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Changes in Gastrointestinal Function and Patient-scored Symptoms after Bariatric Surgery

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Abstract

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The obesity pandemic is rapidly increasing. Individuals with obesity are affected by obesity-related comorbidities, reduced life expectancy, and reduced quality of life. The most effective treatment for obesity and its comorbidities is bariatric surgery, restoring the physical component of quality of life. These procedures change bowel anatomy and physiology, giving rise to different gastrointestinal symptoms.

In the first paper, we used data on quality of life from the Scandinavian Obesity Surgery Registry (SOReg) together with two validated disease-specific questionnaires to study bowel function and fecal incontinence after Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion with duodenal switch (BPD/DS). In the second paper, we collected SOReg data on acid-related symptoms and diarrhea before and up to 5 years after RYGB, sleeve gastrectomy (SG) and BPD/DS. The association between the two symptoms and postoperative complications was studied. In the third paper, we studied bowel transit times and intraluminal pressure with a wireless motility capsule (WMC) before and after BPD/DS, comparing the result to lean controls. In the fourth paper, we analyzed gut peptide profiles before and after BPD/DS.

In Paper I, RYGB resulted in reduced bowel motions but increased problems with abdominal pain, whereas BPD/DS resulted in increased number of bowel motions and more problems with flatus. General quality of life was improved after both operations. Paper II showed that the presence of acid-related symptoms and diarrhea was associated with increased risk for postoperative complications. RYGB relieved acid-related symptoms, but SG worsened them. Diarrhea increased 6-fold after BPD/DS. In Paper III, small bowel transit time was shortened, and motility was decreased in the distal small bowel after BPD/DS. Paper IV showed a clear reduction in postprandial levels of glucose and insulin and described in detail gut peptide profiles.

In conclusion, general quality of life was improved after bariatric procedures although BPD/DS negatively affected bowel habits. The presence of acid-related symptoms and diarrhea increased the risk of postoperative complications. The novel use of WMC was safe, allowing future use for evaluation of bowel motility, both pre- and postoperatively. Glucose homeostasis was improved after BPD/DS with resolved insulin resistance. Postoperative hormone profiles will aid in maintaining weight loss.

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To my beloved family
Reem, Victoria, Sanna and Victor

List of Papers

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

I. Elias, K. Bekhali, Z. Hedberg, J. Graf, W. Sundbom, M. (2018) Changes in bowel habits and patient-scored symptoms after Roux-en-Y gastric bypass and biliopancreatic diversion with duodenal switch. Surgery for Obesity and Related Diseases, 14(2):144-149

II. Elias, K. Hedberg, J. Sundbom, M. (2020) Prevalence and impact of acid-related symptoms and diarrhea in patients undergoing Roux-en-Y gastric bypass, sleeve gastrectomy, and biliopancreatic diversion with duodenal switch. *Surgery for Obesity and Related Diseases*, 16(4):520-527

III. Elias, K. Hellström, PM. Webb, DL. Sundbom, M. (2021) Gastrointestinal Physiology Before and After Duodenal Switch with Comparisons to Unoperated Lean Controls: Novel Use of the SmartPill Wireless Motility Capsule. Obesity Surgery, 31(8):3483-3489

IV. Elias, K. Webb, DL., Diaz-Tartera, H. Hellström, PM. Sundbom, M. Impact of biliopancreatic diversion with duodenal switch on glucose homeostasis and gut hormones and their correlations to appetite perception. *Manuscript*

Contents

Abbreviations

%BMI loss	Percentage body mass index loss
BMI	Body mass index
BPD/DS	Biliopancreatic diversion with duodenal switch
CCK	Cholecystokinin
CI	Confidence interval
EEC	Enteroendocrine cells
ELISA	Enzyme-Linked Immunosorbent Assay
FIQL	Fecal incontinence quality of life
FRC	Functional residual capacity
GERD	Gastroesophageal reflux disease
GIP	Glucose-related insulinotropic polypeptide
GLP-1	Glucagon like peptide-1
GSRS	Gastrointestinal symptom rating scale
HRQoL	Health-related quality of life
LOS	Length of stay
MCS	Mental component summary
MMC	Migrating motility complex
ObRb	Long form of leptin receptor
OHS	Obesity hypoventilation syndrome
OP	Obesity-related Problems Scale
OR	Odds ratio
PCS	Physical component summary
PYY	Peptide tyrosin-tyrosin
QoL	Quality of life
RMR	Resting bariatric rate
RYGB	Roux-en-Y Gastric bypass
SF-36	Short form – 36
SG	Sleeve gastrectomy
SOReg	Scandinavian Obesity Surgery Registry
SOS	Swedish obese subjects
T2DM	Type 2 diabetes mellitus
TWL	Total weight loss
VAS	Visual analogue scale
WHO	World Health Organization

Introduction

The search for an optimal treatment for obesity is ongoing in parallel with the increasing obesity pandemic and type 2 diabetes [1]. Until now, the best-known treatment for morbid obesity is bariatric surgery [2]. The surgery improves obesity-related diseases, as well as life expectancy and quality of life (QoL) [3]. Obesity surgery has evolved since its start in 1950s with many optimizations to the operative technique, minimal invasive surgery; currently more than 99% of the primary operations are completed with laparoscopy [4]. Despite the continuing improvements in operative technique with low complication rate [5], the presence of gastrointestinal symptoms burdens QoL [6]. Therefore, we studied the effect of bariatric surgery on bowel habits and various physiological changes in the gastrointestinal tract after bariatric surgery.

Data on QoL and postoperative complications were collected from the Scandinavian Obesity Surgery Registry (SOReg), which is a national quality registry for obesity surgery in Sweden. At present, SOReg contains data on more than 79 000 operations [7].

In Paper I, we studied bowel habits and QoL in a cohort of patients before and after Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion with duodenal switch (BPD/DS). We studied the effect of symptoms related to the lower gastrointestinal tract and fecal incontinence on QoL, embarrassment, and social and sexual contacts.

In Paper II, we studied the prevalence of two gastrointestinal symptoms, acid-related symptoms and diarrhea, before and up to 5 years after three types of obesity surgery (RYGB, sleeve gastrectomy (SG), and BPD/DS) and its relation to postoperative complications.

In Paper III, we studied patients with BMI $\geq$ 50 scheduled for BPD/DS. By using a wireless motility capsule (WMC) for the first time in this group of patients, we were able to calculate transit times and motility indexes before and after surgery. The results were compared to a control group, investigated earlier at our lab.

In Paper IV, blood samples were collected in conjunction with the above-mentioned WMC testing for a detailed analysis of glucose homeostasis and gut hormones before and after BPD/DS. The relation to appetite control and bowel motility was examined.

Background

Obesity is a physiological state with surplus energy stored as fat that occurs when caloric intake exceeds expenditure. Although the cause of this imbalance between intake and expenditure is multifactorial, the most effective therapy today for severe obesity is bariatric surgery.

Definition and prevalence of obesity

The most used measure for obesity is body mass index (BMI=weight [kg]/height [m]^2) and is used to define the relation between weight and height. This classification of body weight was developed by Adolphe Quetelet during the 19th century [8]. Because BMI is easy to measure and calculate, it has become a commonly used tool worldwide (Table 1).

Table 1. Definition of body mass index (BMI)

BMI (kg/m^2)	Nutritional status
Below 18.5	Underweight
18.5–24.9	Normal weight
25.0–29.9	Pre-obesity
30.0–34.9	Obesity class I
35.0–39.9	Obesity class II
Above 40	Obesity class III

Obesity class II and III (BMI is more than or equal to 35 kg/m^2) can be treated by bariatric surgery. Class III is often called morbid obesity in surgical literature. When BMI exceeds 50, the term super obesity is often used [9].

Globally, the prevalence of obesity is increasing and according to the World Health Organization (WHO), obesity has nearly tripled since 1975 [10]. In Sweden, 56% of the men and 41% of the women were classified as

overweight or obese in 2018. This is however favorable compared to the American population among others [11].

Development of obesity

Several hypotheses have been proposed to explain the rapid rise in the prevalence of obesity around the world. A simple explanation to start with is changes in lifestyle and behavior, leading to reduced physical activity on a regular basis and increased caloric intake [12]. One could simply think that lifestyle modifications in the form of hypocaloric diets and increased physical activity is enough to amend this problem, but almost all individuals start to regain weight after a therapy period of 6 to 12 months of life-style intervention [13]. Additional weight loss can be achieved by adding pharmacotherapy as an adjunct to lifestyle changes in patients with BMI above 30 kg/m² (or BMI >27 kg/m² if having an obesity-related comorbidity) [2]. Combination therapy with two medications leads to a weight reduction of about 8% of the total body weight [14]. However, medical treatment seems to fail in lowering morbidity and mortality from cardiovascular diseases [15]. The poor results in conservative and medical treatment leave bariatric surgery as the most effective treatment method because it gives a long-term weight loss and improves comorbidities [16].

Epidemiological studies suggest a strong genetic influence on the development of obesity. Studies on adoptees show that body weight of adoptees is strongly related to their biological parents [17]. Moreover, studies on twins show that genetics strongly influences obesity [18, 19]. Another factor that might affect weight gain is the resting metabolic rate (RMR) because some studies have shown a lower RMR per kg for the obese than in normal-weight individuals [20].

