About 2 billion people are overweight worldwide and one third of them are obese. This study shows that a small intestinal length is associated with levels of serum triglycerides before and after laparoscopic Roux-en-Y gastric bypass (LRYGB). In addition, serum plant sterols were lower in patients with gallstone disease independent of weight loss after LRYGB, history of cholecystectomy and non-alcoholic fatty liver disease. Genetic risk score did not predict weight loss.
Impact of obesity and Roux-en-Y gastric bypass on comorbidities with special emphasis on cholecystolithiasis and related lipid metabolism
Impact of obesity and Roux-en-Y gastric bypass on comorbidities with special emphasis on cholecystolithiasis and related lipid metabolism

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ABSTRACT

Obesity is one of the major public health concerns worldwide. About 2 billion people are overweight worldwide and one third of them are obese. Bariatric surgery is an excellent treatment for severely obese patients.

The rising prevalence of gallstone disease (GD) in western countries has been associated with increasing prevalence of obesity and rapid weight loss induced by bariatric surgery. Obesity increases the risk for GD three-fold when the BMI exceeds 30 kg/m². Laparoscopic Roux-en-Y gastric bypass (LRYGB) adds to the risk by altering the enterohepatic circulation and normal gallbladder physiology. Bariatric surgery can also predispose patients to cholecystolithiasis even if they have no history of GD. Furthermore, asymptomatic gallstones may become symptomatic and induce postoperative complications.

Genetic factors play an important role in the regulation of weight and obesity. A reliable method of profiling patients preoperatively to predict the outcome of obesity surgery has not been established. We need more knowledge of the associations of obesity, cholelithiasis and bariatric and gallbladder surgery with cholesterol, bile, and fatty acid metabolism in the liver and also of predictors of surgical outcomes.

The aim of this thesis was to analyze the associations of obesity, cholelithiasis and bariatric and gallbladder surgery on cholesterol, bile, and fatty acid metabolism, and to analyze predictors of surgical outcome.

The main findings were that obesity or any of its comorbidities did not associate with an elevated risk for postoperative complications after LCC. In symptomatic GD, obesity and related comorbidities increased the conversion rate, but not the operative risks of LCC. In addition, serum plant sterols were lower in patients with GD independent of weight loss after LRYGB, history of LCC and non-alcoholic fatty liver disease (NAFLD). Low serum plant sterols in patients with GD suggest potentially inherited alterations in sterol absorption and biliary transport in subjects susceptible to GD. We also found that a small intestinal length was associated with levels of serum triglycerides (TG) before and after LRYGB. This suggests that intestinal length regulates TG metabolism, and thus also regulates the levels of serum TG after obesity surgery. Finally, a genetic risk score (GRS) did not predict weight loss while BMI below 45kg/m² at baseline predicted greater weight loss.

National Library of Medicine Classification: QU 85, QU 477, WD 210, WI 500, WI 755, WI 980
Medical Subject Headings: Obesity; Gallstones; Cholecystolithiasis; Gastric Bypass; Bile; Comorbidity; Phytosterols; Postoperative Complications; Triglycerides; Weight Loss; Intestine, Small; Non-alcoholic Fatty Liver Disease
VII

Käkelä Pirjo
Mahalaukun ohitusleikkauksen ja lihavuuden vaikutus liitännäissairauksiin ja näiden yhteyttä sappikivivaiuteen ja rasvaa-aineenvaihduntaan.

Itä-Suomen yliopisto, terveytieteen tiedekunta
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TIIVISTELMÄ:

Lihavuus on yksi maailman suurimmista terveydenhuollon ongelmista. Maailmassa on noin 2 miljardia ylipainoista ihmistä ja yksi kolmasosa näistä on lihavia. Lihavuus on erinomainen vaihtoehto vakavasti lihaville potilaille.

Sappikivivaivan määrän kasvu länsimaissa on katsottu liittyvän lihavuuteen ja toisaalta nopeaan painonlaskuun, jota edesauttaa lihavuuskirurgia. Lihavuus aiheuttaa kolmikertaisen sappikivitaudin riskin, kun BMI lähenee 30 kg/m². Mahalaukun ohitusleikkaus lisää sappikiviriskiä muuttamalla enterohopaattista kiertoa ja normaalia sappirakon toimintaa. Sappikiviä saattaa ilmaantua myös potilaille, joilla niitä ei ole aikaisemmin todettu. Oireet saattavat muuttua oireisiksi lihavuusleikkauksen jälkeen ja aiheuttaa potilaille sappirakkotulehduksen tai sappikivikohtauksia.


Tämän väärtoskirjatyön tarkoitus on analysoida lihavuuden, sappikiviutaudin, lihavuus- ja sappikivikirurgian yhteyttä kolesteroli-, sappihappo- ja rasvaa-aineenvaihduntaan sekä löytää lihavuusleikkauksen vaikuttavuutta ennustavista tekijöistä.


Luokitus: QU 85, QU 477, WD 210, WI 500, WI 755, WI 980
Yleinen Suomalainen asiasanasto: lihavuus; sappikivet; sappirakko; sappihapit; leikkaushoito; liitännäistaudit; kasvisterolit; komplikaatiot; triglyseridit; painoindeksi; ohutsuoli; rasvamaksu
To Ilpo,

Mother † and Father †
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You all made my day.

Kuopio, November 2018

Pirjo Käkelä
List of the original publications

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<td>ATP-binding cassette G5/8</td>
</tr>
<tr>
<td>AL</td>
<td>Alimentary limb</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>ASA</td>
<td>American Society of Anesthesiologists</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>BPD</td>
<td>Biliopancreatic diversion</td>
</tr>
<tr>
<td>BPD-DS</td>
<td>Biliopancreatic diversion with duodenal switch</td>
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<tr>
<td>BPL</td>
<td>Biliopancreatic limb</td>
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<td>CC</td>
<td>Common channel</td>
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<td>CCK</td>
<td>Cholecystokinin</td>
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<td>%EWL</td>
<td>Percent of excess weight loss</td>
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<td>GD</td>
<td>Gallstone disease</td>
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<td>GLP-1</td>
<td>Glucagon-like peptide-1</td>
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<td>GRS</td>
<td>Genetic risk score</td>
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<td>HDL</td>
<td>High-density lipoprotein</td>
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<td>KOBS</td>
<td>Kuopio Obesity Surgery Study</td>
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<tr>
<td>LCC=LC</td>
<td>Laparoscopic cholecystectomy</td>
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<td>LRYGB</td>
<td>Laparoscopic Roux-en-Y gastric bypass</td>
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<tr>
<td>LSG</td>
<td>Laparoscopic Sleeve gastrectomy</td>
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<td>NAFLD</td>
<td>Non-alcoholic fatty liver disease</td>
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<td>NASH</td>
<td>Non-alcoholic steatohepatitis</td>
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<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
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<tr>
<td>PYY</td>
<td>Peptide YY</td>
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<tr>
<td>SNP</td>
<td>Single nucleotide polymorphism</td>
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<tr>
<td>SOS</td>
<td>Swedish Obese Subjects</td>
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<td>T2DM</td>
<td>Type 2 diabetes mellitus</td>
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<td>TG</td>
<td>Triglyceride</td>
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<tr>
<td>%TWL</td>
<td>Percent of total weight loss</td>
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<tr>
<td>VLCD</td>
<td>Very low-calorie diet</td>
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<tr>
<td>WHR</td>
<td>waist/hip ratio</td>
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1 Introduction

Weight loss is recommended for all obesity-related diseases, but weight loss programs with conventional therapy are successful only for a fraction of obese people, and the long-term results are very modest (Ribaric-Buchwald-McGlennon 2014). Laparoscopic Roux-en-Y gastric bypass (LRYGB) is the most frequently performed surgical procedure for weight loss and for resolution of comorbidities (Miller-Pump-Hell 2007). However, in recent years, the role of different procedures has been revised following the postoperative outcomes from a metabolic and functional point of view. The superiority of bariatric surgery is recognized worldwide as a cost-effective treatment both in terms of weight loss, maintenance of weight loss and remission of comorbidities, such as type 2 diabetes (T2DM), hypertension, hyperlipidemia and non-alcoholic fatty liver disease (NAFLD) (Deitel-Dixon 2010, Hatoum-Kaplan 2013).

Gallstones are associated with obesity and rapid weight loss induced by bariatric surgery. Rapid weight loss mobilizes cholesterol from tissue stores and increases gallstone risk via increased hepatic secretion of cholesterol in bile, resulting stones and increased biliary concentration in the gallbladder (Shiffman-Shamburek et al. 1993, Shiffman-Sugerman et al. 1993). The risks of developing gallstones may differ among weight reduction procedures. LRYGB adds to the risk by altering enterohepatic circulation and normal gallbladder physiology (Li VK et al. 2009). Bariatric surgery can predispose patients to cholecystolithiasis even if they have no history of gallbladder disease (Abdallah et al. 2017). Furthermore, bariatric surgery can cause asymptomatic gallstones to become symptomatic and induce postoperative complications due to gallstones (Stender-Nordestgaard-Tybetaerg-Hansen 2013). In the western world, about 80-90% of gallstones consist of cholesterol (Abdallah et al. 2017).

Accurate measurement of the whole small intestinal length may be important peroperatively, because the standard limb lengths used today may have a limited impact on patient weight loss and cholesterol metabolism (Stefanidis-Kuwada-Gersin 2011). Measurement is not done routinely and that is why the data of normal small intestinal length is mostly based on old cadaver studies (Chewal 1995, Evers 1999, Fanucci et al. 1984, Guzman et al. 1977). It has been proposed that to achieve more metabolic benefits, the bariatric procedure should focus on the length of the common channel (CC), rather than the alimentary limb (AL) or biliopancreatic limb (BPL) when constructing a gastric bypass (Stefanidis-Kuwada-Gersin 2011).

Genetic factors play an important role in the regulation of weight and obesity. A reliable method of profiling patients preoperatively to predict the outcome of obesity surgery has not been established. However, some predictors of outcome, such as clinical phenotype, have been identified (Alger-Mayer-Polimeni-Malone 2008, Livhits et al. 2012, Kadeli et al. 2012, Alvarado et al. 2005).

In this doctoral thesis the aim was to evaluate the impact of obesity and associated comorbidities on complications after laparoscopic cholecystectomy (LCC) in 1581 consecutive obese individuals. We also analyzed the association of serum plant sterols and gallstone disease (GD) in NAFLD after gastric bypass in 242 consecutive obese individuals. The third aim was to analyze the association of serum triglyceride (TG) levels on the length of the small intestine before and after LRYGB. The whole small intestine was measured routinely in 70 consecutive obese individuals during the elective LRYGB.

The fourth aim was to assess whether 20 loci associated with body mass index (BMI) and 13 loci
associated with waist/hip ratio (WHR) and a genetic risk score (GRS) predict the outcome of LRYGB in 163 consecutive obese individuals.
2 Review of literature

2.1 OBESITY

2.1.1 Epidemiology of obesity
Obesity is defined as an excess of body fat that may cause problems to an individual’s health. Clinically obesity is defined based on BMI (Li-Bowerman-Heber 2005). BMI is defined as weight in kilograms divided by the square of the height in meters. BMI between 25 kg/m² and 29.9 kg/m² is considered overweight and BMI ≥ 30 kg/m² obese (Falaschetti-Malbut-Primatesa 2002). Obesity is categorized into three classes: BMI between 30 kg/m² and 34.9 kg/m² is class I, moderately obese, BMI between 35 kg/m² and 39.9 kg/m² is class II, severely obese, and BMI ≥ 40 kg/m² is class III, morbidly obese (NICE 2002). Any individual with BMI ≥ 50 kg/m² is considered super obese (MacLean-Rhode-Forse 1990).

BMI has some limitations. It does not consider body fat distribution, muscle mass, bone density or overall body composition. Also, it does not take account sex differences or ethnicity. These all influence the correlation between BMI and health. At the same BMI, people of African ethnicity are likely to carry less fat while people of south Asian ethnicity carry more fat than the general population (Nightingale et al. 2011). This indicates that BMI overestimates obesity among Africans and underestimates obesity in South Asians. Using adjusted thresholds for these ethnic groups could improve obesity estimates.

About 2 billion people are overweight worldwide and one third of them obese (Seidell-Halberstadt 2015). There are great regional and gender differences (WHO 2016) (Figure 1 and Figure 2). In the USA almost 70% of adults are overweight and about 36% of those are obese (Flegal et al. 2012). The prevalence rates in Central, Eastern, and Southern Europe are higher than in Western and Northern Europe (Berghófer et al. 2008). Even though the prevalence is generally lower in low-income and middle-income countries, it is increasing faster in these countries than in high-income countries (Seidell-Halberstadt 2015).

In the 1960s 8% of men and 17% of women in Finland were obese according to Finnish national epidemiological surveys. After the 1960s increase in prevalence of obesity in both sexes, in all age groups and in different educational groups has been very strong (Prättälä et al. 2012). In 2002 the prevalence of obesity was 21% in men and 24% in women (Lahti-Koski et al. 2010). According to FINRISKI 2017 national survey, the prevalence of obesity in men is 26%, and combined overweight and obesity is 72%. In women, the corresponding figures are 27% and 63%. Central obesity (waist circumference over 100 cm in men and over 90 cm in women) is found in 45% of Finns (THL report 4/2018). Even though the estimated need for bariatric operations in Finland is at least 3000 per year (THL Report 16/2009), the number of bariatric operations has stayed at 1000 operations per year, 76% of them LRYGBs (www.limery.fi).
Figure 1. In 2014, the prevalence of overweight individuals was highest in the WHO region of the Americas and lowest in the WHO region for South-East Asia. Adapted from WHO 2016.

Figure 2. In 2014, in all WHO regions women were more likely to be obese than men. Adapted from WHO 2016.
2.1.2 Obesity-related comorbidities

A worldwide increase in obesity, metabolic syndrome and T2DM is likely to increase the risk for symptomatic GD and subsequent requirement for LCC (Bell-Allbright 2007). About 25% of T2DM patients have GD, and one fifth of the patients undergo LCC (Pagliarulo et al. 2004).

The risk for GD increases three-fold when the BMI exceeds 30 kg/m² (Aslar et al. 2003). In humans, cholesterol homeostasis is maintained by the interaction between intestinal uptake, de novo synthesis, hepatic output, and fecal disposal. Intestinal uptake and biosynthesis represent the sole sources of new cholesterol. The mechanism of cholecystolithiasis can be attributed to the formation of lithogenic bile that is highly saturated with cholesterol. This bile eventually precipitates, forming cholesterol stones (Miettinen et al. 1996, Lamri-Senhadji et al. 2002). Risk factors for cholecystolithiasis such as age over 40 years old, T2DM, obesity, and female sex are well known (Stender-Nordestgaard-Tybjærg-Hansen 2013). In the general population, symptomatic gallstones seem to occur up to 20 years after diagnosis of uncomplicated disease with a prevalence of 6-20% (Table 1), (Aerts-Penninckz 2003). Only 1–5% of these patients require cholecystectomy due to symptomatic gallstone formation. It has been estimated that up to 45% of patients with obesity develop cholecystolithiasis (Brandão De Oliveira-Chaim-Da Silva 2003). The incidence of gallstone formation is eight times greater in patients with BMI over 40 kg/m² (Teres 1993). The risk also increases especially in patients who lose over 1.5 kg per week (Amaral-Thompson 1985, Brandão De Oliveira-Chaim-Da Silva 2003).

Obesity-related health risks start to increase already when BMI exceeds 25 kg/m² and the risk increases exponentially above a BMI of 30 kg/m². The risk of developing T2DM doubles with every 5–7.9 kg gain in weight (Chan et al. 1994, Colditz et al. 1995). About 80% of T2DM subjects are obese or overweight and obese subjects have a seven-fold risk to develop T2DM compared to normal weight subjects (Smith-Smith 2016). In 2014, the global prevalence of T2DM (defined as fasting plasma glucose ≥ 7.0 mmol/l or a medication for raised blood glucose) was 9% (Table 1), (WHO 2014). The prevalence of diabetes has been increasing particularly in low- and middle-income countries because of lower physical activity, overweight and obesity (Finucane et al. 2011). In Finland about 250 000 patients were diagnosed with T2DM in 2007. Between 1997 and 2007 the growth was 77%. According to the national health survey, only half of the cases of T2DM are diagnosed. The actual number of T2DM patients in Finland is closer to 500 000 (Koski 2011).

Obesity and overweight account for about 45% of the increased risk for cardiovascular diseases: hypertension, coronary heart disease, angina pectoris, stroke and atrial fibrillation (Table 1), (Bogers et al. 2007, Jones et al. 1994). The risk of developing heart failure increases 5% in men and 7% in women with every 1 kg/m² increment in BMI (Kenchaiah et al. 2002). NAFLD and GD have both been associated with a high incidence of cardiovascular disease (Ahmed-Ali 2014).

