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BARIATRIC SURGERY IN THE TREATMENT OF MORBID OBESITY: LONG-TERM OUTCOMES AND COMPARISON OF LAPAROSCOPIC SLEEVE GASTRECTOMY WITH ROUX-EN-Y GASTRIC BYPASS

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To Eero, Oiva and Päivi

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ABSTRACT

Obesity is currently one of the greatest global health problems. It is associated with increased morbidity and mortality, worsened quality of life (QOL) and significant health care costs. For morbidly obese patients, bariatric surgery is the only effective treatment option showing good and sustainable long-term weight loss and remission or improvement of obesity related comorbidities. Laparoscopic Roux-en-Y gastric bypass (LRYGB) is the gold standard of bariatric surgery with demonstrated long-term efficacy. During the last years, laparoscopic sleeve gastrectomy (LSG) has become the most common bariatric procedure despite the lack of long-term follow-up results at that time.

The main aim of this thesis was to compare the short and long-term outcomes on weight loss, obesity related co-morbidities, and QOL after LSG and LRYGB in the treatment of morbid obesity in a randomized clinical multicenter equivalence trial (SLEEVEPASS). In addition, this thesis aimed to assess the QOL improvement after laparoscopic gastric banding (LGB) and to compare it with the QOL of the general population.

The operative time of LSG was shorter with no difference in early (30 days) overall morbidity between LSG and LRYGB. At 5-year follow-up, the primary endpoint of percent excess weight loss (%EWL) was 57% after LRYGB and 49% after LSG. The mean difference was not statistically significant based on the prespecified equivalence margins. At 5 years, there were no differences regarding the long-term resolution of type 2 diabetes or dyslipidemia, improvement of QOL, morbidity, and mortality, but hypertension resolution was superior after LRYGB. QOL improved significantly after LAGB and was maintained at five-year follow-up but did not reach the level of the general population.

KEYWORDS: Bariatric surgery, Morbid obesity, Laparoscopic gastric bypass, Laparoscopic sleeve gastrectomy, Laparoscopic gastric banding

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MIKA HELMIÖ: Bariatrinen kirurgia sairaalloisen lihavuuden hoidossa: pitkäaikaistulokset ja vertailu mahalaukun kavennusleikkauksen ja ohitusleikkauksen välillä
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TIIVISTELMÄ

Lihavuus on yksi suurimpia maailmanlaajuisia terveysongelmia. Siihen liittyy lisääntynyt sairastavuus ja kuolleisuus, huonontunut elämänlaatu sekä merkittäviä terveydenhuollon kustannuksia. Lihavuuskirurgia on ainoa hoitomuoto, jolla saavutetaan hyvät pitkäaikaistulokset painonlaskun sekä sairaalloiseen lihavuuteen liittyvien liitännäissairauksien paranemisen osalta. Mahalaukun ohitusleikkaus (bypass) on vakiintunut leikkausmenetelmä, jonka teho on osoitettu pitkäaikaisseurannassa. Viime vuosina mahalaukun kavennusleikkauksesta (sleeve) on tullut yleisin lihavuuskirurginen leikkausmenetelmä ilman käytettävissä olevia pitkäaikaistuloksia.

Tämän väitöskirjatyön tarkoituksena oli vertailla mahalaukun kavennus- ja ohitusleikkauksen tuloksia painonlaskun, liitännäissairauksien paranemisen sekä elämänlaadun osalta satunnaistetussa kliinisessä monikeskus-ekvivalenssitutkimuksessa (SLEEVEPASS). Lisäksi tutkittiin mahapantaleikkauksen jälkeistä elämänlaadun paranemista ja vertailtiin sitä väestön yleiseen elämänlaatuun.

Varhaisvaiheen tuloksissa kavennusleikkauksen leikkausaika oli lyhyempi, mutta komplikaatioiden määrässä ei ollut eroa ohitusleikkaukseen verrattuna. Tutkimuksen ensisijainen päätetapahtuma eli ylipaino-osuuden prosentuaalinen lasku (%EWL) viiden vuoden seurannassa oli ohitusleikkauksen jälkeen 57% ja kavennusleikkauksen jälkeen 49%. Keskimääräinen ero ei ollut tilastollisesti merkitsevä perustuen ennalta määriteltyihin ekvivalenssirajoihin. Leikkausmenetelmien välillä ei ollut eroa tyypin 2 diabeteksen, hyperkolesterolemian ja elämänlaadun paranemisessa, eikä sairastavuudessa ja kuolleisuudessa, mutta verenpainetauti parani useammin ohitusleikkauksen jälkeen. Mahapantaleikkauksen jälkeen elämänlaatu parani merkitsevästi viiden vuoden seuranta-aikana, mutta lihavuuskirurgisten potilaiden elämänlaatu oli vertailuväestöä huonompi.

