due to for example kinking at the JJ, which may be mitigated by revisional surgery of the JJ⁹⁵.

Another long-term complication after RYGB is chronic abdominal pain. After rapid and substantial weight loss, the incidence of gallstones is high (10–32%)^{96,97}, and symptomatic gallstone disease and IH are seen most frequently during the first years after RYGB. Among patients with abdominal pain after RYGB where investigations show no clear cause, there is a subset of patients with abdominal pain in the upper left quadrant, and sometimes nausea, for whom we have reason to suspect that a dysfunctional JJ is at the heart of the matter, as described further in Paper III.

2.4 SLEEVE GASTRECTOMY

SG was recognized as a stand-alone bariatric procedure by ASMBS in 2012⁹⁸, and rapidly became the most popular bariatric procedure in the USA and many other regions. SG made its way slowly into Scandinavian bariatric surgery but there was a steep increase in its use after 2012.

Initial data implied that SG was associated with somewhat less weight loss and resolution of comorbidities as compared to RYGB⁹⁹, but with a lower risk of complications¹⁰⁰⁻¹⁰². The BMI change over time after SG in Swedish bariatric surgery can be seen in figure 3. Kraljevic *et al.*¹⁰³ recently presented follow-up of more than 10 years showing a mean excess BMI loss of 54% and a significant improvement in comorbidities, but also a re-operation rate with conversion to other procedure in 19% of patients due to GERD or insufficient weight loss (8–15% revision in RYGB^{84,104} and 64% excess BMI loss⁸³).

2.4.1 SG TECHNIQUE

The surgical technique to create the sleeve should include the inspection of the left crusiate ligament and dissecting if needed, to identify a possible hiatal hernia. A small hernia could arguably be sutured before proceeding with the sleeve construction. The presence of a large hernia could lead to different actions; it could be repaired, an alternative chosen by many surgeons, without clear support in literature^{105,106}, or it could initiate consideration of aborting further surgery or choosing an alternative procedure with less risk of inducing or worsening GERD, i.e., RYGB.

The gastrocolic ligament is separated from the major curvature of the stomach, starting a few centimeters from the pylorus until the angle of His. The stomach is resected starting from 2-6 cm orally of the pylorus, to 1-2 cm from the angle of His, with a large (32-36 Charrière) gastric tube in the lumen as a guide. Repeated firings of linear staplers are used for the resection. In general, a higher staple height is used in the antrum and a lower staple height closer to the fundus. The staple line can be reinforced either by buttressing or suturing the whole staple line, or parts of it, or not reinforced at all. In shaping the sleeve, the surgeon must take care to avoid a narrowing at the angle of the stomach, and to avoid discrepancies between the front and back wall to avoid twisting which can create functional passage problems.



Figure 5. Gastric sleeve. Illustration by Jan Funke.

2.4.2 SG COMPLICATIONS

The general non-procedure-related complications for SG are the same as for RYGB (section 2.2).

The most common early complication after SG is bleeding, usually from the staple line or from the division of the gastrocolic ligament, and may require blood transfusion and/or re-operation. Staple line failure and/or leakage are relatively uncommon but often result in serious problems when occurring. Leaks most frequently occur at the top of the staple line near the hiatus, posing the risk of not only peritonitis but also mediastinitis and intrathoracic complications. The unique problem with the sleeve leak is that the sleeve is a high-pressure system where the leaking site may be the point of least resistance for stomach contents. Continuous leakage of gastric juices may prevent healing even when adequately drained. Specially designed stents and suction devices have been introduced to facilitate healing, but the leaking sleeve is often a longer-term problem with months of treatment before healing and sometimes requiring conversion to a RYGB¹⁰⁷.

Over time it became obvious that GERD is a long-term issue after SG. When studies suggested a prevalence of Barrett's esophagus (BE) of 15–18.8% it was indeed concerning¹⁰⁸⁻¹¹¹. In a recent meta-analysis by Yeung *et al.*, a 19% increase of GERD (compared to baseline) after SG and 23% de novo GERD were demonstrated¹¹². The prevalence of BE at endoscopy was 8% and endoscopically confirmed esophagitis 28%. In the 10-year follow-up of the SLEEVEPASS trial (RCT: RYGB or SG), Salminen *et al.* showed similar numbers for esophagitis in the sleeve group (31%) compared to RYGB (7%), but only 4% BE, which interestingly was at the same level after RYGB¹¹³. The Norwegian Oseberg trial showed a higher risk for GERD and new onset esophagitis in SG compared to RYGB, and demonstrated that many patients with esophagitis were asymptomatic¹¹⁴. In 2022 Johari *et al.* showed that after biopsy the rate of histologically-verified BE post-SG was 3.8%, but also reported a 70.8% prevalence of glandular-type gastric mucosa, thus implying a tubularized herniation of cardia¹¹⁵, and that this altered histopathological picture may be behind the high numbers of BE previously reported, rather than true BE.

Thus, recent studies have tempered previous alarming BE rates, and Johari *et al.* may have identified an underlying cause for previous disparate results. A herniation of the tubular cardia could easily be mistaken for de novo BE^{113,115}. But while the threat of cancer may not in itself question the use of SG, we will still have to deal with the high prevalence of esophagitis that is demonstrated across most studies.

In contrast to many other countries and the position statement from the IFSO¹¹⁶, Swedish health care has not been using routine endoscopy either before or during the follow-up after bariatric surgery, regardless of procedure. Based on the emerging data on GERD after SG, the Swedish Society for Metabolic and Obesity Surgery (SFOK) have been discussing the need of advocating for at least 1 mandatory gastroscopy 5 years after SG and a recommendation to consider preoperative endoscopy before SG^{112,114}. The final decision was, however, to wait for conclusive prospective evidence, in light of the less alarming recent reports on BE^{113,115,117}.

The Swedish healthcare system is still under extra pressure from the Covid-19 pandemic, a new screening program for colorectal cancer is being implemented, and the healthcare system would have struggled to harbor an additional new “screening procedure”, which furthermore may not be needed. At present there is not a national consensus for endoscopic surveillance after SG, but a rising awareness of the problem among bariatric surgeons has led to a very low threshold to refer patients with SG for endoscopy.

2.5 PARTICIPANTS

The demographics of the Swedish patients undergoing bariatric surgery are described in the SOReg annual reports⁷⁶. In comparison to worldwide demographic data from a survey by IFSO¹¹⁸, it can be concluded that with regards to BMI, age, and proportion of males, Sweden is fairly average. It does, however, appear as though the Swedish patient has a slightly lower degree of comorbidities than the average global patient.

In table 1, demographic data from SOReg (2014-2020) is presented together with demographic data for cohorts studied in this thesis¹¹⁹.

Table 1. Demographics at time of surgery in Papers II - IV, as compared to the Scandinavian Obesity Surgery Registry (SOReg, 2014-2020).

