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UNIVERSITY OF TURKU

# LONG-TERM OUTCOMES OF LAPAROSCOPIC SLEEVE GASTRECTOMY VS. LAPAROSCOPIC ROUX-EN-Y GASTRIC BYPASS

## Special focus on procedure selection, gastroesophageal reflux, and quality of life

Sofia Grönroos

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*To my dearest family and fantastic friends*

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ABSTRACT

**Background**: Severe obesity is an increasing global epidemic. To date, metabolic bariatric surgery (MBS) is the only treatment for severe obesity with good and sustainable long-term weight loss and remission of obesity related comorbidities. The gold standard procedure is laparoscopic Roux-en-Y gastric bypass (LRYGB), but since 2014, laparoscopic sleeve gastrectomy (LSG) has been the most common MBS procedure in the world. This transition took place before any available long-term data for LSG. As obesity is a chronic disease, the long-term outcomes are of vital clinical importance in outcome assessment and procedure selection.
**Aims**: The main purpose of this thesis was to assess long-term outcomes of MBS. The first and second study assessed the outcomes of the Sleeve vs. Bypass (SLEEVEPASS) randomized clinical equivalence trial at 7 and 10 years. Firstly, the aim was to compare both weight loss (percentage excess weight loss, %EWL) and quality of life (QOL) and their possible association after LSG vs. LRYGB at 7 years. The second predefined 10-year analysis assessed weight loss and remission of comorbidities, QOL, and overall morbidity and mortality. In addition, a special focus was added to evaluate both symptoms and endoscopic findings of gastroesophageal reflux and more specifically the prevalence of Barrett's esophagus (BE). The third aim of this thesis was to assess the feasibility of Individualized Metabolic Surgery (IMS) score in facilitating procedure selection in patients with severe obesity and type 2 diabetes (T2DM) using a large merged individual patient 5-year data of the two largest RCTs comparing LSG and LRYGB (SLEEVEPASS and SM-BOSS).
**Results**: The mean %EWL was 47% after LSG vs. 55% after LRYGB at 7 years, and 44% vs. 51% at 10 years, respectively. The two procedures were not equivalent, but the difference was not clinically relevant based on the predefined equivalence margins. There was no difference in long-term QOL or in the remission of T2DM, dyslipidemia, obstructive sleep apnea, or complication rate or BE prevalence between LSG and LRYGB at 10 years. Hypertension remission was superior after LRYGB. Esophagitis was more prevalent after LSG. In all IMS score severity stages, there was no difference between the procedures in T2DM remission rates.
**Conclusions**: %EWL was greater after LRYGB, and the procedures were not equivalent for weight loss, but both resulted in good and sustainable weight loss at long-term. Long-term QOL and remission of comorbidities were similar between the procedures except for hypertension and esophagitis, where LRYGB had superior outcomes. IMS score did not facilitate procedure selection.

KEYWORDS: IMS score, long-term outcomes, metabolic bariatric surgery, Roux-en-Y gastric bypass, randomized clinical trial, sleeve gastrectomy

TURUN YLIOPISTO
Lääketieteellinen tiedekunta, Kirurgian oppiaine
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TIIVISTELMÄ

**Tausta**: Vaikea lihavuus on maailmanlaajuinen epidemia. Lihavuuskirurgia on tutkitusti ainoa vaikean lihavuuden hoitomuoto, jolla pitkäaikaisseurannassa saavutetaan hyvä ja pysyvä painonlasku sekä liitännäissairauksien paraneminen. Laparoskooppinen Roux-en-Y mahalaukun ohitusleikkaus (LRYGB) on edelleen lihavuuskirurgian leikkausmenetelmien kultainen standardi, vaikka 2014 lähtien laparoskooppinen mahalaukun kavennusleikkaus (LSG) on ollut maailman eniten käytetty. Tämä muutos tapahtui ennen kuin LSG:n pitkäaikaistuloksia oli saatavilla. Vaikean lihavuuden ollessa krooninen sairaus pitkäaikaistulokset ovat kliinisesti olennaisia hoidon tulosten arvioinnissa ja leikkausmenetelmän valinnassa.
**Tavoitteet**: Väitöskirjassa tutkitaan lihavuuskirurgian pitkäaikaistuloksia. Ensimmäinen ja toinen osatyö käsittelivät satunnaistetun Sleeve vs. Bypass (SLEEVEPASS) –tutkimuksen 7- ja 10-vuotistuloksia. 7v-seurannassa verrattiin painonlaskua (percentage excess weight loss, %EWL) ja elämänlaatua sekä niiden assosiaatiota. 10v-seurannassa arvioitiin painonlaskua, liitännäissairauksia, elämänlaatua ja komplikaatioita sekä refluksitaudin oireita ja endoskooppisia löydöksiä ja Barrettin ruokatorven (BE) esiintyvyyttä. Kolmanneksi tutkittiin Individualized Metabolic Surgery (IMS)-pisteytyksen käytettävyyttä leikkausmenetelmän valinnassa tyypin 2 diabeetikoilla (T2DM) käyttäen kahden satunnaistetun tutkimuksen 5-vuotisyhdistelmädataa (SLEEVEPASS ja SM-BOSS).
**Tulokset**: %EWL 7 ja 10 vuoden kohdalla oli LSG:n jälkeen 47% ja 44% ja vastaavasti 55% ja 51% LRYGB:n jälkeen. Leikkaukset eivät olleet ekvivalentteja, mutta niiden ero ei ollut kliinisesti merkittävä etukäteen asetettujen ekvivalenssimarginaalien pohjalta. Elämänlaadussa ei ollut eroa. Liitännäissairauksien paranemisessa (T2DM, dyslipidemia, uniapnea), komplikaatioissa, tai BEn esintyvyydessä ei ollut eroa 10v-seurannassa. LSG:n jälkeen oli enemmän esofagiittia. Verenpainetaudin paraneminen oli tehokkaampaa LRYGB:n jälkeen. T2DM remissiossa ei ollut eroa toimenpiteiden välillä missään IMS-pisteytyksen T2DM-vaikeusasteissa.
**Johtopäätökset**: LRYGB:n %EWL oli korkeampi, mutta ero ei ollut tutkimusasetelman pohjalta kliinisesti merkittävä, molemmissa leikkauksissa todettiin hyvä ja pysyvä painonlasku. Liitännäissairauksien paranemisessa, elämänlaadussa tai BEn esiintyvyydessä ei ollut eroa. Esofagiittia oli enemmän LSG:n jälkeen, LRYGB oli parempi verenpainetaudin hoidossa. IMS-pisteytys ei helpottanut leikkausmenetelmän valintaa.

AVAINSANAT: IMS-pisteytys, lihavuuskirurgia, mahalaukun kavennusleikkaus, mahalaukun ohitusleikkaus, pitkäaikaistulokset, randomoitu tutkimus

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# Abbreviations

| | |
|---|---|
| 15D | 15-dimensional |
| ADA | American Diabetes Association |
| ANOVA | Analysis of variance |
| AOM | Anti-obesity medication |
| ASMBS | American Society for Metabolic and Bariatric Surgery |
| BAROS | Bariatric Analysis and Reporting Outcome System |
| BE | Barrett's esophagus |
| BMI | Body mass index |
| BPD | Biliopancreatic diversion |
| BPD-DS | Biliopancreatic diversion with duodenal switch |
| CI | Confidence interval |
| DSQOL | Disease-specific quality of life |
| EAC | Esophageal adenocarcinoma |
| EBMIL | Excess body mass index loss |
| EWL | Excess weight loss |
| EP | Endoluminal procedure |
| GERD | Gastroesophageal reflux disease |
| GIP | Glucose-dependent insulinotropic polypeptide |
| GLP-1 | Glucagon-like peptide-1 |
| HbA1C | Glycated hemoglobin |
| HDL | High-density lipoprotein |
| HRQOL | Health-related quality of life |
| IFSO | International Federation for the Surgery of Obesity and Metabolic Disorders |
| IMS | Individualized Metabolic Surgery |
| IPDMA | Individual patient data meta-analysis |
| JIB | Jejunoileal bypass |
| LAGB | Laparoscopic adjustable gastric banding |
| LDL | Low-density lipoprotein |
| LES | Lower esophageal sphincter |
| LRYGB | Laparoscopic Roux-en-Y gastric bypass |

| | |
|---|---|
| LSG | Laparoscopic sleeve gastrectomy |
| MBS | Metabolic bariatric surgery |
| NIH | National institute of health |
| OAGB | One anastomosis gastric bypass |
| OR | Odds ratio |
| OSAS | Obstructive sleep apnea syndrome |
| PPI | Proton pump inhibitor |
| QOL | Quality of life |
| RCT | Randomized clinical trial |
| SADI-S | Single-anastomosis duodenoileal bypass with sleeve gastrectomy |
| T2DM | Type 2 diabetes mellitus |
| TWL | Total weight loss |
| VBG | Vertical banded gastroplasty |
| WHO | World Health Organization |

# List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Grönroos S, Helmiö M, Juuti A, Tiusanen R, Hurme S, Löyttyniemi E, Ovaska J, Leivonen M, Peromaa-Haavisto P, Mäklin S, Sintonen H, Sammalkorpi H, Nuutila P, Salminen P. Effect of Laparoscopic Sleeve Gastrectomy vs Roux-en-Y Gastric Bypass on Weight Loss and Quality of Life at 7 Years in Patients with Morbid Obesity: The SLEEVEPASS Randomized Clinical Trial. *JAMA Surg*. 2021 Feb 1;156(2):137-146.

II Salminen P, Grönroos S, Helmiö M, Hurme S, Juuti A, Juusela R, Peromaa-Haavisto P, Leivonen M, Nuutila P, Ovaska J. Effect of Laparoscopic Sleeve Gastrectomy vs Roux-en-Y Gastric Bypass on Weight Loss, Comorbidities, and Reflux at 10 Years in Adult Patients with Obesity: The SLEEVEPASS Randomized Clinical Trial. *JAMA Surg*. 2022 Aug 1;157(8):656-666.

III Saarinen I*, Grönroos S*, Hurme S, Peterli R, Helmiö M, Bueter M, Strandberg M, Wölnerhanssen BK, Salminen P. Validation of the individualized metabolic surgery score for bariatric procedure selection in the merged data of two randomized clinical trials (SLEEVEPASS and SM-BOSS). *Surg Obes Relat Dis*. 2023 May;19(5):522-529.
*equal contribution

# 1 Introduction

Obesity is increasingly becoming the rule rather than the exception. Since 1975, the prevalence of obesity has nearly tripled. This increase has happened in all parts of the world, in all age groups, and in all sexes. (Chooi et al., 2019) According to Finhealth2017 report, 28% of women and 26% of men aged over 30 years are obese in Finland (Koponen P, 2018). This obesity epidemic has derived to concurrent increase in obesity-related comorbidities such as type 2 diabetes (T2DM), cardiovascular diseases, obstructive sleep apnea syndrome (OSAS), and obesity is also associated with increased cancer incidence and cancer related mortality (Aminian et al., 2022). In 2015 excess body weight was evaluated to account for approximately four million deaths and 120 million disability-adjusted life-years globally (Afshin et al., 2017). Besides increased morbidity and mortality, and worsened quality of life (QOL), obesity is also truly a major economic burden worldwide (Withrow et al., 2011).

Obesity is a chronic disease. Regarding patients with severe obesity, metabolic bariatric surgery (MBS) is to date the only effective treatment of obesity resulting in good and sustainable weight loss and remission or alleviation of obesity-related comorbidities. (Adams et al., 2017; Courcoulas et al., 2015; Ikramuddin et al., 2018; Rubino et al., 2016; Schauer et al., 2017) Furthermore, MBS is associated with considerably better long-term survival than usual obesity management (Syn et al., 2021).

As a result, the number of bariatric procedures has doubled during the years 2011 to 2016, from ca 350 000 to ca 700 000 annual surgical procedures worldwide, not to mention the increase from about 40 000 operations in 1998. However, despite the solid evidence of MBS, the access to treatment is very low, as only 1-2% of eligible patients have access to surgery (Campos et al., 2020). Currently the two most common bariatric procedures are laparoscopic sleeve gastrectomy (LSG) and laparoscopic Roux-en-Y gastric bypass (LRYGB), LSG being the most common procedure worldwide since 2014. (Angrisani et al., 2018) This shift for global preference of LSG over the former gold standard LRYGB has happened before any long-term data for LSG were available.

The long-term outcomes from MBS are somewhat scarce due to the lack of randomized clinical trials (RCTs) with sufficient long-term patient follow-up and comparative studies of LSG vs LRYGB (Puzziferri et al., 2014). There are, however, two larger RCTs comparing LSG and LRYGB; the Sleeve vs. Bypass study (SLEEVEPASS) being the largest one with 240 patients (primary endpoint percentage excess weight loss [%EWL] at 5 years) (Salminen et al., 2018), and the Swiss Multicenter Bypass or Sleeve Study (SM-BOSS) being the second largest with 217 patients randomized (primary endpoint percentage excess BMI loss [%EBMIL] at 5 years) (Peterli et al., 2018). The 5-year outcomes of these studies were published in 2018 in JAMA, in which in brief, both LSG and LRYGB resulted in good and sustainable weight loss outcomes, similar remission of T2DM and dyslipidemia, and no difference in QOL or morbidity, but for hypertension remission LRYGB was superior.

Patients with severe obesity are shown to have lower QOL compared to general population (Andersen et al., 2015; Kolotkin et al., 2017), and therefore QOL plays an important role in evaluating the outcomes of MBS. MBS is associated with better QOL (Hachem et al., 2016; Macano et al., 2017; Major et al., 2015), but this has only been shown in short- or midterm follow-up, or in retrospective assessments. Recent studies have also shown a high incidence of de novo gastroesophageal reflux disease (GERD) and worsening of GERD, esophagitis, and alarming rates of Barrett's esophagus (BE) after LSG (Bevilacqua et al., 2020; Csendes et al., 2019; Felsenreich et al., 2018; Genco et al., 2017). However, long-term results from RCTs comparing LSG and LRYGB especially on GERD are lacking as well as long-term results on QOL covering both disease-specific and health-related QOL.

The aim of MBS is naturally to optimize its outcomes, and therefore selecting the best surgical treatment for all MBS patients is under active research. An important factor in this issue is the severity of T2DM and its predicted remission. The Individualized Metabolic Surgery (IMS) score (Aminian et al., 2017) was created to facilitate procedure choice, but it has not been validated in a prospective setting.

This doctoral thesis addresses the long-term comparative outcomes of LSG vs LRYGB including weight loss and comorbidities, with a special focus on GERD and QOL based on the SLEEVEPASS RCT. Additionally, this thesis reports the feasibility of IMS score in facilitating procedure selection using the merged data of the SLEEVEPASS and SM-BOSS studies.

# 2 Review of the Literature

## 2.1 Obesity

### 2.1.1 Obesity is a chronic disease

Obesity is a very complex multifactorial chronic disease, which poses a major health threat to humans of the 21st century. In 1948, obesity was included in the International Classification of Diseases, and yet nowadays, many people still see it as a lifestyle choice or lack of self-discipline. In March 2021, obesity was defined as a “chronic relapsing disease, which in turn acts as a gateway to a range of other non-communicable diseases” by the European Commission (Burki, 2021). The pathophysiology of obesity is mainly derived from excess adipose tissue but understanding the substantial causes of obesity and the complex biology behind the disease requires moving away from the erroneous line of thinking of just “eating less and exercising more”.

Causes and predisposing factors of obesity are multitude, and all too often the patient with obesity is blamed and stigmatized for it. This weight stigma can cause both physical and psychological harm, and at its worst, delay or even stop the patient from seeking MBS. (Rubino et al., 2020) Naturally, in patients with overweight or only mild obesity, identifying of unhealthy eating habits and encouragement to physical activity, as well as patients’ own motivation to healthy lifestyle changes is very important. Besides excessive energy intake and lack of physical activity, several predisposing factors for obesity are known, such as genetical factors, endocrine disorders, medication, psychiatric illnesses, gut microbiota, impaired brain circuit regulation, and neuroendocrine hormone dysfunction. In addition, broader social, economic, and environmental factors affect our well-being.

Measuring the amount of pathologic adipose tissue is not very convenient, and thus, the most common measure of obesity is still body mass index (BMI). According to World Health Organization (WHO), normal BMI is 18.5-24.99kg/m$^2$, BMI≥25kg/m2 indicates overweight, and BMI≥30kg/m2 indicates obesity. Furthermore, obesity is classified into three categories: BMI 30.0-34.99kg/m2 (class I) as moderately obese, BMI 35.0-39.9 kg/m2 (class II) as severely obese, and BMI≥40 kg/m2 (class III) as very severely (former “morbidly”) obese. The categories can be extended to class IV (BMI≥50kg/m$^2$) and class V (BMI≥60kg/m$^2$), which used to be referred to as superobesity and supersuperobesity, but these stigmatizing terms are not in use anymore.

Higher BMI increases the risk of co-morbid chronic diseases such as T2DM, cardiovascular diseases, OSAS, many types of cancer, and musculoskeletal disorders resulting in lower QOL and shorter life expectancy (Lin et al., 2021). Obesity has also an enormous impact on economy. Compared with healthy-weight adults, people with obesity incur higher inpatient and outpatient costs, higher amount of physician visits, and increased number of prescription drugs (Wang et al., 2011). This reflects also to working as reduced productivity at work, increased sick leaves, and earlier retirement. Men with obesity are found to have 0.5 to 5.9 more missed annual workdays compared to people with healthy-weight. (Finkelstein et al., 2010)

Luckily, in the past decades the understanding of obesity has extended, and gradually moving towards the acknowledgement that obesity is not only a risk factor, but also a chronic disease itself (Burki, 2021). Given this chronic and relapsing nature of obesity, study on long-term outcomes of MBS is of major importance.

### 2.1.2 Epidemiology of obesity

The prevalence of obesity has almost tripled between the years 1975 and 2016 worldwide. To date, the amount of people with obesity has exceeded the amount of underweight people in every region of the world except parts of sub-Saharan Africa and Asia. (WHO, 2016) According to WHO's report in 2016 over 1.9 billion adults were overweight, and 650 billion obese, meaning that 39% of world's population were overweight (39% of men, 40% of women) and 13% obese (11% of men and 15% of women).

Obesity is not solely a problem among the adults but also in children and adolescents. From 4% in 1975, the prevalence of overweight in children aged 5 to 19 years has multiplied to over 18% in 2016. Obesity during childhood and adolescence is also associated with increased cardiovascular and all-cause mortality in adulthood. (Twig et al., 2016) Furthermore, there used to be a perception that overweight and obesity were problems only in high-income countries, but is actually increasing also in low- and middle-income countries (**Figure 1**). (WHO, 2016)

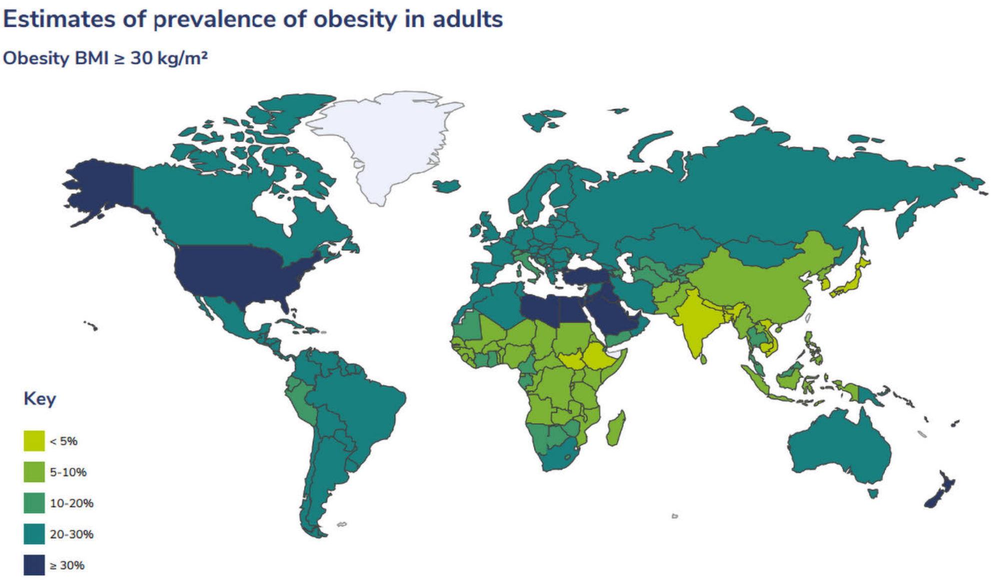


**Figure 1**. Prevalence of obesity (BMI≥30kg/m$^2$) in adults. Reproduced with the permission of © *World Obesity Federation, London.* Original figure can be found in https://data.worldobesity.org/maps/?mapid=69&agegroup=AT&area=maps.

In Finland, the prevalence of obesity is even higher than the world's average. Up to 28% of women and 26% of men aged over 30 years are obese. Similar trend is seen in the ages from 2 to 16 years in Finnish children; 4% of girls and 9% of boys are obese. (Koponen P, 2018)

### 2.1.3 Obesity related comorbidities and mortality

#### 2.1.3.1 Type 2 diabetes mellitus (T2DM)

T2DM is one of the major comorbidities of obesity, and simultaneously one of the most important factors associated with cardiovascular morbidity and mortality (Afshin et al., 2017; Flegal et al., 2016; La Sala et al., 2020). The pathogenesis, in brief, is that the excess adipose tissue leads to elevated levels of free fatty acids and inflammation, which along with pancreatic β-cell dysfunction causes impaired insulin signalling and insulin-resistance, and finally, T2DM (Heymsfield et al., 2017).

The increasing prevalence of obesity means also rising numbers of patients diagnosed with T2DM. The global prevalence of T2DM according to WHO2014 report was 9% (WHO, 2016). In Finland, it is estimated that up to 15% of adult men and 10% of women have T2DM either aware of it or not (Koponen P, 2018).

It has been estimated that more than 80% of T2DM is linked to overweight, and obesity is associated with up to seven times higher risk of T2DM compared to healthy-weight population. (Abdullah et al., 2010; Seidell et al., 2015; Smith et al., 2016) Additionally, the duration of obesity adds to the risk of developing T2DM. (Abdullah et al., 2011) Obesity does not only increase the probability of having T2DM, but also complicates its treatment and enhances its health risks (Maggio et al., 2003).

#### 2.1.3.2 Other comorbidities and mortality

Through excess adipose tissue, obesity predisposes to several chronic diseases (**Figure 2**). These include cardiovascular diseases such as hypertension, dyslipidaemia, coronary artery disease, congestive heart failure, chronic kidney disease, and stroke. Excess body weight can also cause osteoarthrosis, gallbladder disease, OSAS, asthma, depression, polycystic ovarian syndrome, and infertility. (Heymsfield et al., 2017; Martin-Rodriguez et al., 2015; Nguyen et al., 2010; Seidell et al., 2015; Smith et al., 2016) In liver, the burden of obesity can be seen as non-alcoholic fatty liver disease (NAFLD), steatohepatitis (NASH), and cirrhosis. NAFLD affects 25% of the world's population with increasing prevalence and is the biggest risk factor for cirrhosis and hepatocellular carcinoma. It is also strongly linked to cardiovascular diseases and metabolic syndrome. (Aminian et al., 2021; Powell et al., 2021) GERD and its relation to obesity, and vice versa, is addressed in detail in chapter 2.5.

