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Gastrointestinal Physiology and Results following Bariatric Surgery – the

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Abstract
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The number of operations for morbid obesity is rising fast. We have examined aspects of postoperative physiology and results after bariatric surgery.

The pH in the proximal pouch after Roux-en-Y gastric bypass (RYGBP) was investigated with catheter-based and wire-less technique. Gastric emptying, PYY-levels in the fasting state and after a standardized meal was evaluated after biliopancreatic diversion with duodenal switch (DS). A clinical trial was undertaken, comparing DS to RYGBP in patients with BMI>48. Main outcome variables were safety and long-term weight results as well as abdominal symptoms and laboratory results.

Patients with stomal ulcer had significantly lower pH in their proximal gastric pouch as compared to asymptomatic control subjects. Long-time pH measurements with the wire-less BRAVO-system were feasible and demonstrated pH<4 in median 10.5% of the time in asymptomatic post-RYGBP patients. After DS, the T_{50} of gastric emptying was 28±16 minutes. PYY-levels were higher after DS than in age-matched control subjects. BMI-reduction was greater after DS (24 BMI-units) than after RYGBP (17 BMI-units) in median 3.5 (2.0-5.3) years after surgery ($p<0.001$). Fasting glucose and HbA1c levels were lower one and three years after DS as compared to RYGBP. On the other hand, DS-patients reported having more diarrhea and malodorous flatus.

This thesis has resulted in deepened knowledge. Acid produced in the proximal pouch is an important pathogenetic factor in the development of stomal ulcer after RYGBP. However, symptom-free patients have an acidic environment in the proximal Roux-limb as well. After DS, gastric emptying is fast, but not instantaneous, and PYY-levels are high. DS results in superior weight reduction and better glucose control as compared to RYGBP in patients with BMI>48. We believe that DS has a place in surgical treatment of the super-obese, even though symptoms of diarrhea and malodorous flatus are more common after DS.

Keywords: Bariatric surgery, gastric bypass, biliopancreatic diversion with duodenal switch, PYY, stomal ulcer, gastric emptying

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″Οί παχὲες σφὸδρα κατὰ φὺσιν, ταχυθὰνατοι
γὶνονται μᾶλλον τῶν ὶσχνῶν″

“Those who are constitutionally very fat have less
power to successfully resist a severe disease”.

Hippocrates aphorisms II

Till Anna, Ebba och Agnes

List of Papers

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

I Hedberg J, Hedenström H, Nilsson S, Sundbom M, Gustavsson S. (2005) Role of gastric acid in stomal ulcer after gastric bypass. *Obesity Surgery*, 15(10): 1375-1378

II Hedberg J, Hedenström H, Sundbom M. Wire-less pH-metry at the level of the gastrojejunostomy after Roux-en-Y gastric bypass-a novel use of the BRAVO™-system. Submitted

III Hedberg J, Hedenström H, Karlsson FA, Edén-Engström B, Sundbom M. (2010) Gastric emptying and postprandial PYY-response after biliopancreatic diversion with duodenal switch. Obesity Surgery, E-pub ahead of print sept 2010

IV Hedbeg J, Gustavsson S, Sundbom M. Superior weight loss and glucose control three years after duodenal switch compared to Roux-en-Y gastric bypass. Submitted

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Abbreviations

BMI	Body mass index
BPD	Biliopancreatic diversion (=Scopinaro procedure)
CT	Computed thomography
DS (=BPD-DS)	Biliopancreatic diversion with duodenal switch
EBW	Excess body weight
E(B)WL	Excess (body) weight loss
JIB	Jejunoileal bypass
LRYGBP	Laparoscopic Roux-en-Y gastric bypass
PYY	Peptide YY
RYGBP	Roux-en-Y gastric bypass
SAGB	Silicone adjustable gastric banding
VBG	Vertical banded gastroplasty

Introduction

A major dietary shift took place among humanoid primates about two million years ago with increased reliance on meat[1]. This was made possible by tool use and social organization and the changed diet was instrumental for human evolutionary divergence from our primate relatives[2]. The adaptation to more energy dense food compensated for the increased metabolic cost of a larger brain size[3] and the drive to obtain energy dense food is therefore an integral part of human nature. The ability to store calories when possible is important in an environment with seasonal differences in food availability[4]. A distinct change in energy availability occurred with the invention of agriculture and animal husbandry about 10000 years ago[5]. In recent decades, food availability has increased in large parts of the world, at the same time as the requirements for manual labor has decreased, resulting in a major increase in obesity[6-9]. Today overweight is the most common form of malnutrition[10].

Many efforts to treat obesity have been made. The use of diets of varying composition in order to loose weight have been advocated since the time of Hippocrates[11]. In the 20th century, medical treatment has been introduced. These drugs were introduced with great hope of solving the problem of obesity, but systematic evaluation has shown limited efficacy in the long run[12]. Bariatric surgery was introduced in the 1950s and has been refined up until today[13-21]. The refinement of surgical techniques has led to increasing safety and efficacy and today, there is a wide spread consensus that surgery is the best treatment modality for the morbidly obese patient[22]. Bariatric surgery (from the Greek word for weight: baros) is currently expanding rapidly in the world[23], as are the efforts to optimize the operations and studying the post-operative physiology. In the present thesis the focus will be on the results of surgical treatment for obesity in the adult patient. The topic of overweight and obesity in children and adolescents is also very important, but beyond the scope of the present summary.

Background

Definitions and diagnostic methods

The most commonly adopted method to define overweight and obesity is to calculate the BMI (Body Mass Index). BMI is defined as body weight in kg divided by body length in meters squared. This gives the unit measure of kg/m^2, which is often left out. With this method a normal BMI is 18.5-24.9. Obesity is divided into classes of severity; Class I is BMI 30-34.9, Class II is BMI 35-39.9 and class III is BMI of 40 or above, also often referred to as morbid obesity [24, 25]. With increasing numbers of obese patients with very high BMI, further subdivision has been developed, and patients with BMI>50 are referred to as super-obese, and those with BMI>60 as super-super obese. Many other definitions of overweight and obesity have been in use over the years. The Metropolitan Life Insurance Company has defined the weight at which the mortality is the lowest for any given body length[26]. In the American literature Excess Body Weight (EBW) is often used. This is the weight above the ideal weight according to these tables. Excess weight loss (EWL) or excess body weight loss (EBWL) is often used as a measure of success of weight reduction programs. It is often expressed as % EBWL, which refers to the weight reduction divided by the former EBW.

Although BMI is the most commonly used description of weight, it has some drawbacks. It does not reflect the body composition, and for instance, someone with a very big muscular mass can have a high BMI without health risks. Nor does it take into account the distribution of fat in the body. Visceral fat is known to be associated with more cardiovascular risks than subcutaneous fat[27] and waist circumference as well as waist to hip ratio addresses this. To refine measurements of body composition, more advanced diagnostic methods, such as bioimpedance[28], air displacement pletysmograghy (the so called BOD POD)[29] or radiological methods[30] have been developed but are generally not used outside scientific studies. BMI is a very simple and straightforward measurement and it can also be calculated with self-reported weight. This gives an opportunity to evaluate treatments without a visit to the health care facility and a rising use of BMI is seen in the literature.

Epidemiology of obesity

In the last 25 years, obesity has become a worldwide epidemic, beginning in the western countries. The prevalence has been estimated to be as high as 1.7 billion people[10], and for the first time in the western civilization the coming generation may have a shorter life expectancy than its parents as a result of this[31]. In the US, more than one third of the population is obese and nearly two thirds overweight[8]. This represents more than a 100% increase of the obese population in the last 25 years. Given that other western countries often tend to follow USA, it is encouraging to see that since 2004, the trend of increasing obesity may have abated in the US[32]. In Sweden, obesity is rising fast and it is mostly widespread in the lower socioeconomic population[33, 34]. In the male population, 52 % have a BMI>25, of which 11 % are obese. For the female population these percentages are 36 and 9 respectively [35].

Risks of obesity

Mortality in cardiovascular diseases, such as stroke, coronary heart disease, congestive heart failure and cardiomyopathy, is higher in the overweight and the obese[36, 37]. In addition to mortality related to these risk factors, mortality is also independently linked to overweight per se[38-40]. A man in his twenties with a BMI>45 statistically loses 13 years of his life compared to a normal weight person, and this can represent a loss of 22% of expected life span[41].

Hyperlipidemia and hypertension are linked to obesity[42]. Moreover, the visceral fat accumulated in morbidly obese patients gives rise to an inflammatory drive, which is an important factor in the development of artherosclerosis[36, 43].

Type 2 diabetes mellitus has an independent relationship with a high BMI, as well as with weight gain in adult life[44, 45]. The level of insuline resistance and risk of diabetes is also correlated to the amount of visceral fat[46].

Obstructive sleep apnoea, a condition with nighttime desaturations due to apnoeic episodes, is another important comorbidity in obese patients. Of the patients with sleep apnoea, 70% are obese[47]. This condition leads to daytime drowsiness and risk of accidents, but is also in itself a risk factor for cardiovascular disease[47, 48].

Increasing evidence for the relationship between obesity and cancer are mounting. Several types of cancer are linked to obesity, abdominal fatness or both. These are adenocarcinoma of the esophagus, pancreatic cancer, colorectal cancer, breast cancer in postmenopausal women, endometrial cancer, kidney cancer and gallbladder carcinoma[49]. It is estimated that the proportion of cancer attributable to overweight or obesity in the US is as high as 14 % in men and 20 % in women[50].

Diets and behavioral treatment of obesity

A plethora of self-help literature is on the market. The claim to have found the solution to overweight is a good base for commercial success. Weight-loss in the short term is not hard to accomplish, but weight maintenance over time is very hard to achieve. There is support in the literature that weight maintenance is possible for up to 20% of patients undergoing diets, when defined as loosing 10% of their original body weight for at least a year[51]. In the few studies with long-term follow up these figures are less encouraging[52].

Medical treatment of obesity

Over the years, many drugs have been tried in the pharmacological treatment of obesity. Different amphetamines have been in use since the 1940s[53]. Today, there are two drugs for treatment of obesity on the Swedish market:

- Orlistat is a lipase inhibitor and decreases the ability of pancreatic lipase to absorb intestinal fat with about 30%. It has side effects related to this mechanism of action in the form of steatorrhea. The weight loss has been reported to be 8-10 kg after one year and 5-8 kg after two years[12, 54].
- Sibutramin is an inhibitor of serotonine and noradrenaline reuptake in the central nervous system. This leads to decreased feeling of hunger, and a decreased calorie intake. It is contraindicated in patients with coronary heart disease, congestive heart failure or a history of stroke. The weight effect is similar to Orlistat and positive effects on serum lipids have been shown[12, 55].

Surgical approaches to the treatment of obesity

The only treatment with proven effect on the negative consequences of morbid obesity is surgical modification of the gastrointestinal tract[56]. Over the years, various surgical principles have been utilized with the goal to achieve lasting weight-loss whilst minimizing undesirable side effects.

The jejunoileal bypass or shunt (JIB), in which a large part of the small intestine is bypassed was first described in the 1960s[57]. Initial encouraging results led to a rise in popularity of this method. However, metabolical medium to long-term complications in the form of liver imparement, renal stones and electrolyte disturbances as well as problems with weight regain eventually led to abandonment of this procedure[13, 58-61].

In the 70's, horizontal gastroplasty was used in an effort to hinder excessive food intake without interfering with the normal food pathway[14]. This

technically straightforward operation was well tolerated but had the problem of dilatation of the fundus and staple line disruption, both of which led to weight regain.

The vertical stapled gastroplasty (VBG) was developed in the 80's, in an effort to overcome these problems [15]. In this operation a fixed band is placed from a hole made in the corpus of the stomach to the lesser curvature. From this hole a staple line is constructed up to the angle if His and in this fashion all ingested food is led into a small pouch. When constructed along the lesser curvature, the pouch does not dilate and the synthetic band maintains a tight outlet. Band complications, such as band erosion, esophagitis and dysphagia as well as weight regain due to staple line disruption or adaptation of oral intake are associated with this operation[62, 63].