The hypothalamus plays an important role in informing the brain of the energy status and in the regulation of body weight, appetite, and physical activity. Preclinical studies on animal models show that deep brain stimulation of the hypothalamus and nucleus accumbens induces weight loss [21]. It is now clear that obesity is a neuroendocrine disorder in which environmental factors and genetic disposition both influence the development of the disease. Insulin and leptin are important adiposity signals [22] reflecting the stored amount of energy. Some studies have showed a higher plasma leptin in obesity without suppressing appetite, suggesting a leptin resistance [23, 24]. The increased insulin release in obesity is linked both to the development of diabetes type 2 and insulin resistance [25]. Moreover, obesity is associated with an inflammatory state [26] because the stored nutrients in adipose tissue stimulate the release of inflammatory markers that contribute to the reduced insulin sensitivity and to a chronic inflammatory response in the hypothalamus [27].

Glucose metabolism

Obesity is closely related to diabetes type 2; according to WHO 13% of adults are obese and about 6% of the world's population have diabetes type 2 [28]. Moreover, about 85% of people with type 2 diabetes mellites are overweight or obese [29]. Obesity causes insulin resistance and worsening of diabetes. Therefore, diabetes remission is one of the most important outcomes of bariatric surgery. Insulin and glucagon work together to maintain normal blood glucose concentration, where insulin facilitates glucose transport into the cell but glucagon exerts the opposite effect. Glucose dependent insulinotropic polypeptide (GIP) also stimulates lipogenesis and promotes obesity [30]. Moreover, together with Glucagon like peptid-1 (GLP-1) it comprises almost 70% of insulin release from pancreatic B-cells in response to ingested glucose [31].

Role of hormones

Leptin is released by adipocytes and its levels are correlated to body fat mass, thus decreasing during weight loss. Leptins act on leptin receptors (ObRb) in the arcuate nucleus of the hypothalamus. Decreased leptin levels increases food consumption and minimizes energy expenditure [32]. However, in high-fatty diet-derived obesity, appetite is not suppressed due to nonfunctional leptin signaling despite high leptin levels [33]. Leptin seems to affect meal size [34]. Leptin is also released by parietal cells of the gastric mucosa into the GI tract where part of it is absorbed into the bloodstream. In the intestinal lumen leptin seems to promote cell proliferation [35], also increasing host resistance against infections (bacteria and parasitic) [36] and controlling gut flora [37]. Leptin effect on gut flora might explain the difference in gut flora between obese and lean individuals. In the GI tract, leptin might be involved in the onset and progression of cell carcinogenesis [38] because reports show a lower incidence of colorectal cancer in bariatric operated individuals [39].

Cholecystokinin (CCK) is secreted by the duodenal cells in response to the presence of fat and protein in the duodenum. CCK inhibits gastric emptying, and stimulates contraction of the gallbladder, bowel movement and pancreatic enzyme secretion. CCK levels increase after meals and infusion of CCK agonists suppresses food intake [40].

Ghrelin, a 28-amino-acid peptide, is an important hunger hormone secreted into the bloodstream by endocrine cells lining the fundus of the stomach. Ghrelin secretion is stimulated by fasting, increases preprandially, and is suppressed by food intake [41]. Ghrelin levels are suppressed after SG and BPD/DS but it is currently unclear whether ghrelin levels after RYGB decrease [42].

Motilin is secreted by Mo cells in the duodenum and upper jejunum; its release initiates the third phase of MMC in the stomach, helping to empty the

stomach before the next meal. Individuals with defective MMC can suffer from dyspeptic symptoms after food intake [43].

GIP is released from K cells in the upper jejunum. It has an incretin effect by stimulating pancreatic B-cells insulin release in response to presence of glucose and fat in the duodenum [44]. Moreover, it is a lipogenic hormone, enhancing fatty acid synthesis and its incorporation into triglycerides promotes fat deposition and obesity. The reduction of GIP is believed to play a role in maintaining weight loss after bariatric surgery.

Glucagon-like peptide-1 (GLP1) is secreted into the bloodstream by intestinal L cells of the ileum and colon in response to the presence of nutrients in the lumen. GLP-1 has a very short half-life. It increases insulin secretion (incretin effect) and decreases glucagon secretion, inhibits gastric emptying, and decreases food intake. GLP-1 is thought to signal from the hindbrain via stimulation of GLP-1 receptor on the vagal nerve [45]. The administration of GLP-1 analogs has been used to treat diabetes type 2 [46] and also in some cases as an adjunct to treat persistent diabetes type 2 after failed bariatric surgery [47].

Peptide tyrosin-tyrosin (PYY) is released into the bloodstream by intestinal endocrine L-cells of the distal gut (ileum and colon) after food ingestion and in response to the presence of fat in the lumen. PYY3-36, the major form of circulating PYY, binds to hypothalamic receptors and reduces food intake. Individuals with obesity have lower PYY levels after a test meal than individuals without obesity [48].

Complications due to obesity

Obesity negatively affects cardiovascular and respiratory systems; it impairs cardiac function and leads to heart failure [49], ischemic heart diseases, pulmonary hypertension, decreases functional residual capacity (FRC) of the lungs predisposing to airway closure and atelectasis and obesity hypoventilation syndrome (OHS) in extreme obesity [50]. Moreover, excess weight burdens the musculoskeletal system causing low back pain and degenerative joint diseases [51]. Metabolic complications [52] of obesity with insulin resistance and type 2 diabetes mellitus have a major consequence on the whole body. These, can result in heart diseases [53], stroke [54], blindness, peripheral vascular disease, hypertension [55] and renal failure. BMI increase is also a major risk factor for some cancers [56], for example in endometrium, breast, ovaries, prostate, liver, gallbladder, kidney and colon, as well as obstructive sleep apnea syndrome [57], gastroesophageal reflux disease [58], cholecystolithiasis [59], fungal skin rashes [60], infertility [61, 62], depression [63] and surgical site infections [64].

Quality of life

It is important to measure quality of life when evaluating the influence of obesity-related conditions in an individual, both before and after treatment. Social relations, and emotional, environmental, and economic factors, together with physical and mental health, affect the individual's well-being. Health related quality of life (HRQoL) is therefore used when the focus is on the impact of the disease on functional status as perceived and reported by the individual. It is known that obesity adversely affects QoL [65] but most patients report markedly improved QoL after bariatric surgery [3].

Short Form 36 (SF-36) is commonly used to evaluate HRQoL; it measures general QoL across eight health domains: physical function, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue and general health perception [66].

Individuals with functional bowel symptoms such as diarrhea and dyspepsia score poorer QoL compared to individuals without these symptoms [67]. However, it is not clear why patients with gastrointestinal symptoms have lower QoL scores. Diffuse abdominal pain, nausea, bloating and vomiting after meals in symptomatic patients could affect general well-being, perhaps in combination with other comorbidities or unknown conditions. The presence of these symptoms also seems to complicate the postoperative recovery after bariatric surgery [68]. Because gastrointestinal symptoms also may emerge after bariatric surgery due to the performed anatomical changes, the use of disease-specific tools focusing on bowel function [69], fecal incontinence [70], and assessing gastrointestinal symptoms [71] are of high value.

The Obesity-related Problems Scale (OP) developed within the Swedish Obese Subjects (SOS) study, measures the specific effect of obesity in eight everyday items (0-100, lower score indicate less psychosocial dysfunction) [72].

Bariatric surgery

Bariatric surgery was introduced in the 1950s to help patients with obesity to reduce their intake, and/or absorption of ingested nutrients by altering the gastrointestinal anatomy.

Several intestinal bypasses emerged in the 60s, but these procedures were abandoned because of severe side-effects such as malabsorption leading to intractable diarrhea and liver failure. In 1969, Mason performed the first gastric bypass by connecting a loop of jejunum to a proximal gastric pouch, created after completely dividing the upper 10% of the stomach from the remaining part [73]. Because the new procedure led to severe bile reflux esophagitis, Griffin and colleagues modified Mason's operation into the Roux-en-Y gastric bypass (RYGB) in the late 70s [74]. Later, Mason introduced the vertical

banded gastroplasty [75] which gained popularity in the USA and Europe. When this operation was abandoned because of inferior weight results and band-related problems that caused vomiting and GERD, Roux-en-Y gastric bypass was considered the golden standard procedure [76]. The biliopancreatic diversion was developed by Scopinaro in the 80s in order to achieve a better weight reduction and to avoid the former liver failure after jejunoileal bypass [77]. The biliopancreatic diversion with duodenal switch was developed from Scopinaro's original procedure by Hess and Marceau [78, 79]. They divided the stomach vertically and preserved the pylorus, thus giving the advantage of being both restrictive and malabsorptive and minimizing the high risk of marginal ulcers associated with Scopinaro's operation.

The laparoscopic approach was developed in the 90s when Wittgrove and Clark performed the first laparoscopic gastric bypass [80]. The improved instrumentation and increased number of bariatric procedures, with standardization of the operative technique [4], has led to shortened operating time. Since the start of SOReg in 2007, national average for operative time has reduced from 115 to 58 min [81]. Furthermore, the overall risk of procedure-related morbidity and mortality has been dramatically reduced in recent years [82]. Sleeve gastrectomy emerged as a modification to the original biliopancreatic diversion. It was done as part of one stage laparoscopic BPD/DS but due to high complication rate, Regan et al. adopted a two-stage operation and in 2000, SG received status as a stand-alone procedure [83, 84]. SG has gained popularity because of fewer severe complications, it is easier to perform compared to RYGB, and the lower risk of developing nutritional deficiencies [85, 86].

Presentation of currently used procedures

Today several bariatric procedures exist, but RYGB, SG and BPD/DS are the most used. In the first two procedures, food intake is reduced whereas the shorter passage through the small bowel in BPD/DS creates true malabsorption. The BPD/DS procedure leads to superior weight loss, but also increased risk of problems with diarrhea [87].