AVAINSANAT: Lihavuuskirurgia, Sairaalloinen lihavuus, Laparoskooppinen mahalaukun ohitusleikkaus, Laparoskooppinen mahalaukun kavennusleikkaus

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Abbreviations

ADA	American Diabetes Association
ANOVA	Analysis of variance
BMI	Body mass index
BPD	Biliopancreatic diversion
BPD-DS	Biliopancreatic diversion with duodenal switch
CI	Confidence intervals
DSQOL	Disease-specific quality of life
EAS	European Atherosclerosis Society
EBMIL	Excess body mass index loss
ESC	European Society of Cardiology
EWL	Excess weight loss
GERD	Gastroesophageal reflux disease
GLP-1	Glucagon-like peptide-1
HbA1C	Glycated hemoglobin
HDL	High-density lipoprotein
HR	Hazard ratio
HRQOL	Health-related quality of life
JIB	Jejunoileal bypass
LAGB	Laparoscopic adjustable gastric banding
LDL	Low-density lipoprotein
LRYGB	Laparoscopic Roux-en-Y gastric bypass
LSG	Laparoscopic sleeve gastrectomy
MGB	Mini gastric bypass
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NIH	National Institutes of Health
OSA	Obstructive sleep apnea
OAGB	One anastomosis gastric bypass
PCOS	Polycystic ovarian syndrome
PPI	Proton pump inhibitor
QOL	Quality of life

RCT	Randomized controlled trial
SADI	Single-anastomosis duodenoileal bypass
SAGB	Single anastomosis gastric bypass
SOS study	Swedish Obese Subjects study
T2DM	Type 2 diabetes mellitus
TG	Triglyceride
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 Helmiö M, Salminen P, Sintonen H, Ovaska J, Victorzon M. A 5-Year Prospective Quality of Life Analysis Following Laparoscopic Adjustable Gastric Banding for Morbid Obesity. Obes Surg 2011; 21(10): 1585-91

II Helmiö M, Victorzon M, Ovaska J, Leivonen M, Juuti A, Jaser N, Peromaa P, Tolonen P, Hurme S, Salminen P. SLEEVEPASS: A randomized prospective multicentre study comparing laparoscopic sleeve gastrectomy and gastric bypass in the treatment of morbid obesity – preliminary results. Surg Endosc 2012; 26(9): 2521-6

III Helmiö M, Victorzon M, Ovaska J, Leivonen M, Juuti A, Peromaa-Haavisto P, Nuutila P, Vahlberg T, Salminen P. Comparison of short-term outcome of laparoscopic sleeve gastrectomy and gastric bypass in the treatment of morbid obesity: A prospective randomized controlled multicentre SLEEVEPASS study with six-month follow-up. Scand J Surg 2014; 103(3):175-181

IV Salminen P, Helmiö M, Ovaska J, Juuti A, Leivonen M, Peromaa-Haavisto P, Hurme S, Soinio M, Nuutila P, Victorzon M. Effect of Laparoscopic Sleeve Gastrectomy vs Laparoscopic Roux-en-Y Gastric Bypass on Weight Loss at 5 Years Among Patients With Morbid Obesity: The SLEEVEPASS Randomized Clinical Trial. JAMA 2018; 319(3):241-254

1 Introduction

Obesity, defined as an excess of body fat, is a chronic disease. During the last decades, the obesity epidemic has become one of the biggest global health problems with increasing prevalence around the world. It is considered a major contributor to poor health in most countries (NCD-RisC 2016). It has been estimated that in 2015 approximately 604 million adults and 108 million children were obese representing a doubling in obesity prevalence in 70 countries and an increase in the prevalence in almost all countries since 1980 (Afshin et al. 2017). In the year 2000, it was estimated that the number of overweight adults surpassed the number of underweight adults for the first time in the world (Caballero 2007).