<i>Variable</i>	<i>SOReg</i>	<i>Paper II</i>	<i>Paper III</i>	<i>Paper IV</i>
<i>Number of patients (n)</i>	<i>37 915</i>	<i>1 735</i>	<i>115</i>	<i>22 641</i>
<i>Sex (% male)</i>	<i>22.4</i>	<i>26.1</i>	<i>10.0</i>	<i>24.0</i>
<i>Age at time of surgery (years)</i>	<i>41.0</i>	<i>42.9</i>	<i>N/A</i>	<i>40.6</i>
<i>Body mass index (kg/m2)</i>	<i>41.0</i>	<i>40.8</i>	<i>42.8</i>	<i>41.7</i>
<i>Diabetes (%)</i>	<i>12.1</i>	<i>12.9</i>	<i>13.0</i>	<i>13.8</i>
<i>Hypertension (%)</i>	<i>23.9</i>	<i>29.3</i>	<i>N/A</i>	<i>25.6</i>
<i>Dyspepsia (%)</i>	<i>10.2</i>	<i>4.5</i>	<i>N/A</i>	<i>12.8</i>
<i>Smokers (%)</i>	<i>12.4</i>	<i>9.8</i>	<i>25.0</i>	<i>31.1</i>

As moderate and severe dyspepsia was an exclusion criterion for BEST, the lower proportion of dyspepsia was expected among the patients in Paper II. The low number of men in Paper III has no clear explanation (speculatively it could be associated with a larger diameter of intestine and thereby a lower sensitivity to kinking at the JJ). More prevalent smoking in cohorts in Paper III and IV may be due to primary surgery being performed earlier, when smoking was more prevalent among the general public (14% daily smokers in 2006 versus 6% in 2022)¹²⁰.

3 AIM

The overall aim of this thesis is to improve outcomes in bariatric surgery by optimizing procedure selection and surgical technique.

More specifically, a large-scale RCT comparing SG and RYGB in adults undergoing primary bariatric surgery, BEST, was designed and initiated (Paper I).

In addition, the following questions were addressed:

- What are the comparative perioperative outcomes after SG and RYGB? (Paper II)
- Can revisional surgery entail sustained amelioration of postprandial negative symptoms after RYGB? (Paper III)
- Is the surgical strategy for construction of the JJ in RYGB associated with early and late risk of small bowel obstruction? (Paper IV)

3.1 AN OVERVIEW OF THE PAPERS IN THE THESIS

Table 2. Papers in this thesis at a glance. JJ, Jejunojejunostomy. RCT, randomized controlled trial. RYGB, Roux-en-Y gastric bypass. SG, sleeve gastrectomy. SOReg, Scandinavian Obesity Surgery Registry.

	<i>Paper I</i>	<i>Paper II</i>	<i>Paper III</i>	<i>Paper IV</i>
Study Design	Registry-based RCT	Registry-based RCT	Retrospective cohort	Observational registry
Study Period	2015-2022	2015-2022	2013-2017	2012-2019
Intervention /Exposure	Randomization to SG or RYGB	Randomization to SG or RYGB	Re-operation for dysfunction of the JJ	Method of JJ construction
Data Sources	SOReg, national registries	SOReg, Swedish Total Population Register	Medical records, patient interviews	SOReg, Swedish National Patient Registry
Number of Patients	-	1 735	115	23 448
Primary Outcomes	Weight loss and Substantial adverse events over 5 years	Perioperative outcome	Amelioration of symptoms suggestive of JJ dysfunction	Small bowel obstruction at short- and long-term follow-up

4 BEST (PAPERS I AND II)

4.1 BEST BACKGROUND

In the time leading up to initiating BEST, the proportion of patients undergoing SG was increasing in Swedish bariatric surgery. There was a growing interest in the procedure, including from surgeons, other healthcare professionals, and patients. The surgical results in the short- and intermediate-term seemed comparable to those after RYGB. Over time, emerging data suggested that the small- and intermediate-sized RCTs that had been conducted were insufficiently sized to demonstrate any true differences between SG and RYGB¹²¹⁻¹²⁴.

The time frame for introduction of SG in Swedish bariatric surgery coincided with an increase in long-term complications after RYGB (pain syndrome after internal herniations etc., see section 2.3.2 and 5) and the potential of similar outcomes in terms of weight loss, but fewer complications was alluring. There was also a group of patients for whom RYGB was never a good choice (adhesions, etc.) and in those situations SG seemed to offer a good alternative.

With the introduction of SG there was suddenly a possibility for patients to express a preference for having either procedure. There is a wide variety of reasons behind the individual patient's preferences that should be thoroughly explored in the preoperative decision-making.

4.2 THE BEST METHOD

BEST is a pragmatic randomized registry-based clinical trial comparing SG and RYGB in adults with a BMI between 35 and 50. It was of importance that the protocol did not deviate too far from the standard of care for this large multicenter trial to be feasible, and thus some (minor) local variations were allowed. The aim was that the randomization should essentially be the only major deviation from standard care, which allowed many hospitals to participate. A strength of this approach lies in its generalizability to real-world health care.

4.2.1 ENDPOINTS

Data from previous studies suggested that excess weight loss 5 years after RYGB was slightly larger than after SG, but that the number of substantial adverse events of SG might be lower compared to after RYGB^{102,125}.

Considering the balance between the possibility of better outcome in terms of weight loss or reduced risk of adverse events led to evaluating two co-primary objectives in BEST:

- The hypothesis for non-inferiority; that the efficacy of SG as compared to RYGB will be within a 5% non-inferiority margin.
- The hypothesis for superiority; that patients randomized to SG will experience >35% less substantial adverse events than those randomized to RYGB.

If both these hypotheses are true, the SG should in general terms constitute a superior option compared to RYGB in primary bariatric surgery.

The advantage of the design with two co-primary endpoints is its applicability to clinical practice, as we assess the two most important outcomes in the same trial. The design also considers that weight loss is not the only, and sometimes not even the most important, outcome in bariatric surgery. Weight loss can to a certain extent be a surrogate variable for many of the general health improvements but should be balanced to the flip side of the coin, i.e. the adverse outcomes associated with surgery.

In considering possible long-term adverse outcomes after surgery, and striving to capture more than the serious adverse events (SAE), a list of predefined “substantial” adverse events was created (Paper I, table 1). The strength of this construction is in capturing the reality of which outcomes may matter and substantially effect patients, the weakness in that it has no clear comparators in literature.

4.2.2 REGISTRY-BASED RCT

Several members of the study group had recently been involved in conducting a registry-based RCT to study closure of mesenteric defects within SOReg, and it was clear to all that this was a successful concept^{86,126}. Using the registry as a case report form (CRF) would mean minimal extra time and effort for the participating hospitals. The follow-up timepoints in SOReg had been considered to be clinically relevant, which suited the BEST trial well, and the detailed questions in the registry covered most questions outlined in the study

protocol. Many variables are non-mandatory in SOReg but all collaborators participating in BEST agreed to report on all of them. Additionally, 4 extra questions were added to the follow-ups from 1 year and beyond to capture the predetermined substantial adverse events.