Obesity is also associated with increased risk of many cancers, such as esophageal, thyroid, renal, breast, endometrial, gallbladder, pancreatic, colon cancer, and malignant melanoma, multiple myeloma, and leukemia. (Renehan et al., 2008) It is reported, that obesity does not only predispose to developing an obesity-related cancer, but also increases the risk of cancer-specific and all-cause mortality. (Aminian et al., 2022; Arnold et al., 2016)

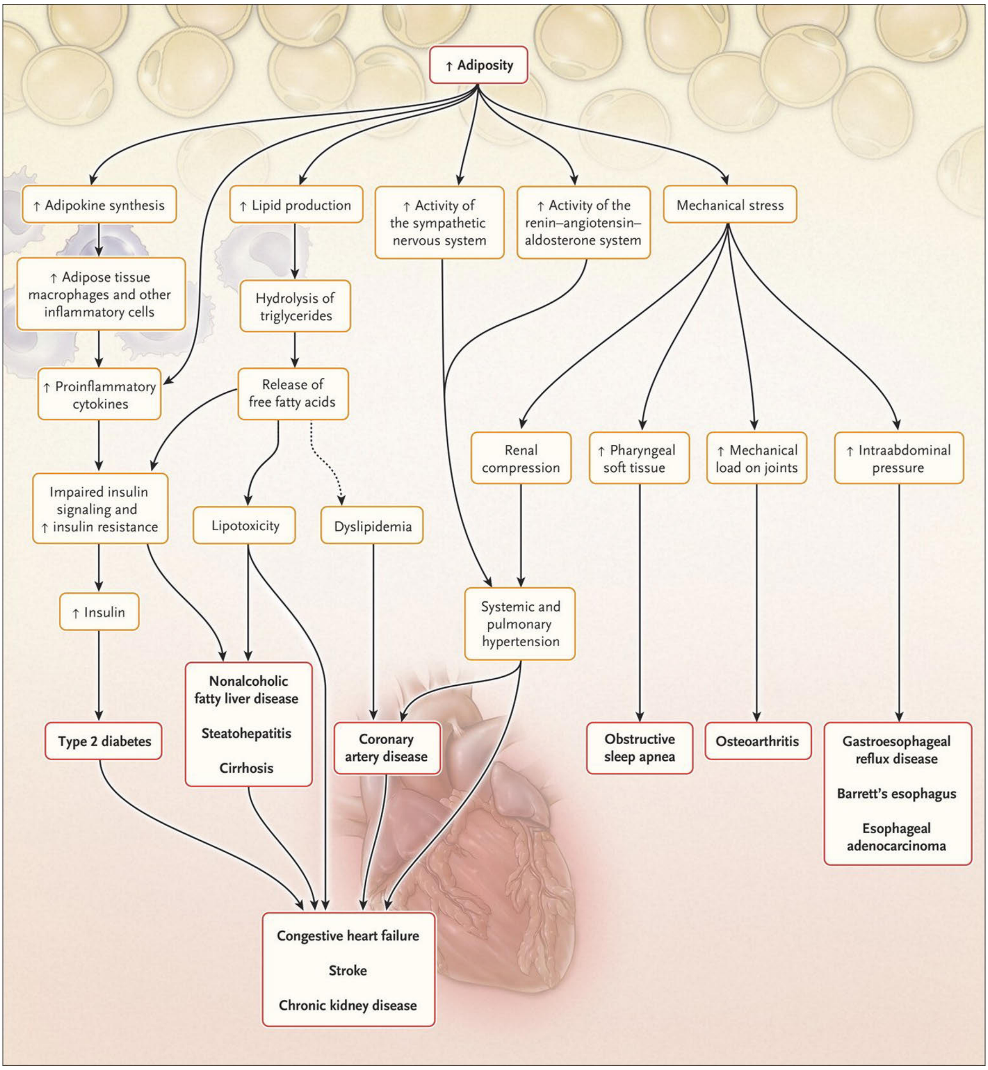


**Figure 2.** Some pathways through which excess adiposity leads to major risk factors and common chronic diseases. Reproduced with permission from Heymsfield SB, Wadden TA. N Engl J Med 2017;376:254-266. © *Massachusetts Medical Society*.

Obesity-related cancers are not the only way in which obesity multiplies global mortality. (Global et al., 2016) According to a large analysis from Afshin et al. including 195 countries in 25 years, excess weight contributed to 4.0 million deaths (7.2% of all-cause mortality), and 120 million disability-adjusted life years in 2015 globally (Afshin et al., 2017). The leading cause of mortality related to high BMI was cardiovascular disease, whereas T2DM was the second. A report from Whitlock et al. including 57 prospective studies found that having BMI 30-35 kg/m$^2$ reduced life expectancy 2-4 years and BMI 40-45 kg/m$^2$ up to 10 years, which equates to the effects of life-long smoking (Whitlock et al., 2009).

The negative effects of obesity can be improved with weight loss. A weight loss of 5-10% is found to reduce cardiovascular risk factors (Wing et al., 2011), and >15% is related to decreased mortality, and naturally other health benefits as well (Ryan et al., 2017). MBS is the key to efficient and long-lasting weight loss, and the effect of MBS on morbidity and mortality is further discussed in chapter 2.4.

## 2.2 Conservative treatment of obesity

### 2.2.1 Lifestyle modifications

The traditional treatment of obesity has been lifestyle interventions. Despite obesity becoming more and more common and its causes better acknowledged, it is still seen solely as a self-inflicted condition by many people, even by health-care professionals. Furthermore, even if the causes were better recognized, many of them are hard to affect for an individual, for example genetics, taxation, growth environment, and prejudices of oneself and others. Perhaps consequently, despite proven lack of efficacy at long-term, lifestyle interventions alone are still recommended to comprise the foundation of the treatment of obesity (Waxman, 2004).

Lifestyle interventions for obesity consist of nutritional counselling (individual or in groups), dietary therapy, physical activity counselling, and behavioural therapy. Screening and assessment of patients with obesity and the initiation of treatment should happen in primary care practice settings, as well as recognition of the patients that would benefit from weight loss (BMI≥30kg/m$^2$ or BMI≥25kg/m$^2$ with one comorbidity or risk factor). Weight loss of 5% to 10% is the usual goal in conservative treatment. (Kushner et al., 2014)

However, the results of lifestyle interventions remain low, especially at long-term follow-up (Adams et al., 2017; Courcoulas et al., 2015; Ikramuddin et al., 2013; Rubino et al., 2016; Schauer et al., 2017). A review by Wirth et al. stated that in 1-2 years 4-6kg weight loss can be achieved by dietary therapy, and 2-3kg by exercise therapy, whereas 20-40kg with MBS (Wirth et al., 2014). In the prospective Swedish Obese Subjects (SOS) study, with over 2000 patients and a 20-year follow-up, MBS resulted in -18% weight loss compared to -1% weight loss achieved by lifestyle interventions (Sjöström, 2013). Furthermore, in the Look AHEAD trial in which patients with obesity and T2DM reached a relatively good weight loss of 7-10% in 10-years by intensive lifestyle modifications, still no significant reduction in cardiovascular morbidity or mortality was found (Wing et al., 2013).

### 2.2.2 Pharmacotherapy with anti-obesity medications

Pharmacotherapy with anti-obesity medications (AOMs) has currently truly stepped into the arena in the treatment of obesity with many new drugs also in the future pipeline. AOMs and MBS are not either-or, but rather as synergy or an additive effect enabling more patients to have access to efficient treatment of severe obesity.

In Finland, there are currently three medications used officially for obesity, including liraglutide (glucacon like peptide-1 receptor agonist, GLP-1), a combination of bupropion and naltrexone, and orlistat. In addition, semaglutide, more commonly used for the treatment of T2DM, has offered a clear improvement in the pharmacological treatment of obesity. Semaglutide is used in Finland also in patients with obesity, but as off-label use. In addition, the 2.4 mg dose (Wilding et al., 2021) is not yet available in the Finnish markets. Another promising product in the pipeline and already in use in some countries is tirzepatide, a dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist (Jastreboff et al., 2022).

Orlistat inhibits pancreatic enzymes and causes reduced intestinal uptake of fat. Its popularity has suffered from modest results and gastrointestinal side effects. In three-year follow-up, Orlistat led to -2.4kg extra weight loss combined with lifestyle therapy. (Richelsen et al., 2007)

The combination of bupropion and naltrexone reduces appetite and increases energy expenditure. A large systematic review and meta-analysis by Khera et al. found bupropion-naltrexone to boost weight loss with -5.0kg in average compared with placebo in one-year follow-up. (Khera et al., 2016)

Liraglutide is a GLP-1 analogue that suppresses appetite. It is better known as medicine for T2DM and is used as subcutaneous injection. In the meta-analysis by Khera et al. liraglutide was associated with -5.3kg weight reduction. When compared with orlistat and bupropion-naltrexone, GLP-1 analogues were associated with best likelihood of ≥5% weight loss (Khera et al., 2016; Shi et al., 2022).

Semaglutide, like liraglutide, is a GLP-1 receptor agonist, and applied as subcutaneous injections once weekly. The preferred dose for obesity is 2.4mg. In a randomized study of Rubino et al. semaglutide resulted in -7.9% body weight loss (vs. +6.9% in placebo group), and waist circumference of -9.7cm in 48 weeks. (Rubino et al., 2021) Another study of Wilding et al. with 68 weeks of follow-up found that semaglutide combined with lifestyle interventions achieved -14.9% (15.3kg) mean weight loss, and had a greater improvement in cardiovascular risk factors compared to placebo treatment. Nausea and diarrhoea were the two most common side effects, but were graded as mild to moderate, and subsided with time. (Wilding et al., 2021) Furthermore, semaglutide seems to be also more effective in comparison with liraglutide (O'Neil et al., 2018; Shi et al., 2022).

Tirzepatide, a dual GLP-1 and GIP receptor agonist, together with semaglutide is another promising medicine for obesity (Bray et al., 2021). Tirzepatide is even newer than semaglutide and is currently under active research. There are promising results in which tirzepatide 5.0 mg was associated with -15.0% weight loss in 72 weeks and improvements in cardiometabolic profile of the patients, and even up to 20% weight loss with higher doses of tirzepatide (Jastreboff et al., 2022).

## 2.3 Surgical treatment of obesity

### 2.3.1 History of metabolic bariatric surgery

Although more an extending health problem of our times, obesity has troubled the humans already hundreds of years ago. A folklore indicates that back in the tenth century in Spain the king of Leon's, D. Sanco's, lips were sutured together, and he could only receive liquid diet (Faria, 2017; Hopkins et al., 1995). In the early 1950's, the first actual weight-reducing procedure was done by a Swedish surgeon, Viktor Henriksson, when he performed a 105 cm small intestine resection on a 32-year-old woman (Henriksson, 1952).

In 1953, Dr Richard Varco at the University of Minnesota performed the first jejunoileal bypass (JIB), in which most of the small bowel was bypassed with an end-to-end jejunoileal anastomosis (Buchwald, 2014). This case was never published, but later in 1954 Kremen et al. were the first to publish this operation (Kremen et al., 1954). This technique was highly effective concerning weight loss but was not without major complications, such as malabsorption of vitamins and minerals, malnutrition, electrolyte imbalances, diarrhoea, kidney stones, steatorrhea etc. There were subsequent innovations on the grounds of JIB, the most popular one by Payne and DeWind (Payne et al., 1969), but these techniques were eventually abandoned due to the challenging side effects described above.

The first gastric bypass was introduced in 1966 by Edward E. Mason at the University of Iowa (Mason et al., 1996). To achieve weight loss with less complications compared to JIB, he proposed a horizontal division of the stomach and constructed a loop gastrojejunostomy to the proximal gastric pouch. During the next decade, the gastric bypass evolved owing to Mason, Alden (Alden, 1977), Pories and Griffen, and in 1977, the gastric bypass with Roux-en-Y gastrojejunostomy (RYGB) was first introduced by Griffen et al (Griffen et al., 1977). This included the addition of jejuno-jejunostomy in addition to the gastrojejunostomy. In 1994, the classic RYGB was converted to laparoscopic approach for the first time (Wittgrove et al., 1994), and since then, it developed into the gold standard of bariatric procedures (Wiggins et al., 2020). The technique of LRYGB is further described in chapter 2.3.3.2.

The original version of gastroplasty, a horizontal partial gastroplasty leaving a greater curvature conduit, was reported first by Printen and Mason in 1973 (Printen et al., 1973). In 1981, the pouch was made vertical and restricted with a silastic ring by Laws and Piatadosi. A year after, a modification of this procedure was introduced by Mason and named as vertical banded gastroplasty (VGB). It came popular for a while, but later in the 1990s VGB was largely dismissed because of the development of laparoscopic gastric banding (LAGB), first introduced in 1993 (Belachew et al., 1994). Regarding both VGB and LAGB, the mid-term results were relatively good, but in long-term the number of complications rose, and the weight loss results were unsatisfactory (Suter et al., 2006). The technique of LAGB is further explained in chapter 2.3.4.

Aiming to the weight reducing ability of JIB but less complications, Nicola Scopinaro performed biliopancreatic diversion (BPD) in 1979 (Scopinaro et al., 1979). It included a partial gastrectomy with the distal part of jejunum anastomosed to the gastric pouch (alimentary limb), and the proximal section of the jejunal loop anastomosed to the distal ileum (biliary limb). Later in 1998, Hess and Hess introduced the BPD with duodenal switch (DS); a sleeve gastrectomy, with pyloric preservation, duodenal division, a proximal duodenoileostomy, and a common channel of approximately 100 cm (Hess et al., 1998). This procedure was highly effective for weight loss, but resulted also in many complications, and consequently was mainly performed to patients with class IV obesity (Wiggins et al., 2020). The technique of BPD-DS is further presented in chapter 2.3.4.

As stated above, laparoscopic sleeve gastrectomy (LSG) was initially designed as a part of BPD-DS. As a free-standing first-stage procedure it was later popularized by Gagner (Milone et al., 2005) with surprisingly effective initial results also at longer-term (Sarela et al., 2012). LSG gained popularity worldwide, and with 53.8% of all the bariatric procedures, it has become the most common one (Angrisani et al., 2018). However, still no long-term comparative outcomes from prospective trials have been available to justify its growing popularity. The technique of LSG is further introduced in chapter 2.3.3.1.

A gastric bypass with only one anastomosis was introduced in 1997 (Rutledge, 2001). This procedure was previously called mini gastric bypass or single anastomosis gastric bypass, however, as the term “mini” is misleading, it is currently known as one anastomosis gastric bypass (OAGB). Its popularity has increased, and currently covers about 8% of the bariatric procedures performed (Welbourn et al., 2019). Another recently developed bariatric procedure on the grounds of BPD-DS is the single anastomosis duodenoileal bypass with sleeve gastrectomy (SADI-S) designed by Torres et al. in 2010 (Sánchez-Pernaute et al., 2010). Both the techniques of OAGB and SADI-S are further discussed in chapter 2.3.4 along with modern endoscopic techniques.

### 2.3.2 Indications and contraindications of metabolic bariatric surgery

Over 30 years ago, in 1991, National Institute of Health (NIH) set guidelines for the treatment of patients with severe obesity, including how to select optimal patients for MBS (NIH, 1992). These guidelines were followed since then, until in 2022 the International Federation for the Surgery of Obesity (IFSO) and the American Society for Metabolic and Bariatric Surgery (ASMBS) published an updated consensus of the indications for MBS (**Table 1**). (Eisenberg et al., 2022) The major differences compared to NIH 1991 consensus include MBS being recommended for patients with BMI≥35 kg/m$^2$ irrespective of comorbidities, and that it should be considered also to patients with BMI 30-34.9 kg/m$^2$. No upper BMI- or age-limit was set. The other main revision was to highlight the need to actively implement MBS in appropriately selected children and adolescents. In clinical practice, there are no absolute contraindications for MBS except ongoing substance or alcoholic abuse. Every patient must be encountered as an individual and decide what is the best option for them.

**Table 1**. Indications and relative contraindications of metabolic bariatric surgery. Composed based on the article of Eisenberg et al. *2022 American Society of Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) Indications for Metabolic and Bariatric Surgery*. Obes Surg. 2023 Jan;33(1):3-14.

| INDICATIONS | CONTRAINDICATIONS |
|---|---|
| BMI≥35kg/m$^2$, regardless of presence, absence, or severity of comorbidities | Severe eating disorder or severe active psychiatric disease? |
| BMI≥30kg/m$^2$ and T2DM | Severe substance or alcohol abuse? |
| BMI 30-34.9kg/m$^2$ and substantial or durable weight loss or comorbidity improvement not achieved using non-surgical methods | Inability to understand instructions? |

### 2.3.3 Laparoscopic sleeve gastrectomy (LSG) and laparoscopic Roux-en-Y gastric bypass (LRYGB)

LSG became the leading bariatric procedure worldwide in 2014 and has maintained its popularity with some 350 000 operations a year accounting for 54% of all bariatric procedures done according to the IFSO world survey 2016 (Angrisani et al., 2018).

LSG consists of subtotal vertical gastrectomy retaining the pylorus and creating a tubular shaped duct (**Figure 3**). Approximately 75% of stomach is typically resected. All of the mechanisms of LSG are still not fully understood, but the rapid gastric emptying and accelerated intestinal transit are considered to cause distal intestine stimulation stimulating hormonal changes, such as increasing levels of GLP-1 and peptide YY, and decreased ghrelin production. (Peterli et al., 2012; Ramón et al., 2012; Wickremasinghe et al., 2022) The popularity of LSG is probably based on both the long-term benefits of an intact gastrointestinal tract omitting the risk of internal hernias associated with LRYGB and the technically simpler nature of the procedure compared to other bariatric procedures. (Benaiges et al., 2015; Felsenreich et al., 2020)

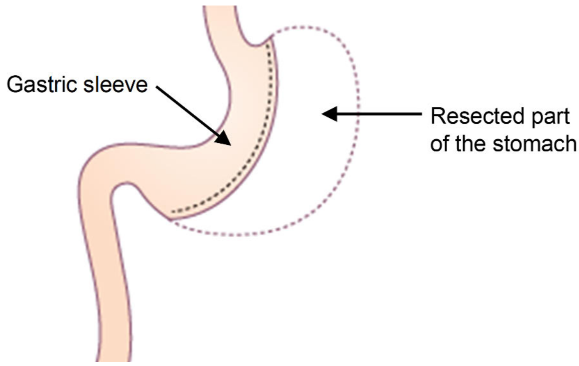


**Figure 3**. Laparoscopic sleeve gastrectomy, LSG. Leppäniemi et al., Surgery, Duodecim Publishing Company, 2018. Artist: Tiina Ripatti-Toledo. Modified and reproduced with the permission of the copyright holders.

LRYGB is the gold standard in the field of MBS. Currently, it is the second most common procedure with around 191 000 annual procedures covering 30% of all bariatric procedures done. (Angrisani et al., 2018)

The standardized surgical technique of LRYGB entails first creating a small gastric pouch of 30 to 50ml. The biliopancreatic limb is then measured at 50 to 80cm and an end-to-side gastrojejunostomy is constructed. Then, the alimentary limb is measured approximately at 150cm and a side-to-side jejunojejunostomy is constructed between the alimentary limb and the biliopancreatic limb (**Figure 4**). Thus, from the gastric pouch the food proceeds straight to distal jejunum bypassing both duodenum and proximal jejunum. The mesenteric defects are also usually routinely closed to avoid internal herniation (Samur et al., 2019; Stenberg et al., 2016). Despite this standard design, many variations exist depending on pouch size (Boerboom et al., 2020), the diameter of the gastrojejunostomy (Abu Dayyeh et al., 2011), and the length of both the biliopancreatic and alimentary limb (Eskandaros et al., 2022).

The weight reducing mechanisms behind LRYGB are diverse. The small gastric pouch reduces food intake, and the nutrient flow is rerouted straight to jejunum resulting in the feeling of satiety. Additionally, the rearrangement of the gastrointestinal track induces changes in circulating gut hormones such as ghrelin, peptide YY, GLP-1 and anti-incretin factors as well as changes in intestinal nutrient-sensing mechanisms regulating insulin sensitivity, and increase in gut microbiota richness, which effects on lipid metabolism (Akalestou et al., 2022; Rubino et al., 2010; Yousseif et al., 2014).

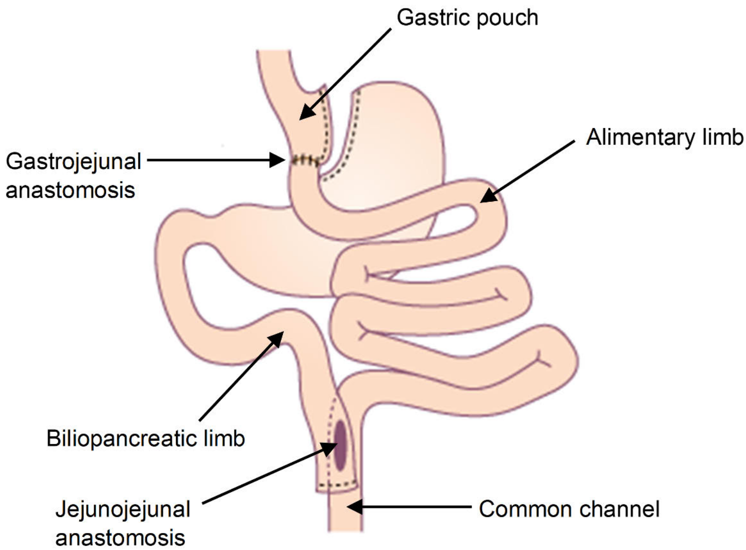


**Figure 4**. Laparoscopic Roux-en-Y Gastric Bypass, LRYGB. Leppäniemi et al., Surgery, Duodecim Publishing Company, 2018. Artist: Tiina Ripatti-Toledo. Modified and reproduced with the permission of the copyright holders.

## 2.3.4 Other common techniques

### 2.3.4.1 Laparoscopic adjustable gastric banding (LAGB)

Being the first minimally invasive bariatric procedure, LAGB became popular in the late 1990s, and was the second common bariatric procedure worldwide in 2008. However, due to its poor long-term results and frequent complications (band migration, vomiting etc.) leading to band removal (Suter et al., 2006), it is currently almost obsolete (Angrisani et al., 2018).

LAGB is solely a restrictive procedure. The band refers to a tight adjustable silicone ring that is set around the cardia of the stomach (**Figure 5**). The band is connected via a tube to an infusion port that is situated subcutaneously and can be adjusted through this port. To achieve satisfying weight reduction with LAGB, the patient must be followed-up and the band frequently adjusted.

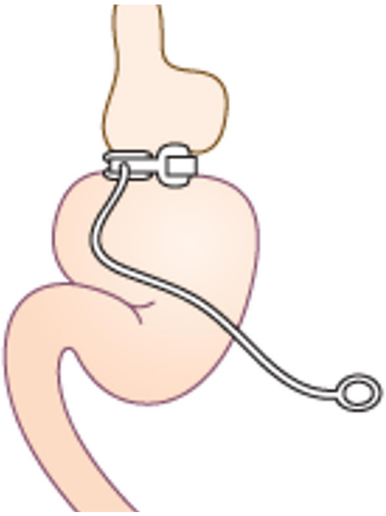

**Figure 5**. Laparoscopic adjustable gastric banding, LAGB. Leppäniemi et al., Surgery, Duodecim Publishing Company, 2018. Artist: Tiina Ripatti-Toledo. Modified and reproduced with the permission of the copyright holders.

#### 2.3.4.2 One anastomosis gastric bypass (OAGB)

OAGB was first introduced (Rutledge, 2001) in 2001 as a modification of LRYGB. In 2016, the OAGB constituted 5% of bariatric procedures with 30 000 procedures a year globally, and its popularity is steadily increasing (Angrisani et al., 2018).

The difference in the surgical technique of OAGB compared to LRYGB is that the pouch is longer, and only one anastomosis is created, i.e., gastrojejunostomy with a jejunal loop 200cm distal to the ligament of Treitz (**Figure 6**) and no enteroenterostomy is created.

