

UPPSALA UNIVERSITET

Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 1324

Gastric bypass

Technical aspects and long-term results

EDUARDO SIMA





ACTA UNIVERSITATIS UPSALIENSIS UPPSALA 2017

ISSN 1651-6206 ISBN 978-91-554-9889-4 urn:nbn:se:uu:diva-319510 Dissertation presented at Uppsala University to be publicly examined in Enghoffsalen, Akademiska sjukhuset, Uppsala, Saturday, 27 May 2017 at 09:15 for the degree of Doctor of Philosophy. The examination will be conducted in Swedish. Faculty examiner: Professor Mikael Wirén (Institutionen för klinisk och experimentell medicin, Linköpings universitet).

Abstract

Sima, E. 2017. Gastric bypass. Technical aspects and long-term results. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 1324. 67 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-554-9889-4.

Roux-en-Y gastric bypass (RYGBP) achieves superior short- and long-term weight loss compared to other weight loss modalities. Different operative techniques have been developed to technically facilitate the surgical procedure, with consequences in the form of an array of postoperative complications and gastrointestinal symptoms. Furthermore, as our follow-up on operated patients extends beyond the first postoperative years, it becomes apparent that a significant number of patients experience unsatisfactory weight result. Current research is just starting to chart factors associated with postoperative long-term weight regain with the ultimate goal of preventing it.

In Paper I it is found that the linear stapled technique for the gastrojejunostomy in laparoscopic RYGBP is associated with shorter operative time, in-hospital stay and a lower incidence of surgical site infections and anastomotic strictures compared to the circular stapled technique. Paper II demonstrates that, despite no differences in weight result, the 21-mm circular stapled technique for the gastrojejunostomy is associated with a higher incidence of vomiting and endoscopic anastomotic dilatations compared to the 25-mm circular stapled technique and the linear stapled technique in the long-term after RYGBP. Paper III shows that despite differences in body composition, long-term weight responders and non-responders after RYGBP did not differ in resting, glucose-induced or activity-related energy expenditure. Lastly Paper IV shows long-term weight result is associated with fasting levels of leptin and ghrelin, and that the response of these hormones to a glucose load might contribute to perpetuate obesity.

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ISSN 1651-6206 ISBN 978-91-554-9889-4 urn:nbn:se:uu:diva-319510 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-319510)

Till min familj

"Estar contigo o no estar contigo es la medida de mi tiempo" Jorge Luis Borges

List of Papers

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

- I **Sima E**, Hedberg J, Ehrenborg A, Sundbom M. (2014) Differences in early complications between circular and linear stapled gastrojejunostomy in laparoscopic gastric bypass. *Obesity Surgery*, Apr;24(4):599–603.
- II Sima E, Hedberg J, Sundbom M. (2016) Gastrointestinal symptoms, weight loss and patient satisfaction 5 years after gastric bypass: a study of three techniques for the gastrojejunal anastomosis. Surgical Endoscopy, Apr;30(4):1553-8.
- III Sima E, Holmbäck U, Eriksson, JW, Berglund M, Sundbom M. (2017) Non-responders after gastric bypass surgery: assessment of body composition, glucose metabolism and energy expenditure. Manuscript.
- IV **Sima E**, Webb DL, Hellström P, Sundbom M. (2017) Non-responders after gastric bypass: hormone response and glucose homeostasis during an oral glucose tolerance test. Manuscript.

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Abbreviations

AEE	Activity-related energy expediture
BMI	Body mass index
DEE	Diet-induced energy expenditure
EBMIL	Excess BMI loss
ELISA	Enzyme-linked immunosorbent assay
EWL	Excess weight loss
FFM	Fat free mass
GERD	Gastroesophagueal reflux disease
GJ	Gastrojejunostomy
iAUC	Incremental Area-Under-the-Curve
NIDDM	Non-insulin dependent diabetes mellitus
OGTT	Oral glucose tolerance test
REE	Resting energy expenditure
RQ	Respiratory quotient
RYGBP	Roux-en-Y gastric bypass

Introduction

Morbid obesity is acknowledged as a concern of epidemic proportions worldwide (1, 2). Roux-en-Y gastric bypass (RYGBP) is the most common procedure for the treatment of morbid obesity in Sweden (71% of all bariatric surgeries in 2015) (3). The operation is routinely performed laparoscopically (3), which facilitates the postoperative course of treatment, especially regarding the duration of in-hospital stay and postoperative convalescence (4). Bariatric surgery produces a significant and more durable weight loss compared to any non-surgical treatment modality (5, 6). A low incidence of postoperative complications, both on the short- and the long-term, is however important, in addition to good postoperative weight loss results.

The operative technique in RYGBP has changed in the last decade, often to cater a need for simpler technical handling. Particularly the gastrojejunostomy (GJ) can be constructed with circular or linear staplers, and it can be partially or completely hand-sutured. New operative techniques have been evaluated regarding short-term results (7), but results several years after surgery are uncommon in the literature.

In our clinical practice, we have been able to readily identify different factors associated to suboptimal postoperative results. When these factors have been found to have a direct association to postoperative complications and when these complications have been quickly identified, we have been able to remove these factors from our practice. Other factors that have been more loosely related to postoperative complications, we have chosen to follow-up and study.

Furthermore, about 50% of RYGBP patients regain weight after two years(8), and after 10 years about one fifth of patients regain enough weight to classify their weight result as failed (9). To develop strategies to treat these patients, it is important to first determine the cause of the poor weight result.

In Paper I, we followed a cohort of patients who underwent laparoscopic RYGBP with two different techniques for the GJ. We studied differences between the groups regarding operative time and in-hospital stay. Moreover, we aimed to investigate whether there was a difference in the incidence of shorttime complications, and whether the choice of stapler was associated to any of these complications as registered at the patients' 6-week visit at the outpatient clinic. In Paper II, we followed a group of patients who underwent RYGBP with three different techniques for the GJ: linear stapled, 21-mm circular stapled and 25-mm circular stapled. We aimed to study differences in patient-rated gastrointestinal symptoms, weight loss, overall satisfaction and need for endoscopic interventions 5 years after gastric bypass between patients who underwent RYGBP performed with different techniques for establishing the GJ.

For Papers III and IV, we followed 40 patients that underwent gastric bypass more than 5 years ago. Patients were matched regarding their preoperative age, weight and years since surgery. Patients were selected depending on their 5-year weight result: non-responders if they had achieved <40% excess BMI loss (EBMIL) and responders if they had achieved >70% EBMIL.

In Paper III, we examined body composition and energy expenditure in responders and non-responders. The aim of the study was to determine whether, adjusting for body composition, there were any differences in energy expenditure between the two groups during fasting and during an OGTT.

In Paper IV, we investigated glucose homeostasis and levels of peptide hormones in responders and non-responders. Leptin, ghrelin, GLP-1, GIP and PYY are all hormones known to affect satiety and glucose metabolism. The aim of the study was to investigate whether peptide hormones in fasting and during an OGTT differed between the groups.

Background

Morbid obesity

Overweight is measured using the body mass index (BMI, kg/m²), calculated as the weight in kilograms divided by the square of the height in meters. According to WHO, normal BMI lies between 20 and 25 kg/m², overweight between 25 and 30 kg/m² and obesity above BMI 30 kg/m² (1). Obesity is further classified as class 1 obesity (BMI 30-35 kg/m²), class 2 obesity (BMI 35-40 kg/m²) and class 3 obesity (BMI 40 kg/m² and above). Obesity classes 2 and 3 are usually classified as morbid obesity. According to national (10) and international (11) guidelines, a BMI of 35 kg/m² and above makes a patient eligible for bariatric surgery.

RYGBP

Modern RYGBP is an operation resulting from several modifications of a surgical procedure described by Mason in 1969 (12). This surgical procedure, designed after an observation that patients achieved a consequent and significant weight loss after gastrectomy, includes the construction of a small gastric pouch of the proximal stomach containing a volume of about 15-30 ml, with the remaining stomach separated from ingested contents. The gastric pouch is connected to the jejunum by a GJ and the gastro-pancreatico-biliary produces are reconnected to the gastrointestinal tract by means of an enteroanastomosis, some 100 cm distal to the GJ (Figure 1).



Figure 1. Roux-en-Y gastric bypass (13)

Weight loss after RYGBP

A combination of restriction of ingested contents and elevated satiety have been described as mechanisms causing weight loss after RYGBP (14), while malabsorption and dumping nowadays are considered to play a minor role (15). Studies have reported a 50-80% of excess weight loss after RYGBP. Different prospective RCTs showed 77% EWL (excess weight loss) at one year (16), 68%, at four years (17), 67% at five years (18) and 70% EWL at ten years (19). Earlier studies have shown no short-term differences in weight loss between hand-sewn, circular stapled and linear stapled GJ (20).