The gastric banding procedure, where a band is placed from the pars flaccida to the angle of His was introduced in the same decade as the VBG and it won some popularity[16]. Refinement of this operation resulted in the silicone adjustable gastric banding procedure (SAGB), in which an inflatable band is placed around the cardia and connected to a subcutaneous port which can be inflated or deflated in order to adjust the stoma size. As in the previously mentioned restrictive procedures, problems of esophagitis, vomiting, dysphagia and band erosion in combination with suboptimal long-term weight results are all described in the litterature[64-66]. Despite this, the SAGB operation is gaining in popularity in the US whereas it is less commonly used in Europe[23].

Gastric bypass, RYGBP

Gastric bypass for treatment of obesity was fist described by Ed Mason in 1967[17]. In this first series, the proximal pouch was constructed by dividing the fundus horizontally and a loop gastrojejunostomy was added, thus creating an operation similar to the Billiroth II procedure, but without the distal resection. A number of modifications of the technique have been made over the years of which the most important ones are the construction of a Roux-limb instead of a loop[67], and making the proximal pouch along the lesser curvature instead of the fundus[68]. These alterations, resulting in the Roux-en-Y gastric bypass (RYGBP), have minimized the problem of bile reflux from an afferent limb[69], and pouch dilatation in the fundic area of the proximal pouch (Figure 1).

With the introduction of surgical staplers, the level of technical complexity decreased and the use of gastric bypass became more widespread even though restrictive operations dominated the bariatric field throughout the 80's. When the laparoscopic era started in the early 90's, the increased popu-

larity of simpler restrictive procedures led to smaller numbers of gastric bypass operations being performed. In 1994, Wittgrove published the first series of five laparoscopic Roux en Y Gastric Bypass (LRYGBP) operations with encouraging results[18]. Handport-assisted laparoscopic gastric bypass does not show any advantages to open surgery in a randomized trial[70].The totally laparoscopic approach however, resulted in fewer wound complications, shorter hospital stay, less morphine use, less incisional hernias and a faster rise in quality of life[71-73].

Today, the number of patients undergoing gastric bypass is increasing rapidly. In Sweden, solely restrictive procedures have become rare and LRYGBP has come to dominate the field. As is the case with the before mentioned bariatric operations, there are specific complications with this technique as well, and they will be discussed in more detail below.

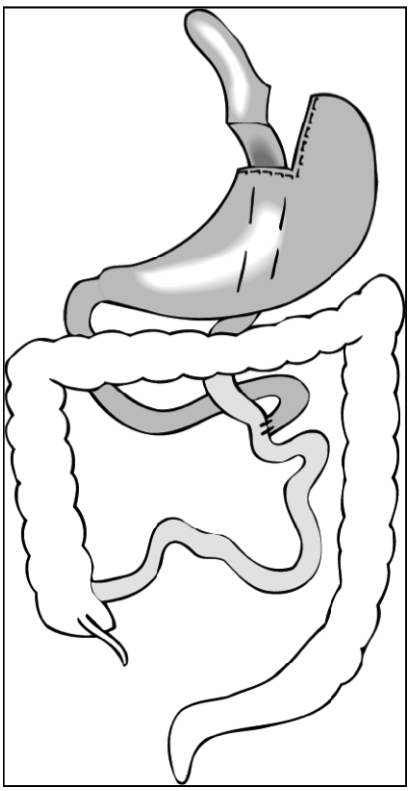


Figure 1 Roux-en-Y gastric bypass, RYGBP. A small proximal gastric pouch is created below the gastroesophageal junction from the lesser curvature. The Roux-limb is created by dividing the jejunum distal to the ligament of Treitz' and connecting the aboral part to the gastric pouch. Continuity of bile and pancreatic flow is restored with an enteroenterostomy

Biliopancreatic diversion with duodenal switch, DS

The duodenal switch is a combination of two operations. De Meester originally described the duodenal switch for the treatment of duodenogastric reflux[74]. The biliopancreatic diversion (BPD) was first described in 1979 by Scopinaro[21] and is also known as the Scopinaro procedure. It is devised to induce a decreased fat absorption by creating a distal Roux-en-Y and thus only allowing uptake of fat in the distal ileum, where the bile and pancreatic juices meet the food-stream. In addition to this, the Scopinaro procedure includes a distal gastrectomy to reduce the gastric volume. Hess later used the Scopinaro procedure after failed restrictive procedures, but the distal gastrectomy proved difficult in revisional operations due to adhesions, and the relatively large gastric remnant gave rise to stomal ulcers in the Roux limb. He therefore created a tube along the lesser curve of the stomach, ie. sleeve gastrectomy, and added the duodenal switch. Hess and Marceau published their first series of biliopancreatic diversion with duodenal switch (DS) in 1998[19, 20]. The promising results from revisional procedures led them to adopting DS as a primary bariatric procedure. Hess et al., with more than 1400 operations and follow up of 92% after ten years[75], have proved the method to be safe and effective. DS has not, however, become widely popular and we believe that this is partly due to the technical difficulty of the operation, especially in the laparoscopic setting, and partly due to concern of metabolical and/or gastrointestinal disturbances following the operation. Comparisons between RYGBP and DS show superior weight loss after DS[76-78] with one exeption[79].

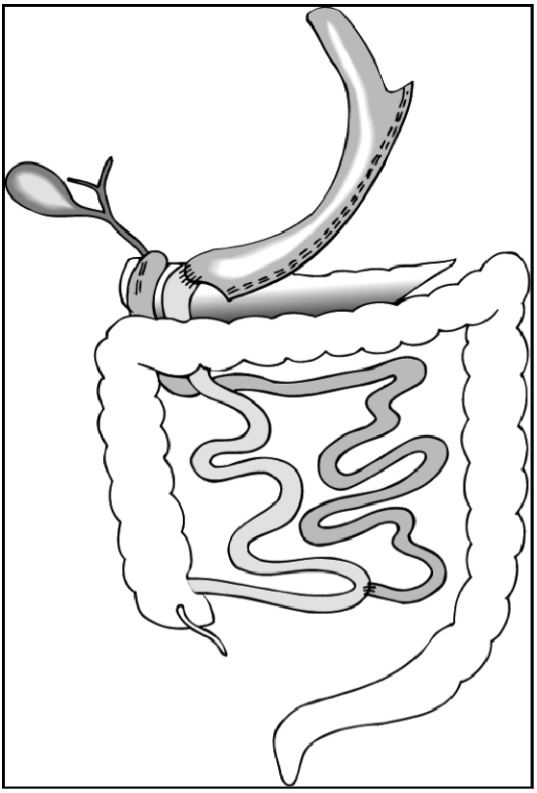


Figure 2 Biliopancreatic diversion with duodenal switch, DS. The small intestine is divided 250 cm oral to the ileocaecal valve and the cephalad part is connected to the distal ileum one meter from the ileoceacal valve, thus creating the one meter long common channel. A sleeve gastrectomy is then performed and the duodenal bulb divided two to four centimeters distal to the pylorus. Finally, a duodenoileostomy is created to restore continuity of the gastrointestinal tract

Complications to RYGBP and DS

Leakage

The most feared complication in the immediate postoperative period is a leakage in one of the anastomoses. It is a life-threatening complication, which demands prompt intervention with repair (if made possible by early detection), adequate drainage and broad-spectrum antibiotics[80, 81]. Symptoms include disproportional epigastric pain, tachycardia, shortness of breath, anuria and hypotension. Leakages are more frequent after RYGBP than after DS[20, 75, 80, 82].

Bleeding

Postoperative bleeding can arise after all types of surgery, and bariatric surgery is no exception. In addition to bleeding into the peritoneal cavity, intraluminal bleeding in the gastrojejunostomy or other anastomoses can arise in the early postoperative period, and require reoperation[83, 84].

Pulmonary Embolism

Although being a rare complication, pulmonary embolism is one of the leading causes of death after bariatric surgery[85, 86].

Small bowel obstruction

With the intestinal transpositions involved in modern bariatric operations, mesentery defects are constructed. These can become sites of internal herniation. Intermittent colicky pain after meals should raise suspicion of this complication. Diagnosis can be difficult with ordinary computed tomography (CT), since the affected small bowel can be on the biliopancreatic limb, and thus not cause classical radiologic signs of obstruction, since it is not in the food-stream. It is important that the surgeon reviews the radiographic pictures. CT can be deemed normal by the radiologists in 60% of cases with internal herniation when the pathology is clear to the operating surgeon[87]. However, coeliotomy sometimes has to be undertaken on clinical suspicion alone since an overlooked gangrene can be disastrous for the patient. Postoperative adhesions can also lead to obstruction[82, 88].

Nutritional deficiencies

A number of nutritional deficiencies are described after bariatric surgery. Protein malnutrition are described after RYGBP[89] and DS[75, 90]. Folate deficiencies can occur and vitamin B^{12} is not readily absorbed since the production of intrinsic factor is decreased[91]. Iron and calcium are normally absorbed in the duodenum and proximal jejunum, both of which are bypassed in modern bariatric surgery, why supplementation of these are necessary[92]. Fat-soluble vitamins; A, D and K are also reported to decrease in serum over time after DS[93]. Thorough preoperative information on the importance of maintainance to nutritional supplementation programs as well as careful follow-up of these patients is therefore important.

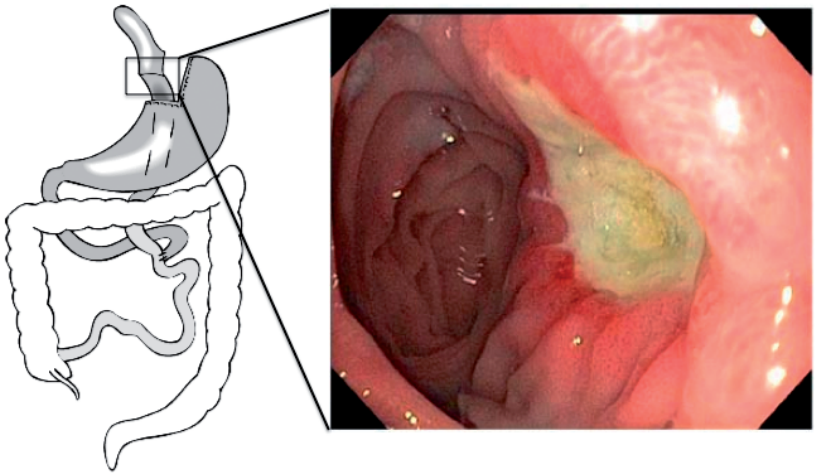


Figure 3 Stomal ulcer distal to the gastrojejunostomy

Stomal ulcer (Figure 3), also called marginal ulcer is a well-known clinical entity after gastric resections[94, 95]. This clinical problem also occur in <1%-9% after RYGBP[96-99], often requiring long-term medication and sometimes reoperation. It can cause significant bleeding, leading to the need of transfusions and endoscopic intervention, or even perforation with peritonitis[100, 101].

Symptoms of stomal ulcer typically arise during the first month after surgery[102], and consist of dull epigastric pain and/or nausea which are often aggravated by food intake. Stenosis with dysphagia can be the only symptom as can upper gastrointestinal bleeding with anemia or signs of hypovolemia. The diagnosis is readily made with endoscopic examination and treatment with proton pump inhibitors (PPI) often suffice. A higher dose than normal is often required and relapse of symptoms after cessation of the medication is not uncommon. Sometimes life-long therapy is warranted.

The observation that stomal ulcers often occur in patients with gastro-gastric fistulae from the bypassed stomach led to the assumption that acid from the bypassed stomach caused these ulcers[103, 104]. Efforts have been made to reduce the size of the pouch, in order to minimize the amount of parietal cells above the gastrojejunostomy[98]. The practice of complete transsection of the proximal pouch reduces the number of gastro-gastric fistulae.

However, the problem with stomal ulcers does not resolve completely with these measures even if the frequency seems to go down[98].

Death

Mortality rates after bariatric surgery varies in the literature between 0.1 and 7,6 %[105, 106]. The bariatric postoperative mortality in Sweden is 0.16%[107]. Although this figure is low, every postoperative death is a tragedy for all concerned in this type of preventive surgery and this risk must always be communicated to the patient and preferably next of kin before a decision to operate can be made.