An Indian RCT with 5-year follow-up from comparing OAGB and LSG showed better weight loss (%EWL 65% vs. 56%, respectively), comorbidity remission and improvement in QOL after OAGB vs LSG (Jain et al., 2021). Furthermore, a French RCT compared standard LRYGB with OAGB and found it not inferior compared to LRYGB in terms of weight loss (%EBMIL 88% after OAGB and 86% after LRYGB) and metabolic improvement at two years (Robert et al., 2019). However, due to the 200cm long biliopancreatic limb, OAGB was reported to result in more malabsorptive effects, such as diarrhea, steatorrhea, and nutritional adverse events (Robert et al., 2019), and after the trial, OAGB was initially banned in France. Bile or acid reflux are additionally potential drawbacks of OAGB.

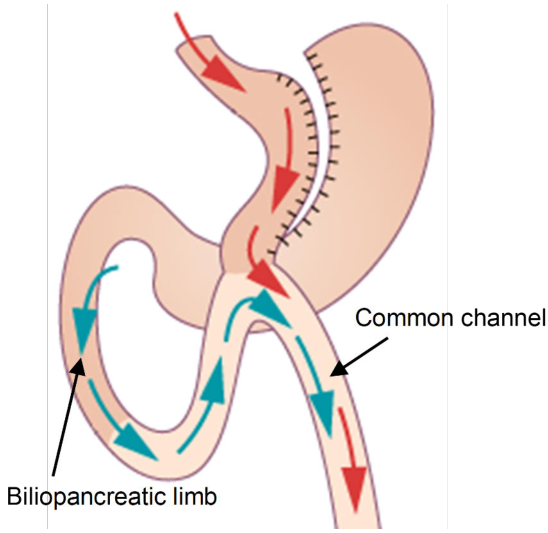


**Figure 6**. One anastomosis gastric bypass, OAGB. Leppäniemi et al., Surgery, Duodecim Publishing Company, 2018. Artist: Tiina Ripatti-Toledo. Modified and reproduced with the permission of the copyright holders.

#### 2.3.4.3 Single anastomosis duodenoileal bypass with sleeve gastrectomy (SADI-S)

SADI-S is a relatively new procedure first published in 2010 (Sánchez-Pernaute et al., 2010). It is a variation of DS incorporating a sleeve gastrectomy and bypass. It is used both as a first-stage procedure and a revisional procedure after LSG.

In SADI-S, LSG is created first, and then an ileal loop 200 to 300cm proximal to the ileocaecal valve is anastomosed to the duodenum (**Figure 7**). As in OAGB, no enteroenteral anastomosis is created.

Long-term outcomes of this relatively new procedure are still lacking, but short- and midterm results appear positive with %EWL ranging from 62 to 104% at 12 months, and %TWL from 22 to 38% at 5 years, as well as promising improvements in metabolic health (Brown et al., 2021).

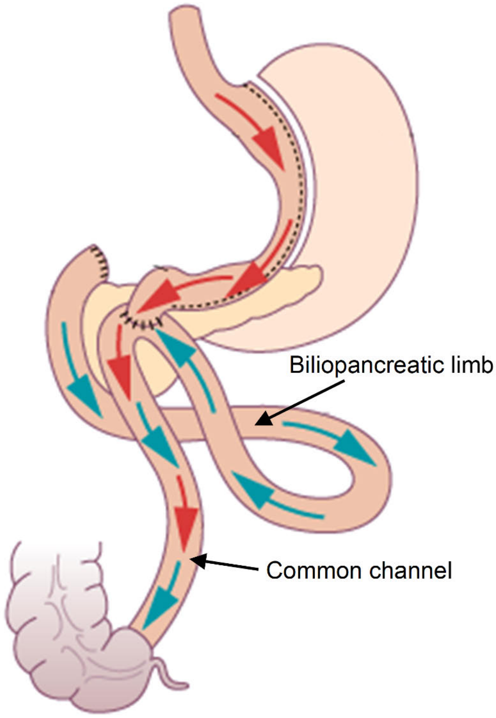


**Figure 7**. Single anastomosis duodenoileal bypass with sleeve gastrectomy, SADI-S. Leppäniemi et al., Surgery, Duodecim Publishing Company, 2018. Artist: Tiina Ripatti-Toledo. Modified and reproduced with the permission of the copyright holders.

#### 2.3.4.4 Biliopancreatic diversion (BPD) and biliopancreatic diversion with duodenal switch (BPD-DS)

BPD and BPD-DS represent only 0.5% of bariatric procedures done globally, with about 3300 procedures per year, although being the most effective one regarding weight loss and T2DM remission outcomes. This is due to the complexity of the procedure, and higher complication and mortality rate. (Angrisani et al., 2018) However, for selected patients such as patients with a BMI over 50 kg/m2 (Skogar et al., 2017) and patients with advanced T2DM (Roslin et al., 2015), BPD and BPD-DS may be the best options.

The surgical technique of BPD consists of partial distal gastrectomy with closing of the duodenal stump, transection of the small bowel about 200-250 cm proximal to the ileocecal valve, and this distal part of the small bowel is then anastomosed to the gastric pouch. A biliopancreatic limb is anastomosed to this alimentary limb 50 cm before the ileocecal valve forming a common channel of only 50 cm which leads to the extreme hypoabsortive effect of this procedure (**Figure 8**).

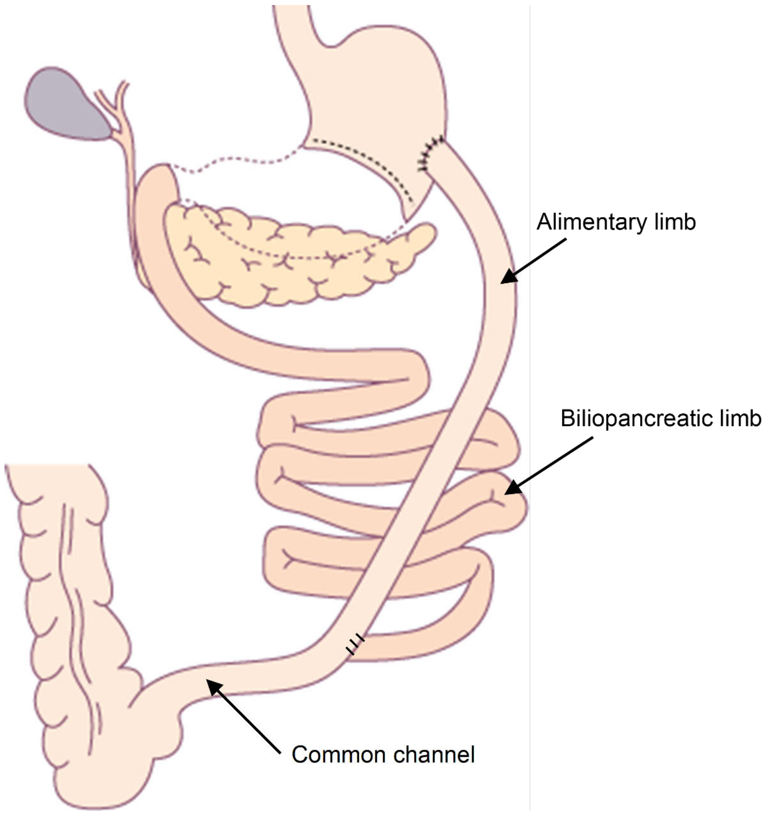


**Figure 8**. Biliopancreatic diversion, BPD. Leppäniemi et al., Surgery, Duodecim Publishing Company, 2018. Artist: Tiina Ripatti-Toledo. Modified and reproduced with the permission of the copyright holders.

To reduce the complications related to BDS (such as malnutrition, anaemia, electrolyte disturbances etc.), BPD-DS was introduced as an option. In this procedure, first a vertical sleeve gastrectomy is performed, usually as a separate first-stage operation. Later, the duodenum is transacted below the pylorus, and the alimentary limb is measured 250 cm from the ileocecal valve and anastomosed to the proximal part of the duodenum. Then the biliopancreatic limb is anastomosed to the ileum about 100cm prior to the ileocecal valve, creating 100cm of common channel (**Figure 9**). A potential disadvantage of BPD-DS is the possible macro- and micronutrient insufficiencies requiring close monitoring (Wiggins et al., 2020).

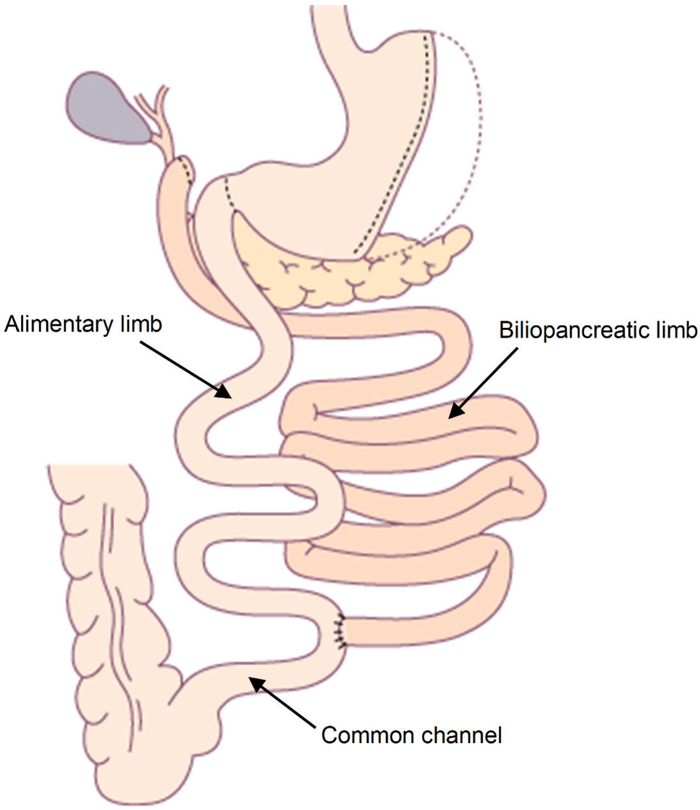


**Figure 9**. Biliopancreatic diversion with duodenal switch, BPD-DS. Leppäniemi et al., Surgery, Duodecim Publishing Company, 2018. Artist: Tiina Ripatti-Toledo. Modified and reproduced with the permission of the copyright holders.

#### 2.3.4.5 Endoluminal procedures

In 2016, 4% (n=25 000) of all bariatric procedures globally were endoluminal procedures (EP) (Angrisani et al., 2018). EPs have gained popularity bridging the gap between surgical bariatric procedures and lifestyle interventions. Their outcomes do not reach the benefits of surgical bariatric procedures but are shown to be more effective than conservative treatments. Due to EP's low morbidity and complication rates and the reversibility in most EPs, they might be a good option for patients who do not qualify for MBS or do not want surgery (Pajot et al., 2017; Turkeltaub et al., 2019).

The traditional and most well-known endoscopic procedure is the use of intragastric balloon (IGB), in which a silicone balloon is placed in the stomach occupying space and delaying gastric emptying leading to early feeling of satiety (Staudenmann et al., 2021). There are several types of traditional IGBs, as well as a novel swallowable IGB that does not require endoscopy at all resulting in 7.9% TWL at 1 year (Jamal et al., 2019).

Endoscopic sleeve gastroplasty mimics LSG. The greater curvature of the stomach is sutured to reduce gastric capacity but unlike LSG it is considered reversible as nothing is resected. The weight loss and comorbidity remission results have been somewhat positive in the available short-term studies of endoscopic sleeve gastroplasty (Abu Dayyeh et al., 2022; Staudenmann et al., 2021).

Another possible endoscopic treatment is aspiration therapy, where an aspire assist device allows for controlled postprandial aspiration of gastric content and thus lowers calorie intake inducing weight loss. The device is inserted endoscopically similarly to percutaneous endoscopic gastrostomy and is also removable. (Pajot et al., 2017; Staudenmann et al., 2021)

Other EPs also exist such as EndoBarrier® (a 60cm plastic sheath from proximal duodenum to the jejunum mimicking a duodenojejunal bypass) and the ValenTx® (a 120cm barrier device from gastroesophageal junction to jejunum), but both of these have relatively high rates of early removal due to patient intolerance (Pajot et al., 2017).

Several EPs are under vast research and development, and very likely not all will be applied in clinical use. However, with relatively positive short-term weight loss results combined with the mini-invasive and reversable nature of the procedures, they certainly may have their specific place in the growing need of bariatric procedures.

## 2.4 Effects of metabolic bariatric surgery

The heterogeneity in reporting MBS outcomes has made it difficult to compare the results from different trials. In 2015, Brethauer et al. published ASMBS standardized reporting guidelines for weight loss and other outcomes of MBS aiming to unify the reporting enabling comparison of different studies in the future (Brethauer et al., 2015). However, compliance for these guidelines has been low despite ease of use (Burger et al., 2020; Shahwan et al., 2022).

### 2.4.1 Effect on weight loss

Weight loss has traditionally been the primary endpoint of MBS studies. There are several ways to define weight loss, which has caused problems when comparing different studies with each other.

Previously in the surgical literature, percent excess weight loss (%EWL) was the most common method in defining weight loss after MBS. It is calculated as (initial weight – follow-up weight)/(initial weight – ideal weight corresponding to BMI 25) x100%. The limitations of %EWL is that it may not reflect successful weight loss in patients with very high BMI, and it is also very hard to understand both for the patients and also health care professionals unlike percent total weight loss (%TWL). %TWL has been recommended to be the outcome measure of choice when reporting weight loss after LRYGB because it is less influenced by preoperative BMI (Corcelles et al., 2016).

Change in BMI (ΔBMI, weight/height$^2$), percent excess BMI loss [%EBMIL, change in BMI/(initial BMI-25) x100], total absolute weight loss (TWL, weight loss in kilograms), and %TWL [(Initial Weight) – (Postop Weight)/(Initial Weight)× 100] are other common variables for reporting weight loss. Despite the guidelines, according to a recent study significant heterogeneity in reporting weight loss outcomes remains (Shahwan et al., 2022).

The superiority of MBS compared to conservative treatments of obesity has been shown in many studies (Adams et al., 2017; Puzziferri et al., 2014; Sjöström, 2013). In a 12-year follow-up by Adams et al. with 1150 patients MBS resulted in -35kg weight loss compared to -2 to 0kg weight loss in the non-surgery group (Adams et al., 2017). Similar results were found in the SOS study with over 4000 patients as MBS led to -18% weight loss at 20 years compared to -1% in patients who received usual care (Sjöström, 2013). In a meta-analysis of O'Brien et al. with ≥10 years of follow-up, %EWL after LRYGB, LSG, BPD (+/- DS), and LAGB were 57%, 58%, 74%, and 46%, respectively (O'Brien et al., 2019). All procedures were associated with substantial and long-lasting weight loss. Another meta-analysis from Yang et al. consisting of RCTs with five-year follow-up showed %EWL of 59% after LSG and 69% after LRYGB (Yang et al., 2019). The merged data of the 5-year results of two largest RCTs comparing LRYGB and LSG reported 56% %EBMIL after LSG and 63% after LRYGB (Wölnerhanssen et al., 2021).

### 2.4.2 Effect on obesity-related comorbidities

#### 2.4.2.1 Effect on T2DM

One of the most important comorbidities of obesity is T2DM due to its micro- and macrovascular complications and increased mortality. Therefore, remission of T2DM is one the most positive outcomes of all means of weight loss. The remission of T2DM has been traditionally defined according to American Diabetes Association criteria (Buse et al., 2009) as HbA1c <6.5% or 48 mmol/mol for at least 1 year's duration in the absence of active pharmacologic therapy or ongoing procedures. However, a new recommendation and consensus of American Diabetes Association (Riddle et al., 2021) has been introduced, in which a remission is defined as HbA1c

< 6.5% or 48 mmol/mol that persists for at least three months in the absence of usual glucose-lowering pharmacotherapy.

According to several studies, MBS results in long-term remission of T2DM (Adams et al., 2017; Puzziferri et al., 2014; Rubino et al., 2016), and already according to 2016 Diabetes Surgery Summit guideline, MBS should also be considered for patients with BMI 30 to 34.9kg/m$^2$ and poorly controlled T2DM (Rubino et al., 2016). It is proven to be superior compared to conservative treatments in achieving T2DM remission in various studies (Courcoulas et al., 2020; Ikramuddin et al., 2018; Mingrone et al., 2015; Schauer et al., 2017). In the RCT of Courcoulas et al. with 5-year follow-up comparing MBS vs lifestyle intervention for T2DM treatment, partial or complete T2DM remission was achieved by 30% of LRYGB patients and by 0% of lifestyle intervention patients at 5 years (Courcoulas et al., 2020). The Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial also showed both LRYGB and LSG superior to medical therapy alone in T2DM remission at 5 years of follow-up (Schauer et al., 2017). A meta-analysis of Sheng et al. with long-term follow-up ≥5 years showed that MBS significantly increased T2DM remission, reduced micro- and macrovascular complications and reduced mortality compared to non-surgical treatment (Sheng et al., 2017).

Recent meta-analyses have shown no significant difference in T2DM remission between LRYGB and LSG (Han et al., 2020; Lee et al., 2021). In the merged data of the two largest RCTs comparing LSG an LRYGB there was no difference in the remission of T2DM; complete or partial remission was achieved in 49% after LSG and 56% after LRYGB at 5 years (Wölnerhanssen et al., 2021). In a large cohort study with 9710 patients, LRYGB resulted in slightly higher T2DM remission rates compared to LSG (McTigue et al., 2020). Similarly, in the Oseberg RCT of Hofsø et al., LRYGB was found superior for T2DM remission at 1 year (Hofsø et al., 2019).

There are many factors affecting the probability of T2DM remission after MBS, such as the duration of T2DM, number of medications, and the preoperative level HbA1c, and these are further discussed in chapter 2.6.

#### 2.4.2.2 Effect on hypertension, dyslipidemia, and obstructive sleep apnea syndrome

MBS has positive effects on several other obesity-related comorbidities as well. These include for example hypertension (Buchwald et al., 2004; Schiavon et al., 2020), hyperlipidemia (Buchwald et al., 2004; Wölnerhanssen et al., 2021), OSAS(Buchwald et al., 2004; Furlan et al., 2021), asthma (Xie et al., 2023), stroke, coronary artery disease and heart failure (van Veldhuisen et al., 2022), PCOS and infertility (Tian et al., 2021), and cancer (Zhang et al., 2020). The remission of hypertension is usually defined by no anti-hypertensive medications, as objective blood pressure measurements are hard to get (Brethauer et al., 2015). The remission of dyslipidemia is defined based on European Society of Cardiology/European Atherosclerosis Society guidelines (Catapano et al., 2011) as no need for medication and normal lipid values (low-density lipoprotein cholesterol <115.8 mg/dl [3.0 mmol/l]). The remission of OSAS is usually assessed as discontinuation of continuous positive airway pressure (CPAP) use (Brethauer et al., 2015).

In the RCT of Ikramuddin et al., MBS patients had an average of 3.0 fewer medications for T2D, hypertension, and dyslipidemia, compared with lifestyle therapy (Ikramuddin et al., 2013). In the systematic review of Puzziferri et al. with 8000 patients and at least 2-year follow-up, MBS resulted in up to 38% remission of hypertension, and 60% remission of hyperlipidemia (Puzziferri et al., 2014).

In the meta-analysis of Lee et al. comparing LSG and LRYGB, they found no difference in hypertension remission, but LRYGB resulted in higher rates of dyslipidemia remission (Lee et al., 2021). Furthermore, in the meta-analyses of Han et al., LRYGB was superior to LSG in managing hypertension and dyslipidemia (Han et al., 2020). In the merged data of SLEEVEPASS and SM-BOSS, LRYGB was associated with higher rate of hypertension remission (LSG, 45% vs LRYGB, 60%) and less medication for dyslipidemia but there was no statistical difference in the remission of OSAS (LSG, 60% vs LRYGB, 54%) or dyslipidemia (LSG, 34% vs LRYGB, 48%) at five years (Wölnerhanssen et al., 2021). Still, long-term evidence from RCTs to detect differences in the remission of comorbidities between LSG and LRYGB are lacking.

### 2.4.3 Effect on quality of life (QOL)

Quality of life is an important outcome of MBS. QOL can be measured in many ways but is usually divided into health-related QOL (HRQOL) and disease-specific QOL (DSQOL). QOL questionnaires include for example physical, psychological, and social aspects of life. People with severe obesity are known to have lower QOL compared to normal-weight population (Kolotkin et al., 2017; Taylor et al., 2013). Not only do they have lower physical success in QOL but also lower self-esteem, more depression and eating disorders, and poorer social relations (Kolotkin et al., 2017).

MBS has proven to improve QOL by many studies (Andersen et al., 2015; Hachem et al., 2016; Macano et al., 2017; Major et al., 2015). In the study of Schauer et al. comparing MBS with conservative treatment, QOL was addressed with RAND 36-Item Health Survey ranging from 0 to 100, with higher scores indicating better health. Significant mean (±SD) changes from baseline in general health scores of LSG, LRYGB, and medical therapy (16±22, 17±20, and 0.3±16, respectively;

P<0.05 for both) and changes in bodily pain scores (0.5±21, −2.4±25, and −17±25; P<0.05 for both) were noticed at 5 years, with results favouring the MBS groups. Higher weight loss was associated with better QOL. (Schauer et al., 2017) In the SOS study significantly better HRQOL outcomes were found after MBS compared to conventional group in current health perceptions, social interaction, psychosocial functioning, and depression at 10-year follow-up (Karlsson et al., 2007).

There seems to be no difference in QOL between LSG and LRYGB in short- and mid-term (Hu et al., 2019; Major et al., 2015; Nickel et al., 2017; Versteegden et al., 2018; Wölnerhanssen et al., 2021). In the merged data of SLEEVEPASS and SM-BOSS, the Moorehead-Ardelt QOL score was significantly higher at 5-years compared to baseline (LSG, 0.1 vs 1.1; LRYGB, 0.2 vs 1.2, P<0.01) with no significant difference between the procedures (P=0.38). However, long-term assessments from RCTs comparing LSG and LRYGB including both HRQOL and DSQOL are not available.

### 2.4.4 Effect on mortality

Obesity is major risk factor for increased mortality (Whitlock et al., 2009). MBS improves life-expectancy and lowers all-cause mortality at long-term (Wiggins et al., 2020). In a large cohort study of Arterburn et al. with 10 000 patients, mortality rate was 13.8% in MBS group compared to 23.9% in the control group at 10 years of follow-up (Arterburn et al., 2015). In a recent meta-analysis of Syn et al. with 175 000 participants, MBS was associated with 6.1 years longer life expectancy compared to control group, and for people with T2DM life expectancy was up to 9.3 years longer after MBS (Syn et al., 2021).

MBS is also related to lower cancer-risk and lower cancer-related mortality (Zhang et al., 2020). In the SPLENDID study including 30 000 patients, the cumulative risk for 13 types of obesity-related cancers was 2.9% in the MBS group and 4.9% in the control group at 10 years, and the cumulative risk for cancer-mortality was 0.8% and 1.4%, respectively (Aminian et al., 2022).

Bariatric procedures are considered safe and have improved especially since early 2000s. According to a review article from Arterburn et al., the perioperative mortality ranges from 0.03 to 0.2% (Arterburn et al., 2020). In a meta-analysis of Cardoso et al. with 4030 patients from 38 RCTs, short-term (≤30 days) all-cause mortality after MBS was 0.18% (Cardoso et al., 2017). In a Finnish registry study 30-days mortality was 0.08% after MBS in Finland. In comparison, the mortality after elective cholecystectomy was significantly higher (HR 2.38) according to the same study. (Böckelman et al., 2017)

### 2.4.5 Morbidity of metabolic bariatric surgery

Surgical complications are usually categorized into early (<30 days) and late (≥30 days). Complications are commonly specified with the Clavien-Dindo classification (Dindo et al., 2004) or the Comprehensive Complication Index (Cotton et al., 1991).