The use of the registry as CRF comes also with the added possibility to compare the study participants with the registry since all data is collected in the same manner at the same timepoints, and can thus show clearly if the randomized study patients are representative of the registry population¹²⁶.

4.2.3 RANDOMIZATION

The trial initially used envelope randomization, but when funding was secured, a computerized randomization module was introduced in SOReg. When identifying an eligible patient (age, BMI), a pop-up window asked if the patient should be included in BEST. If not, questions on reason for non-participation were posed, facilitating upcoming analyses on the trial's generalizability. If the patient agreed to participate and was to be included in BEST, randomization was automatically performed within the registry (figure 6).

BEST-studien, inkludera eller exkludera patient	
Stämmer nedanstående information från basregistreringen?	
Har skriftligt intyg inhämtats	Ja
Patienten bedöms olämplig att opereras med någon av metoderna	Nej
Tidigare genomgången bariatrisk kirurgi eller antirefluxkirurgi	Nej
Finns medelsvår-svår refluxsjukdom eller större hiatusbräck	Nej
Planeras annan samtidig signifikant kirurgi	Nej
Har patienten inflammatorisk tarmsjukdom	Nej
Har fyllt i EQ5D-5L och SF36/OP	Ja

Till basregistreringen Exkludera patienten Inkludera patienten

Figure 6. The BEST randomization module pop-up in SOReg. [Translation: BEST-Study, include or exclude patient; Is the following information from baseline registration correct?; Written consent obtained (Yes/No); Patient considered unsuitable for surgery with either one of the procedures (Yes/No); Prior bariatric surgery or anti-reflux surgery (Yes/No); Presence of moderate-severe gastroesophageal reflux disease or larger hiatal hernia (Yes/No); Is larger concomitant surgery planned (Yes/No); Is patient diagnosed with inflammatory bowel disease

(Yes/No); Have EQ5D-5L and SF36/OP (questionnaires) been completed (Yes/No); To baseline registration; Exclude patient; Include patient.]

4.2.4 BLINDING

For obvious reasons it is hard to blind the surgeons in an interventional surgical study such as BEST. But could it be blinded to the patient? This was considered but eventually abandoned, mainly for safety reasons. The primary concern was that time could be wasted in trying to unblind the procedure in critically ill patients.

If blinding was to be used, there was also the question of when to unblind. Although the primary endpoint was at 5 years, the intention has always been to follow-up even longer. We also considered that the hard endpoints, such as death, re-operations, etc., would not be affected by patients' knowledge.

In the initial protocol the patients were to be informed about allocation post-operatively. Among the initial eligible patients there were, however, several who declined participation based on the lack of information before surgery on which procedure was to be performed. Additionally, "in-theater randomization" was a challenge for logistic reasons for those hospitals having different equipment for the two procedures.

The steering committee took the pragmatic decision that randomization could be performed at earliest 24 hours before surgery, and that patients could be informed about allocation either before or after surgery. It was also emphasized that patients should confirm consent before randomization to avoid cross-over.

4.2.5 POWER

The primary power calculation in 2014 was based on an assumption of an incidence of 5% substantial adverse events in the RYGB group, a 35% lower incidence in the SG group, and 15% of participants lost to follow-up. These assumptions suggested that 4000 patients were needed in order to detect a statistically significant difference between the groups (at 2.5% level) with 90% power for both co-primary endpoints.

However, an analysis of SOReg data in 2017 showed that the incidence of substantial adverse events for RYGB was at least 13%, prompting a recalculation, and an update of numbers needed to include to 2100¹²⁷. New data from Courcoulas *et al.*¹²⁸ and Howard *et al.*¹²⁹ revealed an even higher SAE rate over 5 years for RYGB (> 25%). Together with the severe consequences the Covid-19 pandemic had on performing elective surgery, this prompted the

BEST steering committee to, in late 2021, perform an additional analysis for primary endpoints^{128,129}.

In this analysis, performed by an independent statistician, not only data from the above-mentioned papers, but also the available 2-year follow-up data for included BEST patients were used. The conclusion was that BEST most likely had reached a sufficient power to analyze both primary endpoints and it was decided to end recruitment to BEST on December 31, 2021, with the last operating day for recruited patients set for March 31, 2022. In total, 1735 patients were included and operated.

The argument can be made that maintaining the higher participant numbers would have resulted in better power to detect differences in outcomes between the pre-defined subgroups (sex, age, BMI) and perhaps enable stronger conclusions regarding secondary endpoints. However, when there are enough patients included to address the primary endpoints, it would be unethical to include additional patients.

There was also a practical argument; including patients in this trial had proven to be harder than expected, and with Covid-19 slowing inclusion rates down even further, there had already been an extended recruitment period in BEST. Thus, we had science, ethics, and “reality”, all in agreement to end inclusion.

4.2.6 GASTROSCOPY – PREOPERATIVELY AND AT 5 YEARS POST-OPERATIVELY?

Preoperative gastroscopy has not been mandatory for RYGB nor SG patients in Sweden (as this very rarely changes surgical approach¹³⁰). Virtually all patients participating in BEST are publicly funded, and thus not offered a preoperative gastroscopy. When emerging data showed an increased risk of GERD and BE after SG^{108,131}, the BEST steering committee issued a complementary statement recommending preoperative gastroscopy, but the reality in many hospitals was, that if gastroscopy was mandatory for patients in BEST, several sites would stop including patients. This is an example of when the very best of scientific intentions can collide with clinical (and political) reality.

After further discussion, the BEST steering committee decided to amend the protocol with a non-mandatory gastroscopy at 5 years post-operatively, which was strongly encouraged. If applicable, participants sign an additional informed consent as gastroscopy was not originally planned.

Data concerning GERD and BE will likely not be conclusive in BEST but considering the size of the trial, the data generated will likely still be of interest.

4.2.7 PER-PROTOCOL ANALYSIS

The standard analysis of randomized trials is the intention-to-treat analysis, where participants are analyzed with the group they were randomized to, regardless of which treatment they actually received¹³². This maintains the balance created by randomization and reduces the risk of over-estimating the possible treatment effect.

When considering the perioperative outcomes and the surgical safety perspective in BEST, we assumed that the procedure actually performed is of greater interest than the procedure randomized to, and thus the BEST perioperative analysis is a per-protocol analysis. The patients who crossed over and received the procedure they were not randomized to are analyzed according to treatment received. With an intention-to-treat analysis the possible adverse events of the cross-over patients may be assigned to the “wrong method” and skew information regarding perioperative risk.