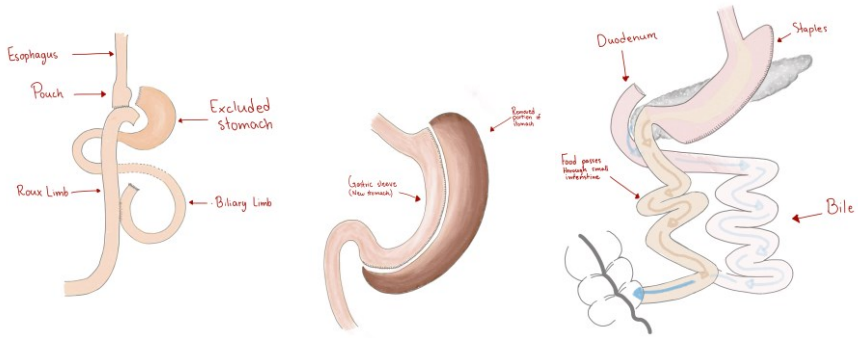

Figure 1. RYGB to the left, SG in the middle and BPD/DS to the right

Roux-en-Y gastric bypass

RYGB is still considered the golden standard weight-loss operation [88]. It is now surpassed by SG both in Sweden and USA [89, 90]. RYGB is done by first constructing a small gastric pouch of about 30 ml. Next, the small intestine is divided about 50-60 cm from the ligament of Treitz. The distal end of the divided small bowel (Roux limb) is brought up in an antecolic fashion and anastomosed to the small gastric pouch. The length of the Roux limb is about 100 cm where the proximal end of the divided small bowel is reconnected (Figure 1). In Sweden, most surgeons use the double omega-loop technique developed by Lönroth and Olbers [91]. The operation works by limiting the amount of ingested food, in combination with several hormonal changes such as increased GLP-1 secretion [92].

Sleeve gastrectomy

Sleeve gastrectomy is performed by removing about 75% of the lateral part of the stomach, leaving a narrow tube along the lesser curvature to limit food intake. Sleeve gastrectomy also results in reduction in ghrelin levels because this hunger hormone is produced mainly in the resected fundus of the stomach.

Biliopancreatic diversion with duodenal switch

BPD/DS is a more complex operation. In addition to performing a gastric sleeve, the duodenal bulb is divided just distal to the pylorus. About 2.5 m proximal to the ileocecal valve, the small bowel is divided and anastomosed in an antecolic fashion to the remaining part of the duodenal bulb, just below the pylorus. The oral part of the divided small bowel is anastomosed to the ileum at about 100 cm proximal to the ileocecal valve. This creates a state of malabsorption as well as restriction and a hormonal change that improves the glucose metabolism.

Outcome of bariatric surgery

Depending on the performed procedure, a mean %TWL of about 28, 19 and 41 is expected after RYGB, SG and BPD/DS respectively at 5 years, thus resolving or ameliorating obesity related complications. In a study for SOReg the prevalence of diabetes type 2 reduced 61%, hypertension reduced 34%, dyslipidemia reduced 51%, and sleep apnea reduced 73% at 5 years [93].

The long-term sustainable weight loss after bariatric surgery leads to improved quality of life [94]. The SF-36 health survey is most commonly used instrument to measure QoL; it summarizes a mental and a physical component. Moreover, more improvement is found in the physical component; SOReg shows as much as 26% improvement, which is mainly due to the improved physical function and reduced bodily pain.

Bowel physiology

The enteroendocrine cells (EEC) in the gut are the source of many hormonal, neuronal and metabolic signals that regulate hunger and satiety feeling in the brain. EEC exist in the lower part of the mucosal crypts and produce more than 30 hormones; they mainly populate the proximal small intestine, their population falls in the colon and rises again in the rectum [95]. Obesity itself affects bowel motility and function giving different symptoms such as gastroesophageal reflux (GERD), and both diarrhea and constipation [96]. The strong association between obesity and GERD is mainly due to the increased intraabdominal pressure in obesity and increased number of relaxations in the gastroesophageal junction [97], permitting reflux. Leptin is higher in individuals with obesity, and its high levels have been associated with both esophageal dysmotility [98] and delayed gastric emptying.

The higher amount of nutrients and fat entering the distal part of small bowel increases GLP-1 and PYY release from L-cells, which in turn decreases bowel motility allowing for higher nutrient absorption. This ileal break which is mainly activated by fat, leads to food stagnation and bacterial overgrowth that can give different symptoms such as abdominal pain, diarrhea, and gas building. Moreover, bacterial fermentation produces gases such as methane that can contribute to constipation.

Obesity surgery modifies bowel anatomy, leading to different gut hormone profiles. Together, these anatomical and hormonal modifications can affect bowel habits and cause different gastrointestinal symptoms, depending on the performed procedure, i.e., Roux-en-Y gastric bypass, sleeve gastrectomy or duodenal switch. Moreover, some gastrointestinal symptoms are decreased, such as acid-related symptoms after RYGB, whereas the same condition is known to increase after SG. Due to the exclusion of small bowel, problems with diarrhea can increase after BPD/DS.

Motility and transit times

The migrating motility complex (MMC) is characterized by contractions that start in the stomach and migrate caudally to the terminal ileum [99]. This is controlled by neuronal and hormonal stimulus. The length of this cycle ranges from 1.5 to 2 hours. Motilin initiates phase 3 MMC in the stomach, but the presence of food in the stomach or the proximal small bowel interrupts this cycle. Vagus nerve stimulation maintains the postprandial motility [100]. Functioning MMC between the meals is important for a normal gastrointestinal health because disturbed MMC may lead to bacterial overgrowth, irritable bowel syndrome, and functional dyspepsia [99].

The use of a catheter, placed from the lower esophageal sphincter to the duodenum, with internal and external pressure transducers (manometry) is a reliable method to measure MMC [101].

A wireless motility capsule (WMC) with a pressure, temperature and pH sensor can be used to study and measure bowel transit times and motility [102]. However, because the capsule has only one sensor, in contrast to the manometry catheter which has many sensors placed 1 cm apart, accurate assessment of MMC is not possible. WMC detects gastric emptying by the increase in pH which is associated with antral contractions of MMC when the capsule passes the pylorus. The time from pylorus passage to the decrease of at least one unit in pH when the capsule passes through the ileocecal valve is defined as the small bowel transit time. Colon transit time is the time from entering the cecum until a decreased temperature and absence of contractions is observed, as the capsule leaves the body (Figure 2).

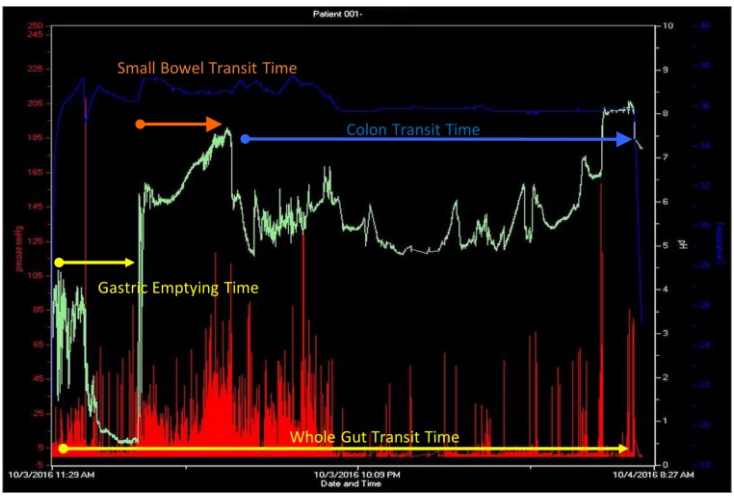

Figure 2. Wireless motility capsule reading. Vertical red spikes represent pressure. Green line represents pH, blue line represents temperature.

Enzyme-linked immunoassay (ELISA) was used to measure hormone concentrations in Paper IV. Commercial plates coated with antibodies for detection of hormones in serum were used. Plates were then placed in a plate reader that uses a high-resolution camera to detect light emitted from the plates (Figure 3).

Figure 3. Picture to the left shows plates and to the right is plate reader.

Aims

The aim of this thesis is to study bowel function and patient-reported gastrointestinal symptoms before and after bariatric surgery and to study bowel physiology (transit times and gut hormones) before and after surgery.

The specific aims are:

I. To investigate bowel function and its impact on quality of life, before and two years after RYGB and BPD/DS by using three validated questionnaires

II. To determine the prevalence of acid-related symptoms and diarrhea before and during the first five years after three types of bariatric surgeries (RYGB, SG, and BPD/DS) in a large cohort and to study possible associations between the two symptoms and postoperative complications, weight loss and QoL

III. To investigate changes in gastrointestinal transit time and other physiological factors after BPD/DS. A secondary aim was to compare pre- and postoperative WMC measurements to lean controls

IV. To investigate glucose homeostasis and changes in gastrointestinal hormone profiles before and after BPD/DS with special focus on the correlation to appetite control

Material and methods

Paper I

We recruited 268 adult patients (mean age of 42.5 yrs, BMI 44.8, 67.9% female) listed for RYGB and BPD/DS. Patients were asked to answer our local validated questionnaire about bowel function and the Fecal Incontinence Quality of Life Scale (FIQL) by Rockwood et al [70]. The Swedish Obesity Registry (SOReg) was used to collect data on general quality of life (SF-36) before and 2 years after surgery as well as the incidence of postoperative complications. The bowel function questionnaire includes 49 questions, covering four items: Bowel motion; Incontinence and urgency; Abdominal pain and urological symptoms; and Social and physical issues [69]. FIQL contains 29 items, forming four scales that describe how incontinence affects Lifestyle (10 items), Coping and behavior (9 items), Depression and self-perception (7 items), and Embarrassment (3 items). All answers are categorical and registered in a score from one to four, with higher values indicating fewer difficulties [70]. The aim was to assess changes in gastrointestinal function and patient-scored symptoms after RYGB and BPD/DS.