Acid secretion after RYGBP

The parietal cells of the gastric mucosa produce hydrochloric acid by actively transporting H^+ -ions into the gastric lumen with H^+-K^+-ATPase. Cloride ions are transported passively into the lumen. The parietal cells are activated during a meal, and the resting H^+ secretion of 2 mmol/h can increase tenfold. The most important stimulant of gastric acid secretion is gastrin. This hormone, released by G-cells in response to vagal nerve signals, or mechanical stimulation of the gastric mucosa, induces histamine secretion from ECL-cells which in turn acts in a paracrine way to stimulate H^+-K^+-ATPase in the parietal cells[108, 109]. After gastric bypass, acid production in the bypassed stomach is suppressed[110] and measurements with a perfused orogastric tube have failed to demonstrate significant amounts of acid in the proximal pouch after RYGBP[111]. This group has demonstrated that the acid-secreting parietal cells are present in the cardiac area all the way to the gastroesophageal junction[112], and one of the aims of this thesis was to evaluate the pathogenic role of acid production from these cells in ulcer formation at the gastrojejunostomy after RYGBP.

Gastric emptying and pylorus function

Gastric emptying is normally characterized by two phases. The first phase is called lag-phase. It can be measured as the time from ingestion to the first appearance of solids in the proximal small bowel. A linear emptying-phase then ensues[113, 114]. The pylorus acts as a regulator of the flow from the stomach to the duodenum and vice versa. The pylorus is innervated mainly from the vagal nerve[115]. It has a number of responses to different stimuli. For instance, when the duodenum is exposed to fat or acid, the pylorus responds with increased baseline activity and phasic contractions[116]. Unlike most sphincters of the gastrointestinal canal, the pylorus maintains a lumen most of the time[117].

PYY

A number of gastrointestinal peptides are involved in gastric emptying and satiety regulation[118, 119]. One of these, peptide YY (PYY), is studied in this thesis. PYY is a 36-amino-acid peptide of the neuropeptide Y family. It is secreted from the enteroendocrine L-cells in the small and large intestine with increasing concentration distally[120]. The active N-terminally truncated PYY_{3-36} inhibit gastric emptying and increase intestinal transit time[121, 122]. The ileal brake, which slows transit through the gastrointestinal tract in response to fat, protein and carbohydrates in the ileum, depend on PYY among other transmittors[123]. Active PYY_{3-36} has high affinity to Y2-receptors in the hypothalamus, inducing satiety in humans[124] and non-operated obese subjects have low[124] or normal[125-127] levels of PYY. While its effect on food intake in humans has been disputed[128], elevated levels of this PYY is seen after JIB[129]. A recent study shows decreased food intake after orally administered PYY[130] and it could be one among other mechanisms whereby food intake is decreased after bariatric surgery.

Aims of this thesis

In light of the massive rise in bariatric surgery in Sweden and internationally, the need for study of the postoperative physiology increases. Certain complications of bariatric surgery will increase in prevalence and efforts to understand the underlying patophysiology is vital for development of correct treatment strategies. The aim of this thesis was to investigate certain changes in gut physiology, and results of bariatric surgery. The specific aims were:

I to study the pathogenetic role of hydrochloric acid in the formation of stomal ulcer after gastric bypass with a case-control study of pH in the proximal pouch in patients with stomal ulcer. A secondary aim was to describe results of revisional operations for stomal ulcer.

II to introduce a new use of wire-less pH-monitoring and to describe the level of the acidity at the gastroenteroanastomosis after RYGBP in asymptomatic patients.

III to describe gastric emptying after DS and to study PYY levels after DS in relation to age-matched control subjects. To investigate the occurrence of dumping symptoms after DS.

IV to compare DS and RYGBP in a randomized controlled trial. Major outcome variables were perioperative complications and weight results. Gastrointestinal symptoms and biochemical evaluation more than two years after surgery were secondary outcome variables.

Patients and methods

Paper I

Six patients (one male) with endoscopically verified stomal ulcers were included. The time from operation to diagnosis was in median 3.5 weeks (3 weeks to 5 years). Barium swallow x-ray studies were obtained to exclude gastro-gastric fistula. Control subjects were six asymptomatic women who had undergone RYGBP at least 5 years earlier. After discontinuation of proton pump inhibitor use for at least one week, a pH-sensitive probe (Digitrapper.pH, Medilab) was passed transnasally to the proximal pouch as guided by calculated distance and pH-response. The probe was left in place for four hours during which time the subjects could eat and drink at their leisure. The proportion of time with pH<4 was calculated and compared between stomal ulcer patients and controls by Wilcoxon´s Rank-sum analysis. Three revisional operations were performed. Two of these included total resection of the gastroenterostomy as well as reduction of the proximal pouch. In the third operation, a large part of the proximal pouch could be resected without touching the gastroenterostomy.

Paper II

Patients

In total, 25 patients (4 men), median age 44 years (range 31-60) and BMI 29.3 (range 22.7-40.1) kg/m^2, who had undergone RYGBP 4 years (range 2-8 years) earlier were studied. Twenty-one of these patients had no symptoms or history of stomal ulcer, nor did they use PPI or NSAID. Four patients with symptoms from the epigastric area and who were under PPI-treatment (continous or occasional) were also recruited. Their data are reported separately. In an attempt to evaluate reproducibility, two of the 21 asymtomatic patients underwent double measurements. In one patient the measurement was repeated after one month and in the other patient two Bravo-capsules were applied side by side.

All operations had been performed at the Department of Surgery, Uppsala University Hospital. A small proximal pouch was constructed at the lesser curvature by dividing the stomach horizontally 5 cm below the gastroeso-

phageal junction with a cutting linear stapler (45-mm blue cartridge). The pouch was then totally transected using one to three vertical firings with identical cartridges. After placing a purse sting suture just above the initial horizontal staple line, it was cut and the anvil of a 25-mm circular stapler was entered into the pouch. This and the forthcoming stapling of the upper anastomosis reduced the length of the pouch by about one cm. The jejunum was divided 30 centimeters from the ligament of Treitz and a classical Roux-limb of 70 centimeters was constructed. Finally, the gastrojejunostomy was performed end-to-end with the circular 25-mm stapler. For study proposes, the number of 45-mm cartridges that were used to construct the vertical part of the pouch was noted, as a rough measurement of the pouch size.

pH-metry

After a fasting period of at least 6 hours, an upper endoscopy was performed. The anastomotic area was checked for ulcers and other pathology, such as gastrogastric fistula, and the distance to the incisors was measured. A calibrated BRAVO™-capsule was then inserted transorally and followed by the endoscope, so the capsule could be applied to the anastomotic region under direct visual control (Figure 7). After applying suction (510 mm Hg) for initially one minute, later two minutes, to obtain a portion of mucosa in the positioning hole of the capsule, the locking pin was activated to secure the capsule to the wall. No fluoroscopy was used. Nine patients had lidocain spray in the pharynx, and four patients also had a mild sedation with 5 mg of diazepam intravenously. During the 48-hour registration, the study patients could eat and drink at their leisure. Data were recorded in the receiving device, carried in a band over the shoulder or kept within one meter from the body.

Data analysis

The pH-plots were analyzed using the software Polygram NET ® version 4.2 (Given Imaging, Yoqneam, Israel). The plots were truncated if the pattern suddenly changed and showed a consistently neutral environment indicating a premature capsule detachment (Figure 8). The total registration time before detachment, time with pH<4, number of episodes with pH<4 as well as number of episodes with pH<4 for more than 5 minutes were registered. The percentage of time with pH<4 was calculated, as well as its distribution during daytime (08.00-22.00) and night (22.00-08-00). The graphs were adapted for publication with Pixelmator version 1.4.1, Pixelmator team ltd, London, UK.

Statistics

Descriptive statistics were used. In calculating relationship between the number of cartridges needed for the vertical part of the pouch and level of acidity, linear regression was used and when comparing the proportions of daytime and night, Wicoxons matched pair test was used. $p<0.05$ was considered significant. In the two patients who had double measurements, the plot with longest registration time was included in the main study.

Paper III

Patients and operation

Twenty patients who had undergone DS at our centre at least 18 months previously (median 3.5 years) volunteered to participate in a scintigraphic study of gastric emptying. The group, which included 12 men, had a median age of 43 years (range 31-57) and a median BMI of 31.1 kg/m^2 (range 21.8-46.3). They were weight stable and had had a BMI before surgery of 51.7 kg/m^2. Out of these 20 patients, 10 patients also volunteered for PYY measurements after a standardised meal (5 men, median age 38 years and median BMI 27.0). For comparative reasons, the PYY-results were related to postprandial PYY-measurements of 9 non-operated, normal-weight, age-matched subjects (median BMI 22.4 kg/m^2, range 19.9-25.8) from previously published work [131].

The DS had been performed at the Department of Surgery at Uppsala University Hospital. The operation consisted of transection of the small intestine 250 cm oral to the ileocaecal valve. The distal end of the cephalad part was anastomosed to the ileum 100 cm from the ileocaecal valve, creating an alimentary limb of 150 cm and a common channel of 100 cm. The remaining small bowel, the biliopancreatic limb, was in median 3.6 m (range 2.5-5.5m). A sleeve gastrectomy was performed along the lesser curvature with cutting staplers, lateral to a 38 French bougie and a one-centimetre free margin. The resection started at the greater curvature, 5 cm oral to the pylorus after division of the right gastroepiploic artery. For technical reasons, the right gastric artery was divided as well as all tissue lateral to the pyloric region. The duodenal bulb was transected two to four centimetres distal to the pylorus and anastomosed to the oral end of the alimentary limb with a hand-sown end-to-side anastomosis (Figure 2).

Gastric emptying studies

The scintigraphic measurements were performed at the Department of Nuclear Medicine after an overnight fast. A 10 MBq ^{99m}Tc-labeled omelette (1/2 egg, one table spoon wheat flour, 25 ml milk, 1-2 g margarine and salt, 77.5 kcal) and an unlabelled soft drink (150 ml, 70 kcal) were consumed within 2 minutes. The energy composition of the meal was 30 % fat, 12 % protein and 58 % carbohydrates. The solid component was reduced to a quarter of normal size used in our lab[132], in order to ensure that the subjects could ingest the whole meal within two minutes. Anterioposterior scans (Infinia™ Hawkeye®4, GE Healthcare, Waukesha, Wisconsin, USA) with the subject in sitting position were then obtained immediately and repeated every 5 minutes for the first 50 minutes, then every 10 minutes up until 120 minutes in total. The region of interest was outlined in the first scan and included the whole gastric tube down to the level of the pylorus. Half-emptying time was calculated, as well as percentage of tracer remaining in the gastric tube at the above-mentioned time-points. Any lag-phase was also registered.

PYY-analyses

For PYY analyses, the ten DS-patients were presented at the Clinic for Obesity Care after an overnight fast, which was sustained until a standardised meal was served at 1300 hours. The meal consisted of 574 kcal (21% fat, 18% protein and 61% carbohydrates). Blood samples were drawn at 0800, 1000, 1200, 1300, 1330, 1400, 1430, 1500 and 1600 hours and then stored in -70 °C prior to laboratory analyses. Serum concentrations of total PYY were measured with a commercial radioimmunoassay kit (Linco Research Inc. Michigan, USA). The kit uses radioactive iodine-labelled PYY, guinea pig PYY antiserum and goat anti-guinea pig antibody/PEG technique. Sensitivity of the assay was 10 pg ml $^{-1}$, specificity was 100 % for human PYY_{1-36}, PYY_{3-36}, [Pro34] PYY and [Leu31,Pro34] PYY and <0,1% for rat/porcine PYY_{1-36}, PYY_{3-36} and neuropeptid Y. Double samples were analyzed from all patients and a mean from these were calculated. All samples were assayed in the same batch. Inter- and intra-assays coefficient of variance (CVs) were <9%.

Evaluation of dumping symptoms

All patients undergoing bariatric surgery at our institution are given education concerning recommended eating behaviour postoperatively and get information about both early and late dumping. Dumping symptoms were evaluated on an ordinal scale (symptoms occurring daily, weekly, monthly, yearly or never). No distinction between early and late dumping was made.

Statistics

Descriptive statistics were used in the gastric emptying study. In the PYY analyses, repeated measures ANOVA was used and $p<0.05$ was considered significant. Mean and standard deviation are presented, unless otherwise stated.