Possible early complications after LSG can include venous thromboembolism, gastro-intestinal or intra-abdominal bleeding, staple line leak or wound infection. Early complications of LRYGB include bowel obstruction, venous thromboembolism, gastrointestinal or intra-abdominal bleeding, anastomotic leakage, wound infection and internal herniation. The risk of <30 days' serious adverse events (such as reoperation, prolonged hospitalization, and venous thromboembolism) ranges from 0.8% to 5.6% after LSG and 1.4% to 9.4% after LRYGB (Arterburn et al., 2020). In the meta-analysis of Lee et al. involving 33 studies with 2500 patients, there was no difference in the rate of 30-day minor and major complications (Lee et al., 2021), but the meta-analysis of Han et al. showed more early complications after LRYGB (Han et al., 2020). In the SLEEVEPASS trial, LSG was associated with fewer early minor complications than LRYGB (7.4% vs 17.1%) but there was no difference in early reoperations (2.5% vs 3.3%) (Helmio et al., 2012). The same was observed in SM-BOSS study, <30 days complications occurred more often after LRYGB than LSG (17.2% vs 8.4%) but there were no significant differences in early severe complications (Peterli et al., 2013). In the SLEEVEPASS trial, the most typical major early complication after LSG was bleeding (2.5%) and after LRYGB bleeding (6.0%) and intra-abdominal infection (2.6%) (Salminen et al., 2018).

Possible late (≥30 days) complications after LSG include sleeve stricture, gastroesophageal reflux disease, cholelithiasis, incisional hernia, and nutritional and vitamin deficiencies. Possible late complications after LRYGB are anastomotic stricture, bowel obstruction, marginal ulceration, cholelithiasis, incisional hernia, nutritional and vitamin deficiencies, dumping syndrome, malabsorption, gastrogastric fistula, and internal hernia (especially if mesenteric defects are left unclosed). In most studies, the late complications are assessed as the rates of reoperation, which has found to be higher for LRYGB than LSG in many studies (Courcoulas et al., 2020; Lewis et al., 2019; Li et al., 2021), except for bariatric conversion or revision procedures which are more common after LSG (DuPree et al., 2014). In a large cohort study of Li et al. with 35 000 patients the overall risk for reinterventions (nutritional, endoscopic, radiologic, or surgical) was 21.3% for LSG and 28.3% for LRYGB at five years. In the SLEEVEPASS trial, the late overall morbidity rate was 19% after LSG and 26% after LRYGB at five years, and all the late major complications were reoperations (8% after LSG and 15% after LRYGB). The reasons for reoperations after LSG were GERD (5.8%) and incisional hernia (2.5%), and after LRYGB suspected internal herniation (14.3%) and incisional hernia (0.8%). (Salminen et al., 2018)

In a ten-year follow-up cohort study of LRYGB, adverse effects (anastomotic stricture, marginal ulcer, internal hernias, adhesions) were reported in 21.3%, and 14.6% of patients required re-laparoscopy (Duvoisin et al., 2018). Internal hernias are the feared complication of LRYGB and thus the mesenteric defects are nowadays usually closed. In a recent meta-analysis from Muir et al. the rate of internal herniations was reduced when the defects were closed (2% vs 6%) as well as re-operations for small bowel obstructions (2% vs 10%) (Muir et al., 2023).

In a ten-year follow-up of LSG, up to 57% of patients had reflux symptoms, in as much as 14% prevalence of BE was detected, and the reoperation rate was 33% (Felsenreich et al., 2018). Indeed, GERD is the major problem concerning LSG, however, no long-term RCTs with preoperative upper gastrointestinal endoscopies are available to address this issue. GERD and its effect on MBS, and vice versa, is further discussed in chapter 2.5.

## 2.5 Gastroesophageal reflux disease (GERD)

### 2.5.1 Pathophysiology and prevalence of GERD in patients with obesity

GERD is a condition where acid-containing gastric contents persistently regurgitate into the esophagus. Normally, the regurgitation is blocked by the so-called gastro-esophageal barrier consisting of the lower esophageal sphincter (LES), the crural diaphragm and the back-stroke valve mechanism of the esophagogastric junction. When this barrier is compromised, usually due to LES dysfunction, the esophageal mucosa is repeatedly exposed to digestive enzymes, and bile and gastric acids. The back flow of these harmful contents may result in typical GERD symptoms of heartburn and regurgitation. This cascade can finally lead to metaplastic and dysplastic transformation of the esophageal mucosa. The clinical findings of GERD can include esophagitis, esophageal strictures, and intestinal metaplasia (Barrett's esophagus, BE). (Tack et al., 2018)

Obesity is a major risk factor for GERD. Other risk factors include older age, male sex, white race, and smoking (Richter et al., 2018). The prevalence of GERD is hard to determine due to the heterogeneity of the assessments of GERD symptoms, but is ranging between 8.8 to 25.9% in Europe, 18.1 to 27.8% in North America, and 2.5 to 7.8% in East Asia (El-Serag et al., 2014). The prevalence of GERD is markedly higher in patients with obesity (OR 1.73) (Eusebi et al., 2018), and central adiposity is associated with higher risk of esophagitis (OR 1.87), BE (OR 2.04), and esophageal adenocarcinoma (OR 2.51) (Singh et al., 2013). The mechanism behind the connection of obesity and GERD is the increase of intra-abdominal pressure, which again leads to distension of crural diaphragm, and finally often can result in sliding hiatal hernia, which compromises the gastroesophageal barrier and leads to GERD (Tack et al., 2018).

### 2.5.2 Diagnosis of GERD

There is a lack of standard definitions in diagnosing GERD, which makes it difficult to define the accuracy of patients' reporting typical symptoms of GERD and their actual correlation on GERD existence (Richter et al., 2018). In a study from Dent et al. with 300 patients with typical GERD symptoms (heartburn and regurgitation), only 66% had GERD based on endoscopic findings and/or 24h pH-measurements. GERD-questionnaires did not perform better, the sensitivity and specificity were 62% and 67%, respectively. Furthermore, symptom response to esomeprazole was neither sensitive nor specific for the diagnosis of GERD. (Dent et al., 2010) In 2018, the Lyon consensus statement on diagnosis of GERD was published, and accordingly, no individual method is sufficient for diagnosing GERD, and combined information from several available method is required. (Gyawali et al., 2018) Useful methods suggested in the consensus statement are presented next in brief.

Endoscopy is the most common and clinically valid way to examine the upper gastrointestinal tract. Photographs and biopsies can be taken during the endoscopy. The specific findings of esophagitis, BE, and adenocarcinoma are described further. Different questionnaires can be helpful in determining the type and complexity of GERD symptoms. Proton pump inhibitor (PPI) trial as first-line intervention can be useful and is less costly than endoscopy in patients without alarming symptoms. A combined 24h impedance and pH measurement detects objectively the frequency and acidity of the refluxate and can be compared with subjective symptoms. Esophageal high-resolution manometry can provide information on esophageal motility and esophagogastric junction function. (Gyawali et al., 2018)

### 2.5.3 Complications of GERD

#### 2.5.3.1 Esophagitis

Esophagitis is an inflammation of the esophagus. It is caused by the repeated reflux of gastric acid juices, which dilate the intercellular spaces of esophageal squamous epithelium, and this results in the presence of inflammatory cells (Tack et al., 2018). Esophagitis is diagnosed in upper gastrointestinal endoscopy. Los Angeles - classification (Armstrong et al., 1996) is used to evaluate the grade of esophagitis, and is presented in **Figure 10**. The grades from A to D include the length and the continuity of the mucosal breaks caused by esophagitis.

#### 2.5.3.2 Barrett's esophagus

In Barrett's esophagus (BE), the distal esophageal squamos cells are histologically replaced with intestinal metaplasia. The pathogenesis is not completely known, but it is a consequence of continues tissue injury due to GERD, resulting in the mucus-secreting columnar cells replacing the reflux-damaged esophageal squamos cells (Burke et al., 2012). The exact prevalence of BE in the general population remains unclear due to endoscopies usually performed for GERD symptoms, but it ranges between 1.6% in the Swedish population and up to 5.6% in the American population (Ronkainen et al., 2005; Spechler et al., 2014). Major risk factors include age>50, male sex, obesity, hiatal hernia, and smoking (Spechler et al., 2014).

The diagnosis of BE requires upper gastrointestinal endoscopy. A typical finding of BE is presented in **Figure 11**, where the normal esophageal mucosa is replaced with intestinal metaplasia. The diagnosis of BE needs both endoscopic and histologic confirmation. The endoscopic biopsies have to be taken above the gastroesophageal junction (Z line) preferably according to the American Society for Gastrointestinal Endoscopy Seattle biopsy protocol: 4-quadrant biopsy sampling at 1- to 2-cm intervals starting from the top of the gastric folds up to the most proximal extent of the suspected BE, along with targeted biopsy sampling from any mucosal abnormality (Qumseya et al., 2019). According to the American Gastroenterological Association, the histological diagnosis of BE must include the presence of intestinal metaplasia, i.e. goblet cells in the histologic sample (Spechler et al., 2011), and preferably verified by two gastrointestinal pathologists. In contrast, according to the British Society of Gastroenterology definition the presence of only gastric metaplasia is also diagnosed as BE (Fitzgerald et al., 2014), which causes contradictions for example in comparing results from different studies.

BE is a premalignant finding, and a risk factor for esophageal adenocarcinoma (EAC). However, the annual risk of patients with BE for developing EAC seems to be relatively low, ranging from 0.12% to 0.5% (de Jonge et al., 2010; Hvid-Jensen et al., 2011). Nevertheless, according to the European Society of Gastrointestinal Endoscopy (ESGE), all patients with a BE ≥10 cm, a confirmed diagnosis of low-grade dysplasia, high-grade dysplasia, or early cancer should be referred to a BE expert centre for surveillance and/or treatment. The endoscopic follow-up should be 5 years for BE ≥1cm to <3cm, and 3 years for BE ≥3cm to <10cm. Long (≥10cm) BEs as well as all BEs with detected dysplasia of any degree should be treated (usually with radiofrequency ablation therapy) and all visible abnormalities should be removed by endoscopic resection to obtain optimal histopathological staging. (Weusten et al., 2017)

The risk factors for EAC are similar to BE; smoking, alcohol, obesity, prolonged GERD symptoms, BE, and a diet with lack of fruits and vegetables (Pennathur et al., 2013). The risk of developing adenocarcinoma of BE is relatively low, and an estimated 95% of patients with a new diagnosis of adenocarcinoma do not have a previous diagnosis of BE (Hvid-Jensen et al., 2011). In the Finnish cancer registry report, in 2020 there were 273 new esophageal carcinomas, and the incidence was higher in men (n=196). The prognosis remains poor; 31% of men and 45% of women are alive after one year of diagnosis, and 9% and 18% at five years, respectively. The poor survival rate is due to both diagnosis at a later and advanced stage, and the metastasis-sending nature of even superficial esophageal tumors (Pennathur et al., 2013).

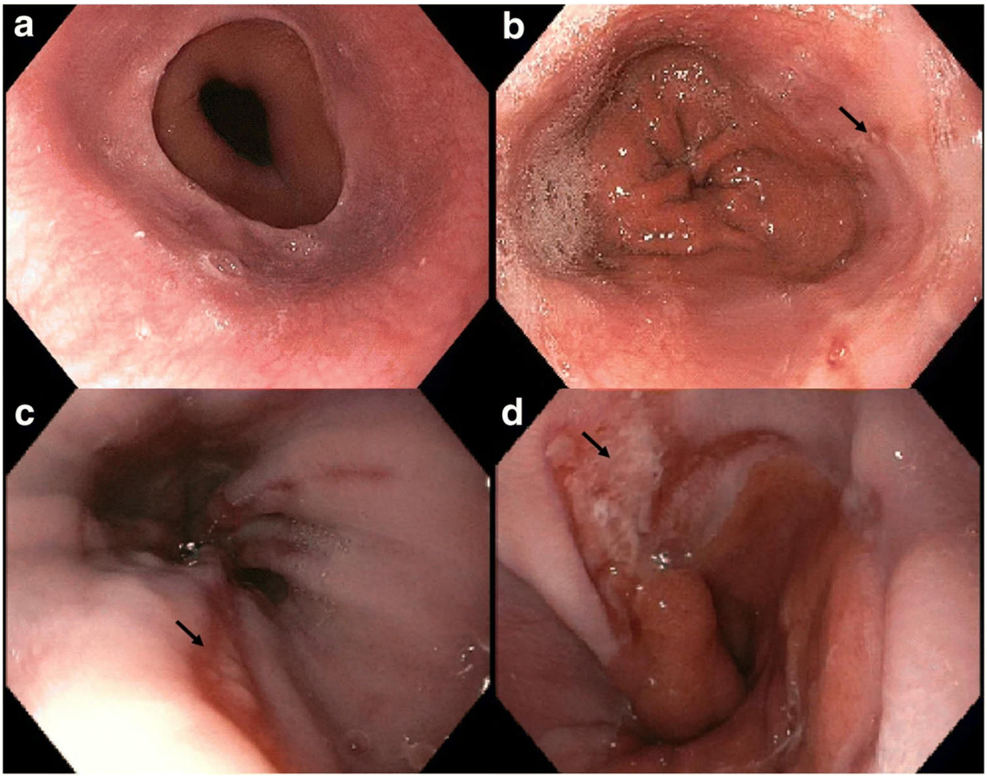


**Figure 10.** Los Angeles -classification. (**A**) Mucosal breaks confined to the mucosal fold, each no longer than 5 mm. (**B**) At least one mucosal break longer than 5 mm confined to the mucosal fold but not continuous between two folds. (**C**) Mucosal breaks that are continuous between the tops of mucosal folds but not circumferential. (**D**) Circumferential mucosal break with one portion being of significant depth.
Reproduced with permission from Lim CH et al. Correlation Between Symptomatic Gastro-Esophageal Reflux Disease (GERD) and Erosive Esophagitis (EE) Post-vertical Sleeve Gastrectomy (VSG). Obes Surg. 2019 Jan;29(1):207-214, *Copyright Clearance Center's RightsLink® service.*

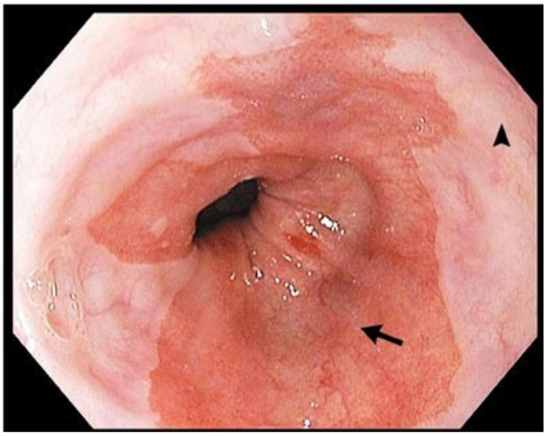

**Figure 11**. Endoscopic Detection of Barrett's Esophagus. The red, columnar-lined esophagus (arrow) and the contrast between the squamous (arrowhead) and columnar (arrow) epithelium are characteristic of Barrett's esophagus. Reproduced with permission from Sharma P. Clinical practice. Barrett's esophagus. N Engl J Med. 2009 Dec 24;361(26):2548-56, *Massachusetts Medical Society©.*

### 2.5.4 Effect of GERD on metabolic bariatric surgery

GERD has been reported in up to 62% of MBS candidates (Bou Daher et al., 2019). Recently, some studies have shown alarmingly high incidence of worsening or de novo GERD, esophagitis, and BE after LSG (Bevilacqua et al., 2020; Csendes et al., 2019; Felsenreich et al., 2018; Genco et al., 2017). As LSG is the most common bariatric procedure worldwide, this has raised questions of the need for preoperative endoscopy and endoscopic follow-up of LSG patients. The diagnosis of GERD is difficult since the correlation between GERD symptoms and findings is relatively weak. In other words, the absence of symptoms does not rule out the presence of GERD. Still, there is no consensus on whether upper gastrointestinal endoscopy should be offered to all MBS candidates. (Bou Daher et al., 2019) In practice, LSG is nowadays probably rarely performed in patients with diagnosis of GERD, but there is still no consensus on whether preoperative GERD and/or hiatal hernia (and up to what extent) should be a contraindication for LSG (Gagner et al., 2016; Mechanick et al., 2019). However, according to the 2019 updated American clinical practise guidelines: “significant gastrointestinal symptoms should be evaluated before bariatric procedures, and the use of pre-operative endoscopy may be considered in all patients being evaluated for LSG” (Mechanick et al., 2019).

In the light of above, LRYGB is usually the procedure of choice for patients with preoperative GERD. It has been studied, that LRYGB is actually superior to fundoplication in patients with severe obesity as an anti-reflux procedure (Gorodner et al., 2022; Varela et al., 2009). Furthermore, it has been shown that hiatal hernia is not a contra-indication for LRYGB, and concomitant hiatal hernia repair with

LRYGB appears to be safe and feasible (Kothari et al., 2012), although more common in LSG patients (Docimo et al., 2019).

### 2.5.5 Effect of metabolic bariatric surgery on GERD

LSG creates a narrow gastric high-pressure conduit with delayed emptying. The angle of His is altered and this compromises the integrity of the gastroesophageal barrier, which results in increased intragastric pressure, and possible worsening of or de novo GERD (Mion et al., 2016). In the 5-year report of SM-BOSS trial, remission of GERD was seen in 25% in LSG group and 60% in LRYGB group, but on the other hand, de novo GERD was reported in 31.6% after LSG and 10.7% after LRYGB. (Peterli et al., 2018) Several studies have shown new onset of GERD, esophagitis, and even BE after LSG (Bevilacqua et al., 2020; Csendes et al., 2019; Felsenreich et al., 2018; Juodeikis et al., 2017). In an Italian study, de novo BE was detected in up to 17.2% at five years after LSG (Genco et al., 2017), and in an Austrian study in 15% (Felsenreich et al., 2018) but these findings are markedly higher than in other studies. For example, in a recent study of Wölnerhanssen et al. the prevalence of de novo BE at five years was only 3.6%, and similar after LRYGB (Wölnerhanssen et al., 2023).

The effects of LRYGB on GERD are very positive in patients with obesity (Alimi et al., 2021; Ashrafi et al., 2020; Gorodner et al., 2022). In a recent meta-analysis, LRYGB was proved efficient and safe also as a revisional procedure in symptomatic patients after fundoplication failure (Bhat et al., 2022). According to another meta-analysis, BE is also significantly improved after LRYGB (Adil et al., 2019).

GERD is the most frequent complication of LSG, and the biggest reason for conversions from LSG to LRYGB. 9% of LSG patients in SM-BOSS study and 6% in SLEEVEPASS study were converted to LRYGB due to GERD at 5 years. (Peterli et al., 2018; Salminen et al., 2018) Conversion from LSG to LRYGB seems to be effective for alleviation of GERD in most cases (Alimi et al., 2021; Matar et al., 2021; Parmar et al., 2017).

LSG is the leading bariatric procedure worldwide, but the fear of GERD and especially BE with extensive follow-up overshadows its popularity. Even though LSG's effect on GERD and GERD's effect on LSG has been a hot topic since LSG became the most popular bariatric procedure, there is a lack of comparative long-term RCTs with comparable upper gastrointestinal endoscopies performed preoperatively and at long-term follow-up.

## 2.6 The effect of T2DM on metabolic bariatric procedure choice

T2DM is one of the most significant comorbidities related to obesity, and is a major factor in the growing numbers of cardiovascular morbidity and mortality (La Sala et al., 2020). Selecting the best bariatric procedure is a multifactorial issue, and optimizing the outcomes of MBS has been under active research. T2DM plays a very important role in the decision making, and the presence of preoperative T2DM and its severity, as well as its predicted remission after MBS must be considered. Recognizing the preoperative factors that affect the likelihood of T2DM relapse and selecting the best bariatric procedure for each individual to achieve T2DM remission is of greatest importance, and these topics are discussed in the next chapter.

### 2.6.1 The preoperative factors affecting T2DM remission

#### 2.6.1.1 Duration of T2DM

The preoperative duration of T2DM plays an important role in the success of MBS. MBS is shown less effective in patients with longer preoperative duration of T2DM, and the literature is unanimous on this subject (Moradi et al., 2022; Panunzi et al., 2016; Sharma, 2014; Wang et al., 2015; Wölnerhanssen et al., 2021). In the Swedish Obese Subjects (SOS) study with 343 surgery patients with T2DM at baseline and ten years of follow-up, short diabetes duration was associated to both high remission rate at two years and low relapse rate between two and ten years of follow-up (Sjostrom et al., 2014). Aminian et al. found that LSG patients with preoperative T2DM duration of ≥5 years had 16% T2DM remission rate at 6 years of follow-up, while in the whole study population the T2DM remission rate after LSG was 63% at 6 years (Aminian et al., 2016). It seems that surgical intervention within 5 years of diagnosis of T2DM results in higher rate of long-term remission (Brethauer et al., 2013).

#### 2.6.1.2 Glycemic control and beta cell function

Another important preoperative predictor of T2DM remission after bariatric surgery is the baseline glycemic control of the patient. Lower fasting plasma glucose and lower HbA1c-values at baseline predict better remission of T2DM, and the literature seems to be unanimous also on this matter (Jiménez et al., 2012; Moradi et al., 2022; Panunzi et al., 2016; Souteiro et al., 2017; Wang et al., 2015; Yan et al., 2017). In a cohort study of Souteiro et al. with 363 diabetic patients, the patients achieving T2DM remission had a mean of 0.90 mmol/mol lower HbA1c and 1.35 mmol/l lower fasting plasma glucose at baseline compared to those who did not achieve remission (Souteiro et al., 2017).

Recently, the function of pancreatic insulin-secreting beta cells has also been under active research as a predictive factor for T2DM remission after MBS. C-peptide is a widely used measure of pancreatic beta cell function as the level of it depends on the amount of insulin produced by pancreas and is thus a sign of endogenous insulin-production. Considering this, it is easy to understand that studies have shown better beta cell function and higher preoperative C-peptide values as good predictors of T2DM remission (Souteiro et al., 2017; Wang et al., 2015; Yan et al., 2017). In one study with 226 patients with T2DM, who underwent MBS, a C-peptide level > 2.72 ng/ml was associated with T2DM remission two years postoperatively (Salman et al., 2021).

#### 2.6.1.3 Number of medications and insulin therapy

The preoperative number of anti-diabetic oral medications and insulin therapy have also been evaluated as possible predictive factors of T2DM remission. In a 5-year follow-up study of Aminian et al. with 134 patients with T2DM they found that taking two or more anti-diabetic medications at baseline predicted less long-term remission: 13% remission rate at five years (Aminian et al., 2016). Some other studies have also found less oral medication as a positive predictive factor for T2DM remission (Panunzi et al., 2016; Salman et al., 2021). However, this remains controversial, as in the study of Souteiro et al. the use of oral anti-diabetics and insulin therapy did not reach statistical significance when they were adjusted for age and preoperative HbA1c (Souteiro et al., 2017).

Many other studies have found insulin therapy at baseline as a negative predictive factor for achieving T2DM remission (Jiménez et al., 2012; Moradi et al., 2022; Wang et al., 2015). It seems that especially the absence of long-acting insulin predicts better chance of T2DM remission (Dang et al., 2019).

#### 2.6.1.4 Age and BMI

Other predictors for T2DM remission found in the literature are patient age and preoperative BMI. It seems that younger age relates to better chance of achieving T2DM remission (Panunzi et al., 2016; Souteiro et al., 2017; Wang et al., 2015).