Weight recidivism after RYGBP

After RYGBP, excess weight loss decreases from about 66% at 1-2 years to 50% at ten years (21). Despite being a fairly common occurrence, weight recidivism after RYGBP has no consensus about how to be defined and measured. To begin with, the definition for weight recidivism varies with different parameters. A common parameter for weight loss is percent of excess BMI loss. Excess BMI is defined as all BMI units above 25 kg/m². Thus a widespread criterion for weight recidivism is whether the patient loses less than 50% of EBMIL at the time of measurement (22). Criticism about this criterion is that, because there might be differences in baseline BMI, lighter patients may achieve higher results as measured in %EBMIL (23). Other methods of measuring weight loss are percent of total weight loss (%TWL), and amount of lost BMI units. To measure weight recidivism, the question rises as to which point the recidiving weight is compared. Usually it is considered that most patients achieve their nadir weight one year after surgery. Compared to that, weight recidivism is considered to occur in 30-50% of patients. Five years after RYGBP, patients had lost about 28% of their total preoperative weight corresponding to 71% EBMIL, and regained about 14% of their weight and BMI lost, compared to their two-year weight result (24). Ten years after RYGBP, patients had lost about 25% of their total preoperative weight, regained about 30% of their weight lost, compared to nadir, and about 30% of them regained most of their lost weight (25).

Paper I: Short-term complications

Early complications to RYGBP

According to the Scandinavian Obesity Surgery Registry (SOReg), it is uncommon to register major surgical complications to RYGBP, such as anastomotic leak (1.1%), intraperitoneal abscess (0.9%), postoperative thromboembolism (0.1%) and postoperative bleeding (2.0%) at the six-week follow-up visit. Other short-term complications are also uncommon, such as surgical site complications (1.0%), anastomotic ulcers (0.5%) and anastomotic strictures (0.2%) (26). The risk for early complications is higher if there are adverse events during surgery, if a laparoscopic RYGBP is converted to an open one or during the learning curve of the procedure.

Anastomotic leak

The GJ is the most common location for anastomotic leak in RYGBP (27, 28). The incidence of leak from the GJ in RYGBP is about 1% in large series (28, 29) and it has not been found to differ between open and laparoscopic RYGBP in a randomized trial (4). According to data from SOReg, anastomotic leak has been shown to occur in 0.9% of patients operated with laparoscopic RYGBP, with an odds ratio for anastomotic leak of 2.8 with the circular stapler compared to the linear stapler in the same group of patients (29). An anastomotic leak occurring hours after surgery is often caused by a technical error in the construction of the anastomosis. With anastomotic leaks showing several days after surgery, one must also consider ischaemia in the area of the anastomosis. The management of anastomotic leaks has been suggested to include prompt surgery (28), which makes it of utmost importance to observe

the postoperative patients regarding early signs as tachycardia and accentuating upper abdominal pain postoperatively. For early leaks the preferred option consists of primary repair, whereas for late leaks it is recommended to drain the area of the leakage, and the use of endoscopically applied stents has been discussed (30, 31).

Surgical site infections

Surgical site infections (SSI) in laparoscopic surgery of obese patients occur in about 1.6% of patients (32). In laparoscopic RYGBP, surgical site infections have been more frequently found when using a circular stapler, with a large retrospective study showing a 4.7% incidence of SSI using the circular stapler (33) and a recent meta-analysis showing a significantly reduced incidence of SSI associated to the use of a linear stapler for the GJ (33). However, most of the studies included were relatively small, and the size of the instruments used and the participating surgeons' skill could not be standardized. No standardized course of preoperative antibiotics was accounted for in these studies either. Although increased BMI and diabetes seem to increase the overall frequency of postoperative SSI (34, 35), these factors do not seem to affect the incidence of SSI after RYGBP in particular (36).

Anastomotic ulcer

Anastomotic ulcers after RYGBP(Figure 2), often presenting as upper abdominal pain, nausea or vomiting, have been showed to occur in 4.6% of laparoscopic RYGBP patients in a recent review (37). According to SOReg, 1.0% of all patients operated with laparoscopic RYGBP developed an anastomotic ulcer within one year of surgery (29). The ulcers seem to occur most commonly on the jejunal side of the anastomosis, with the majority presenting within the first year after surgery (38). Anastomotic ulcers entail epigastric pain, and can lead to bleeding or perforation. The pathogenesis has been theorized to be impaired microcirculation in the anastomosis and/or an elevated acidity in the gastric pouch, perhaps secondary to unintentional construction of a large gastric pouch, with a higher exposure to gastric acid of the GJ (39). Risk factors such as diabetes, peptic ulcer history and high doses of aspirin are related to a higher incidence of anastomotic ulcers (40).



Figure 2. Fibrin-coated anastomotic ulcer located on jejunal mucosa. (Courtesy of M. Sundbom)

Anastomotic stricture

Narrowing of the GJ typically presents several months after surgery. Its cause has been postulated to be an ulcer healing with fibrosis or ischaemia of the anastomotic area. The condition is discovered as the patient requires care due to food intolerance (with solid or liquid ingested contents), epigastric pain and/or emesis. Although the incidence of anastomotic stricture in Sweden has been reported to be 0.2% at the six-week visit (26), a recent randomized trial between laparoscopic RYGBP and laparoscopic gastric banding found the incidence of anastomotic stricture to be 14.6% in post-RYGBP patients with a mean follow-up of 4.2 years (17). A meta-analysis found a higher risk for anastomotic stricture using the circular stapler (33) compared to the linear stapler although most included studies supporting this conjecture compared small groups of patients. A recent review of the literature has shown a higher incidence of anastomotic stricture using a 21-mm circular stapler compared to using a 25-mm circular stapler (41). In most cases, anastomotic strictures can be treated successfully with endoscopic dilatations (42, 43) (Figure 3).



Figure 3. Left: Normal anastomosis after RYGBP. Middle: Anastomotic stricture. Right: Endoscopic dilatation using balloon dilator. (Courtesy of M. Sundbom)

Operative time

In Sweden, the mean operative time for all laparoscopic RYGBP surgeries between 2007 and 2013 was 73 minutes (29). The linear stapled technique for the GJ in RYGBP has in several studies been found to result in shorter operative time compared to the circular stapled (29, 33, 44). Operative time clearly depends on the surgeon's experience and familiarity with the procedure as well as the technique used and thus, studies including the learning curve of a procedure present longer operative times (18).

In-hospital stay

A laparoscopic operative technique for the RYGBP results in a short in-hospital stay compared to an open technique for the same procedure (45). Duration of stay was a mean of 2.1 days for all RYGBPs between 2007 and 2013 in Sweden and was found to be shorter with the linear stapled technique (29). However, in a meta-analysis of studies including large groups of patients operated with laparoscopic RYGBP, no difference was found regarding in-hospital stay between the two stapling techniques (33). As with operative time, in-hospital stay depends on the experience of the surgical team as well as whether the learning curve for the procedure is included in the study presented. It is also affected by the postoperative dietary regime and the rate of postoperative complications.

Paper II: Long-term gastrointestinal symptoms

Reflux

In a Swedish population study, reflux as a gastrointestinal symptom was reported to occur in 25% of the population (46). Gastroesophageal reflux disease (GERD) is common in the morbid obese population, as common in 50% of patients with BMI>30 (47, 48). This has been postulated to be caused by a high intra-abdominal pressure together with a defective anti-reflux barrier, due to a malfunctioning lower esophageal sphincter and a higher incidence of hiatal hernias in the obese (49). RYGBP alleviates reflux symptoms in 56-94% of patients within the first year after surgery and patients with higher excess weight loss experience more relief (50-52).

Dumping

Dumping refers to the symptoms secondary to the fast passage of the undigested bolus to the small bowel, which causes a local osmotic reaction and a systemic hyper-insulinemic effect (53). It is a well-known consequence of gastric and esophageal surgery. Dumping occurs in a highly varying percentage of patients after bariatric surgery (12-75% of RYGBP patients) (54, 55). In a recent study, dumping presents itself most commonly as fatigue and nausea, but other symptoms such as the sensation of impending fainting, flushing, abdominal cramps and diarrhoea have been described (54). Although considered a mechanism important to initial weight loss, the prevalence of dumping after RYGBP is not associated with long-term weight loss (55).

Vomiting

Vomiting has been reported in 2.3% of the general population (46) and at least once per month in about 7% of patients with BMI > 35 (56). Reports on vomiting after RYGBP have been varied, ranging from 7% of patients reporting having it more than once a week six months after surgery in an RCT (57) to 33% of patients reported vomiting at least once weekly in a five-year prospective study based on interviews (58). Vomiting is not physically possible in the same way after RYGBP because the patient lacks the reservoir capacity of the stomach from which to vomit. Frequent vomiting in the immediate postoperative period is an ominous sign, symptomatic of a total or subtotal obstruction in the gastrointestinal tract. As a late gastrointestinal symptom after RYGBP surgery, it has been attributed to overfilling the gastric pouch during meals and could be associated to failed attempts at binge-eating (58).