Obesity and overweight are mainly associated with the risk of knee osteoarthritis, but not to a large extend with hip osteoarthritis (Table 1). Weight loss improves the functional consequences of knee osteoarthritis (Sridhar et al. 2012, Sabharwal-Root 2012).

Obesity is a significant risk factor for obstructive sleep apnea. The prevalence of obstructive sleep apnea is 17% to 24% in men and 5% to 9% in women (Ashrafian et al. 2012). Up to 80% of obese and overweight patients may have undiagnosed obstructive sleep apnea (Chau et al.
2012). The incidence is 12 to 30 times higher in the obese population compared to the general population. In bariatric patients’ prevalence ranges from 60% to 83% (Table 1), (Ashrafian et al. 2012). Obstructive sleep apnea is also strongly linked to metabolic abnormalities and T2DM (Tuomilehto et al. 2008, Tasali-Mokhlesi-Van Cauter 2008). In diabetic patients, the prevalence is 78% (Fredheim et al. 2011).

Overweight and obesity account for approximately 20% of all cancer cases (Table 1), (Wolin-Carson-Colditz 2010). At a BMI ≥ 40 kg/m², mortality from all causes of cancer is 52% higher in men and 62% higher in women than in those with a normal BMI (Pi-Sunyer 2009). In a study from the United Kingdom, increasing BMI was associated with a significant increase in risk for 12 out of 17 of the most common types of cancer such as endometrial cancer, adenocarcinoma of the oesophagus, kidney cancer, leukaemia and multiple myeloma, pancreatic, liver and gallbladder cancer and non-Hodgkin's lymphoma, ovarian, breast and colorectal cancer (Reeves et al. 2007). Over 67% of these are diagnosed in developed countries and these cancers comprise 27% of the global burden (Arnold et al. 2016). A rise in BMI between age 30 and 50 years leads to a rise in the risk of colorectal cancer. Weight loss in men is associated with reduced risk of colon cancer (Arnold et al. 2016).

Obesity is an independent risk factor for increased mortality. Worldwide obesity and overweight are the fifth leading cause of death and account for 3.4 million deaths each year (Smith-Smith 2016, WHO 2014, Lim et al. 2012). The mean obesity mortality rate is 2.5% during 8-14 years of follow-up (Table 1), (Telem et al. 2015). Obesity and overweight are considered to decrease the life expectancy by seven years in obese women and more than six years in obese men (Peeters et al. 2003). Obesity in adulthood is a powerful predictor of prematurely shortened life expectancy in older ages.

NAFLD is tightly associated with obesity and metabolic syndrome (Musso-Gambino-Cassader 2010). Some individuals develop non-alcoholic steatohepatitis (NASH), the progressive form of NAFLD. Approximately 10-20% of those with simple steatosis have NASH (Vernon-Baranova-Younossi 2011, Adams et al. 2005). The prevalence of NASH in the USA is between 3% and 5%. The population prevalence of NASH in 45-74 year-old Finnish subjects is approximately 5% (Hyysalo et al. 2014). Worldwide the prevalence rate of NAFLD ranges from 6% to 35%, with a median of 20% (Table 1), (Amarapurkar et al. 2007). About 2-3% of patients with steatosis develop NASH during a five-year follow-up, and 8% of those with NASH will develop cirrhosis in five years (Musso-Gambino-Cassader 2010, Vernon-Baranova-Younossi 2011, Adams et al. 2005).

Overweight and obesity account for approximately 30-70% of all polycystic ovarian syndrome cases, including anovulation, infertility and miscarriage (Table 1), (Loret de Mola 2009). The rise in infertility seems to plateau when BMI exceeds 35 kg/m² (Loret de Mola 2009).

Obesity and overweight are a major risk factor for gastroesophageal reflux disease and its complications, erosive esophagitis, Barrett’s esophagus and esophageal adenocarcinoma (Nguyen-El-Serag 2010). The prevalence of gastroesophageal reflux disease is 44% (Table 1), (Locke et al. 1997). A weight loss of 3.5 kg results in a significant decrease in the frequency of symptoms of gastroesophageal reflux disease (Emmanuel-Coppack 2016).

Obese patients with asthma have more severe symptoms and have less responsive to medication therapy than non-obese asthma patients (Marceau et al. 2007). The prevalence of asthma is 12.3% (Table 1), (Sutherland 2014). Asthma increases progressively with increasing BMI. Increase is 12% with a BMI of 25.0 kg/m² to 29.9 kg/m² and almost 250% with a BMI ≥ 50
kg/m² (Koebnick et al. 2016). The association between obesity and asthma risk is greater in women. Obesity is associated with poorly controlled and high-risk asthma (Koebnick et al. 2016).

Obesity is an independent risk factor for urinary incontinence (Danforth et al. 2006, Khullar et al. 2014, Townsend et al. 2008). Each five-unit increase in BMI above normal weight is associated with a 40% to 70% increase in prevalence of urinary incontinence over 5 to 10 years (Brown et al. 1996). The prevalence of urinary incontinence has been reported to be 70% among severely obese women (Burgio et al. 2007, Deitel et al. 1988, Laungani-Seleno-Carlin 2009, Richter et al. 2005) and 24% among severely obese men (Table 1), (Ranasinghe et al. 2011).

Table 1. Obesity-related comorbidities and their prevalence.

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Prevalence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallstone disease</td>
<td>6-20 %</td>
<td>Aerts-Penninckz 2003</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>9 %</td>
<td>WHO 2014</td>
</tr>
<tr>
<td>Cardiovascular and cerebrovascular diseases, arterial hypertension</td>
<td>45 %</td>
<td>Bogers et al. 2007, Jones et al. 1994,</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>12-37 %</td>
<td>Sridhar et al. 2012, Sabharwal-Root 2012</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td>60-83 %</td>
<td>Ashrafian et al. 2012</td>
</tr>
<tr>
<td>Certain types of cancers</td>
<td>20 %</td>
<td>Wolin-Carson-Colditz 2010</td>
</tr>
<tr>
<td>Increased risk of mortality</td>
<td>2.5 %</td>
<td>Telem et al. 2015</td>
</tr>
<tr>
<td>Non-alcoholic fatty liver disease</td>
<td>6-35 %</td>
<td>Amarpurkar et al. 2007</td>
</tr>
<tr>
<td>Polycystic ovary disease</td>
<td>30-70 %</td>
<td>Loret de Mola 2009</td>
</tr>
<tr>
<td>Gastro-oesophageal reflux disease</td>
<td>44 %</td>
<td>Locke et al. 1997</td>
</tr>
<tr>
<td>Respiratory disorders and asthma</td>
<td>12.3 %</td>
<td>Sutherland 2014</td>
</tr>
</tbody>
</table>
2.2 OBESITY SURGERY

2.2.1 History of bariatric surgery

Bariatric surgery can be classified into four different categories: malabsorptive procedures, malabsorptive/restrictive procedures, restrictive procedures, and experimental procedures (Buchwald-Buchwald 2002). The chronological overview of procedures for morbid obesity is seen in Table 2. By the early 1950s Swedish surgeon Viktor Henriksson resected 105 cm of small bowell (Henriksson 1994). However, the prototype of malabsorptive procedures specifically to induce weight loss was the jejunoileal bypass performed by Varco (Kremen-Linner-Nelson 1954, Buchwald-Rucker 1987). It was a highly effective weight reduction operation. However, it had problems with gas bloating, steatorrhea, electrolyte imbalance, liver fibrosis and other adverse effects, and finally it was abandoned early 1970s.

In 1963 Payne et al. published the results of the first massive intestinal bypass. They bypassed almost the entire small intestine, the right hemicolon and half of the transverse colon (Payne-DeWind-Commons 1963). Because of the massive adverse effects, they had to do reversal of the bypass. Scopinaro developed biliopancreatic diversion (BPD) in 1976 (Scopinaro et al. 1980) and Hess further developed it into a BPD with duodenal switch (BPD-DS) (Buchwald 2014, Salameh 2006). These operations induce a malabsorption and contain a risk for malnutrition (Skroubis et al. 2002, Larrad-Jimenez et al. 2007).

In 1966, the first version of the gastric bypass was developed by Mason and Ito. This operation had less malabsorption than BPD (Mason-Ito 1967). Gastric bypass had favourable metabolic improvements because of the modifications in the entero-endocrine axis (Yousseif et al. 2014, Mans et al. 2015, Korner et al. 2005). In 1994, the laparoscopic approach became one of the most commonly performed procedure worldwide (Wittgrove-Clark-Tremblay 1994). In 1980 Mason performed the vertical banded gastroplasty (Mason 1982). Due to enlargements of pouches, poor weight loss and development of gastro-gastric fistulas, it was abandoned. Laparoscopic adjustable gastric banding, became rather popular in the 1990s and early 2000s (Belachew-Legrand-Jacquet 1993, Forsell-Hallberg-Hellers 1993). The mid-term results up to five years were as good as in vertical banded gastroplasty, but the long-term results were disappointing because of slippages and band erosions (Sampalis-Sampalis-Christou 2006, Pontiroli et al. 2005). Many of the adjustable gastric banding operations have been reversed to LRYGB or laparoscopic sleeve gastrectomy (LSG) (Tolonen 2008). LSG is a restrictive procedure and previously used only as a first stage operation in BPD-DS. In 2000, McMahon performed the first LSG (Sarela et al. 2012). In 2013-2014 it became the most rapidly growing bariatric procedure (Buchwald 2014, Salameh 2006).

In Helsinki university hospital, 47 jejunoileal bypasses were performed between 1972 and 1980, and 33 vertical banded gastroplasties between 1983 and 1990. Adjustable gastric banding procedures were initiated in Kuopio, Oulu, Helsinki and Vaasa in the beginning of 1990s. The first open gastric bypass in Finland was performed in Lahti in the end of 1990s (THL report 16/2009), and the first LRYGB in Finland was performed in Kuopio university hospital in May 2000.
Table 2. Chronological overview of procedures for morbid obesity.

<table>
<thead>
<tr>
<th>Name</th>
<th>Year</th>
<th>Procedure</th>
<th>Category</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henriksson</td>
<td>1950s</td>
<td>105 cm small bowel resection</td>
<td>malabsorptive</td>
<td>Henriksson 1994</td>
</tr>
<tr>
<td>Payne et al.</td>
<td>1963</td>
<td>Massive intestinal bypass</td>
<td>malabsorptive</td>
<td>Payne-DeWind-Commons 1963</td>
</tr>
<tr>
<td>Mason and Ito</td>
<td>1966</td>
<td>Open gastric bypass</td>
<td>restrictive/malabsorptive</td>
<td>Mason-Ito 1967</td>
</tr>
<tr>
<td>Scopinaro</td>
<td>1976</td>
<td>Biliopancreatic diversion</td>
<td>malabsorptive</td>
<td>Scopinaro et al. 1980</td>
</tr>
<tr>
<td>Mason</td>
<td>1980</td>
<td>Vertical banded gastroplasty</td>
<td>restrictive</td>
<td>Mason 1982</td>
</tr>
<tr>
<td>Wittgrove et al.</td>
<td>1994</td>
<td>Laparoscopic gastric bypass</td>
<td>restrictive/malabsorptive</td>
<td>Wittgrove-Clark-Tremblay 1994</td>
</tr>
</tbody>
</table>

2.2.2 Indications and contraindications for bariatric surgery

Bariatric surgery is an effective choice for severe or morbid obese patients. There is not enough information or reliable indicators to predict which procedure is best for an individual patient or which patients will successfully lose weight and see an improvement of their obesity-related diseases.

In 1991, the National Institutes of Health (NIH) Consensus Development Panel gave a significant number of recommendations for bariatric surgery (NIH conference 1991). These recommendations are a majority consensus, rather than evidence based and they are accepted with very minor variations in most western countries. Same recommendations are used in Finland and worldwide (Table 3). Age limits are set in Finland between 18 and 65 years, but an individual evaluation is possible (Current Care Guidelines, Käyppä hoito-suositus, 2013).

In 2011, the International Diabetes Federation recommended bariatric surgery to patients with a BMI between 30 kg/m² and 35 kg/m² who, regardless of weight loss and conventional medical therapy, have uncontrolled diabetes (Dixon et al. 2011). Also, the National Institute for Health and Care Excellence and the American Diabetes Association recently recommended the same (National Institute for Health and Clinical Excellence 2014). In 2004, Asian Pacific Bariatric Surgery Group was founded and they also establish modified criteria because of the physiological differences in Asian populations.

In Finland KELA (Social Insurance Institution) has set even higher criteria for bariatric operations: BMI over 45 kg/m² without weight-related comorbidities or 40 kg/m² with
comorbidities. Also, in the United Kingdom, obesity surgery is recommended even in a higher BMI and with much more comorbidities than in Finland (Guh et al. 2009).

Contraindications for bariatric operation in adults are listed in Table 3. Previous intra-abdominal operations influence applicability of the laparoscopic approach, because residual adhesions may totally preclude access to the intra-abdominal cavity. In Finland, all patients are instructed to follow a very low-calorie diet (VLCD) for three to five weeks with the aim to reach average 10% weight loss preoperatively to decrease fatty liver size and visceral fat content and improve access to the intra-abdominal cavity. In this way, the surgery candidate establishes also the motivation for the life style change. There are no absolute contraindications to bariatric surgery but all individual complicating factors must be examined carefully (Sarkar-Sedman 2016).

Table 3. Indications and contraindications for bariatric surgery in adults according to the National Institutes of Health (NIH) Consensus Development Panel (NIH conference 1991).

<table>
<thead>
<tr>
<th>Indications</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI over 40 kg/m²</td>
<td>severe eating disorder</td>
</tr>
<tr>
<td>BMI over 35 kg/m² with obesity related diseases;</td>
<td>severe and active psychiatric disease</td>
</tr>
<tr>
<td>- type 2 diabetes mellitus</td>
<td>drug or alcohol abuse</td>
</tr>
<tr>
<td>- obesity-induced cardiomyopathy</td>
<td>active gastric ulcer</td>
</tr>
<tr>
<td>- severe osteoarthritis</td>
<td>inability to understand instructions</td>
</tr>
<tr>
<td>- obstructive sleep apnea</td>
<td></td>
</tr>
<tr>
<td>- hypertension</td>
<td></td>
</tr>
<tr>
<td>- polycystic ovary syndrome</td>
<td></td>
</tr>
<tr>
<td>- conservative treatment has failed</td>
<td></td>
</tr>
<tr>
<td>- familial hyperlipidemia</td>
<td></td>
</tr>
<tr>
<td>Age between 18-60 years</td>
<td></td>
</tr>
</tbody>
</table>

2.2.3 The most common bariatric procedures

Roux-en-Y gastric bypass

LRYGB is the gold standard and the most frequently executed restrictive, malabsorptive (Miller-Pump-Hell 2007) and hormonal (Rubino et al. 2010) operation at the moment. Almost 470 000 bariatric operations were performed worldwide in 2013. About 50% of them were gastric bypasses and 96% were carried out laparoscopically (Angrisani et al 2015).

In LRYGB a small gastric pouch of about 15 to 30 ml in capacity is divided from the upper part of the stomach. The gastric pouch is then anastomosed to the distal end of the jejunum which is transected approximately 60–75 cm distal to the ligament of Treitz, configuring the AL. The gastric remnant in continuity with the duodenum and proximal jejunum represents the
BPL, which is connected to the alimentary channel through a jeuno-jejunostomy usually about 100–150 cm distal to the gastric pouch (Figure 3). As a result of this configuration, absorption of nutrients occurs mostly distal to the jeuno-jejunostomy, when food particles interact with the digestive pancreatic enzymes. Thus, the length of functionally absorptive small intestine is decreased by 160-225 cm as a result of the operation. The degree of malabsorption can be modified by altering the length of these limbs. As a result, food is diverted from the small gastric pouch directly into the jejunum and bypassing the gastric remnant, duodenum, and proximal jejunum.

When altering the gastrointestinal anatomy and physiology, the amount of food intake is reduced and nutrients are delivered more rapidly to the distal small intestine. Patients will lose weight and they will also have favorable metabolic improvements because of the modifications in the entero-endocrine axis (e.g., increase of peptide YY (PYY), glucagon-like peptide-1 (GLP-1) levels), (Yousseif et al. 2014, Mans et al. 2015, Korner et al. 2005). This all can lead to a loss of hunger and increase in satiety (le Roux et al. 2007). Exclusion of the proximal small intestine reduces the secretion of upper gastrointestinal factors such as anti-incretins, which are assumed to suppress insulin secretion or promote insulin resistance (Rubino et al. 2010). Changes in gut microbiota after the bypass may also influence weight by reduction of low-grade inflammation associated with obesity (Abdeen-le Roux 2016).