Statistics

Wilcoxon signed ranks test and Mann-Whitney U test used for numerical values. McNemar and Chi-square test was used for categorical values to compare the outcomes of the two operations with baseline data. A Bonferroni adjustment was used, leading to a p-value of 0.001 or less for statistical significance.

Paper II

We studied 58 823 individuals who underwent primary bariatric operations (RYGB: 87.5%, SG: 11.7% and BPD/DS: 0.7%) according to SOReg during 2007-2017 with the aim to determine the prevalence of acid-related symptoms and diarrhea, before and up to five years after the three different types of bariatric surgeries. We also studied the associations between these two gastrointestinal symptoms and postoperative complications, weight loss, and quality of life. Data was collected from SOReg preoperatively and up to five years after surgery.

Statistics

A multivariate logistic regression model was used adjusted for age, gender, baseline, BMI, and year of surgery. A Holm-Bonferroni correction was used and led to a significance level corresponding to a p-value of 0.002 or less.

Paper III and IV

In Paper III, we focused on gastrointestinal (GI) motility by measuring transit times throughout the GI tract: stomach, small bowel, and large bowel. By using an ingestible 13x26 mm wireless measuring capsule (WMC) 'SmartPill', we were also able to monitor local intraluminal pressure and bowel motility [103] throughout the GI tract. We studied 28 patients (35 ± 11.3 years, 14 females) with BMI ≥ 50 before and one year after BPD/DS and compared the results to 41 normal-weight unoperated controls (28.4 ± 12.8 years, 20 females), previously investigated at our lab.

At our outpatient clinic, patients were given a standard meal of 260 kcal with 150 ml of tap water before swallowing the WMC. Blood samples were collected at baseline and at 10, 20, 30, 60, 90, 120 and 180 min after the meal. Thus, the collection times mimicked the setup of an oral glucose test. All blood samples were put on ice and a protease inhibitor was added. Plasma was separated at the lab and stored at -70ºC until assayed. A carry-on external recorder received wireless data of pH, pressure, and temperature during WMC passage through the GI tract.

Motility Index (MI) values, calculated as MI = Ln (sum of amplitudes × number of contractions + 1), were analyzed for separate 30-minute intervals just before and after WMC passes through pylorus and ileocecal valve.

Appetite control was documented by all participants by using a 100-mm visual analogue scales (VAS) [104] before and up to 3 hours after meal ingestion.

Gastrointestinal Symptom Rating Scale (GSRS), a validated disease-specific instrument, was used to measure changes in the following gastrointestinal symptoms: reflux, abdominal pain, indigestion, diarrhea, and constipation [105].

Statistics

Kruskal-Wallis test was used for VAS scores. Paired sample t test was used for GSRS. Paired-sample Wilcoxon signed-rank test was used for all other parameters.

In Paper IV, we used the blood samples collected in conjunction with the abovementioned WMC testing to evaluate the postoperative changes in various variables after BPD/DS. Blood samples were analyzed for glucose and

triglycerides at the accredited clinical chemistry laboratory, Uppsala University Hospital. Leptin, insulin, ghrelin, GIP, GLP-1 and PYY were analyzed by ELISA at Rudbeck Laboratory, Uppsala, in duplicates on 96-well multisport plates coated with specific capture antibodies (Meso Scale Diagnostics, Rockville, USA). The Mesoscale Diagnostic imager was used to read the plates. Motilin was assayed by human motilin ELISA kit (Novus Biological, Littleton, CO, USA) and plates read by TECAN spark microplate reader (Tecan group, Männedorf, Switzerland). Hormone concentrations were correlated to bowel motility data from WMC and VAS scores that were acquired parallel with the WMC test.

Statistics

Paired-sample Wilcoxon signed-rank test was used for concentrations. Spearman rank correlation was used. Paired sample t test was used for normally distributed variables.

Ethical consideration

The included studies were evaluated and approved by an ethics committee and informed consent was obtained from all included patients.

Study 1 was approved by the regional ethical committee in Uppsala (Dnr: 2012/024).

Study 2 was approved by the regional ethical committee in Stockholm (Dnr: 2013/535-31/5).

Study 3 and 4 were approved by the regional ethical committee in Uppsala (Dnr: 2012/142).

Results

Paper I

Postoperatively, 208 patients (78.2% of 266 eligible patients) answered the questionnaires after losing 78% and 68% of their former excess BMI (Table 2).

Table 2. Patient characteristics at 2 years follow up.

	RYGB (n=173)	BPD/DS (n=35)	p-value
Age	42.9 ± 11.1	40.4 ± 9.4	0.076
Gender (% male/female)	26/74	52/48	0.001
Preoperative BMI	42.7 ± 5.3	57.1 ± 5.8	<0.001
Postoperative BMI	29.5 ± 4.7	35.3 ± 4.5	<0.001
BMI reduction	13.4 ± 4.0	22.2 ± 5.6	<0.001
% excess BMI loss	78.1 ± 21.4	68.4 ± 12.7	0.004

RYGB=Roux-en-Y gastric bypass; BPD/DS=Biliopancreatic diversion with duodenal switch; BMI=Body mass index. Data as mean ± standard deviation

Compared to baseline, RYGB patients had fewer bowel motions per week (8 versus 10) and more abdominal pain postoperatively (P<.001). Postoperatively, 69% versus 23% of the 35 BPD/DS patients needed to empty their bowel twice or more than twice daily. In conjunction with this, they reported more flatus and urgency, and increased need for keeping a diet (p<.001) (Table 3).

Table 3. Summary of the postoperative changes in bowel habits that remained statistically different after Bonferroni correction (p <0.0012) due to multiple comparison.

	RYGB			BPD/DS		
	Preop n=219	Postop n=173	p-value	Preop n=47	Postop n=35	p-value
Number of bowel movements	10	8	<0.001	13	21	0.010
Deferring time for hard stools (min)	15.8	13.8	<0.001	16.6	13.0	0.024
Flatus n, (%)	88, (41%)	80, (46%)	0.356	18, (38%)	28, (80%)	0.001
Urgency n, (%)	102, (47%)	83, (48%)	0.896	18, (39%)	29, (83%)	0.001
Need for diet n, (%)	28, (13%)	26, (17%)	0.248	2, (4%)	17, (49%)	<0.001
Abdominal pain n, (%)	37, (17%)	56, (32%)	<0.001	9, (18%)	13, (37%)	0.344

n=number
Errata: The p-values for Urgency and Need for diet have been corrected in the table above

Concerning the Fecal Incontinence Quality of Life Scale (Figure 4), coping and behavior were slightly reduced but depression and self-perception scores were improved after RYGB. Lifestyle, coping and behavior, and embarrassment were reduced after BPD/DS (P<.05). In the 36-Item Short Form Health Survey (Figure 5), physical scores were markedly improved, but mental scores were largely unaffected.

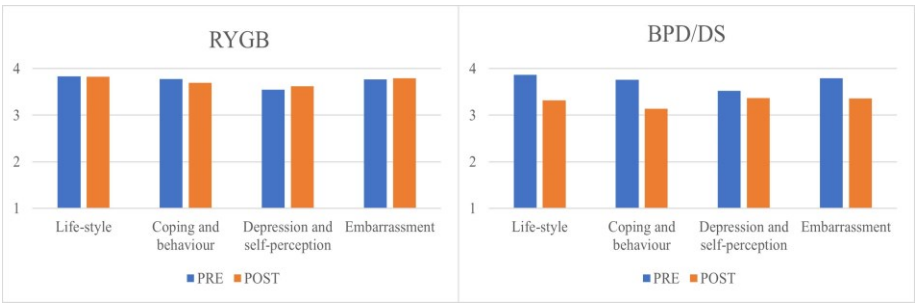

Figure 4. Fecal incontinence quality of life scale (FIQL) in Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion with duodenal switch (BPD/DS).