Abdominal pain

Abdominal pain has been reported as a functional symptom in 0.5-2.0% of the general population (59) and in about 20% of patients with BMI>30 kg/m² (56, 60). Postoperatively, there is a range of conditions secondary to the surgery that can cause abdominal pain, such as behavioral and functional disorders, biliary disease, and diseases of the gastric pouch and the small bowel (61), including internal herniation.

Diarrhoea

Diarrhoea has been reported in 9.8% of the population (46). BMI >30 kg/m² is associated with higher incidence of diarrhoea, with as many as 30% of these patients reporting symptoms more than once a week (56, 60, 62). Five percent of patients operated with RYGBP experience symptoms of diarrhoea on a daily basis four years after surgery (63) and about one-third of RYGBP patients develop a worsening of existing diarrhoea after RYGBP (64-66). This should be considered when choosing the bariatric procedure to recommend to a patient with these symptoms.

Paper III: Body composition and energy expenditure

Body composition

Women, compared to men, have higher general adiposity (predominantly subcutaneous) for any given BMI (67). Diet-induced weight loss is commonly believed to be constituted by 75% of the weight lost as fat mass and 25% as fat free mass (68). Loss of FFM caused by non-surgical interventions range between 14-23% and is influenced by caloric restriction and exercise (69). To assess body composition different methods have been developed, such as body impedance analysis (BIA), doubly labelled water, dual-energy X-ray absorptiometry (DXA), air-displacement plethysmography and hydrostatic weighing. Hydrostatic weighing assumes that fat- and fat-free mass are constant among all people and may underestimate body fat in athletes (70). BIA is a quick and non-invasive method to estimate body composition (71), but it assumes no anomalies in fluid and electrolyte balances. Air displacement plethysmography agrees well with hydrostatic weighing, assumes small variations in intra-thoracic air and a fasting state (72). After RYGBP, a loss of a median of 31.2% of FFM was observed 3-14 months postoperatively (69).

Energy expenditure

Energy expenditure or the amount of energy the body uses during the day is divided in resting and non-resting energy expenditure. Non-resting energy expenditure is in turn divided into diet-induced energy expenditure (DEE) and activity-related energy expenditure (AEE).

Resting energy expenditure (REE) constitutes about 60% of the body's energy expenditure (73). In healthy humans, the amount of fat-free mass and respiratory quotient are the principal determinants for REE, whereas insulin sensitivity and abdominal obesity are determinants for DEE after glucose intake, so-called glucose induced thermogenesis (74). REE can in healthy, normal-weight subjects be estimated using height, weight, age and sex. Prediction equations, such as the Harris–Benedict (75) and Mifflin–St. Jeor. (76) equations, are then used to reach an approximation of REE without more time-consuming measurements. A more exact estimate of REE is achieved using indirect calorimetry. Earlier studies have shown that obese subjects have higher absolute REE compared to non-obese subjects but that the found difference disappears when adjusting for fat-free mass (77). No difference in REE was observed between good and poor weight responders one year after RYGBP (78).

DEE is known to vary with the substrate in responders and non-responders. Amongst non-obese subjects, no difference was found in DEE in response to a glucose load in non-diabetic individuals regardless of insulin resistance (79), and it was found to be mainly determined by insulin sensitivity and abdominal obesity (74). Obese subjects have lower DEE in response to an OGTT than non-obese subjects (80) and this reduction is associated to insulin resistance (81, 82).

Indirect calorimetry

A more exact parameter for energy expenditure is achieved by measuring expired carbon dioxide (VCO₂) in relation to inspired oxygen (VO₂) using Weir's equation: REE = [3.94(VO2) + 1.11(VCO2)] 1.44, measured as kCal per 24 h. The examination is usually performed with subjects in the supine position. After being informed about the examination, a transparent hood to collect expired air is placed around the subject's head and a first measure is performed for calibration. A review suggests that the optimal conditions for this measurement is after 5 h fasting, a minimum rest of 10-20 min, restriction of 2 h of moderate exercise and at least 14 h from heavy exercise, in room temperature (20-25 °C), with the aim to achieve $\leq 10\%$ coefficient of variation for each measure. Within the same subjects, repeated measures over 24 h vary 3-5%, or less than 100 kCal (83).

Respiratory quotient

Respiratory quotient (RQ) is a dimensionless measure of glucose oxidation and indirectly a factor identifying which substrate the body is using at any time, with an RQ of over 1.0 signaling ongoing lipogenesis. RQ is assessed using indirect calorimetry by dividing ventilated CO_2 with ventilated O_2 (VCO₂/VO₂). When interpreting indirect calorimetry results for resting energy expenditure, optimal values for RQ should lie between 0.7 and 1.0 (83). In young subjects (25-30 years of age), high fasting RQ has been found to be predictive for weight gain during a 12-month period (84)

Paper IV: Glucose homeostasis and peptide hormones

Insulin and weight gain

In normoglycaemic obese subjects, larger insulin responses during an OGTT were associated with lower food intake and less weight gain (85). Insulin sensitivity has been identified as a risk factor for weight gain (86). Gower et al. found that in non-operated weight-reduced women, insulin sensitivity predicts changes in adiposity and fat distribution (87), and proposed that a high insulin response could lead to energy partitioning towards adiposity. This supports the hypothesis that insulin resistance can protect against weight gain in obese subjects.

Measures of glucose hemostasis

Matsuda index correlates well with the euglycaemic clamp method (88) in subjects with normal glucose tolerance (r= 0.73) and impaired glucose tolerance (r= 0.66)(89). Insulinogenic index is a surrogate measure of first-phase insulin responses to a glucose load and a commonly used measure of β -cell function (90)

Leptin

Produced in the white adipose tissue, leptin, a 168-amino acid peptide, exerts its effect of reducing appetite by binding to the leptin receptor in the brain (91). Leptin production is higher in subcutaneous tissue than visceral adipose tissue (92). Levels of leptin are not only proportional to amounts of adipose tissue but also to overfeeding (93). Circulating leptin levels are higher in obese than lean subjects (94) and thus, leptin resistance has been postulated as a factor predisposing for the development and maintenance of obesity (95). Pos-

sible mechanisms behind leptin resistance are impaired transport of serum leptin over the brain-blood barrier (96), blunted neuronal response (97) and reduced receptor activity (98). Physical activity has been postulated as a way to overcome leptin resistance (99). After being fed a mixed meal and monitored for postprandial leptin levels over 120 minutes, obese women showed lowerthan-baseline values at the 90- and 120-min control points (100) compared to normal weight women.

Two weeks after RYGBP and after losing two BMI units, patients with BMI 45 kg/m² showed lower levels of leptin during fasting and in response to a mixed meal test (101) compared to preoperative levels. Other data also support the idea that leptin levels decrease after RYGBP, and that these changes correlate to anthropometric measurements (102). Earlier studies have been both supporting (103) and disputing (104) of a positive correlation between leptin and RMR.

Ghrelin

Ghrelin is a 28-amino acid peptide that, in its acylated form, crosses the brain barrier and binds to the growth-hormone-secretagogue receptor (GHS-R1a) in the brain, stimulating gastric motility and appetite (105). It is produced in the fundus and antrum of the stomach (106), as well in the α -cells in the pancreas (107). Acylated ghrelin is the active peptide regarding appetite stimulation, whereas non-acylated ghrelin (>90% of total ghrelin) is considered to be nonfunctional in this regard (108). Circulating ghrelin levels are lower in obese than lean subjects (109), and higher in obese subjects after starvation or weight loss (110) although this change is transient despite weight maintenance (111). In normal-weight individuals there are diurnal and postprandial variations in levels of ghrelin. Post-prandial variations are blunted in obese individuals (112) and thus existence of central ghrelin resistance has been postulated (113). Interestingly, 1-2 years after RYGBP, postprandial ghrelin levels are markedly blunted (114), prompting the question whether they remain blunted in the long-term term or revert to a preoperative pattern (115). Ghrelin effects on glycaemic control may depend on inhibition of insulin secretion (116), stimulation of glucagon secretion (117) or promoting gastric emptying (118).

GLP-1

Glucagon-like peptide-1 is a neuroendocrine peptide secreted by enteroendocrine L cells in the distal ileum and colon. Of its two active isoforms, GLP-1₇₋₃₇ and GLP-1₇₋₃₆, the latter is the most frequently prevalent and active in humans (119). GLP-1 exerts its anorexigenic and antiglycaemic effects by delaying gastric emptying, amplifying glucose induced insulin secretion and inhibiting glucagon secretion. Although oral intake of predominantly fats and carbohydrates stimulate the release of GLP-1 (120) the peptide can be released in response to a mixed meal or to fat, carbohydrates or proteins individually (121). Oral administration of 75 g glucose lead to peak levels of GLP-1 at 15-30 min (122) with a return to baseline at 180-240 min in lean subjects (123). Meal induced GLP-1 secretion was lower in obese subjects compared to lean subjects, and it increased after diet-induced weight loss to resemble lean-subject levels (124). After an oral glucose load, GLP-1 secretion was decreased in obese subjects (BMI 34) compared to lean subjects (BMI 22) (125). Lower GLP-1 in diabetics compared to healthy subjects is believed to be caused by a lower secretion because elimination between the two groups does not differ (126). After RYGBP, postprandial GLP-1 levels increase compared to preoperative levels in non-diabetic subjects (127). Postprandial GLP-1 levels were also found to be higher in subjects with good weight result (EBMIL >60%) 1 year after RYGBP compared to subjects with poor weight result (EBMIL <50%) (78).