Figure 3. Roux-en-Y gastric bypass.
Sleeve gastrectomy
The number of LSG has progressively increased from an estimated 37% in 2003, becoming the most popular restrictive bariatric procedure in the USA and in North America, and the second common worldwide even though the long-term data is lacking (Angrisani et al. 2015).

In LSG a narrow tube is resected longitudinal along the lesser curvature starting from the antrum about 5 cm proximal from the pylorus. It involves the complete excision of the fundus, two thirds of the body and antrum, yet preserving a portion of the later and the pylorus itself. The tube-shaped gastric “sleeve” has a capacity of approximately 100 ml (Figure 4). LSG has been found to generate weight loss not only through the simple restriction of food intake but also through hormonal mechanisms. LSG may generate hunger suppression through a decrease in ghrelin plasma levels. However, ghrelin may not be as important as previously thought, because LSG has been equally effective in ghrelin-deficient and ghrelin-intact mice (Miras-le Roux 2013). In addition, ghrelin levels increase after adjustable gastric banding and increase, decrease, or remain unaltered after LRYGB (Miras-le Roux 2013). The beneficial effects on glycemic control has been suggested to derive also from the rapid passage of undigested food arriving into the small intestine and the release of gastrointestinal hormones like GLP-1, PYY, and cholecystokinin (CCK) (Yousseif et al. 2014, Mans et al. 2015).

Biliopancreatic diversion and biliopancreatic diversion with duodenal switch
At the moment the most popular malabsorptive procedures are BPD and BPD-DS, even though seldom carried out (Buchwald-Buchwald 2002). In the BPD, the lower two-thirds portion of the stomach is removed, and the small intestine is transected approximately 200 cm to 250 cm proximal the ileo-caecal valve. The distal part of the small intestine is anastomosed to the gastric pouch, and the BPL is anastomosed to the distal ileum about 50 cm from the ileo-caecal valve. In this way, the CC is 50 cm (Figure 5). In BPD eating capacity is greater than in other
procedures because the volume of gastric pouch is between 300 ml to 500 ml. It is important to maintain proper nutrition, but the malabsorption maintains the weight loss (Resa et al. 2004, Larrad-Jimenez et al. 2007, Crea et al. 2011).

BPD-DS is a metabolic operation very seldom carried out. Incidence is approximately 1.5% of all bariatric and metabolic procedures worldwide (Angrisani et al. 2015). BPD-DS is particularly suitable and successful in extremely obese patients, either as a single or double-staged procedure. Sleeve gastrectomy is usually performed as a first-step operation. In a second-step operation, if needed, the duodenum is transected below the pylorus and the AL is measured 250 cm from the ileo-caecal valve and anastomosed to the proximal part of duodenum. The BPL is anastomosed about 100 cm from the ileo-caecal valve, creating a 100 cm long CC (Figure 6). BPD-DS has the greatest efficacy concerning weight loss but it has also a relatively high rate of short- and long-term complications and mortality. Metabolic complications are usually malnutrition, nutrient- and vitamin deficiencies, increased bowel movements, diarrhea, anastomotic or gastric leaks, anastomotic strictures, internal hernias, and gastroesophageal reflux (Gissey-Mariolo-Mingrone 2016).
2.2.4 Effects of bariatric surgery

2.2.4.1 Effect on cholesterol metabolism and gallstone formation

Gallstones are associated with obesity and rapid weight loss induced by bariatric surgery. The risk of GD increases three-fold when the BMI exceeds 30 kg/m² (Aslar et al. 2003). Rapid weight loss mobilizes cholesterol from tissue stores and increases gallstone risk via increased hepatic secretion of cholesterol in bile, resulting stones and increased mucin, calcium, prostaglandins and arachidonic acid concentration in the gallbladder (Shiffman-Shamburek et al. 1993, Shiffman-Sugerman et al. 1993). A significant decrease in gallbladder emptying and hypomotility may happen after LRYGB, which also contributes to biliary sludge and stone formation (Bastouly et al. 2009), (Figure 7). Another theory is postprandial gallbladder dyskinesia, secondary to decreased circulating CCK levels that occur from the altered anatomy and the exclusion of the duodenum following bariatric surgery (Ahmed et al. 2007). LRYGB results in reduction of CCK levels due to food stream diversion. This may favor bile stasis, incomplete gallbladder contraction, and gallstone formation (Shiffman-Shamburek et al. 1993). LRYGB has major effects on the serum lipid profile, which may also alter cholesterol saturation (Jamal et al. 2011).

Insulin resistance has been reported to be related to impairment in gallbladder motility, especially in ejection function, and bile composition (Biddinger et al. 2008). Insulin resistance increases the cholesterol content of the bile due to a direct increase in gene expression of bile carriers of cholesterol, and decreases the expression of enzymes that synthesize bile acids.
(Biddinger et al. 2008). It is reasonable to hypothesize that the surgery may trigger gallstone formation in this group of subjects exposed to greater risk due to their metabolic disturbance (Cazzo et al. 2016).

The risks of developing gallstones between the different weight reduction procedures may be different. LRYGB adds the risk by altering enterohepatic circulation and normal gallbladder physiology (Li VK et al. 2009). Interestingly, bariatric surgery can predispose patients to cholecystolithiasis even if they have no history of GD (Abdallah et al. 2017). Furthermore, bariatric surgery can cause asymptomatic gallstones to become symptomatic and induce postoperative complications of gallstones (Stender-Nordestgaard-Tybjaerg-Hansen 2013). However, few studies have looked at the effect of the physiological nature of the LSG. Asymptomatic gallstones found before LSG tend to have less risk of becoming symptomatic than those formed after weight loss (Conley et al. 2016).

There are some other well-known risk factors for developing gallstones, such as female sex, aging and metabolic syndrome (Shaffer 2006). Postoperative weight loss of more than 25% at 10 months or 50% at three months is a predictive risk factors for the development of symptomatic gallstones and thus can help selecting patients for postoperative ultrasound surveillance and subsequent LCC once gallstones are identified (Li VK et al. 2009). The incidence is eight times greater in patients with BMI ≥ 40 kg/m² (Teres 1993), and the risk increases especially in patients losing more than 1.5 kg per week (Amaral-Thompson 1985, Brandão de Oliveira-Chaim-Da Silva 2003). After bariatric operation, one-year gallstone formation rates are between 30% and 53%, with incidence of symptomatic stones between 7% and 16% (Shiffman et al. 1991, Li VK et al. 2009, Brandão de Oliveira-Chaim-Da Silva 2003). Most gallstones form during the first 6 to 10 months after the bariatric operation and decrease when weight stabilizes around 24 months (Shiffman et al. 1991). Former observations indicate a significantly higher incidence of gallstone formation or sludge up to 28–71% after bariatric surgery (Melmer et al. 2015). Gallstones develop significantly more often in the white race, and in women. No significant differences in age or BMI exist between patients who developed gallstones or sludge and those who do not. Patients who develop sludge have less cholesterol and lower cholesterol saturation in their gallbladder bile than persons who develop gallstones (Shiffman et al. 1991). However, there are conflicting data reporting that preoperative characteristics seem to be associated with increased weight loss and also post-LRYGB symptomatic GD. These characteristics are younger age, lower BMI, or less obesity-associated comorbidities, such as T2DM, lower fasting glucose, HbA1c or TG concentrations (Ortega et al. 2012, Faria et al. 2013, Faria et al. 2014). Longer obesity evolution, lower insulin levels, and lower hepatic enzymes might be related to the development of symptomatic gallstones, maybe through a surrogate action through rapid weight loss (Morais et al. 2016). A Cochrane review showed that males have 5.4 times increased incidence of LCC after obesity surgery (Colquitt et al. 2005).
2.2.4.2 Effect on weight loss

The superiority of bariatric surgery is recognized worldwide as a cost-effective treatment in terms of weight loss, maintenance of weight loss and remission of comorbidities. Weight loss after bariatric surgery is usually reported as percent of total weight loss (%TWL), percent of excess BMI loss or percent of excess weight loss (%EWL), (Deitel-Dixon 2010, Hatoum-Kaplan 2013). In recent years, the role of different procedures has been revised following the postoperative outcomes from a metabolic and functional point of view. These outcomes have given rise to further possible indications for bariatric procedures that could be applied to non-obese patients with comorbidities in the future (Dixon et al. 2011).

In 2004, Buchwald et al. reported a systematic review and meta-analysis of outcomes of different bariatric procedures. The %EWL following LRYGB was 61.6% and 70.1% after BPD (Buchwald et al. 2004). Different outcomes of BPD and BPD-DS on weight loss have also been reported (Table 4), (Bolckmans-Himpens 2016, Biertho et al. 2016).

In the Swedish Obese Subjects (SOS) Study only a small portion of the patients were treated by gastric bypass and even a smaller portion participated in the 15- and 20-year follow-up.
Those who participated in the follow-up, had a maximal weight loss of 32% after two years, decreasing to 25% at ten years and maintaining this up to 20 years of follow-up (Sjöström 2013). Similar results have also been reported previously (Table 4), (Mehaffey et al. 2016, Käkelä-Torpström et al. 2013). Most patients can expect to lose more than 50% of their excess weight but modest weight regain is not unique to LRYGB.

In 2014, a systematic review of long-term follow-up data from LRYGB and LSG was reported. In this review the mean %EWL was 65.7% after LRYGB at three to five years and 64.5% after LSG at three years (Puzziferri et al. 2014). In a multicenter, retrospective, matched cohort study comparing LRYGB and LSG, the %EWL was 65.1% following LRYGB and 62.5% following LSG at five years (Table 4), (Dogan et al. 2015). Himpens et al. documented a mean %EWL of 72.8% three years after LSG, which decreased to 57.3% after six years (Table 4), (Himpens-Dobbeleir-Peeters 2010). Weight regain appears in LSG between the third and the sixth postoperative year. Diamantis et al. evaluated the long-term weight loss results after LSG and compared them with the short-term and mid-term weight loss results. He found out that the overall mean %EWL at five years after LSG remains about 50% and after eight years still 54.8% (Diamantis et al. 2014). LSG was originally performed as the restrictive part of laparoscopic BPD-DS. Now LSG is recognized as a stand-alone procedure, but direct comparison between the two procedures is still very few. Biertho et al. compared the outcomes of the LSG and laparoscopic BPD-DS on weight loss at three years. He found that EWL was 51% in LSG group and 83% in laparoscopic BPD-DS group at three years (Table 4), (Biertho et al. 2014).

Table 4. Effect of bariatric surgery on weight loss during long-term follow-up.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>1 year (%)</th>
<th>2 year (%)</th>
<th>3 year (%)</th>
<th>5 year (%)</th>
<th>10 year (%)</th>
<th>20 year (%)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>LRYGB</td>
<td>-32</td>
<td></td>
<td></td>
<td>-25</td>
<td>-25</td>
<td></td>
<td>Sjöström 2013</td>
</tr>
<tr>
<td>LRYGB</td>
<td>74 (EWL)</td>
<td></td>
<td></td>
<td>52 (EWL)</td>
<td></td>
<td></td>
<td>Mehaffey 2016</td>
</tr>
<tr>
<td>LRYGB</td>
<td>-25</td>
<td></td>
<td></td>
<td>-23</td>
<td></td>
<td></td>
<td>Käkelä et al. 2013</td>
</tr>
<tr>
<td>LRYGB</td>
<td></td>
<td></td>
<td></td>
<td>65.1 (EWL)</td>
<td></td>
<td></td>
<td>Dogan et al. 2015</td>
</tr>
<tr>
<td>BPD-DS</td>
<td>81 (EWL)</td>
<td>83 (EWL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Biertho et al. 2016</td>
</tr>
<tr>
<td>BPD-DS</td>
<td></td>
<td>83 (EWL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Biertho et al. 2014</td>
</tr>
<tr>
<td>BPD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40.7 (TWL)</td>
<td></td>
<td>Bolckmans 2016</td>
</tr>
<tr>
<td>LSG</td>
<td>72.8 (EWL)</td>
<td>62.5 (EWL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Himpens et al. 2010</td>
</tr>
<tr>
<td>LSG</td>
<td></td>
<td>51 (EWL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dogan et al. 2015</td>
</tr>
<tr>
<td>LSG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Biertho et al. 2014</td>
</tr>
</tbody>
</table>
2.2.4.3 Effect on mortality
An added life expectancy of 6.7 years might be gained with bariatric surgery for a 45 year-old female with T2DM and a BMI of 45 kg/m² (Schauer et al. 2015). Similar results are seen for both men and women in all age groups (Schauer et al. 2015). In a study by Adams et al., a long-term mortality in the surgery group decreased by 40%, as compared with that in the control group (Adams et al. 2007). Cause-specific mortality in the surgery group decreased by 56% for coronary artery disease, by 92% for T2DM, and by 60% for cancer (Adams et al. 2007).

The SOS study has shown that bariatric surgery reduces the number of cardiovascular deaths and lowers the incidence of cardiovascular events (Sjöström et al. 2012). The cumulative overall mortality during a 16-year follow-up was 6.3% in the control group and 5.0% in the surgery group (Sjöström et al. 2007). In a study comparing the general population to the bariatric population, the long-term mortality rates of bariatric patients were significantly improved regardless of bariatric procedure performed. The mean bariatric mortality rate was 2.5% with 8 to 14 years of follow-up, while in general population it was 3.1%. Additionally, perioperative complications did not increase long-term mortality risk (Telem et al. 2015). Specific patient risk factors associated with an earlier time to death were age, male gender, congestive heart failure, rheumatoid arthritis, pulmonary circulation disorders and T2DM (Telem et al. 2015).

Early (less than 30 days) and late (more than 30 days) mortality rates for different procedures are presented in Table 5 (Hutter et al. 2011, Marceau et al. 2007, Biertho et al. 2014). The death rate for LRYGB is 0.2%, whereas open RYGB is 2.1% (Buchwald et al. 2004, Flum et al. 2009). Despite significant early improvements of comorbidities, obesity surgery does not seem to reduce mortality rates until ten years after surgery. In the SOS study, the mortality benefits of weight loss surgery did not become apparent until 13 years after bariatric operation (Sjöström 2013). Same kind of results was noted in the high-risk patient study (Maciejewski et al. 2011). Conclusive data showing a long-term mortality benefits between different procedures are very few. In one Finnish center, early and late postoperative mortality in LRYGB was 0% and in LSG 0% (Käkelä-Torpström et al. 2013). In randomized clinical trials, regardless of the bariatric procedure performed, the early mortality rate was 0.08%, and the late mortality rate was 0.31% (Chang et al. 2014). However, according to Adams et al. the mortality at the 12-year follow-up was 6.2% in LRYGB. It is possible that the combination of psychological problems with over-expectations after surgery may lead to these deaths (Adams et al. 2017).

Table 5. Early and late mortality rates for different bariatric procedures. Adapted from Hutter et al. 2011, Marceau et al. 2007, Biertho et al. 2014.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>&lt;30 days</th>
<th>1 year</th>
<th>3 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>LRYGB</td>
<td>0.2-0.5 %</td>
<td>0.34 %</td>
<td></td>
</tr>
<tr>
<td>LSG</td>
<td>0.1 %</td>
<td>0.21 %</td>
<td></td>
</tr>
<tr>
<td>BPD</td>
<td>1.1 %</td>
<td>0.13 %</td>
<td></td>
</tr>
<tr>
<td>BPD-DS</td>
<td>1.0 %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2.2.4.4 Effect on morbidity

T2DM

In SOS Study, remission of T2DM was achieved in the surgery group after two years of follow-up in 72% of patients and after ten years in 36%, respectively (Sjöström et al. 2004). Within Buchwald’s meta-analysis, T2DM remission occurred in 80% of LRYGB patients and in BPD it was 98% (Buchwald et al. 2004). In 2012, Mingrone et al. presented their results of T2DM remission at 2 years (Mingrone et al. 2012) and Bolckmans et al. at 10 years (Table 6), (Bolckmans-Himpens 2016). Puzziferri et al. presented a systematic review for T2DM in which remission rates were 66,7% for LRYGB (Puzziferri et al. 2014).

Lee et al. organized a randomized controlled trial comparing T2DM resolution in diabetic patients with BMI 25–35 kg/m² undergoing either LRYGB or LSG. They showed that T2DM remission occurred in 93% of patients in the LRYGB group and in 43% of patients in the LSG group at one-year follow-up (Table 6), (Lee et al. 2011). This effect was also noted in another study in patients with BMI ≥ 35 kg/m² (Schauer et al. 2012).

