

Department of Gastrointestinal Surgery, Helsinki University Central Hospital Faculty of  
Medicine, University of Helsinki, Finland

## **Complications in Bariatric Surgery**

Mervi Javanainen

Doctoral dissertation

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SUPERVISORS:

Docent Marja Leivonen, MD, Ph.D.

Department of Gastrointestinal Surgery

Seinäjäki Central Hospital, Seinäjoki, Finland

Docent Tom Scheinin, MD, Ph.D.

Department of Gastrointestinal Surgery, Abdominal Center,

Helsinki University Hospital, Helsinki, Finland

Docent Harri Mustonen, DSc, Ph.D.

Biomedicum Helsinki,

Helsinki University Central Hospital, Helsinki, Finland

REVIEWERS:

Docent Jyrki Kössi, MD, Ph.D., Päijät-Häme Central Hospital, Lahti, Finland,

Docent Timo Heikkinen MD, Ph.D., University of Oulu, Oulu, Finland

Opponent:

Docent Vesa Koivukangas, MD, Ph.D.

Department of Gastrointestinal Surgery,

Oulu University Hospital, Oulu, Finland

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## List of original publications

1. Retrospective analysis of three different antithrombotic prophylaxis regimens in bariatric surgery. Javanainen MH, Scheinin T, Mustonen H, Leivonen M. *Surg Obes Relat Dis*. 2016 Mar-Apr; 12(3):675-680. doi: 10.1016/j.soard.2015.12.017.
2. Do Changes in Perioperative and Postoperative Treatment Protocol Influence the Frequency of Pulmonary Complications? A Retrospective Analysis of Four Different Bariatric Groups. Javanainen MH, Scheinin T, Mustonen H, Leivonen MO *Obes Surg*. 2017 Jan; 27(1):64-69. doi: 10.1007/s11695-016-2236-7.
3. A Retrospective Two-Year Follow-up of Late Complications Treated Surgically and Endoscopically After Laparoscopic Roux-en-Y Gastric Bypass (LRYGB) and Laparoscopic Sleeve Gastrectomy (LSG) for Morbid Obesity. Javanainen MH, Penttilä A, Mustonen H, Juuti A, Scheinin T, Leivonen M. *Obes Surg*. 2017 Oct 28. doi: 10.1007/s11695-017-2967-0.
4. Two-year nutrition data in terms of vitamin D, vitamin-B12 and albumin after bariatric surgery and long-term fracture data compared with conservatively treated obese patients—a retrospective cohort study. Javanainen M, Pekkarinen T, Scheinin T, Leivonen M. *Obes Surg*. 2018 Jun 23. doi: 10.1007/s11695-018-3336-3.

## Abbreviations

|        |  |
|--------|--|
| AGB    | adjustable gastric banding                     |
| AHI    | apnea-hypopnea index                           |
| AT     | adaptive thermogenesis                         |
| BMI    | body mass index                                |
| BPD    | biliopancreatic diversion                      |
| BPD/DS | biliopancreatic diversion with duodenal switch |
| CI     | confidence interval                            |
| COPD   | chronic obstructive pulmonary disease          |
| CPAP   | continuous positive airway pressure            |
| CT     | computed tomography                            |
| DMT2   | diabetes Mellitus Type 2                       |
| DS     | duodenal switch                                |
| DVT    | deep vein thrombosis                           |
| EGD    | esophagogastroduodenoscopy                     |
| EMA    | European Medicines Agency                      |
| ERAS   | enhanced recovery after surgery                |
| EWL%   | excess weight loss percentage                  |
| FDA    | Food and Drug Administration                   |
| GGF    | gastrogastric fistula                          |
| GERD   | gastroesophageal reflux disease                |

|       |   |
|-------|---|
| GED   | gastric electrical stimulation  |
| GLP-1 | glucagon-like peptide 1   |
| HRQOL | health-related quality of life  |
| ICU   | intensive care unit   |
| IFSO  | The International Federation for the Surgery of Obesity and Metabolic Disorders |
| IH    | internal hernia   |
| IPS   | intermittent pneumatic compression devices                                      |
| LMWH  | low-molecular-weight heparin  |
| MGB   | mini gastric bypass   |
| MU    | marginal ulcer  |
| NICE  | the National Institute for Health and Care Excellence                           |
| NIH   | National Institutes of Health   |
| NUD   | non-ultra descriptus  |
| OSA   | obstructive sleep apnea   |
| PCOS  | polycystic ovarian syndrome   |
| PE    | pulmonary embolism  |
| PP    | postoperative pneumonia   |
| PPI   | proton-pump inhibitor   |
| PRF   | postoperative respiratory failure   |
| RR    | relative risk   |
| RCT   | randomized controlled trial   |



|        |   |
|--------|---|
| RYGB   | Roux-en-Y gastric bypass                |
| SADI-S | single-anastomosis duodeno-ileal bypass |
| SBO    | small bowel obstruction                 |
| SG     | sleeve gastrectomy                      |
| SOS    | the Swedish Obese Subjects              |
| UGI    | upper gastrointestinal series           |
| WC     | waist circumference                     |
| WHR    | waist-to-hip circumference ratio        |
| VTE    | venous thromboembolism                  |
| VLCD   | very low-calorie diet                   |

## Abstract

Since 1975, the prevalence of obesity has nearly tripled, and 39% of the world's population is now overweight. Bariatric surgery has proven to be the most effective treatment for obesity and obesity-related diseases. Roux-en-Y gastric bypass (RYGB) is one of the most popular and well-studied operation types worldwide. However, in recent years, the popularity of sleeve gastrectomy (SG) has risen rapidly, surpassing the RYGB.

Bariatric surgery has proven to be safe; however, there is still limited information about some of the complication types. The complications that occur after bariatric surgery can be divided into early complications (under 30 days after the operation) and late ones (over 30 days after the operation); late complications can further be divided into surgical and non-surgical complications.

This thesis consists of four different studies on the common complication types related to bariatric surgery. Study I analyses the relationship between bleeding/venous thromboembolic complications and different enoxaparin protocols, and Study II reviews the changes in pulmonary complications under different perioperative protocols. The last two studies compare late complications, vitamin deficiencies, and fractures between RYGB and SG operations. In Study IV, we also compare the number of fractures that occur after surgery to fractures in non-surgically treated patients.

All the data from the patients were collected between 2007 and 2016 at Peijas Hospital, affiliated to Helsinki University Hospital. The patient characteristics and the data from the first two years were collected prospectively and later retrospectively. In addition to analyzing the patients who underwent operations, Study IV includes 199 non-surgically treated obese patients as a control group. In Studies I and II, the follow-up times were 30 days. In Study III, the follow-up time was two years, and, in Study IV, the follow-up time was at least six years.

The results of Study I showed that enoxaparin was safest when administered in a 40-mg dose once a day. Study II revealed that, alongside avoiding the use of drains and urinary catheters, fast mobilization was favorable to prevent postoperative pneumonia and shorten the hospital stay. The last two studies compared RYGB to SG. It was observed that, compared to the SG patients, the RYGB patients had more late complications treated surgically or endoscopically. In Study IV, vitamin D, albumin, and B12 levels were at an acceptable level two years after either operation. It was shown that the bariatric patients had a higher risk of fractures compared to the non-surgically treated

patients. Higher age, bariatric surgery, and lower body mass index (BMI) at the two-year control mark increased the risk of fracture after obesity treatment.

## Tiivistelmä

Lihavuuden määrä on kolminkertaistunut 1975-vuodesta lähtien ja nykyään 39% maapallon ihmisistä on ylipainoisia. Lihavuuskirurgia on todetusti lihavuuden ja siihen liittyvien sairauksien tehokkain hoitokeino. Leikkaustyypeistä ohitusleikkausta on tutkittu eniten ja se oli suosituin leikkaustyyppi. Kuitenkin kavennusleikkaus on ohittanut maailmalla ohitusleikkauksen suosion.

Lihavuuskirurgia on tutkitusti turvallista, mutta monista komplikaatioista on vielä vähän tutkittua tietoa. Lihavuuskirurgian komplikaatiot voidaan jakaa välittömiin (alle 30 päivää leikkauksesta) ja myöhäisiin (yli 30 päivää leikkauksesta).

Väitöskirja koostuu neljästä osatutkimuksesta, joissa tutkitaan neljää eri lihavuuskirurgiaan liittyvää komplikaatiota. Osajulkaisu I selvittää enoksapariini- tromboosiprofylaksian muutosten vaikutusta vuoto- ja tukoskomplikaatioihin. Osajulkaisussa II tutkitaan leikkausta edeltävän ja leikkauksenjälkeisen toiminnan vaikutusta keuhkokomplikaatioihin. Osajulkaisut III ja IV vertailevat mahalaukun kavennus- ja ohitusleikkauksen myöhäiskomplikaatioiden määrää, vitamiinipuutoksia ja murtumia. Osajulkaisussa IV oli mukana myös konservatiivisesti hoidettu vertailuryhmä.

Kaikkien tutkimusten seurantatiedot on kerätty vuosien 2007-2016 välillä Peijaksen sairaalassa hoidetuista potilaista. Leikattujen potilaiden lisäksi osajulkaisussa IV on mukana 199 konservatiivisesti hoidettua ylipainoista potilasta. Kahdessa ensimmäisessä artikkelissa käsiteltiin varhaiskomplikaatioita, joten potilaita seurattiin 30 päivän ajan leikkauksesta. Kolmannessa artikkelissa seuranta-aika oli 2 vuotta ja neljännessä artikkelissa vähintään 6 vuotta.

Osatutkimuksessa I saatiin selville, että enoksapariini-annostus on turvallisin annosteltuna 40mg kerran päivässä. Osatutkimuksen II tuloksena on, että nopea mobilisointi ja laskuputkien käytön minimointi aiheuttivat vähiten keuhkokomplikaatiota ja nopeuttivat kotiin lähtöä.

Kaksi viimeistä osatutkimusta vertailivat kavennus- ja ohitusleikattuja potilaita. Osatutkimuksen III tuloksista nähdään, että ohitusleikatuilla potilailla on enemmän myöhäisiä komplikaatioita. Osatutkimuksessa IV selviää, että molemmissa leikkaustyypeissä D-vitamiini, albumiini ja B12 arvot olivat hyväksyttävät. Lisäksi huomattiin lihavuuskirurgian lisäävän murtumariskiä verrattuna ei-

kirurgisesti hoidettuihin potilaisiin. Murtuman riskiä lisäsivät vanhempi ikä, kirurginen hoito, ja matalampi BMI-lukema kahden vuoden kontrollissa.

## 1 Introduction

Obesity is said to be a chronic disease, resulting from the combination of genes and environment (1). Modern humans' lifestyle of decreased physical activity and the great abundance of food have led to an obesity pandemic around the globe (2). In the United States, obesity is the second most common cause of preventable deaths, right after smoking (3).

Obesity is a lifelong problem; it is a chronic relapsing condition with only a few successful long-term solutions (4). Compared to conservative weight-loss methods, such as lifestyle interventions and pharmacotherapy, bariatric surgery has proven to be the most effective weight-loss method (4, 5, 6). Bariatric surgery is also effective in improving obesity-related comorbidities, such as diabetes, hypertension, and hypercholesterolemia (7).

Bariatric surgery began to evolve in 1954 from the notion that a shortened small intestine and secondary malabsorption led to sustained weight loss. Since its inception, several restrictive and malabsorptive bariatric procedures have been proposed. However, the majority of these techniques are no longer used because of their severe complications (8).

Between 1998 and 2002, the number of bariatric surgeries increased by more than 400%. One reason for this increase was a change in operation type from open to laparoscopic; compared to the open approach, the laparoscopic method is associated with a significantly lower number of complications and a shorter hospital stay (9).

In 2013, the total number of bariatric operations performed globally was estimated to be 468,609. The most popular operations were Roux-en-Y gastric bypass (RYGB) (45%), sleeve gastrectomy (SG) (37%), and adjustable gastric banding (AGB) (10%). The most notable trend in the last 10 years has been the rise of popularity of SG from zero to 37% between 2003 and 2013 (10).

As with all surgical procedures, the number of complications in bariatric surgery is one factor related to the results of the operation type. Complications can be divided into short-term complications (under 30 days after the operation) and long-term ones (over 30 days after the operation) (11). In a large meta-analysis, the total complication rate after bariatric surgery was 17% (95% CI, 11–23%), and

the reoperation rate was 7% (95% CI, 3–12%). The total mortality rate within 30 days of the operation was 0.08% (95% CI, 0.01–0.24%) (12).

Pulmonary embolism (PE) is one of the most common reasons for early mortality after bariatric surgery (13). In this doctoral thesis, Study I presents the relationship of enoxaparin, thromboembolic complications, and bleeding complications after bariatric surgery.

Another common early problem is postoperative pneumonia (PP), which, together with respiratory failure (RF), accounts for 20% of total mortality, following bariatric surgery (14). The second study analyzes how changes in peri- and postoperative treatment protocol toward enhanced recovery after surgery protocol (ERAS) affect the incidence of pulmonary complications in bariatric patients.

Early complications are now well studied and documented; however, there is a paucity of information about late complications. Some of the most common late complications are internal hernias, biliary complications, and nutritional deficiencies (11). Recently, it has been suggested that RYGB is associated with more late complications than SG (15, 16). In the third study, we compare whether there is a difference in late complications between RYGB and SG two years after the operation.

In the fourth study, we monitor changes in B12, albumin, and vitamin D levels for two years in RYGB and SG patients; we will also compare the number of fractures that occurred to patients who had undergone these operations to a non-surgically treated cohort group.

## 2 Review of the literature

### 2.1 Epidemiology of obesity

For a long period, people had to fight against famine and diseases in order to survive (17). The controversial “thrifty gene” hypothesis suggest that the ability to store fat in times of nutritional abundance in order to deal with periodic starvation is a positive trait that has evolved over many thousands of years of human evolution (18, 19).

The median weight of the human population started to grow at the onset of the Industrial Revolution, based on the notion that, compared to being underweight, soldiers and farmers performed better when their weight was closer to a normal range. Therefore, the shift in the population’s body mass index (BMI) from being underweight to a normal range of BMI was a significant political and economic development (20).

Historical records suggest that height and weight increased progressively, particularly during the 19<sup>th</sup> century. During the 20<sup>th</sup> century, the population began to approach its genetic potential in terms of longitudinal growth and began to gain more weight than height, resulting in an increase in the average BMI (17). By the year 2000, it was observed for the first time that the number of overweight humans exceeded those who were underweight (21). Until recently, obesity was associated with countries of high socioeconomic status. However, in the early 20<sup>th</sup> century, obesity also began to increase rapidly in the developing countries (22).