PYY

Peptide YY and GLP-1 are secreted by enteroendocrine L-cells in the distal ileum and proximal colon. Of its two circulating forms, PYY₁₋₃₆ and PYY₃₋₃₆, the latter is most common (128). The anorexigenic effect of PYY is attributed to its effect on delaying gastric emptying (129, 130). Although it is postulated that PYY reduces food intake in humans (131), there is not consistent evidence to support this theory (132). There is both supporting and opposing evidence to lower fasting or post-prandial PYY levels in obese subjects compared to lean subjects (132). Obese subjects do not seem to be resistant to the anorexigenic effects of PYY (133), as is the case with leptin. Diet-induced weight loss leads to decreased PYY and increased hunger after 2-3 weeks (134) and 12 months after weight maintenance (135). RYGBP results in higher PYY levels after 75 g oral glucose (136) or post-prandially (102) compared to normal-weight or obese subjects although it does not seem to affect fasting levels (132). Inability to maintain high PYY levels after RYGBP has been postulated as a cause for postoperative weight recidivism (137).

GIP

Initially named gastric inhibitory peptide, but later shown to have negligible effect on gastric motility (138), the glucose-dependent insulinotropic polypeptide (GIP) is produced by the K-cells in the duodenum and proximal jejunum after ingestion of predominantly fat but also carbohydrates. Through the GIP receptor in the pancreas and adipose tissue, GIP induces insulin secretion and liposynthesis (121). Despite a short-term increase after a diet-induced 13% TWL, postprandial GIP returned to baseline levels after 1 year of weight maintenance (139). Two years and 36% TWL after RYGBP, a group of non-diabetic obese women showed a decrease in postprandial GIP, but not fasting

GIP compared to obese controls (140). Most studies show a decrease in postprandial GIP, whereas decreases in fasting GIP are not as well documented (141). Furthermore, changes in GIP after RYGBP have been attributed to patients' glucose metabolism.

Baseline GIP is similar to or slightly elevated in type 2 diabetics compared to healthy subjects (142), but elimination does not differ between the groups (143). Two weeks after RYGBP, there were no changes in fasting or postprandial GIP in non-diabetic subjects in response to a glucose load or a mixed meal (127). RYGBP decreased GIP levels in type 2 diabetic patients but not in nondiabetic obese patients (144).

Aims

The aim of this thesis is to investigate different technical approaches to RYGBP surgery and to evaluate long-term effects of surgery.

The specific aims were:

Ι	To evaluate two operative techniques for the stapled GJ, the circular and linear, and to investigate the risks for developing complications using a multivariate logistic regression model.
Π	To study patient-graded gastrointestinal symptoms, weight loss, overall satisfaction and need for endoscopic interventions 5 years after RYGBP performed with three different techniques for establishing the GJ.
III	To study, in weight responders and non-responders after RYGBP, differences in energy expenditure in relation to their body composition.
IV	To study, in weight responders and non-responders after RYGBP, differences in hormone peptides during fasting and in response to an oral glucose tolerance test.

Patients and methods

Patients

In Paper I, we followed 560 patients operated between 2008 and 2012 with laparoscopic primary RYGBP, where 288 patients had a GJ constructed with a 25-mm stapler and 272 patients had a GJ constructed with a linear 45-mm stapler (Table 1). Data were collected from the patients' medical chart from their 6-week follow-up visit according to national register's guidelines. SSI were identified as infections in a laparoscopic port site that required antibiotics or surgical drainage or both.

Table 1. Paper I, baseline and perioperative characteristics of 560 patients having had laparoscopic gastric bypass

	CS, n=288	LS, n=272	p-value
Age (years, mean ±SD)	41.1±10.1	42.2±10.2	0.17
Gender (f/m)	236/52	211/61	0.20
BMI (kg/m ² , mean ±SD)	41.9±3.5	42.6±3.9	0.02
HbA1c (mmol/mol, mean ±SD)	42.8±10.4	41.7±9.5	0.24
Operative time (minutes, mean ±SD)	122±37	83±24	< 0.001
In-hospital stay (days, median (range))	4 (2-28)	3 (1-74)	< 0.001

In Paper II, we followed 593 patients operated between 1996 and 2007 with open, hand-port assisted and laparoscopic primary RYGBP. Patients received a questionnaire about gastrointestinal symptoms and their need for additional surgery and endoscopic interventions at their five-year control (Appendix A). This study is based on the 489 patients who answered, and data from the questionnaire was checked and complemented with data from the patients' medical charts. The GJ was constructed with 21-mm stapler in 88 patients, with a 25-mm circular stapler in 298 patients and with a linear stapler in 103 patients (Table 2). No patients underwent a secondary bariatric procedure prior to the five-year control.

	Patients	Age	Preop BMI	BMI 5vear	BMI re-	%EWL	%TWL
	(Females)	Median (IQR)	Mean ±SD	Mean ±SD	Mean ±SD	Median (IQR)	Median (IQR)
LS	103 (88.3%)	37 (15)	43.8 ±6.6	31.5 ±5.9	12.3 ±4.8	67% (34%)	28% (12%)
C21	88 (89.8%)	36 (11)	46.0 ±6.1	31.1 ±5.8	14.7 ±5.9	75% (31%)	34% (16%)
C25	298 (74.5%)	40 (14)	45.0 ±5.5	31.6 ±5.8	13.3 ±5.1	69% (35%)	30% (13%)
Total	489 (80.2%)	38 (14)	44.9 ±5.9	31.5 ±5.8	13.3 ±5.2	70% (34%)	30% (13%)

Table 2. Paper II, baseline data and weight results. LS Linear stapler, C21 Circular stapler 21-mm, C25 Circular stapler 25-mm

In Paper III and IV, we screened within our quality register for 40 patients who had had RYGBP surgery more than five years before. Patients were selected for their weight result at five years after surgery, and were classified as responders (EBMIL >70%) and non-responders (EBMIL<40%). At examination weight and height were measured and as patients had changed their weight from the five-year control to examination, the resulting groups consisted of 22 non-responders (EBMIL <50%) and 18 responders (EBMIL >50%). Patients were matched at screening for preoperative BMI, age and years from surgery. Only female participants were recruited for the sake of uniformity (Table 3).

	Non-responders	Responders	p-value
Number of participants	22	18	
Age at surgery (years)	41.0 (15.8)	38.5 (14.5)	0.56
Weight at surgery (kg)	124.5 (21.3)	119.0 (19.3)	0.18
Height at surgery (m)	1.65 ± 0.06	1.65 ± 0.05	0.92
BMI at surgery (kg/m ²)	45.3 (5.5)	42.5 (5.0)	0.12
Age at exam (years)	52.0 ± 7.5	53.2 ± 11.4	0.71
Weight at exam (kg)	109.6 ± 17.1	79.7 ± 9.7	< 0.01
Height at exam (m)	1.64 ± 0.06	1.65 ± 0.06	0.86
BMI at exam (kg/m ²)	40.6 ± 6.0	29.5 ± 3.5	< 0.01
%EBMIL	26.0 ± 15.9	74.9 ± 18.3	< 0.01
%TWL	12.5 ± 6.3	32.4 ± 8.4	< 0.01
Follow-up (years)	11.5 (8.0)	9.5 (7.0)	0.38

Table 3. Papers III and IV, group characteristics at surgery and at the metabolic examination

Operative techniques

All patients received preoperative antibiotic prophylaxis using Cefuroxim 1.5 g i.v. and Metronidazole 2.0 g p.o. on the morning of the procedure. Tromboprophylaxis (LMWH) was administered to all patients pre- and postoperatively. The laparoscopic procedure was performed in all patients using a fivetrocar technique where, after establishing pneumoperitoneum, a 12-mm camera trocar was placed supraumbilically in the midline. Two 12-mm trocars were placed in the epigastrium and an additional 12-mm trocar was placed in the right hypochondrium for the liver retractor. A 5-mm trocar was placed in the left hypochondrium for the assistant. In the hand-assisted laparoscopic procedure, the trocar in the left epigastrium was replaced with a hand-port. The open procedure involved access to the abdomen by means of a short upper midline incision. In Paper I, the RYGBP was performed with a 100-cm Roux limb and a 50-cm biliary limb. In Paper II, a 70-cm Roux limb with a 30-cm biliary limb were used. 354 patients underwent an open RYGBP and 135 patients were operated using laparoscopic techniques (96 completely laparoscopic and 39 hand-assisted laparoscopy). In Paper III and IV, Roux limbs were a median of 70 cm with biliary limb of 30 cm. A total of 26 open RYGBP were performed (20 non-responders), 13 laparoscopic procedures (12 responders) and 1 non-responder was converted from laparoscopic to open RYGBP due to bleeding. All patients followed the same postoperative course and follow-up, and were operated by the same team of surgeons.