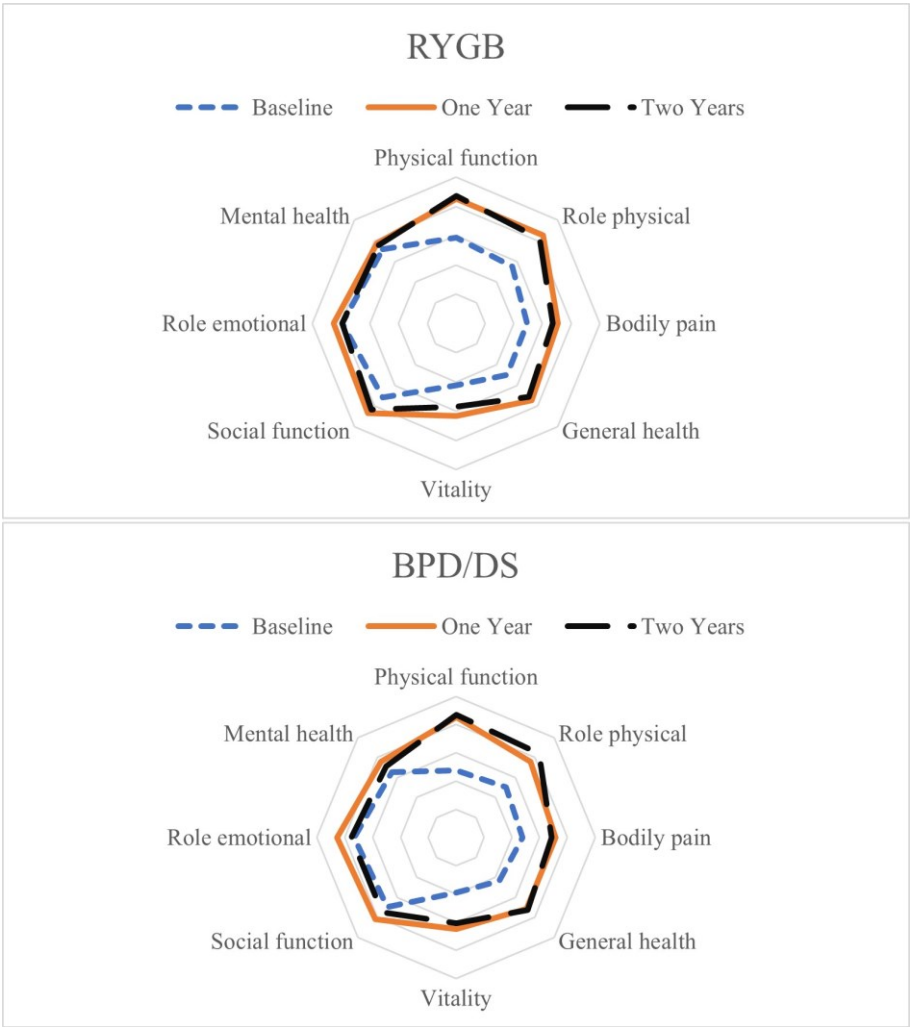

Figure 5. Short form 36 (SF-36) health survey showing the changes in general quality of life at baseline to one and two years postoperatively.

Paper II

At baseline, acid-related symptoms were the most common before RYGB, with an overall prevalence of 9.4%, while diarrhea was rare at 1.3%. In general, patients with acid-related symptoms and diarrhea were older, had more comorbidities and lower quality of life as well as more previous, and additional perioperative surgical procedures compared with other patients. More importantly, bariatric procedures in the symptomatic patients were associated with more complications and reoperations. Acid-related symptoms affected

the operative time (decreased in RYGB and increased in SG) and resulted in poorer weight reduction at two years in SG.

Postoperatively, the prevalence of acid-related symptoms was decreased in RYGB but increased in SG. Diarrhea increased two- and six-fold in RYGB and BPD/DS, respectively (Figure 6).

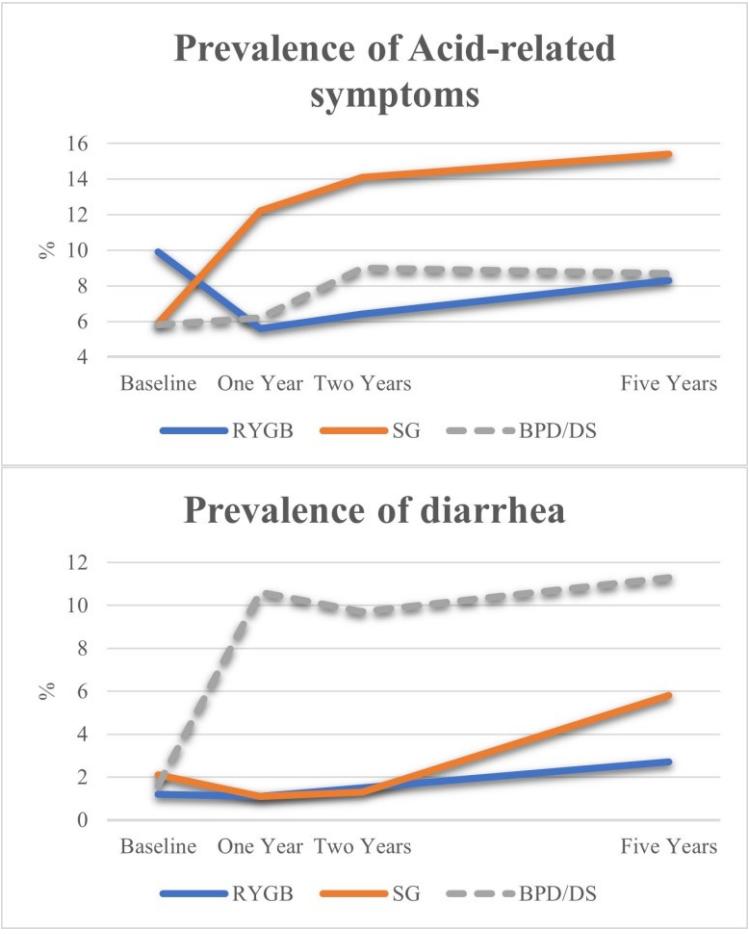

Figure 6. Prevalence of acid-related symptoms and diarrhea before and after the three studied bariatric operations (RYGB = Roux-en-Y gastric bypass; SG = sleeve gastrectomy; BPD/DS = biliopancreatic diversion with duodenal switch).

In a multivariate analysis adjusted for age, sex, year of operation, and BMI, acid-related symptoms after RYGB were associated with reduced risk for longer operative time, but the opposite was observed after SG. The risk of developing a complication after surgery was 24% higher after RYGB but more than doubled after SG. The risk of bleeding/infection/leakage was higher for RYGB patients with acid-related symptoms. Reoperations were also more frequent, but the risk was decreased for prolonged length of stay (LOS). After

SG, preoperative diarrhea was associated with higher risk for prolonged LOS and a doubled risk for complications (Table 4).

Table 4. Multivariate analysis adjusted for age, gender, baseline BMI and year of surgery.

		Acid-related symptoms			**Diarrhea**		
Variable	Operation	OR	CI 95%	p-value	OR	CI 95%	p-value
Operative time (above 75th percentile)	RYGB	0.79	0.73-0.85	<.001	0.98	0.81-1.19	.863
	SG	1.29	1.03-1.63	.026	1.77	1.23-2.56	<.001
	BPD/DS	1.98	0.77-5.05	.267	1.29	0.22-7.31	.772
Complication (total)	RYGB	1.24	1.12-1.36	<.001	1.26	0.96-1.64	.088
	SG	2.19	1.55-3.08	<.001	2.13	1.23-3.70	.007
	BPD/DS	1.05	0.34-3.22	.930	1.03	0.11-9.05	.977
Leak/Deep infection	RYGB	1.44	1.17-1.76	<.001	1.62	0.98-2.68	.057
	SG	2.26	0.99-5.17	.052	-	-	-
	BPD/DS	-	-	-	-	-	-
Bleeding	RYGB	1.24	1.02-1.51	.029	1.41	0.85-2.32	.179
	SG	1.06	0.42-2.67	.897	2.84	1.01-7.97	.047
	BPD/DS	-	-	-	-	-	-
Reoperation	RYGB	1.36	1.17-1.57	<.001	1.17	0.78-1.76	.455
	SG	1.72	0.93-3.20	.083	2.27	0.90-5.71	.080
	BPD/DS	-	-	-			
LOS (above 75th percentile)	RYGB	0.71	0.67-0.76	<.001	1.04	0.88-1.24	.613
	SG	1.07	0.87-1.32	.476	1.24	0.88-1.75	.218
	BPD/DS	1.01	0.36-2.81	.973	3.98	0.79-19.87	.092
EWL>50% at 2y	RYGB	0.88	0.76-1.03	.114	1.00	0.67-1.50	.966
	SG	0.78	0.46-1.13	.158	1.21	0.50-2.95	.661
	BPD/DS	1.12	0.13-9.14	.871			

RYGB, Roux-en-Y gastric bypass; SG, Sleeve gastrectomy; BPD/DS, Biliopancreatic diversion with duodenal switch; OR (odds ratio); CI (confidence interval); LOS (Length of stay)

Paper III

Eighteen out of 28 (64%) patients returned for their second WMC testing. Patients with obesity were older than lean controls (Table 5).

Table 5. Characteristics for the BPD/DS patients and lean controls.

	BPD/DS		p-value	**Lean controls**	p-value	p-value
	Preop (n=28)	Postop (n=18)		(n=41)	Lean vs preop	Lean vs postop
Patient demographics						
Age (years)	35.0 ± 11.3	36.8 ± 11.1	<.005	28.4 ± 12.8	<.005	.019
Gender m/f, (% female)	14/14 (50.0)	8/10 (44.4)	.713	21/20 (51.2)	.558	.632
Obesity-related diseases n, (%)						
Diabetes	10/28 (35.7%)	0/18 (0%)	.031	-		
Hypertension	12/28 (42.9%)	3/18 (16.7%)	.250	-		
Dyslipidemia	3/28 (10.7%)	0/18 (0%)	.999	-		
Osteoarthritis	7/28 (25%)	4/18 (22.2%)	.999			
BMI (kg/m^2)	56.5 ± 5.1	35.8 ± 8.3	<.005	22.6 ± 2.1	<.005	<.005
%EBMIL	-	67.2 ± 23.4		-		
%TWL	-	34.3 ± 13.4		-		
Time to second visit (years)	-	1.8 ± 0.7		-		

Data are in mean ± SD

Patients with obesity had higher median gastric pH compared to lean controls, but operated patients had both higher lowest and median gastric pH compared to lean controls. Motility index (MI) in the stomach did not differ after surgery, but in the ileum, it was lower compared to both the preoperative state and lean controls. A trend toward a lower small bowel pressure was observed in operated patients (Table 6).