Cho et al. presented their systemic review for T2DM in which T2DM remission rates were similar for LSG and LRYGB over a one-year follow-up (Cho et al. 2015). Biertho et al. presented their remission rates of T2DM in LSG and in BPD-DS (Table 6), (Biertho et al. 2014). Direct comparison between these two procedures are still very few.

Mingrone et al. compared bariatric surgery with the conventional medical treatment of T2DM in obese patients. Five-year outcomes showed surgery to be superior to medical treatment in achieving glycemic control (Mingrone et al. 2015). Bariatric surgery reduces the risk of T2DM by 84% at ten years and by 78% at 15 years compared to conventional treatment (Sjöström 2013). Some studies support the growing consensus on the effectiveness of bariatric surgery also for the non-obese diabetic patients (Dixon et al. 2011).

In 2007 Parikh et al. published research in which they compared the rate of T2DM resolution after different bariatric operations. At one and two years follow-up, the proportion of patients requiring oral diabetic medication was 22% and 13% for LRYGB and 11% and 13% for laparoscopic BPD-DS (Parikh et al. 2007). The proportion of patients requiring insulin at one and two years follow-up was 7% and 13% for LRYGB and 11% and 13% for laparoscopic BPD-DS (Parikh et al. 2007). What is amazing is that despite the large difference in %EWL at the one and two years follow-up between LRYGB and laparoscopic BPD-DS, the rate of resolution of T2DM was equivalent (Parikh et al. 2007). An article reporting the data from one Finnish center showed similar resolution of T2DM in LRYGB. At the one- and ten-year follow-up, the proportion of patients requiring oral diabetic medication was 21% and 19% for LRYGB and patients requiring insulin 6% and 3%, respectively (Käkelä-Torpström et al. 2013).
Table 6. Surgery-induced remission rates of T2DM.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>1 year</th>
<th>2 year</th>
<th>10 year</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>LRYGB</td>
<td>75 %</td>
<td></td>
<td></td>
<td>Mingrone et al. 2012</td>
</tr>
<tr>
<td>LRYGB</td>
<td>93 %</td>
<td></td>
<td></td>
<td>Lee et al. 2011</td>
</tr>
<tr>
<td>BPD-DS</td>
<td>90 %</td>
<td></td>
<td></td>
<td>Biertho et al. 2014</td>
</tr>
<tr>
<td>BPD</td>
<td>95 %</td>
<td></td>
<td></td>
<td>Mingrone et al. 2012</td>
</tr>
<tr>
<td>BPD</td>
<td></td>
<td>87.5 %</td>
<td></td>
<td>Bolckmans-Himpens 2016</td>
</tr>
<tr>
<td>LSG</td>
<td>43 %</td>
<td></td>
<td></td>
<td>Lee et al. 2011</td>
</tr>
<tr>
<td>LSG</td>
<td>56 %</td>
<td></td>
<td></td>
<td>Biertho et al. 2014</td>
</tr>
</tbody>
</table>

Hyperlipidemia

Hypercholesterolemia and hypertriglyceridemia improve significantly due to bariatric surgery. In Buchwald’s meta-analysis, hyperlipidemia improved more than in 70% of patients in all surgical procedures including the mixed bariatric surgery. The maximum improvements were in BPD (99.1%) and in LRYGB (96.9%) (Buchwald et al. 2004). In LSG, 35% of hyperlipidemia resolve one year after the surgery (Hutter et al. 2011), and the resolution was 25% after eight years (Gadiot et al. 2017). In BPD-DS remission rates were 93.3% at ten years follow-up (Bolckmans-Himpens 2016). In a randomized control trial of T2DM patients randomized in medical therapy or bariatric surgery, after 2 years total cholesterol levels were normalized in 27.3% of patients in the medical therapy group, as compared with 100% of those in the LRYGB and BPD groups. Triglyceride levels normalized in 0% after medical therapy, in 85.7% after LRYGB and in 92.3% after BPD. High-density lipoprotein (HDL) levels normalized in 11.1% after medical therapy, in 100% after LRYGB and in 72.7% after BPD (Mingrone et al. 2012). In the SOS study, a significant increase in HDL and a significant decrease in serum TG levels were shown in the bariatric surgery compared to conventional care. No significant difference was found in total cholesterol between groups (Romeo et al. 2012). These results suggest that metabolic parameters should be used to select obese patients for surgery (Sjöström et al. 2012).

NAFLD

NAFLD is the most common reason for chronic liver disease in the Western countries (Musso-Gambino-Cassader 2010). NAFLD covers a wide spectrum of liver pathology from steatosis, through NASH to cirrhosis and liver cancer (Musso-Gambino-Cassader 2010). NAFLD increases the risk of hepatocellular carcinoma and is found in 35% of cases (Dyson et al. 2014). About 2-3% of patients with steatosis develop inflammatory state NASH during five year follow-up (Musso-Gambino-Cassader 2010, Vernon-Baranova-Younossi 2011, Adams et al. 2005). In NAFLD, TG content is over 5-10% in the liver (Chalasani et al. 2012). The population prevalence of NASH in 45-74 year-old Finnish subjects is approximately 5% (Hyysalo et al. 2014). NASH increases liver-related mortality five to six-fold (Matteoni et al. 1999, Rafiq et al. 2009) when comparing to those without NASH.
Higher age is associated with the risk of NAFLD (Amarapurkar et al. 2007, Chen et al. 2007) and based on some other studies NAFLD is more frequent in males (Caballeria et al. 2010, Williams et al. 2011). Previous studies have shown that about 20% of GD patients have NAFLD (Loria et al. 2005, Fracanzani et al. 2012, Roesch-Dietlen et al. 2008) and GD has been proposed to be an independent risk factor for NAFLD (Koller et al. 2012).

Weight loss induced by bariatric surgery has been shown to lead to resolution of NASH in nearly 85% of patients after one year, in addition to significant reductions in mean levels of alanine aminotransferase (ALT), but this varies according to the procedure and the bypassed length of the small bowel (Lassailly et al. 2015). The grade of steatosis (Silverman-Sapala-Appelman 1995), hepatic inflammation (Clark et al. 2005) and fibrosis (Mottin et al. 2005) decrease after bariatric surgery. T2DM is a strong predictor of NAFLD (Williamson et al. 2011, Targher et al. 2007). Surgery decreases insulin resistance, mean levels of ALT and γ-glutamyltransferase (Lassailly et al. 2015).

Effects on other comorbidities

Cardiovascular diseases and hypertension
The SOS study has shown that bariatric surgery reduces the number of cardiovascular deaths and lowers the incidence of myocardial infarction and stroke (Sjöström et al. 2012). The study demonstrated a 44% reduction in the incidence of myocardial infarction at 13 years in obese individuals with T2DM (Romeo et al. 2012). The effect of surgery in reducing myocardial infarction incidence was stronger in individuals with higher serum total cholesterol, TG (Romeo et al. 2012) and with high fasting serum insulin levels at baseline, suggesting that those with dyslipidemia and hyperglycemia should be prioritized (Sjöström et al. 2012). The rate of recovery from hypertension in the surgical group was 34% at 2 years and 19% at 10 years (Sjöström et al. 2004). An article reporting the data from one Finnish center also showed resolution of hypertension in LRYGB. At baseline 59% of patients who underwent LRYGB had hypertension, and after a ten-year follow-up it was 48% (Käkelä-Torpström et al. 2013).

Osteoarthritis
Obese women treated with obesity surgery have a lower 2-year and 6-year incidence of work-restricting pain in the knee and ankle joints than conventionally treated obese women (Peltonen-Lindoos-Torgerson 2003). Bariatric surgery increases physical activity over 2 (Sjöström et al. 2004, Karason et al. 2000) and 10 (Sjöström et al. 2004) years of follow-up.

Obstructive sleep apnea
A randomized trial compared the effect of intensive lifestyle intervention against LRYGB on obstructive sleep apnea. LRYGB had a 66% remission of obstructive sleep apnea rate while the control group had a 40% remission rate. These benefits were directly attributable to weight loss alone (Fredheim et al. 2013). The severity of obstructive sleep apnea could not be reliably predicted by preoperative BMI, but weight loss following LRYGB resulted in profound improvement in obstructive sleep apnea (Rasheid et al. 2003). Obstructive sleep apnea was resolved in 85.7% of patients after surgery (Buchwald et al. 2004). As many as 71% of bariatric
patients may have residual obstructive sleep apnea one year after obesity surgery (Lettieri-Eliasson-Greenburg 2008).

Cancer
Epidemiological studies suggest that the beneficial effect of weight loss on cancer is greater in women than in men (Williamson et al. 1995, Williamson et al. 1999). Obesity surgery is associated with decreased cancer incidence in women (Adams et al. 2009, McCawley et al. 2009) but not in men (Adams et al. 2009). BMI is significantly associated with higher rates of death due to cancer of the esophagus, colon and rectum, liver, gallbladder, pancreas, kidney, non-Hodgkin lymphoma, and multiple myeloma (Pi-Sunyer 2009). Overweight or obesity during early adulthood is associated with a greater risk of pancreatic cancer and a younger age of disease onset, independent of diabetes status (Li D et al. 2009). Obesity at an older age is associated with a lower overall survival in patients with pancreatic cancer, regardless of disease stage and tumor resection status (Li D et al. 2009). In a study by Adams et al. there were 16 (1.4 %) cancer-related deaths in LRYGB and in non-surgery groups during 12 years of follow-up (Adams et al. 2017).

Polycystic ovarian syndrome
LRYGB has been shown to achieve excellent results in amelioration of manifestations of polycystic ovarian syndrome and in improvement in fertility rates in up to 100% (Jamal et al. 2012). In a systematic review and meta-analysis, the preoperative incidence of polycystic ovarian syndrome was 45.6%, and it decreased to 6.8% one year after LRYGB (Skubleny et al. 2016).

Gastroesophageal reflux disease
A systematic review comparing LSG and LRYGB has shown that LRYGB is significantly better at resolving gastroesophageal reflux disease (Li et al. 2014). Disease rates fell from 56% (Li et al. 2014) up to 75% (Peterli et al. 2013) over a 12-month period following LRYGB. Symptoms significantly improve and use of antireflux medications is reduced after LRYGB independent of weight loss (Nelson et al. 2005).

Asthma
Bariatric surgery induced weight loss has a positive impact on asthma symptoms, lung function, need for medication, hyper-responsiveness and inflammation in the airways (Marceau et al. 2007). After bariatric surgery medication for asthma decreases in 88% (Marceau et al. 2007). In a study of bariatric surgery patients with and without asthma, a great improvement was seen in small airway function and systemic inflammation in both groups after bariatric operation (van Huisstede et al. 2015). In the asthma group small airway function, hyper-responsiveness and asthma control improved. However, weight loss did not influence the obstruction of larger airways among asthma patients (van Huisstede et al. 2015).

Urinary incontinence
In a large study, the prevalence of urinary incontinence was 49.3% in women and 21.8% in men before surgery and one year postoperatively it was 18.3% and 9.8%. Three years after obesity surgery the prevalence was higher than one year after surgery for both sexes, but significantly
lower than baseline (24.8% and 12.2%), (Subak et al. 2015). Weight loss and younger age was independently related to urinary incontinence remission (Laungani-Seleno-Carlin 2009).

2.2.4.5 Effect on quality of life
The impact of excess weight on physical health is mostly due to comorbidities but also to decreased physical activity. In the SOS intervention study, health-related quality of life was significantly more improved in the surgery group than in the conventionally treated obese group. The surgery group had more social interaction and better psychosocial functioning due to a greater and more sustained weight reduction. However, no significant differences between these two groups were found for overall mood and anxiety after 10 years (Karlsson et al. 2007). The quality of life improves during the first two years after the surgery with greater improvements in physical than in mental health (Hachem-Brennan 2015). Long term improvement in physical and mental health was found 5 to 25 years after surgery (Driscoll et al. 2016).

2.2.5 Predictors of outcome

2.2.5.1 Clinical characteristics

Weight loss
A key finding of the SOS trial was that high insulin or glucose levels in patients with baseline BMI less than 35 kg/m² predicted a favorable treatment effect of bariatric surgery, whereas higher BMI did not. According to the SOS study, more importance should be given to metabolic variables in selecting patients to bariatric surgery (Sjöström 2013). Analysis of patients BMI ≥ 50 kg/m² revealed significantly greater %EWL in the laparoscopic BPD group than in LRYGB group at 2 years (79% vs 67%), (Nelson-Blair-Martin 2012). The BPD patients achieved better weight control benefits among the superobese. This is why the most appropriate procedure should be tailored based on individual BMI (Gissey-Mariolo-Mingrone 2016). Younger age, lower baseline BMI (Ortega et al. 2012) and male gender (Ma et al. 2006) predict a higher EWL. Preoperative weight loss is also a significant predictor of long-term success following LRYGB (Alger-Mayer-Polimeni-Malone 2008, Alvarado et al. 2005). Several factors have been associated with postoperative weight loss failure, including longer duration of T2DM and older age (Bradley-Magkos-Klein 2012). The influence of age on weight loss is interesting. For example, higher fasting glucose (McLaughlin et al. 2011) levels and higher levels of benzoapyrenes (Irigaray et al. 2006) in adipose tissue decrease lipolysis. This seems to be the most important mechanism behind the difficulty of older people to respond to weight-losing interventions.

T2DM
The risk of developing T2DM approximately doubles with every 5–7.9 kg gain in weight (Chan et al. 1994, Colditz et al. 1995). Obese subjects have a seven-fold risk to develop T2DM compared to normal weight subjects (Smith-Smith 2016). According to SOS study, high insulin
or glucose concentrations at baseline predicted favorable treatment effects (Sjöström 2013, Dixon et al. 2011). In 2009, Buchwald summarized in a systematic review and meta-analysis that clinical and laboratory manifestations of T2DM are resolved or improved in the majority of patients after bariatric procedures, and the responses are associated with a greater %EWL (Buchwald et al. 2009). Younger age, T2DM or higher HbA1c are associated with better results in obesity surgery (Ortega et al. 2012). However, there is also a conflicting data reporting that higher preoperative fasting glucose seems to be associated with a worse weight loss at the one-year follow-up (Faria et al. 2014). Several factors have been associated with treatment failure, including longer duration of T2DM and more severe T2DM requiring insulin therapy before surgery (Bradley-Magkos-Klein 2012).

**Dyslipidemia**
There are some characteristics that predict treatment results. Veilleux suggested that age and hormonal (menopausal) status are independent predictors of hypertriglyceridemia in women (Veilleux et al. 2011). Hainer et al. presented that female sex, age and baseline BMI together with hormones, predicted 49.8% of the variability in weight loss and dyslipidemia (Hainer et al. 2008). According to Ortega et al., higher TG concentrations predict higher EWL and lower risk of a nonsuccessful surgery (Ortega et al. 2012). Campbell et al. found that weight loss significantly lowered serum estrogens and free testosterone regardless of baseline BMI (Campbell et al. 2012). Hyperlipidemia improves in about 70% of patients after surgery (Jammah 2015, Pinheiro et al. 2008). There are several studies that have found that the CC length associates with more than 95% resolution or improvement in obesity-related comorbidities including hyperlipidemia (Buchwald et al. 2004, Søvik et al. 2011, Nelson-Blair-Martin 2012, Stefanidis-Kuwada-Gersin 2011).

### 2.2.5.2 Gut length
An inadequate bypass with a long CC may fail to reach its malabsorptive goal (Gleysteen 2009, Mahawar et al. 2016), while a too short AL and CC may drive the patient to protein-calorie malnutrition in up to 20–25% of LRYGB procedures (Kalfarentzos et al. 2011). Individual total small intestinal length maybe important in predicting the weight loss and resolution of metabolic comorbidities (Stefanidis-Kuwada-Gersin 2011, Pinheiro et al 2008). The flexible elasticity of bowel makes its measurement sometimes rather subjective and variable and there is no recommended standard method for intestinal measurement.

Intestinal growth rates continue at a 7.6% increase in youth to the age of 20 years and a 7.2% decrease until the age of 80 years (Bryant 1924). Older women have a shorter small intestine than older men (Teitelbaum et al. 2013). Gender, age and small intestinal length may be strong predictors of weight (Tacchino 2015). A shorter small intestine could predispose to weight loss. Men have a longer small bowel, a larger body mass and these could predispose to weight gain and older people have difficulties to lose weight (Tacchino 2015). Also, according to Nordgren et al. increased weight is positively associated with the small intestinal length (Nordgren et al. 1997). However, there is conflicting data reporting that age does not correlate with the small intestinal length (Tacchino 2015, Lohsiriwat-Wiangphoem-Lohsiriwat 2014) and patients with increased weight do not have longer small intestine (Teitelbaum et al. 2013). Measuring the
entire small intestine before LRYGB and tailoring the small intestinal limbs according to the BMI, may prevent the risk of nutritional consequences in malabsorptive, revisional, and metabolic procedures (Tacciino 2015).