In Paper I, all Roux limbs followed an antecolic, antegastric route. Because the construction of the GJ followed an antecolic, antegastric route, the greater omentum was routinely divided to lessen the tension on the GJ. In Paper II all Roux limbs followed a retrocolic, retrogastric route, except for 15 patients in the 25-mm circular stapled group (3% of all patients).

In patients where the circular stapling technique was used, we introduced the anvil of the circular stapler transorally with the help of the anaesthesiologist in-theatre. The tip of the anvil was then pushed out of the gastric pouch through a small opening in the horizontal stapler line. A blunt-ended tip was attached to the distal end of stapler to facilitate the passage through the abdominal wall. The shaft of the stapler was introduced through the abdomen after enlarging the skin incision at the lateral left 5-mm trocar site. The tip was removed and the end of the stapler was introduced into the end of the Roux limb and placed antemesenterically to perform an end-to-side anastomosis to the gastric pouch. The opening in the Roux limb was closed by a linear stapler and resected. The enlarged opening in the fascia was sutured shut (Figure 4).

The linear stapled technique included the use of a 30 to 45-mm linear stapler inserted into the gastric pouch and the end of the Roux limb through small openings to create a GJ. The remaining opening at the anterior aspect of the anastomosis was closed with a running suture.



Figure 4. Construction of the GJ using a 25-mm circular stapler. Upper left: insertion of the stapler through the abdominal wall. Upper middle: Insertion of the stapler into the end of the Roux limb. Upper right: docking of the anvil to the stapler. Lower left: Anastomosing of the gastric pouch to the Roux limb. Lower middle: Resection of the end of the jejunum. Lower right: suture of the abdominal wall. (Courtesy of M. Sundbom)

Anthropometric measurements

Height and weight were assessed using a stadiometer and a standardized scale, respectively. Height was measured twice (mean is the result). The abdominal circumference was measured on a patient lying flat down with a flexible tape just below the ribcage and above the navel, with extended legs. SAD (Sagittal Abdominal Diameter) was carried out with the subject lying down flat on a hard surface with knees bent and feet down on surface. The measurement was done with an abdometer at the level of iliac crest (L4–5) to the surface below to the nearest 0.1 cm after a normal expiration. The area of measurement was without clothes allowing the caliper arm to touch the abdomen slightly but without compression when the subject exhales. The measuring was repeated until two identical measurements were obtained.

Body composition

To assess body composition a three-compartment model was applied, with the use of air displacement plethysmography and bioimpedance analysis to estimate fat mass and fat-free mass.

BIA (Bioelectrical Impedance Analysis)

Inbody S20 (Biospace, Seoul, Korea), a multi-frequency body composition analyser, was used to detect intra/extracellular fluid. Subjects lay down during measurement. Adhesive electrodes were placed on the back of the hands and feet. On each hand, one electrode was placed just below the long finger knuckle and the other electrode was placed distal of the wrist. On each foot, one electrode was placed at the toe base and the other electrode was placed just below the crest that shows when the foot is flexed.

Air displacement plethysmography

Subjects wore only a cap and underwear during the examination, to eliminate faulty volume measurement. Subjects sat inside the BodPod (BodPod air displacement plethysmograph, Life Measurements, Inc. Concord, CA, US) chamber during two 40 sec measurements and if a faulty outcome was obtained, the measurement was repeated.

Indirect calorimetry

Subjects lay down in a comfortable relaxing environment and after brief information about the procedure and calibrations of the machine, measurements started. Two calibrations occurred prior to testing: mass flow sensor calibration and gas calibration. The instrument was started and warmed up, and calibration verified and approved before measurement starts. Data were collected with the subject breathing under a ventilated hood. Measurements start between 08:30- 09:00 with the subject having fasted since the previous evening. Information was given that no food or medication should be consumed after 22:00 the day before data collection. Temperature and air humidity were standardized and the subject had an option to watch a film while resting. After 15-30 min of REE measurements and having achieved stable continuous data acquisition, measuring was paused. The subjects consumed 75 g glucose mixed with 250ml water and time measurements started directly after the last sip was taken. Indirect calorimetry measurements were repeated at 30, 60, 90 and 120 min after the glucose load for 15 min at a time.

Oral glucose tolerance test

Participants were asked to fast overnight and not to take any medications on the day of the exam. Upon arriving to the laboratory at 08:30 AM, they were informed about the details of the OGTT. An intravenous line was inserted into

an antecubital vein and anthropometric data (length and weight) was collected. Fasting blood samples were collected before ingestion of 75 grams of glucose dissolved in 250 mL water. Additional blood samples were drawn at 30, 60, 90 and 120 min after the oral glucose load. Samples were later assayed for leptin and ghrelin, the incretins GIP and GLP-1 as well as PYY, insulin and glucose.

Measures of glucose homeostasis

Whole body insulin sensitivity was estimated using the Matsuda Index (145). β -cell function was estimated by the insulinogenic index, using the formula: Insulinogenic Index = (30 min insulin – fasting insulin)/((30 min glucose – fasting glucose) x 18) (146).

Glucose and insulin responses were calculated as the incremental area under the curve (iAUC) by use of the trapezoid rule on values obtained by calculating the difference between of measures in each control point and baseline (fasting values).

Blood sample handling

A protease inhibitor cocktail was prepared, as previously described (147-149), consisting of 5.5 μ L 10 mM KR-62436 (150) (DPP4 inhibitor) in DMSO and a SIGMAFAST[®] protease inhibitor tablet (151) (both produced by Sigma-Aldrich Corp., St. Louis, MO, USA Cat# K4264 and S8830) dissolved in 2100 μ L of distilled water (50X stock). Inhibitor tablets contained the following well known protease inhibitors (mM final concentrations): AEBSF 2; Phosphoramidon 1; Bestatin 130; E-64 14: Leupeptin 1; Aprotinin 0.2; Pepstatin A 10. Blood samples were drawn using 6 mL EDTA plasma tubes, immediately put on ice and 160 μ L of the 50X protease inhibitor cocktail was added. Tubes were vortexed for 10 s and centrifuged at 4 °C, 10 min, 2500 RCF. The resulting supernatant (plasma) was then pipetted into Eppendorf tubes (450 μ L each) and immediately frozen at -25 °C until assayed. Blood was also drawn into 6 mL serum tubes in parallel for insulin and glucose analyses. These were sent at room temperature for analysis at the hospital clinical chemistry laboratory immediately after the examination was completed.

Multiplex ELISA by electrochemiluminescence

Plasma concentrations of GLP-1, GIP, PYY, ghrelin and leptin were assayed by multiplexed ELISA using electrochemiluminescence detection. Plasma samples were thawed and vortexed. Samples were then analyzed in duplicate on 96-well multispot plates (Meso Scale Diagnostics, Rockville, MD, USA) coated with capture antibodies against acyl-ghrelin, GIP, active GLP-1, leptin and total PYY according to manufacturer's instructions. The Meso Scale Diagnostics QuickPlex SQ120 imager was used to read the plates. Resulting duplicate sample values were used to calculate CV% values, which were (intra/inter-assay): GIP 3.6/6.9; active GLP-1 8.8/27.5; acylated ghrelin 19.8/3.5; leptin 4.4/9.1; total PYY 5.1/4.0. Intra-assay CV% was possible using a quality control plasma sample on all plates. Lower limits of detection calculated from 5 standard curves were (ng/L): GIP 4.0; active GLP-1 0.5; acylated ghrelin 6.4; leptin 65; total PYY 12.5.

Statistical methods

In Paper I, normally distributed parametric numerical data were analysed using the two-tailed student's t test, categorical data were evaluated with Chi square test, and ordinal data were analysed using the Wilcoxon–Rank sum test. Differences in postoperative complications were first analysed with unadjusted logistic regression analysis and when found significant were further analysed using multivariate logistic regression. All analyses were performed using STATA 11.2 (Stata, College Station, TX).

In Paper II, ordinal data and non-parametric numerical data were analysed using the Kruskal–Wallis test. Dichotomous data were analysed using Pearson's Chi square test. All analyses were performed using R software (R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

In Paper III and IV, variables were investigated for normality using the Shapiro-Wilks test. Parametric variables are presented using mean \pm SD, differences between groups is analysed with Welch's t-test and differences within groups are analysed using paired t-test. Non-parametric variables are presented using median and interquartile range, differences between groups is analysed using Wilcoxon's rank sum test and differences within groups are analysed using Wilcoxon's signed rank test. In Paper IV we present correlations analyses between %EBMIL and fasting hormone levels using Pearson's product moment correlation test, as all variables are parametric. All analyses were performed using R software (R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

Ethics

All studies were approved by the Regional Ethical Review Board at Uppsala University.