Paper IV

Patients

During 2004-2007, 99 patients referred to us with a BMI>48 were assessed for eligibility for the study. Nine patients were excluded on medical grounds or due to language difficulties. Of the remaining 90 patients, 47 patients (23 men, age 39.1±9.9 yrs, BMI 54.5±6) agreed to have their operation (DS or RYGBP) randomized. The remaining 43 patients (8 men, age 36.4±8.3 yrs, BMI 53.3±4.8) agreed to take part in the extended follow-up but not in randomization. These patients were thus free to choose type of operation (Figure 4, Table 1).

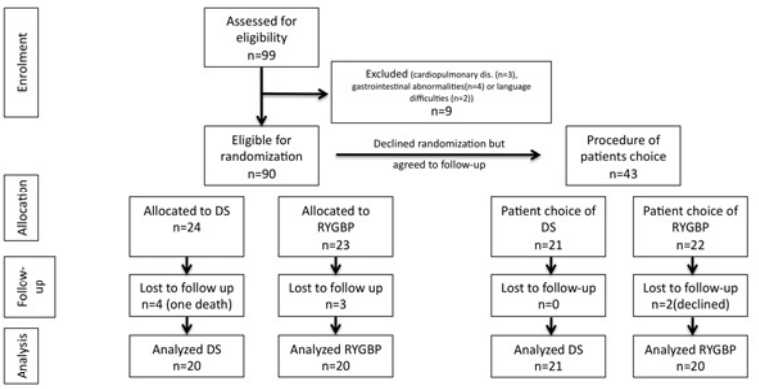


Figure 4 Inclusion flow illustrated

Table 1 Antropometrics and comorbidities of patients included in the study. † Students t-test, ¶ Fisher exact test

	Randomized patients (n=47)			**Procedure of patients choice (n=43)**			**Total (n=90)**		
	DS (n=24)	RYGBP (n=23)		DS (n=21)	RYGBP (n=22)		DS (n=45)	RYGBP (n=45)	
Age (years)	40.2±9.5	37.9±10.4	p=0.432†	35.8±7.3	37.0±9.5	p=0.649†	38.1±8.8	37.4±9.9	p=0.724†
Gender (M/F)	12/12	13/10	p=0.438¶	4/17	4/18	p=0.624¶	16/29	17/28	p=0.500¶
BMI (kg/m^2)	54.5±6.7	54.5±5.6	p=0.963†	53.8±4.6	52.7±5.2	p=0.501†	54.2±5.8	53.6±5.4	p=0.637†
Hypertension	6	7	p=0.464¶	7	8	p=0.545¶	13	15	p=0.410¶
Hyperlipidemia	0	0	-	5	3	p=0.322¶	5	3	p=0.357¶
Sleep apnoea	4	3	p=0.525¶	4	0	p=0.049¶	8	3	p=0.098¶
Diabetes mellitus (oral/insuline-treated)	6/1	1/0	p=0.055/ p=0.511¶	5/1	2/1	p=0.187/ p=0.744¶	11/2	3/1	p=0.039/ p=0.500¶

Pre-operative evaluation

All patients referred to our centre for bariatric surgery were first thoroughly examined at the centre for metabolic medicine. This included individual evaluation of internist, dietician and psychologist as well as education on postoperative diet. Abnormalities were treated before surgery.

Operations

All operations were performed by laparotomy with an upper midline incision, typically sparing five to ten centimetres above the umbilicus. For the DS, the same technique as in paper III was used (Figure 2). For RYGBP, the technique described in paper II was used (Figure 1), with the modification that the biliopancreatic limb was made 50 cm long (instead of 30 cm) and the alimentary limb 120 cm (instead of 70 cm). All patients received thromboprophylaxis with high-dose LWMH and single-dose of broad-spectrum antibiotics (Cefuroxime 1.5 grams IV and Metronidazol 1.5 grams per orally). In two patients in the DS-group, with symptomatic cholecystolithiasis, a cholecystectomy was also performed.

Perioperative registration

Perioperative data was prospectively registered for all randomized patients, with special emphasis on postoperative problems, C-reactive protein, mor-

phine consumption (PCA-pump, patient controlled analgesia), time to ingestion of fluids and solids as well as all early complications. For non-randomized patients, the data was collected retrospectively.

Follow up

Postoperatively, all patients were seen at our out-patient clinic, where multivitamin and vitamin B_{12} substitution was started. Patients were then followed by dietician at 3, 6 and 12 months and internist at 6 and 12 months, at the centre of metabolic medicine. Routine laboratory examinations were also undertaken. At one year, the majority of the patients were doing fine and could be referred to their primary care physician for subsequent annual follow up, including treatment of comorbidities, laboratory tests and further prescription of life long nutritional supplement therapy.

Laboratory evaluation

Routine chemistry, including haemoglobin, vitamin B_{12}, folate, albumin, glucose, HbA1c, HDL, LDL and triglycerides was analysed preoperatively, at one year and three years postoperatively. The latter laboratory data was taken from primary care physician follow-up (2.9 ± 0.5 yrs postoperatively).

Study data for the extended follow-up

For the purpose of this study, a mail questionnaire was sent out to all patients at least two years postoperatively (n=90). We used our standard questionnaire for long term follow up; current weight, medication, subsequent surgery as well as an extended inquiry on abdominal symptoms (appendix 1, Paper IV). The median time to this follow up was 3.5 years (2.0-5.3 years).

Statistics

Power analysis was based on the historical standard deviation in BMI-reduction in our super-obese patients. To find a difference in weight loss of 5 BMI-units with a power of greater than 90 % (two-sided t-test $p<0.05$), a sample size of 40 patients in each group was needed. The randomization was stratified to sex and BMI (above or below BMI 53). Normally distributed values are reported with means (standard deviation), and non-normally distributed as median (range). For comparison of proportions between groups Fisher exact test was used. For continuous variables, Students t-test was employed for normally distributed data and Mann-Whitney-U test for non-normally distributed data. Mann-Whitney-U test was used for data on ordinal scales. ANOVA repeated measures analysis was used for the laboratory follow up. Two-sided $p<0.05$ was considered significant. The data have been analyzed both separately for the randomized and non-randomized groups, as well as for the total sample of 90 patients.

Ethics

All four studies were approved by the Regional Ethics Committee at the University of Uppsala, Sweden, and informed consent was obtained from all patients.

Results

Paper I

No gastrogastric fistulae were found on barium swallow x-ray studies. pH measurements were feasible in all patients and no adverse events occurred. The proportion of time with pH<4 was significantly grater in the patients with stomal ulcer (median 95.5%, range 49.6-100%) as compared to the asymptomatic control subjects (median 20%, range 6.7-43.9%), $p<0.01$, Wilcoxons rank sum test. In fact none of the controls reached the lowest value of the ulcer patients (Figure 5).

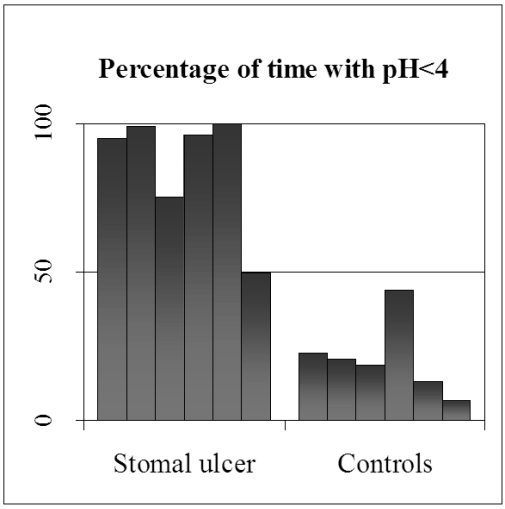


Figure 5 Representation of proportion of time with pH<4. The percentage is shown on the y-axis and each bar represents one patient

Three of the patients underwent revisional surgery because of epigastric pain that did not subside with PPI-medication. In one, a repeated pH-measurement was made and the percentege of time with pH<4 was decreased from 100% to 6%. This patient became symptom free. The second patient had clear reduction of her symptoms and no longer needed PPI, but she refused repeated pH-metry. In the third revisional patient, a bleeding stomal ulcer occurred while she was waiting for a new pH-measurement and she was put on life-long PPI.

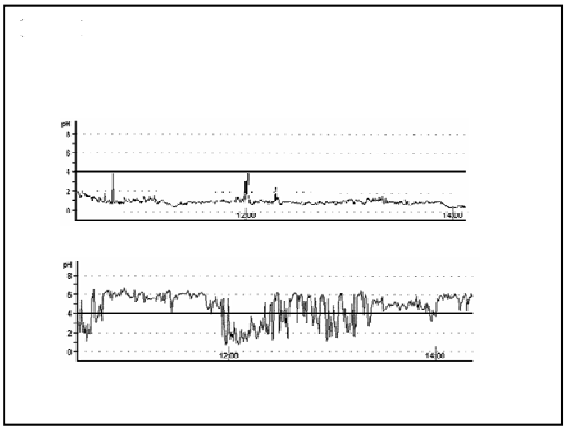


Figure 6 pH-plots of one stomal ulcer patient (upper panel) and an asymptomatic control patient (lower panel). pH is given on the y-axis and pH 4 is marked with a horizontal line. Time of day is given in the x-axis

Paper II

The BRAVO™-capsule could be positioned at the level of the gastro-jejunostomy under direct vision of the endoscope in all 25 patients (Figure 7).

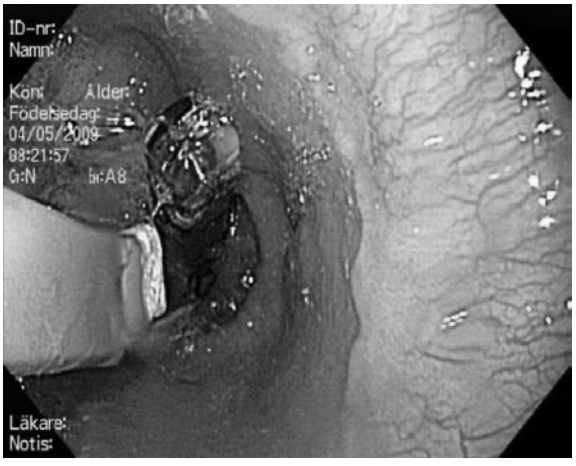


Figure 7 The BRAVO™-capsule is attached to the mucosa of the gastric pouch just above the gastrojejunostomy. The pH-sensor is located in the proximal Roux-limb. The applicator is seen to the left. Squamous epithelium of the esophagus is seen in the right hand side of the picture

In two patients, it was not secured enough to the mucosa and was lost into the Roux limb when the applicator was removed. Three additional patients had early detachment, judged by the consistent neutral environment until the

signal was lost. These five patients were therefore excluded, giving pH data from 16 asymptomatic individuals and 4 symptomatic subjects. No gastro-gastric fistula was found.

Interpretable pH-data from the region of interest was obtained for a median of 25.7 hours (6.1-47.4, n=20). Registration time increased during the study period, i.e. the time before capsule detachment (indicated by a sudden and continuous shift to neutral pH, Figure 8), since four of the five immediate detachments occurred in the first half of the series. In the second half, the locking pin was always attached to gastric mucosa, but leaving the pH-electrode in the jejunum, and the suction time was increased to 2 minutes. These measures yielded fewer failures and a trend towards longer registration times, 26.9 vs. 18.8 hours (p=0.11).