4.3 BEST PERIOPERATIVE RESULTS

BEST included, randomized, and operated 1735 patients from October 6, 2015 to March 31, 2022. A total of 878 patients received SG and 857 RYGB. Inclusion started in 5 centers and in total 23 hospitals included patients, 20 in Sweden and 3 in Norway. As seen in figure 7, there are large differences in the number of patients included at the different hospitals. Some centers, including the 3 with the lowest inclusion numbers, stopped performing bariatric surgery during the trial. Participants recruited at those hospitals were transferred to other “BEST centers” to ensure adequate follow-up.

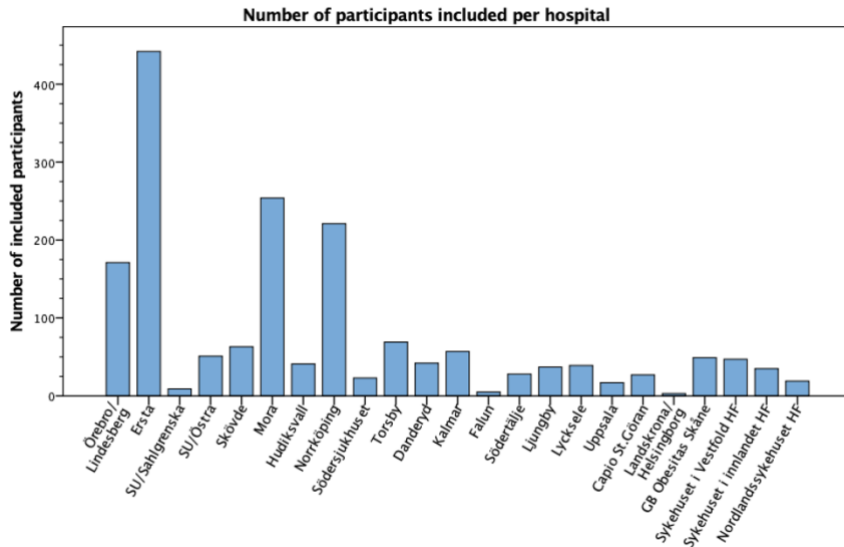


Figure 7. Participants in the Bypass Equipose Sleeve Trial and including hospitals.

An analysis of demographic and baseline data (age, sex, BMI, comorbidities, etc.) showed that the SG and RYGB groups are comparable, as we would expect in a large, randomized trial. The minor existing statistical differences were not deemed clinically relevant (Paper II, Table 1).

Surgical data showed that the procedures were in general, performed in accordance with the protocol.

There were 10 patients who crossed over from SG to RYGB (8 with hiatal hernia), and 8 from RYGB to SG (6 with adhesions/short mesentery).

There was a high 30-day follow-up rate (99.3%) and no 90-day mortality (100% follow-up). The rate of adverse events at 30 days were low in both groups; 4.6% in SG and 6.3% in RYGB, ($P = 0.11$); odds ratio (OR) 0.71 (95% CI 0.47–1.08). For SAE (Clavien-Dindo score \geq IIIb) the corresponding figures were 1.7% and 2.7% ($P = 0.19$); OR 0.63 (95% CI 0.33–1.22).

In a deeper analysis of the re-operations within 30 days of bariatric surgery (table 3), it was found that bleeding was more common in SG whereas bowel obstruction was more abundant in RYGB, with only the latter showing statistically significant.

Table 3. Re-operations post-operative day 0-30 after sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB). Number of re-operations as defined by diagnosis and proportion of participants with complications within each group (SG/RYGB), (n (%)).

	SG (N=14)	RYGB (N=23)
<i>Abscess</i>	0 (0)	2 (9)
<i>Bleeding</i>	8 (57)	5 (22)
<i>Bowel obstruction</i>	0 (0)	7 (30)
<i>Leakage</i>	3 (21)	8 (35)
<i>Bowel injury</i>	2 (14)	0 (0)
<i>Abdominal wall hernia</i>	1 (7)	1 (4)
<i>Diagnostic laparoscopy without diagnosis</i>	1 (7)	2 (9)
<i>Revision (e.g. SG to RYGB)</i>	1 (7)	0 (0)

4.4 A PROMISING START

The perioperative outcomes (Paper II) suggested that BEST has laid a solid foundation to eventually address the primary endpoints in order to compare the long-term efficacy and safety of SG and RYGB. For a multinational, multicenter setting, the complication numbers show a reasonable homogeneity between clinics as well as similar complication rates between procedures.

Although complication rates did not differ statistically, there was a trend of higher numbers of adverse events after RYGB compared to SG. The pattern of adverse events also varied between the procedures. For most complications, the rates were very similar, whereas, unsurprisingly, small bowel obstruction occurred only in RYGB. One can note that re-operation for small bowel obstruction alone was responsible for the absolute majority of the higher numbers of re-operations after RYGB (7/23 vs. 0/14).

From an international perspective, the most interesting results in Paper II are perhaps not the low number of adverse events for SG, but the lack of statistically significant differences compared to RYGB. Such a low risk of complications when using the RYGB is somewhat in contrast to international reports^{125,133} and may reflect the larger experience in performing RYGB surgery in Scandinavia. Thus, BEST will indeed compare a low-risk RYGB to SG. Interpretation of BEST results in clinical practice may therefore need to

be evaluated regarding whether the context of complication rates is relevant for the current practice.

The multicenter, multi-surgeon design shows that low complication rates are achievable in both SG and RYGB on a national bariatric surgical level. We believe that annual surgical quality conferences with sharing and discussing the topic of surgical safety and continuous follow-up via SOReg in Scandinavian bariatric surgery, has contributed to a broadly high quality of care. This is also reflected in that the risk of any complication or a severe complication in Swedish bariatric surgery has halved over 15 years^{76,83}.

5 ACKNOWLEDGING A SURGICAL PROBLEM (PAPER III)

5.1 BACKGROUND - IS THERE A PROBLEM AT THE JJ?

In the years from 2012 and onwards we noticed an increasing number of post-RYGB patients with severe abdominal pain. At our tertiary center, Sahlgrenska University Hospital, the numbers of these patients were growing. Indeed, we were at a surgical peak, with nearly 9000 procedures in Sweden in 2011 (figure 2), but the increase in the number of patients with problems still appeared disproportionate. Standard investigations with computer tomography, ultrasound, and gastroscopy most often did not help identify any problem, and therefore diagnostic laparoscopy became a standard measure. Surprisingly, the laparoscopy often revealed problems at the JJ with kinking or adhesions, and when performing surgical correction, the patients often did better, sometimes for a short period and sometimes lasting.

The typical patient reported postprandial pain where often solid food made symptoms worse than liquids. An additional observation at the time was that patients also presented with complex postprandial hypoglycemia, which did not improve by dietary treatment, and with hypoglycemia episodes that were difficult to predict⁹⁵. Yet another observation was that a number of patients reported a fully functioning RYGB without abdominal pain until an episode of IH with emergency surgery and closure of mesenteric defects, whereafter the acute symptoms disappeared, but chronic problems began.