The effect of preoperative BMI on T2DM remission remains somewhat controversial. One study indicated lower preoperative BMI as a predictive factor of T2DM remission (AbdAlla Salman et al., 2022), while another study stated higher BMI to predict better remission (Mateo-Gavira et al., 2021). In the two meta-analyses of Wang et al. and Yan et al., they found no connection between preoperative BMI and remission of T2DM (Wang et al., 2015; Yan et al., 2017). The same result was observed in the study of Panunzi et al., but they found waist circumference as a predictive factor with lower baseline waist to be associated with higher HbA1c reduction (Panunzi et al., 2015).

## 2.6.2 T2DM remission and procedure choice

### 2.6.2.1 T2DM remission after LRYGB vs LSG

As T2DM has a major effect on cardiovascular morbidity and mortality, the possible difference between T2DM remission after LRYGB vs LSG has been under active research, especially since LSG became the most common bariatric procedure. There has been some evidence that LRYGB might be superior to LSG in treatment of T2DM, especially in some older studies (Brethauer et al., 2013), but also in some more recent registry studies and one RCT (Aminian et al., 2021; Hofsø et al., 2019; McTigue et al., 2020). In the large cohort study of McTigue et al. with 9710 patients comparing LSG and LRYGB, T2DM remission rate was approximately 10% higher in patients after LRYGB compared to LSG at 5 years of follow-up (McTigue et al., 2020).

However, in the merged data of SLEEVEPASS and SM-BOSS with 156 patients with T2DM, there was no significant difference in T2DM remission between LRYGB and LSG at 5 years; complete or partial remission of T2DM was seen in 49% after LSG and in 56% after LRYGB (Wölnerhanssen et al., 2021). This is in line with several meta-analyses (Han et al., 2020; Lee et al., 2021; Shoar et al., 2017; Zhao et al., 2019) on this issue, which also found no difference on T2DM remission between the two procedures. This seems to apply also in non-severely obese patients (Sha et al., 2020).

Although T2DM remission outcomes after MBS are proven to be superior compared to other treatments, T2DM relapse appears at long-term in some patients (Aminian et al., 2020). This, however, should not be reflected as a failure, as the trajectory of the disease and its related cardiometabolic risk factors is changed favourably after MBS. LRYGB might be associated to less T2DM relapse at long-term compared to LSG (Aminian et al., 2020). Recurrent weight gain seems to be a risk factor for T2DM relapse (Jiménez et al., 2012).

Altogether, international collaboration and individual patient data meta-analysis (IPDMA) are needed to determine the possible differences in long-term T2DM remission after LRYGB vs LSG.

#### 2.6.2.2 Individualized Metabolic Surgery (IMS) score

The IMS score (Aminian et al., 2017) was presented by Aminian et al. in 2017. It was created to facilitate procedure selection between LSG and LRYGB in patients with severe obesity and T2DM. The IMS score categorizes patients into three categories depending on the severity of T2DM; mild, moderate, and severe, and aims to predict which procedure is the best for each severity stage.

There are four preoperative predictive factors that are used in the calculation of the IMS score including the duration of T2DM (in years), glycemic control (HbA1c <7%), the number of T2DM medications, and insulin use. According to their calculated IMS score, patients are categorized into three stages of T2DM severity: mild (IMS score ≤25, moderate (IMS score >25 but ≤95), and severe (IMS score >95). They suggested LSG as the procedure of choice for the severe stage due to its better risk-benefit ratio compared to LRYGB. LRYGB was recommended for the moderate stage, because in their retrospective cohort LRYGB resulted in better rate of T2DM remission in the moderate stage (60% vs 25%). For mild stage, both procedures were found highly effective. (Aminian et al., 2017)

The IMS score has only been studied in retrospective cohorts (Aminian et al., 2017) or at short- or mid-term follow-up (Chen et al., 2018; Ohta et al., 2021; Park et al., 2020), but not validated in a prospective cohort with a longer-term follow-up.

#### 2.6.2.3 Other scores for predicting T2DM remission after metabolic bariatric surgery

According to a recent meta-analysis (Singh et al., 2021), there are altogether 16 prognostic models for predicting T2DM remission following MBS. Four of them are presented in brief below.

The ABCD score (Lee et al., 2013) was created by Lee et al. in 2013. It consists of four predictive factors of T2DM hailing from the initials of the score: age, BMI, C-peptide level, and duration of T2DM. The score ranges from 0 to 10 with 10 representing the best likelihood of achieving T2DM remission.

The DiaRem (Still et al., 2014) score was presented in 2014 by Still et al. Four preoperative variables are included in the score: age, insulin use, HbA1c level, and type of antidiabetic medication. The score ranges from 0 to 22 with low scores indicating better probability of T2DM remission.

The advanced-DiaRem (ad-DiaRem) (Aron-Wisnewsky et al., 2017) was created in 2017 to improve the accuracy of the original DiaRem score. Two clinical variables were added in the original DiaRem score: duration of T2DM and the number of glucose-lowering agents. The ad-DiaRem score ranges from 0 to 21, and the predictive improvement compared to the DiaRem was most noticeable in patients with low (0-5) or high (15-21) scores (Aron-Wisnewsky et al., 2017).

The DiaBetter score (Pucci et al., 2018) designed by Pucci et al. in 2017 consists of three variables: duration of T2DM, HbA1c level, and antidiabetic medications. Each of them is scored from 0 to 3 with the total score ranging from 0 to 9, with higher points indicating poorer chance of achieving T2DM remission.

#### 2.6.2.4 Comparing the IMS score with other predictive scores of T2DM remission after metabolic bariatric surgery

The different predictive scores have been compared with each other to find the best score in determine T2DM remission after MBS. Chen et al. compared the IMS score and the ABCD score in their retrospective 5-year follow-up study and found that both scores predicted the success of surgery, however, the ABCD score was better in patients with IMS moderate scores (Chen et al., 2018). Ohta et al. found the IMS score and the ABCD score comparable in predicting T2DM remission at 3 and 5 years (Ohta et al., 2021).

Plaeke et al. compared altogether 11 different predictive scores and found the IMS score to be the most accurate one. Along with the IMS score, DiaBetter score, ad-DiaRem score, and DiaRem score best predicted T2DM remission. (Plaeke et al., 2021) In contrast, in another recent study by Karpinska et al., the DiaBetter demonstrated the best predictive performance. Nevertheless, none of the predictive scores were found accurate in patients with advanced stages of T2DM. (Karpińska et al., 2022) In the meta-analysis of Singh et al., the ABCD score and the DiaRem were found to be the most widely validated and showed acceptable to excellent discrimination power (Singh et al., 2021). However, the performance of the IMS score was not reported in this study due to insufficient data in the original IMS publication for comparison calculations. In conclusion, further studies on validating newer models and studies with long-term follow-up of T2DM remission are needed. (Singh et al., 2021)

# 3 Aims

This doctoral thesis focuses on comparing the long-term outcomes after LSG and LRYGB in patients with severe obesity with special emphasis on QOL, reflux, and procedure selection. The specific aims of the present study were:

1. To determine the equivalence of LSG and LRYGB for long-term weight loss at 7 and 10 years, and to compare the remission of obesity-related comorbidities and late complications after LSG and LRYGB at 10 years.

2. To assess the 7-year QOL after LSG and LRYGB covering both DSQOL and HRQOL with comparison of the HRQOL to general population, as well as to evaluate the effect of weight loss outcomes on long-term DSQOL.

3. To compare the long-term GERD symptoms, PPI use, endoscopic esophagitis, and BE after LSG and LRYGB at 10 years.

4. To validate the IMS score and determine its feasibility in both facilitating procedure selection between LSG and LRYGB and in predicting long-term remission of T2DM.

# 4 Patients and Methods

## 4.1 Patients

### 4.1.1 Study I-II (SLEEVEPASS trial)

The SLEEVEPASS trial is a multicentre, multisurgeon, open-label, randomized clinical equivalence trial conducted between March 2008 and June 2010 in three participating hospitals in Finland; Turku, Helsinki, and Vaasa. A total of 240 patients with severe obesity were randomized to undergo either LSG or LRYGB.

The eligibility criteria included age 18 to 60 years, BMI >40 kg/m$^2$ or >35 kg/m$^2$ with a significant obesity-related comorbidity, and previous failed adequate conservative treatment. Exclusion criteria were BMI >60 kg/m$^2$, significant psychiatric or severe eating disorder, active alcohol or substance abuse, active gastric ulcer disease, severe GERD with a large hiatal hernia, and previous MBS.

A preoperative multidisciplinary evaluation according to standard treatment protocol including endocrinologist, dietician, and surgeon was carried out for all the participating patients. Additionally, psychiatric evaluation (if necessary), laboratory tests, upper gastrointestinal endoscopy, and abdominal ultrasound was carried out. Possible Helicobacter Pylori infections and gastric ulcers were treated preoperatively as well as symptomatic gallstones.

Randomization was carried out with closed-envelope method with 1:1 equal allocation ratio. The treating surgeons were all part of the study team.

### 4.1.2 Study III (SLEEVEPASS and SM-BOSS trials merged)

Study III is based on the merged data of Finnish SLEEVEPASS and Swiss SM-BOSS RCTs. The SLEEVEPASS trial is described in detail above. Like SLEEVEPASS, SM-BOSS was also designed as two-group, randomized, controlled, multicentre trial. The SM-BOSS trial was carried out from January 2007 to November 2011 randomizing 225 patients to either LSG or LRYGB at four bariatric centres in Switzerland.

The merged data of SLEEVEPASS and SM-BOSS consists of 240 patients from Finland and 225 patients from Switzerland, with similar exclusion and inclusion criteria as described above. Raw data from the original RCTs were combined, and outcomes were standardized. Additional five-year data were retrieved on T2DM (preoperative T2DM duration and number of T2DM medications). Out of the 398 patients (398/465, 85.6%) available for follow-up in this merged data, 155 patients had T2DM at baseline and were included in this study of IMS score validation.

### 4.1.3 Long-term follow-up

The patients in the SLEEVEPASS trial have been followed-up at the predefined time points of 6 months, 1 year, 3 years, and 5 years (primary end point assessment). The last follow-up date for the seven-year follow-up was September 26, 2017, and for the ten-year follow-up January 27, 2021. The follow-up plan for the SLEEVEPASS trial extends for up to 15 and 20 years. The patients lost to follow-up were contacted several times by telephone and mail, and search of electronic hospital records was performed to retrieve information about them.

## 4.2 Methods

### 4.2.1 Operation techniques

#### 4.2.1.1 LSG

The procedure was performed either by first dividing the stomach or by first mobilizing the greater curvature upward until the angle of His by dissection of the short gastric vessels using the Harmonic Scalpel™ depending on the surgeon's preference. Two sequential 4.8/60-mm green-load firings for the antrum were used followed by approximately four sequential 3.5/60-mm blue-load firings with all the staple lines reinforced (buttressed). The resection was initiated 4–6 cm proximal to the pylorus and, thus, most of the antrum was preserved. A 33–35-Fr calibration bougie was used to create the narrow sleeve. The removal of the resected stomach was done through one of the trocar sites by a plastic retrieval bag (EndoCatch™, Covidien). A methylene blue test was routinely performed after LSG at two of the three participating hospitals.

#### 4.2.1.2 LRYGB

First, a small (~20–40 ml) gastric pouch was created. The lesser curvature was dissected using a Harmonic Scalpel™ and the stomach was divided horizontally and vertically with linear staplers using reinforced 3.5/45 and 3.5/60-mm cartridges with blue loads. The biliopancreatic limb was measured at 50–80 cm (50cm in the SM-BOSS trial) distal to the ligamentum of Treitz. An antecolic end-to-side gastrojejunostomy was constructed as either a 25-mm circular stapler anastomosis (OrVil™, Covidien) or a 3.5/45-mm blue-load linear stapler (Covidien) anastomosis depending on the surgeon's preference. The omentum was not routinely transacted. The jejunal opening in the circular stapler anastomosis was closed with a reinforced 3.5/45-mm blue-load linear stapler firing. A continuous suture either manually or using EndoStitch™ (Covidien) was used for closing of the opening in the linear stapler anastomosis. The alimentary limb was measured at 150 cm and a linear stapler using a 2.5/60-mm cartridge with white load was used to create a side-to-side jejunojejunostomy. The opening in the anastomosis was closed depending on the surgeon's preference with either by a totally stapled technique using two reinforced 3.5/60-mm linear stapler firings with blue loads or with a continuous suture. The gastrojejunostomy was checked for leaks with a methylene blue test. The mesenteric defects were not routinely closed at the time of the surgery.

### 4.2.2 Weight loss (primary outcome of the SLEEVEPASS trial)

The primary end point of the SLEEVEPASS trial was weight loss defined by percentage excess weight loss (%EWL), calculated as (initial weight – follow-up weight) / (initial weight – ideal weight for BMI 25) × 100 (Brethauer et al., 2015). The primary end point was predefined to be assessed at five years of follow-up(Salminen et al., 2018).

In addition to %EWL, BMI, percentage excess BMI loss, %TWL, and weight in kilograms are reported at ten years. Furthermore, the prevalence of percentage total weight loss (%TWL) less than 5% was assessed and weight regain was determined as percentage of maximum weight lost: (100 × (postnadir weight – nadir weight) / (presurgery weight – nadir weight), which seems to best associate with most clinical outcomes (King et al., 2018).

### 4.2.3 Comorbidity outcomes

The remission of T2DM was assessed in terms of the new recommendation and consensus of American Diabetes Association (Riddle et al., 2021) (a return of HbA1c to < 6.5% or 48 mmol/mol that occurs spontaneously or following an intervention and persists for at least three months in the absence of usual glucose-lowering pharmacotherapy). The preoperative duration of T2DM was classified and defined in 3 categories: 0 to 2 years, 2 to 10 years, and more than 10 years.

The remission of dyslipidemia was assessed based on European Society of Cardiology/European Atherosclerosis Society guidelines (Catapano et al., 2011) as no need for medication and normal lipid values (low-density lipoprotein cholesterol <115.8 mg/dl [3.0 mmol/l]).

Hypertension was defined by persisting (no change in medications compared to baseline), improved (reduction in medications), or remission (no medications).

OSAS was assessed in terms of CPAP mask use as persisting (no change in CPAP settings), improved (reduction in CPAP settings), or remission (discontinuation of CPAP use).

### 4.2.4 Morbidity and mortality

Postoperative complications were classified as major or minor (Cotton et al., 1991). Major complication was defined by morbidity resulting in death, reoperation, hospital stay exceeding 7 days, or need for blood transfusions of 4 or more units. All other complications were assessed as minor. The complications were also defined according to the Clavien-Dindo classification (Dindo et al., 2004); I: any deviation in postoperative recovery; II: requiring pharmacological treatment, blood transfusions, or parenteral nutrition; III: requiring intervention (a: no general anesthesia, b: under general anesthesia); IV: life-threatening complication requiring intensive care unit; V: death of patient.

All additional complications between 5 and 7 years, and between 7 and 10 years postoperatively were reviewed and added to the previously reported complications. The Official Statistics Finland registry on causes of death was utilized.

### 4.2.5 Quality of life

#### 4.2.5.1 Moorehead-Ardelt questionnaire

For DSQOL evaluation, the Moorehead-Ardelt Quality of Life questionnaire of the Bariatric Analysis and Reporting Outcome System (BAROS) was applied (Oria et al., 1998). The 1-page analysis consists of self-esteem (score ranging from −1 to 1) and four daily activities (physical activity, social life, work conditions, and sexual activity [score ranging from −0.5 to 0.5 for each activity]) with the total score of −3 to 3 points with higher scores indicating better QOL.

#### 4.2.5.2 15D questionnaire

For HRQOL evaluation, the 15-dimensional (15D) questionnaire was applied (Sintonen, 2001). It is a generic, comprehensive, standardized, and self-administered questionnaire including 15 dimensions: breathing, mental function, speech (communication), vision, mobility, usual activities, vitality, hearing, eating, elimination, sleeping, distress, discomfort and symptoms, sexual activity, and depression. All dimensions scale from 0 to 1 and there is an additive aggregation formula for all dimensions, with 1 indicating full health and 0 indicating death. A change of more than 0.015, on average, has been studied to indicate clinical importance (Alanne et al., 2015).

The validity, sensitivity, reliability, responsiveness to change, and discriminatory power of the 15D questionnaire has been well tested in the Finnish population (Sintonen, 2001). The data on HRQOL of the Finnish general population is available (Koskinen et al.) enabling the comparison with the age- and sex-standardized general population.

## 4.2.6 GERD

### 4.2.6.1 PPI use and GERD-HRQL questionnaire

At the time of study initiation in 2008, systematic investigation on GERD symptoms was not performed due to lack of scientific knowledge of the relative importance of GERD related to MBS. However, at ten years of follow-up, a retrospective subjective assessment of GERD symptoms and PPI use (yes or no, daily or on demand) comparing present and preoperative GERD symptoms was collected among the study-patients.

The GERD symptom assessment was performed with the gastroesophageal reflux disease-health related quality of life (GERD-HRQL) questionnaire (Velanovich, 2007). There are 15 questions in the questionnaire of heartburn, regurgitation, medication, and swallowing all ranging from 0 to 5 points (0 indicating no symptoms and 5 indicating that symptoms are incapacitating daily activities). PPI use and an overall evaluation of satisfaction to present condition are also assessed in the questionnaire.

### 4.2.6.2 Upper gastrointestinal endoscopy

Prior to randomization, all patients underwent upper gastrointestinal endoscopy. At ten years, after adding the GERD assessments in the study protocol, endoscopy was offered for all trial patients with a separate written informed consent. This allowed the comparison with preoperative endoscopic findings. In Finland all digestive surgeon specialists routinely perform all of their own endoscopies, and thus, all endoscopies were performed by experienced surgeons.

For esophagitis, the Los Angeles classification (Armstrong et al., 1996) was used (Grade A: 1 or more mucosal breaks confined to the mucosal folds, each no longer than 5 mm; Grade B: at least 1 mucosal break more than 5 mm long confined to the mucosal folds but not continuous between the tops of 2 mucosal folds; Grade C: at least 1 mucosal break continuous between the tops of 2 or more mucosal folds but not circumferential; Grade D: circumferential mucosal break; see also **Figure 10**).

BE was endoscopically assessed as columnar mucosa extending above the gastroesophageal junction (Z line) (Spechler et al., 2014). The possible finding of BE was photographed and defined by the Prague C&M criteria (Sharma et al., 2006) ("C" for circumferential and "M" for maximal measurements of BE). From the suspected BE, endoscopic biopsies were taken above the Z line according to the American Society for Gastrointestinal Endoscopy Seattle biopsy protocol (Qumseya et al., 2019) (4-quadrant biopsy sampling at 1 to 2 cm intervals starting from the top of the gastric folds up to the most proximal extent of the suspected BE, along with targeted biopsy sampling from any mucosal abnormality).

If possible, hiatal hernia evaluation with inversion inspecting the gastroesophageal flap valve was performed using the Hill classification (Hill et al., 1996); grading from I to IV depending on the size of the hernia.

#### 4.2.6.3 Histopathology

All endocopic findings of suspected esophagitis and BE were confirmed by histopathology. The diagnosis of BE required the histopathological presence of columnar intestinal metaplasia with goblet cells according to American Society for Gastrointestinal Endoscopy definition (Qumseya et al., 2019; Spechler et al., 2011). As opposed to the British Society of Gastroenterology definition (Fitzgerald et al., 2014), the histological finding of only gastric metaplasia was not diagnosed as BE. The preoperative and the long-term ten-year follow-up endoscopic examinations and biopsies were compared to confirm de novo BE.

### 4.2.7 IMS score calculations

Four different independent preoperative domains predicting long-term remission of T2DM were used for IMS score calculations. The four variables were: duration of T2DM (in years), the number of diabetes medications, insulin use, and glycemic control (HbA1c <7%). Patients were categorized according to their calculated IMS scores to three different groups of T2DM severity stage: mild (IMS score ≤25), moderate (IMS score >25 to ≤95), and severe (IMS score >95). For all three severity stages, the remission rates of T2DM were defined. Long-term T2DM remission was defined according to ADA consensus statement(Buse et al., 2009) as HbA1c <6.5%

(<48 mmol/mol) and a fasting glucose level of <126 mg/dl, and off T2DM medications at 5 years or more after surgery. Furthermore, the changes in BMI were calculated according to T2DM severity. The change in BMI was used as a variable to facilitate the comparison with the original IMS score publication(Aminian et al., 2017). Weight loss was also defined by %TWL.

### 4.2.8 Statistical analysis

In studies I-II, sample size calculations were based on a test of mean difference between LSG and LRYGB in %EWL in one year. A mean of 60 and standard deviation (SD) of 20 in the LRYGB group were assumed and an $\alpha$ level of 0.05 was used in calculations. By using an equivalence design with a margin of equivalence of 15 % (–9 to 9 percent units), a sample size of 108 patients per group were needed for 90 % power. When a 10 % drop out was considered, 120 patients per group were enrolled in the study.

In studies I-II, equivalence of %EWL between LSG and LRYGB at different time points was estimated using a linear mixed model for repeated measures. Model-based estimates with 95% CIs were calculated for difference between operations to be able to evaluate the predefined margins for equivalence (−9 to 9).

In studies I-II, the main analyses were performed using modified intention-to-treat population (patients who did not undergo surgery at all were excluded). For the primary outcome of %EWL, a per-protocol analysis was also performed at ten years by excluding all the patients who had undergone conversion to another bariatric procedure. Missing data were excluded from the analyses. Multiple imputation was used for the primary end point sensitivity analyses. Multivariate imputation by fully conditional specification method was performed. The predictive mean matching method was used to construct 10 imputed data sets and a linear mixed model for repeated measures was fitted for each. Results were combined for the inference and compared with the original analyses.

In study I, continuous variables were summarized with mean (SD) values and categorical variables with numbers and percentages. Pearson correlation was calculated between %EWL and DSQOL. Similarly, as in equivalence of %EWL calculations, comparisons for DSQOL at seven years were estimated with in linear mixed models suitable for repeated measures. In the model, intervention, time, and their interaction was included. Study site was handled as a random factor. An unstructured covariance structure was used; otherwise, the same details as in %EWL analyses were followed. The Moorehead-Ardelt QOL score dimensions were compared between interventions separately for each time point using the Fisher exact test. Similarly, the number of patients with complications was compared between interventions with the $\chi 2$ tests.

In study I, for the HRQOL the 15D responses in which more than three dimensions were left blank were excluded. Other possible missing 15D values were estimated using a regression analysis according to Sintonen (Sintonen, 2001). If two or more alternatives were reported for a single dimension, the worst value chosen was included in the analysis. All the estimates were calculated for each time point. The 15D results were compared with age- and sex-standardized general population values. Population values were drawn from a national survey (the Health 2011 survey) on changes in the health status, functional capacity, and welfare of the population (Koskinen et al.). Differences between the groups in median 15D scores were compared with the control group using a Mann-Whitney test. Differences in 15D scores between time points were compared using an independent samples *t* test. The 15D statistical analyses were conducted using Stata, version 14 (Stata Corp). Other statistical reporting in study I was performed using SAS software, version 9.4 for Windows.

In study II, linear mixed models suitable for repeated measures were used to evaluate the differences between operations in BMI, %EBMIL, %TWL, weight, fasting plasma glucose, HbA1c, total cholesterol, LDL, high-density lipoprotein cholesterol, HDL, triglycerides, and Moorehead-Ardelt QOL total score. Logarithmic transformation was used for skewed variables (fasting plasma glucose, HbA1c, HDL, and triglycerides) and for those variables, estimates were transformed back to the original scale. Assumptions for models were checked with studentized residuals. For categorical variables, differences between study groups and other associations between categorical variables were tested using $\chi 2$ test or Fisher exact test in case of small frequencies. To compare the total score of GERD-HRQL questionnaire and weight regain between study groups, nonparametric Mann-Whitney *U* test was used. Statistical analyses were performed using SAS version 9.4 (SAS Institute) and all figures were drawn with R version 4.0.3 (R Foundation for Statistical Computing).