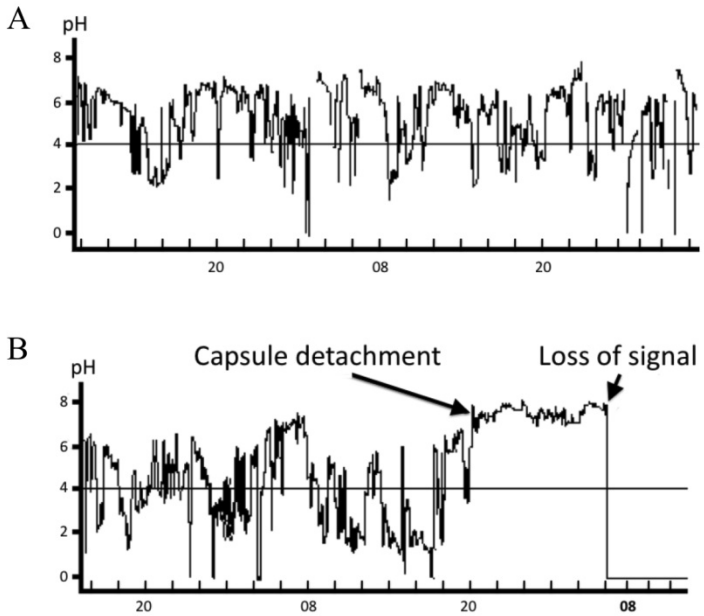


Figure 8 Two pH curves showing; A: A successful two-day recording B: Capsule detachment after 30.6 hours (at 20.00) and subsequent loss of signal when the capsule passes (at 07.00)

When analyzing the 16 asymptomatic patients, the median percentage of time with pH<4 was 10.5 (0.3- 37.7) (Figure 9). When dividing the registration time in day (08.00-22.00) and night (22.00-06.00), the percentage of time with pH<4 was 8.4 and 6.3, respectively, (p=0.08). The median number of episodes per hour with pH<4 was 10.2 (0.1-26.2, Table 2). No correlation was found between the number of cartridges used for the vertical division of the gastric pouch, in median 2 (1-3), and the measured level of acidity.

The two patients examined with two capsules had consistent results. The patient with a repeated measurement after one month had pH<4 in 0.9 vs. 0.3% of the total registration time (20.0 and 23.9 h, respectively). In the patient with two capsules side-by-side, one capsule was lost after 8 hours, but during that time pH<4 was registered in 13.9% and 11.6%, respectively. The remaining capsule (11.6%), stayed in place for 21.7 hours, and during that time pH<4 was noted in 9.6% of the registration time.

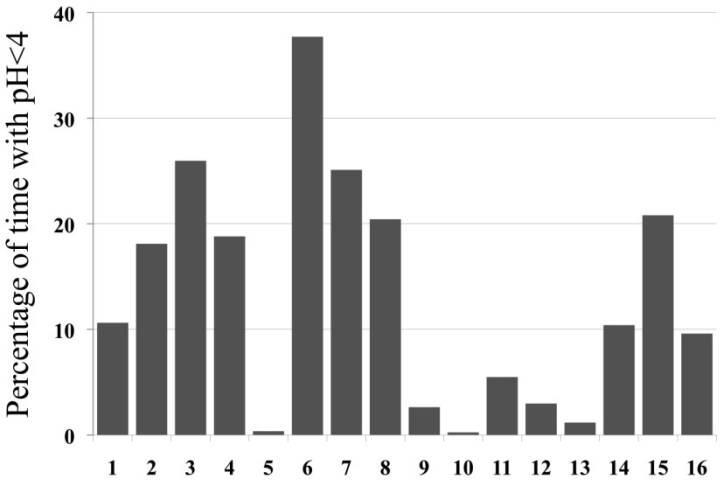


Figure 9 Proportion of time with pH<4 is presented on the y-axis. Each column represents one asymptomatic patient

Table 2 Data of 16 consecutive recordings of pH in the proximal Roux-limb in asymptomatic post RYGBP-patients

Patient m=male	BMI	Registration Time (h)	Episodes pH<4	pH<4 >5 min	Longest Episode pH<4(min)	Time pH<4(min)	Episodes pH<4/hour	% time pH<4 Day	% time pH<4 Night	Total % time pH<4
1	37.2	34.1	228	10	21	217	6.7	8.4	17.8	10.6
2	35.1	7.8	204	1	10	85	26.2	-	-	18.1
3	34.4	6.1	99	6	13	95	16.2	-	-	26.0
4	30.0	11.1	232	1	8	125	20.9	-	-	18.8
5	27.3	22.2	7	0	2	3	0.3	0.3	0.2	0.4
6(m)	40.1	27.5	554	34	19	622	20.1	39.1	34.0	37.7
7	26.0	20.8	361	15	24	313	17.4	32.4	6.3	25.1
8	24.7	30.6	566	10	13	375	18.5	24.0	9.9	20.4
9	29.3	46.9	212	1	8	74	4.5	3.7	0.7	2.6
10(m)	25.3	20.0	3	0	2	3	0.2	0.3	0.6	0.3
11	32.3	47.4	390	4	8	156	8.2	8.2	0.4	5.5
12	25.5	47.0	246	1	11	84	5.2	2.6	3.7	3.0
13	28.7	8.5	1	1	6	6	0.1	-	-	1.2
14	26.2	8.5	139	0	4	53	16.3	-	-	10.4
15	28.2	47.1	577	24	25	588	12.3	25.4	11.1	20.8
16(m)	36.1	21.7	161	7	12	125	7.4	12.5	10.1	9.6
Median	**29.0**	**22.0**	**220.0**	**2.5**	**10.5**	**110.0**	**10.2**	**8.4**	**6.3**	**10.5**

Of the four symptomatic patients, two patients could not discontinue their PPI-treatment due to the severity of their symptoms. The percentage of time with pH<4 was found to be 0% in both these patients. The remaining two patients interrupted their PPI-medication two weeks prior to the Bravo-capsule placement. Their plots showed a percentage of time with pH<4 of 11.3 and 10.0%. A small stomal ulcer was seen at endoscopy in one of these patients.

Symtoms	PPI	BMI	Registration Time (h)	Episodes pH<4	pH<4 >5 min	Time pH<4(min)	Episodes pH<4/hour	% time pH<4
Epigastralgia	Discont 2 wks	39.3	21.2	63	8	143	3.0	11.3
Epigastralgia/ stomal ulcer	Discont 2 wks	33.0	45.5	421	6	275	9.3	10.0
Epigastralgia	On demand	24.7	44.7	5	0	1	0	0.0
Epigastrlgia	Continously	33.1	38.8	0	0	0	0	0

Table 3 pH in the gastrojejunostomy in symptomatic patients after RYGBP

No complications occurred during placement or passing of the capsule. One patient reported mild retrosternal discomfort when returning the receiving device (two days after placement), but an additional endoscopy was normal and the discomfort soon subsided.

Paper III

Gastric emptying

All subjects could ingest the meal within the stipulated two minutes. Data were extracted at 5, 10, 15, 20, 30, 45, 60, 75, 90 and 120 minutes and the mean percentages of remaining tracer in the gastric tube were plotted. The mean half-emptying time was 28±16 minutes, and areas of normal lag-phase and half emptying time used in our lab[133] have been included in the figure to give an idea of gastric emptying in normal subjects (Figure 10). A lag-phase was seen in six patients (30%). In the remaining patients, the emptying was linear already from the first scan (5 minutes).

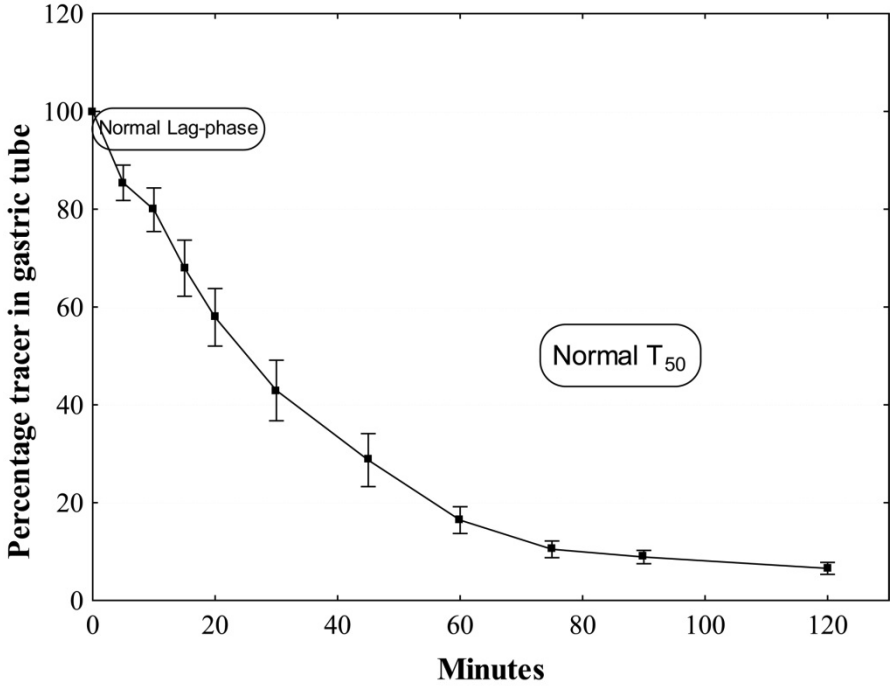


Figure 10 The mean percentage of remaining tracer in the gastric tube after ingestion of the ^{99m}Tc-labeled omelette (77.5 kcal) for all study patients is plotted. Bars show the standard error. For comparison, the areas of the normal lag-phase and half-emptying time in our lab after a standard meal (310 kcal) in normal subjects are indicated with ovals

PYY

The fasting PYY-levels were significantly higher in the DS-group compared to the non-operated age-matched controls ($p<0.001$). Thirty minutes after the

meal, PYY had risen from a mean of 161 to 277 pg/ml, an elevation of 72%. PYY-levels were continuously high in the DS group during the study period, with a declining trend three hours after the test meal. In the controls, a slow and continuous rise was seen postprandially (Figure 11).

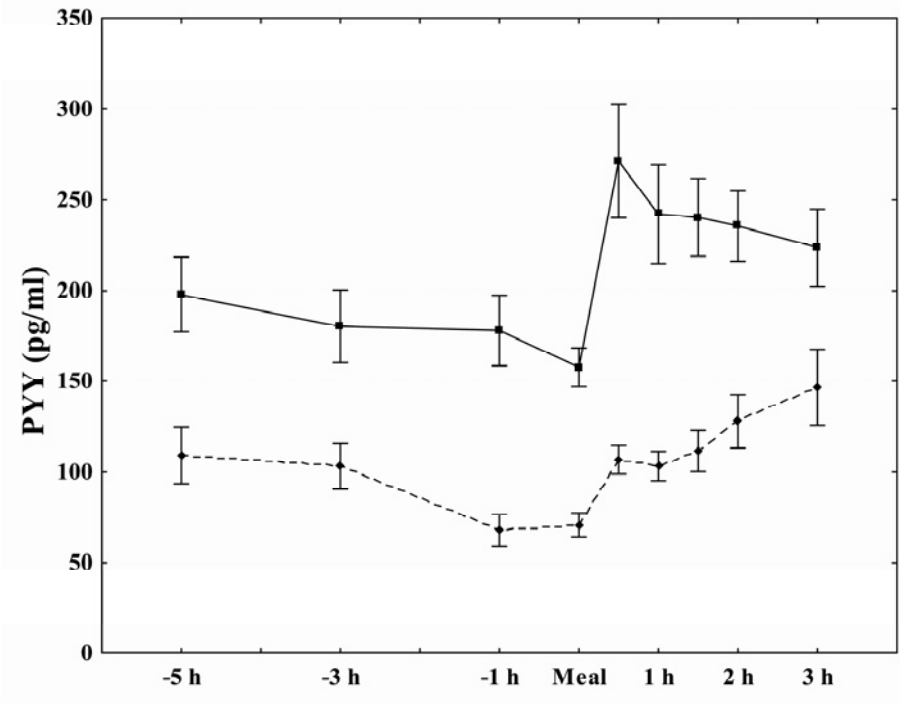


Figure 11 PYY levels in ten DS patients (squares, solid line) and nine age-matched controls (diamonds, dotted line). Time is given in relation to the test meal, consumed after an overnight fast. Note the marked response to the test meal as well the constantly elevated PYY levels in the DS-patients. $p<0.001$, ANOVA repeated measures analysis. Bars show the standard error

Dumping

No patient reported daily dumping symptoms. One patient reported weekly dumping symptoms, two patients monthly and eight patients once or a few times a year. The remaining nine patients reported that they never experienced dumping. We found no correlation between reported dumping symptoms and gastric emptying times.