In the years 2010-2011, an RCT on routine closure of mesenteric defects⁸⁶ was conducted, and although official results had not been reported yet, there was a clinical impression that closure should become routine. However, there were also reports from many Swedish hospitals of small bowel obstruction after mesenteric defects closure.

A hypothesis was that the JJ was sensitive to angling and kinking, and that this occurred more often when closing the mesenteric defect behind the JJ. It appeared also to be a learning-curve effect as modification of closure technique could mitigate those problems. Most bariatric surgeons in Sweden were learning how to close mesenteric defects simultaneously, and Stenberg *et al.* later showed that there was indeed a learning curve¹³⁴. However, it could also

be speculated that a new phenomenon was introduced by closure of mesenteric defects and that symptoms may not always arise immediately after surgery.

In 2015 we decided to perform a retrospective analysis of patients having undergone a surgical intervention for symptoms suggested to be related to JJ problems to see if our hypothesis — “a problem at the JJ” —had any bearing (Paper III).

5.2 A RETROSPECTIVE STUDY DESIGN

We were unable to identify all patients who had been assessed for abdominal pain after RYGB in health care, but a local surgery registry made it possible to identify patients whom had been operated, within the time frame, by a bariatric surgeon with specific surgical codes registered. This may have introduced a risk of selection bias, but there had been a liberal indication for a diagnostic laparoscopy in patients with problems after RYGB.

Repeated data collection was performed to ensure the longest possible follow-up after intervention. The study plan included both a review of medical records as well as patient interviews. The interviews and reviews of medical records were conducted mainly by medical students to minimize bias, and the amassed data was reviewed by a senior bariatric colleague from another hospital to further validate our findings.

More than anything this study aimed at assessing whether there could be a “proof of concept”; that “mechanical problems at the JJ” existed, and that surgical intervention could be helpful.

5.3 RESULTS - ESTABLISHING THE PROBLEM

There were 115 patients included who were re-operated after RYGB due to abdominal pain with a mean age of 41 years (range 19–67 years; 90% women). We managed to define outcomes over a minimum follow-up of 2 years after first surgical revision.

Data demonstrated that RYGB patients that presented with abdominal pain in the upper left quadrant, either only postprandially or with postprandial aggravation, with or without concomitant nausea and complex postprandial hypoglycemia (figure 8) could become symptom-free, or substantially improved after surgical correction of problems at the JJ.

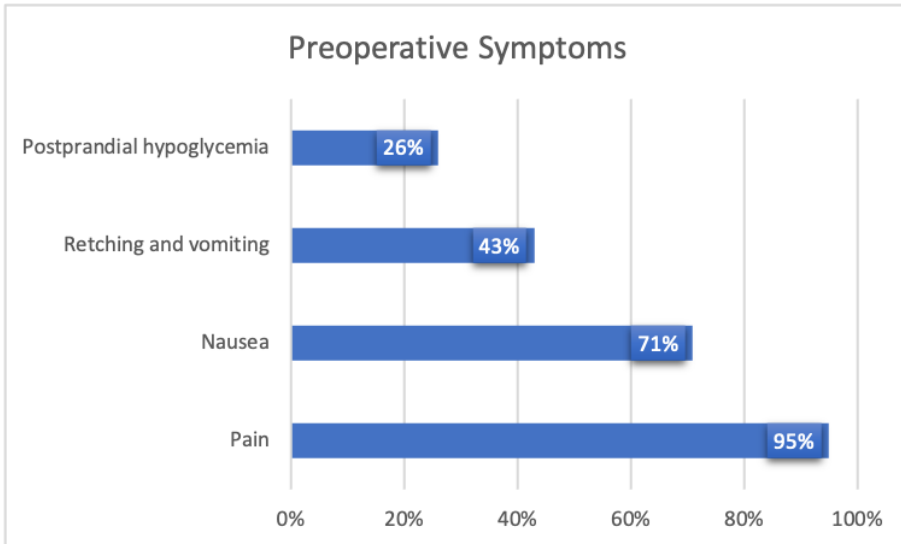


Figure 8. Preoperative symptoms of dysfunction at the JJ. Of the 6 patients who did not have pain as a main problem, 3 had complex postprandial hypoglycemia, 3 had nausea and vomiting.

After surgical revision of the JJ, 44 (38%) patients were symptom-free and 32 (28%) improved. There was no lasting improvement for 31 (27%) patients, and of them, 16 (14%) eventually had a reversal of the anatomy. Eight (7%) patients were lost to follow-up.

Twenty-seven percent of the patients had a history of no symptoms prior to emergency surgery for IH, and of these patients only 3 had had closure of the mesenteric defects at primary RYGB. Thirty-nine percent of patients had both defects sutured at primary RYGB (missing data 21%). Thus, the hypothesis that closure of the mesenteric defects may influence the function of the JJ was supported by our analyses.

Initially, there were often minor adhesiolysis performed, but with time, a more radical approach was employed where simple adhesiolysis was tried initially, but if not successful a complete revision of the JJ was performed. As can be seen in figure 9, multiple re-explorations usually did not add any benefit. As both IH and re-operations performed at other (non-bariatric) hospitals were included in the total, the numbers of surgeries must be interpreted with care. If the problem cannot be identified and rectified after a few surgeries at a bariatric specialist center, multiple surgeries may become a part of the problem and probably rather add to further issues such as chronic pain.

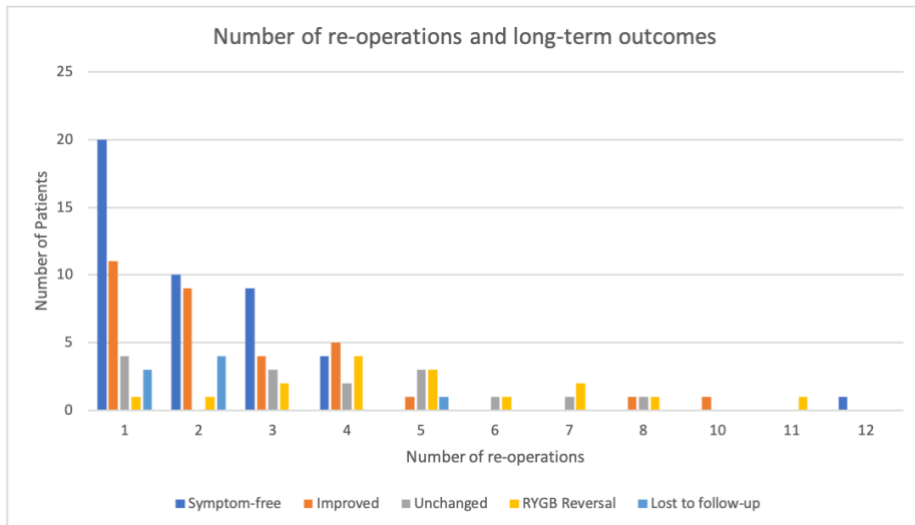


Figure 9. Graph depicting the number of re-operations- and the long-term outcomes. Due to the method of registry, operations for internal herniation may be included in the total number of re-operations. Total number also includes procedures at other hospitals.