In study III, continuous variables were described using as means with SDs or, if the data were skewed, as medians with 25th (Q1) and 75th (Q3) percentiles. Nonparametric Kruskal-Wallis's test was used to test differences in continuous baseline variables between the IMS T2DM severity stages. Categorical variables were characterized using frequencies and percentages and tested using Pearson's Chi Squared test or Fisher's exact test when appropriate. To be able to compare the results to the original publication, Pearson's Chi Squared test was used to compare the remission rates of T2DM between the operations separately in three severity stages, and one-way analysis of variance (ANOVA) was used to evaluate the differences in BMI between the severity stages separately in two operations. In addition, logistic regression analysis was used to evaluate the effect of T2DM severity stage, operation, and %TWL on T2DM remission. In contrast to the original article, we used %TWL in the model to represent the weight loss instead of change in BMI used in the original article. In the severe T2DM stage, there was no remission after LRYGB and thus, we combined the severe stage with the moderate stage and this modified variable was used in the first reported model. First model included T2DM severity stage (severe and moderate stages combined), operation, %TWL, and interaction of severity stage and operation. The final model included only the main effects of T2DM severity stage (original variable with three categories) and operation because using this simple model enabled the use of severity stage with original categories. The results of logistic regression models were quantified using odds ratios (OR) with 95% CIs. Statistical analyses were performed using SAS version 9.4 (SAS Institute).

In all studies, two-sided tests were used and P values <.05 were considered statistically significant.

### 4.2.9 Ethics

For the SLEEVEPASS trial (studies I-III), the complete study protocol was approved by institutional ethics committees, and written informed consent was obtained from all patients. At ten years, one amendment to the study protocol was added: the GERD assessments. The trial was carried out at three Finnish hospitals: Turku, Vaasa, and Helsinki. The study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline. The SLEEVEPASS trial is registered at ClinicalTrials.gov (Identifier: NCT00793143).

For the SM-BOSS trial (study III), the complete study protocol was approved by each local ethical committee of the participating hospitals, and all patients gave written informed consent. The SM-BOSS trial is registered at ClinicalTrials.gov (Identifier: NCT00356213).

# 5 Results

## 5.1 Studies I-II: Long-term comparative outcomes of weight loss, QOL, and complications after LSG vs LRYGB at 7 and 10 years

**Table 2**. The simplified main results on long-term comparative outcomes of weight loss, QOL, and complications after LSG vs LRYGB.

| OUTCOME | LSG | LRYGB | COMPARISON |
|---|---|---|---|
| %EWL (AT 10 YEARS) | 43.5% (95% CI, 39.8-47.2) | 51.9% (95% CI, 48.1-55.6) | Not equivalent (difference: 8.4 [95% CI, 3.1-13.6]) |
| DSQOL[A] (AT 10 YEARS) | 0.64 (SD 1.24) | 0.41 (SD 1.23) | No difference (P=.91) |
| HRQOL[B] (AT 7 YEARS) | 0.88 (IQR 0.78-0.95) | 0.87 (IQR 0.78-0.92) | No difference (P=.37) |
| COMPLICATIONS (AT 10 YEARS) | | | |
| MINOR[C], N (%) | 42/121 (34.7%) | 29/119 (24.4%) | No difference (P=.08) |
| MAJOR[D], N (%) | 19/121 (15.7%) | 22/119 (18.5%) | No difference (P=.57) |

[a] Moorehead-Ardelt QOL total score
[b] 15D questionnaire total score
[c] Clavien Dindo I-IIIa
[d] Clavien-Dindo IIIb

Among the initial 240 patients randomized in the SLEEVEPASS trial 167 (69.6%) were women, mean age was 48.4 years (range 23 to 67, SD 9.4) and mean baseline BMI was 45.9 kg/m$^2$ (range 35 to 66, SD 6.0). 121 of the patients were randomized to undergo LSG and 119 to LRYGB. The baseline characteristics of the study population are shown in **Table 3**.

**Table 3**. Baseline characteristics of the patients in the SLEEVEPASS trial. Reproduced with the permission of the copyright holders from the original studies I and II.

| **CHARACTERISTICS** | **LSG (N=121)** | **LRYGB (N=119)** |
|---|---|---|
| FEMALE NO. (%) | 87 (71.9) | 80 (67.2) |
| MALE NO. (%) | 34 (28.1) | 39 (32.8) |
| AGE (YEARS), MEAN (SD) | 48.5 (9.6) | 48.4 (9.3) |
| WEIGHT (KG), MEAN (SD) | 130.1 (21.5) | 134.9 (22.5) |
| BMI ($KG/M^2$), MEAN (SD)[A] | 45.5 (6.2) | 46.4 (5.9) |
| T2DM NO. (%) | 52 (43.0) | 49 (41.2) |
| HYPERTENSION NO. (%) | 83 (68.6) | 87 (73.1) |
| DYSLIPIDEMIA NO. (%) | 39 (32.2) | 45 (37.8) |
| MOOREHEAD-ARDELT QOL TOTAL SCORE[B], MEAN (SD) | 0.10 (0.94) | 0.12 (1.12) |
| HOSPITALS PARTICIPATING IN THE STUDY | | |
| TURKU (N) | 40 | 40 |
| VAASA (N) | 40 | 40 |
| HELSINKI (N) | 41 | 39 |

Abbrevations: BMI, Body mass index; T2DM, Type 2 diabetes mellitus; QOL, Quality of life
[a]Calculated as weight in kilograms divided by height in meters squared.
[b]Score range -3 to +3 with higher score indicating better QOL.

The flow of participants through the ten-year follow-up of the SLEEVEPASS trial is shown in **Figure 12**. The seven-year follow-up rate was 75.8% (182/240); 91 patients (75.2%) in the LSG group and 91 patients (76.5%) in the LRYGB group.

At ten years, there were altogether ten deaths (five in LSG and five in LRYGB group) during the follow-up period, all unrelated to intervention). Of the 228 available patients, 193 (84.6%) completed the ten-year follow-up on weight loss, remission of comorbidities, QOL, and GERD symptoms, and 176 (77.2%) underwent upper gastrointestinal endoscopy.

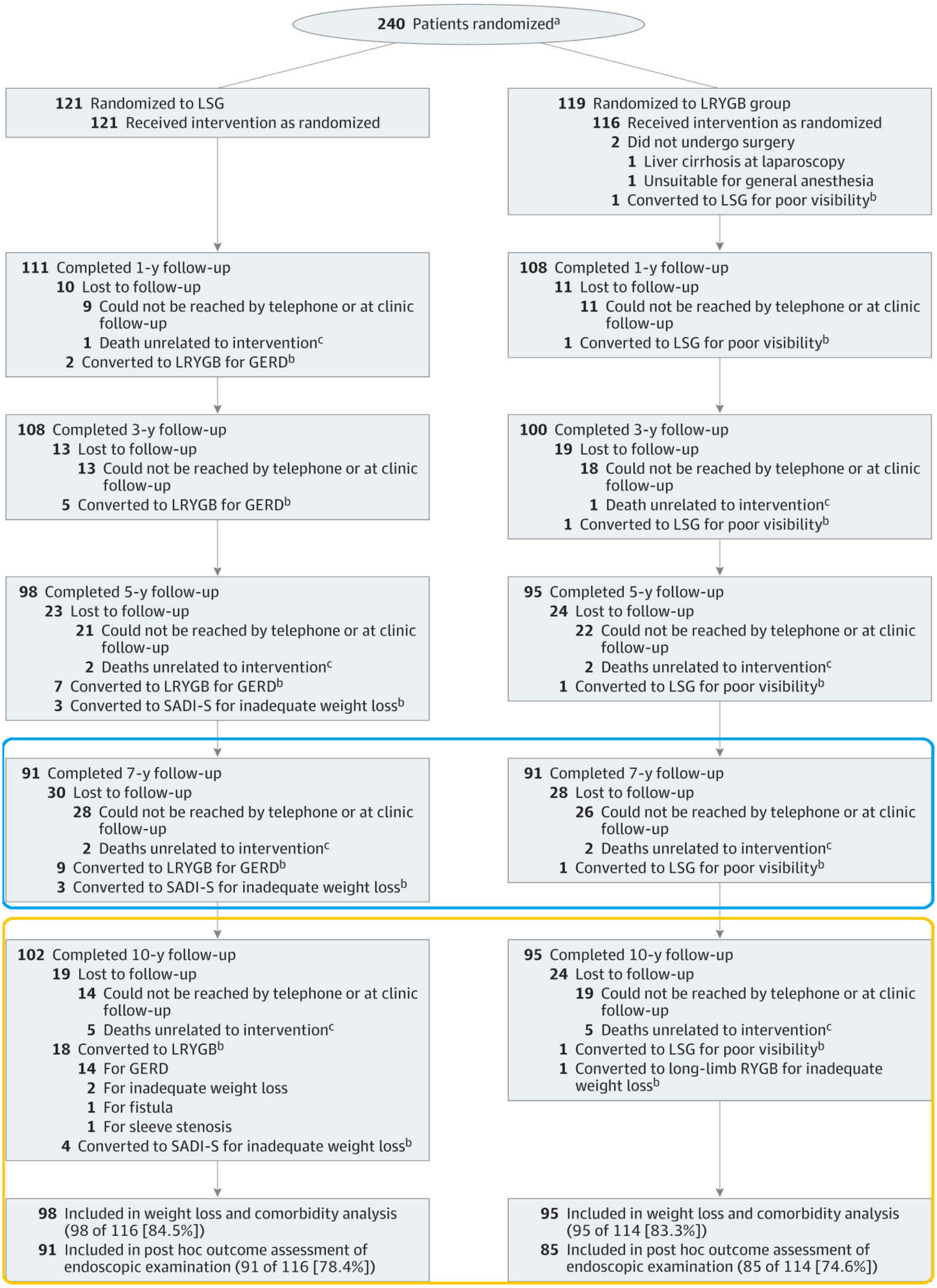


**Figure 12.** Flow Diagram. Reproduced and modified with the permission of the copyright holders from the original study II. [a]The number of patients assessed for eligibility was not adequately recorded. [b]Analyzed according to intention-to-treat. [c]The specific causes of death were: 1 traffic incident, 1 drowning, 1 ketoacidosis, 1 pulmonary embolism, 1 uterine cancer, 1 cholangiocarcinoma, 1 lung cancer, 1 pancreatic cancer, and 2 alcohol overdoses.

### 5.1.1 Weight Loss

The %EWL and %TWL trajectories after LSG and LRYGB for each follow-up point (0.5, 1, 3, 5, 7, and 10 years) is presented in **Figure 13**.

At seven years, the estimated mean %EWL was 47% (95% CI 43%-50%) after LSG and 55% (95% CI 52%-59%) after LRYGB. The model-based estimate of mean %EWL was 8.7 percentage units (95% CI 3.5-13.9 percentage units), higher after LRYGB.

At ten years, the estimated mean %EWL was 43.5% (95% CI, 39.8-47.2) in LSG group and 51.9% (95% CI, 48.1-55.6) in LRYGB group. The model-based estimate of mean %EWL was 8.4 percentage points (95% CI, 3.1-13.6), higher after LRYGB. As both at seven and at ten years the whole confidence intervals are not within the predefined margins of equivalence (−9 to 9), the two procedures were not equivalent for %EWL. Although weight loss after LRYGB was statistically greater compared with LSG in both follow-up points, the difference was not clinically relevant in terms of the predefined 95% CIs and margins of equivalence.

In the per-protocol analyses at ten years, the difference between the procedures was 10.4 percentage units (95% CI 5.1-15.8), and thus the results were similar (not equivalent). The %EWL results were similar after using multiple imputation for missing values. The detailed %EWL, BMI, percentage excess BMI loss, and %TWL data from baseline to ten-years of follow-up are presented in **Table 4**.

%TWL less than 5% at ten years was detected in 5/98 patients (5.1%) in LSG group and in 3/95 (3.2%) in LRYGB group ($P = .72$). Median (range) weight regain, assessed as the percentage of maximum weight lost, was 35.0% (0-95.5) after LSG and 24.7% (0-95.5) after LRYGB ($P = .16$).

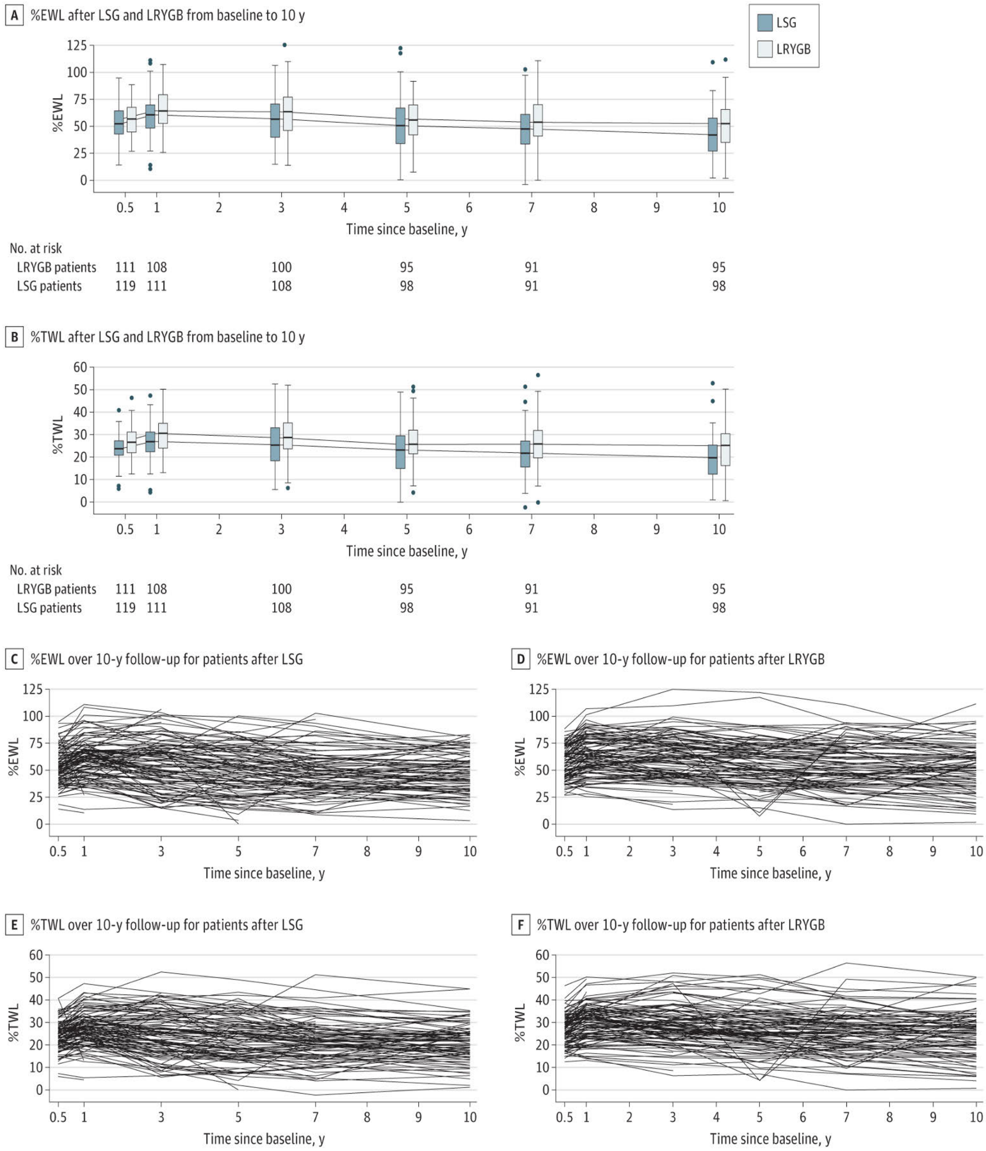


**Figure 13.** %EWL and %TWL for all patients and individual patients after LSG and LRYGB from baseline to 10 years. Reproduced with the permission of the copyright holders from the original study II.

**Table 4**. Model-based estimates of %EWL, BMI, %EBMIL, and %TWL.[a] Reproduced with the permission of the copyright holders from the original study II.

| | TIME | LSG | LRYGB | DIFFERENCE (LRYGB VS. LSG, 95% CI) | P VALUE |
|---|---|---|---|---|---|
| **%EWL**, NO. [B,C,D] | **Baseline** | N=121 | N=119 | | NA |
| | **0.5 y** | n=119 | n=111 | 4.7 (-0.4–9.7) | NA |
| | **1 y** | n=111 | n=108 | 5.7 (0.6–10.8) | NA |
| | **3 y** | n=108 | n=100 | 8.6 (3.4–13.7) | NA |
| | **5 y** | n=98 | n=95 | 8.4 (3.1–13.7) | NA |
| | **7 y** | n=91 | n=91 | 9.0 (3.6–14.3) | NA |
| | **10 y** | n=98 | n=95 | 8.4 (3.1–13.6) | NA |
| **BMI**, MEAN ESTIMATE (95% CI)[C,E,F] | **Baseline** | 47.3 (46.2–48.4) | 48.4 (47.2–49.5) | | |
| | **0.5 y** | 35.8 (34.7–37.0) | 35.3 (34.1–36.5) | -0.5 (-2.1–1.1) | .73[g] |
| | **1 y** | 34.4 (33.3–35.6) | 33.6 (32.4–34.8) | -0.9 (-2.5–0.8) | .73[g] |
| | **3 y** | 35.3 (34.2–36.5) | 34.0 (32.8–35.2) | -1.3 (-2.9–0.3) | .73[g] |
| | **5 y** | 36.5 (35.4–37.7) | 35.4 (34.2–36.6) | -1.1 (-2.8–0.6) | .73[g] |
| | **7 y** | 37.1 (36.0–38.3) | 35.8 (34.6–37.0) | -1.3 (-3.0–0.4) | .73[g] |
| | **10 y** | 37.8 (36.6–39.0) | 36.5 (35.3–37.7) | -1.3 (-3.0–0.4) | .73[g] |
| **%EBMIL**, MEAN ESTIMATE (95% CI)[C,E,G] | | 50.8 (48.0–53.7) | 58.2 (55.3–61.2) | 7.4 (3.4–11.5) | <.001 |
| **%TWL**, MEAN ESTIMATE (95% CI)[C, E, H] | | 23.4 (22.1–24.7) | 26.9 (25.6–28.2) | 3.5 (1.6–5.4) | <.001 |

[a]All results adjusted for center and diabetes status.
[b]Equivalence design was used in the analyses, and equivalence margins were set from -9 to +9
[c]Repeated-measurements ANOVA
[d]Percentage excess weight loss calculated as (initial weight - follow-up weight)/(initial weight- ideal weight for body mass index 25)
[e]Superiority design was used in the analysis
[f]p<.001 for operation x time interaction
[g]p=.36 for operation x time interaction, p<.001 for main effect of operation, p<.001 for main effect of time
[h]p=.49 for operation x time interaction, p<.001 for main effect of operation and p<.001 for main effect of time

## 5.1.2 QOL

### 5.1.2.1 Disease-specific QOL

At baseline, the mean (SD) DSQOL (Moorehead-Ardelt QOL) total score was 0.10 (0.94) in LSG group (n=117) and 0.12 (1.12) in LRYGB group (n=118).

At ten years, the mean (SD) DSQOL total score was 0.64 (1.24) after LSG and 0.41 (1.23) after LRYGB with no significant difference between the procedures (P=.91). The total DSQOL was significantly better at ten years (mean estimate 0.49;

95%CI 0.34-0.63) compared with baseline (mean estimate 0.11; 95% CI, 0.00-0.23) (P = .001). The mean (SD) DSQOL total scores were 1.20 (1.08) for LSG and 1.32 (1.05) for LRYGB at one year; 0.91 (1.17) for LSG and 1.13 (1.13) for LRYGB at three years; 0.85 (1.08) for LSG and 0.76 (1.01) for LRYGB at five years; and 0.50 (1.14) for LSG and 0.49 (1.06) for LRYGB at seven years.

In the detailed DSQOL analysis at seven years, there were no significant differences in any of the Moorehead-Ardelt QOL dimensions between LSG and LRYGB (See the original Study I, Table 2). %EWL was associated with the DSQOL total score; greater weight loss resulted in superior DSQOL (r=0.26; P<.001) (**Figure 14**).

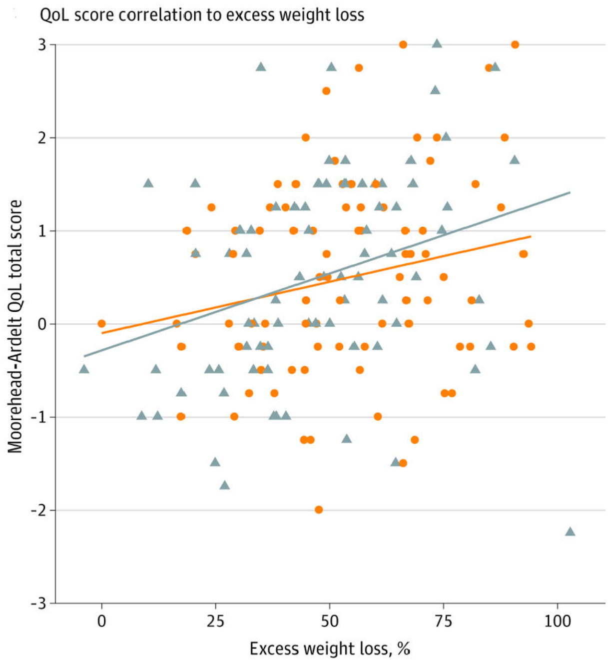


**Figure 14**. DSQOL (Moorehead-Ardelt QOL) total score correlation to %EWL. Orange: LRYGB, blue: LSG. Reproduced and modified with the permission of the copyright holders from the original study I.

#### 5.1.2.2 Health-related QOL

The analyses on HRQOL (15D questionnaire) and comparison with that of general population were assessed in the detailed QOL-report at seven years. At baseline, the median HRQOL total score was 0.87 (interquartile range [IQR] 0.78-0.90) for LSG (n=116) and 0.85 (IQR 0.77-0.91) for LRYGB (n=117).

At seven years, the median HRQOL total score was 0.88 (IQR 0.78-0.95) after LSG (n=83) and 0.87 (IQR 0.78-0.92) after LRYGB (n=88) (P=.37). During the first five years of follow-up after both procedures, HRQOL was higher compared with baseline, but at seven years it decreased close to baseline, with no significant difference in HRQOL compared with baseline (LSG, 0.88 [IQR 0.78-0.95] vs 0.87 [IQR 0.78-0.90]; and LRYGB, 0.87 [IQR 0.78-0.92] vs 0.85 [IQR 0.77-0.91]; P=.07).

A comparison between the HRQOL of the trial patients and the age- and sex-standardized general Finnish population was also made. At baseline, the mean (SD) HRQOL total score of trial patients was 0.84 (0.10) and that of the general population was 0.93 (0.01) (P<.001). At seven years, the mean (SD) HRQOL total score was 0.84 (0.12) for trial patients and 0.92 (0.01) for the general population (P < .001). Both at baseline and at seven years, the HRQOL of the trial patients remained significantly lower compared with the general population.

### 5.1.3 Morbidity and mortality

The morbidity and mortality after LSG and LRYGB from baseline to five years of follow-up have been reported earlier (Helmio et al., 2012; Helmio et al., 2014; Salminen et al., 2018). At seven years, the additional complications between five and seven years were assessed. The late minor complication rate (Clavien Dindo I-IIIa) between five and seven years was 5.0% (n=6) for LSG, and 3.4% (n=4) for LRYGB (P=.75). The late major complication rate (i.e., reoperation rate, Clavien-Dindo IIIb) between five and seven years was 0.8% for LSG (n=1) and 2.5% (n=3) for LRYGB (P=.37). At seven years, the overall complication rate was 24.0% (n=29) for LSG and 28.6% (n=34) for LRYGB (P=.42). There were no deaths reported among the trial patients between five- and seven-years of follow-up.