Results

Paper I

We found operative time to be shorter with the linear stapler (83 min) than with the circular stapler (122 min, p<0.001). In-hospital stay was also found to be shorter with the linear stapler (3 vs 4 days, p<0.001). The incidence of surgical site infections was found to be higher in the circular stapled group than in the linear stapled group (5.2 vs 0.4%, p<0.001), as was the incidence in stomal ulcers (2.4% vs 0.4%, p<0.06, respectively). In a multivariate analysis, the use of the circular 25-mm stapler was found to be an independent predictor of surgical site infections and anastomotic ulcers. Moreover, age at surgery was found to be a predictor for surgical site infections, and BMI was found to be a predictor for the development of anastomotic ulcer.

Paper II

Five years after surgery, dumping was the most commonly reported symptom (14.1% of patients reported having it on a daily to weekly basis). Dumping was less common amongst patients who had their GJ constructed with the 25-mm stapler (p<0.05). Vomiting was reported by 2.9% of all patients on a daily to weekly basis and most common in patients operated with the 21-mm circular stapler (p<0.01). Reflux, abdominal pain and diarrhoea (3.6%, 9.4% and 13.3% on a weekly to daily basis) did not differ between the different operative modalities for the GJ (Figure 5). No difference was found in weight loss (a median of 70% EWL in all patients), overall satisfaction with the procedure (88% of all patients were satisfied) and inclination to recommend the procedure to an acquaintance in the same situation (92% of all patients would).



Figure 5. Gastrointestinal symptoms after RYGBP

We found that 24.5% of all patients developed symptoms that merited a gastroscopy and 9.4% of all patients were diagnosed with anastomotic ulcers, with no statistically significant difference between the groups. In total, 4.5% of all patients needed dilatation of the GJ, and this was found to be more common in the 21-mm circular stapled group (12.5%) than in the others (3.9% for the linear stapled and 2.3% in the 25-mm circular stapled groups, p<0.01) (Figure 6).



Figure 6. Endoscopic interventions and anastomotic ulcers after RYGBP

Paper III

Our non-responder group exhibited larger fat mass (56.2 vs 31.8 kg and 50.9% vs 39.6%, p<0.01 for both) and fat-free mass (53.4 vs 47.9 kg) compared to our responder group (Table 4).

	Non-responders	Responders	p-value
Fat mass (%)	50.9 ± 5.0	39.6 ± 6.1	< 0.01
Fat mass (kg)	56.2 ± 13.0	31.8 ± 7.6	< 0.01
Fat-free mass (%)	49.1 ± 5.0	60.4 ± 6.1	< 0.01
Fat-free mass (kg)	53.4 ± 6.6	47.9 ± 5.6	< 0.01
Abdominal circumference (cm)	117.3 ± 10.4	92.0 ± 13.4	< 0.01
SAD (cm)	29.9 ± 4.2	22.1 ± 2.5	< 0.01
Resting heart rate (bpm)	62.0 (14.5)	65.0 (14.0)	0.53

Table 4. Paper III, body composition and resting heart rate. SAD: sagittal abdominal diameter

Between weight responders and non-responders, no long-term differences were found in REE when adjusted for FFM (33.8 vs 33.0 kcal d-1 kg-1). DEE in response to a glucose load was similar between the groups (iAUC 12.8 vs 11.4 kcal) despite non-responders having lower insulin sensitivity. AEE adjusted for body weight showed no differences between responders and non-responders after RYGBP (14.4 vs 15.9 kcal d-1 kg-1) (Table 5).

During fasting	Non-responders	Responders	p-value
REE	1786 ± 154	1563 ± 139	< 0.01
REE/FFM	33.8 ± 3.9	33.0 ± 3.8	0.49
RQ	0.86 (0.4)	0.82(0.3)	< 0.05
During OGTT			
DEE at 30 min	195 ± 166	178 ± 86	0.69
DEE at 60 min	227 ± 152	210 ± 140	0.72
DEE at 90 min	161 ± 160	168 ± 166	0.90
DEE at 120 min	80 ± 170	-19 ± 78	< 0.05
iAUC DEE	13 ± 9	11 ± 7	0.58
Activity-related			
AEE foot	1166 ± 348	867 ± 221	< 0.01
AEE foot / BW	11 ± 4	11 ± 3	0.86
AEE hand	1551 ± 383	1255 ± 296	< 0.05
AEE hand / BW	14 ± 3	16 ± 4	0.23

 Table 5. Paper III, energy expenditure and respiratory quotient in responders and non-responders after RYGBP

Paper IV

We found that fasting levels of leptin and ghrelin correlate to %EBMIL in patients operated with gastric bypass more than five years ago (Figures 7, 9). Furthermore, circulating leptin and ghrelin levels in response to an OGTT seen to resemble those earlier reported in obese non-operated subjects, perhaps contributing to the perpetuation of the obese state (Figures 8, 10. Appendix B).



Figure 7. Scatterplot of %EBMIL vs fasting leptin in responder (R) and non-responders (N) after RYGBP. Rho=-0.75 p<0.01. Spearman's rank correlation



Figure 8. Leptin during an OGTT in responders and non-responders after RYGBP



Figure 9. Scatterplot of EBMIL vs fasting ghrelin in responders (R) and non-responders (N) after RYGBP. Rho=0.31 p=0.05. Spearman's rank correlation.



Figure 10. Acyl ghrelin during an OGTT in responders and non-responders after RYGBP.

Non-responders exhibited lower insulin sensitivity and lower fasting glucose levels compared to responders (Table 6).

	Non-responders	Responders	p-value
Fasting glucose (mmol/L)	5.9 (1.1)	5.2 (0.6)	< 0.05
Fasting insulin (mU/L)	8.6 (6.2)	6.6 (3.0)	0.06
HbA1c (mmol/mol)	37.0 (3.8)	36.5 (4.8)	0.58
Glucose iAUC (mmol/L x h)	5.4 (6.0)	5.3 (4.7)	0.60
Insulin iAUC (mU/L x h)	93.4 (85.9)	82.8 (88.5)	0.25
Matsuda Index	3.4 (2.2)	4.4 (2.0)	< 0.05
Insulinogenic Index	0.97 (1.23)	0.55 (0.65)	0.10

Table 6. Paper IV, measures of glucose metabolism in responders and non-respond-ers after RYGBP

Discussion

Paper I shows a higher incidence of laparoscopic surgical site infections in patients operated using a circular stapled compared to another group who received the same course of prophylactic antibiotics and postoperative care. It suggests that a higher rate of SSI is associated with the passage of the circular stapler through the abdominal wall. In open surgery the use of wound protectors has been evaluated in a meta-analysis where it has been found to reduce wound infections by 45% when used in gastrointestinal and biliary surgery (152), making an argument for the use of physical barriers on surgical wounds larger than those caused by a laparoscopic trocar. In laparoscopic colectomy, where the incidence of surgical site infections is higher than in laparoscopic bariatric surgery, wound protectors have not been found to lower the risk for infection (153).

We also found that the use of a circular stapler for the GJ was associated with an increased risk for the development of anastomotic ulcers. Pouch size, among others, have been identified as a risk factor for the development of anastomotic ulcers in the GJ (154). We believe that the circular technique, because it required a larger gastric pouch in order to fit the anvil, is therefore more prone to the development of ulcers. Anastomotic ulcers in the GJ have been proposed to be treated with amelioration of risk factors, extended high dose PPI therapy and endoscopic controls until remission (38). Although the study in Paper I is not randomized by design, we standardized the included patients' peri- and postoperative care and follow-up, and the data included in the study were collected prospectively.

Paper II shows that RYGBP-related, self-reported gastrointestinal symptoms related to RYGBP that have been found in short-term studies (57), can be found five years after surgery. Furthermore, size restriction in the construction of the GJ seem to have consequences several years after surgery. It is shown that stapling with a 21-mm circular stapler is associated with a significantly higher frequency of endoscopic dilatations due to stricture in the GJ and a higher incidence of vomiting.

We have also been able to observe that although patients that underwent an endoscopic dilatation achieved a higher %EWL than those who did not, no single operative technique for the GJ was associated with a significantly higher weight loss, as expressed in %EWL.

Although our non-randomized study lacks preoperative percentages of the presented gastrointestinal symptoms and the questionnaire used is not validated, we believe that this study yields reliable five-year data supported by a high follow-up rate and a standardized questionnaire. We believe that our results can be considered when choosing which technique to use for the GJ.