5.4 ACKNOWLEDGING THE PROBLEM

Abdominal pain after RYGB appears to be a problem, but data are conflicting and it's hard to get a good view of the issue. The limited data available suggests an incidence of approximately 30%¹³⁵. However, indications of pre-existing abdominal pain were identified in approximately 17% of patients¹³⁵⁻¹³⁷. The severity of pain is of great heterogeneity, with most studies using pain affecting daily activities and quality of life at least once a month as the definition of chronic abdominal pain. Bruze *et al.* has shown an increase in hospital admission in a 6-year follow-up after RYGB, both for all cause admission and for gastrointestinal surgery, as compared to the general population¹³⁸.

This study (Paper III) shows that dysfunction of the JJ can be part of the problem and should be a differential diagnosis for the bariatric surgeon treating patients after RYGB.

There is currently no diagnostic tool with sufficient precision to identify dysfunction of the JJ. Although computer tomography and upper

gastrointestinal follow-through (often with food and barium) may add clues, such as a modestly dilated remnant stomach, contrast moving in a retrograde direction in the biliopancreatic limb or even up in the duodenum, or a slow passage over the JJ, the predictive negative value for such investigations appears low.

Based on conclusions in Paper III and clinical experience, we suggest an initial clinical work-up addressing all the common causes of abdominal pain, but indeed also suggest a low threshold for a diagnostic laparoscopy at a center with experience of RYGB complications. Apart from kinking/adhesions at the JJ, findings can include open/partially open mesenteric defects and symptoms stemming from intermittent IH, as well as intussusception. Preoperative discussions should include the possible findings and subsequent remedial intervention including total revision of the JJ. While adhesiolysis sometimes may be enough, there may be a need for revision of the JJ in the next step. If a total revision of the JJ does not resolve the problem, further surgery is often not warranted.

If surgery cannot improve a patient's symptoms, they may benefit from multimodal pain management. In some severe cases, patients eventually might need a reversal of the RYGB anatomy. Although reversal of the anatomy is an option, studies have demonstrated a high risk of complications^{139,140}. Further studies of the effect following reversal of anatomy are needed, and underway.

Psychiatric comorbidities may cloud the picture in patients with complex problems after RYGB. There was a higher level of psychiatric disease among patients with complications in study III. Psychiatric disease and post-traumatic stress disorder (PTSD) were not formally assessed at time of surgery and follow-up. During the study period, the multidisciplinary team at Sahlgrenska University Hospital was expanded through the addition of a psychologist; and it was noted that among the patients with chronic pain and ongoing complex surgical situations there was a substantial number of patients with complex PTSD and other serious psychiatric comorbidities that might impair well-being and affect the perception of, and ability to cope with, abdominal pain¹⁴¹. A clinical observation is that it becomes very difficult when complex surgical problems and complex psychiatric/PTSD problems occur in the same patients. To the best of our knowledge this area has not been previously investigated, although there are studies suggesting an increased risk of worsening of psychiatric symptoms after bariatric surgery, as well as studies suggesting an overlap between benign abdominal symptoms and PTSD¹⁴¹⁻¹⁴⁴.

On a side note, the extensive review of the medical records led to a deeper understanding of the problem, if not to scientifically crystal-clear answers.

6 DOES THE CONSTRUCTION OF THE JJ MATTER? (PAPER IV)

6.1 BACKGROUND

While the scientific process, at least theoretically works strictly step-by-step, the surgical mind does not always follow suit. Working with patients in Paper III, and in the clinic, we became convinced that a problem to solve in RYGB surgery was a dysfunctional JJ. It appeared that the JJ was sensitive to kinking and adhesions, and several different preventative measures were suggested but had not been formally assessed.

6.1.1 TECHNICAL VARIATIONS IN CONSTRUCTION OF THE JJ

The overall aim of the above-mentioned surgical variations was to create a mobile JJ without kinks or hang-ups, and there were mainly 3 ways to achieve this:

1. Closure of the mesenteric defect at the JJ with sutures/clips positioned “deep” in the mesentery (away from the bowel), where special care is taken not to create a kinking at the JJ. (This approach is not a matter of controversy and is generally applied in modern RYGB surgery.)
2. Radial division of the mesentery between the GJ and the JJ (figure10). This provides more mobility to the JJ and prevents adhesion between the staple line of the blind end of the JJ and the proximal Roux-limb.
3. Bi-directional stapling (figures 11 and 12) with transverse hand-sutured closure of the remnant defect aims to minimize the risk for a “waist” formation at the transition from the distal Roux limb to the common channel, where kinks usually occur.

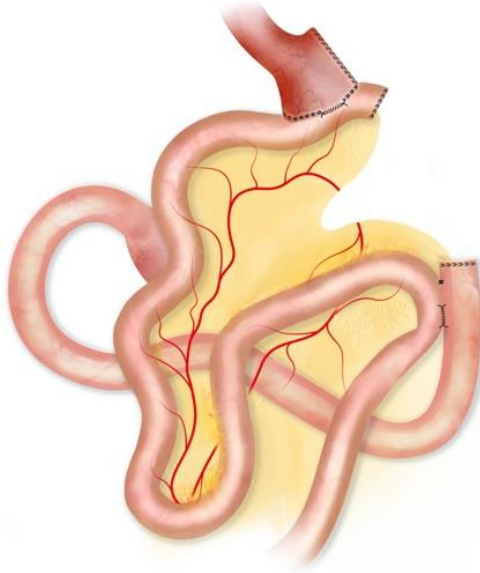


Figure 10. Roux-en-Y gastric bypass with long mesenteric division (unidirectional jejunojunction). Illustration by Jan Funke.

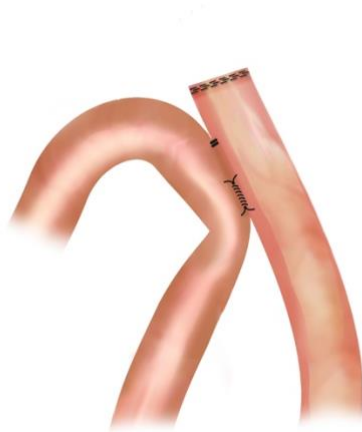


Figure 11. Close up illustration of an original unidirectional jejunojunction with possible kinking. Illustration by Jan Funke.