Paper IV

Perioperative

All patients underwent surgery as planned (randomized or chosen procedure). The outcome was similar between randomized and non-randomized patients, in both types of operation. In short, DS-patients had longer duration of surgery (156 ±30 vs. 117 ±33 min, $p<0.001$), higher mean postoperative C-reactive protein levels (138.5 ±54.7 vs. 117.6 ±43.2, $p=0.047$) and higher total morphine consumption postoperative day one to three (133.3 ±84.8 mg vs. 89.3 ±72.9 mg, $p=0.010$) than RYGBP-patients (n=90). The resume of oral intake; liquids (2.2 ±2.8 vs. 1.2 ±0.5 days, $p<0.001$, n=90) and solids (4.4 ±1.1 vs. 3.3 ±0.8 days, $p<0.001$, n=90) was delayed after DS compared to RYGBP. The average length of stay was 7.0 ±4.1 and 5.2 ±1.2 days, $p=0.004$, n=90, for DS and RYGBP, respectively (Table 4).

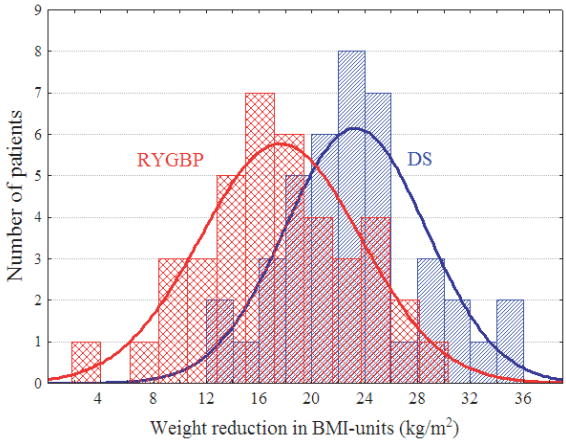
In total, three reoperations were made (two DS, one RYGBP). One DS patient was drained due to a bile collection without obvious source and she could be discharged ten days postoperatively. The other DS patient was reoperated due to postoperative bleeding causing elevated intraabdominal pressure and leakage at the divided duodenal bulb. After drainage, this subsided and the patient could be discharged after 32 days. One RYGBP patient had a negative laparotomy on the first postoperative day due to a suspected leak and had an uneventful recovery. One patient died, due to pulmonary embolism, occurring in her home three weeks after a DS, in spite of a previous uneventful postoperative course.

Follow up

A follow-up of 90% was achieved and the median time from operation was 3.5 (2.0-5.3 years). The weight loss was significantly greater in the DS-group (24.0±6.8 vs. 17.3±6.1 BMI-units, respectively, $p<0.001$). In the RYGBP group, 10 percent of the patients had a weight reduction of less than 10 BMI-units. This was not seen in the DS-group (Figur 12). The percentage excess weight loss (EWL%) was 81.1% in the DS group, and 63.2% in the RYGBP group ($p<0.001$). 91.1 % of the DS patients and 75.6% of the RYGBP-patients achieved an EWL of more than 50% ($p=0.004$). The BMI-reduction was independent of whether the patients operation had been randomized or not.

Table 4 Perioperative data, † Students t-test, ‡ Mann Whitney U test, ¶ Fisher exact test

	Randomized patients n=47			**Procedure of patients choice n=43**			**Total n=90**		
	DS, n=24	RYGBP, n=23		DS, n=21	RYGBP, n=22		DS n=45	RYGBP, n=45	
Duration of surgery (min)	153.2±23.6	117.4±40.7	p<0.001†	160.2±36.6	116.2±22.3	p<0.001†	156.5±30	116.8±32.7	p<0.001†
Mean CRP day 1-3(mg/L)	137.8±59.3	125.0±50.8	p= 0.433†	139.4±50.5	110.0±32.4	p=0.028†	138.5±54.7	117.6±43.2	p=0.047†
Morphine-consumption day 1-3 (mg)	140.4±96.3	92.9±60.7	p=0.050‡	125.2±71.0	85.5±85.1	p=0.105‡	133.3±84.8	89.3±72.9	p=0.010‡
Time to liquids per mouth (days)	2.8±3.8	1.3±0.6	p<0.001‡	1.6±0.7	1.1±0.3	p<0.015‡	2.2±2.8	1.2±0.5	p<0.001‡
Time to food per mouth(days)	4.5±1.3	3.5±0.9	p<0.003‡	4.4±0.7	3.1±1.0	p<0.001‡	4.4±1.1	3.3±0.8	p<0.001‡
Length of stay (days)	7.6±5.4	5.5±1.2	p=0.073‡	6.4±1.6	4.9±1.1	p<0.001‡	7.0±4.1	5.2±1.2	P<0.004‡
Mortality	1	0	p=0.511¶	0	0	-	1	0	p=0.500¶
Reoperations	2	1	p=0.516¶	0	0	-	2	1	p=0.500¶
Postoperative transfusions	0	2	p=0.234¶	2	1	p=0.482¶	2	3	p=0.500¶



Figur 12 Histogram of BMI-reduction after DS (blue columns) and RYGBP (red columns. p<0.001 Students t-test

In the DS group, ten of the eleven patients with diabetes had been able to stop oral anti-diabetic medication and two of thirteen had discontinued their antihypertensive treatment. Of the three diabetics in the RYGBP-group, none had medication at follow up and four of fifteen had discontinued the antihypertensive treatment.

No base-line differences between the two operations were seen in the laboratory tests. DS-patients had significantly lower glucose (4.64 ±0.44 vs. 5.29 ±1.04 mmol/L, p=0.008) and HbA1c (3.97 ±0.34 % vs. 4.67 ±0.32 %, p=0.005) tree years postoperatively compared to RYGBP (Figure 13).

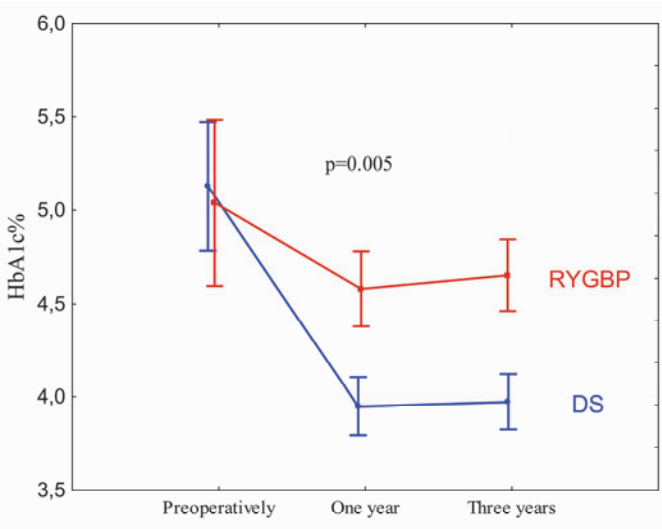


Figure 13 DS yielded significantly lower HbA1c levels, p=0.005, ANOVA repeated measures analysis. Bars denote 95 % confidence interval

At one year, one DS-patient (2.4%) and four RYGBP-patients (9.5%) had a fasting glucose above 6 mmol/l (p=0.187). The corresponding proportions at three years were 0 and 12% respectively (p=0.083). No differences in haemoglobin or albumin were seen. Nor was the frequency of anaemic or hypoalbuminemic patients different between DS and RYGBP (data not shown). Improvements were seen in folate and vitamin B_{12}-values in both groups, probably due to supplements and diet counselling (Table 5).

Concerning abdominal symptoms, diarrhea and malodorous flatus were more frequent after DS, and mostly occurred weekly, while dumping was more common after RYGBP (Figure 14). On the effect of the operation on their general well being, 100% of the DS-patients, and 85% of the RYGBP-patients responded that they were satisfied or very satisfied in an ordinal scale of four steps (appendix 1) (p=0.086). The five RYGBP-patients who were dissatisfied (n=5) or very dissatisfied (n=1) had lower weight loss, 8.4 BMI-units (1.8-13.0) as compared to the whole RYGBP group (p=0.002).

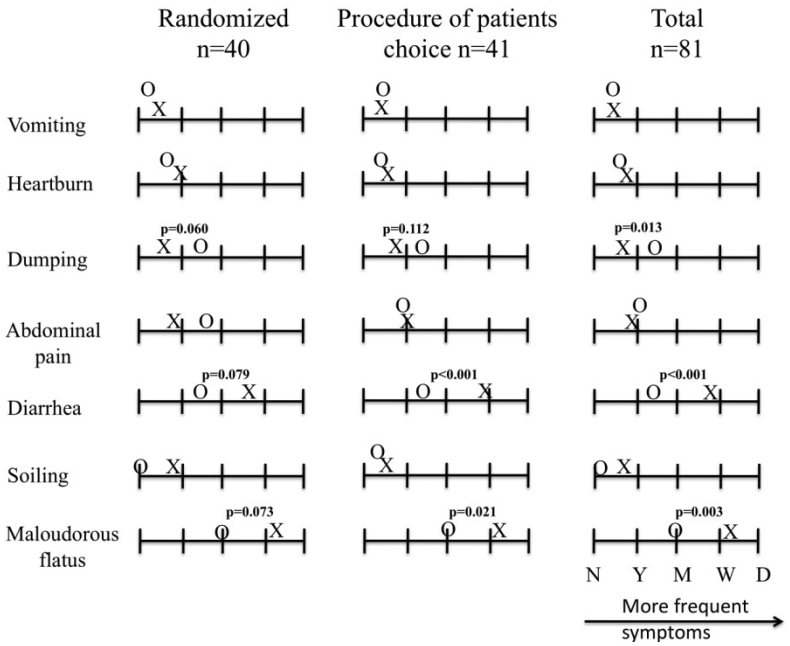


Figure 14 The DS group is represented by X and the RYGBP group by O. Abdominal symptoms were evaluated on an ordinal scale with five steps. N=never. Y=yearly symptoms, M=monthly symptoms, W=weakly symptoms and D=daily symptoms (indicated on the bar on the bottom right). These answers were recoded to numbers (0-4) and means calculated for visual representation only. p-values are calculated non-parametrically (Mann-Whitney-U-test)

Table 5 Laboratory follow up after DS and RYGBP. ANOVA repeated measures analysis is used

	DS	RYGBP	
Hemoglobin (g/L)			
Preoperatively	141±13 (n=45)	139±11(n=44)	
One year postop	135±14 (n=40)	138±15 (n=42)	p=0.280
Three years postop	128.7±14 (n=39)	133±16 (n=35)	
Kobalamines (pmol/L)			
Preoperatively	283±130 (n=45)	280±107 (n=43)	
One year postop	491±370 (n=40)	403±297 (n=44)	p=0.458
Three years postop	478±321 (n=35)	478±280 (n=30)	
Folate (nmol/L)			
Preoperatively	9.5±5.9 (n=45)	11.0±9.2 (n=43)	
One year postop	21.3±15.7 (n=40)	16.8±11.9 (n=44)	p=0.977
Three years postop	67.3±205 (n=38)	61.0±176 (n=28)	
Albumine (g/L)			
Preoperatively	38.2±2.8 (n=45)	39.0±2.4 (n=44)	
One year postop	38.3±3.1 (n=42)	37.8±2.8 (n=45)	p=0.363
Three years postop	38.5±3.3 (n=35)	38.6±3.3 (n=22)	
Glucose (mmol/L)			
Preoperatively	6.43±3.35 (n=43)	5.74±1.20 (n=44)	
One year postop	4.56±0.45 (n=41)	4.94±0.68 (n=42)	p=0.008
Three years postop	4.64±0.44 (n=35)	5.29±1.04 (n=25)	
HbA1c (%)			
Preoperatively	5.24±1.27 (n=38)	4.89±0.87 (n=37)	
One year postop	3.90±0.42 (n=42)	4.41±0.39 (n=43)	p=0.005
Three years postop	3.97±0.34 (n=30)	4.67±0.32 (n=17)	
HDL (mmol/L)			
Preoperatively	1.32±1.21 (n=44)	1.14±0.23 (n=43)	
One year postop	1.07±0.24 (n=42)	1.29±0.37 (n=44)	p=0.149
Three years postop	1.17±0.37 (n=32)	1.34±0.35 (n=17)	
LDL (mmol/L)			
Preoperatively	2.83±0.89 (n=44)	2.93±0.69 (n=44)	
One year postop	1.90±0.64 (n=42)	2.36±0.52 (n=44)	p=0.057
Three years postop	2.00±0.69 (n=28)	2.60±0.63 (n=14)	
Triglycerides (mmol/L)			
Preoperatively	2.38±1.84 (n=44)	1.82±0.76 (n=44)	
One year postop	1.18±0.75 ((n=42)	1.11±0.35 (n=44)	p=0.138
Three years postop	1.00±0.51 (n=32)	1.15±0.62 (n=17)	

During the follow up, one DS-patient had undergone coeliotomy due to internal herniation with incarcerated small intestine and another had undergone cholecystectomy. In addition, nine DS patients had been readmitted due to abdominal pain (whereof five were diagnosed with cholecystolithiasis). In the RYGBP-group, one patient had been operated due to small intestinal obstruction and another had undergone cholecystectomy. Five additional readmissions had been made due to unclear abdominal pain. Five patients (DS, n=3 and RYGBP, n=2) had undergone incisional hernia repair during the follow-up period.