Limitations of the available literature include variation in the length of the small intestinal limbs, which makes comparison of results between the studies difficult. It is difficult to compare different studies, since the same AL or BPL is considered short in some studies and long in others. Furthermore, the criteria used to determine the length of the limbs vary significantly among surgeons (Savassi-Rocha et al. 2008). A few publications have shown that after LRYGB a short CC, which is 100 cm or less, leads to a resolution of more than 95% of comorbidities with 65% EWL, and this has a better outcome than a long CC, more than 100 cm (Stefanidis-Kuwada-Gersin 2011, Pinheiro et al. 2008). When the length of the CC approaches 100 cm, a significant impact on comorbidities and lipid metabolism, is observed due to malabsorption (Stefanidis-Kuwada-Gersin 2011). A range of 100-200 cm for combined length of BPL or AL gives optimum results with LRYGB in most patients (Mahawar et al. 2016). A long AL of more than one third of the length of the whole small intestine, predicts both early and five-year follow-up weight loss outcomes in superobese (BMI ≥ 50 kg/m²) but not in morbidly obese (BMI < 50 kg/m²) patients (Gleysteen 2009). Choban et al. prefer an AL of approximately one-half of the length of the whole small intestine (Choban-Flancbaum 2002). For patients with a BMI < 50 kg/m², limb-lengths are not as crucial to successful weight loss (Stefanidis-Kuwada-Gersin 2011). When the length of the CC approaches 100 cm, a significant impact on weight loss is observed (Stefanidis-Kuwada-Gersin 2011). Further reduction in the length of the CC may lead to an increased incidence of metabolic and nutritional complications (Choban-Flancbaum 2002). The ratio of the BPL to the total length of the small intestine maybe crucial. In patients with BMI ≥ 60 kg/m², a ratio of > 45% was associated with higher %EWL at 2 and 3 years (Hamoui et al. 2008). In patients with BMI < 60 kg/m², the benefits of a longer BPL diminished during long-term follow-up (Hamoui et al. 2008).

During the first 12 weeks following obesity surgery, T2DM control maybe achieved in 93% of patients with a short CC (1/3 of the total length of the small bowel) and in 58% of patients with a long CC (2/3 of the total length of the small bowel), (Pinheiro et al. 2008). Dyslipidemia was improved in 70% of patients with a short CC, whereas only 57% of the patients with a long CC showed improvement in dyslipidemia (Pinheiro et al. 2008). Nelson et al. found out that dyslipidemia was resolved in 68% of patients with a short CC, whereas only 44% of the patients with a long CC, showed improvement (Nelson-Blair-Martin 2012). In contrast, Valera-Mora et al., suggested that changes in serum lipids in response to surgery are independent of the length of the CC (Valera-Mora et al. 2005). In distal bypass with a short, 100 cm CC, resolution of T2DM reached 94% at the four-year follow-up (Nelson et al. 2006). The %EWL was faster with the short CC but was similar in both groups at 48 months (70% vs 74%) (Nelson et al. 2006).

2.2.5.3 Genetics
Genetic factors play an important role in the regulation of weight and obesity. Genome-wide association studies have identified > 50 genetic loci to be robustly associated with obesity-related traits (Frayling et al. 2007, Scuteri et al. 2007, Willer et al. 2009, Thorleifsson et al. 2009, Loos et al. 2008, Speliotes et al. 2010). The fat mass and obesity associated (FTO) gene was identified in 2007 and it was the first locus unequivocally associated with BMI. The genetic
regulation of body fat distribution involves genetic loci and have influence on BMI (Heid et al. 2010). Sarzynski et al. performed a study estimating the effect of genetic factors on the outcome of the obesity surgery in 1,443 patients (Sarzynski et al. 2011). They tested an association of single nucleotide polymorphisms (SNPs) in 11 obesity candidate genes with obesity-related phenotypes, weight loss and weight regain. However, they found no evidence that these SNPs affect weight regain or weight loss over 6 years of follow-up.

Bandstein et al. demonstrated a significant impact on weight loss two years after LRYGB with two genetic risk scores (GRS) composed of BMI and WHR-associated SNPs (Bandstein et al. 2016). Young patients and patients with lower baseline BMI had the best outcome. These findings suggest the effect of genetic variants on LRYGB, as much as about 1.9 kg/m² average weight loss (Bandstein et al. 2016). Speliotes et al. reported a per-allele impact of 0.17 kg/m² for the strongest BMI-associated SNP, FTO (Speliotes et al. 2010).

Genetic association studies have identified over 100 loci that influence T2DM risk (Fuchsberger et al. 2016). Physiological, epigenomic and gene expression data suggest that the genetic basis of T2DM is largely a consequence of many small effect variants that affect pancreatic islet regulation (Fuchsberger et al. 2016). Putative target genes of T2DM variants have been defined at an increasing number of loci, such as FTO. Each locus, however, contains different molecular and cellular mechanisms through which risk variants functionally contribute to disease (Gaulton 2017). Genetic predictors of T2DM associated with increased insulin resistance and increased risk of T2DM have also been identified (Kilpeläinen et al. 2011). Steemburgo et al. found that the common polymorphism in the FTO gene has been associated with T2DM but it had no predictive value on the outcome after weight loss or weight gain (Steemburgo et al. 2013).

Genetic predictors of dyslipidemia risk have been associated with several genes. More than 25 independent common variants have been found to associate with individual variation in lipid concentrations. Some are found in previously implicated loci, and others are found in loci where genetic variants have not been previously implicated in lipid metabolism (Willer et al. 2008). Family studies suggest that LRYGB was associated with weight loss and improvements in dyslipidemia among patients having an extreme form of central adiposity, T2DM, dyslipidemia and NAFLD (Melvin et al. 2017). About half of the variation in these traits is genetically determined, and the genetic variance was typically larger in females and in younger individuals (Pilia et al. 2006). Despite the heterogeneity in effect sizes the same loci appear to contribute to variance in young and old, and in males and females (Pilia et al. 2006). There is a strong association between coronary artery disease and the impact of most alleles on TG concentrations. However, there are also some alleles that have a strong association with TG concentrations but no significant association with coronary artery disease (Willer et al. 2008). Dyslipidemia is strongly influenced by the genetic constitution of each individual.
3 Aims of the study

The aim of this thesis was to analyze the associations of obesity, cholelithiasis and bariatric and gallbladder surgery on cholesterol, bile, and fatty acid metabolism in the liver and to analyze predictors of surgical outcome. The more specific aims were to:

1. Evaluate the impact of obesity and associated comorbidities on complications after LCC (I)

2. Analyze the association of serum plant sterols and GD in NAFLD after LRYGB (II)

3. Analyze the association of serum TG on the small intestinal length before and after LRYGB (III)

4. Assess whether the 20 loci for BMI and 13 loci for WHR and GRS predict the outcome of obesity surgery (IV)
4 Patients and methods

4.1 MIKKELI STUDY

Patients
In study I, from January 1995 to the end of year 2008 altogether 1581 consecutive patients with symptomatic gallstones underwent LCC in Mikkeli Central Hospital. Preoperative data and operative outcome of the 437 obese patients (302 with BMI 30-35 kg/m² and 135 with BMI ≥ 35.1 kg/m² of which 43 BMI ≥ 40.1 kg/m²) and 1144 non-obese controls (BMI ≤ 29.9 kg/m²) undergoing LCC were compared. Figure 8 shows the comparisons between different study groups.

Methods
During 14 years, 28% of LCCs were performed in the obese patients, 8.5% of the patients had BMI ≥ 35.1 kg/m² and 2.7% had BMI ≥ 40.1 kg/m². Fifteen percent of the LCCs in obese patients was performed because of acute cholecystitis. Comorbidities, age and sex, American Society of Anesthesiologists (ASA) classification and BMI of the patients were recorded. Preoperative routine laboratory tests (including plasma bilirubin, plasma glucose and transaminases), electrocardiography, chest x-ray, and abdominal ultrasound scan were examined in all patients. The results of operative data (elective/emergency operation, duration of operation, bleeding, complications, conversion rate, and number of cholangiographies) were recorded. Postoperative complications were divided into surgical site infections (superficial or deep wound infection), pulmonary (pneumonia, increased pleural fluid, atelectasis), urinary (infections, retention), and bleeding disorders. Acute cholecystitis was diagnosed on the basis of clinical findings, laboratory tests (plasma bilirubin, transaminases and CRP), and abdominal ultrasound. If an acute cholecystitis was diagnosed, an emergency cholecystectomy was usually performed in the same or the following day. In acute cholecystitis, an intravenous infusion of 1.5 g ceftriaxone was also administered 3 times per day for 5 to 6 days. Percutaneous cholecystostomy was not used routinely to delay emergency operation. All removed gallbladders were histologically examined and categorized as acute cholecystitis (including gangrenous type), chronic cholecystitis, or normal gallbladder. Perioperative cholangiogram was performed selectively in LCC, if there was a suspicion of common bile duct stones or unclear anatomy. Patients outcome was assessed by using clinical examination, laboratory tests, and imaging findings (abdominal ultrasound, endoscopic retrograde cholangiopancreatography, computerized tomography, or magnetic resonance imaging) at one month postoperatively.

The definition of T2DM was based on medical history. Type 1 was defined as onset of under age of 30 years and treated initially and subsequently with insulin. The rest were considered to have T2DM (treated with diet only, oral drugs, and/or insulin) and onset after the age of 30 years. Type 1 diabetes and T2DM were joined together in this analysis. Coronary heart disease was recorded based on a history of hospital-verified myocardial infarction and/or chronic heart failure or a history of hospital-treated acute coronary syndrome or drug-imbursement for these
conditions. History of chronic obstructive pulmonary disease was obtained from medical records and mainly classified as having drug reimbursement for bronchial asthma or chronic bronchitis or daily need for medications for these disorders. History of hypertension was based on the use of antihypertensive agents indicated for chronic hypertension. Renal insufficiency was determined by using multiple measurements of serum creatinine (>130 mmol/L).

**Figure 8.** Flow chart for study 1.

### 4.2 KUOPIO OBESITY SURGERY STUDY (KOBS)

**Patients**

The primary study population of this thesis was Kuopio Obesity Surgery Study (KOBS) subjects. It had almost 500 well characterized subjects with detailed liver histology. Patients accepted to LRYGB surgery at Kuopio University Hospital have been recruited to the ongoing KOBS study since 2005 (Pihlajamäki et al. 2012). All patients met the NIH guidelines for bariatric surgery (BMI ≥ 40 kg/m² or ≥ 35 kg/m² with obesity related comorbidity and failed conservative weight loss attempts), (NIH Conference 1991, Kotronen et al. 2007). The exclusion criteria were patients under 18 years old or over 65 years old, severe alcohol or drug abuse, severe eating disorder or severe and active psychiatric disease, active gastric ulcer, disability to understand instructions or other severe disease contraindicating bariatric surgery. Patients were accepted for obesity surgery by a multi-disciplinary team consisting of a specialist in internal medicine, a dietician, an anaesthesiologist, and a bariatric surgeon. All patients were encouraged to follow a very low-calorie diet (VLCD) for 4 weeks preoperatively aiming to 10% weight loss to make the operation technically possible.
In study II, from May 2005 to November 2013 a total of 242 obese individuals were included to the KOBS and LRYGB operation.

In study III, from October 2012 to December 2014 a total of 70 obese individuals were included to the KOBS and LRYGB operation.

In study IV, from May 2005 to April 2011 a total of 163 obese individuals were included to the KOBS. One hundred and fifty-seven patients underwent LRYGB (96%) and six patients underwent LSG (4%).

Methods
In studies II, III and IV fasting blood samples were drawn after 12 hours of fasting before and one year after bariatric operation. Also, histological analysis of liver biopsy to diagnose NAFLD was performed. A standard 60 cm BPL and 120 cm AL was performed in all KOBS subjects. A small gastric pouch was divided from upper part of stomach with linear staplers. The omentum was divided with ultrasound scissors. A standard BPL of 60 cm, measured from the ligamentum of Treitz, was lifted up beside the pouch and a gastro-jejunostomy was created with linear stapler and suturing. A standard AL of 120 cm was measured onward from the gastro-jejunostomy and the jejunojejunostomy was stapled and sutured. The gastro-jejunostomy anastomose was tested with the water air test for leakage. The pathway between the anastomoses was transected.

In study II, the clinical characteristics, previous LCC and the use of cholesterol lowering medication were recorded. Ultrasound of the gallbladder was performed before the operation to diagnose GD. Bile fluid was taken transhepatically from the gallbladder with a fine needle aspiration during the bariatric operation. Associations of GD with serum non-cholesterol sterol to cholesterol ratios, bile and fatty acid metabolism in the liver were analysed. Figure 9 shows the comparisons between different study groups of KOBS. The main comparison was between those with and without GD. Furthermore, we investigated if previous LCC had an effect in those with GD.

In study III, the clinical characteristics and use of cholesterol-lowering medication were recorded. The whole small intestinal length was measured as a sum of BPL, AL and CC. The small intestinal lengths were always measured simultaneously by the same two surgeons in patients undergoing elective LRYGB. Since there is no recommended standard method for intestinal measurement, it was measured according to Isreb et al. (Isreb et al. 2009). This was done step by step. At first, a standard 60 cm BPL and 120 cm AL was made. After this, the CC was measured without any tension or traction along the mesenteric border from the entero-entero anastomosis to ileocecal valve with a laparoscopic Babcock instrument in which the distal 10 cm was marked. Gas pressure was held stable 12 mmHg during the operation. The CC measurement was performed as early in the course of the operation as possible, immediately after bypass. The association of the small intestinal length with the weight, serum cholesterol levels and the mRNA expression of genes participating in the cholesterol and fatty acid metabolism in the liver, were analyzed. Figure 10 shows all the participants of the KOBS and cohort of operated subjects divided to those with the small intestinal length below 700.0 cm, between 700.0-780.0 cm and above 780.0 cm.

In study IV, data for weight regain and medication were collected with a questionnaire sent by mail. Twenty BMI- and 13 WHR-related SNPs were genotyped.
Figure 9. Flow chart for study II.
4.3 CLINICAL METHODS

In studies I, II, III and IV, body weight was recorded using a calibrated weighing scale. It was measured with a 0.1 kg precision. Height was measured to the nearest 0.1 cm. BMI was calculated as weight (kilogram) divided by height (meter) squared. Diabetes was defined by the WHO criteria of diabetes (Alberti-Zimmet 1998).

For study IV, genotypes were coded 0, 1, or 2 according to the number of published BMI-/WHR-increasing alleles (resulting in a score ranging from 0 to 40 for BMI and 0 to 26 for WHR). The combined GRS was created by summing the number of BMI and WHR increasing alleles to estimate the total BMI and WHR increasing effect. The combined GRS was included in the statistical models as a continuous score.

Figure 10. Flow chart for study III.
4.4 LABORATORY METHODS

In study I, preoperative routine laboratory tests were examined in all patients (fasting plasma glucose, plasma bilirubin, transaminases and CRP), but not one year after LCC. In studies II, III and IV fasting plasma glucose, serum insulin, serum TG, serum cholesterol, HDL cholesterol and ALT were analyzed before and one year after LRYGB. Plasma glucose was measured by enzymatic hexokinase photometric assay (Konelab Systems Reagents, Thermo Fischer Scientific, Vantaa, Finland). Glucose tolerance was classified according to the American Diabetes Association criteria (American Diabetes Association 2004) using fasting values. Serum insulin was determined by immunoassay (ADVIA Centaur Insulin IRI, no 02230141, Siemens Medical Solutions Diagnostics, Tarrytown, NY). Cholesterol, HDL cholesterol and TG levels from serum were assayed by standard automated enzymatic methods (Roche Diagnostics, Mannheim, Germany).

In study II, non-cholesterol sterols in serum and bile were measured with gas liquid chromatography in a 50-m capillary column (Ultra 2; Agilent Technologies, Wilmington, DE) using 5α-cholestane as the internal standard (Miettinen 1988). Serum cholesterol precursors squalene, cholestenol, desmosterol, and lathosterol reflect whole-body cholesterol synthesis, whereas serum cholestanol and plant sterols campesterol, sitosterol and avenasterol reflect cholesterol absorption efficiency (Simonen-Gylling-Miettinen 2008). The non-cholesterol sterol values in serum and bile are given as ratios to cholesterol of the same gas liquid chromatography run (10² x mmol/mol of cholesterol).