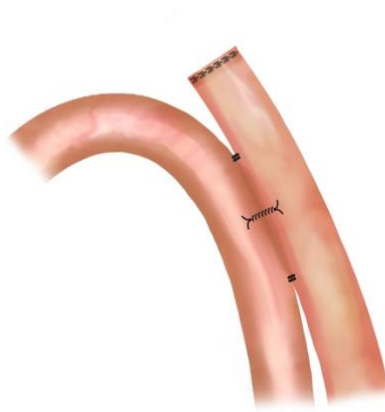


Figure 12. Close up illustration of a jejunojunction constructed with bidirectional stapling and transverse hand sutured closure. Illustration by Jan Funke.

6.2 PREVENTING THE PROBLEM AT THE JJ – AN OBSERVATIONAL STUDY

The registration of several technical procedural variables in SOReg enables observational studies regarding outcomes after various variations in surgical technique for RYGB. For example, SOReg registers whether uni- or bi-directional JJ construction has been used, length of division of mesentery (between GJ and JJ), and closure of mesenteric defects. We used re-operations for small bowel obstruction as the primary endpoint and separated between early interventions (< 30 days) and late interventions. For completeness we also used data from the Swedish National Patient Registry (PAR)¹⁴⁵.

6.3 RESULTS - CONSTRUCTION MATTERS

The study included 23 448 patients who underwent RYGB with closure of mesenteric defects during 2012–2019, and for whom length of mesenteric division and number of cartridges used at the JJ were registered. There was a 30-day follow-up rate of 96.2% and a mean follow-up time for small bowel obstruction of 4.3 ± 2.2 years.

Bidirectional stapling was associated with a lower risk of small bowel obstruction in the short term (HR 0.52, 95% CI 0.29–0.95, $P < 0.05$). Bidirectional stapling was associated with a slightly increased risk of small bowel obstruction in the long term. In the short term, a limited mesenteric division (1–4 cm) appeared to increase the risk of small bowel obstruction (HR 1.66, 95% CI 1.14–2.42, $P < 0.01$), but the long-term risk was unaffected. Mesenteric division did, however, ameliorate the long-term increased risk of small bowel obstruction in patients with a bidirectionally stapled JJ (1–4 cm, HR 0.59, 95% CI 0.38–0.90, $P < 0.05$; ≥ 5 cm, HR 0.30, 95% CI 0.14–0.65, $P < 0.005$).

In a post-hoc multivariate analysis of the original JJ (unidirectional, no mesenteric division) compared to the most modified JJ (bidirectional, ≥ 5 cm mesenteric division) the latter was associated with a lower long-term risk (adjusted OR 0.24, 95% CI 0.12–0.50, adjusted $P < 0.001$) of small bowel obstruction.

In discussions after presenting this study, a hypothesis was proposed that the directionality of the unidirectional JJ may be of importance; whether it is

stapled in oral or aboral direction. A variable concerning the directionality of the unidirectional JJ was added to the SOReg a few years ago, however, it was not in use during the study period and therefore this hypothesis could not be tested in this study.

6.4 IS THE CORRELATION CAUSAL?

Paper IV showed a correlation between bidirectionally stapled JJ and a lower 30-day risk of small bowel obstruction. Our interpretation is that the association, at least to a certain degree, is causal. The hypothesis behind the bidirectional JJ is to allow passage for food (and blood clots), even if a swelling or narrowing should occur. As swelling or clot formation normally happens early post-operatively, it also seems reasonable that this effect should be larger in the short term, a finding that is corroborated by Munier *et al.*¹⁴⁶. In the longer term, bidirectional stapling was associated with a slightly increased risk of small bowel obstruction. The reasons for this are unknown, but there have been speculations regarding a possible increased risk of intussusception due to the larger sized anastomosis.

That mesenteric division alone did not alter the risk of small bowel obstruction in the longer term and increased the risk in the short term with an intermediate length division was unexpected. But as mesenteric division mitigated the long-term risk of small bowel obstruction after bidirectional stapling, it appears to have an impact. The interpretation of our data is that ideally, a long mesenteric division should be added when using bidirectional stapling.

It can of course be argued that the surgeon might matter more than the method. However, this cannot be ascertained as SOReg does not register the individual surgeon for a procedure but instead the surgical site. Surgeons at a certain hospital (site) will most often use the same method. This leads to, that for example bidirectional stapling and long mesenteric division is used both by the very experienced, but also by the younger surgeon in learning, which should mitigate the “surgeon-effect” in this study.

Another measure to decrease the risk of small bowel obstruction after RYGB is to divide the greater omentum, as observed by Josefsson *et al.*¹⁴⁷, and to use sutures instead of clips when closing the mesenteric defects⁸⁷.

7 METHODOLOGICAL CONSIDERATIONS

The method of any study should be tailored to answer the research questions posed. The study method chosen must be not only scientifically valid, but also ethically sound, and the proposed study must be possible to conduct. For example, in situations where there is no clearly formed hypothesis, it would be impossible to construct a good RCT, but a retrospective study can clarify the questions, generate the hypothesis, and take the first steps on the way to answers.

Further, when RCTs are difficult to perform, large observational studies may be a better choice. The large observational study is the basis of registry studies, where prospectively collected data pertaining to a large number of patients can be used. In large registries, even uncommon outcomes may be prevalent enough to show whether there are correlations that may support a hypothesis.

A correctly powered RCT might give reliable answers to the question posed, but the generalizability may be limited by the protocol used. It can be assumed that registry-based RCTs are more generalizable than other RCTs since they capture a real-world situation rather than well-organized best-case scenarios¹²⁶. Using the registry as CRF ensures a higher degree of follow-up at a lower cost, and provides a high degree of information also regarding the non-randomized population and thereby a possibility to assess external validity.

The predefined outcome that is being addressed in an RCT needs to be prevalent enough to be studied in a reasonable number of included patients. What is realistic may depend not only on the actual number of included patients but also on the setting and on the research question, as well as the probability that patients will consent to participate. Trends in society out of the scope and reach of the investigators may influence patients' interest in participating in studies. The increasing numbers of patients with a clearly formed idea of which procedure they preferred influenced the inclusion rate of BEST, as patients who were eligible according to the protocol declined participation to a higher degree than expected. There was also a large variation between centers in the ability to recruit, but overall, 12% of eligible patients consented to participate in BEST, in comparison to 97% in the closure of mesenteric defects trial⁸⁶.

Retrospective studies have several drawbacks and a high risk of bias but can be hypothesis generating. In the review of medical records one can note that the presence of certain symptoms or findings may not be noted, most likely because there was no suspicion/knowledge of a possible link at the time.

An example of this is the presence of hypoglycemia in Paper III where there is a lot of missing information regarding hypoglycemia. It appeared that if surgeons and dieticians did not actively ask for symptoms the information was not captured. Documentation improved when the suspicion of an overlap between symptoms was established in the clinic.

8 ETHICAL CONSIDERATIONS

As in all studies involving humans in health care, we must always act according to the ethics outlined in the World Medical Association's Declaration of Helsinki¹⁴⁸. Which level of invasiveness is acceptable? How do possible harms relate to possible gains – for the study participants and for future patients? Are the questions we pose important and relevant? Can the method used deliver reliable answers? At the core of every research proposal are the questions: Could it be done? Should it be done?