Obesity is associated with increased morbidity and mortality, worsened quality of life (QOL) and significant health care costs. All of these associations are based mainly on obesity-related comorbidities, such as type 2 diabetes mellitus (T2DM), hypertension and other cardiovascular diseases, hyperlipidemia, obstructive sleep apnea (OSA) and depression. (Calle et al. 1999)

Results with conservative treatment, such as nutritional counseling, dietary therapy, physical activity counseling, behavioral therapy and pharmacological therapy, have been disappointing, in particular in the long term. Bariatric surgery is considered the only effective treatment option for morbidly obese patients showing good and sustainable weight loss and remission or improvement of obesity related comorbidities. (Adams et al. 2018, Puzziferri et al. 2014, Sjöström 2013) For many years, laparoscopic Roux-en-Y gastric bypass (LRYGB) was the most frequently performed bariatric procedure in the world (Angrisani et al. 2018) and considered the gold standard of bariatric surgery. Its long-term efficacy regarding weight loss, resolution of obesity-related comorbidities and complication rates has been well demonstrated (Adams et al. 2018, Buchwald et al. 2004).

As the first laparoscopic minimally invasive bariatric procedure, laparoscopic adjustable gastric banding (LAGB) became popular in the 1990s and early 2000s (Angrisani et al. 2018). However, the long-term results have been rather disappointing due to increasing number of complications, such as band slippage requiring band removal, and insufficient weight loss (Suter et al. 2006). Nowadays, LAGB is performed less frequently, and has been almost abandoned in Europe

(Angrisani et al. 2018), and many of the earlier LAGB patients have been converted to other bariatric procedures.

Laparoscopic sleeve gastrectomy (LSG) is currently the most common bariatric procedure worldwide and in 2014, the number of LSGs surpassed the number of LRYGBs (Angrisani et al. 2018). LSG was initially developed as a first stage procedure in biliopancreatic diversion with duodenal switch (BPD-DS) in super obese patients to reduce surgery related morbidity and mortality (Hess and Hess 1998). As weight-loss results following LSG were more promising than expected, it started to gain popularity as a single stage procedure in morbidly obese patients. The advantages of LSG over LRYGB include a technically less complex procedure with shorter operation time, no risk of internal herniation, the remnant stomach still accessible for endoscopy, less dumping due to preservation of the pylorus, and that various second stage procedures are possible, if required.

In this doctoral thesis, the aim of study I was to assess the changes in QOL after LAGB performed for morbid obesity. In addition, the QOL of the LAGB bariatric surgery patients was compared to the QOL of an age and gender standardized general population. Studies II, III, and IV were parts of a randomized, clinical, multicenter equivalence study (SLEEVEPASS trial). The aim of study II was to compare perioperative outcomes and 30-day morbidity after LSG and LRYGB for the treatment of morbid obesity. In study III, the six-month results on weight loss, remission of obesity-related comorbidities and overall morbidity after LSG and LRYGB were assessed. The aim of study IV was to determine the outcomes of LSG and LRYGB at 5-year follow-up regarding the primary endpoint percent excess weight loss (%EWL) and the secondary outcomes remission of obesity-related comorbidities, overall morbidity, and improvement of QOL.

2 Review of the Literature

2.1 Obesity

2.1.1 Classification and epidemiology of obesity

Obesity is defined as an excess of body fat that may cause problems to an individual's health. Body mass index (BMI) calculated as weight in kilograms divided by the square of height in meters (kg/m^2) is used for classifying the degree of obesity. The recommended classifications for BMI adopted by the National Institutes of Health (NIH) and World Health Organization (WHO) are: people with BMI < 18.5 kg/m^2 are considered underweight, 18.5 to 24.9 kg/m^2 normal weight, 25.0 to 29.9 kg/m^2 overweight, and people with BMI ≥ 30.0 kg/m^2 are considered obese. Obesity is further categorized into three classes: class I (moderately obese) for BMI 30.0 to 34.9 kg/m^2, class II (severely obese) for BMI 35.0 to 39.9 kg/m^2, and BMI ≥ 40.0 kg/m^2 is class III, very severely obese or morbidly obese. (National Institutes of Health 1998, World Health Organization 2000)