4.5 HISTOLOGICAL ASSESSMENT OF THE LIVER SAMPLES

In studies II, III and IV liver biopsies were obtained using a Trucut needle (segment IV) (Radiplast AB, Uppsala, Sweden) or with ultrasonic scissors (segment III) during the elective LRYGB from all the patients participating the KOBS study. Histological assessment of NAFLD was performed by one pathologist according to Brunt et al. (Brunt et al. 1999). Chronic hepatitis B and C were excluded using serology if ALT values were elevated prior to surgery. Hemochromatosis was excluded by histological analysis of liver biopsies, and by normal serum ferritin levels in subjects that had elevated serum ALT level.

In study II, bile fluid was taken transhepatically from the gallbladder with a fine needle aspiration during the elective LRYGB.

4.6 LIVER GENE EXPRESSION

In studies II, III and IV, all liver samples for gene expression analysis were immediately frozen in liquid nitrogen. Total RNA from liver tissue was extracted using Tri-Reagent (Applied Biosystems (ABI) Foster City, CA, USA). TruSeq Targeted RNA Expression (Illumina, San Diego, CA, USA) was used for measuring the gene expression levels of genes related to cholesterol, bile acid and lipid metabolism in the human liver according to instructions provided by the manufacturer using MiSeq system (Illumina). Total RNA (150ng) was reverse-
transcribed using the ProtoScript II Reverse Transcriptase (New England BioLabs). Oligo pool targeted regions of interest were hybridized to cDNA. Next, hybridized cDNA was extended by DNA polymerase followed by ligation using DNA ligase. The extension-igation products were amplified with PCR and AMPure XP beads (Beckman Coulter) were used to clean up the PCR products. Equal volumes of the products were pooled together and quantitated with DNA 1000 chip (Agilent Technologies). Finally, the pooled sample was diluted, denatured and sequenced with MiSeq.

4.7 GENOTYPING

In study IV, genomic DNA was isolated from human leukocytes by the salt-precipitation method. DNA was available for 163 patients at baseline. Twenty BMI- and 13 WHR-related SNPs were selected based on previous literature (Speliotes et al. 2010, Heid et al. 2010). The genotyping was completed by the Sequenom iPLEX gold SBE platform. Genotypes of 20 risk SNPs for BMI comprised the following variants: NEGR1 rs2815752, TNNI3K rs1514175, TMEM18 rs2867125, ETV5 rs9816226, GNPDA2 rs10938397, SLC39A8 rs13107325, FLJ35779 rs2112347, NUDT3 rs206936, TFAP2B rs987237, LRRN6C rs10968576, RPL27A rs4929949, BDNF rs10767664, MTCH2 rs3817334, FAIM2 rs7138803, PRKD1 rs11847697, MAP2K5 rs2241423, GPRC5B rs12444979, SH2B1 rs7359397, FTO rs9939609, and MC4R rs571312. Genotypes of 13 risk SNPs for WHR comprised the following variants: TBX15-WARS2 rs984222, GRB14 rs10195252, ADAMTS9 rs12444979, SH2B1 rs7359397, FTO rs9939609, and MC4R rs571312. Genotypes of 13 risk SNPs for WHR comprised the following variants: TBX15-WARS2 rs984222, GRB14 rs10195252, ADAMTS9 rs6795735, LY89 rs1294421, VEGFA rs6905288, RSPO3 rs9491696, HOXC13 rs1443512, ZNRF3-KREMEN1 rs4823006, DNLM3-PIGC rs1011731, LYPLAL1 rs4846567, CPEB4 rs6861681, NFE2L3 rs1055144 and ITPR2-SSPN rs718314.

4.8 STATISTICAL METHODS

Characteristics of the study groups are given as means and standard deviations. P-value less than 0.05 was considered statistically significant. In study I, the data analysis was carried out using SPSS 18.0 for Windows (SPSS, Chicago, IL). In studies II and III statistical analyses were performed using SPSS 19.0 for Windows (SPSS, Chicago, IL) and in study IV, the data analysis was carried out using SPSS 23.0 for Windows (SPSS, Chicago, IL).

In study I, univariate analyses for categorical variables were calculated with the \( \chi^2 \) test and for continuous variables with the Mann-Whitney U test. The odds ratio served as an approximate estimate of relative risk for postoperative complications. Factors associated with postoperative complications were determined in univariate and multivariate binary logistic regression models with a forward selection process. The impact of obesity, diabetes, cholecystitis, coronary heart disease, pulmonary disease, hypertension, and renal insufficiency on the postoperative outcome was analyzed by using multiple logistic regression analysis. The following operative factors and independent coexisting diseases were included in the regression analysis: BMI \( \geq 35.1 \) kg/m\(^2\), ASA classification, diabetes, presence of acute cholecystitis, and other coexisting diseases.

In studies II and III, general linear model univariate analyses were used to study the differences between the study groups (adjusted for sex, BMI and use of statin, when
appropriate). In addition, paired samples T-test was used to assess the significance of changes in response to obesity surgery. For the TREx analysis, the expression levels for each gene per sample in the gene panel were normalized based on the total number of aligned reads of the corresponding sample and the results are shown as percentage of total transcript reads. Independent samples T-test was used to compare gene expression levels between the study groups (statin users were excluded from the analysis) and the changes during the year after surgery.

In study IV, normality of variable distributions was tested with the Kolmogorov–Smirnov test or by plotting the residuals of each statistical test. Logarithmic transformation was used to improve normality when necessary. Genotypes were coded 0, 1, or 2 according to the number of published BMI-/WHR-increasing alleles (resulting in a score ranging from 0 to 40 for BMI and 0 to 26 for WHR). The combined GRS was created by summing the number of BMI and WHR increasing alleles to estimate the total BMI and WHR increasing effect. The combined GRS was included in the statistical models as a continuous score. General linear model univariate analyses were used to study the effect of individual SNPs and the combined GRS on obesity and related traits at baseline and during the changes. In addition, separate analyses for multiple linear regression were used to assess the influence of combined GRS, age, sex, fasting plasma glucose, serum insulin concentrations and NASH diagnosis on the variation of BMI or %EWL change during the first year and on the BMI regain. Logistic regression was used to assess the influence of same variables on T2DM incidence.

4.9 APPROVALS

Studies of this thesis follow the recommendations for biomedical research involving humans (Declaration of Helsinki of the World Medical Association 1964 including the revisions up to Hong Kong 1989 and Edinburgh, Scotland 2000) and a Finnish law concerning information protection. The KOBS project has been approved by the Ethics Committee of the Northern Savo Hospital District (54/2005, 104/2008 and 27/2010). The Ethical Committee of Mikkeli Central Hospital approved the study protocol. All methods have been previously used in humans and are known not to pose an additional risk for the patients. The KOBS population consist of individuals who were eligible for LRYGB and were willing to take part in the study. In Mikkeli Central Hospital all LCCs were performed on the patients with symptomatic GD. The nature and potential risks of the study were explained to all subjects before obtaining their written informed consent.
5 Results

5.1 OBESITY AND COMORBIDITIES DO NOT ELEVATE OPERATIVE RISKS OF LCC (STUDY I)

The finding of study I was that obesity or any of the comorbidities did not associate with an elevated risk for postoperative complications after LCC (Table 7). In symptomatic GD, obesity and obesity-related comorbidities increased the conversion rate, but not the operative risks of LCC (Table 8).

Obese patients undergoing LCC were younger and they were more frequently female. They had also T2DM and a higher ASA classification than non-obese controls. The preoperative mean concentration of glucose, total bilirubin, and transaminases were comparable with obese and non-obese patients, but the mean concentration of C-reactive protein was elevated in obese patients (p= 0.0001). In obese patients with BMI ≥ 40 kg/m², the mean value of C-reactive protein was the highest (113±85 mg/dL).

The total number of complications was not increased with obesity-related comorbidities. There were surgical site infections in 3.7% of obese patients vs in 1.6% of non-obese patients, port hernias in 2.2% vs in 1.0% and bleeding in 0% vs 1.3% of obese vs non-obese patients. Only surgical site infections were significant in obese patients (p=0.0186). Table 8 shows the operative data and outcome of LCC in obese patients and non-obese control subjects.

Table 7. Univariate and multivariate regression analyses of risk factors for complications in laparoscopic cholecystectomy in obese patients.

<table>
<thead>
<tr>
<th>Factors</th>
<th>95% CI</th>
<th>P</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (&gt; 35.1 kg/m²)</td>
<td>-0.148 to 0.065</td>
<td>0.446</td>
<td>0.657</td>
<td>0.215 to 2.010</td>
<td>0.461</td>
</tr>
<tr>
<td>ASA (III-IV)</td>
<td>0.067 to 0.228</td>
<td>0.0001</td>
<td>3.271</td>
<td>1.650 to 6.488</td>
<td>0.010</td>
</tr>
<tr>
<td>Multiple (≥ 2) disease</td>
<td>-0.298 to 0.387</td>
<td>0.798</td>
<td>1.501</td>
<td>0.062 to 36.13</td>
<td>0.803</td>
</tr>
<tr>
<td>Acute cholecystitis</td>
<td>-0.240 to 0.144</td>
<td>0.161</td>
<td>1.714</td>
<td>0.825 to 3.561</td>
<td>0.149</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-0.160 to 0.171</td>
<td>0.946</td>
<td>1.057</td>
<td>0.229 to 4.871</td>
<td>0.944</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>-0.198 to 0.134</td>
<td>0.703</td>
<td>0.761</td>
<td>0.166 to 3.473</td>
<td>0.724</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>-0.227 to 0.106</td>
<td>0.474</td>
<td>0.587</td>
<td>0.118 to 2.926</td>
<td>0.516</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-0.199 to 0.157</td>
<td>0.816</td>
<td>0.847</td>
<td>0.165 to 4.340</td>
<td>0.842</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>-0.227 to 0.699</td>
<td>0.318</td>
<td>2.463</td>
<td>0.128 to 47.49</td>
<td>0.550</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; CI, confidence interval.
Table 8. Operative data and outcome of laparoscopic cholecystectomy in obese patients and non-obese control subjects.

<table>
<thead>
<tr>
<th></th>
<th>Class II-III Obese BMI &gt; 35.1 (kg/m²)</th>
<th>Class I Obese BMI = 30-35 (kg/m²)</th>
<th>Nonobese Controls BMI ≤ 29.9 (kg/m²)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 135 (%)</td>
<td>n = 302 (%)</td>
<td>n = 1144 (%)</td>
<td></td>
</tr>
<tr>
<td>Conversion rate</td>
<td>20 (15)</td>
<td>31 (10)</td>
<td>70 (6.1)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Mean operative time (min ± SD)</td>
<td>88 ± 42</td>
<td>80 ± 40</td>
<td>73 ± 36</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mean bleeding (mL ± SD)</td>
<td>86 ± 140</td>
<td>60 ± 140</td>
<td>40 ± 90</td>
<td>NS</td>
</tr>
<tr>
<td>Mean hospital stay (d ± SD)</td>
<td>4.4 ± 2.3</td>
<td>4.4 ± 3.1</td>
<td>4.1 ± 2.5</td>
<td>NS</td>
</tr>
<tr>
<td>Cholecystectomy rate</td>
<td>4 (3.0)</td>
<td>12 (4.0)</td>
<td>32 (2.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Cholangiography rate</td>
<td>24 (18)</td>
<td>74 (25)</td>
<td>266 (23)</td>
<td>NS</td>
</tr>
<tr>
<td>No. reoperations</td>
<td>2 (1.5)</td>
<td>5 (1.7)</td>
<td>17 (1.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Operative complications</td>
<td>15 (11)</td>
<td>40 (13)</td>
<td>131 (11)</td>
<td>NS</td>
</tr>
<tr>
<td>Surgical site infection</td>
<td>5 (3.7)</td>
<td>12 (4.0)</td>
<td>18 (1.6)</td>
<td>0.0186</td>
</tr>
<tr>
<td>Port hernia</td>
<td>3 (2.2)</td>
<td>4 (1.3)</td>
<td>11 (1.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
<td>7 (0.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0 (0)</td>
<td>2 (0.7)</td>
<td>15 (1.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>6 (4.4)</td>
<td>22 (7.3)</td>
<td>80 (7.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Mortality</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (0.2)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Percentages are presented in parenthesis.
BMI indicates body mass index.

5.2 ASSOCIATION BETWEEN SERUM PLANT STEROLS AND GALLSTONE DISEASE (STUDY II)

The main finding of the study II was that serum plant sterols campesterol (p=0.003), sitosterol (p=0.002) and avenasterol (p=0.015) were lower in patients with GD than in those without GD. Serum plant sterols were lower in patients with GD independent of NAFLD, history of LCC or use of statin medication. Levels of sitosterol (p=0.001) and campesterol (p=0.001) remained lower in obese individuals with GD also after obesity surgery. Figure 11 shows the comparison of serum sitosterol and campesterol values in study groups divided by the presence of GD at baseline (panel A) and at one-year follow-up (panel B) after obesity surgery. In addition, there was no difference in liver histology between those with and without GD.
**Figure 11.** Serum sitosterol and campesterol values ($10^2$ mmol/mol of cholesterol) in study groups divided by the presence of gallstone disease (GD) at baseline (panel A) and at 1-year follow-up (panel B) after the obesity surgery. Those with GD have also been divided into those who have and have not been operated with laparoscopic cholecystectomy (LCC). General linear model, adjusted for sex, body mass index and use of statin medication. * P<0.05, ** P<0.01. Data is presented as mean±standard deviation.

### 5.3 SMALL INTESTINAL LENGTH ASSOCIATES WITH SERUM TRIGLYCERIDES BEFORE AND AFTER LRYGB (STUDY III)

The findings of study III were that female sex (p=0.006), serum TG (p=0.016), serum ALT (p=0.007) and liver steatosis (p=0.001) associated with the small intestinal length at baseline (Table 9). Association remained significant between levels of serum TG and CC length (p=0.048) at one-year follow-up (Table 10).
Table 9. Characteristics of the study subjects divided to tertiles by the small intestinal length at baseline.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Small intestinal length</th>
<th>P value*</th>
<th>Adjusted P value **</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=23</td>
<td>n=23</td>
<td>n=24</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>1/22</td>
<td>4/19</td>
<td>10/14</td>
</tr>
<tr>
<td>Age (years)</td>
<td>46.8±10.6</td>
<td>48.5±9.7</td>
<td>48.1±9.7</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>41.8±4.5</td>
<td>42.3±4.0</td>
<td>41.5±4.6</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L)</td>
<td>5.7±1.0</td>
<td>6.4±2.8</td>
<td>6.5±1.7</td>
</tr>
<tr>
<td>Fasting serum insulin (pmol/L)</td>
<td>15.1±9.2</td>
<td>14.0±8.2</td>
<td>20.4±16.8</td>
</tr>
<tr>
<td>Total serum cholesterol (mmol/L)</td>
<td>4.4±0.8</td>
<td>4.2±0.9</td>
<td>4.3±1.0</td>
</tr>
<tr>
<td>Serum triglycerides (mmol/L)</td>
<td>1.3±0.7</td>
<td>1.2±0.5</td>
<td>1.7±0.7</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.3±0.4</td>
<td>1.2±0.3</td>
<td>1.1±0.3</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>33.7±19.8</td>
<td>30.1±13.0</td>
<td>55.3±35.8</td>
</tr>
<tr>
<td>Steatosis grade (n)</td>
<td>22</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td>&lt;5%</td>
<td>14</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>5-33%</td>
<td>6</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>33-66%</td>
<td>1</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>&gt;66%</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Lobular inflammation (n)</td>
<td>22</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>None</td>
<td>16</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>&lt;2 foci per 200x field</td>
<td>6</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>2-4 foci per 200x field</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>&gt;4 foci per 200x field</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fibrosis stage (n)</td>
<td>22</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td>0</td>
<td>17</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ballooning (n)</td>
<td>22</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td>None</td>
<td>18</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Few balloon cells</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Many cells/prominent</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Liver phenotype (n)</td>
<td>18</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Normal liver</td>
<td>14</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Simple steatosis</td>
<td>2</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>NASH</td>
<td>2</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

*One-way ANOVA over all study groups. **Adjusted variables between all groups sex, BMI and statin use. Mean±SD shown. P values <0.05 are bolded.

ALT = serum alanine aminotransferase. NASH = nonalcoholic steatohepatitis.
Table 10. Characteristics of the study subjects divided by the top tertiles by the CC length at one-year follow-up.