At ten years, all minor and major complications from 30 days to ten years were cumulatively evaluated. The overall minor complication rate at ten years was 34.7% (42/121) after LSG and 24.4% (29/119) after LRYGB (P=.08). The overall major complication rate was 15.7% (19/121) after LSG and 18.5% (22/119) after LRYGB (P=.57). All major complication were reoperations. After LSG most reoperations (14/19) were because of GERD, and after LRYGB (18/22) because of internal herniation. There were altogether 12 deaths (seven in LSG and five in LRYGB group), all unrelated to the procedures, ten of which occurred before the ten-year follow-up. The cumulative minor and major complications from 30 days to ten years are presented in **Table 5**.

**Table 5**. Minor and major late complications after LSG and LRYGB reported cumulatively after 30 days to 10 years of follow-up. Reproduced with permission of the copyright holders from the original study II.

| | LSG (N=121) | LRYGB (N=119) | P VALUE |
|---|---|---|---|
| **MINOR COMPLICATIONS, NO. (%)** | | | |
| VOMITING/DEHYDRATION | 0 (0.0) | 3 (2.5) | |
| GASTROESOPHAGEAL REFLUX | 38 (31.4) | 8 (6.7) | |
| ULCER/STRICTURE AT GASTROJEJUNAL ANASTOMOSIS | 2 (1.7) | 8 (6.7) | |
| DUMPING | 1[a] (0.8) | 3 (2.5) | |
| FISTULA AND ABSCESS | 1[b] (0.8) | 0 (0.0) | |
| URETHEROLITHIASIS | 0 (0.0) | 1 (0.8) | |
| ADHESION RELATED INTESTINAL OBSTRUCTION | 0 (0.0) | 1 (0.8) | |
| VENTRAL HERNIA | 0 (0.0) | 1 (0.8) | |
| SUSPECTED INTERNAL HERNIATION | 0 (0.0) | 1 (0.8) | |
| NONSPESIFIC ABDOMINAL PAIN | 0 (0.0) | 1 (0.8) | |
| ANEMIA | 0 (0.0) | 1 (0.8) | |
| HYPOKALEMIA | 0 (0.0) | 1 (0.8) | |
| **TOTAL** | 42 (34.7) | 29 (24.4) | 0.08[d] |
| **MAJOR COMPLICATIONS, NO. (%)** | | | |
| FISTULECTOMIA | 1[b] (0.8) | 0 (0.0) | |
| GASTROESOPHAGEAL REFLUX | 14[a] (11.6) | 0 (0.0) | |
| INTERNAL HERNIATION | 0 (0.0) | 18[c] (15.1) | |
| INCISIONAL HERNIA | 3 (2.5) | 3[c] (2.5) | |
| CANDY CANE/BLIND LOOP RESECTION | 0 (0.0) | 1 (0.8) | |
| ABDOMINAL PAIN AND STRICTURE | 0 (0.0) | 1 (0.8) | |
| SLEEVE STENOSIS | 1 (0.8) | 0 (0.0) | |
| **TOTAL** | 19 (15.7) | 22[c] (18.5) | 0.57[d] |

[a]One patient converted from LSG to LRYGB for GERD at 6 years, and later at 10 years dumping as a complication from LRYGB
[b]Conversion from LSG to LRYGB for fistula and abscess, and later fistulectomy
[c]One patient underwent laparotomy one year after LRYGB, and later at nine years incisional hernia, calculated only once in total count of major complications
[d]P values calculated with Chi-Squared -test

## 5.2 Study II: Long-term comparative outcomes of obesity-related comorbidities, including GERD, after LSG vs LRYGB at 10 years

**Table 6**. The simplified main results on comparative outcomes of obesity-related comorbidities and GERD after LSG and LRYGB at 10 years.

| OUTCOME AT 10 YEARS | LSG | LRYGB | COMPARISON |
|---|---|---|---|
| FASTING PLASMA GLUCOSE, MEAN | 6.9 mmol/l (95% CI 6.6-7.3) | 6.8 mmol/l (95% CI 6.4- 7.1) | No difference (P=.42) |
| HBA1C, MEAN | 6.9% (95% CI 6.6-7.2) | 7.0% (95% CI 6.7-7.4) | No difference (P=.64) |
| T2DM REMISSION[A], N(%) | 11/42 (26%) | 13/39 (33%) | No difference (P=.63) |
| DYSLIPIDEMIA REMISSION[B], N(%) | 4/21 (19%) | 11/31 (35%) | No difference (P=.23) |
| HYPERTENSION REMISSION[C], N(%) | 6/72 (8%) | 16/68 (24%) | Significant difference (P=.04) |
| OSAS REMISSION[D], N(%) | 5/31 (16%) | 9/29 (31%) | No difference (P=.30) |
| PPI INTAKE, N (%) | 58/90 (64) | 30/84 (36) | Significant difference (P<.001) |
| GERD-HRQL TOTAL SCORE, MEDIAN | 10.5 (min-max 0.0-47.0) | 0.0 (min-max 0.0-47.0) | Significant difference (P<.001) |
| ESOPHAGITIS, N (%) | 28/91 (31%) | 6/85 (7%) | Significant difference (p<.001) |
| BARRETT'S ESOPHAGUS, N (%) | 4/91 (4%) | 3/85 (4%) | No difference (p=0.29) |

[a] The new consensus of American Diabetes Association; a return of HbA1c to < 6.5% (<48 mmol/mol) that occurs spontaneously or following an intervention and that persists for at least 3 months in the absence of usual glucose-lowering pharmacotherapy
[b] No medication and LDL cholesterol <115.8 mg/dl (3.0 mmol/l)
[c] No medication
[d] No CPAP use

### 5.2.1 Remission of comorbidities

Regarding T2DM, 101 patients (42%) (52/121 [43%] in LSG and 49/119 [41%] in LRYGB) had T2DM at baseline. Remission of T2DM was seen in 11/42 patients (26%) in LSG group and in 13/39 (33%) in LRYGB group (P=.63) at ten years. Similarly, there was no statistically significant difference between the groups in estimated mean of fasting plasma glucose level value (6.9 mmol/l [95% CI 6.6-7.3] after LSG and 6.8 mmol/l [95% CI 6.4- 7.1] after LRYGB; P=.42) or in mean estimated values of HbA1c (6.9% [95% CI 6.6-7.2] after LSG and 7.0% [95% CI 6.7-7.4] after LRYGB; P=.64) at ten years. The preoperative duration of T2DM was significantly associated with T2DM remission: 0 to 2 years, 12/23 (52%), >2 to 10 years, 12/48 (25%), and > 10 years, 0/9 (0%) (P=.01).

For dyslipidemia, 84 patients (35%) (39/121 [32%] in LSG and 45/119 [38%] in LRYGB) had dyslipidemia at baseline. Remission of dyslipidemia (normal lipid values and no medication) was seen in 4/21 patients (19%) after LSG and in 11/31 patients (35%) after LRYGB (P=.23) at ten years of follow-up.

Regarding hypertension, 170 patients (70.8%) had medication for hypertension (83/121 [69%] in LSG and 87/119 [73%] in LRYGB) at baseline. Remission of hypertension (no medication) was seen in 6/72 patients (8%) after LSG and in 16/68 (24%) after LRYGB, improved hypertension status (reduction in antihypertensive medications) in 23/72 (32%) vs 16/68 (24%) and persisting hypertension (no change in medication) in 43/72 (60%) vs 36/68 (53%), respectively (P=.04), at ten years.

For OSAS, 65 patients (27.1%) (30/121 [24.8%] in LSG and 35/119 [29.4%] in LRYGB) had OSAS at baseline. Remission of OSAS (no CPAP) was seen in 5/31 patients (16%) after LSG vs 9/29 patients (31%) after LRYGB, improved OSAS (reduced CPAP settings) in 8/31 (26%) vs 4/29 (14%) and persisting (no change in CPAP settings) in 18/31 (58%) vs 16/29 (55%), respectively (P=.30), at ten years.

### 5.2.2 Upper gastrointestinal endoscopy and GERD symptoms

The outcomes on GERD assessments including PPI intake, GERD symptoms, GERD-HRQL total scores, esophagitis, and BE at ten years are presented in detail in **Table 7**.

PPI intake was significantly higher after LSG than LRYGB (58/90 [64%] vs 30/84 [36%]; P<.001). Similarly, LSG resulted in higher GERD-HRL total scores (10.5 vs 0.0; P<.001), and more reflux symptoms (Table 5, P<.001) compared to LRYGB at ten years.

For findings in the upper gastrointestinal endoscopy, the prevalence of esophagitis at ten years was in 28/91 (31%) after LSG vs in 6/85 (7%) after LRYGB (P<.001). Patients with esophagitis after LSG had significantly more de novo GERD symptoms compared with the retrospective subjective assessment of the preoperative status (Table 5, P=.02) and higher GERD-HRQL total scores (15.0 vs 0.0; P=.03) compared with patients in the LRYGB group presenting with esophagitis.

No significant difference was found in BE; de novo BE was present in 4/91 patients (4%) after LSG and in 3/85 (4%) after LRYGB (P=.29). In the LSG group, one patient was excluded from the BE analysis due to a very short-segment BE with mild dysplasia already at baseline in retrospective assessment, and this remained unchanged at ten years (i.e., the finding was not de novo BE). All de novo BE findings were short-segment BEs with no dysplasia at histopathology.

**Table 7**. PPI intake, GERD symptoms, GERD-HRQL, and endoscopic findings between LSG vs LRYGB at 10 years. Reproduced with the permission of the copyright holders from the original study II.

| | | LSG (N=91) | LRYGB (N=85) | P VALUE |
|---|---|---|---|---|
| **ALL PATIENTS WHO UNDERWENT ENDOSCOPY, NO./TOTAL(%)** | | 91/121 (75.2) | 85/119 (71.4) | |
| PPI INTAKE PREOPERATIVELY, NO./TOTAL(%) | | 11/89 (12) | 5/81 (6) | 0.20[c] |
| PPI INTAKE AT 10 YEARS, NO./TOTAL(%) | | 58/90 (64) | 30/84 (36) | < 0.001[c] |
| GERD SYMPTOMS, NO./TOTAL(%) | | | | |
| | *No symptoms preop or at any point* | 18/90 (20) | 39/85 (46) | < 0.001[c] |
| | *Symptoms similar to preop* | 16/90 (18) | 6/85 (7) | |
| | *Symptoms alleviated postop* | 12/90 (13) | 32/85 (38) | |
| | *Symptoms worsened postop* | 44/90 (49) | 8/85 (9) | |
| GERD-HRQL TOTAL SCORE, MEDIAN (MIN-MAX) | | 10.5 (0.0-47.0) | 0.0 (0.0-47.0) | < 0.001[d] |
| HIATAL HERNIA, NO./TOTAL(%)[A] | | 57/91 (63) | N/A | N/A |
| **ESOPHAGITIS** | | 28/91 (31) | 6/85 (7) | < 0.001[e] |
| LOS ANGELES CLASSIFICATION, NO./TOTAL(%) | | | | |
| | *Gradus A* | 14/28 (50) | 3/6 (50) | 0.66[c] |
| | *Gradus B* | 12/28 (43) | 2/6 (33) | |
| | *Gradus C* | 2/28 (7) | 1/6 (17) | |
| | *Gradus D* | 0/28 (0) | 0/6 (0) | |
| PPI INTAKE PREOPERATIVELY, NO./TOTAL(%) | | 3/28 (11) | 1/5 (20) | 0.50[c] |
| PPI INTAKE AT 10 YEARS, NO./TOTAL(%) | | 16/28 (57) | 2/5 (40) | 0.64[c] |
| GERD SYMPTOMS, NO./TOTAL(%) | | | | |
| | *No symptoms preop or at any point* | 6/28 (21) | 3/6 (50) | 0.02[c] |
| | *Symptoms similar to preop* | 6/28 (21) | 0/6 (0) | |
| | *Symptoms alleviated postop* | 4/28 (14) | 3/6 (50) | |
| | *Symptoms worsened postop* | 12/28 (43) | 0/0 (0) | |
| GERD-HRQL TOTAL SCORE, MEDIAN (MIN-MAX) | | 15.0 (0.0-47.0) | 0.0 (0.0-18.0) | 0.03[d] |
| HIATAL HERNIA, NO./TOTAL(%)[A] | | 26/28 (93) | N/A | N/A |

| | | LSG (N=91) | LRYGB (N=85) | P VALUE |
|---|---|---|---|---|
| **BARRETT'S ESOPHAGUS[B]** | | 4/91 (4) | 3/85 (4) | 0.29[c] |
| PPI INTAKE PREOPERATIVELY, NO./TOTAL(%) | | 0/4 (0) | 1/2[f] (50) | 0.33[c] |
| PPI INTAKE AT 10 YEARS, NO./TOTAL(%) | | 3/4 (75) | 2/3 (67) | 0.99[c] |
| GERD SYMPTOMS, NO./TOTAL(%) | | | | |
| | *No symptoms preop or at any point* | 0/4 (0) | 1/3 (33) | 0.49[c] |
| | *Symptoms similar to preop* | 1/4 (25) | 0/3 (0) | |
| | *Symptoms alleviated postop* | 0/4 (0) | 1/3 (33) | |
| | *Symptoms worsened postop* | 3/4 (75) | 1/3 (33) | |
| GERD-HRQL TOTAL SCORE, MEDIAN (MIN-MAX) | | 11.0 (3.0-20.0) | 4.5 (0.0-9.0) | 0.25[d] |
| HIATAL HERNIA, NO./TOTAL(%)[A] | | 2/4 (50) | N/A | N/A |

[a]Descriptive data; hiatal hernias in LRYGB group cannot be evaluated reliably due to problems with inverse
[b]All short-segment de novo Barretts
[c]Fisher´s exact test
[d]Non-parametric Mann-Whitney U test
[e]Chi-squared -test
[f]One patient had missing info

## 5.3 Study III: Validation of the IMS score in a large, randomized data set

The flow of participants is shown in **Figure 15**.

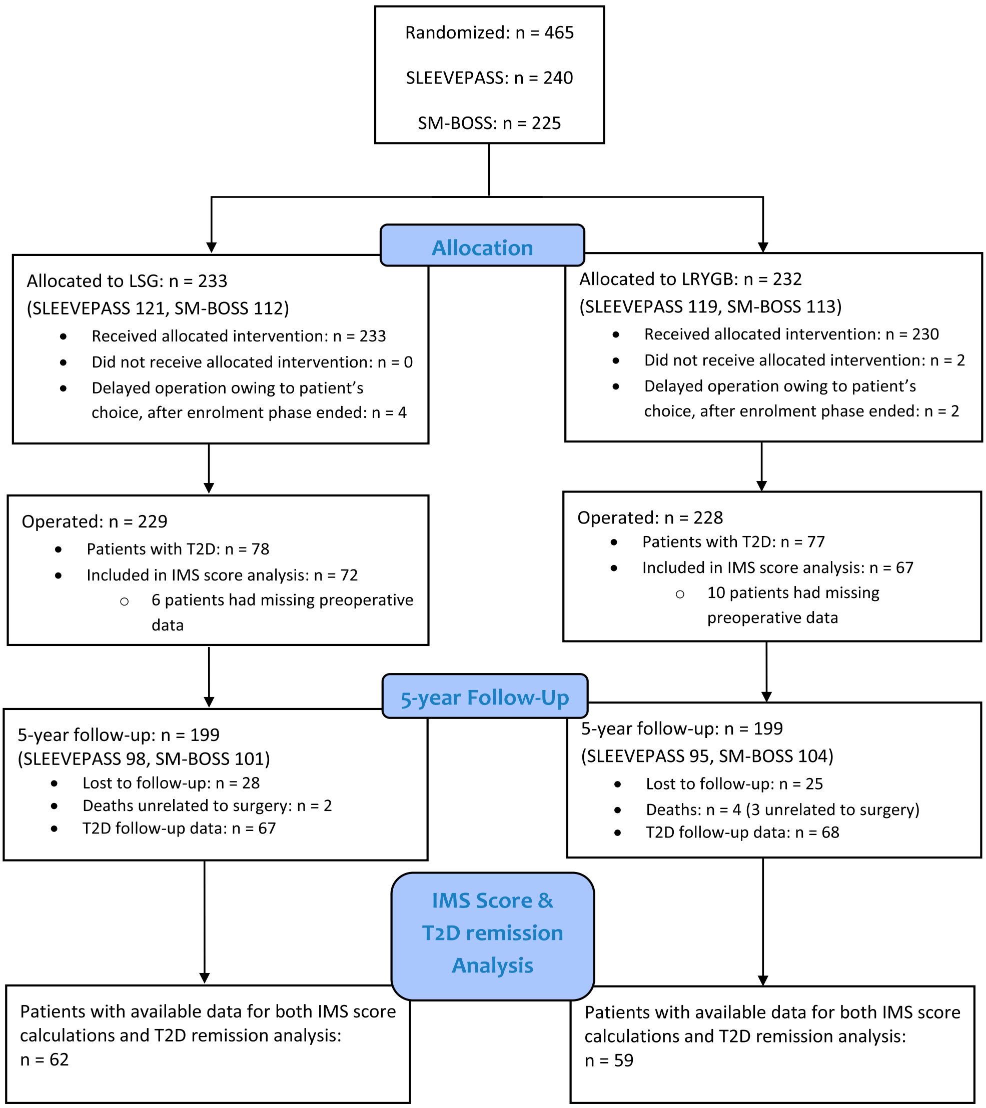


**Figure 15**. Flow diagram of the merged SLEEVEPASS and SM-BOSS trials. Reproduced with the permission of the copyright holders from the original study III.

There were altogether 155 patients with T2DM in the merged SLEEVEPASS and SM-BOSS data at baseline. Of them, 139/155 (89.7%) had the preoperative data for

IMS calculations, and 135/155 (87.1%) were available for follow-up at five years. At five years, remission of T2DM was seen in 49.3% (33/67) after LSG and 55.8% (38/68) after LRYGB (P=.418). The baseline characteristics of the SM-BOSS and SLEEVEPASS trials and the merged LSG and LRYGB groups are shown in **Table 8**.

**Table 8**. Baseline characteristics of the patients in SM-BOSS and SLEEVEPASS trials, and in the merged LSG and LRYGB groups. Reproduced with the permission of the copyright holders from the original study III.

| BASELINE CHARACTERISTICS | SM-BOSS (N=54) | SLEEVEPASS (N=101) | LSG (N=78) | LRYGB (N=77) |
|---|---|---|---|---|
| AGE (YEARS), MEAN (SD) | 47.9 (10.3) | 51.6 (8.1) | 50.4 (8.9) | 50.2 (9.2) |
| SEX: FEMALE/MALE, N (%) | 30/24 (55.6%) | 62/39 (61.4%) | 43/35 (55.1%) | 49/28 (63.6%) |
| BODY MASS INDEX, BMI ($KG/M^2$), MEAN (SD) | 44.7 (10.3) | 46.9 (6.2) | 46.1 (6.2) | 46.1 (6.0) |
| PREOPERATIVE DURATION OF T2DM (YEARS), MEDIAN ($Q_1$-$Q_3$) | 1.0 (0.5-7.0) | 5.0 (2.0-8.0) | 5.0 (1.1-7.5) | 4.0 (1.0-7.0) |
| NO T2DM MEDICATION, N (%) | 17/44 (38.6%) | 0/100 (0.0%) | 9/75 (12.0%) | 8/69 (11.6%) |
| ONE T2DM MEDICATION, N (%) | 22/44 (50.0%) | 51/100 (51.0%) | 32/75 (42.7%) | 41/69 (59.4%) |
| TWO T2DM MEDICATIONS, N (%) | 5/44 (11.1%) | 40/100 (40.0%) | 31/75 (41.3%) | 14/69 (20.3%) |
| THREE T2DM MEDICATIONS, N (%) | 0/44 (0.0%) | 8/100 (8.0%) | 3/75 (4.0%) | 5/75 (7.3%) |
| FOUR T2DM MEDICATIONS, N (%) | 0/44 (0.0%) | 1/100 (1.0%) | 0/75 (0.0%) | 1/69 (1.5%) |
| INSULIN USE, N (%) | 10/54 (18.5%) | 32/101 (31.7%) | 24/78 (30.7%) | 18/77 (23.4%) |
| GLYCATED HEMOGLOBIN, HBA1C (%), MEDIAN ($Q_1$-$Q_3$) | 6.8 (6.1-7.9) | 6.6 (6.3-7.2) | 6.7 (6.3-7.5) | 6.6 (6.1-7.7) |
| GLYCEMIC CONTROL (HBA1C<7%), N (%) | 31/51 (60.8%) | 67/101 (66.3%) | 51/77 (66.2%) | 47/75 (62.7%) |

### 5.3.1 IMS score calculations and T2DM severity stages

Of the 139 patients that had the preoperative data for IMS score calculations, 41/139 (29.5%) were categorized as mild stage, 77/139 (55.4%) as moderate stage, and 21/139 (15.1%) as severe stage. The baseline characteristics for each severity stage and for LSG and LRYGB are presented in **Table 9**.

**Table 9**. Baseline characteristics by T2DM severity stage and procedure according to the calculated IMS score. Reproduced with the permission of the copyright holders of the original study III.

| | **MILD (N=41)** | | **MODERATE (N=77)** | | **SEVERE (N=21)** | |
|---|---|---|---|---|---|---|
| | **LSG (N=19)** | **LRYGB (N=22)** | **LSG (N=41)** | **LRYGB (N=36)** | **LSG (N=12)** | **LRYGB (N=9)** |
| AGE (YEARS), MEAN (SD) | 46.4 (9.2) | 50.6 (11.0) | 52.2 (8.0) | 49.2 (8.0) | 51.8 (8.0) | 52.5 (9.7) |
| SEX: FEMALE/MALE, N (%) | 12/7 (63.2%) | 15/7 (68.2%) | 24/17 (58.5%) | 22/14 (61.1%) | 5/7 (41.7%) | 7/2 (77.8%) |
| BODY MASS INDEX, BMI (KG/M$^2$), MEAN (SD) | 47.6 (6.4) | 47.8 (5.7) | 46.1 (6.4) | 46.8 (6.4) | 42.9 (6.0) | 43.8 (6.2) |
| GLYCATED HEMOGLOBIN, A1C (%), MEDIAN ($Q_1$-$Q_3$)) | 6.2 (5.8-6.7) | 6.1 (5.7-6.5) | 6.7 (6.4-7.0) | 6.8 (6.2-7.7) | 8.6 (7.4-9.7) | 8.7 (8.2-9.7) |
| PREOPERATIVE DURATION OF T2D (YEARS), MEDIAN ($Q_1$-$Q_3$) | 1.0 (0.5-1.5) | 1.0 (0.5-1.0) | 5.0 (4.0-7.0) | 5.0 (4.0-7.0) | 11.0 (8.0-20.5) | 15.0 (13.0-26.0) |
| NO T2D MEDICATION, N (%) | 7/19 (36.8%) | 8/22 (36.4%) | 1/41 (2.4%) | 0/36 (0.0%) | 0/12 (0.0%) | 0/9 (0.0%) |
| ONE T2D MEDICATION, N (%) | 12/19 (63.2%) | 14/22 (63.6%) | 19/41 (46.3%) | 22/36 (61.1%) | 0/12 (0.0%) | 4/9 (44.4%) |
| TWO T2D MEDICATIONS, N (%) | 0/19 (0.0%) | 0/22 (0.0%) | 20/41 (48.8%) | 10/36 (27.8%) | 10/12 (83.3%) | 3/9 (33.3%) |
| THREE T2D MEDICATIONS, N (%) | 0/19 (0.0%) | 0/22 (0.0%) | 1/41 (2.4%) | 4/36 (11.1%) | 2/12 (16.67%) | 1/9 (11.1%) |
| FOUR T2D MEDICATIONS, N (%) | 0/19 (0.0%) | 0/22 (0.0%) | 0/41 (0.0%) | 0/36 (0.0%) | 0/12 (0.0%) | 1/9 (11.1%) |
| INSULIN USE, N (%) | 0/19 (0.0%) | 0/22 (0.0%) | 10/41 (24.4%) | 7/36 (19.4%) | 12/12 (100.0%) | 9/9 (100.0%) |
| GLYCEMIC CONTROL (HBA1C<7%), N (%) | 18/19 (94.7%) | 22/22 (100.0%) | 28/41 (68.3%) | 19/36 (52.8%) | 1/12 (8.3%) | 1/9 (11.1%) |

## 5.3.2 T2DM remission rates by severity stage and operation

Altogether 121 patients had available data for both IMS score calculation and T2DM remission analysis. At five years, complete long-term remission of T2DM was seen in 52.6% (63/121) of the patients. Of these, 86.5% (32/37) were in the mild stage group, 43.9% (29/66) in the moderate stage group, and 11.1% (2/18) in the severe stage group (P<.001). The odds for achieving T2DM remission were the highest in the mild stage (mild versus moderate OR, 8.3; 95% CI, 2.8–24.0; P<.001 and mild versus severe OR, 52.2; 95% CI, 9.0–302.3; P<.001), and also significantly higher in the moderate stage compared to the severe stage (OR, 6.3, 95% CI, 1.3–29.8;

P=.020). The T2DM remission rates by severity stage and operation are presented in **Table 10**.