Table 6. Motility index (MI) and gastric pH in BPD/DS patients and lean controls.

	BPD/DS		p-value	**Lean controls**	p-value	p-value
	Preop (n=28)	Postop (n=18)		(n=41)	Lean vs preop	Lean vs postop
Motility index						
Stomach MI	81.6 ± 61.6	90.1 ± 74.9	.663	85.2 ± 68.7	.875	.818
Ileal MI	262.5 ± 223.5	136.5 ± 143.9	.011	254.0 ± 231.4	.627	.012
Gastric pH						
Lowest pH	0.2 ± 4.0	1.5 ± 1.6	.161	.6 ± .3	.127	.018
Median pH	2.6 ± 1.6	2.9 ± 2.2	.632	1.2 ± 1.1	<.001	<.001

VAS scores showed higher hunger and desire to eat at 3 hours after meal compared to the preoperative state and higher satiety score 1 to 3 hours after meal for unoperated obese patients compared to lean controls (Figure 7). Patients with obesity showed a higher GSRS score vs lean controls (1.7, 2.3 and 1.2 for obese preoperatively, postoperatively and lean respectively). Surgery increased problems with indigestion and diarrhea.

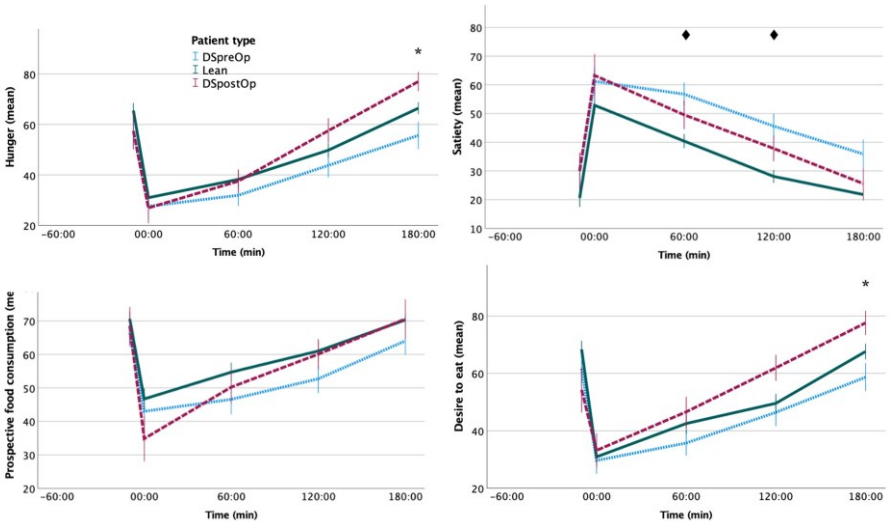

Figure 7. Visual analogue scales (VAS0–100) demonstrating appetite control (hunger, satiety, prospective food consumption, and desire to eat) in BPD/DS patients preoperatively (n = 28) and postoperatively (n = 18) as well as lean controls (n = 41). Values in mean, error bars: Standard error of the mean. Asterisk and diamond denote $p < 0.05$ between preoperative and postoperative BPD/DS patients and lean vs preoperative BPD/DS patients, respectively.

GET did not differ between the three groups (preoperative, postoperative and controls), SBTT was clearly faster in patients with obesity compared to lean controls. SBTT was shortened considerably after surgery. CTT in patients with obesity tended to be slower compared to lean controls, resulting in a longer WGTT. WGTT was shortened after surgery and therefore similar to lean controls (Figure 8).

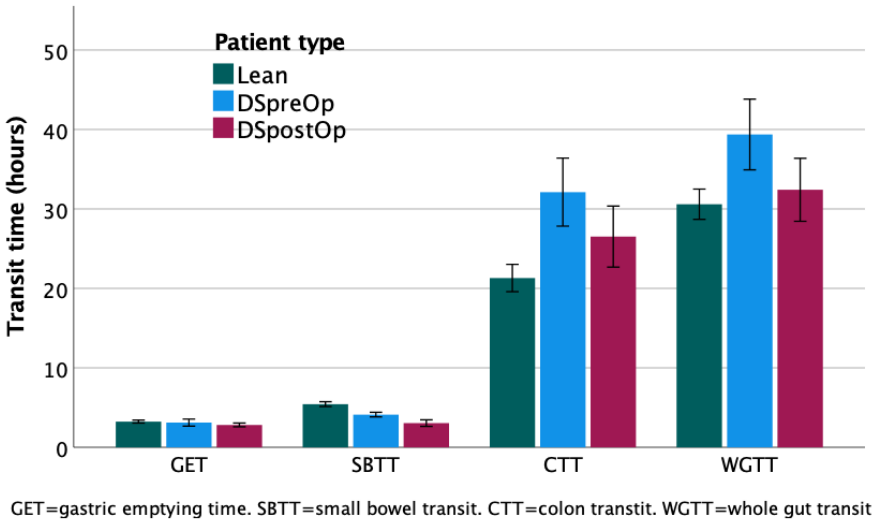

Figure 8. Gastrointestinal transit times, values in mean, error bars: Standard error of the mean.

Paper IV

Blood samples were available for 27 out of the 28 patients who underwent WMC testing. A second blood sampling by 68% of patients (Table 7).

Table 7. Characteristics of BPD/DS patients. Data in mean ± SD. Abbreviations: BMI, body mass index; %EBMIL, percent excess BMI loss; %TWL, percent total weight loss; HOMA-IR, homeostatic model assessment for insulin resistance.

	Preoperative (n=28)	Postoperative (n=19)	p-value
Biometric measures			
Age (years)	35.5 ± 11.2	37.3 ± 10.9	<.001
Gender m/f, (% female)	14/14 (50%)	11/8 (42%)	
BMI (kg/m2)	56.6 ± 5.1	36.1 ± 8.1	<.001
Obesity-related diseases*, n (%)			
Type 2 Diabetes Mellitus	10 (36%)	0 (0%)	.031
Hypertension	12 (43%)	3 (16%)	.250
Dyslipidemia	3 (11%)	0 (0%)	.999
Osteoarthritis	7 (25%)	4 (21%)	.999
Time until second visit (yrs)		1.8 ± 0.7	
%EBMIL	-	66.1 ± 23.3	
%TWL	-	36.6 ± 12.1	
HOMA-IR	13.9 ± 11.4	4.8 ± 2.8	.005

* Obesity-related diseases are defined by continuous use of disease-specific medication

Leptin levels were almost halved after surgery (Figure 9) and correlated negatively with weight loss. Glucose and insulin postprandial peaks between 30 and 60 minutes resolved after surgery. Ghrelin was reduced at baseline, 10 and 60 minutes but showed a rapid rise at 20 minutes after meal. Motilin was significantly decreased at 90 minutes with a 44% decrease in AUC, and also showed a rapid rise after meal but at 30 minutes. GIP levels were decreased between 30 and 180 minutes rendering a 42% decrease in AUC. GLP-1 levels showed 6.2-fold increase with earlier peak postprandially. PYY showed a rapid rise postprandially with a 3-fold increase in AUC. Hunger correlated negatively with motilin before operation. HOMA-IR correlated positively to both insulin and GIP. Stomach MI correlated negatively with weight loss.