General discussion

Continuous evaluation of all surgical methods is vital to optimizing patient treatment. Bariatric surgery is no exception. In this thesis we examine aspects of the postoperative gastrointestinal function in relation to complications, symptoms and metabolical markers after weight reducing surgery.

In Paper I, the role of hydrochloric acid in patients with stomal ulcer is evaluated. Stomal ulcers are known to occur after gastric resections, and in frequencies of 0.6-16% after RYGBP[95, 97, 99, 100, 102-104, 134]. The pathogenesis of stomal ulcer has been under some debate. Gastric acid is produced mainly in the fundus and corpus of the stomach where parietal cells are abundant. Cardiac mucosa has been considered to be solely mucus producing and thus devoid of acid output[135]. The proximal pouch in RYGBP is constructed high on the lesser curvature, and measurements with a perfused orogastric tube has failed to detect any significant amounts of acid in an intact proximal pouch[111]. Some authors have therefore ascribed gastrogastric fistulation, when acid from the bypassed stomach gains entrance to the proximal pouch, to be the mechanism whereby the Roux-limb can be exposed to acid[104]. However, autopsy studies have challenged the existence of gastric mucosa[136], and reports from our group demonstrate presence of parietal cells all the way up to the gastroesophageal junction[112].

The main finding in paper I was the more acidic environment in stomal ulcer patients as compared to asymptomatic controls. Indeed, the ideal anastomosis for avoiding stomal ulceration would be an esophagojejunostomy, but this gives, in my opinion, an unacceptably high risk of anastomotic leakage, which is reported in up to 11 % after gastrectomy for malignancy[137]. Therefore, all efforts to minimize the pouch size should be made without risking the reliability of the anastomosis. After the pH-measurements, three of the patients with stomal ulcer were reoperated with reduction of their proximal pouches in order to reduce the amount of acid producing parietal cells. In two of these, discontinuation of PPI and resolution of symptoms were obtained, but one patient relapsed with a bleeding stomal ulcer and lifelong PPI was prescribed. The anastomosis and the ulcer itself were not resected in the patient who relapsed, and one could speculate that this contributed to the relapse.

All patients in this study had discontinued their PPI for at least one week prior to the investigation. A weakness of this design can be an acid rebound seen in response to PPI-withdrawal[138]. The majority of the patients, however,

had only had PPI for a short time and I do not believe that this explains the whole difference in acidity demonstrated in this study.

Interestingly, some patients seem to be impervious to acid exposure in the Roux-limb since not all patients with gastro-gastric fistulation develop stomal ulceration even though they have a low pH in their proximal pouch[104]. This notion is also supported by the fact that early routine endoscopy reveals a high frequency of stomal ulceration (7.9%) one month after surgery and only 0.3% one to two years postoperatively[102]. There are no data on how many of the "early" stomal ulcer patients who were under PPI-treatment at the later follow up point in this study, but it seems likely that the jejunal mucosa is more susceptible to acid in the early postoperative period, and that an adaptation occurs over time. Lublin et al. advocate a routine 30-day PPI-course in order to avoid these early ulcerations, but still, late ulcerations appear and they seem prone to perforate[101]. It is worth notice that all eight perforated stomal ulcers in this series arose on antecolic Roux-limbs in a patient material where both antecolic (n=499) and retrocolic (n=403) Roux-limbs were included ($p<0.05$). Furthermore, perforated stomal ulcers seem to have an intriguingly consistent location at the top of the antimesenteric side of the Roux-limb[101, 139], which could imply a circulatory facet to the ulcerogenesis.

In paper II, we adopted the wire-less BRAVO-system™ to study the pH in the proximal jejunum after RYGBP. We were able to present long-time registrations (exceeding 24h) of pH in the proximal Roux-limb for the first time. Certain modifications in the placement of the capsule gave longer registration times. I chose to place all capsules under direct visual control with the endoscope to be sure of their position. In some patients, the egress from the pouch to the Roux-limb was not straightforward, and in these cases the endoscope was very useful to guide the applicator in the right direction, in order to position the pH-sensor in the jejunal lumen. The positioning-hole of the BRAVO™-capsule was ideally placed on gastric mucosa for a more reliable placement. During the study, I also increased the time with applied suction to two minutes instead of one. With these measures, a registration of more than 24 hours was generally obtained (mean 25.7 hours).

We found a median of 10.5% of time with pH<4 at the level of the gastrojejunostomy in the 16 asymptomatic patients with successful recordings. We adopted the cut-off level at pH<4, used in the evaluation of gastroesophageal reflux disease, for several reasons. First, a pH-level below 4 gives rise to heartburn in normal subjects[140] suggesting an erosive effect on mucosa normally only subjected to neutral pH. Second, normal subjects without heartburn have a pH greater than 4 in 98,5% of the time in a 24 hour registration[141]. Third, and maybe most relevant to the present study, pepsinogen is activated into pepsin, which plays a fundamental role in formation of ulcers in the gastrointestinal tract, below a pH of 4[142]. Fourth, in an experi-

mental setting, jejunal ulcers have been produced with pepsin and hydrochloric acid [142, 143]. This is, in our opinion the most plausible pathogenesis for stomal ulcers seen after RYGBP and further studies of pepsin activation in the gastrojejunostomy are warranted.

The fact that asymptomatic patients can have as much as 37.7% of time with pH<4 without ulcer formation or symptoms is interesting and in line with the before mentioned report of patients without ulcers but low pH because of gastrogastric fistulation [104]. Our data from paper II is also in line with the acidity found in the proximal pouches of the control group in paper I (6.7-43.9 % of time with pH<4). The conclusion that pH is closely related to ulcer formation is supported by the results in paper I, but the nature of the defense mechanisms, which seem to develop in the jejunal mucosa of the Roux-limb, remains to be completely understood. Smoking and non-steroid anti-inflammatory drugs have been linked to stomal ulceration[144]. Helicobacter pylori infection, even if successfully treated could also predispose for stomal ulcer formation[97] but other authors have not found this association[145]. Other microbial factors of this normally sterile locale might play a role here, as might histological changes that occur after RYGBP[146], but this has not been addressed from an acid-protection point of view and further study of this would be interesting.

We also investigated four symptomatic patients. Of these, two had discontinued their treatment for two weeks, and their pH-results were in line with the asymptomatic group (10.0 and 11.3% of time with pH<4), thus no obvious rebound phenomenon could be seen. Two patients were studied during PPI-therapy and in these, no time with pH<4 was registered at all, which is reassuring considering the wide-spread use of PPI.

In paper III rapid gastric emptying after DS, with a mean half-emptying time of 28 minutes, is demonstrated. Gastric emptying after DS is not previously described. In this study, we aimed primarily at describing the postoperative gastric emptying since normal gastric emptying in normal weight and obese subjects are described prieviously[132, 147, 148]. In order to achieve this, we reduced the solid meal to about 80 ml (75 kcal) since studies of the stomach remnant after DS have demonstrated volumes as low as 80ml[149]. With the hypothesis of fast emptying, we also stipulated that the subjects should ingest the meal in two minutes. The half emptying time of the gastric tube with this method was 28±16 minutes. There are two studies in the literature where emptying of the gastric tube after sleeve gastrectomy is investigated[150, 151]. Different protocols are used for scintigraphic studies in the literature, why comparisons of our results must be made with great caution. Braghetto[22] et al used an egg sandwich with approximately 200 g of bread, consumed within ten minutes, and obtained a postoperative half-emptying time of 38 minutes, while Bernstine [23] et al found a postoperative half emptying time of 57 minutes using a 230 kcal meal consisting of bread (60 g) and scrambled eggs

(35% fat, 47 % carbohydrates and 18% protein, ingestion time not specified). We interpret our result of 28±16 minutes as being quicker than after sole sleeve gastrectomy. This could be explained by denervation during the dissection around the pylorus, which takes place in the duodenal switch part of DS.

The normal lag-phase[113] was absent in all but six of the study subjects. The definition of the lag-phase in gastric emptying has been under some debate[152]. In this setting of postoperatively deranged anatomy and pylorus function, a description of emptying cannot readily be compared to normal gastric emptying. It seems illogical to attribute any of the emptying curve as lag-phase when it is essentially linear from the first (five minutes) scan, even if the crossing of the regression line at 90% is normally used for lag-phase definition in our lab[132]. We have therefore studied the graphs individually, and designated a lag-phase in those patients who demonstrated any biphasic emptying pattern. Indeed, the frequent lack of lag-phase and quick gastric emptying is also described after truncal vagotomy and pyloroplasty for ulcer disease[153]. There was nor correlation between gastric emptying rate and weight reduction, nor to time since surgery (data not shown).

In the fasting state, higher levels of circulating PYY were found in the DS-group compared to the controls. Elevated PYY levels have also been reported in jejuno-ileal bypass patients[129], having a similar alternation of the small bowel. In contrast, non-operated obese subjects have low[124] or normal[125-127] levels of PYY. In the present study, a marked PYY response to the test meal was also seen in the DS-group. This finding, as well as our earlier report of an exaggerated PYY-response in gastric bypass patients compared to controls[131], are likely due to the rapid appearance of nutrients in the ileum. Active PYY_{3-36} has high affinity to Y2-receptors in the hypothalamus, inducing satiety in humans[124]. Even though its effect on food intake in humans later has been disputed[128], one might speculate that in addition to the restrictive and malabsorptive effects of DS, the patients also benefit from a hormonal mechanism with constantly elevated PYY and rapidly rising levels at meals.

Disturbing dumping symptoms were surprisingly uncommon in our DS-patients. In other procedures with swift passage to the small bowel (total/subtotal gastrectomies and gastric bypass) dumping can be a considerable and long-lasting problem. In a small study of six patients with dumping problems after gastric surgery, increased PYY-levels in response to orally administered glucose was reported[154]. In our study, however, dumping was uncommon and the now demonstrated reservoir function of the gastric tube might explain this. In accordance, postprandial proinsulin, insulin and glucose levels in BPD-DS patients are similar to those of normal-weight control subjects, as earlier demonstrated[155]. This is not the case after gastric bypass, where ingested food immediately reaches the small bowel, giving rise to a high glucose and insulin levels, as well as an elevated frequency of dumping.

However, the relatively long time after surgery (3.5 years) might also have given our BPD-DS patients a chance to adapt their eating behaviour to avoid dumping.

In paper IV, the aim to achieve a prospective controlled randomized trial, was only partly met. Since both operations were part of the treatment arsenal, we complied with patients who wanted DS outside the study. As time passed, it became obvious that as much as half of the patients chose their type of operation themselves. These decisions were often influenced by successful cases in their surroundings and since we aimed at randomizing as many as possible, we did not favor either procedure. Since the patients choosing DS turned out to be well matched with those choosing RYGBP, we decided to do a follow up of these patients as well. In this way we feel that as much information as possible is extracted from our experience.

Our BMI-cut-off at 48 units was chosen in order to include 80 patients within three years based on our referral rate. Some might argue that this is a low BMI for DS and indeed, some authors recommend lap-RYGBP as the standard operation in this group of patients[156]. On the other hand, Hess et al, with extensive experience of over 1300 cases, prefer the DS in all morbidly obese patients regardless of BMI[75]. Furthermore, other criteria are also important (distribution of fat, diabetes, gender) in selecting patients for a specific type of operation.