Until the 1970s, the “ideal” body size was derived from actuarial tables from the life insurance industry. These tables were based on the notion that a body weight within the ideal range had a lower risk of premature death. In the 1980s, the ideal body weight approach was replaced by the BMI system, where the cutoff limits for being overweight (BMI 25 to 30) and obesity (BMI under 30) were introduced (17).

The BMI model is still commonly utilized. However, it has faced some critiques, in that the risks of mortality and BMI may vary in different ethnic groups (23, 24). Some Asian countries have already lowered their cutoff number for obesity (24). The BMI risk assessment is not flawless, and new methods for determining body fat quickly and reliably are needed. Waist circumference (WC) and the waist-to-hip circumference ratio (WHR) have been suggested as new methods (25).

More than 1.9 billion adults, aged 18 or older, were overweight in 2016, and 650 million of them were obese; this means that 39% of the world’s adult population is overweight and 13% is obese. The prevalence of obesity has nearly tripled since 1975 (26). In Finland, the mean BMI has risen from the 1970s. Over half of the population in Finland (46% women, 66% men) are overweight (BMI over 25 kg/m<sup>2</sup>) and 20% are obese (BMI over 30 kg/m<sup>2</sup>) (27).

In 2015, obesity accounted for 4 million deaths annually and 120 million disability-adjusted life years worldwide (28). Obesity is the cause of substantial direct and indirect costs, which puts a strain on both healthcare and social resources. Diagnosis, prevention, and treatment constitute the direct costs related to obesity. Indirect costs can be far higher but are often neglected; they can derive from decreased productivity, illness, and premature death, for example (29). It has been estimated that in 2015, 29% of the U.S. national health expenditures were allocated to obesity-related diseases (30), and the European nations spent 0.09% to 0.62% of their country’s gross domestic budgets on treating obesity (31).

## 2.2 The physiology and consequences of obesity

By definition, obesity is a state of increased adipose tissue of a sufficient amount to produce adverse health effects. Under normal circumstances, when a person has normal nutrient absorption, energy can only be stored in the body if energy intake exceeds the body's total energy expenditure. Energy expenditure is generated from basal metabolism, physical activity, and adaptive thermogenesis (AT). Physical activity refers to all voluntary movements, while basal metabolism refers to the number of biochemical processes, aimed at maintaining life (32). AT refers to the underfeeding-associated fall in resting and non-resting energy expenditure (33). The term metabolic adaptation is also sometimes used as a synonym for AT (34).

Multiple factors contribute to obesity, for example, excessive eating arising from increased hunger, decreased satiety, or both. Besides, highly processed foods with added fat and refined carbohydrates (e.g., chocolate, pizza, and chips) are associated with behavioral indicators of addictive eating (35).

The pathology of the subcortical area in the brain, which controls the appetite, has a genetically determined susceptibility, which is then affected by environmental factors (36). Environmental factors include the advertising and marketing of food, increased portion sizes, the availability of high-calorie food, and increased automation (37). Current research is trying to determine how the neural pathways involved in regulating food intake and energy control work and are modulated by environmental and genetic factors. Gut hormones such as cholecystokinin, peptide YY, and glucagon-like peptide 1 (GLP-1) appear to play critical roles (38).

Small adipocytes in normal-weight people release adipokines, which do not affect metabolic homeostasis, while enlarged adipocytes in obese people release adipokines in larger amounts, promoting inflammation and insulin resistance (39). Obesity is an essential contributor to the pathophysiology of insulin resistance and diabetes by dysregulating cellular metabolism (39). These conditions will eventually lead to significant atherosclerosis and, together with obesity and insulin resistance, will constitute metabolic syndrome (40).

In addition, obesity contributes to immune dysfunction, where the secretion of inflammatory adipokines is a risk factor for many types of cancer, including esophageal, hepatocellular, and colon cancer (39). Adipocytes have been studied intensively, and it is hypothesized that adipocytes might also be relevant to the control of body weight (41).

Compared to normal weight, obesity (BMI > 30) is associated with significantly high mortality (42). In a Swedish study that collected data from military personnel, it was observed that the protective effect of fitness against death was reduced in obese subjects, and a normal-weight unfit subject had a lower risk of death than a fit obese subject (43).

We have learned in the last few decades that the risk of obesity is highly hereditary (44) and that several genes are associated with weight gain (45, 46). Gut microbes, inflammation, and insulin resistance are also under rigorous investigation to find an explanation for the current obesity epidemic (47, 48).

## 2.3 Conservative treatment of obesity

### 2.3.1 Lifestyle modifications

Expert panels from the World Health Organization and the National Institute of Health have recommended that for obese individuals attempting to lose weight, lifestyle modifications should comprise the foundation of the treatment and management of obesity (22, 49). More recent guidelines have also added behavior therapies to the recommendations (50). An initial modest weight loss of 5% to 10% of total body weight is recommended in most guidelines to improve results in cases of diabetes, hypertension, and disability, without incurring significant risks (22, 49). However, in the Look AHEAD trial, in which the participants with diabetes Mellitus Type 2 (DMT2) underwent an intensive lifestyle intervention and achieved a median weight loss of 7% to 10% over 10 years, no significant reduction in cardiovascular morbidity and mortality was found compared to the control group (51).

Lifestyle modification can be achieved with a variety of dietary approaches (52); however, traditionally, a diet high in carbohydrates and low in fat (under 30% calories from fat) with an emphasis on vegetables, fruits, and whole grains is recommended (53). Another popular trend is low-carbohydrate diets, which concentrate on high-protein and low-carbohydrate intake (52). Severely obese patients, who had DMT2 or metabolic syndrome, were assigned either a low-carbohydrate diet or a low-fat diet. Compared to those in the low-fat diet (1.9 kg), those in the low-carbohydrate diet group lost significantly more weight in six months (5.8 kg) and exhibited greater changes in insulin sensitivity (54). However, in a review comparing a restrictive carbohydrate diet and a balanced diet, no difference was found in weight loss or changes in cardiovascular risk factors for up to two years between the two diet protocols (55). Therefore, the choice of a specific diet can be left to the



discretion of the patient, as superior diet programs are not available. The key is to find a popular calorie-reduced program to which the patient can adhere (56).

Behavior treatment is usually held by dietitians, behavior psychologists, or other healthcare professionals (57). It has been shown that group therapy yields a more considerable initial weight loss than individual care, even in patients who indicated a preference for individual treatment (58). Physical activity plays an important role in cardiovascular health (59). However, physical activity alone offers limited benefits or none at all in inducing weight loss (60).

From a meta-analysis of weight-loss studies, it was determined that in two to four years, dietary and lifestyle therapies yield a weight loss of under 5 kg, while surgical therapy yields a weight loss of 25 kg to 75 kg (6). The failure of lifestyle change alone to produce durable weight loss is partly due to the use of biological responses that promote weight regain (61); these include a reduction in energy expenditure (34), changes in hunger and satiety (62, 63), and changes in adipocytes and insulin sensitivity to favor fat storage. Longitudinal studies suggest that these changes are probably permanent (63, 64).

### 2.3.2 Pharmacotherapy

Pharmacotherapy concerns patients with a BMI of  $\geq 30$  kg/m<sup>2</sup> or a BMI of at least 27 kg/m<sup>2</sup> in the presence of obesity-related diseases or risk factors (65). If a patient fulfills the BMI criteria and fails to lose weight alone or with professional help, anti-obesity drugs should be started promptly (66). Anti-obesity drugs provide a weight loss of 5 kg to 10 kg in one to two years (6). In a recent meta-analysis of 20 randomized controlled trials (RCTs), it was observed that anti-obesity drugs improved the maintenance of weight loss compared to placebo by 3.5 kg in 18 months (60).

Currently, there are three categories of anti-obesity drugs: (a) central nervous system modifiers, (b) endocannabinoid inhibitors, and (c) fat absorption inhibitors (67). In North America, there are currently six Food and Drug Administration-approved anti-obesity medications available, and these include phentermine, orlistat, phentermine/topiramate, lorcaserin, naltrexone/bupropion, and liraglutide (66).

Orlistat is an anti-obesity drug approved by the European Medicines Agency (EMA) (67) and therefore one of the few available anti-obesity drugs in Finland (68). Orlistat is a pancreatic lipase inhibitor that prevents the normal metabolism of dietary fat and hence reduces fat absorption (69). In a Cochrane

meta-analysis of 13 double-blind placebo RCTs on Orlistat, participants lost, on average, 2.9% more weight (95% CI, 2.5–3.4%) than those given a placebo (70).

In early 2018, a new weight-loss product, Mysimba (naltrexone/bupropion), was brought to the Finnish market. Naltrexone is an opioid antagonist, and bupropion is an antidepressant of the aminoketone class, which is an inhibitor of the neuronal reuptake of dopamine and norepinephrine (71). Naltrexone/bupropion was brought to the United States as a second combination therapy in 2014. A weight loss of 3.3% to 4.8% was seen in placebo-controlled studies after one year. Nausea and an increase in blood pressure are common adverse effects (72).

Another medicine for Finnish customers is liraglutide, which is a GLP-1 receptor agonist that works in the hypothalamus to reduce hunger and increase satiety (72). Liraglutide is administered daily as a subcutaneous injection. In placebo-controlled studies, Liraglutide yielded a 4% to 5.4% weight loss in one year (72).

## 2.4. Surgical treatment of obesity

### 2.4.1 History

The idea of bariatric surgery originated in 1954 when Kremen et al. reported that the resection of a controlled length of the small intestine in dogs resulted in impaired fat absorption and weight loss. They also noticed that patients who had lost a part of their small intestine began to lose weight, despite increased intake of calories (73).

In 1963, Payne et al. (74) performed the first obesity surgery procedure for weight loss on an obese patient. The operation was a jejunocolic bypass, in which the small intestine was divided 30 cm to 50 cm from the ligament of Treitz. The proximal segment was then anastomosed to the proximal transverse colon, and the distal end was closed, leaving a long blind loop of the small intestine. The operation yielded significant weight loss and a decrease in serum cholesterol and lipoproteins; however, fatty stool, diarrhea, and anal complications were also observed in nearly all the patients (75). Other problems included poor absorption of vitamins, dehydration, electrolyte imbalance, anemia, fatty infiltration of the liver, hepatic cirrhosis, and even hepatic failure. Because of the severe complications, the jejunocolic bypass was abandoned (76).

The next modification was presented in 1969 by Payne and Dewind, who recommended jejunioileostomy for the surgical treatment of obesity. In this procedure, the small intestine was

divided 35 cm distally to the ligament of Treitz, and the proximal segment of jejunum was anastomosed with the terminal ileum 10 cm proximal to the ileocecal valve (77).

The reported overall mortality of the jejunioileal bypass was 4% in the first two postoperative years, mostly due to liver failure (78). The weight loss that accompanied the jejunioileal bypass was most significant shortly after the operation and then leveled out. Subsequently, the jejunioileal bypass was also abandoned, and most of the patients had to have a revision surgery (79).

In 1967, Mason noticed that with partial gastrectomy, patients were able to lose weight. Based on that notion, he developed a simple gastric bypass procedure by surgically isolating a portion of the stomach along with a retrocolic loop gastrojejunostomy (80). A small pouch was created, which permanently restricted the food volume, sustaining weight loss. However, several complications such as dumping syndrome, marginal ulcers, and bile reflux were also observed. In 1977, Alden modified the operation by cross-stapling the stomach and switching to an antecolic gastrojejunostomy (81). Around the same time, Griffen et al. introduced Roux limb modification (82). Since then, several variations have been suggested, leading to the current technique used in RYGB.

In 1979, the idea of adding a malabsorptive component to previous restrictive procedures was raised, which led to the first biliopancreatic diversion (BPD) by Scopinaro. The operation was a modification of the jejunioileal bypass and consisted of a 200 ml to 250 ml horizontal gastric pouch with a distal gastrectomy, closure of the duodenal stump, and a gastroenterostomy with a 250-cm Roux limb (83).

There were fewer problems with the BPD patients than the jejunioileal bypass patients, as the increased bowel length decreased frequent diarrhea, protein malnutrition, and vitamin and electrolyte deficiencies. However, there was an increased risk of calcium, a fat-soluble vitamin, and protein deficiencies. Patients were also experiencing post-gastrectomy syndrome, including marginal ulcers and dumping syndrome (80). Because of the high incidence of the post-gastrectomy syndrome, BPD was modified with a duodenal switch (DS), which was first described by Marceau in 1993. In a BPD with a DS (BPD/DS), the major curvature is resected, leaving a tube-like gastric remnant, while saving the pylorus. The enteric limb (250-cm Roux limb) is then anastomosed to the post-pyloric duodenum. A long duodenal biliopancreatic limb is anastomosed to the Roux limb 50 cm proximal to the ileocecal valve (84).

SG originated in 1988 as a variation of BPD/DS (85, 86, 87). Compared to BPD, in SG the pylorus and duodenum were preserved (88). In the beginning, SG was performed openly and was first performed laparoscopically in the 1990s (89). In 2000, a high complication rate in patients with high BMIs was reported, and Regan et al. described a two-step surgical approach in which SG was performed as the first step, followed by RYGB or BPD (90). However, it was observed that good results were usually obtained with SG only, and no second-step operation was needed (91, 92, 93).

Another restrictive operation type, previously used widely, is gastric banding, whereby a band is wrapped round the stomach, and a narrow passage is created from the proximal to the distal stomach. Gastric banding gained high popularity in the late 1990s; however, it has nowadays been nearly abandoned due to long-term complications and failure in weight loss (8).

Laparoscopic surgery was initially introduced early this century by Dimitri Ott et al. to inspect the abdominal cavity of a pregnant woman. For several years, laparoscopy was used mainly for diagnostic purposes. In 1987, the first laparoscopic cholecystectomy was performed on humans. Since then, it has been widely used in abdominal surgery (94). The change from an open to a laparoscopic operation type also affected the popularity of bariatric surgery, as the complication rate and the number of re-operations were significantly lower; the length of the hospital stay was also shorter with the laparoscopic approach (9).

Some newer operations include the single-anastomosis gastric bypass and the single-anastomosis duodeno-ileal bypass with sleeve gastrectomy (SADI-S). The mini-gastric bypass was first introduced in 2001 by Rutledge, and it consists of two stages. First, a long and narrow lesser curvature gastric pouch is created, followed by a single antecolic gastrojejunostomy (GJ) anastomosis for the second stage (95). SADI-S was first presented by Sánchez-Pernaute et al. in 2007 as a technical simplification of the DS to reduce its complexity (96).