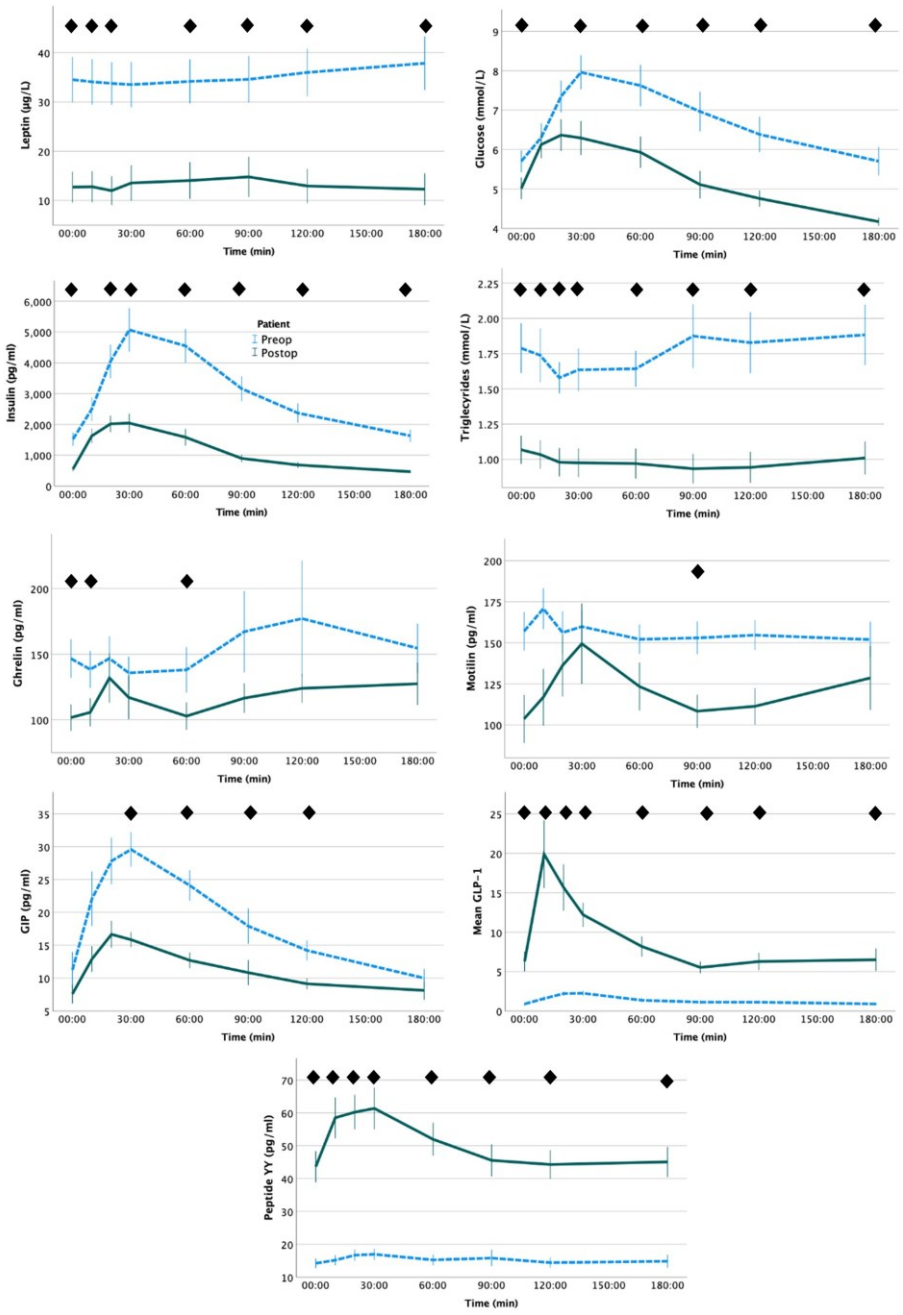

Figure 9. Gastrointestinal peptides in BPD/DS patients before (n=27, ----) and after (n=19, ——). Data are mean ± SEM. "♦" indicated $p < .05$.

Discussion

Paper I

Weight loss was significant after both procedures, 38 kg after RYGB and 66 kg after BPD/DS, which is in line with other publications [106, 107].

Changes in gastrointestinal symptoms and their impact on quality of life

We were able to demonstrate that RYGB patients experienced fewer bowel movements, with a shift toward one movement per day. This is probably due to decreased food intake and altered gastrointestinal hormones postoperatively. RYGB was associated with an increased frequency of abdominal pain. The anatomical changes after BPD/DS led to more bowel motions (2 or more daily for 69% of patients) and looser stools. We were also able to demonstrate troublesome flatus and urgency and an increased need to keep a diet after surgery. By looking at the FIQL, we saw a limitation in social activities after BPD/DS because patients avoided longer journeys and had an increased need to identify nearby toilets. Furthermore, the change in bowel habits was also considered bothersome in sexual contacts. The present results provide important information to patients seeking bariatric surgery.

Paper II

Acid-related symptoms were most common before RYGB with an overall prevalence of 9.9%. We believe that this is mainly due to patient selection at the preoperative counseling because surgeons choose RYGB for patients with acid-related symptoms due to the well-known curative effect after RYGB [108]. Likewise, RYGB and BPD/DS are often avoided when the patient has inflammatory bowel disease or problems with diarrhea preoperatively.

Prevalence

The literature shows a prevalence of acid-related symptoms ranging between 20-50% for patients with BMI ≥ 30 [58, 109]. The lower prevalence of acid-related symptoms observed in our material is mostly due to the strict definition of SOReg, i.e., continuous pharmacological treatment. In line with the literature, acid-related symptoms were more common in females and older age [110, 111] as well as in individuals with higher BMI [112, 113]. We therefore

adjusted for age, gender, baseline BMI, and year of surgery in our analysis. Except for the higher prevalence of depression in patients with functional gastrointestinal symptoms [6] we have no other explanation than increased age for the almost doubled rate of diabetes, hypertension, and dyslipidemia in our patients.

Increased operative risks

The risk of developing severe complications, i.e., leakages/deep infections and reoperations, was higher in patients with acid-related symptoms. Theoretically, the interruption of treatment with proton-pump inhibitors could lead to a rebound effect with increase acid secretion and a more hostile milieu, leading to an increased risk for leakage. In an earlier paper from our group, we showed that larger pouch sizes increased the risk for stomal ulcers at the gastrojejunostomy [114]. Somewhat surprisingly, the risk of developing severe complications was also increased in SG patients having diarrhea at baseline.

Development over time

Surgery changed the prevalence of both acid-related symptoms and diarrhea. RYGB led to 75% decrease in acid-related symptoms at one year, but the incidence of acid-related symptoms was increased by twice after SG. The increase in acid-related symptoms after SG could be due to increased intraluminal pressure [115] or postoperative problems such as persisting hiatal hernia, narrowing or twisting of the sleeve [116]. The marked increase in the incidence of diarrhea after BPD/DS from 1.6% to 11.3% is related to the anatomical changes, i.e., the short common channel (often only one meter), leading to a state of fat malabsorption and steatorrhea. The doubled rate of diarrhea after SG could be due to rapid gastric emptying [117].

Quality of life

Patients with acid related symptoms and diarrhea scored worse in SF-36, showing that these two gastrointestinal symptoms negatively impact quality of life [6]. Although QoL scores improved markedly after surgery, patients with acid-related symptoms continued to show inferior scores compared to patients without acid-related symptoms and diarrhea.

Paper III

The effect of surgery on appetite control

We observed a higher hunger and desire to eat score at 3 hours postprandially in operated individuals compared to before operation; this finding is difficult to explain but could be the effect of a faster propagation of contents in the gastrointestinal tract after surgery. Hunger contractions did not differ after

surgery despite the smaller stomach size and the expected ghrelin decrease. This indicated that the stomach preserved its motility which might explain why VAS ratings are largely unchanged.

The effect of surgery on transit times and motility

GET was reported in the literature as both increasing and not differing after performing SG, [118, 119]; we found no difference in GET in our study. pH values did not differ after surgery despite the smaller stomach size indicating a normal function in the sleeve. However, compared to the lean controls, patients with obesity, had higher pH. This interesting finding of higher pH may explain the difference in bacterial flora between obese and lean and needs further investigation. A recent study on pH after SG supports our results with a higher pH after surgery [120]. Compared to lean controls, patients with obesity had faster SBTT, which could be due to bowel adaptation to higher nutrient intake, which might in turn lead to increased contractility [121]. SBTT was faster after surgery because of bowel shortening (Roux limb of 2.5 m), creating a state of malabsorption. However, the small bowel probably adapts to increased nutrient uptake which we observed from WMC measurements with the lowered motility after surgery. Moreover, the higher GLP-1 after surgery probably plays a role in decreasing small bowel motility. The faster SBTT is an important factor for losing weight. The trend of slower CTT in patients with obesity compared to lean controls led to a longer WGTT. WGTT came close to the lean after the operation showing the adaptive capability of the human body. GSRS showed increased problems with indigestion and diarrhea as a result of bowel shortening and likely change in bowel flora.

The effect of surgery on GSRS

Patients with obesity scored higher in GSRS than lean controls. Individuals with obesity have higher prevalence of gastrointestinal symptoms [96], which is supported by our study. Although, increased problems with indigestion and diarrhea, BPD/DS-operated reported mild symptoms (score ≤ 3).

Paper IV

Glucose metabolism

After surgery, metabolic control was superior by alleviating the high glucose and insulin excursions between 30 and 60 minutes postprandially, thus improving glycemic control as well as HOMA-IR index, and amending insulin resistance. This illustrates the important role of bariatric surgery in diabetes remission as diabetes type 2 is common in obesity with a prevalence of up to 40% [122]. While GIP is a lipogenic hormone that promotes obesity, it has an

incretin effect but its action in obesity seems to be disturbed [123]. GIP correlated positively with HOMA-IR index after surgery indicating that a lower GIP level is more favorable for glycemic control; and therefore, bypassing GIP producing cells in the upper intestine seems to be effective in decreasing insulin resistance.

Leptin

Leptin decreases food intake and balances energy metabolism. The high leptin levels in obesity are often referred to as "leptin resistance". We found that leptin levels were halved and significantly correlated with weight loss suggesting that "leptin resistance" is resolved.

Ghrelin and motilin

Both ghrelin and motilin were decreased at some timepoints; they also shared a similar pattern of rapid postprandial surge at 20-30 minutes but correlated differently to hunger and satiety suggesting opposite actions. Motilin is mostly studied in the hungry stomach where its release stimulates MMC in the stomach facilitating gastric emptying before meals. Increased motilin levels in this study seems to reduce hunger and desire to eat. While ghrelin reduction is mainly due to the sleeve gastrectomy as part of the operation, this reduction is favorable for weight loss.

GLP-1 and PYY

It is known that fat in the duodenum stimulates GLP-1 and PYY release, which in turn delays stomach emptying and inhibit appetite. Both hormones have a potent incretin effect. The high hormone levels after surgery are considered beneficial and are the cornerstone behind the success of bariatric surgery. However, the decreased insulin levels after surgery are probably due to a decreased metabolic demand due to reduced intake. BPD/DS keeps the first part of duodenum available for food contact, which might further boost GLP-1 and PYY levels in comparison to RYGB which completely bypasses the duodenum. GSRS from Paper 3 did not show side-effects related to high GLP-1 and PYY levels, i.e., nausea and vomiting which is considered as a considerable advantage over using GLP-1 analogs as a sole treatment for obesity.