When results are available, should the patients be sought out and informed of the results? Particularly if one treatment/procedure is superior, do we have a moral obligation to find, inform, and treat participants who did not receive the better option? In surgery, this question is even more complex since revisional surgery may not be possible, or may come with a higher risk than the primary procedure. These questions do not have clear answers but are highly relevant for BEST in the future.

In accordance with the Swedish Act (2003:460) concerning the ethical review of research involving humans, the Swedish Ethical Review Authority has an important role in the research process, by reviewing and approving ethical review applications in order to clarify many of the questions above¹⁴⁹.

Another core question is of course that of informed consent. As a rule, the patient must receive both written and oral information, and be given a possibility to have their questions answered before they are asked to participate in a study.

In Paper III the patients were mailed a letter with information about the study and the possibility to contact the research team to decline participation. The patients were contacted by telephone and asked about participation. There were generally not many questions about the study, and it appeared that the participants decided whether to participate based mostly on the written information. The medical students calling could contact a surgeon if anything was mentioned that needed medical attention.

In Paper II the patients usually received the written information by mail, and trial participation was further discussed at a preoperative meeting. In this trial it appeared that the oral information and questions/discussions were of utmost importance to the patients. Discussing inclusion/exclusion criteria and what is known/not known played an important part in allowing the patients to consent to inclusion with confidence.

In Paper IV we analyzed data from SOReg and PAR. SOReg has an opt-out design where patients are given written information about the register, including how to opt out if not consenting to take part. Very few patients opt-out and a handful contact the registry to have their data removed. But in general, people are happy to participate and contribute to the knowledge concerning the different aspects of bariatric surgery. The register allows analysis of data without individual consent by each participant for each study, as long as the study is approved by the Swedish Ethical Review Authority.

9 GENERAL DISCUSSION

Bariatric surgery has a pivotal role in the treatment of severe obesity and metabolic diseases. Outcomes regarding weight loss, and improvement or even resolution of comorbidities, are overall excellent.

As with all surgery, there is certainly still room for improvement. As discussed by Fearon and Pournaras in their comment to study IV, there are two main routes for improving surgery¹⁵⁰:

1. Finding new, better surgical options; and
2. Improving the existing procedures.

These two routes are not necessarily in conflict with one another, as could be argued simply by the existence of this thesis. BEST (Paper I and II) compares an old (RYGB) procedure to a newer one (SG), whereas Papers III and IV on the dysfunctional JJ strive to improve the RYGB.

There is a risk of “throwing the baby out with the bathwater” when discarding an existing surgical technique. A true comparison between SG and RYGB must ensure that both procedures are performed with a high surgical standard; only then can we find true differences that are not surgeon-dependent. This requires large multicenter studies and long-term follow-up, in order to ascertain the safety and efficacy of the procedures.

Understanding the advantages and disadvantages of the procedures in both the short- and long-term allows us to tailor the choice of procedure to the individual patient, improving outcomes and setting realistic expectations for both patients and surgeons.

As surgeons we must acknowledge the myriad of surgical technical variations and consider whether we are indeed sometimes comparing apples and pears. There are vast differences in method, opinion, and capabilities within the fairly homogeneous group that Scandinavian surgeons encompass. On a worldwide scale, surgical techniques and variations abound, and need to be taken into account when trying to place surgery and science in context, in order to learn and evolve.

Historically, the prejudice and stigma towards persons with obesity have been abundant, not only in society but also in medicine. The idea that you should “just get a grip and lose the weight” is common. Adding to the actual knowledge about obesity and its treatment helps to counteract this

disinformation. Persons seeking or referred for bariatric surgery should be given high quality information regarding expected outcomes and inherent risks, as well as receive updated information on obesity and its complex causality. Health care should thus help the patients to make informed decisions and help lighten the burden of stigma.

10 CONCLUSIONS

With this thesis I conclude that:

- Both SG and RYGB can be performed safely and with similar low perioperative risk in adult patients undergoing primary bariatric surgery, although the pattern of complications may differ.
- Most patients having negative postprandial symptoms after RYGB can improve or even become symptom-free after surgical revision of the JJ.
- Variations in the surgical construction of the JJ are associated with the risk of small bowel obstruction, in the short- as well as long-term.
- Bidirectional stapling of the JJ with a long mesenteric division was associated with the lowest risk of small bowel obstruction (figure 13).

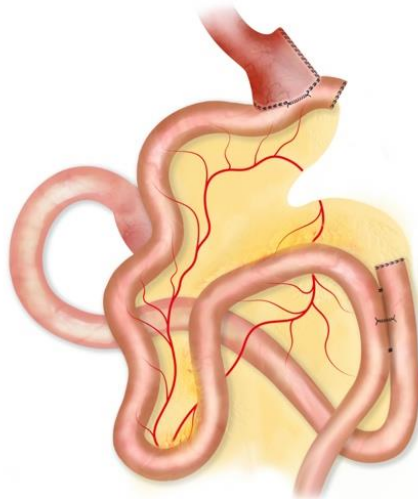


Figure 13. Roux-en-Y gastric bypass with bidirectional jejunojunction and long mesenteric division. Illustration by Jan Funke.

11 FUTURE PERSPECTIVES

In Papers I and II we report an outline for the BEST trial and a good start to set the stage for what is to come. In the future for BEST lies 2-year outcomes (weight loss and comorbidities), a comparison to unrandomized SOReg patients, and of course the 5-year outcomes of weight loss and substantial adverse events. And after that - onwards for long-term follow-up.

In Papers III and IV we have concluded that the JJ is indeed the Achilles heel of RYGB, and that it is possible, to some extent prevent the problems of the JJ. In study III we also show that revision of the JJ can help the patients. There are, however, several unanswered questions:

- Can we refine our diagnostics? There are variations of upper gastrointestinal swallow /follow-through studies with food and contrast, or contrast in food, but to the best of our knowledge, no consensus on how to perform nor interpret them. This is an area for future improvement together with our colleagues in radiology.
- How do we resolve the problem once it exists? We have an idea about what to do – revise the JJ – but in which way is it best done?
- When we look at the preventive measures, does the directionality of the unidirectional JJ matter?
- Is it possible to take the next scientific step comparing surgical techniques for construction of the JJ in a prospective randomized study?

Surgery often moves faster than science. In order to advance surgery, we need to be innovative, brave, and humble. We must have inquisitive minds, striving to find new answers and new solutions to help our patients, but humble in knowing what we do not yet know, seeking the answers as we go. And we must always strive to follow the science; retrospectively to generate hypotheses, observationally to see if a hypothesis can be dispelled, and finally, with the RCT see if we can prove its worth. Surgery may be partially an intuitive craft, but science gives a structure and framework, and a way to move knowledge forward.

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