Compared to the existing surgical approaches, endoluminal interventions, performed by flexible endoscopy, offer a new, safe, and cost-effective approach; the weight-loss effect is typically higher than that of drugs but lower than that of surgical operations. The field of endoluminal techniques includes promising methods, such as endoscopic gastroplasty, intragastric balloon, endoluminal malabsorptive bariatric procedures, and gastric electrical stimulation (GES) (97).

#### 2.4.2 Epidemiology of bariatric surgery

Despite the good results obtained from bariatric surgery, only a fraction of patients who fulfill the eligibility criteria and benefit from obesity surgery undergo operations or are even referred for surgery (98). For example, in 2013, only about 0.01% of the world's population underwent bariatric surgery (10). The most recent estimation of the total number of bariatric surgeries is from 2013. There were an estimated 468,609 bariatric procedures worldwide, 95.7% of which were carried out laparoscopically. The highest number of operations (33%) was performed in the United States and Canada. The most common procedures were RYGB (45%), SG (37%), and AGB (10%).

Globally, the popularity of RYGB decreased by 16% between 2011 and 2013, while the popularity of SG rose from zero to 37% between 2003 and 2013. The number of AGB plummeted between 2008 and 2013 from 68% to 10%. In Latin/South America and Europe, RYGB remains the most popular operation, while in other regions (United States, Canada, and the Asia Pacific), it has been surpassed by SG (10).

The International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) report (2013–2015), covering 31 different countries and a total of 142,748 operations, indicates that the median age of operated patients was 42 years; 73.3% of the patients were women, 49.4% of the operations were RYGB, and 40.7% were SG. The one-year total weight loss percentage (TWL%) was 30.53% (95% CI, 30.22–30.84%) (99).

It has been estimated that 1.4% to 7% of all health costs result from obesity in Finland and, compared to other Scandinavian nations, Finnish people are more obese (100). In Finland, approximately 400 bariatric operations were performed in 2008, which peaked at slightly over 1,000 patients in 2011. Afterward, the number of procedures has slowly decreased and stabilized at 800 to 900 operations a year. In comparison, the number of procedures performed in Sweden has been steady, 5000 to 7000 operations per year. The incidence of bariatric procedures in Finland is one of the lowest in Western Europe (101).

#### 2.4.3 Indications of operative treatment

The criteria for bariatric surgery were first established in 1991 by a National Institutes of Health consensus panel (NIH) (102). Since then, the recommendations have only changed a little. The Interdisciplinary European Guidelines on Metabolic and Bariatric Surgery recommend obesity surgery for the age group ranging between 18 and 60 with a BMI  $\geq 40$  kg/m<sup>2</sup> or a BMI of 35 kg/m<sup>2</sup> to 40

kg/m<sup>2</sup> with co-morbidities, whereby surgically induced weight loss is expected to improve the disorder (e.g., DMT2, hypertension, dyslipidemia, cardiovascular disease, stroke, sleep apnea, osteoarthritis, polycystic ovarian syndrome (PCOS), certain cancers, and obesity-related psychological problems).

To be considered for obesity surgery, patients should have failed to lose weight or maintain weight loss using appropriate conservative treatment protocols, such as nutrition or pharmacotherapy. Before the operation, the patients undergo a comprehensive interdisciplinary assessment by an endocrinologist, surgeon, psychologist, nutritionist, and social worker if needed. Contraindications include non-stabilized psychotic disorders, severe depression, severe eating disorders, alcohol or drug abuse, and an inability to participate in a prolonged medical follow-up (103). Similar multidisciplinary patient selection for obesity surgery is recommended by the Finnish Current Care Guidelines (Käypähoito) (68).

Bariatric surgery should be considered in children/adolescents if their BMI is over 40 kg/m<sup>2</sup>, the patient has one co-morbidity, and weight loss has been monitored for at least six months at a specialist weight reduction center. The patient also has to show skeletal maturity and be capable of committing themselves to a comprehensive medical and psychological evaluation before and after surgery (103). In elderly patients, the risk has to be evaluated individually, and the primary target is to improve the quality of life (104). Candidates for bariatric surgery have to be evaluated prior to the operation for surgical risks, including the presence of cardiovascular, pulmonary, or other system diseases (105).

The current indications for bariatric surgery have been in use for over 24 years and have been widely criticized. The current eligibility criteria for bariatric surgery are mostly based on BMI. However, patients with similar BMIs may have very different levels of health and comorbidities. It has been suggested that instead of concentrating on BMI, the indication criteria should be preferably based on functional effects, overall health variables, and the pathophysiological impact of the surgical approach (106).

Some updates have been added to the newer guidelines. The NIH guidelines from 2014 stated that bariatric surgery should be considered for the treatment of recent-onset DMT2 for patients with a BMI of 30 kg/m<sup>2</sup> to 34.9 kg/m<sup>2</sup> (107).

Another consideration of obesity surgery is ethnic differences. The population prevalence data indicate that Asians have a higher risk of DMT2 and other diseases at lower BMI levels than people in European countries (108). Some emerging data also show that metabolic surgery is effective for Asian patients with DMT2 with lower BMI limits (109, 110). An update to 2014 National Institute for Health and Care Excellence (NICE) guidelines suggested that bariatric surgery should be considered for Asian candidates with a BMI over 35 kg/m<sup>2</sup>, regardless of the existence of comorbidities (107).

#### 2.4.4 Effects on weight loss

There is strong evidence that bariatric surgery is associated with greater weight loss than conservative management (6). It was stated in a Cochrane review that, globally, the two most popular operation types, RYGB and SG, offered similar results in terms of weight loss, and both procedures had better outcomes than AGB. However, most of the studies included in the Cochrane review had a follow-up time of only one to two years (5).

In a meta-analysis of 22,094 patients, the mean excess weight loss percentage (EWL%) was 61.2% (58.1–64.4%) for all bariatric surgery patients, 47.5% for gastric banding, 61.6% for gastric bypass, and 70.1% for biliopancreatic diversion or duodenal switch (111). In one of the analyses, it was also observed that, compared to Europe, RYGB leads to higher EWL% in the United States, Canada, and Asia (112). No differences in baseline age, BMI, and length of follow-up after the operation had significant associations with EWL%. However, a positive correlation between EWL% and the female gender after RYGB, but not AGB and SG, was seen (112). It has been suggested that the differences in weight loss between different ethnic groups may be due to differences in metabolism, dietary intake, and living habits (113).

In 2018, a multicenter RCT of 240 patients with a five-year follow-up was published. The study showed that the mean EWL% with a gastric bypass was 57% (95% CI, 53–61%) and 49% (95% CI, 45–52%) with SG. However, the effect of procedures on weight loss was considered equal because of prespecified equivalence margins (113).

In the Swedish Obese Subjects (SOS) studies, it was noted that the level of energy restriction that was achieved 0.5 years after bariatric surgery predicts the long-term weight loss. More significant weight loss was achieved in patients who favored protein and carbohydrates over fats (115).

#### 2.4.5 Effects on mortality and morbidity

Bariatric surgery improves the long-term mortality rate compared to that of the general population, regardless of the type of bariatric surgery performed (116). The perioperative complications do not increase long-term mortality risk. In a recent study of 7862 bariatric surgery patients with 8- to 14-year follow-up, the mean total mortality in bariatric surgery patients was 2.5%. Between 1999–2000, the actuarial mortality rate for the general population was 2.1% and 2.3% in obese patients versus the observed 1.5% for the bariatric surgery population. The risk factors for earlier death were age, male gender, congestive heart failure, rheumatoid arthritis, pulmonary circulation disorders, and DMT2 (116). In the SOS studies, 2037 bariatric surgery patients were matched to 2037 obese control patients and followed an average of 10.9 years. The unadjusted overall hazard ratio for mortality was 0.76 in the surgery group ( $p = 0.04$ ) (117).

The incidence of DMT2 is growing rapidly worldwide, driven by population growth, aging (118), and the increase in BMI, as BMI and DMT2 have a positive correlation (119). With non-surgical treatments, such as lifestyle interventions and pharmacotherapy, a remission rate under 15% has been achieved (120). In contrast, with bariatric surgery, even 76.8% of the diabetic population can achieve remission (111).

The efficacy of bariatric surgery, compared to non-surgical therapy in DMT2, has been proven in multiple RCTs (121, 122, 123). However, these studies only follow patients for up to two years. In a recently published meta-analysis where patients were followed for more than five years after bariatric surgery, a pooled estimate showed that surgery significantly increased DMT2 remission (RR 5.90; 95% CI, 3.75–9.2) and decreased mortality (RR = 0.21; 95% CI, 0.20–0.21) compared to non-surgically treated patients. The risk of micro- and macrovascular complications was also reduced (124). In another study of 4160 subjects, a 23% reduction in the risk of DMT2 was discovered 12 months after the operation. In the dose-response meta-regression, a decrease of five BMI units reduced the risk of DMT2 by 30% (7).

Bariatric surgery is also effective in treating hypertension (125, 126). In a meta-analysis focusing on hypertension after bariatric surgery, 64% of patients had a resolution of hypertension after surgery (125). There is some evidence that the effect of bariatric surgery on hypertension might wear off over time (127, 128). As there is a repertoire of effective anti-hypertensive medications available (129), bariatric surgery as a treatment for isolated hypertension is less attractive.



Previous studies have suggested that, compared to gastric banding procedures, a bypass or gastric resection type of operation can lead to a better result in the resolution of hypertension (130). In a study comparing RYGB and SG, 65% of patients achieved the remission of hypertension. Baseline BMI, the presence of type DMT2, vitamin D status, baseline waist circumference, the type of surgery, and excess weight loss did not correlate with the remission effect, whereas the duration and severity of pre-surgical hypertension predicted the lack of postoperative remission (131).

In a meta-analysis, it has been shown that bariatric surgery decreased the risk of hyperlipidemia by 33% (7) and, in another meta-analysis of 29,208 patients and 166,200 non-surgical controls, bariatric surgery has also proven to reduce the risk of myocardial infarction and stroke compared to non-surgical controls (132).

An estimated 58% of obstructive sleep apnea (OSA) patients are obese, and, with the increase of obesity, the incidence of OSA also rises (133). OSA is caused by repeated periods of complete or partial upper airway collapse during sleep. With polysomnographic measures, the number of apnea-hypopnea episodes can be monitored (an apnea-hypopnea index (AHI)) (134).

A decline of OSA in bariatric surgery patients from 71% to 44% was found in a recent Finnish study one year after the surgery ( $p < 0.001$ ). The number of AHI also decreased from 27.8 events/h to 9.9 events/h ( $p < 0.001$ ) (134). In another study, which compared the effects of weight loss for both surgically and non-surgically treated patients, beneficial effects on AHI were seen in both groups. However, bariatric surgery may result in greater improvements in BMI and AHI (135).

Obesity has been shown to have a significantly negative impact on asthma control, and weight reduction will lead to an overall improvement in asthma, including airway hyperresponsiveness and inflammation. It has been suggested that weight loss should be the cornerstone in the management of asthma in obese patients (136). A longitudinal study comparing bariatric surgical patients to non-surgically treated patients indicated that bariatric surgery improved the function of the small airways, decreased systemic inflammation, and improved the quality of life (137).

In obesity, adipokine tissue is often in a chronic state of inflammation, and inflammation itself supports the development of DMT2. Several studies have measured mediators such as TNF $\alpha$ , IL-6, and CRP to measure diabetogenic inflammation after bariatric surgery. However, the relationship between these inflammatory mediators and metabolic health improvements, including DMT2

remission after bariatric surgery, is not well understood. The idea of a drop in inflammatory mediators after bariatric surgery has not been consistently supported in the published articles. In future longitudinal studies, the inclusion of different operation techniques and timing will be helpful in clarifying the correlation of DMT2 remission and inflammation (138).

Bariatric surgeries have been found to have a positive effect on infertility (139); however, mothers with previous bariatric operations are at a higher risk of perinatal complications compared to non-operated mothers (140). In a recent multisite cohort study on severe obesity, bariatric surgery was associated with a 33% lower hazard ratio of developing cancer compared to that of matched patients. The risk of obesity-related cancers, such as postmenopausal breast cancer (HR 0.58, 95% CI, 0.44, 0.77,  $P < 0.001$ ), endometrial cancer (HR 0.50, 95% CI, 0.37, 0.67,  $P < 0.001$ ), and colon cancer (HR 0.59, 95% CI, 0.36, 0.97,  $P = 0.04$ ), were particularly decreased (141). Bariatric surgery has also been found to have a positive effect on steatohepatitis (142).

#### 2.4.6 Effects on quality of life

Psychosocial considerations are a somewhat overlooked aspect of bariatric surgery, even if extreme obesity is associated with a number of psychological problems (143, 144). For studying the psychosocial aspects of bariatric surgery, health-related quality of life (HRQOL) questionnaires are often used. Quality of life questionnaires often include different aspects of health, including domains of physical, mental, and social well-being (144).

In obese men, low points on HRQOL were associated with attempts to lose weight. With women, a similar correlation between weight loss and HRQOL or BMI was not seen. These findings suggest that men try to lose weight based on their subjective evaluation of poor health measured by HRQOL, whereas women try to lose weight independent of HRQOL and health (145). It has been suggested that the success of bariatric surgery is not only due to BMI changes and the improvement of obesity-related comorbidities but also changes in HRQOL and the level of patient satisfaction (146).

In Lindekildeit's meta-analysis, it was shown that bariatric surgery is effective in improving the overall quality of life; the improvements were more effective in the physical domain, compared to other domains (e.g., mental) (147). However, there is significant heterogeneity in the results, suggesting that not all patients benefit psychologically from surgery (148).

The results of up to five years of HRQOL after surgery are well documented, showing significant improvements in physical health scores, which often reach typical population values (149, 150, 151).

In a recent meta-analysis of long-term results, significant improvements in physical and mental health were found, favoring the surgical group compared to the controls five to 25 years after surgery (152).