Gastric and intestinal motility

Gastric motility correlated negatively to weight loss, indicating that higher motility in the stomach leads to a lower weight loss. This interesting finding needs further investigation. On the other hand, we observed a reduced motility in the distal small bowel, which we think is an adaptive mechanism counteracting the rapid SBTT to compensate for nutrient malabsorption. A future study to examine whether hypertrophy occurs in the mucosa in the distal small bowel will be needed.

Strengths and limitations

The combination of the three validated questionnaires, bowel function, FIQL and QoL, provides a detailed evaluation, from a different point of view, on patient-rated gastrointestinal symptoms after bariatric surgery. Even if the data from BPD/DS were based on few patients, the results were comparable to earlier publications [124]. Moreover, the response rate of 78% at 2 years after surgery in Paper I, a time point when most weight loss has been reached, provides stable, and clinically valid, data. In Paper II, the large registry cohort from SOReg with wide range of different well-defined parameters and long-term follow-up are the main strengths. The lack of symptom scores and data on symptom severity as well as duration and dosage of medications are clear limitations. The longitudinal analysis, inclusion of lean controls, and the usage of VAS scales in Paper III gave a detailed picture of the changes in gastrointestinal physiology after BPD/DS and are the main strengths. The fact that only 18 postoperative tests were performed after surgery in this study is among its limitations. In Paper IV, the detailed and frequent blood sampling is a major strength. Availability of data on appetite control and motility from WMC in the same cohort of patients is an additional strength. The fact that only 19 patients returned for their second test is a limitation.

Conclusions

Paper I

Bowel function was altered in both groups, with fewer number of bowel movements after RYGB, but BPD/DS resulted in an increased bowel frequency and a need to keep a diet. Although quality of life was influenced in both groups, massive improvements were observed in general health.

Paper II

The two studied gastrointestinal symptoms, acid-related symptoms and diarrhea were associated with increased risk for complications and decreased improvement in QoL. The weight result was not affected. The substantial changes in prevalence postoperatively are likely due to anatomical alterations.

Paper III

The novel use of WMC seems suitable for evaluating gastrointestinal motility pre- and postoperatively. The shortened SBTT and CTT brought WGTT in BPD/DS patients very close to that in lean controls.

Paper IV

Metabolic control was superior after BPD/DS. The increased levels of GLP-1 and PYY, along with decreased GIP concentrations, occurred simultaneously with reduced insulin concentration. The mechanism by which bariatric surgery triggers T2DM remission apparently involves, and may even require, both increased GLP-1 and decreased GIP.

Future work

This thesis corroborates that gastric motility and the changes in gut profiles are important factors for postoperative weight loss and remission of obesity-related comorbidities.

- This observation needs further examination in a larger cohort. Can preoperative assessment of motility data and gut hormones tell us who will lose a reasonable amount of weight?

The Vagus nerve is the link between the gut and the brain, and both thus: Vagus nerve stimulation and blockage causes weight loss; however, only poor weight loss is achieved.

- Can we find a way to treat obesity by effectivization of vagal control on digestion and augment the satiation effect of gut peptides?

The use of disease-specific instruments with focus on bowel function and fecal incontinence provided a different point of view from the generic, regularly used, instruments.

- Could we apply these disease-specific instruments to be regularly used in the registry?
- A long-term follow-up study in the same patients five to ten years postoperatively would be very interesting

We need to compare gut hormones between patients with obesity both before and after surgery to lean controls.

- Can we develop an effective nonsurgical treatment?

In order to examine bowel physiology and gastrointestinal disorders on a wider scope, we could use WMC more often in patients undergoing different types of bariatric surgeries. SG use is increasing, making it the most popular bariatric surgery today. Therefore, WMC testing on patients undergoing SG before and already at 3 months postoperatively to measure the early changes before future bowel adaptations is of high clinical importance.

- What does bowel motility look like in patients undergoing SG? Can we still see the same pattern in gut hormone profiles after two years?
- Can we identify abnormal patterns that can explain chronic abdominal pain after bariatric surgery?

We need to collect stool samples before and after surgery to study changes in bowel flora and be able to compare them with those from lean controls.

- Can manipulation of gut microbiota sustain the efficacy of bariatric surgery?

Populärvetenskaplig sammanfattning på svenska

Fetmaepidemin ökar parallellt med den stigande förekomsten av diabetes. I Sverige har ca 13 % av den vuxna befolkningen fetma och 4–5 % typ 2 diabetes. De vanligaste överviktsoperationerna är idag är gastric bypass (GBP) och sleeve (GS), medan duodenal switch (DS) används vid BMI ≥ 50. Då dessa tre ingrepp förändrar anatomin i mag-tarmkanalen, så påverkas tarmvanor och egenupplevda magsymtom. Eftersom överviktskirurgi inte bara kommer att ge viktnedgång och minskad förekomst av överviktsrelaterade följdsjukdomar, utan även upphov till en del nya mag-tarmsymtom är studier av livskvalitet viktigt.

I denna avhandling har vi undersökt tarmvanor och deras påverkan på livskvalitet samt studerat mag-tarmfysiologin före och efter olika typer av överviktskirurgi.

Arbete I

Vi studerade 266 patienter som hade genomgått GBP och DS med en lokalt validerad enkät med fokus på tarmfunktion och avföringsläckage före och 2 år efter kirurgi. Generella livskvalitetsdata (SF-36) inhämtades från det svenska kvalitetsregistret för obesitaskirurgi (SOReg). Då 208 patienter även besvarade enkäterna efter operation hade vi en svarsfrekvens på 78,2 %. Vi kunde visa att GBP före med sig något färre tarmtömningar, men mer buksmärta. DS-opererade hade ökad tarmtömningsfrekvens, liksom mer malabsorptionsrelaterade symtom såsom uppblåsbarhet och lösare avföring. Fler patienter i DS gruppen ansåg att tarmfunktionen störde deras välbefinnande och sexliv.

Även om DS-patienter fick mer tarmsymtom skattade de sig friskare än före kirurgin.

Arbete II

Mag-tarmsymtomen dyspepsi (magsmärta och uppblåsthet efter måltid) och diarré är vanliga hos överviktiga. För att studera hur dessa symtom förändras

efter operation samt om de påverkar operationsrisken använde vi SOReg-data på 58,823 patienter (GBP: 87,5 %, GS: 11,7 % och DS: 0,7 %). Dyspepsi var vanligast i GBP-gruppen men minskade efter operation, medan tillståndet ökade efter GS. Förekomsten av diarré ökade 6 gånger efter DS. Patienter med mag-tarmsymtom var äldre, hade högre BMI och fler följdsjukdomar samt skattade lägre livskvalitet än övriga. Efter justering för ålder, kön, BMI och operationssår kunde vi se att förekomsten av mag-tarmsymtom var förknippad med ökad risk för komplikationer efter både GBP och GS.

Vår slutsats är att noggrann information till patienter om förekomst och utveckling av dyspepsi och diarré efter överviktskirurgi är viktig, särskilt med tanke på den ökade komplikationsrisk som föreligger.

Arbete III och IV

Mag-tarmfysiologin förändras efter överviktskirurgi. De anatomiska förändringarna förbättrar vissa symtom och följdsjukdomar som diabetes, medan de försämrar andra. Vi har fokuserat på mekaniska och hormonella förändringarna efter avancerad fetmakirurgi med duodenal switch. Genom att för första gången i denna patientgrupp använda en trådlös mätkapsel för att registrera pH samt tryck och temperatur i tarmen kunde vi mäta passagetiderna genom magtarmkanalen och få en uppfattning om tarmens rörlighet. Vi samlade in blodprover upp till 3 timmar efter en standardmåltid för hormonanalyser. 28 patienter deltog i studien.

I arbete III jämförde vi mätkapsels resultat före och efter DS-operation samt även mot en grupp normalviktiga personer som undersökts vid ett tidigare tillfälle. Vi såg en snabbare tunntarmspassage hos feta personer jämfört normalviktiga och passagetiden ökade ytterligare efter utförd operation. Trenden mot en långsammare tjocktarmspassage hos feta försvann efter kirurgi, vilket resulterade i att tiden för total tarmpassage kom nära den för normalviktiga.

Användningen av denna trådlösa mätkapsel verkar säker och förefaller lämplig för att studera rubbningar i mag-tarmkanalens fysiologi både vid fetma och efter överviktsoperation.

I arbete IV analyserade vi glukos, insulin, triglycerider (blodfetter) samt hormonerna leptin, ghrelin, motilin, GIP, GLP-1 och PYY före och efter DS. Vi såg en tydlig normalisering av glukos- och insulinnivåerna efter måltid. Leptin halverades. Hormonerna med så kallad inkretineffekt, GIP minskade medan vi såg en tydlig stegring av GLP-1 och PYY. De sistnämnda förändringarna är viktiga för att bevara en hållbar viktnedgång och bota diabetes.

Korrelationsanalysen visade en positiv korrelation mellan mättnad och GLP-1 samt dess maxkoncentration efter operation. Vi såg också att magsäcksrörligheten hade positiv korrelation till önskan att äta och negativ korrelation till viktnedgång.

Ovanstående resultat för fram de hormonella förändringarna som viktiga mekanismer för en framgångsrik överviktsoperation.

Sammanfattningsvis har vi kunnat konstatera att tarmsymtom har stor betydelse för livskvalitet och social kontakt. Förekomsten av symtom som dyspepsi och diarré ökar risken för operationskomplikationer. Valet av kirurgisk metod har stor betydelse för utveckling av dyspepsi och diarré. De hormonella förändringar som uppstår i samband med överviktskirurgi har stor betydelse för en långvarig och hållbar viktnedgång.

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