Over the years, we have adapted our clinical practice to the results of our research. Our RYGBP practice started in 1996, when we constructed the GJ between a retrocolic, retrogastric Roux limb and the anterior aspect of a gastric pouch by means of a 30-mm linear stapler. By 1999 we had changed the method to circular stapling for the GJ using a 21-mm stapler because we found it less technically demanding. In 2003 we increased the diameter of the stapler to 25 mm due to an initial relatively high frequency of anastomotic strictures. However, the circular stapling technique was associated with a high number of surgical site infections and pain in the left lateral side of the abdominal wall where the stapler had been introduced. Thus, in 2011 we changed our technique to the omega-loop technique using a linear stapler for the laparoscopically constructed GJ but kept the circular stapled technique for the open RYGBP.

In Papers III and IV we use percent of EBMIL to measure suboptimal weight result. Concerns have been raised that using percent of EBMIL to measure weight result after surgery could yield greater results in lighter patients compared to heavier ones (155). Since the groups in these studies were matched for preoperative BMI, we believe we manage to avoid this fallacy and the measurement was therefore used.

Paper III corroborates earlier findings that total REE in obese subjects is higher than in normal-weight subjects (90), and this seems to be the case even if they have been operated with GBP. This would suggest that early postoperative changes in REE notwithstanding, metabolic conditions in subjects with suboptimal long-term weight regain might resemble those of non-operated obese. Furthermore, earlier studies have implied that REE and RQ are markers for appetite and ad-libitum food intake (156, 157), and this might suggest that despite no differences existing in FFM-adjusted REE, a higher absolute REE may indirectly contribute to the maintenance of obesity. Our findings for body composition indicate that non-responders exhibited larger FFM than responders. This is important because an earlier report found that sarcopenic obesity exists within the obese population (158) and that it could negatively influence REE. Because REE is believed to decrease with age (159), we feel confident that our groups are matched for age.

Although it has earlier been reported that DEE decreases after RYGBP (160), no differences were found between subject with optimal and suboptimal weight result after RYGBP when insulin resistance was similar between the groups (161). Together with the findings in this study, where insulin resistance

was higher in our non-responder groups, this suggests that DEE might be influenced to a higher extent by other factors related to glucose metabolism, e.g. insulin response or β -cell function.

The lack of differences in weight-adjusted AEE between the groups, contrary to earlier reports that AEE is reduced with increasing degrees of obesity (162), suggest that we need to look beyond an increased sedentary lifestyle to explain and ultimately treat suboptimal long-term weight result.

Paper IV, together with earlier findings for leptin and ghrelin levels (100, 163), supports the theory that early hormonal changes notwithstanding, hormone levels in non-responders after RYGBP resemble those of non-operated obese. Likewise, earlier reports of an attenuated postprandial ghrelin response reported as an effect of RYGBP (114) could not be duplicated in the long-term, with subjects, both responders and non-responders, showing variations in their postprandial ghrelin response. Leptin and ghrelin levels return to baseline at the end of the OGTT, implying that the interaction between an attenuated anorexigenic hormone and an accentuated orexigenic hormone may contribute to maintain obesity in non-responders. Although earlier studies have stated a relationship between leptin and REE, it seems these effects are mediated by the amount of fat mass (164) and that these effects reverse if the patient regains weight after surgery.

Conclusions

Paper I

Linear stapling for the GJ in laparoscopic RYGBP is associated to shorter operative time, shorter in-hospital stay and a lower incidence of surgical site infections and anastomotic strictures compared to the circular stapled technique.

Paper II

Despite no differences in weight result, the 21-mm circular stapled technique for the GJ is associated with a higher incidence of vomiting and endoscopic anastomotic dilatations compared to the 25-mm circular stapled technique and the linear stapled technique in the long-term after RYGBP.

Paper III

Despite differences in body composition, resting, glucose-induced and activity-related energy expenditure does not differ between long-term weight responders and non-responders after RYGBP.

Paper IV

Long-term weight result correlates negatively to fasting levels of leptin and positively to fasting levels of ghrelin, and the response of these hormones to a glucose load might contribute to perpetuate obesity. Lower fasting ghrelin and PYY are also associated with subjects' glucose metabolism.

Future aspects

Stapling techniques for the GJ in RYGBP show technique-associated differences in short-term complications and long-term gastrointestinal symptoms. An interesting next step to investigate causality would be to randomize patients to the different techniques in a setting where the implementation of the same do not affect the abdominal wall, e.g. an open operative technique. A longitudinal assessment of gastrointestinal symptoms, with pre- and postoperative data would also contribute to establish causality.

Regarding weight regain, routine preoperative measures of energy expenditure and peptide hormones would also contribute to more clearly identify factors causative to poor weight result. As they become more available, measurements of peptide hormones could also be taken for example at the patients' yearly control. Finally, as we learn that levels of peptide hormones, independently of weight result, correlate to glucose metabolism several years after surgery, it would be interesting to explore if they are related to other factors, e.g. the chronic low-grade inflammation associated to obesity and insulin resistance.

Populärvetenskaplig sammanfattning

Sjuklig övervikt sprider sig som en epidemi världen över. Utöver försämrad livskvalitet drabbas patienterna av ett flertal följdsjukdomar som diabetes, hjärt- och kärlsjukdomar och sjukdomar i rörelseorganen. Överviktskirurgi, med målet att åstadkomma en varaktig viktnedgång, har visat sig vara säker och leder till en förbättring i ovan nämnda följdsjukdomar.

Roux-en-Y gastric bypass (RYGBP) är den vanligaste överviktsingreppet i Sverige. I den delas magsäcken i en liten övre magsäcksficka och en urkopplad restmage. Magsäcksfickan kopplas sedan till tunntarmens mellersta del och utgör därmed en förbikoppling av den merparten av magsäcken och första delen av tunntarmen. Under åren har nya tekniker uppkommit med målet att underlätta operationen och bland dem har olika sätt att koppla magsäcksfickan till tunntarmen tagits fram. Nu kan man göra kopplingen med cirkulärstaplers av olika vidd och linjärstaplers av olika längder. Detta urval, tillsammans med implementeringen av titthålskirurgin, leder till ett behov att studera för- och nackdelar med de olika tekniker. Anatomiförändringen efter RYGBP leder dessutom till förändrade matvanor och magtarmsymtom. Därför är det även intressant att ta reda på om förekomsten av magtarmsymtom är kopplad till de olika operationstekniker och till långtids viktnedgången.

Viktnedgången är ett mått på hur framgångsrik operationen har varit på lång sikt. Därför är det bekymrade att uppemot 20% av patienterna drabbas av ett suboptimalt viktresultat, definierat som att de då har förlorat mindre än hälften av sin övervikt. Därför är det viktigt att studera olika faktorer som kan vara relaterade till viktnedgång, som påverkar energiintag och åtgång, och som kan skilja sig mellan patienter med optimalt och suboptimalt viktresultat.

Delarbete I studerar 560 patienter opererade med laparoskopisk RYGBP: hos 288 patienter användes en cirkulärstapler och hos 272 en linjärstapler för att koppla magsäcksfickan till tunntarmen. Grupperna jämfördes beträffande tidiga komplikationer, operationstid och antal vårddagar. Man fann en lägre förekomst av laparoskopiska sårinfektioner (0,4% vs 5,2%), kortare operationstid (83 vs 122 minuter) och kortare vårdtid (3 vs 4 dagar) hos patienterna som opererades med linjärstapler, samtidigt som förekomsten av större komplikationer var oförändrad mellan grupperna. Därtill identifierades ålder och användande av cirkulärstapler som oberoende riskfaktorer för uppkomsten av laparoskopiska sårinfektioner. Delarbete II studerar 593 patienter opererade med öppen och laparoskopisk RYGBP med tre olika tekniker för kopplingen av magsäcksfickan och tunntarmen: 103 patienter opererade med linjärstapler, 88 med en cirkulärstapler med 21 mm i diameter och 298 med en cirkulärstapler med 25 mm i diameter. Grupperna jämfördes beträffande magtarmsymptom, viktnedgång, behov an endoskopiska ingrepp och nöjdhet med operationen. Patienterna opererade med den 21 mm vida cirkulärstaplern hade oftare besvär med kräkningar och större behov av endoskopiska ingrepp (12% jämfört med 4,5% i hela gruppen) jämfört med de andra. Ingen skillnad förelåg beträffande viktnegång mellan grupperna och 88% av patienterna var nöjda med operationen.

Delarbete III och IV studerar 40 patienter opererade med RYGBP sedan mera än 5 år, 22 med suboptimalt viktresultat och 18 med optimalt viktresultat. Delarbete III jämför grupperna beträffande kroppskonstitution och energiåtgång. Man studerade energiåtgång i vila, som svar på en sockerbelastning och energiåtgång under aktivitet. Trots att patienterna med suboptimalt viktresultat hade högre fett- och fettfri massa fanns det ingen skillnad i energiåtgång mellan grupperna.