#### 2.4.7 Operation types

##### *Roux-En-Y-gastric-bypass (RYGB)*

As described by b Cesar Roux, in RYGB, a stable line is created with a staple-cutter device that cuts the stomach into a small gastric pouch and a much larger excluded component. The jejunum is then divided 20 cm to 50 cm distal to the ligament of Treitz, and the distal limb (i.e., Roux limb, alimentary limb) is brought up and anastomosed with the gastric pouch, creating a gastrojejunal anastomose and a short blind-ending jejunal stump. The gastrojejunal anastomose is left small in caliber (8–12 mm) to limit the emptying of solid food from the gastric pouch and thus facilitating weight loss by a restrictive effect. The alimentary limb can be brought up to the gastric pouch either anterior or posterior to the transverse colon. The proximal limb of the divided jejunum (i.e., the afferent or biliopancreatic limb) is anastomosed to the small bowel 75 cm to 150 cm distal to the gastrojejunostomy (153).

Several modifications of RYGB have been presented, with variations in pouch size and limb length. Other modifications include whether the gastrojejunal anastomosis is performed in a circular, linear-stapled, or hand-sewn manner and if the Roux limb procedure is performed in an antecolic or retrocolic manner (154).

In a recent study, it was found that lengthening the alimentary limb from 100 cm to 150 cm did not affect post-RYGB weight loss (155). There was also some evidence that lengthening the biliary limb could result in a greater antidiabetic effect for patients, and it was suggested that the RYGB procedure should be modified to improve DM2 outcomes (156).

The potential mechanism of the antidiabetic effect of RYGB includes increased nutrient stimulation of lower intestinal hormones (e.g., glucagon-like peptide-1), compromised ghrelin secretion, altered physiology, the modulation of intestinal nutrient sensing, and the regulation of insulin sensitivity (157).

##### *Sleeve gastrectomy (SG)*

In SG, the stomach is divided along its axis and the greater curvature, resecting the fundus, body, and proximal antrum, leaving a narrow gastric pouch along the lesser curvature. The remaining stomach has a residual volume of only about 100 ml compared to the original volume of 1800 ml. SG is a

restrictive bariatric operation, and weight loss is achieved by reducing the gastric volume, which leads to reduced food intake (153). SG is mainly a restrictive procedure; however, a large portion of the major curvature is removed and, with it, the fundal ghrelin-producing cells, increasing gastric emptying, which is associated with a variety of metabolic consequences leading to weight loss. A decrease in the ghrelin level is believed to affect appetite regulation. Also, the hindgut mechanism, which includes a post-prandial increase in peptide-YY and GLP-1, is thought to play a role in weight loss (158, 159).

#### *Adjustable gastric band (AGB)*

In AGB, an adjustable silicone gastric band is placed around the stomach about 2 cm below the gastroesophageal junction. The band is sutured to the wall of the stomach to decrease band slippage. The band has an inflatable inner sleeve, which is connected to a subcutaneous port in the abdominal wall. Adjustments of the band can be made by altering the amount of the fluid in the port with a needle. Port adjustment should be made based on the patients' weight loss and symptoms (153).

#### *One-anastomosis gastric bypass (OAGB)/Mini-gastric bypass (MGP)*

In the mini-gastric bypass, which is also called a one-anastomosis gastric bypass or an Omega-loop gastric bypass, the stomach is divided in the junction of body and antrum at a location where the jejunal loop can be brought up comfortably. An Ewald tube, roughly the diameter of the esophagus, is passed inside from the mouth and held against the lesser curvature. The stomach is divided parallel to the lesser curvature up to the angle of His. A point is selected on the small bowel about 200 cm distal to the ligament of Treiz, and the jejunal loop is brought up in an antecolic manner. An anastomose on the small bowel and the gastric tube is formed (95).

In a study of over 2000 mini gastric bypass (MGB) patients followed up for five years, a very acceptable complication rate was found. However, more extensive and longitudinal RCT studies are needed before this operation type gains as much acceptance as the popular RYGB and SG (160).

#### *Biliopancreatic diversion (BPD)*

The BPD operation consists of a partial distal gastrectomy, in which the duodenal stump is closed, followed by a transection of the small bowel and then Roux-en-Y-gastroenterostomy from the gastric pouch to the distal bowel loop, creating an alimentary limb and a biliopancreatic limb anastomosed with the alimentary limb 50 cm before the ileocecal valve (80). In DS, a vertical SG is

combined with duodenoenterostomy and distal biliopancreatic limb anastomosis. DS involves the preservation of the lesser curvature, antrum, pylorus, and the first part of the duodenum (161).

In a study comparing the limb lengths of BPD with the limb lengths of Scopinaro's (50–200 cm) and modified (75–225 cm) procedures, no difference in weight loss was found. However, in Scopinaro's group, malnutrition and iron deficiencies were more common (162).

BPD is considered the most effective weight-loss procedure with 70% EWL (111); however, it only accounts for 2% of the world's operations (5). Explanations for this discrepancy can be the operation's surgical complexity and concerns over the excessive side effects of malabsorption, including protein malnutrition, vitamin deficiencies, and diarrhea (163). However, with the increase in SG, the need for revision in the case of weight regain has brought back interest in adding a malabsorptive component to the SG operation. BPD/DS is also used for superobese patients with BMIs over 50 (163).

#### *Single-anastomosis duodeno-ileal bypass (SADI-S)*

Single-anastomosis duodeno-ileal bypass with sleeve gastrectomy (SADI-S) is a relatively new operation based on BPD. In operation, an SG is followed by an end-to-side duodeno-ileal diversion. The preservation of the pylorus makes reconstruction in one loop possible, which reduces the operating time (164). SADI-S has also been used as a second-step procedure after SG if needed (165).

### 2.5 Complications in bariatric surgery

As in any other surgical procedure, bariatric surgery's results are affected by its morbidity and mortality. In a large meta-analysis, the overall complication rate was 17% (95% CI, 11–23%), and the reoperation rate was 7% (95% CI, 3–12%) (12).

The complications after bariatric surgery can be categorized into immediate (i.e., early) and delayed (i.e., late) complications or according to the type of procedure performed. Late complications can be divided into surgical and non-surgical complications. Early complications such as anastomotic leaks, bleeding, and pulmonary embolism can be fatal, as their recognition may be challenging. Tachycardia and raised C-reactive protein levels may be the only objective signs of a complication (11). Risk factors of complications include high age, male gender, recent myocardial infarction, previous stroke, bleeding disorders, hypertension, and a high BMI (166).

In a recent study of 69,494 patients, open and laparoscopic RYGB were compared in terms of mortality. It was observed that the open procedure had a higher mortality rate of 0.82% (95% CI = 0.49–1.23) compared to the laparoscopic surgery mortality rate of 0.22% (95% CI = 0.09–0.40). Besides, in recent years, a trend of decreasing postoperative mortality and complication rates has been observed (167).

The ERAS protocols (168) are widely accepted for colorectal, thoracic, and urological surgery (169, 170). The content of the different ERAS protocols varies; however, the principles usually include the use of minimally invasive surgical techniques and aggressive postoperative rehabilitation, including early oral nutrition and early removal of drains, tubes, and urine catheters (168). A meta-analysis of the ERAS protocols for bariatric surgery suggests that an ERAS protocol can reduce the length of a hospital stay by 1.5 days without any significant increase in overall major complications or readmission rates (171).

## 2.5.1 Early complications

### 2.5.1.1 Thromboembolic complications

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common cause of morbidity and even mortality after bariatric surgery (172). The incidence of VTE varies from 0.3% to 3.3% (173). PE is the most common reason for death after bariatric surgery (174).

A report on 71,694 patients from the United States showed that 0.3% had DVT and 0.2% had PE. Only 26.1% of the patients who developed PE after discharge had been diagnosed with DVT and the majority of the PE patients were diagnosed after discharge. No differences in patient characteristics were found between early PE and post-discharge PE (175).

Known risk factors for VTE after bariatric surgery are obesity, old age, male gender, previous PE/DVT, obstructive sleep apnea (176), an open operation, and no antithrombotic prophylaxis (177). In addition, postoperative complications after bariatric surgery significantly increase the risk of PE (178); moreover, 50–60% of the variance in VTE incidence depends on genetics. Some genetic susceptibility variants have been found in genes, mostly related to the clotting systems and those responsible for inherited hypercoagulable states (179).

To prevent VTE in patients undergoing abdominal surgery, pharmacologic and/or mechanical methods are recommended (180). In the Interdisciplinary European Guidelines for bariatric surgery, low-molecular-weight heparin (LMWH) is recommended for all patients undergoing bariatric surgery (103).

In the past, several different protocols were presented to improve the efficacy of thromboembolic prophylaxis for bariatric patients, including a higher dosage of the usual pharmacotherapy (for example, 30 mg of enoxaparin twice daily) and weight-adjusted prophylaxis. Recent studies have yielded controversial results on the dose and length of treatment (181–183); there has also been some controversy in the studies about whether a larger dosage causes more bleeding complications. Concerning the lack of clear evidence, no American guidelines currently recommend a specific duration or dosage of LMWH, neither routine screening with venous duplex ultrasound after bariatric surgery has proven to be necessary, even if it might be beneficial for high-risk patients (180).

#### 2.5.1.2 Bleeding complications

The incidence of hemorrhage after laparoscopic RYGB ranges from 1.1% to 4% (185). However, a recent studies suggests that less than 1% of all RYGB patients have bleeding, requiring transfusion or other interventions (186). In early bleeding (under 30 days after the operation), the bleeding usually occurs in the first 12 hours to 24 hours after surgery (185). The bleeding can be intra- or extraluminal. Common sources for extraluminal bleeding are the gastric staple lines, dissection planes, or trocar insertion sites. The most common place for bleeding is the gastrojejunal anastomosis.

The presentation of postoperative bleeding varies with the site and severity of blood loss. The bleeding can present itself as an asymptomatic drop in hematocrit or as a gastrointestinal bleeding and hemodynamic instability (187). Technical factors such as hand-made gastrojejunostomy anastomosis have a lower bleeding rate compared to a stapled anastomosis (188). There is also some evidence that the bleeding rate is slightly elevated after a laparoscopic approach compared to an open approach and with the preoperative administration of LMWH (189).

For hematemesis or melena, endoscopic examination is often used. For reducing the risk of iatrogenic complications, endoscopy should be performed carefully (190). Most of the bleeds are situated in the gastrojejunal anastomosis and are reachable with a normal gastroscope (191, 192). If identified, the bleeding is treated like all other endoscopically treated bleedings. If the bleeding

is suspected to be more distal, enteroscopy might play a role. However, reintervention surgery is most often preferred (190).

Non-operative management of bleeding is feasible with hemodynamically stable patients, whereas surgical intervention is needed for patients who are hemodynamically unstable, who do not respond to blood transfusion, and whose bleeding site cannot be properly identified (186).

After RYGB, the stomach is left in situ after the closure of the upper part of the organ, creating a blind-ended gastric remnant that can cause complications and surgical emergencies. One of the most feared complications is bleeding from the gastric-remnant where the dilatation can cause a "blow-out" situation with subsequent severe peritonitis. This diagnosis can be obtained from computed tomography (CT) (193).

With SG, the bleeding incidence varies between 1.16% and 4.94% (194). Bleeding usually occurs from the staple line, the divided short gastric, or other divided vessels (195). A recent meta-analysis showed that over-sewing the staple line in laparoscopic SG does not decrease the risk of staple line bleeding (196). In a study of risk factors for bleeding after SG, a low level of expertise in bariatric surgery and not using staple line reinforcements were associated with a higher risk of bleeding. Protective factors for bleeding included the patient having no history of obstructive sleep apnea or hypertension (197).

#### 2.5.1.3 Pulmonary complications

Obesity affects pulmonary function and can change cardiopulmonary physiology. These changes are a combination of mechanical- and inflammatory-mediated changes that can result in pulmonary dysfunction (198).

In a database study of 32,889 patients, postoperative pneumonia (PP) was diagnosed in 0.6% of the patients, and postoperative respiratory failure (PRF) was diagnosed in 0.6%. In total, PP and PRF accounted for 18.7% of the total mortality rate (14). In another large meta-analysis, the incidence of pneumonia varied between zero and 2.2% in different bariatric procedure types (166). Risk factors for pneumonia included congestive heart failure, stroke, age, chronic obstructive pulmonary disease (COPD), smoking, diabetes, and the length of anesthesia (14).

In a recent article, it was noted that preoperative smoking and preoperative oxygen saturation could help predict the number of pulmonary complications. In the same study, the total number of



pulmonary complications was 15.3%, with the most typical being atelectasis (14.2%), followed by pleural effusion (10.9%), PRF (5.4%), PP (4.3%), and PE (1.09%) (199).

Obesity is generally associated with decreased lung and chest wall compliance, increased airway resistance, and moderate-to-severe hypoxemia. These alterations are generally more pronounced if the patient has obesity hypoventilation syndrome or sleep apnea. Anesthesia and surgery can worsen respiratory function and increase the risk of postoperative pulmonary complications (200).

Obstructive sleep apnea and asthma are more common in obese patients than in normal-weight patients (134, 201). These conditions are often undiagnosed in bariatric patients. Therefore, bariatric patients are recommended to undergo an assessment for sleep apnea syndrome and pulmonary function before surgery (202).

For early postoperative pulmonary management, aggressive pulmonary toilet, spirometry, oxygen supplementation, and the use of continuous positive airway pressure (CPAP) when clinically indicated are recommended (203).

#### 2.5.1.4 Anastomotic leakage

Anastomotic leakage is defined as a leak of luminal contents from a surgical join between two hollow viscera (204). The etiology of the gastrointestinal leak is multiple; however, it generally includes mechanical or ischemic causes (205). To avoid leakage, careful tissue handling, consideration of the tissue thickness and avoiding tension, twisting or kinking of the mesentery, and other tissues are believed to be helpful (206).

Leakages can be classified by their clinical presentation, time of onset, radiological appearance, and location (206). Csendes et al. classified leakage as “early” when it occurred one to four days postoperatively, “intermediate” between five and nine days, and “late” after 10 days. When classified by appearance and location, type I is a well-localized leak, without dissemination into the pleural or abdominal cavity, and type II is a leak that disseminates into the abdominal or pleural cavity and has systemic manifestations (207).

The reported incidence for leaks after open and laparoscopic RYGB is 0.1% to 8.3% (206). GI leaks after RYGB can occur in many locations, for example, in the gastrojejunal anastomosis, gastric pouch staple line, jejunojunostomy, and gastric remnant staple line. Of these places, leaks occur most often in the gastrojejunal anastomosis (207). It has been suggested that numerous intraoperative

techniques decrease leak rate, such as over-sewing the staple line or reinforcing the staple line with synthetic or biological materials (208, 209). The results obtained with these techniques are still controversial. Besides, intraoperative leak tests conducted with air, dye, or endoscopy have not been able to reduce the incidence of leaks after RYGB procedures (206).