<table>
<thead>
<tr>
<th></th>
<th>Follow-up</th>
<th>*P value</th>
<th>Adjusted P value**</th>
<th>P value*** group 1 vs 2</th>
<th>P value*** group 2 vs 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>&lt;520.0 n=23</td>
<td>520.0-600.0 n=23</td>
<td>&gt;600.0 n=24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>1/22</td>
<td>4/19</td>
<td>10/14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.8±10.6</td>
<td>49.5±9.7</td>
<td>49.1±9.7</td>
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<td>Body mass index (kg/m²)</td>
<td>32.6±5.0</td>
<td>31.5±4.2</td>
<td>31.8±4.0</td>
<td>0.688</td>
<td>0.210</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L)</td>
<td>5.6±0.9</td>
<td>5.4±0.8</td>
<td>5.3±0.5</td>
<td>0.454</td>
<td>0.086</td>
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<td>Fasting serum insulin (pmol/L)</td>
<td>7.0±4.9</td>
<td>5.7±3.4</td>
<td>7.6±6.1</td>
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<td>Total serum cholesterol (mmol/L)</td>
<td>4.6±0.7</td>
<td>4.2±0.8</td>
<td>4.4±0.7</td>
<td>0.244</td>
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<td>Serum triglycerides (mmol/L)</td>
<td>1.0±0.5</td>
<td>1.0±0.4</td>
<td>1.3±0.5</td>
<td>0.048</td>
<td>0.085</td>
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<td>HDL cholesterol (mmol/L)</td>
<td>1.8±0.4</td>
<td>1.6±0.4</td>
<td>1.4±0.4</td>
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<td>ALT (U/L)</td>
<td>30.0±28.5</td>
<td>27.7±13.6</td>
<td>40.1±39.0</td>
<td>0.316</td>
<td>0.258</td>
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</tbody>
</table>

*One-way ANOVA over all study groups. **Adjusted variables between all groups sex, BMI and statin use. ***Independent samples T-test between study groups.
5.4 GENETIC RISK SCORE DOES NOT PREDICT THE OUTCOME OF LRYGB (STUDY IV)

The main finding of study IV was that GRS (p =0.916) did not predict weight loss after LRYGB while BMI below 45 kg/m² at baseline (p =0.0005) predicted greater %EWL (Figure 12). GRS did not associate with weight, BMI, EWL, fasting plasma glucose or serum insulin levels at baseline or at the one-year follow-up. In addition, GRS did not predict weight regain after the one-year follow-up.

![Figure 12](image-url)

*Figure 12. The association of age (a), body mass index (b) and genetic risk score (c) with percentage of excess weight loss during the one-year follow-up (independent samples t-test).*
6 Discussion

6.1 PATIENTS AND METHODS (STUDY I-IV)

The KOBS cohort was the primary study population in this thesis. In studies II-IV we had altogether almost 500 well-characterized subjects with detailed liver histology, clinical and laboratory measurements, taken at baseline and one-year after bariatric surgery. This cohort provided a large prospective study population to investigate the associations of obesity, cholelithiasis, and bariatric and gallbladder surgery on cholesterol, bile and fatty acid metabolism in the liver and to analyze predictors of outcome. In addition, control measurements one year after the bariatric operation provided the opportunity to investigate changes associated with the improvement in these comorbidities and parameters. Since individuals in KOBS were all obese, results cannot be generalized to normal weight subjects. The KOBS cohort was an optimal population for this thesis and gave an opportunity to compare results within the same BMI range and age.

In studies II-IV, all the patients were on a VLCD for 4 weeks before the operation. This could have had an affect on the results in studies II-IV, since it is possible that this had beneficial effects on the serum lipid composition and serum TG levels preoperatively. VLCD also decreases liver fat content and liver size (Yki-Järvinen 2005). However, it is important to notice that despite the preoperative VLCD, the associations between GD and sterol metabolism in study II cannot be explained by the preoperative VLCD. Also, the significant alterations in serum TG remained at follow-up in study III and IV.

In addition, in study II 29% (n = 71) and in study III 20% (n=14) of individuals used cholesterol lowering medication (statins), before the operation. Statins have the ability to inhibit cholesterol synthesis in liver and to diminish cholesterol concentration in bile (Smit et al. 1992). However, we carefully adjusted all our analyses, in studies II and III by the use of statins to control for this effect, although the use of statins did not significantly differ between the study groups. Thus, the associations between GD and sterol metabolism in study II and associations between small intestinal length and TG levels in study III cannot be explained by the use of statins. Several studies have reported a significant reduction in the incidence of symptomatic GD in patients using statin therapy (Cariati-Piromalli 2012).

In studies II-IV, liver biopsy was used for diagnosing NAFLD. Liver biopsy is the gold standard for the diagnosis of NAFLD (Nalbantoglu-Brunt 2014) and thus the optimal method was used. However, liver biopsy presents only a small amount of the liver, which makes limitations for histological analysis. Nonetheless, a better option for diagnosis is not available and multiple biopsies are usually not done, because of the risk of complication (Piccinino et al. 1986). Liver biopsies offered unique opportunities also for analyses other than standard histological evaluation. This included liver gene expression, which gave essential information about metabolic pathways when combined with other results. Furthermore, the possibility to measure liver total cholesterol content and bile metabolism gave deeper understanding about cholesterol metabolism.
The Mikkeli cohort was a larger cohort including 1581 very well characterized individuals operated with LCC during 14 years at Mikkeli Central Hospital. Individuals in the Mikkeli cohort were mostly moderately obese, but there was also a big non-obese, lean control group. Therefore, results may be generalized to normal weight subjects.

6.2 IMPACT OF OBESITY AND COMORBIDITIES ON OPERATIVE RISKS OF LCC (STUDY I)

LCC in obese patients has sometimes been associated with increased operative difficulty and postoperative complications (Ammori et al. 2001, Sidhu et al. 2007, Chang et al. 2009, Simopoulos et al. 2005). In study I, the number of postoperative complications was not increased with obesity-related comorbidities, supporting the view that LCC is a safe procedure in obese patients. Obesity is likely to cause a three to eight times greater risk for symptomatic GD (Aslar et al. 2003) and subsequent requirement for LCC and even for conversion (Bell-Allbright 2007). Our study suggested that, in symptomatic GD, obesity and related comorbidities increase the conversion rate, but not the operative risks of LCC. Obesity is associated with increased cardiopulmonary disease and anesthetic complications during surgery (Eichenberger et al. 2002, Hussien et al. 2002). Obese patients undergoing laparoscopic surgery are at risk for intraoperative adverse effects related to use of CO2 pneumoperitoneum (Hirvonen et al. 2000). LCC in obese patients is also technically more demanding because of enlarged fatty liver. Situation is similar in obesity surgery because of enlarged fatty liver and visceral fat.

In our study, obesity was associated with an increased conversion rate. Some previous studies have suggested that significant independent predictive factors for conversion also include obesity, acute cholecystitis, increasing age, male sex and gallbladder wall thickness (Ibrahim et al. 2006, Pavlidis et al. 2007, Lipman et al. 2007). Our study suggested that obese patients undergoing LCC were younger, more frequently of female sex, and diabetic, and they had a higher ASA classification than non-obese controls. Previous studies have reported that metabolic syndrome and T2DM are likely to cause an elevated risk for symptomatic GD and subsequent requirement for LCC (Bell-Allbright 2007). About 25% of T2DM patients have GD, and one fifth of those undergo LCC at some point (Pagliarulo et al. 2004). Comorbidities occurred more frequently in obese patients than in non-obese subjects. There are no prospective randomized studies comparing laparoscopic with open cholecystectomy in obese patients, because such a study would face ethical problems and difficulty with recruitment. Also, there would be exactly the same problems with enlarged fatty liver and visceral fat, which would cause even more difficulties in open surgery. Laparoscopic approach is the gold standard in obese patients, because of obesity itself (Ammori et al. 2001, Sidhu et al. 2007, Chang et al. 2009, Simopoulos et al. 2005).

Study I supported the concept that LCC was a safe procedure in obese patients and the number of postoperative complications was not increased with comorbidities. There is no gold standard for the management of gallstones in LRYGB. There are studies for and against of LCC. Bariatric surgery can predispose obese patients to cholecystolithiasis even if they have no history of GD (Abdallah et al. 2017). After bariatric operation, one-year gallstone formation
rates are between 30% and 53%, with an incidence of symptomatic stones of almost 16% (Shiffman et al. 1991, Li VK et al. 2009, Brandão de Oliveira-Chaim-Da Silva 2003). Most gallstones form during the first 6 to 10 months after LRYGB, and new gallstone formation decreases when weight stabilizes around 24 months (Shiffman et al. 1991). Earlier observations indicate a significantly higher incidence of gallstone formation or sludge up to 71% after LRYGB (Melmer et al. 2015). Furthermore, bariatric surgery can cause asymptomatic gallstones to become symptomatic and to induce postoperative complications of gallstones, eventually leading to LCC (Stender-Nordestgaard-Tybjaerg-Hansen 2013). The management of gallstones in obese patients should not be different from normal-weight patients. Therefore, performing LCC only in symptomatic patients is an effective approach and asymptomatic gallstones should not be treated at the time of bariatric surgery (Morais et al. 2016).

In a large cohort study from the United States, the T2DM cohort had a 1.91-fold greater risk of biliary disease than non-diabetic controls (Noel et al. 2009). Our study indicated that obesity with T2DM did not predispose to higher risk for complications after surgery. Some previous studies concluded that LCC in the obese is a safe, feasible and efficient operation (Lipman et al. 2007, Vollmer-Callery 2007). In our study, the only factor that significantly increased postoperative morbidity in multivariate regression analysis, was an elevated ASA classification of the patients.

In our study, 1581 LCCs were performed with no transection of common bile duct. In obese patients, the conversion rate was 8.7% in elective operations, compared with 50% in acute emergency operations. In studies carried out 10-15 years ago, biliary injuries were found to occur three times more often when LCC is performed for acute cholecystitis than during elective LCC, and twice as often compared with open cholecystectomy for acute cholecystitis (Khan et al. 2007, Aslar et al. 2003, Vollmer-Callery 2007). Nowadays worldwide reported incidence of major biliary injuries in LCC seems to have stabilized between 0.3% and 0.55% (Karaniakas et al. 2016). A major difficulty in acute cholecystitis is altered anatomy, because of the inflammation in tissues and the amount of visceral fat.

Limitations of this study include insufficient data collection in terms of determining minor postoperative complications, such as wound infections.

### 6.3 ASSOCIATION OF SERUM PLANT STEROLS AND GALLSTONE DISEASE AFTER LRYGB (STUDY II)

The regulation of cholesterol synthesis and transport, mediated by the ATP-binding cassette G5/8 (ABCG5/8) and Niemann-Pick C1-like 1 (NPC1L1) proteins, is key for whole body cholesterol homeostasis. Genetic defects of proteins involved in these processes can distort the overall cholesterol balance, resulting in gallstones (Krawczyk et al. 2012). Obesity surgery and weight loss mobilize cholesterol from tissue stores and increase gallstone risk via increased hepatic secretion of cholesterol into the bile, resulting in stones in the gallbladder (Shiffman-Shamburek et al. 1993). There is a strong connection between GD and NAFLD (Loria et al. 2005, Fracanzani et al. 2012, Roesch-Dietlen et al. 2008). Interestingly, previous studies demonstrate that LCC changes bile metabolism and LCC is independently associated with a significant increase in NAFLD (Ruhl-Everhart 2013).
The most important finding in study I was that serum plant sterols were lower in patients with GD independent of NAFLD, history of LCC, use of statin medication and weight loss after LRYGB. Low serum plant sterols in patients with GD suggest potentially inherited alterations in sterol absorption and biliary transport.

In study II, levels of serum sitosterol and campesterol remained low after obesity surgery in those with GD despite a significant decrease in both weight and serum plant sterols in response to surgery, as published before by our group (Pihlajamäki et al. 2010). This suggested an association of GD with low serum plant sterols independent of obesity. Furthermore, the association of low sitosterol and campesterol with GD was not explained by previous LCC, known to change bile metabolism (Barrera et al. 2015). Our findings that low plant sterol levels in individuals with GD were observed both before and after obesity surgery, in those with and without previous LCC, and independent of NAFLD, support the conclusion that cholesterol and plant sterol metabolism are primarily altered in GD. These results are in line with the results from Krawczyk et al. (Krawczyk et al. 2012) who also found that serum sterols were lower in patients with GD compared to those without GD. These results also support the idea that low levels of serum plant sterols are related to GD itself, potentially partly due to genetic regulation by ABCG5/8 genes (Renner et al. 2013, Buch et al. 2007, Grunhage et al. 2007, Lammert-Wang 2005).

Lower weight and female sex associated with GD in our study. This is mainly in line with the study by Shaffer et al. who suggested that the risk factors for GD has been associated with obesity, female sex, aging, metabolic syndrome and rapid weight loss (Shaffer 2006).

We further investigated the role of sterols transporters in GD. We investigated the liver mRNA expression of genes regulating sterol export, cholesterol metabolism and bile metabolism. Enhanced hepatic protein expression of ABCG5/8 has been described in individuals with GD (Jiang et al. 2008), and functional studies have demonstrated that biliary cholesterol secretion correlates with hepatic expression of ABCG5/G8 (Kosters et al. 2003, Kamisako-Ogawa 2003). Accordingly, we found an increased expression of ABCG8 in those with GD. The increased expression of genes regulating cholesterol synthesis is also in line with previous observations reporting increased cholesterol synthesis in GD (Krawczyk et al. 2012, Liew et al. 2008). The increased expression of proprotein convertase subtilisin/kexin type 9 (PCSK9), encoding a protein regulating LDL receptor levels, in individuals with GD could theoretically contribute to elevated cholesterol levels. Despite the increase in expression of ATP-binding cassette, sub-family B member 11 (ABCB11) and ATP-binding cassette, sub-family C member 2 (ABCC2) we did not observe any association of GD with bile plant sterols, contrary to what was published before that bile plant sterols are increased in those with GD (Krawczyk et al. 2012).

We adjusted our analysis by the use of statins, although the use of statins did not significantly differ between the study groups in our study. Thus, the associations between GD and sterol metabolism in our study cannot be explained by the use of statins. We adjusted by statin use because statins inhibit cholesterol synthesis in liver, which will diminish cholesterol concentration in bile (Smit et al. 1992). Several studies have reported a significant reduction in the incidence of symptomatic GD in patients using statin therapy (Cariati-Piromalli 2012). Previous studies have shown that about 20% of GD patients have NAFLD (Loria et al. 2005, Fracanzani et al. 2012, Roesch-Dietlen et al. 2008). However, we found that there was no
difference in liver histology between those with and without GD, suggesting that any differences between the groups in serum sterols are not related to NAFLD.

Our study has some limitations. We acknowledge that heterogeneity between the individuals may exist and that our sample size was too small to study potential differences in sterol metabolism between individuals with different risk factors for GD (e.g. in men and women separately). Specifically, we acknowledge that our study is too small to properly investigate the potential modifying role of genetic ABCG5/8 variants in the association between GD and sterol metabolism. On the other hand, the strength of our analysis was that we had a detailed metabolic characterization, liver histology and mRNA analysis and perioperative bile fluid samples.

6.4 THE EFFECT OF THE SMALL INTESTINAL LENGTH ON SERUM TRIGLYCERIDE LEVELS BEFORE AND AFTER LRYGB (STUDY III)

The most important finding in study III was that the small intestinal length regulates TG metabolism before and after LRYGB. Therefore, modification of the length of bypassed small intestine based on measured total small intestinal length could optimize the outcomes of the elective LRYGB. The mechanism remains open but could be linked with alterations in lipid absorption. We suggest that the length of the total small intestine should be considered to measure routinely during the bariatric operation with special consideration to the ratio of bypassed lengths.

The length of the CC is not routinely measured during LRYGB, and therefore the length of the whole small intestine remains unknown. Currently, the data of the normal length of the whole small intestine are mostly based on old cadaver studies (Chewal 1995, Evers 1999, Guzman et al. 1977). Limitations of the available literature also include variation in length of the small intestinal limbs, which makes comparison of results between the studies unreliable. It is difficult to compare different studies, since in some studies the same AL or BPL is considered short and long in others. Furthermore, the criteria used to determine the length of the limbs vary significantly among surgeons (Savassi-Rocha et al. 2008). Very few studies compare the ratio of the AL+BPL to the length of the CC, and their impact on resolution of comorbidities. A few publications have shown that after LRYGB a short CC, which is 100 cm or less, leads to a resolution of more than 95% of comorbidities with 65 %EWL, and this has a better outcome compared to the long, more than 100 cm, CC (Stefanidis-Kuwada-Gersin 2011, Pinheiro et al. 2008). When the length of the CC approaches 100 cm, a significant impact on comorbidities and lipid metabolism, is observed due to malabsorption (Stefanidis-Kuwada-Gersin 2011).