Delarbete IV jämför grupperna beträffande sockeromsättning och nivåer av hormoner som påverkar aptit och sockeromsättning. Patienter med suboptimal viktnedgång hade en högre insulinresistens och högre fastenivåer av leptin, ett mättnadshormon. Därtill såg man ett samband mellan viktnedgången och fastenivåer av leptin och ghrelin, ett hungerstimulerande hormon. Mot slutet av sockerbelastningen såg man att leptin sjönk från och ghrelin ökade tillbaka till fastevärden hos patienter med suboptimalt viktresultat.

Sammanfattningsvis är användningen av cirkulärstapler för kopplingen av magsäcksfickan till tunntarmen under RYGBP associerad till flera laparoskopiska sårinfektioner, längre operations-och vårdtid än den linjära tekniken. En snävare koppling mellan magsäcksficka och tunntarm ger inte bättre viktnedgång, men ger mera frekventa kräkningar och behov av endoskopiska ingrepp efter flera år. Patienter med suboptimalt viktresultat skiljer sig inte i energiåtgång från de med optimalt viktresultat. Patienter med suboptimalt viktresultat har andra fastehormonnivåer och annat hormonsvar till sockerintag än de med optimalt viktresultat och detta skulle kunna bidra till att upprätthålla deras övervikt.

Acknowledgements

This thesis would not have been possible without the help from many people, whom I would like to thank.

My main supervisor Magnus Sundbom, for giving me the opportunity to conduct research while at the same time introducing me to the field of bariatric surgery. We are many that benefit from the generosity with your time, your love of teaching and your uncanny ability to multi-task that you display daily. Thank you for revising version after version of the manuscripts with enthusiasm and providing constructive criticism, and for showing me how research and clinical work intertwine to improve each other.

My co-supervisor Jakob Hedberg, for always having time and wise words to spare and for tirelessly revising and commenting on the manuscripts. Thank you for making statistics not only understandable but also applicable, at a time when I found it them barely legible.

My co-author Anna Ehrenborg, and currently in her former role, Lena Ekfjord and Anna Höglin, for diligently assisting us with the follow-up of the patients and for memorable coffee room banter.

My co-author Ulf Holmbäck, for helping us with the design of the study on metabolism and body composition, and for rewarding discussions about statistics and physiology.

My co-author Marie Berglund, for teaching me good laboratory practice by example and for being an immense help carrying out and interpreting the analyses of energy expenditure and body composition.

My co-author Dominic-Luc Webb, for interesting discussions about research and the field of biochemistry. I believe I have never left your lab without learning something new.

My co-author Per Hellström, for assisting with the design of the study on peptide hormones and for patiently revising a seemingly endless number of manuscript versions. My co-author Jan Eriksson, for interesting discussions on the field on diabetes and its consequences on metabolism.

My co-tutor Wilhelm Graf, for your support in various ways.

To bariatric patients and specially the participants in the metabolic studies for, amidst your busy lives and in some cases postsurgical throes, selflessly dedicating one morning to the examination.

Tina Asklöf, Viktoria Wessman and especially Kerstin Norlander for your professionalism and patience when taking care of the study's participants during the metabolic examination.

To Claes Juhlin, current head of the Department of Surgery, Uppsala University Hospital, and Per Hellman and Olle Nilsson, current and former head of the Department of Surgical Sciences, Uppsala University, for providing the opportunity and means to conduct research.

To Steve Scott-Robson, for a skillful and fast linguistic revision of my thesis.

To Josef Urzik and Bengt Isaksson, former and current room mates, for willingly sharing space with me during my most reclusive moments of thesis production.

To Joakim Folkesson and my fellow PhD students, Martin Löfling, Eladio Cabrera, Zakaria Bekhali, Henrik Benoni, Emmanuel Ezra, Kostas Tsimogiannis, Andreas Karakatsanis, Fredrik Linder, Peter Moberger, Christopher Månsson, Ann Langerth, Malin Enblad and Åsa Collin for interesting discussion on and about research.

To Lana Ghanipour and Tammer Hemdan for much appreciated advice on thesis production and dissertation practicalities.

My fellow surgeons, David Edholm, Khalid Elias, Bjarni Vidarsson and Gustav Linder, as well all my colleagues at the Department of Surgery at Uppsala University Hospital for making the day-to-day enjoyable and stimulating with your company, humour and ambition to excel in whichever endeavour you pursue.

My sisters Carol and Roxana (in strict order of appearance), for babysitting beyond the call of duty and for taking me down a notch when my head is getting too big. My parents, Elvinia and Alvaro, for your unconditional support, your motivation throughout the years and for teaching me to persevere in the face of adversity.

Finally but foremost, to my children Noah and William, the light of my life and to my dear wife and best friend Andreea, thank you for your love, understanding and support during these years.

Appendix A

Appendix A. Questionnaire on gastrointestinal symptoms, surgical and endoscopical procedures and overall satisfaction with the gastric bypass procedure

1. Have you undergone additional abdominal surgery after your gastric bypass procedure?

Yes No

If so, state the procedure:

Have you undergone plastic surgery? Yes No

 Have you undergone any other examinations (e.g. gastroscopy or radiology) due to conditions following your bariatric surgery? Yes No

If so, specify the reason:

 Have you been admitted to a hospital since your bariatric surgery (for causes other than those stated above)?
 Yes No

If so, specify the reason:

 Have you been to a physician to follow-up on your bariatric surgery during the last year? Yes No

If so, specify where:

5. Do you have regular check-ups for any other condition? Yes No

If so, specify which condition:

At which health care facility:

6. Gastrointestinal symptoms after surgery:

Do you suffer from any of the following:

Vomiting?
Reflux?
Dumping?
Abdominal pain?
Diarrhoea?
Soiling?
Flatulence?

If so, specify how often:

Daily, once or several times a week, once or several times a month, once or several times a year, never.

7. Do you medicate for any of the following conditions?

Yes	No
Yes	No
	Yes Yes Yes Yes Yes Yes Yes

- 8. Please write down all your current medications (including vitamins and supplements):
- 9. Did you use a CPAP machine to treat sleep apnoea prior to your bariatric surgery?

Yes No

If so, do you use one now?

Yes No

- 10. What is your current weight (wearing light clothes)?
- 11. How do you experience the effects of the bariatric procedure on your overall wellbeing?
 I am very satisfied
 I am satisfied
 I am dissatisfied
 I am very dissatisfied
- 12. Would you recommend the bariatric procedure to others in the same situation?

Yes No

If no, why?

Thank you for your participation!

Appendix B

Hormones Non-responders Responders ¶ ¤ a) (ng/L)(n=22) (n=18) 7800 (7000) <0.01 Leptin at 0 min 31200 (33800) 8100 (4100) <0.01 Leptin at 30 min 34800 (30200) 0.54 0.97 8000 (4800) <0.01 Leptin at 60 min 32900 (20600) 0.39 0.35 7400 (4600) <0.01 <0.05 Leptin at 90 min 29600 (18300) 0.12 8100 (6600) <0.01 <0.05 Leptin at 120 min 25800 (18500) 0.06 75 (140) 111 (83) Acyl ghrelin at 0 min 0.16 Acyl ghrelin at 30 min 0.25 < 0.01 < 0.01 36 (49) 49 (50) Acyl ghrelin at 60 min 28 (42) 48 (37) 0.23 < 0.01 < 0.01 0.19 < 0.01 < 0.01 Acyl ghrelin at 90 min 54 (54) 46 (47) Acyl ghrelin at 120 min 69 (72) 82 (42) 0.36 0.20 < 0.01 Act GLP-1 at 0 min 1.9 (1.2) 0.33 2.6 (1.4) Act GLP-1 at 30 min 31.3 (21.4) 29.7 (28.2) 1.00 < 0.01 < 0.01 Act GLP-1 at 60 min 10.2 (7.0) 10.9 (9.1) 0.51 < 0.01 < 0.01 ActGLP-1 at 90 min 5.2 (4.5) 5.9 (6.1) 0.30 < 0.01 < 0.01 Act GLP-1 at 120 min 2.5 (1.8) 2.7 (1.3) 0.50 0.08 < 0.01

Appendix B. Paper IV, adipose and gut hormone levels in responders and non-responders after RYGBP. \P non-responders vs responders, (a) non-responders vs baseline, \square responders vs baseline

GIP at 0 min	71 (31)	54 (28)	0.26
GIP at 30 min	399 (349)	311 (180)	0.29 <0.01 <0.01
GIP at 60 min	262 (211)	210 (108)	0.38 <0.01 <0.01
GIP at 90 min	139 (80)	120 (53)	0.41 <0.01 <0.01
GIP at 120 min	96 (61)	87 (38)	0.43 <0.01 <0.01
PYY total at 0 min	37 (29)	46 (28)	0.29
PYY total at 30 min	205 (113)	157 (67)	0.49 <0.01 <0.01
PYY total at 60 min	157 (119)	141 (57)	0.80 <0.01 <0.01
PYY total at 90 min	120 (135)	114 (79)	0.87 <0.01 <0.01
PYY total at 120 min	99 (126)	104 (54)	1.00 <0.01 <0.01

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Editor: The Dean of the Faculty of Medicine

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