Postoperative upper gastrointestinal series (UGI) is used in some cases after the operation to detect leaks. There is no clear evidence that routine UGI studies would decrease the leak rate (210, 211, 212). When suspecting a leak, the first step involves evaluating if the patient is clinically stable, and if not, surgical exploration, preferably laparoscopic, is mandatory (206). If the patient is stable, UGI should be performed. However, the reported sensitivity of UGI varies between 22% and 75% (206). CT of the abdomen can detect leaks, abscesses, and bowel obstruction (153). The experience of the radiologist in interpreting the postoperative anatomy and patient positioning can lead to false negative results (206). If UGI and CT are combined, up to 30% of patients with leaks are still missed in both imaging methods (213). Therefore, surgical exploration should always be considered even if the imaging studies are considered normal, and there is clinical doubt of a leak. Management options of the leak depend on the timing and clinical presentation. Non-operative management of leaks may be used in selected and clinically stable patients.

There is a paucity of data on the use of endoscopic stent placements for gastrojejunal leaks after RYGB (206). The problem with self-expandable stents is their tendency to migrate, and they are not always well tolerated. However, when they are working, stents can provide an effective, minimally invasive therapy for the management of leaks (214).

Immediate reoperation is preferred for unstable patients with washout, wide drainage and attempts at suturing the leak, if the tissue conditions permit (215). Non-surgical treatment includes bowel rest, antibiotics, enteral nutrition, percutaneous drainage of collections, and percutaneous access to the remnant stomach for decompression and feeding. A low threshold for operative management should be maintained (206).

The pathophysiology of leaks after SG differs from the leaks that occur after RYGB. In SG, maintaining the pylorus and creating a long narrow conduit yield higher intraluminal pressure compared to the gastric pouch in RYGB. The estimated incidence of a leak after SG is zero to 7% (206). It is estimated that 75% to 85% of the leaks after SG occur at the proximal third of the staple line (215). In a recently published meta-analysis of 4888 SG patients, 79% of the leaks were diagnosed after hospital discharge

and over 10 days after the surgery. The risk for leakage was found to be higher with superobese (BMI over 50 kg/m<sup>2</sup>) patients and with a bougie size of < 40 Fr (216).

Various intraoperative techniques have been suggested to avoid leaks associated with SG; these include staple line reinforcements (absorbable, remodelable, or permanent), biological sealants, and over-sewing the staple line. No clear consensus on their impact is available (217, 218, 219).

As most of the leaks occur after hospital discharge following SG, UGI studies have very low sensitivity. With patients who are clinically stable and are suspected of having a leak, CT with oral and IV contrast is recommended. Likewise, in RYGB, re-operation should always be considered, regardless of the findings of the imaging when a GI leak is clinically suspected (206).

The treatment varies significantly between acute leak (< 5 days) and chronic fistula (over four weeks after the operation). In the acute postoperative leak, the first goal, with surgical management, is to ensure adequate drainage to avoid sepsis, confirm the diagnosis, and also insert a jejunostomy. The goal should not be a definitive repair. However, in very early stages (48–72 hours after the operation), definitive repair may sometimes be possible (220). With proximal leakage, endoluminal stent application is good therapy in the early postoperative course following SG (220).

#### 2.5.1.5 Early intestinal obstruction

In the early post-operative period after RYGB, problems with small bowel obstruction usually arise from technical issues with the Roux limb; these can include complete or partial narrowing of the gastrojejunostomy or jejunajejunostomy, acute angulation of the Roux limb, and narrowing of the Roux limb at the level of the transverse mesocolon. Around 1.8% of patients have an obstruction in jejunajejunostomy site after RYGB, mainly because of technical problems such as acute angulation of the anastomosis or bowel kinking, postsurgical anastomotic edema, ischemia, and staple-line bleeding with intraluminal hematoma formation. Other reasons for small bowel obstruction after RYGB include trocar site hernias, adhesive bands, bezoars, and jejunajejunostomy intussusception. Roux limb obstruction due to edema of the jejunajejunostomy or gastrojejunostomy usually requires conservative treatment consisting of suspending the oral feeding and the administration of intravenous fluids (221).

### 2.5.2 Late complications

#### 2.5.2.1 Late surgical complications

### 2.5.2.1.1 Internal hernia

In a meta-analysis of 31,320 RYGB patients, the incidence of internal hernia varied from zero to 16%, with the lowest incidence (1%) found in groups in which an antecolic approach was combined with the closure of all mesenteric defects (222). The incidence of internal hernias after bariatric surgery is higher than those in other upper gastrointestinal track operations. Internal hernias are not only found after laparoscopic procedures but also after open gastric bypass surgery. However, the incidence has risen significantly with the implementation of laparoscopic interventions (223). With the rise of RYGB operations performed yearly, the incidence of internal hernias has also been growing (10).

There are three potential locations for internal hernias. The most common location is in the opening in the transverse mesocolon, in which the Roux limb is brought posteriorly through the mesocolon to the gastric pouch (mesocolic). Another place for internal hernias is located between the mesenterium of the Roux limb and transverse mesocolon (Petersen's space). The third place for an internal hernia is sometimes observed in the form of a small-bowel mesenteric defect at the jejunojejunostomy site (222).

In a study of 607 RYGB, the patients had a total of 25 IHs, two of which occurred immediately in the postoperative period and 23 of which occurred later at a mean of 29 months after the operation (224). The clinical presentation of IH varies greatly, ranging from mild and intermittent abdominal cramping to acute small bowel obstruction (SBO). The most feared complication of IH is strangulation (222). In a recent study, SBO was found in 1.5% to 3.5% of RYGB patients, and IH is one of the leading causes of it (225). During pregnancy, an internal hernia typically presents itself with subtle symptoms and can cause intestinal ischemia and fetal complications; it should always be kept in mind regarding pregnant women after RYGB (226).

SBO symptoms are clinically recognizable; however, when IH presents itself in an intermittent and subacute manner, the diagnosis can be complicated. The diagnosis of IH is usually established by abdominal CT, although there are limitations to its sensitivity and specificity, with laparoscopy being the only reliable tool for a correct diagnosis (222).

In order to reduce internal hernias, two methods have been studied extensively. The closure of all-mesenteric defects during the operation and the use of the antecolic route for the Roux limb have both proven to be effective operative techniques to prevent internal hernias (222, 227). If the

diagnosis of IH is missed or management is delayed, IH can lead to significant morbidity and mortality. Patients complaining about abdominal pain after RYGB need a high index of suspicion. Early laparoscopy, even with negative imaging studies, is essential for the diagnosis of the internal hernia (228).

#### 2.5.2.1.2 Biliary complications

Biliary diseases including acute and chronic cholecystitis, acute pancreatitis, and choledocholithiasis are common in obese populations, and the risk of these diseases increases after bariatric surgery (229). The incidence of gallstone disease in the United States and Europe has been estimated at 5.9% to 21.9% of the general population (230). An Indian study showed that the prevalence of cholelithiasis and choledocholithiasis was 8.4% after SG and 13.4% in the RYGB group (231). Known risk factors for biliary complications after bariatric surgery include female gender, age (> 50), cholelithiasis at the time of the bariatric procedure, and the Roux-en-Y gastric bypass operation type (232).

No consensus on how to manage gallbladder disease in bariatric surgery patients has been reached. A variety of treatments such as preventive, preoperative, concomitant, or postoperative cholecystectomy has been suggested. Non-surgical treatments with ursodeoxycholic acid and observation have also been suggested (233).

A recent large-scale study suggested that cholecystectomy during SG appears to be safe, with only a slightly increased risk of bleeding and pneumonia compared to SG alone (234). Similar results with concomitant cholecystectomy with RYGB have been presented (235).

#### 2.5.2.1.3 Gastroesophageal reflux

Gastroesophageal reflux disease (GERD) has a high prevalence of morbidly obese patients. Increased body mass and increased intra-abdominal pressure lead to an increase in esophageal acid exposure. There is a growing concern about the effect of SG on GERD. However, recent studies have shown satisfactory postoperative reflux control in the majority of patients. The initial treatment option is medical therapy with proton-pump inhibitors (PPIs). If necessary, conversion from SG to RYGB is the procedure of choice with a satisfactory result in improvement or resolution of reflux symptoms. There is increasing evidence that the shape of the gastric sleeve appears to be the main factor predicting the risk of postoperative GERD (236).

#### 2.5.2.1.4 Incisional hernia

An incisional hernia is one of the most frequent complications after abdominal surgery. In a study of 12,737 open abdominal procedures, including bariatric surgery, a total of 3.5% of patients had surgically treated incisional hernia at the cost of \$17.5 million (237). Different risk factors for an incisional hernia after bariatric surgery have been suggested, including a BMI > 60 kg/m<sup>2</sup>, DM2, malnutrition, prior abdominal surgery, and wound infections (238).

The introduction of laparoscopic operations remarkably reduced the incidence of incisional hernia. In an RCT comparing open and laparoscopic bariatric operations, a significant difference was found in the amount of incisional hernias (7.9% vs. 0%) (239). In a study of 1524 laparoscopic bariatric patients, 0.5% had trocar port hernia, and 0.2% had an incisional hernia from a previous surgery (240).

Previous studies recommended the routine closure of the fascia in 10-mm or larger trocar ports (241); however, this can be considerably complicated with extremely obese patients (240). Little evidence supports the closure of the fascia, and not all bariatric surgery centers close the defects routinely (242).

#### 2.5.2.1.5 Endoscopically treated complications

##### *Stenosis/Stricture*

After RYGB, the incidence of stenosis in a gastrojejunal anastomosis is between 3% and 27% (243) and is one of the most frequent late complications after gastric bypass (190). Risk factors include the use of small (< 25 mm) circular staplers and marginal ulcers. Stenosis is not only most commonly seen in gastrojejunal anastomosis but also enteroenteric anastomosis, the Petersen defect, and the passage through the mesocolon of the Roux limb (1). Stenosis most commonly presents itself one to three months after surgery (190). Up to 90% of patients can be treated with endoscopic dilatations(244, 245); however sometimes more than one dilatation is needed. Dilatations up to 15 mm have been proven to be safe (1).

The rate of stenosis after SG has been reported to range between 0.1% and 3.9 % (246, 247). Post-SG stenosis is often located at the incisura angularis (190). Patients may experience obstructive symptoms such as nausea, vomiting, abdominal pain, and dysphagia. Endoscopic balloon dilatations up to 40 mm have proven to be a safe method of treatment (248). Laparoscopic seromyotomy has also been proven to be effective for long stenosis, which is not possible to treat with endoscopic balloon dilatations (249).

### *Marginal ulcer*

A marginal ulcer (MU) has been defined as an ulcer at or near the gastrojejunostomy. In a systematic review, an MU was found in 4.6% of RYGB patients after surgery (250). In another review, 3% of SG patients were found to have ulcers (251).

The symptoms of ulcers can be epigastric burn, bleeding, nausea, vomiting, and dysphagia (252). The etiology of MU is multifactorial, including *Helicobacter pylori* (*H. pylori*) infection, drugs and toxicity, smoking, surgical techniques, and ischemia (190).

After surgery, the common practice is to begin prophylactic proton pump inhibitor medication. A recent meta-analysis showed that the prophylactic proton pump inhibitor (PPI) significantly decreases MU formation (253). Smoking was found to be the only significant risk factor for MUs. Therefore, smoking cessation should be advised for all patients after RYGB, and smokers should be treated as high-risk patients for MUs (254).

Conservative management is based on PPI therapy, and healing should be monitored with endoscopic controls. Revisional surgery should be reserved for patients with refractory ulcers or anatomical abnormalities (250).

The feared complication of an MU is perforation, the overall rate of which is 1.4%. The best result in the treatment of a perforated MU has been observed with laparoscopic repair (255). Ulcer in the remnant stomach can create a life-threatening blow-out situation if it is not diagnosed (193).

### *Chronic fistula*

Gastrogastric fistula (GGF) occurs in 1% to 6% of patients after RYGB (256). GGF is an abnormal communication between the gastric pouch and the excluded gastric remnant. The leading causes of GGF are suspected to be confirmed leaks/suspected micro leaks, failure to divide the proximal stomach, and MUs (257).

GGF has been classified into type 1 and type 2. Type 1 GGF is located in the higher part of the gastric pouch more than 1 cm above the gastrojejunal anastomosis, and type 2 is located in the lower part less than 1 cm from the gastrojejunal anastomosis (256).

The gold standard for diagnosis is endoscopic and radiologic imaging, such as UGI, esophagogastroduodenoscopy (EGD), and a CT scan with oral contrast. A CT scan can show the presence of contrast or air in the gastric remnant, an indirect sign of GGF (257).

The initial choice for treatment should be conservative, consisting of the eradication of *H. pylori* with high-dose PPI and smoking cessation. The premise of conservative management is to reduce gastric acid secretion (258). Endoscopic treatment has also been suggested, for example, with fibrin sealants, endoclips, and endoscopic suturing systems (259). Surgical treatment has been suggested as follows: for type 1, an excision of the fistula and the preservation of the GJA and type 2, the complete revision of the gastrojejunal anastomosis with fistula excision (256).

In a series of SGs, three types of fistulas after the operation were characterized as follows: type I, a small leak with no collection; type II, a leak with an associated intra-abdominal abscess and type III, a leak with multiple internal or external abscesses—a complex fistula. It was suggested that type I fistulas could be treated conservatively, while type II fistulas needed external percutaneous drainage and/or stenting, and type III fistulas should be treated with an operation. Roux-en-Y gastro-jejunosomy, esophagojejunosomy, or total gastrectomy have been suggested as surgical procedures (260).

#### 2.5.2.2 Late non-surgical complications

##### 2.5.2.2.1 Mineral and vitamin deficiencies

As bariatric procedures significantly affect nutritional intake and reduce nutrient absorption, there is a risk of malnutrition, ranging from micronutrient deficiencies to severe protein-calorie malnutrition; this occurs not only because of changes in the GI tract but also because nutritional behavior patterns are altered after bariatric surgery (261). Studies have shown that after bariatric surgery, patients change their diet habits, for example by reducing their total protein intake (262, 263). Besides, many obese patients have low levels of D vitamin, B12 vitamin, and iron before the operation (264, 265). Several observational cohort studies have reported micronutrient deficiencies following bariatric surgery. Commonly observed deficiencies include B12 vitamin, vitamin D, folate, thiamin, iron, copper, and zinc (261).