There was no statistically significant difference in T2DM remission rates between the operations within any of the severity stages. In the logistic regression analyses for T2DM remission, interaction of operation and IMS severity stage (severe and moderate stages combined) was not significant (P=.524) and thus no further analyses were needed to test the difference between LSG and LRYGB concerning different IMS severity stages.

**Table 10**. T2DM remission rates by severity stage and operation. Reproduced and modified with permission of the copyright holders from the original study III.

| SEVERITY STAGE | REMISSION AFTER SURGERY | REMISSION AFTER LSG | REMISSION AFTER LRYGB | P* |
|---|---|---|---|---|
| MILD [N (%)] | 32/37 (86.5%) | 14/16 (87.5%) | 18/21 (85.7%) | 0.999 |
| MODERATE [N (%)] | 29/66 (43.9%) | 15/35 (42.9%) | 14/31 (45.2%) | 0.999 |
| SEVERE [N (%)] | 2/18 (11.1%) | 2/11 (18.2%) | 0/7 (0.0%) | 0.497 |

*Fisher's Exact test

### 5.3.3 The change of BMI and total weight loss by severity stage and operation

At five years after LRYGB, there was a significant difference in the change of BMI between the severity stages; the highest BMI loss was associated with T2DM mild stage (-14.6 kg/m$^2$ [SD 6.1]) compared with moderate stage (-11.6 kg/m$^2$ [SD 4.2]) and severe stage (-10.0 kg/m$^2$ [SD 3.5]), P=.043. At five years after LSG, there were no significant differences in change of BMI between the severity stages (-11.0 kg/m$^2$ [SD 5.6] in mild stage; -9.3 kg/m$^2$ [SD 4.1] in moderate stage; -10.4 kg/m$^2$ [SD 4.5] in severe stage, P= .454).

The effect of %TWL on T2DM remission was statistically significant (P<.001); greater %TWL resulted in superior T2DM remission (OR, 1.1; 95% CI, 1.0–1.2).

# 6 Discussion

## 6.1 Long-term effect of LSG vs LRYGB on weight loss, comorbidities, and morbidity

In this randomized long-term study with 240 patients, LSG and LRYGB did not meet criteria for equivalence in terms of weight loss assessed with %EWL. Both LSG and LRYGB resulted in good and sustainable weight loss at seven (47% and 55%, respectively) and ten years (44% and 52%, respectively). Weight loss was slightly higher after LRYGB with mean difference in %EWL of 8.7 to 8.4 percentage points. However, due to the prespecified equivalence margins of -9 to 9, there was no clinical difference in weight loss between LSG and LRYGB in our study. There was no statistically significant difference in remission of T2DM, dyslipidemia, or OSAS after LSG vs LRYGB, but hypertension management was better after LRYGB. Long-term late complication rates were similar after both procedures.

In all follow-up points of the SLEEVEPASS trial, LRYGB has resulted in greater %EWL compared to LSG, and the procedures have not been equivalent for weight loss in the primary endpoint assessment at five years (Salminen et al., 2018) or in any of the previous follow-up points (Helmio et al., 2012; Helmio et al., 2014). To our knowledge, so far SLEEVEPASS trial is the largest randomized trial with the longest follow-up comparing these two procedures while the Swiss SM-BOSS trial is the second largest with 217 patients. In the SM-BOSS trial, weight loss assessed with %EBMIL was similar after LSG and LRYGB at five years (Peterli et al., 2018). Nevertheless, in the merged data of SLEEVEPASS and SM-BOSS, LRYGB resulted in superior %EBMIL at five years (Wölnerhanssen et al., 2021). Similarly, in the SLEEVEPASS trial weight loss in terms of %TWL was significantly higher after LRYGB compared with LSG, which is in accordance with a large cohort study from McTigue et al. with almost 10 000 patients. Three meta-analyses found also %EWL to be higher after LRYGB at five years (Gu et al., 2020; Hu et al., 2019; Yang et al., 2019). A recent meta-analysis of Lee et al. including 33 RCTs found change of BMI higher after LRYGB at one and three years (Lee et al., 2021), but there was insufficient evidence of weight loss differences at five years, which however, may be explained with the mixing results of the retracted article of Ruiz-Tovar et al (Ruiz-Tovar et al., 2019).

Altogether, prospective comparative studies of LRYGB and LSG with over five years of follow-up are lacking, and further studies with prospective settings, sufficient number of patients, and even longer-term follow-up are needed. In the SLEEVEPASS trial, the weight loss trajectories after LRYGB and LSG have been similar at all follow-up time points, and the individual variability in weight loss outcomes among the study population has been high in concurrence with the literature. All this underlies the importance of patient selection and the need for further investigation of preoperative factors affecting the success of MBS, as well as the importance of uniform standardized reporting of weight loss outcomes enabling easier comparison of different studies (Shahwan et al., 2022).

In the present thesis, no difference was found in remission of T2DM, dyslipidemia, or OSAS between LSG and LRYGB at ten years. Hypertension remission was superior after LRYGB. This was the finding also in the merged five-year data of SLEEVEPASS and SM-BOSS trials (Wölnerhanssen et al., 2021). Some meta-analyses have also found LRYGB superior in hypertension (Gu et al., 2020; Han et al., 2020; Zhao et al., 2019) or dyslipidemia (Gu et al., 2020; Han et al., 2020; Lee et al., 2021) remission, while others have shown similar remission of comorbidities after LRYGB and LSG (Hu et al., 2019; Lee et al., 2021; Shoar et al., 2017). As MBS is shown to be associated with markedly lower all-cause mortality and longer life expectancy compared with usual obesity management, especially in patients with T2DM, the possible differences in T2DM remission after LRYGB and LSG have been under active research. Our ten-year follow-up study showed no statistically significant differences in T2DM remission after the two procedures, and this was the case also in the five-year follow-up of the merged data (Wölnerhanssen et al., 2021), and in the meta-analyses of 33 RCTs from Lee et al (Lee et al., 2021). However, in the large PCORnet registry cohort study (McTigue et al., 2020), LRYGB seemed to result in slightly higher T2DM remission rate. Nevertheless, the comparative RCTs available are all underpowered in detecting clinically relevant differences in the remission of comorbidities. It has been calculated that over 700 patients with T2DM would be needed to detect a 10% difference in T2DM remission after LRYGB vs LSG, which highlights the need for international scientific collaboration and an IPDMA to assess this highly important topic.

Concerning complications, there has been no statistically significant differences in the complication rates of LSG vs LRYGB in any of the follow-up points of the SLEEVEPASS trial, except for early (<30 days) minor complication rate, which was higher after LRYGB (Helmio et al., 2012), nor treatment-related mortality. At ten years, there was no difference in the overall reoperation rate after LSG vs LRYGB; majority of the reoperation after LSG were because of GERD and most of the reoperations after LRYGB due to suspected internal herniation. In contrast, the five-year merged data of SLEEVEPASS and SM-BOSS trials showed higher late complication rate after LRYGB evaluated with comprehensive complication index (Wölnerhanssen et al., 2021), although in the individual trials the complication rates were similar after both procedures (Peterli et al., 2018; Salminen et al., 2018). This finding of the merged data is in accordance with the large PCORnet cohort study with over 33000 patients indicating more adverse events (interventions, operations, and hospitalization) after LRGYB compared with LSG (Courcoulas et al., 2020). As MBS overall is related to low complication rate (Gero et al., 2019) in experienced centers, large numbers of patients is needed to identify potential differences between the procedures. Moreover, as discussed earlier in regard to weight loss, definitions and reporting of complications should be standardized and uniformed to allow the comparison of different studies (Brethauer et al., 2015). As all surgical procedures, both LSG and LRYGB have their own typical specific complications and these should be preoperatively discussed and evaluated together with the patient. Patient selection for both procedures should be based on the outcomes of long-term follow-up studies and the procedure choice regarding for example preoperative GERD assessments may have a crucial effect on future reoperation rates. Similarly, the risk for internal herniation and other possible major complications should be considered before LRYGB.

## 6.2 Long-term effect of LSG vs LRYGB on QOL

In this thesis study, long-term QOL was similar after LSG and LRYGB. MBS resulted in significant improvement of DSQOL, and greater weight loss led to superior DSQOL. However, the QOL of the trial patients remained significantly lower when compared with the age- and sex-standardized general population.

The detailed QOL-analysis of the SLEEVEPASS trial at seven years of follow-up including long-term QOL assessing both DSQOL and HRQOL, to our knowledge, is unique. At seven years (study I), there was no difference in either DSQOL or HRQOL after LSG vs LRYGB. For DSQOL, a significant improvement from baseline to seven, and also at ten years (study II), was detected. Superior weight loss was associated with superior DSQOL. This is in line with the literature, as MBS has been reported to have positive effect on QOL in previous studies as well (Cooiman et al., 2019; Hachem et al., 2016; Macano et al., 2017; Sha et al., 2020; Versteegden et al., 2018), with no difference between LSG and LRYGB (Hu et al., 2019; Major et al., 2015; Sha et al., 2020; Versteegden et al., 2018; Wölnerhanssen et al., 2021)

For the HRQOL assessments, the trajectories were similar after both procedures; up to five years of follow-up the HRQOL of the trial patients stayed higher compared to baseline but at seven years it reached baseline levels again. Despite the positive effects of MBS on QOL, the HRQOL of the trial patients stayed lower than that of the Finnish general population throughout the follow-up. The decline between five and seven years in the HRQOL of the trial patients can be at least in part interpreted as a normal phenomenon, as this trend along aging is also seen in normal population without obesity (Sintonen, 2001). The finding of HRQOL declining back to baseline levels after seven years is naturally somewhat discouraging, and maybe not all parts can be explained by aging. However, even seven years of better HRQOL and at least up to ten years of better DSQOL can still be seen as a success compared to impaired QOL with no change at all.

## 6.3 Long-term effect of LSG vs LRYGB on reflux

Based on this thesis, the prevalence of GERD, PPI use, and esophagitis were significantly higher after LSG compared to LRYGB. However, there was no difference in the prevalence of de novo BE, and BE occurred markedly less frequently than in earlier studies.

The growing number of bariatric procedures worldwide with LSG being the most popular one, LSG's effect on GERD and endoscopic findings has become a major concern. The previous studies of Felsenreich et al. (Felsenreich et al., 2020) and Genco et al. (Genco et al., 2017) have reported discouraging high cumulative incidence of BE ranging from 14% to 17%. To our knowledge, the data in this thesis (study II), reports the first long-term RCT data on GERD also including the comparison with preoperative endoscopic findings. The markedly lower cumulative incidence of BE in our study (4% after both procedures) compared with the previously mentioned studies (Felsenreich et al., 2020; Genco et al., 2017) probably derives from possible differences in the definition of BE (gastric vs intestinal metaplasia (Spechler et al., 2014)), and the potential variability in the endoscopic techniques and sampling. The findings of this thesis are in accordance with a recent prospective ten-year follow-up after LSG showing similarly 4% prevalence of de novo BE (Csendes et al., 2019), and with a recent prospective clinical study showing also 4% prevalence of de novo BE at five years after LSG (Wölnerhanssen et al., 2023). Furthermore, a large registry trial with over 48000 patients showed no difference in the incidence of BE or esophageal adenocarcinoma after LSG vs LRYGB (Bevilacqua et al., 2020). These convergent findings may reduce the fear of BE and esophageal adenocarcinoma after LSG. However, the significantly higher rates of endoscopic esophagitis, PPI use, and GERD symptoms after LSG compared with LRYGB in our study also in concurrence with Bevilacqua et al. strongly suggest systematic and careful preoperative assessment of GERD along with preoperative endoscopy.

## 6.4 The ability of IMS score in facilitating procedure selection and predicting T2DM remission

In study III of this thesis with large merged prospective data, IMS score did not facilitate procedure selection between LSG and LRYGB in patients with severe obesity and T2DM, as there were no differences in T2DM remission rates between the two procedures in any of the three T2DM severity stages of the IMS score. Nevertheless, the patients in the mild stage group achieved T2DM remission more often compared with moderate and severe stage groups indicating that IMS score might be useful in predicting T2DM remission in MBS patients even though this most likely is due to the preoperative duration of T2DM. Greater %TWL was associated with superior T2DM remission.

To our knowledge, this is the first randomized long-term data validating the IMS score. The IMS score, based on a large retrospective patient cohort with 5 900 patients, suggested LRYGB as the procedure of choice for moderate stage T2DM severity group, as they found superior remission of T2DM after LRYGB in the moderate group (Aminian et al., 2017). This is in contrast with our results, and also with the retrospective validation of Chen et al. (Chen et al., 2018), which in concurrence with our study found no difference in T2DM remission between the two procedures in the T2DM moderate stage at five years. In contrast to above, a recent study by Ohta et al. showed LSG superior in T2DM remission with moderate stage T2DM compared with LRYGB, even though patients in their LSG group had higher BMI compared to patients in the LRYGB group.

The finding of similar T2DM remission rates after LSG and LRYGB of our study is in line with the meta-analyses of Lee et al. consisting of 33 RCTs comparing these two procedures (Lee et al., 2021). However, the Oseberg trial (Hofsø et al., 2019), which found superior remission of T2DM after LRYGB, is not included in the meta-analyses of Lee et al. Nevertheless, as stated earlier, all the available RCTs are underpowered for comorbidities, and international scientific collaboration would be needed to further address this issue.

As described in the literature review, many scoring systems consisting of different predictive factors have been developed to predict T2DM remission after MBS. In a study of Plaeke et al. comparing 11 different predictive scores of T2DM remission (Plaeke et al., 2021), IMS score, Ad-DiaRem (Aron-Wisnewsky et al., 2017), and DiaBetter (Pucci et al., 2018) performed best in the prediction of T2DM remission after MBS. They all include similar predictive factors such as HbA1c, preoperative T2DM medication, and insulin use, all related to odds of achieving T2DM remission (Panunzi et al., 2016; Park et al., 2020; Pucci et al., 2018; Still et al., 2014). The strongest predictive factor for T2DM remission seems to be the duration of T2DM (Aron-Wisnewsky et al., 2017; Dixon et al., 2013; Moradi et al., 2022; Panunzi et al., 2016; Schauer et al., 2003; Schauer et al., 2017), which is also included in all three best performing scores above. As T2DM is usually a progressive disease, the important role of T2DM duration is understandable: higher levels of HbA1c, medications and insulin use can be seen as a consequence of longer duration of T2DM, and signs of progression of disease severity (Turner et al., 1999).

## 6.5 Strengths and limitations of the studies

This thesis has several strengths, including the randomized setting, and multicenter and multisurgeon design of the SLEEVEPASS trial. A clear strength of the trial is the long-term follow-up, with 76% follow-up rate at seven years (study I), and up to 85% follow-up rate at ten years (study II). A special strength in QOL assessments is the long-term QOL covering both DSQOL and HRQOL from baseline up to seven years. Finally, a major advantage of the ten-year report is the preoperative careful assessment of upper gastrointestinal endoscopy findings and the high endoscopic follow-up rate of 77%, enabling the comparison with preoperative findings and the assessment of de novo -findings.

The SLEEVEPASS (studies I-III) randomized trial naturally has several limitations. First, during the enrolment of the study in 2008-2010 only a small number of bariatric procedures was performed in Finland which may have caused a potential learning curve effect, and none of the study hospitals at that time could be seen as a specialized high-volume bariatric center. This may affect the rather high reoperation rate in our trial. However, this learning curve effect applies for both groups, and although not experienced in MBS at the time of study initiation, all the treating surgeons were experienced laparoscopic surgeons. Another limitation concerning study enrolment is that patients not included in the study were not adequately recorded. However, owing to the small number of bariatric procedures done in Finland at the study initiation, the majority of the patients were enrolled in the study mitigating the selection bias.

Secondly, the SLEEVEPASS trial, as all RCTs, is obliged to follow the original study design and setting, which always sets limitations, especially at long-term follow-up. The equivalence trial design was selected, and the equivalence margins of minimal clinical important difference had to be predefined somewhat arbitrarily, as there was very limited clinical information of the longer-term follow-up weight loss outcomes especially regarding LSG at the time of study initiation.

Third, the preoperative assessment of GERD was insufficient and not standardized, even though patients with severe GERD and large hiatal hernia were excluded. Preoperative gastrointestinal endoscopy was performed for all patients, but no standardized reporting of GERD symptoms or PPI use was collected, and these we had to address retrospectively in study II. As GERD was the most frequent reason for reoperations in the LSG group, a more structured preoperative GERD evaluation might have led to better patient selection. However, owing to little clinical and scientific knowledge of the connection of LSG and worsening of GERD at the study initiation, a standardized GERD assessment was not performed.

Fourth, regarding reoperations in the LRYGB group, suspected internal herniation was the most frequent reason for late reoperation. This is partly due to the fact that at the time of study enrolment, the mesenteric defects were not routinely closed, a procedure which nowadays is routinely done (Stenberg et al., 2016). This may have caused the relatively high number of reoperations after LRYGB in our study.

Fifth, as discussed earlier in this thesis, the SLEEVEPASS trial like other RCTs addressing this issue, are underpowered for differences in comorbidities, especially for T2DM. To detect 10% difference in T2DM remission between LSG and LRYGB, 700 patients should be enrolled, and to achieve this, we need international collaboration and merging of individual patient level data.

Limitations for study III include the above stated limited number of patients with T2DM, which however, to our knowledge, is to date the largest randomized cohort of patients with T2DM and severe obesity with the longest follow-up and high follow-up rate comparing LSG and LRYGB. Two limitations can be seen in comparison of the original IMS report (Aminian et al., 2017): our trial patients had relatively better glycemic control and shorter duration of T2DM than the patients in the original trial, and the surgical technique of LRYGB (especially limb length) was not reported in the original IMS report. These facts may have affected the differences in the study outcomes.

## 6.6 Future aspects

The obesity epidemic is still increasing worldwide. Although MBS has proven to be efficient and safe even at long-term (Adams et al., 2017; Angrisani et al., 2018; Puzziferri et al., 2014), and superior in comparison to conservative treatment (Schauer et al., 2017), it is still very rarely performed as only about 1% of patients with severe obesity eligible for MBS actually have access to surgery (Campos et al., 2020). The causes of the low prevalence of MBS remain somewhat unclear, but given its excellent safety profile (Arterburn et al., 2020), the overestimation of surgical risks at primary care and by the possible patients may set barriers in this issue (Rajeev et al., 2023). Even to date, severe obesity is not recognized as a chronic disease. The exposing factors of obesity are not identified, and a major negative stigma and lack of knowledge still dominates the field of obesity management. These factors slow down or at their worst prevent the patients from getting active treatment (Rubino et al., 2020). Furthermore, enhanced awareness of the positive effects of MBS should be obtained among physicians and patients to increase utilization of bariatric procedures. As the number of bariatric procedures is slowly but steadily growing, and MBS results in longer life-expectancy and lower all-cause mortality at long-term (Arterburn et al., 2020; Wiggins et al., 2020), especially in patients with T2DM (Syn et al., 2021), MBS patients are expected to live longer. Considering this and the chronic nature of obesity, even longer-term studies are needed to assess the course of effects of bariatric procedures. In some cases, revisional or conversional procedures will be required, and these should be evaluated individually considering the best option for the patient in question with respect to best possible quality of life. In addition, international collaboration is needed in the future to have power to detect potential differences in comorbidity remission, especially in T2DM, between the two procedures.

LSG and LRYGB are currently the most popular bariatric procedures worldwide, both with their pros and cons. The more one immerses in comparison of these two procedures, the harder it gets to form an unambiguous opinion, as there are multiple factors that needs to be assessed in decision making. The key is to find the best bariatric procedure for each individual patient considering risk-profiles, patient's characteristics, and associated diseases as well as naturally the availability of different bariatric procedures, and patient's opinion. In the future, an algorithm for a prognostic scoring system including all relevant individual patient's characteristics for decision making should be created to tailor the best bariatric procedure for each patient. In addition, a standardized uniform reporting system of MBS outcomes should be created to enable better comparison and interpretation of the outcomes of different trials and treatment options regarding not only procedure selection, but also anti-obesity medical treatments.

What about in the further future? Obesity and climate change are probably the two greatest threats to humankind. The overconsumption of food, as well as the resources of our planet, is not a sustainable way of living. With rising temperatures due to climate change, people may become even less physically active, and this leads to an even higher number of people with obesity and larger carbon footprints. Fruits and vegetables will become more expensive, and maintaining a healthy diet will be even harder than nowadays. Actions will be needed from all of us.

Luckily, the treatment of obesity has taken huge steps during the last decades, and none of us can predict what happens next. I hope for good things. Learning more and more about genetics can help us map obesity-related genes and develop targeted treatments. Maybe the inescapable global warming will encourage people to go vegan and diminish at least the prevalence of class I and II obesity. Maybe somebody will invent superfood that tastes great, is healthy, and environmental-friendly. Maybe advanced medical therapy will solve the problem of obesity, and bariatric surgery is not even needed in the future. Slightly a discouraging thought for my thesis, but fantastic for the world and its inhabitants.

# 7 Conclusions

The present thesis assessing the comparative long-term outcomes of LSG and LRYGB results in the following conclusions:

1. At seven and ten years of follow-up, %EWL is greater after LRYGB compared with LSG, and the two procedures are not equivalent for weight loss. There was no difference in remission of T2DM, dyslipidemia, or OSAS, but LRYGB resulted in superior hypertension remission. There was no difference in late minor or major complication rates after LSG and LRYGB at ten years.

2. MBS leads to significant long-term QOL improvement with no difference between LSG and LRYGB. The overall HRQOL of all study patients remains lower than that of age- and sex-standardized general population. Greater weight loss after MBS was associated with better DSQOL.

3. GERD symptoms, PPI use, and endoscopic esophagitis were more prevalent after LSG compared to LRYGB at ten years underlining the importance of preoperative GERD assessment and patient selection, as well as careful long-term follow-up after MBS. However, the cumulative incidence of BE was markedly lower than in previous studies, and there was no difference between the procedures.

4. IMS score does not seem to facilitate procedure selection between LSG and LRYGB, as in our prospective cohort there were no differences in the T2DM remission rates between the two procedures in any of IMS score's T2DM severity stages. However, IMS score was useful in predicting long-term T2DM remission after MBS most likely based on preoperative T2DM duration.

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