In this study we chose to use our standard technique in super obese patients, the open approach. First, when enrolment began, no standard procedure for laparoscopic DS existed and second, we did not want a steep learning curve to interfere with the results. The overall complication level in the study was indeed low and we believe that three reoperations (bile leakage, haemorrhage, negative exploration) in a patient cohort like this is acceptable. Kim et al has compared open and laparoscopic DS, with a mortality of 7.6% in the laparoscopic group[106] and in the literature, mortality after DS varies from 0-3.5%[75-77, 106, 157]. Our only death, due to pulmonary embolism, occurred in the DS-group (2.2%). Fatal pulmonary embolism is a very rare occurrence and hard to ascribe to the specific type of operation. Duration of surgery does however, play a role in the risk for tromboembolic complications.

The duration of surgery was longer in the DS group. This is not surprising since DS implies a larger operative field, with extended dissection and a hand-sutured anastomosis. However, our mean operating time, 153 minutes for DS, is shorter than earlier reported (259 minutes)[106]. The length of stay as well as the time to ingestion of fluids and solids were longer after DS. The more extensive operation will most likely lengthen the postoperative gastrointestinal paralysis, thus prolonging the time requiring nil per mouth. Our demand that all patients must to be able to eat normal food before discharge inevitably results in an extended length of stay after DS and a longer length

of stay after DS is in accordance with the literature[79, 158, 159]. The significantly higher levels of C-reactive protein and morphine consumption during the first three postoperative days after DS also reflect the more complex nature of this operation.

The major finding was the large difference in BMI-reduction, 24 BMI-units and 17 BMI-units, for DS and RYGBP, respectively. This is in line with earlier studies comparing the two procedures[76-78]. DS can therefore be recommended to super-obese patients who need massive and reliable weight loss. A sizable portion of the super obese patients obtains dissatisfactory weight results from RYGBP. Eleven of the RYGBP-patients in our study (24%) had not achieved a 50% excess weight loss, which is a common measure for successful bariatric surgery, as compared to 4 patients (8.9%) in the DS group. Moreover, the RYGBP group included five patients (12.5%) who had a weight loss of less than 10 BMI-units, whereas the lowest weight loss in the DS group was 12.1 BMI-units. Further treatment of the patients who fail to loose weight after bariatric surgery or regain weight over time represents a big and increasing challenge to the medical community.

Lower glucose and HbA1c levels were found after DS and after three years, no hypergycemia was found in the DS-group. Recently, DS-patients were demonstrated to have fasting glucose levels below that of normal weight control subjects after DS[155]. Apart from superior glucose control, a high resolution-rate of other comorbidities (diabetes, hypertension and hypercholoesterolemia) are reported after DS[20].

No symptomatic hypoalbuminemia occurred in either group. This is otherwise a rather common complication after DS, especially in patients with a short common channel. We can confirm earlier reports stating that hypoalbuminemia is rare using a constant 100-centimetre common channel in all patients[20]. It is, nevertheless, our clinical impression that an elevated suspicion of nutritional defects is warranted, and since normal multivitamin substitution may be inadequate even in RYGBP[160] and a greater risk of vitamin A- and D-deficiencies after DS has been reported[90], additional supplements could be advantageous in this more malabsorptive procedure.

The risk of gastrointestinal problems is important for the patient. Diarrhea and malodorous flatus is a more common problem after DS, even though these symptoms can occur after RYGBP as well. Higher frequency of bowel movements after bariatric surgery are reported prieviously[161, 162] and some improvement over time is reported[157]. Wasserberg et al, however, found no difference in bowel function between DS and RYGBP[163]. Soiling, a social handicap, was rare in our material. As expected, RYGBP was more prone to give rise to dumping symptoms. Neither heartburn nor vomiting was a common problem. This is to be expected since none of the operations have a pronounced restrictive component. Overall, patients reported a very high level of satisfaction, 100% of the DS-patients, and 85% of the RYGBP patients, were satisfied or very satisfied (p=0.086). As mentioned before, non-

satisfied patients had lost less weight than the RYGBP-group as a whole, again implying that the weight result is of utter importance for quality of life.

One drawback of the present study is the rising number of patients that declined randomization between the two operations. There were no differences in weight or age between the two groups and we believe that the weight result and metabolic parameters are unlikely to be affected by the patients' choice. The subjective symptom-scores could be influenced by anticipation, but the overall results of the randomized and non-randomized patients were similar. Randomization aside, the operations were not blinded for the patient, and the experience of gastrointestinal symptoms could be influenced by expectation in relation to the performed procedure as well.

In summary, DS produces superior weight loss and better glucose control compared to RYGBP in the long run, with acceptable nutritional risks and without intolerable complications for the patient. We believe that DS has a place in future surgical treatment of super obese patients, an increasing patient cohort, as well as in surgical treatment of failed RYGBP.

Conclusions

Paper I

Patients with stomal ulcer after RYGBP, have lower pH in their proximal pouch as compared to asymptomatic control subjects. Acid seems to play a fundamental role in stomal ulcer formation. Reduction of the pouch size did not eliminate stomal ulcers completely.

Paper II

Wire-less pH monitoring in the proximal Roux-limb after RYGBP is feasible and safe. The mucosa of the proximal Roux-limb is exposed to pH below four in median of 10.5% of the time even in asymptomatic patients.

Paper III

Although the pylorus is preserved in DS, gastric emptying is fast. After DS, PYY levels are elevated in the fasting state as well as after a standardized meal compared to controls. The marked postprandial response could be caused by the rapid appearance of nutrients in the distal ileum and despite this, dumping symptoms are uncommon.

Paper IV

DS produces superior weight results and glucose control as compared to RYGBP in patients with BMI>48. Both operations are safe and yield high satisfaction-rates but a higher risk of diarrhea and malodorous flatus arise after DS.

Svensk sammanfattning (summary in Swedish)

Övervikt och fetma är växande problem i Sverige och globalt. Detta innebär att en allt större del av befolkningen riskerar sänkt livskvalitet, sjukdom eller för tidig död till följd av detta. Ett stort antal behandlingsmetoder för behandling av fetma har provats, men den enda behandling med varaktigt resultat på vikt och följdsjukdomar är kirurgi. Gastric bypass (RYGBP), som innebär att magsäcken ”kopplas ur” och att en liten magsäcksficka kopplas direkt till tunntarmen, är den i särklass vanligaste operationsmetoden i Sverige idag. Av de överviktiga är det gruppen med de allra tyngsta som ökar mest och i denna grupp har gastric bypass sämre resultat. Vi har sedan 2003 därför även använt biliopankreatisk divergering med duodenal switch (DS), för att hjälpa patienter med BMI>48. Både RYGBP och DS har specifika för- och nackdelar och denna avhandling studerar de förändringar i magtarmkanalen som uppkommer efter överviktskirurgi.

Delarbete I

I detta arbete studeras en av de vanligaste komplikationerna efter gastric bypass; stomalt sår som uppkommer i den tunntarmsslynga som kopplas till den lilla magsäcksfickan. Varför vissa patienter får denna komplikation vet man ej. Man har tidigare inte kunnat visa någon signifikant syraproduktion i den lilla magsäcksfickan och därmed ansett att gastro-gastrisk fistel (då saltsyra från den urkopplade magsäcken kommer över till fickan), ligger bakom all sårbildning. Huvudfyndet i delarbete I är ett mycket lågt pH i den lilla magsäcksfickan vid mätning med nasogastrisk pH-givare hos patienter med stomalt sår, jämfört med symtomfria kontroller. Detta låga pH förelåg trots att gastro-gastrisk fistel uteslutits med röntgen. Tre av patienterna i studien opererades med förminskning av magsäcksfickan och av dessa blev två symtomfria. Den tredje fick dessvärre ett nytt sår och får fortsätta med livslång medicinsk behandling.

Delarbete II

Tekniken för trådlös pH-mätning i magtarmkanalen, det så kallade BRAVO™-systemet, anpassas i detta arbete till att undersöka surhetsgraden i det område där stomala sår bildas. Gastric bypass-opererade patienter utan symtom på stomalt sår undersöktes genom att man med hjälp av gastroskop pla-

cerade en BRAVO™-kapsel vid tunntarmens koppling till magsäcksfickan och på detta sätt kunde pH registreras i upp till 48 timmar medan patienten levde som vanligt. Metoden fungerade och kapslarna kunde placeras i önskat läge under ögats kontroll med hjälp av gastroskopet. Tekniken för att fästa kapseln modifierades och allt längre registreringstider erhölls i och med detta. Med denna metod fann vi en relativt sur miljö, med ett pH<4 under 10.5% av registreringstiden. Fyra undersökningar av patieneter med symtom gjordes också. Två undersöktes under pågående syradämpande behandling och de hade aldrig lägre pH än 4. Resultaten visar en signifikant produktion av magsyra trots att magsäcksfickan görs liten. Att de flesta patienter trots detta inte utvecklar sår talar för att en adaptation av slemhinnan i tunntarmen sker.

Delarbete III

Vid DS görs magsäcken om till ett smalt rör. Nedre magmunnen bevaras vid denna operation, men dess funktion efter operationen är inte undersökt. Ett stort antal hormoner är inblandade i reglering av magsäckstömning och många av dessa har också hungerreglerande funktioner. I detta arbete fokuserar vi på PYY, som hos icke-opererade personer har betydelse för magsäckstömning och hungerupplevelse. Vi undersökte magsäckstömning på 20 patienter efter DS med hjälp av en radioaktivt märkt omelett. På tio av dessa undersöktes också PYY-nivåer i fasta och efter en standardiserad måltid. Vi utvärderade också det symtomkomplex som kallas dumping och som ofta förekommer efter magsäcksoperationer. De fynd som gjordes kan sammanfattas med en snabb magsäckstömning, sannolikt till följd av att nedre magmunnens nervförsörjning påverkats av operationen, höga PYY-nivåer och få dumpingsymtom. Även om magsäckstömningen var snabbare än normalt, så var den inte momentan utan hade en halveringstid på 28 minuter i genomsnitt. Detta förklarar att dumping är sällsynt efter denna operation. De höga PYY-nivåerna är ett intressant fynd och man kan spekulera i om dessa nivåer har en särskild effekt på mättnadskänslan. Det skulle kunna bidra till den goda vikteffekt som uppnås med DS på lång sikt.

Delarbete IV

Superobesitas (BMI>50) är den snabbast växande patientkategorin bland de sjukligt överviktiga i USA. Gastric bypass ger inte optimalt viktresultat hos dessa patienter. Vi har i en randomiserad studie mellan DS och RYGBP jämfört perioperativa risker, viktresultat och gastrointestinala symtom. Utvärderingen är gjord i median 3,5 år efter operationen och innehåller även biokemiska jämförelser. Huvudfyndet är en kraftigare viktnedgång efter DS (24 BMI-enh) jämfört med gastric bypass (17 BMI-enh). Duodenal switch ger mer besvär av diarréer och illaluktande gaser, medan gastric bypass ger

dumping. Större förbättring av glukos- och HbA1c-nivåer förelåg efter DS. Patienterna är mycket nöjda med effekten av operationen på deras allmänna välbefinnande efter både DS och RYGBP. De viktresultat vi kan visa är i nivå med de flesta andra studier. Att DS har en mycket god effekt på diabetes är känt, men skillnaden i fasteglukosvärden har inte hittats tidigare.

Konklusioner

I Trots att magsäcksfickan görs liten finns en signifikant syraproduktion kvar vilket kan leda till mycket låga pH och stomala sår i tunntarmens första del.

II Den trådlösa BRAVO-kapseln kan användas för att undersöka patienter och mäta pH kontinuerligt under två dygn efter gastric bypass. Den första delen av tunntarmen utsätts för låga pH-värden även hos symtomfria patienter, vilket antyder att en adaptation av slemhinnan sker över tid efter operationen.

III Tömningen av magsäckstuben efter duodenal switch är snabb, men inte momentan vilket kan förklara att så få patienter får dumpingsymtom postoperativt. PYY-nivåerna är höga i fasta och stiger kraftigt efter måltid jämfört med åldersmatchade kontroller.

IV Duodenal switch ger större viktnedgång och lägre blodsockernivåer än gastric bypass vid BMI>48. Detta sker till priset av mer besvärande diarréer och illaluktande gaser. Riskerna vid de två ingreppen är låga och likvärdiga.

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