Protein-calorie malnutrition should be suspected if a patient continues to lose weight for a prolonged period, extending over two years after surgery. Other clinical signs include fatigue, muscle mass



wasting, and other persistent micronutrient deficiencies (261). The diagnosis of protein malnutrition should be established on a clinical basis and might be supported by measuring visceral protein store markers, such as albumin or prealbumin (266).

In a systematic review of 51 observational studies examining vitamin D levels in bariatric surgery patients, the mean 25-hydroxyvitamin D level (25(OH)D) was less than 30 ng/ml before and after bariatric surgery, despite vitamin D supplementation (267).

Current guidelines suggest varying amounts of vitamin D supplementation after bariatric surgery: after RYGB and SG, the American Association of Clinical Endocrinologists (AACE), the Obesity Society (OS), and the Society for Metabolic and Bariatric Surgery (ASMBS) recommend vitamin D supplementation of at least 3000 IU daily (203). The British Obesity & Metabolic Surgery Society (BOMSS) Guidelines recommend a minimum of 800 IU vitamin D daily (268) and, in the new guidelines for Nordic countries, vitamin D is also recommended at 800 to 900 IU daily (269).

Reduced calcium absorption is observed following malabsorptive procedures and commonly causes hyperparathyroidism (270). In order to prevent bone loss and hyperparathyroidism after bariatric surgery, calcium supplementation after malabsorptive procedures is also recommended (203).

Vitamin B12 deficiency is quite common following bariatric surgery (261). The two important causes of vitamin B12 deficiency are malabsorption and insufficient oral intake (271). Despite recommendations for nutrient supplementation, the B12 deficiency rate has been reported to be approximately 5% to 15% following AGB, 20% following SG, 20% to 40% following BPD/DS, and 30% to 60% following RYGB (261). Baseline and postoperative monitoring of B12 vitamin levels are recommended for all bariatric patients as well as continuous supplementation (203).

Alterations in GI physiology include diminished stomach acid production after RYGB, BPD/DS, and SG, which contributes to the relatively high iron deficiencies reported after these operations. Another mechanism for affecting iron absorption is the bypassing of the duodenum in RYGB and BPD/DS (261). Regular testing for serum iron levels at six-month intervals and appropriate supplementation is recommended (203). Iron is recommended at a dosage of 45 to 60 mg daily via multivitamins (261).

Pregnancy may exacerbate micronutrient deficiencies after bariatric surgery due to pregnancy-related symptoms, along with increased maternal and fetal demand. For patients who become pregnant after bariatric surgery, laboratory screening for deficiencies and nutritional surveillance

should be offered in every trimester, including iron, folate, B12, calcium, and fat-soluble vitamins (203)

The iron requirement increases to 800 mg of elemental iron, of which around 300 mg is required by the fetus and the placenta, while the rest goes to maternal hemoglobin mass expansion (272). Maternal iron deficiency can lead to an increased risk of pre-term delivery and subsequent low birth weight (273).

Adequate folate intake is also necessary to prevent neural tube defects in the fetus. The pre-conception supplementation dosage is 400 micrograms per day until the 12<sup>th</sup> week of pregnancy in normal pregnancy; however, for high-risk patients, such as bariatric surgery patients, the dosage is recommended to be 5 mg a day (272).

#### 2.5.2.2.2 Fractures

It was previously believed that obesity protected against osteoporosis and osteoporotic fractures; however, several recent studies have suggested that obesity is indeed a risk factor for osteoporosis and fractures (274). Several prospective studies show a reduction in bone mineral density (BMD) or bone mineral content one to four years after gastric bypass surgery (275). These studies have their problems, such as limited patient numbers and a lack of randomized control groups. However, we know that obesity has a negative impact on bones.

Until now, the clinical implications of the bone changes that occur after bariatric surgery have remained unclear. In a recent meta-analysis of 35,770 bariatric surgeries and 57,395 control subjects, the risk for any fracture was higher in the bariatric surgical group compared to the non-surgical group (risk ratio [RR] 1.29, 95% CI, 1.18–1.42). Besides, patients who underwent mixed restrictive and malabsorptive procedures had an even higher risk of fracture (RR 1.54, 95% CI, 0.96–2.46) (276).

#### 2.5.2.2.3 Hypoglycemia

Hypoglycemia symptoms usually occur later than 1–2 years from the operation. After bariatric surgery, glycemic and hormonal profiles are modified with an early peak of insulin after glucose, turning to lower glucose concentrations in the subsequent postprandial period. These metabolic changes have been associated with dumping syndrome, which occurs to 70% of patients after RYGB consuming high glycemic index carbohydrates. These symptoms are usually responsive to dietary modifications.

A much smaller percentage of patients may develop severe hypoglycemia with neuroglycopenia, leading to altered consciousness, seizures, and motor vehicle accidents. These patients might need medications, such as somatostatin analogs or diazoxide, to suppress insulin production. Mild hypoglycemia may be more frequent than clinically recognized; however, the long-term significance remains unknown (277).

### 3 Aims of the study

- I To determine the optimal antithrombotic prophylaxis dose of enoxaparin to use with patients undergoing bariatric surgery to avoid bleeding and thromboembolic complications;
- II To evaluate the effect of modifications of peri- and postoperative treatment of bariatric patients on pulmonary complications;
- III To compare the number of surgically and endoscopically treated late complications between RYGB and SG patients for two years after the operation;
- IV To compare two-year vitamin D, albumin, and B12 vitamin status in RYGB and SG patients and to compare the long-term fracture incidence of the two cohorts: bariatric patients (RYGB and SG) and non-surgically treated, severely obese patients.

## 4 Patients and methods

### 4.1 Patients

#### Studies I–IV

All the follow-up data were collected retrospectively from patients operated at Peijas Hospital, the Bariatric Surgery Unit of Helsinki University Central Hospital. With all the operated patients, the selection criteria for bariatric surgery followed the current European Guidelines on Metabolic and Bariatric Surgery (91). The inclusion criteria for the patients were as follows: BMI > 40 kg/m<sup>2</sup> or > 35 kg/m<sup>2</sup> with comorbidities, aged 18 to 65 years, and previously failed attempts at weight loss with a non-surgical obesity program. The exclusion criteria included current psychiatric problems, alcohol/drug abuse, and severe cardiopulmonary disease. All surgical patients were on a very low-calorie diet (VLCD) for five weeks before surgery. The recommended nutritional supplementation was initiated after the operation; this included a multivitamin and a combination of 30 micrograms of vitamin D (cholecalciferol) and calcium supplementation of 1 g daily.

The selection of the operation type was based on patients' and surgeons' preferences. However, SG was recommended for patients who were extremely obese or had additional risk factors, including severe intra-abdominal adhesions after previous abdominal operations, liver cirrhosis, chronic obstructive pulmonary disease, chronic renal failure, coagulopathy, and risk factors for malignancy in the stomach. Between 2009 and 2010, Peijas Hospital participated in a multicenter study during which patients were randomized to RYGB or SG.

After the operation, the first follow-up was at the one-month time and was conducted by the surgeon; afterward, follow-ups were conducted by an endocrinologist at 3, 6, 12, and 24 months. After this time, follow-ups were continued at the primary health care provider.

### 4.2 Methods

#### 4.2.1 Operation techniques

##### *Gastric bypass*

Three 12-mm and two 5-mm dilating ports were used—three on the left side of the abdomen, one on the right side, and one under the xiphoidium—to hold the liver retractor. A 20-ml gastric pouch was formed with three to five linear-stapler firings (Endo-GIA; Medtronic; Minneapolis, MN, USA). The first 100 gastro-jejunal anastomoses were formed using a circular-stapler technique (Circular

stapler; Orvil; Medtronic; Minneapolis, MN, USA); subsequently, a linear-stapler technique with hand-sewing was used to close the stapler-device hole. The length of the biliopancreatic limb was between 60 cm and 80 cm; the alimentary limb was 150 cm. The loop was antecolic. The jejuno-jejunal anastomosis was made with a linear stapler and hand-sewing to close the stapler-device hole. The biliary and alimentary channels were divided after the entero-anastomosis was formed. Mesenteric openings were closed using various methods with absorbable or non-absorbable suturing or metallic clips. The gastro-jejunal anastomosis was tested using 50 ml of methylene blue dye.

#### *Sleeve gastrectomy*

Two 12-mm and one 5-mm dilating ports were employed on the left upper abdomen, one 15-mm port on the right abdomen, and one 5-mm port under the xiphoidium to hold the liver retractor. The sleeve was formed with the help of a 35-Fr bougie. The procedure was initiated by dividing the vessels along the greater curvature, from 6 cm proximal from the pylorus up to the angle of His, and the adhesions behind the stomach were cut. The resection was started from the antrum with 45-mm and 60-mm green staplers (Endo-GIA; Medtronic; Minneapolis, MN, USA) and then with blue/golden 60-mm staplers along the bougie and up to the angle of His, where a 1-cm corner of the stomach was left. Reinforcements (Peri-Strip dry; Synovis; USA) were used on the stapler line, and the line was tested with 200 ml of methylene blue dye.

#### 4.2.2 Study methods

##### Study I

We followed the first 400 consecutive operated bariatric patients for bleeding complications for thromboembolic complications in the unit between 2008 and 2013. The patients were divided consecutively into three subgroups with different enoxaparin regimens. The first 100 patients (high-dose group) received enoxaparin at a dose of 40 mg twice daily starting one day before the operation. For the next 100 patients (intermediate-dose group), 40 mg of enoxaparin were administered twice daily without the dose on the morning of the operation. The last 200 patients (low-dose group) received 40 mg of enoxaparin once daily starting one day before the operation and without the dose being given on the morning of the operation. Besides, intermittent pneumatic compression devices (IPS), and graded compression stockings were used with all patients.

### Study II

The same first 400 bariatric surgery patients were included as in Study I. The patients were divided into four different approaches in postoperative treatment. The first 100 patients (ICU group) were treated in the intensive care unit (ICU) with minimal mobilization. They had a urinary catheter, a drain, and arterial blood pressure monitoring. Patients also performed blow bottle exercises 10 times per day, 10 times per exercise. Patients 101 to 200 (ICU-CPAP group) were similar to the patients in the first group; however, they also used a CPAP device intermittently four times per day, one hour at a time. Patients 201 to 300 (the ward-slow group) recovered on a normal ward with regular daily rehabilitative routines and without a urinary catheter, a drain, or an arterial needle. They did their blow bottle exercises like the other groups, and their CPAP therapy was initiated in the recovery room immediately after the operation. On the ward, they had CPAP four times per day, continuing one hour at a time. Patients 301 to 400 (ward-fast group) walked to the operating room and were mobilized in the recovery room during the first two hours after the operation. Blow bottle exercises and CPAP were used as in the previous groups. In all groups, pain medication was mainly given orally, avoiding opioids.

### Study III

The data included the first 760 consecutively operated RYGB and SG patients, who were operated on between 2008 and 2013. Of the patients, 545 were RYGB patients, and 215 were SG patients. The data included both primary and revisional bariatric surgery patients. Twelve patients with different operation types were excluded from the study. The follow-up period was two years.

Before the operation, an upper stomach ultrasound and gastroscopy were performed. If an *H. pylori* infection was diagnosed, it was treated before the operation. Diagnosed gallstones were not removed before the bariatric operation; however, if symptomatic, they were removed electively two to six months after the bariatric surgery.

### Study IV

The data included the first 395 patients who underwent bariatric surgery between 2007 and 2010 and 191 non-surgically treated obese patients. The non-surgically treated patients were treated as outpatients in the obesity clinic at Peijas Hospital. The inclusion criteria for non-surgically treated patients were similar to those for surgically treated patients.

Of the surgically treated patients, 253 were RYGB patients, and 142 were SG patients. Of the surgically treated patients, 69 were excluded. These included one band operation, six band removals, one duodenal switch, eight patients who did not show up in the controls, and 53 patients who were followed in different hospital regions after the operation.

Data on the control group of 199 obese patients were collected between 2002 and 2006. This fracture study was an extension of the previously reported trial (278). They received lifestyle intervention, and weight loss was measured after one and two years. Fracture data were collected retrospectively from both groups at the end of 2016. Serum 25 hydroxyvitamin D [25(OH)D], vitamin B12, albumin concentrations, and weight were measured from bariatric surgery patients after one and two years.

#### 4.2.3 Statistical analyses

Statistical analysis was performed using SPSS version 21 (IBM Corp.; New York, NY, USA) and SAS version 9.4 (SAS Systems; SAS Institute Inc.; Cary, NC, USA).

In Study I, the differences between groups with continuous variables were tested with the Kruskal-Wallis test or with the Mann-Whitney U test. Differences in binominal or categorical variables were tested with Fisher's exact test or the Fisher-Freeman-Halton test. Logistic regression analyses were used, and these results were given as an odds ratio and 95% confidence intervals (CI). Forward conditional stepping was used to select variables for the logistic regression model among the following variables: group, age, BMI, operation type, atrial fibrillation, and arterial hypertension.

In Study II, continuous data were tested for normality using the Shapiro-Wilk test. Differences between groups in continuous variables were tested with the Kruskal-Wallis test or Mann-Whitney U test and differences in binominal or categorical variables with Fisher's exact test or Fisher-Freeman-Halton- test. Logistic regression analysis was used, and the results were given as an odds ratio and 95% confidence intervals (CIs). Group, gender, COPD, asthma, OSA, and operation time were included in the model.

In Study III, continuous data were tested for normality using the Shapiro-Wilk test. Differences in continuous variables between groups were analyzed using the Kruskal-Wallis test or the Mann-Whitney U test, and differences in binominal or categorical variables were analyzed using the Fisher's exact test or the Fisher-Freeman-Halton test. Univariate and multivariate logistic regression analyses were used to identify significant risk factors for complications. The Firth's penalized logistic regression



was used in multivariate regression regarding complications without cholecystectomies. EWL% was calculated as the ideal body weight to yield a BMI of 25 kg/m<sup>2</sup>.

In Study IV, the differences between groups with continuous variables were tested with the Mann Whitney U test or with the Kruskal-Wallis test. Differences in binominal or categorical variables were tested with Fisher's exact test or the Fisher-Freeman-Halton test. Hazard ratios were calculated with the Cox regression proportional hazard model, and multivariate models were constructed with stepwise selection. Kaplan-Meier analysis was used to illustrate cumulative risks for fracture with exact 95% confidence interval (CI). In all studies, P 0.05 was considered statistically significant, and two-tailed tests were used.