Our aim was to investigate if the different length of the whole small intestinal length is associated with NAFLD and lipid metabolism at baseline, and if the length of the CC is associated with weight loss and changes in lipid metabolism in response to surgery. First, we found that the small intestinal length was longer among women. Second, we also found that the weight loss was equal despite the length of the CC, as reported before (Hosseinpour-Behdad 2008). Third, we found that serum TG levels associated with the small intestinal length before and the length of the CC after LRYGB, suggesting that the small intestinal length regulates lipid metabolism, as published before (Buchwald et al. 2004, Søvik et al. 2011, Nelson-Blair-Martin...
2012). Finally, there was a difference in liver steatosis between groups with different baseline small intestinal length, suggesting that the small intestinal length also associates with NAFLD. It is important to note that CC length after surgery was variable between the study groups, while the length of the AL and BPL was the same in every group. Therefore, the differences between the study groups after the surgery are likely to be due to different lengths of the CC. Small bowell length did not predict the outcome of obesity surgery at one-year follow-up since the weight loss was equal despite the length of the small intestine.

Hyperlipidemia improved in about 70% of patients after surgery in our study, which is in line with previous studies (Jammah 2015, Pinheiro et al. 2008). Importantly, we demonstrated that small intestinal length before and the CC length after the LRYGB associated with serum TG levels. Earlier Pinheiro et al. found out that dyslipidemia was improved in 70% of patients with a short CC (1/3 of the total length of the small bowel), whereas only 57% of the patients with a long CC (2/3 of the total length of the small bowel), showed improvement in dyslipidemia (Pinheiro et al. 2008). Nelson et al. found that dyslipidemia was resolved in 68% of patients with a short CC, whereas only 44% of the patients with a long CC showed improvement (Nelson-Blair-Martin 2012). In contrast, Valera-Mora et al. (Valera-Mora et al. 2005), suggested that changes in serum lipids in response to surgery are independent of the length of the CC. Together, these earlier findings and our results suggest that the small intestinal length regulates lipid absorption, and thus also regulates the levels of serum TG after obesity surgery. Furthermore, our study suggests that more beneficial effects on serum TG levels could be achieved by constructing a shorter CC from the total small intestinal length, as proposed by Pinheiro et al (Pinheiro et al. 2008). Thus, our findings suggest that instead of constructing the standard bypass, the ratio of the bypassed AL+BPL vs CC length should be 2/3 vs 1/3 of the total length of the small bowel when better control of dyslipidemia is aimed for. This requires that the length of the total small intestine be measured peroperatively when constructing a gastric bypass, as was done in our study.

Liver mRNA expression of genes regulating cholesterol synthesis and bile metabolism did not associate with the baseline small intestinal length, suggesting that the small intestinal length does not affect liver histology. Genetic predictors of dyslipidemia risk has been identified and associated with several genes, and more than 25 independent common variants have been found to associate with individual variation in lipid concentrations. Family studies suggest that in many populations, about half of the variation in these traits is genetically determined and the genetic variance was typically larger in females and in younger individuals (Pilia et al. 2006). Despite the heterogeneity in effect sizes the same loci appear to contribute to variance in young and old, and in males and females (Pilia et al. 2006).

Our study has limitations. KOBS subjects were instructed to follow a preoperative VLCD for 4 weeks. This likely had beneficial effects on the serum lipid composition and serum TG levels preoperatively. VLCD also results in significant reduction in liver fat content and in liver size (Yki-Järvinen 2005). It is important to note that even though the liver fat content probably decreased during the preoperative VLCD, there were still significant beneficial alterations in serum TG levels at follow-up, suggesting an effect independent of preoperative diet. We also acknowledge that heterogeneity between the individuals may exist and that our sample size was too small to study potential differences in lipid metabolism between individuals with different CC length. Moreover, small intestinal length associated with the gender, but the study groups were not balanced with respect to gender distribution. However, we carefully adjusted
the analysis for gender to control this effect. Follow-up time was short. Unfortunately, follow-up liver biopsy was not available, because of the risk of complications (Piccinino et al. 1986). Despite the limitations, the strengths of our study include detailed metabolic characterization, liver histology and mRNA analysis.

6.5 GENETIC RISK SCORE IN PREDICTING THE OUTCOME OF LRYGB (STUDY IV)

Genetic factors play an important role in the regulation of weight and development of obesity. A reliable method of profiling patients preoperatively to predict the outcome of obesity surgery has not been established (Alger-Mayer-Polimeni-Malone 2008, Livhits et al. 2012, Kadieli et al. 2012, Alvarado et al. 2005). In our study, we found that the GRS does not predict weight loss after LRYGB while lower baseline BMI predicted the greater weight loss.

We evaluated the benefit of using a combined GRS of SNPs known to influence BMI and WHR in predicting the outcome of LRYGB. We found that GRS did not predict weight loss at baseline or weight regain during a mean 3.1-year follow-up. Each locus, however, contains different molecular and cellular mechanisms through which risk variants functionally contribute to disease (Gaulton 2017). Sarzynski et al. presented similar results suggesting that there was no evidence that obesity-predisposing SNPs in FTO or other obesity candidate genes would affect weight loss or weight regain over six years of follow-up. Of the 11 SNPs, only FTO rs16945088 associated with maximum weight loss but it was after GB, not LRYGB (Sarzynski et al. 2011).

Furthermore, we observed that lower BMI (BMI ≤ 45kg/m²) at baseline predicted greater %EWL after LRYGB. Because preoperative BMI predicted weight loss, our results imply that clinical phenotype is a better predictor of the outcome than the known genetic risk factors for obesity. Our findings are consistent with most previous studies suggesting that lower preoperative weight predicts better weight loss in study populations relatively similar to our study (Alger-Mayer-Polimeni-Malone 2008, Livhits et al. 2012, Kadieli et al. 2012, Alvarado et al. 2005, Ma et al. 2006, Biertho et al. 2003, Magro et al. 2008, Ortega et al. 2012). The decreases in weight (24%), BMI (23%) and %EWL (55%) during the first year were also very similar to the SOS study (Sjöström et al. 2007) and to meta-analyses (Buchwald et al. 2009, Pories et al. 1995, Maggard et al. 2005). According to the SOS study, bariatric operation with baseline BMI ≤ 35 kg/m² in patients with high insulin or glucose, predicted a favorable treatment effect, whereas higher BMI did not (Sjöström et al. 2007).

We also analyzed the role of different factors on the prediction of weight loss and weight regain after LRYGB using multiple linear regression analysis. In the multiple linear regression analysis, age explained the variance of EWL during the first year but did not predict weight loss. Study of Sarzynski et al. reported similas results. In his study, obesity-related phenotypes did not predict weight loss or weight regain (Sarzynski et al. 2011). This is in contrast with some previous studies suggesting that younger age predicts greater weight loss (Ma et al. 2006, Ortega et al. 2012, Bradley-Magkos-Klein 2012).

We also investigated the factors predicting T2DM. Fasting plasma glucose, age and fasting serum insulin associated with T2DM prevalence at baseline, as expected. Baseline fasting
plasma glucose concentration also associated with T2DM prevalence at one-year follow-up. None of the baseline variables (baseline fasting plasma glucose, serum insulin, age, combined GRS, baseline BMI, sex and NASH) associated with T2DM prevalence at the last follow-up (1.58±1.27 years). According to the study by Mingrone, preoperative BMI, weight loss, age, sex and duration of T2DM were not significant predictors of T2DM remission at 2 years (Mingrone et al. 2012). According to Bradley et al., longer duration of T2DM and more severe T2DM requiring insulin therapy before surgery has been associated with postoperative weight loss failure and T2DM resolution failure (Bradley-Magkos-Klein 2012) and higher preoperative fasting glucose seems to be associated with a poorer weight loss at one-year follow-up (Faria et al. 2014). Bariatric surgery may induce durable remission of T2DM in patients with BMI ≤ 30 kg/m² (Pories-Dohm-Mansfield 2010). In some previous studies, young age, lower baseline weight and male sex have been associated with greater weight loss while T2DM has been associated with a lower weight loss (Alger-Mayer-Polimeni-Malone 2008, Alvarado et al. 2005, Ma et al. 2006, Biertho et al. 2003, Magro et al. 2008).

We found that NASH had no effect on weight loss or weight regain. On the contrary, weight loss induced by bariatric surgery has been shown to lead to resolution of NASH in nearly 85% of patients after one-year follow-up (Lassailly et al. 2015).

Our study has some limitations. The number of patients was rather small with a relatively short follow-up for genetic association analyses. We acknowledge that our study was underpowered to detect the effects of the GRS on long-term T2DM risk. In addition, we obtained long-term medication data from a questionnaire which was self-reported. However, it should be highlighted that even with the limited sample size we were able to confirm the effect of lower baseline BMI on greater weight loss after surgery, whereas no genetic effect was observed. The strength of our analysis was that we screened previously established obesity SNPs on a large scale (20 BMI loci and 13 WHR loci) in individuals from a homogenous Finnish population with a detailed metabolic characterization, including liver histology. However, long-term follow-up results are essential before recommendations can be made.
7 Conclusions

The main findings and conclusions of this thesis demonstrated, that:

1. Obesity and its comorbidities did not associate with an elevated risk for postoperative complications after LCC (I).

2. Serum plant sterols were lower in GD independent of weight loss and NAFLD (II).

3. Small intestinal length associates with serum TG before and after LRYGB (III).

4. GRS does not predict the outcome of obesity surgery (IV).
8 Future Perspectives

An interesting issue in GD management is the use of gallstone-lowering prophylaxis after LRYGB. Identification of predictive factors for gallstone formation after LRYGB may be important in selecting patients for prophylactic interventions. We know that the majority of gallstones are of cholesterol and statins inhibit cholesterol synthesis and reduce hypercholesterolemia (Kan et al. 2014). It would be highly valuable to carry out a randomized, multicenter, prospective, placebo-controlled, double-blind trial with a six-month follow-up with prophylactic statins or drugs with similar pharmacokinetic properties to assess their possible efficacy post-LRYGB gallstone prevention.

We suggest that to achieve more metabolic benefits, the bariatric procedure should focus on the length of the CC, rather than the AL or BPL when constructing a gastric bypass. A prospective, randomized trial is warranted to determine whether modified lengths of bypassed small intestine based on measured total small intestinal length could optimize the outcomes of elective LRYGB.

An interesting and rather new procedure is the mini gastric bypass or single-anastomosis gastric bypass, which is a modification of the LRYGB. This is a simplified one-loop DS without an enteroanastomosis. It has shown some promising results in weight reduction and metabolic improvement.
9 References


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function and bronchial and systemic inflammation in morbidly obese subjects with asthma”, *Thorax*, vol. 70, no. 7, pp. 659-667.


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10 Appendices

KUPIOSSA LIHAVUUSLEIKATTUJEN POTILAIDEN SEURANTAKYSELY

Arvoisa _____________________________________________

1. Mikä on tämänhetkinen painonne? ______________ kg

2. Olitteko työelämässä

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</table>

3. Oliko Teillä ennen lihavuusleikkausta todettu jokin seuraavista sairauksista

- Diabetes (sokeritauti)
- Verenpainetauti
- Uniapnea
- Hyperkolesterolemia (korkeat kolesteroliarvot)
- Masennus
- Astma
- Rasitusperäisiä nivelkipuja
- Muu, mikä?

_________________________________________
### 4. Oliko Teillä edellä mainittuihin sairauksiin liittyen lääkitystä / lääkityksiä

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<td>☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐</td>
</tr>
<tr>
<td>Hyperkolesterolemia</td>
<td>☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐</td>
</tr>
<tr>
<td>(korkeat kolesteroliarvot)</td>
<td>☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐</td>
</tr>
<tr>
<td>Masennus</td>
<td>☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐</td>
</tr>
<tr>
<td>Astma</td>
<td>☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐</td>
</tr>
<tr>
<td>Rasitusperäisiä nivelkipuja</td>
<td>☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐</td>
</tr>
<tr>
<td>Muu, mikä?</td>
<td>☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐</td>
</tr>
</tbody>
</table>

### 5. Listatkaa nykyinen lääkitysne (lääkkeen nimi ja annos)

__________________________________________________________________________
__________________________________________________________________________
__________________________________________________________________________

### 6. Käytättekö päivittäin

<table>
<thead>
<tr>
<th>Lääkkeen nimi ja annos</th>
<th>Valmisten nimi ja annos</th>
</tr>
</thead>
<tbody>
<tr>
<td>-monivitamiinivalmistetta</td>
<td>☐ ☐ ☐ ☐</td>
</tr>
<tr>
<td>-kalsium-D-vitamiinivalmistetta</td>
<td>☐ ☐ ☐ ☐</td>
</tr>
<tr>
<td>-B_{12}-vitamiini tablettina</td>
<td>☐ ☐ ☐ ☐</td>
</tr>
</tbody>
</table>

### 7. Saatteko B_{12}-vitamiinia pistoksenä

<table>
<thead>
<tr>
<th>Valmisten nimi ja annos</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ ☐ ☐ ☐</td>
</tr>
</tbody>
</table>
8. Oletteko joutuneet 30 vrk sisällä lihavusleikkauksesta uudelleen sairaalahoitoon
   Ei       Kyllä
   □       □
   Jos kyllä niin miksi? ____________________________________________________________
   ____________________________________________________________
   ____________________________________________________________
   Jouduitteko uudestaan leikkaukseen?
   Ei       Kyllä
   □       □

9. Onko teillä ollut seuraavia ongelmia myöhemmin (yli 30 vrk lihavusleikkauksesta) ja kuinka vakavana koitte ongelman?

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Ongelman vakavuus VAS-asteikolla 1-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kyllä</td>
<td>Ei</td>
<td>(vastatkaa numeroilla; 1 lievä, 10 vakava)</td>
</tr>
<tr>
<td>Pahoinvointi</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Vatsakipu</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Oksentelu, pulauttelu</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Haavatyrä</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Vatsahaava</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Dumping (hiotus, tykytys)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Anemia</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Suolitukos</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Muu, mikä?</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

____________________________
____________________________

____________________________
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____________________________
____________________________
10. Onko lihavuusleikkaus aiheuttanut rajoituksia syömiseenne, esim. tiettyjen ruoka-aineiden syömiseen välittömästi leikkausen jälkeen (alle ½ vuotta lihavuusleikkauksesta)?

Kyllä  Ei

Jos kyllä, niin mitä?

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

11. Onko lihavuusleikkaus aiheuttanut rajoituksia syömiseenne, esim. tiettyjen ruoka-aineiden syömiseen myöhemmin (yli ½ vuotta lihavuusleikkauksesta)?

Kyllä  Ei

Jos kyllä, niin mitä?

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

12. Onko teillä tällä hetkellä lihavuusleikkaukseen liittyviä seurantoja terveydenhuollossa?

- lääkärillä  Kyllä  Ei  Missä ja kuinka usein?

- ravitsemusterapeutilla  Kyllä  Ei  Missä ja kuinka usein?

- muualla  Kyllä  Ei  Missä ja kuinka usein?
13. Millaista lihavuusleikkaukseen liittyvää hoito on ollut

<table>
<thead>
<tr>
<th></th>
<th>Huonoa</th>
<th>Tyydyttävää</th>
<th>Hyvää</th>
<th>Erinomaista</th>
</tr>
</thead>
<tbody>
<tr>
<td>KYS:ssa</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Jatkohoitopaikassanne</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

14. Millaista lihavuusleikkaukseenne saamanne ravitsemusohjaus on ollut KYSissä?

<table>
<thead>
<tr>
<th></th>
<th>Huonoa</th>
<th>Tyydyttävää</th>
<th>Hyvää</th>
<th>Erinomaista</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

15. Miten lihavuusleikkaus on vaikuttanut elämänlaatuunne?

- □ Huonontanut, miten? ____________________________
- □ Pysynyt samanlaisena __________________________
- □ Parantunut, miten? ____________________________

16. Jos nyt saisitte päätää, menisittekö lihavuusleikkaukseen, niin mitä päättäisitte?

- □ Kyllä, miksi? __________________________________
- □ En, miksi? ____________________________________

Terveisiä

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

Kiitos vastauksistasi.
About 2 billion people are overweight worldwide and one third of them are obese. This study shows that a small intestinal length is associated with levels of serum triglycerides before and after laparoscopic Roux-en-Y gastric bypass (LRYGB). In addition, serum plant sterols were lower in patients with gallstone disease independent of weight loss after LRYGB, history of cholecystectomy and non-alcoholic fatty liver disease. Genetic risk score did not predict weight loss.