#### 4.2.4 Study approvals

The Institutional Review Board and the Ethics Committee of the Department of Surgery, Helsinki University Central Hospital, approved the study protocols. The initial patient data were collected prospectively; however, the follow-up data were collected retrospectively from the patient records. No written informed consent for participation in the studies was requested because data were collected retrospectively. In the prospective part, patients were verbally informed of data collection and its use for study purposes.

## 5 Results

### 5.1 Study I

#### *Patient characteristics*

The study included 400 consecutively operated patients. The mean age was 47.7 ± 9.1 years, and the mean preoperative BMI was 48.6 ± 6.9 kg/m<sup>2</sup>. There were 268 women (67%) and 132 men (33%); 60.5% (242) of the patients had RYGB, 38.5% (154) had SG, and 1% (4) had other types of operations. The three groups were similar regarding gender, comorbidities, and baseline weight.

#### *Thromboembolic complications, bleeding complications, and reoperations*

No thromboembolic complications were found in the study. There was a significant difference in the number of major bleeding complications between the three groups (15/6/4.5%). There were six reoperations because of bleeding complications, two of which were conducted endoscopically. No significant differences were found between the number of interventions across the groups.

Table 1: Bleeding complications and interventions;  $p$ -value < 0.05 is considered significant

|  | High-dose group<br>(0–100) | Intermediate-dose group<br>(101–200) | Low-dose group<br>(201–400) | $p$ -value |
|--|----------------------------|--------------------------------------|-----------------------------|------------|
| Bleeding complications % (N)             | 15(15)                     | 6(6)                                 | 4.5(9)                      | 0.004      |
| Interventions for bleeding complications |                            |                                      |                             |            |
| Operative                                | 2                          | 0                                    | 2                           | 0.356      |
| Endoscopic                               | 0                          | 1                                    | 1                           | 1.00       |
| Total                                    | 2                          | 1                                    | 3                           | 1.00       |

### *Risk of complications*

The logistic regression analysis (Table 2) shows that the risk of bleeding complications is lower in the intermediate- and low-dose groups compared to the high-dose group. In the logistic regression model, arterial hypertension significantly increased the risk of major bleeding complications (Table 2).

Table 2: Univariate logistic regression model for major bleeding complications

|                         | HR   | CI 95%    | p-value |
|-------------------------|------|-----------|---------|
| High-dose group         | 1.0  |           |         |
| Intermediate-dose group | 0.32 | 0.12–0.88 | 0.027   |
| Low-dose group          | 0.23 | 0.09–0.56 | 0.001   |
| Arterial hypertension   | 6.77 | 1.55–29.7 | 0.011   |
| Gender (female)         | 1.21 | 0.54–2.72 | 0.637   |

#### *Operation time and hospital stay*

There was no significant difference ( $p = 0.757$ ) in the operation time between patients with or without major bleeding complications ( $98.4 \pm 32.7$  min vs.  $92.8 \pm 38.7$  min, respectively). The mean hospital stay for patients with major bleeding complications was  $9.3 \pm 2.8$  days, and, for others, it was  $5.1 \pm 7.5$  days, with a significant difference ( $p = 0.005$ ).

## 5.2 Study II

### *Patient characteristics*

The mean age was  $47.7 \pm 9.1$  years, ranging from 23 to 67 years, and the mean preoperative BMI was  $48.6 \pm 6.9$  kg/m<sup>2</sup>. There were no differences between the groups regarding age, gender, and baseline weight; 60.5% (242) of the patients had RYGB, 38.5% (154) had SG, and 1% (4) had other operation types. A total of 4.3% (17) of the operations were revision procedures.

### Pulmonary complications

The total number of pneumonia cases was 48 (12%), and the total number of infection NUDs (non-ultra descriptus ) was 30 (7.5%). There was a significant difference in pneumonia cases across the four groups (Table 3).

Table 3: Number of pneumonia cases, infection NUDs, operation times, and hospital stay

|                            | ICU*<br>(n = 100) | ICU + PAP**<br>(n = 100) | Ward-slow<br>(n = 100) | Ward-fast<br>(n = 100) | p-value |
|----------------------------|-------------------|--------------------------|------------------------|------------------------|---------|
| Pneumonia<br>(N/%)         | 20                | 12                       | 10                     | 6                      | 0.020   |
| Infection NUDs<br>(N/%)    | 11                | 8                        | 6                      | 5                      | 0.387   |
| Operation<br>time/min (SD) | 114.3 (37)        | 95.3 (28.1)              | 81.4 (29.5)            | 82.0 (25.5)            | < 0.001 |
| Hospital<br>stay/days (SD) | 6.13<br>(4.9)     | 5.90<br>(4.1)            | 5.06<br>(1.4)          | 4.60<br>(2.4)          | < 0.001 |

\*ICU = Intensive care unit; \*\*CPAP = continuous positive airway pressure

### Operation time and hospital stay

The operation time and the hospital stay were significantly different across the four groups (Table 1). For patients without pulmonary complications, the operation time was 88 min compared to 114 min with pulmonary infections ( $p < 0.001$ ). The hospital stay for patients without infections was significantly shorter (5.2 and 6.3 days, respectively) ( $p < 0.001$ ).

### *Risk of pulmonary complications*

In the logistic regression analysis, a longer operation time increased the risk of pulmonary complications. The risk for pulmonary complications was slightly decreased in the ward-fast group compared to the ICU group (Table 4).

Table 4: Logistic regression model of the risk of pulmonary complications

|   | ODDS | 95% CI     | <i>p</i> -value |
|---|------|------------|-----------------|
| ICU                                       | 1.00 |            |                 |
| ICU + CPAP                                | 0.65 | 0.33–1.28  | 0.212           |
| Ward-slow                                 | 0.57 | 0.28–1.18  | 0.132           |
| Ward-fast                                 | 0.32 | 0.14–0.74  | 0.008           |
| Gender (female)                           | 1.70 | 0.90–3.22  | 0.100           |
| Asthma                                    | 1.93 | 1.00–3.73  | 0.051           |
| COPD                                      | 2.95 | 0.43–20.24 | 0.272           |
| OSA                                       | 0.92 | 0.49–1.76  | 0.810           |
| Operation time<br>(> 88 min vs. ≤ 88 min) | 3.65 | 2.02–6.59  | < 0.001         |

### *Learning curve*

In order to study the learning curve, we compared the first 50 and second 50 patients in the ICU group. We found a difference in the operation time (128 min vs. 100 min) ( $p < 0.01$ ) but none in the number of pulmonary complications (38 vs. 42) ( $p = 0.45$ ).

### 5.3 Study III

#### *Patient characteristics*

The RYGB and SG patient groups were similar regarding gender, comorbidities, and previous operations; however, there were differences in age and preoperative BMI (Table 5).

Table 5: Patient characteristics

|                                | <b>RYGB</b>      | <b>SG</b>        | <b>p-value</b> |
|--------------------------------|------------------|------------------|----------------|
| Patients                       | 545              | 215              |                |
| Gender, female (%)             | 381 (69.9%)      | 143 (66.5%)      | 0.39           |
| Age, median (IQR)              | 47 (23–65)       | 49 (24–67)       | 0.023          |
| Preoperative BMI, median (IQR) | 44.1 (32.4–77.7) | 46.6 (31.7–72.1) | 0.001          |
| Hypertension (%)               | 387 (71%)        | 145 (67.4%)      | 0.34           |
| Diabetes (%)                   | 262 (48.1%)      | 107 (49.8%)      | 0.68           |
| Hypercholesterolemia (%)       | 183 (33.6 %)     | 84 (39.1%)       | 0.17           |
| Prior cholecystectomy (%)      | 80 (14.7%)       | 38 (17.7%)       | 0.32           |
| Prior abdominal surgery (%)    | 49 (9%)          | 10 (4.7%)        | 0.050          |

#### *Complication rate*

There was a significant difference in the number of surgical and endoscopic interventions between the two groups: 9.4% of RYGB patients were treated surgically versus 0.9% of SG patients, and 4.6% of RYGB patients were treated endoscopically versus 1.4% of SG patients (Table 2).

#### *Weight loss*

RYGB patients lost more weight compared to SG patients one year and two years after the procedure, with significant differences in the mean EWL% (Table 6).

Table 6: Endoscopic and surgical interventions with LRYG and LSG patients and EWL%

|  | <b>RYGB (545)</b> | <b>SG (215)</b> | <b>p-value</b> |
|--|-------------------|-----------------|----------------|
| Total number of patients with endoscopic interventions | 25 (4.6%)         | 3 (1.4%)        | 0.034          |
| Total number of patients with surgical interventions   | 51 (9.4%)         | 2 (0.9%)        | < 0.001        |
| 1-year EWL% (SD)                                       | 49.7% (21.2)      | 42.6% (22)      | < 0.001        |
| 2-year EWL% (SD)                                       | 50.5% (22.7)      | 45.5% (25.2)    | 0.024          |

*Time for intervention*

The mean time until the first surgical interventions was 390 days for RYGB and 388 days for SG patients ( $p = 0.98$ ). For endoscopic interventions, it was 127 days for RYGB and 209 days for SG patients ( $p = 0.61$ ).

*Risk of complications*

In the logistic regression model, one-year total weight loss increased the risk for surgical complications, and SG operation decreased the risk (Table 7).

Table 7: Logistic multivariate regression analysis regarding surgical complications

|                        | ODDS  | 95% CI    | p-value |
|------------------------|-------|-----------|---------|
| Age > 55               | 0.381 | 0.23–1.74 | 0.64    |
| Age 44–55              | 0.405 | 0.37–1.50 | 0.74    |
| Age < 45               | 1.0   |           |         |
| Gender (female)        | 0.868 | 0.52–2.15 | 1.06    |
| Hypertension           | 0.139 | 0.30–1.18 | 0.60    |
| Diabetes               | 0.958 | 0.50–1.93 | 0.98    |
| SG                     | 0.05  | 0.01–0.38 | 0.004   |
| Initial EWL% 12 months | 0.025 | 1.00–10.3 | 1.02    |

#### 5.4 Study IV

##### *Patient characteristics*

A total of 762 patients were included in the study: 253 were RYGB patients, 142 were SG patient, and 199 were non-surgically treated.

##### *Vitamin and albumin*

Among the bariatric patients, the mean vitamin 25(OH) D, B12, and albumin levels were at the recommended levels. Albumin and D vitamin levels were similar between RYGB and SG patients; however, B12 vitamin was significantly lower in RYGB patients compared to the SG patients ( $p < 0.05$ ). If the target of 50 nmol/L of vitamin 25(OH) D vitamin was used, 14%/13% of RYGB/SG patients were below the target level at the two-year control. If the higher target of 75 nmol/l was used, only 29/28% of patients were at the recommended levels.



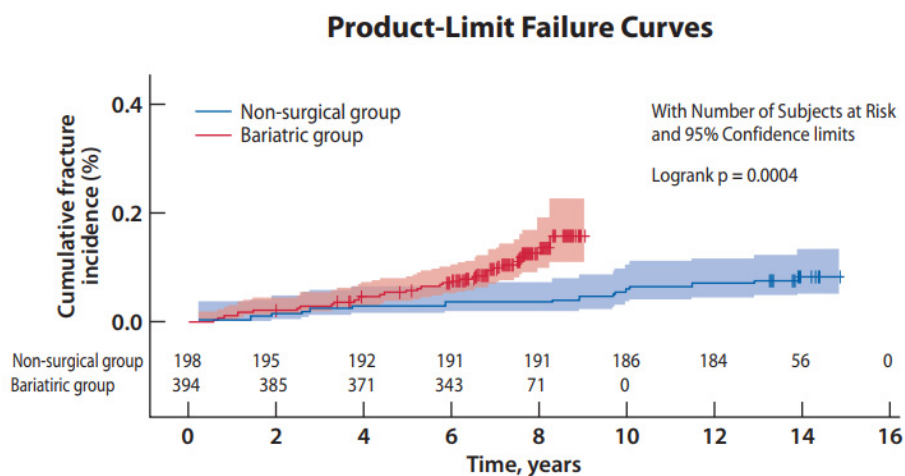
### Fractures

The mean follow-up time was 6.9 years. A total of 31 patients had fractures during the follow-up. There were no significant differences ( $p = 0.26$ ) in the cumulative number of fractures between RYGB, SG, and non-surgical patients (12.3% vs. 7.8% vs. 8.5%, respectively) during the follow-up (Table 1). The risk of fracture started to grow in surgically treated patients after four years compared to non-surgically treated patients.

Table 8: Patient characteristics and number of fractures

|  | <b>RYGB</b><br><b>(n = 253)</b> | <b>SG</b><br><b>(n = 142)</b> | <b>Non-surgical</b><br><b>(n = 199)</b> | <b>p-value</b> |
|--|---------------------------------|-------------------------------|---|----------------|
| Gender, female % (N)                           | 66.8 (169)                      | 71.8 (102)                    | 70.9 (142)                              | 0.507          |
| Age, years, median (IQR)                       | 47.0 (41.5-54.0)                | 48.0 (40.0-57.0)              | 48.5 (38.1-55.4)                        | 0.615          |
| Baseline BMI, kg/m <sup>2</sup> , median (IQR) | 47.5 (43.7-52.6)                | 48 (40.0-57.0)                | 48.5 (38.1-55.4)                        | < 0.001        |
| Diabetes % (N)                                 | 52.2 (132)                      | 50.7 (72)                     | 42.2 (84)                               | 0.092          |
| Hypertension % (N)                             | 75.1 (190)                      | 67.6 (96)                     | 58.3 (116)                              | < 0.001        |
| Hypercholesterolemia % (N)                     | 34 (86)                         | 38.0 (54)                     | 13.1 (26)                               | < 0.001        |
| Fractures % (N)                                | 12.3 (31)                       | 7.8 (11)                      | 8.5 (17)                                | 0.257          |

Figure 1. The cumulative fracture risk for surgically and non-surgically treated patients.



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#### Prediction of fracture risk

In the univariate regression analysis, age over 48 years, surgical treatment, hypertension, diabetes, hypercholesterolemia, one- and two-year TWL%, and a lower BMI after two years increased the risk of fracture. In the multivariate regression analysis with forward stepping, where the model has been adjusted with a different baseline weight, TWL% after one year, age, surgical treatment, and a lower BMI after two years increased the risk of fracture (Table 9).

Table 9: Multivariate adjusted stepwise Cox regression model for the risk factor for fractures

| Multivariate                        | HR   | 95% CI     | p-value |
|-------------------------------------|------|------------|---------|
| Age (> 48 years vs. < 48 year)      | 4.08 | 2.02–8.23  | 0.000   |
| Treatment (surgery vs. non-surgery) | 5.49 | 1.76–17.15 | 0.05    |
| BMI at two-year control             | 0.93 | 0.87–1.00  | 0.004   |

## 6 Discussion

### 6.1 Early complications

Bariatric surgery has proven to be safe, with a 90-day mortality of only 0.35% (279). In a recent nationwide Finnish registry study, the 30-day mortality in bariatric surgery was 0.08%. Mortality rates following bariatric surgery were low or similar compared to other common elective surgeries, such as elective cholecystectomy (HR 2.38, 95% CI 1.39–4.08,  $p = 0.002$ ), hip arthroplasty (HR 11.7, 95% CI 6.90–19.8,  $p < 0.001$ ), and colorectal resections (HR 27.5, 95% CI 16.2–46,  $p < 0.001$ ) (280).

The standardization of the operation probably affects the low mortality and morbidity rate, as well as the change from an open operation type to a laparoscopic operation (9). The risk factors for mortality after RYGB surgery are higher BMI and age, male gender, pulmonary hypertension, congestive heart failure, and liver disease (281).

The number of early complications after bariatric surgery is reported to be under 10%, and, with restrictive procedures, the numbers tend to be lower than restrictive and malabsorption combining techniques. The most common early complications include anastomotic leaks (0.1–8.3%), bleeding (0.5–3.5%), and pulmonary embolism (0.2–1%) (206, 282). In a Polish study on RYGB and SG patients, a higher BMI, longer operation time, and the number of firings in SG increased the risk for early complications; operation type did not affect the number of complications (283).

Obesity surgery was initiated in 2008 at Peijas University Hospital. At that time, knowledge about postoperative complications and ways to avoid them was limited. At our hospital, patients were prospectively monitored for certain factors, such as bleeding complications or postoperative pneumonia, and, if the number of complications seemed high, the protocol would be modified, and, if a positive change were observed, the protocol would continue. After the first 400 operations, the results were retrospectively collected and studied.

As bariatric surgery was initiated at the outset of the study, the learning curve effect should be taken into consideration. All the surgeons who operated on bariatric patients at Peijas Hospital had extensive experience in laparoscopic surgery before the bariatric surgery. The literature suggests a learning curve of between 50 and 500 patients (284, 285). It is clear that the higher spectrum of patients to fulfill the learning curve cannot be achieved in our two first study groups of 400 patients.

In Studies I and II, we monitored the operation time and noticed a decrease after the first 50 patients, suggesting the presence of a learning curve effect. Still, in Studies I and II, no difference was detected in the number of major bleeding complications or pulmonary complications between patients 0–50 and patients 50–100. Other limitations of the two first studies include relatively small follow-up group of 100–200 patients and a lack of randomization.

#### *Thromboembolic and bleeding complications*

Thromboembolic complications are one of the leading causes of morbidity, accounting for 50% of the mortality following bariatric surgery (286). When considering enoxaparin alone for non-weight-adjusted thromboprophylaxis, many variables such as the dosage, frequency, and time of administration related to surgery must be taken into consideration. It is understandable that there are numerous possible regimens available. The best regimen protocol would prevent venous thromboembolic events without increasing bleeding complications.

Current VTE prophylaxis varies greatly depending on the surgeon's preference since no level 1 evidence of the type or duration of therapy is available (287). Our results suggested a correlation between higher enoxaparin dosage and bleeding complications. The recent guidelines on the ERAS protocol after bariatric surgery concluded that there is no evidence to support twice-daily prophylaxis. However, some studies suggest that a dose adjusted to BMI (i.e., 6000 IU of enoxaparin for BMI > 30 kg/m<sup>2</sup>, 8000 IU for BMI > 40 kg/m<sup>2</sup>, 10,000 IU for BMI > 50 kg/m<sup>2</sup>) could be safe (286).

In this study, we noticed a correlation between bleeding complications and hypertension. As hypertension is associated with increased peripheral vascular resistance (288, 289), it can be argued that the changes in the vascular histology and stiffness of the small vessels may cause an increase in the bleeding risk.

The hospital stay for patients with bleeding complications was significantly higher than for patients without bleeding complications (9.3 vs. 5.1 days, respectively), leading to more expenses for both patients and society. As the operation type was new at the outset of the study, all patients had a relatively long period of treatment at the hospital. Today, patients are generally discharged one to three days after the operation. In conclusion, the dosage of 40 mg of enoxaparin once daily was safest regarding bleeding complications. However, the literature lacks a consensus on the amount or timing of prophylaxis

### *Pulmonary complications*

Abdominal surgery and general anesthesia challenge the respiratory function in obese patients (290), and obesity is an independent factor in postoperative respiratory complications (291). As such, it is no surprise that PP and PRF account for most non-wound complications after bariatric surgery (14). Pulmonary complications also increase the length of hospital stay and increase the cost of hospital treatments (292).

ERAS protocols date back to the 1990s; they have offered strong evidence on other types of surgery since then (169, 170). Just recently, two meta-analyses conducted after bariatric surgery and ERAS were released. They suggested that by following the ERAS protocol, hospital length of stay can be reduced by around 1.5 to 3 days without any significant increase in overall major complications (171, 286). In our study, we found a similar trend toward fewer pulmonary complications after changing the treatment protocol to adhere to ERAS principles by, for example, avoiding tubes and mobilizing as early as possible. However, there was a confounding factor as shortened operation affected the number of pulmonary complications in the logistic regression model. In order to understand whether shortened operation time was the only factor decreasing the number of complications, we calculated the operation time in patients 0 to 50 and patients 51 to 100. We noticed that there was a difference in operation time (128/100 min) but none in the number of pulmonary complications (38/42), suggesting that operation time was not the only factor affecting the number of complications. In short, the results from our study support the use of ERAS in bariatric surgery.

### 6.2 Late surgical complications

There is substantial evidence of long-term and very long-term follow-ups for weight loss after RYGB, SG, and AGB (112) as well as the resolution of comorbidities (7); however, information on late complications is scarce. Late complications are essential to consider as many complications, such as stricture or severe dumping syndrome, may pose a significant risk of malnutrition. It is possible that even if obesity and obesity-related comorbidities could be managed with bariatric procedures, late complications would have the potential to create a new set of chronic malnutrition-related health problems.

### *RYGB versus SG*

The number of SG has grown exponentially in the past years. The advantages of SG are its technical simplicity, shorter operation time, maintenance of the bowel, and preservation of the pylorus (248).

However, some questions persist regarding long-term complications and weight regain after SG (293). Besides, the question about the higher incidence of Barrett's esophagus after SG remains unanswered. In a recently published study of a 10-year follow-up after SG, de novo hiatal hernias were found in 45% of the patients, and Barrett's metaplasia was found in 15% of the patients. Moreover, 14% of the patients were shifted to RYGB because of intractable reflux (294). In another study with a mean follow-up of 58 months, Barrett's esophagus was found in 17.2% of the patients (295).

Our third study suggested that RYGB had more late complications, which were treated using both surgical (9.4% vs. 9%) and endoscopic interventions (4.6% vs. 1.4%). Similar results have been suggested in the literature. In a study of 1487 patients, RYGB patients had a significantly higher percentage of cholecystectomies (5% vs. 2%,  $p < 0.01$ ) and other operations (6.9% vs. 0.9%,  $p < 0.01$ ) (116). Nonetheless, some studies indicate no difference in the complication rates (296).

In a meta-analysis of six RCT (695 patients) (297) of late complications in RYGB and SG, with a follow-up time ranging from 30 days to three years, a reduction in the relative odds favoring the SG procedure was observed; however, this did not reach statistical significance (OR, 0.64; 95% CI, 0.21–1.97;  $p = 0.4$ ). The problem with this meta-analysis was the short follow-up time in the included studies; another problem was that different studies categorize and describe complications in different ways.

When analyzing late complications, the technical skills of the operating surgeon should also be taken into consideration. Skills have been recognized as an essential factor in both perioperative and postoperative complications (297). A study by Birkmeyer demonstrated that surgeons with top quartile skills, compared to those with lower quartile skills, had significantly lower operation times and complication and mortality rates (298).

At the moment, no definitive answer can be offered as to which operation is best for treating late complications or very long-time weight changes. In the future, longitudinal follow-ups for late complications are needed to find the most effective and safe bariatric procedure in the long run.

### 6.3 Late non-surgical complications

#### *Vitamin and mineral deficiencies*

All the different obesity surgery procedures induce alterations of the gastrointestinal physiology, which can lead to malnutrition, varying from micronutrient deficiencies to severe protein-calorie

malnutrition (261). It has been concluded in a recent article that macro- and micronutrient deficiencies are common after obesity surgery. The most critical, depending on the operation type, are hypoalbuminemia (3–18%) and deficiencies of vitamins B1 ( $\leq$  49%), B12 (19–35%), vitamin D (25–73%), iron (17–45%), and zinc (12–91%) (299). A recent meta-analysis concluded that there is a clear correlation between obesity and reduced vitamin D concentrations (300). Lower values of D vitamin are also prevalent in the bariatric surgery population (301).

In our fourth study, vitamin D levels were at an appropriate level with the use of supplements after both operation types, when a target level of 50 nmol/l was used. However, if the higher target of 75 nmol/l had been used, less than 30% of the patients would have reached this goal. Further, no significant difference in vitamin D levels in RYGB and SG patients was found one and two years after the operation. Controversial results on the differences in vitamin D levels in patients after RYGB and SG have been reported in the literature, showing that both yielded similar levels (302, 303) or that RYGB patients had lower levels after the operation (304).

After bariatric surgery, two leading causes of B12 vitamin deficiency are malabsorption and insufficient oral intake. It has been shown previously that restrictive procedures, such as AGB and SG, have a lower incidence of postoperative vitamin B12 deficiency (304), which was also noted in our current study, as SG had higher B12 vitamin values. Despite the differences in these values, both groups were at the recommended levels. It has been stated previously that some amount of B12 vitamin deficiencies are missed because measuring B12 vitamin in serum has limited sensitivity and specificity. Thus, many patients may experience clinical symptoms of deficiency, even when B12 is shown to be at the proper level (305).

Protein deficiency can result from intolerance of protein-rich foods and a failure to take protein supplements. Several prospective studies have reported that low albumin is associated with the risk of mortality and cardiovascular diseases (306, 307). In our study, the albumin levels were at the appropriate level; however, the follow-up percentage was under 50%, giving the result a low statistical significance.

In addition to nutritional deficiencies, the currently performed bariatric operation can change the bioavailability of a wide range of drugs. There are very few studies available on the matter (308). Similar to organ transplant patients, bariatric surgery patients require lifelong monitoring of nutrient and vitamin levels to assess their adherence to supplementation and diagnose the variety

of macro- and micronutrient deficiencies that may occasionally develop, even with adequate supplementation (299).

### *Fractures*

Fractures cause workplace absences, inflict short-term disability, and incur high expenses on society (309). Numerous studies have documented the adverse effects of bariatric surgery on bone health. It seems that the negative effects on bones persist beyond the first years following the surgery, varying between different operation types (275).

A recent review of fracture risk after bariatric surgery showed that fracture risk was significantly increased for bariatric surgery patients compared to the non-surgical group. A difference in the number of fractures between restrictive and malabsorptive procedures favoring purely restrictive procedures was also found (276). Interestingly, not earlier but five years after surgery, we found a statistically significant fivefold increase in cumulative fracture risk (HR 5.49, 95% CI, 1.76–17.15) in the bariatric group compared to the non-surgically treated obese patient group.

In this study, the risk factors for fractures included age over 48, a previous surgical procedure, and a lower BMI after two years. Age has previously been proven as a risk factor for fractures (310), and weight loss is associated with high fracture risk, but for postmenopausal women only (311). In older people (over 65), obesity also seems to increase the risk of falling (312).

In the future, more extensive databases and detailed follow-ups explaining factors such as vitamin levels, exercise, smoking, among others, are needed to determine the extent to which bariatric surgery increases the fracture risk.

## 6.4 Strengths and limitations

The most apparent limitation of this thesis is the retrospective nature of the studies included. Another weakness is that data were gathered from a single hospital. Strengths of this thesis include a relatively high number of patients in each study, the calculation of the learning curve effect (whenever possible), and the use of a control group in Study IV.

## 6.5 Future aspects of bariatric surgery

According to a recent report, the global bariatric surgery market was valued at approximately \$1.96 million in 2018 and is expected to generate revenue of around \$3.5 million by the end of 2024 (213). However, only a limited number of eligible patients for bariatric surgery will undergo the operation



(10). One reason for this can be people's attitudes toward bariatric surgery. In a survey in 2016 in the United States, 60% of the participants believed that dieting and exercise were more effective than surgery for long-term weight loss. Bariatric surgery was also seen as ineffective and even dangerous (214). Another problem can be the attitude of physicians. In a study of over 500 doctors, 91% advised their severely obese patients to exercise, with diet following closely behind; only 15% of the doctors recommended obesity surgery (215).

There are still considerable debates over the choice and timing of the operative procedure, duration of the weight loss effect, the mechanism behind the effects, and new surgical procedures (316). Endoluminal interventions offer a promising alternative approach to the treatment of obesity, including endoscopic gastroplasty, intragastric balloon, and endoluminal malabsorptive bariatric procedures. The weight loss effect of endoscopic treatments is higher than drugs but lower than bariatric surgery (97). Other endoscopic procedures under investigation are aspiration therapy (317) and Gastric Electrical Stimulation (GES) therapy (318), among others.

As the treatment of obesity is multidisciplinary and includes more than bariatric surgery, changes in the field of conservative treatment will affect the popularity and progress of bariatric surgery. Several new potential drugs and even vaccines are being studied, leading to better treatment options and personalized approach to obesity care in the future (219). However, for the time being, the bariatric surgery remains the most effective treatment of obesity.

## 7 Conclusions

I: Enoxaparin (40 mg) given once daily was the safest protocol regarding bleeding complications. Arterial hypertension may increase the risk of bleeding complications. No thromboembolic complications were found.

II: A longer operation time increases the risk of pulmonary complications. Changes in perioperative care to follow the ERAS principles may have a positive effect on the frequency of pulmonary complications.

III: RYBG is associated with a higher risk of late complications, treated both surgically and endoscopically compared to SG.

IV: Vitamin D, B12, and albumin were at the recommended level at one and two follow-up years in RYGB and SG patients. The fracture risk was higher for operatively treated patients. The risk factors for fractures after obesity treatment were older age, rapid weight loss, and a lower BMI after two years.

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Mervi

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10 Original publications