Obesity is a chronic disease with an increasing prevalence around the world. It is considered a major contributor to poor health in most countries. (NCD-RisC 2016) It has been estimated that approximately 604 million adults and 108 million children were obese in 2015 globally. This represents a doubling in the prevalence of obesity in 70 countries and increased prevalence in almost all other countries since 1980 (Afshin et al. 2017). There are differences in the prevalence of obesity regarding different regions and countries: 4% to 28% of men and 6% to 37% of women in European countries are obese with Eastern and Southern Europe having higher prevalence rates (Berghöfer et al. 2008). According to a 2014 WHO report, 61% of people in the Americas were overweight and 27% were obese, whereas in South-East Asia only 22% were overweight and 5% obese (World Health Organization 2014). In Finland, according to the FinHealth 2017 study, the prevalence of overweight is 72% and obesity 26% in men, and 63% and 28% in women, respectively (Koponen et al. 2018).

2.1.2 Obesity related morbidity and mortality

Obesity is associated with increased morbidity and mortality (Wang et al. 2011, Haslam and James 2005). Health risks related to obesity start to increase already at BMI > 25 kg/m² (Field et al. 2001). The worldwide incidence of especially T2DM, cardiovascular diseases, OSA, cancer, and osteoarthritis is strongly influenced by the obesity epidemic (Seidell and Halberstadt 2015). Other comorbidities associated with obesity are, for example, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), cirrhosis, gallstones, gastroesophageal reflux disease (GERD), asthma, polycystic ovarian syndrome (PCOS), infertility, urinary incontinence, gout, and depression (Nguyen and El-Serag 2010, Martin-Rodriguez et al. 2015, Bächler et al. 2014).

There is strong evidence from several large epidemiologic studies that obesity is associated with an increased risk of mortality (Adams et al. 2006, Freedman et al. 2006, Pischon et al. 2008). An analysis of a UK primary care database (Clinical Practice Research Datalink, CPRD) between 1988 and 1998 identified the following factors to be associated with increased risk of death in the severely obese population (BMI ≥ 35 kg/m²): T2DM, age, male sex and smoking (Padwal et al. 2013). In addition to these factors, a recent case-controlled analysis from the same UK database including almost 190 000 patients identified also BMI ≥ 60 kg/m², hypertension, and hyperlipidemia at first diagnosis of severe obesity to be independently associated with an increased risk of death (Moussa et al. 2019).

2.1.3 Economic impact of obesity

The treatment of obesity-related conditions accounts for an enormous economic burden (Wang et al. 2011, Finkelstein et al. 2008). In addition to direct health care expenses, obesity also imposes costs in the form of lost work days, lower productivity at work, and permanent disability. It has been described that there is an association between increasing BMI and costs attributable to obesity (Dee et al. 2014, Specchia et al. 2015). In 2014, the global economic impact of obesity was estimated to be 2.0 trillion US dollars or 2.8% of the global gross domestic product (Tremmel et al. 2017).

The Swedish Obese Subjects (SOS) study is a large prospective matched controlled intervention study that started in 1987 and compares bariatric surgery with conservative treatment of morbid obesity (Sjöström 2013). A cross-sectional comparison was conducted between obese patients from the SOS study and randomly selected references. It was found that individuals with obesity had twice as many days of sick leave, were three times as likely to draw a disability pension, and had higher annual drug costs compared with non-obese (Narbro et al. 2002).

2.2 Conservative treatment of obesity

To be successful, conservative treatment of obesity must include multimodal life-style interventions and long-lasting changes in many aspects of life. Conservative treatment of obesity can consist of nutritional counseling, dietary therapy, physical activity counseling, behavioral therapy and pharmacological therapy. Unfortunately, conservative treatment options suffer from a high rate of failure at long-term follow-up and in most of the cases, only slow down the process of obesity and associated comorbidities at the best. (Kissane and Pratt 2011, Picot et al. 2009, Terranova et al. 2015, Franz et al. 2015) In the SOS study the mean change in body weight was -16% in the surgery group and -1% in the conventionally treated control group at 15-year follow-up (Sjöström et al. 2012). In reality, the outcome of conservative treatment in the SOS study may be even more disappointing as the results are only presented according to intention-to-treat analysis, and a considerable number of patients in the control group have ultimately undergone bariatric surgery later during the follow-up.

Pharmacological therapy is seldom recommended as a first-line treatment option for obesity. However, it can be used as an additional weight-reducing intervention to other conservative treatment modalities. Medical therapy can be considered for patients with BMI over 30 kg/m² or for patients with BMI over 28 kg/m² with obesity-related comorbidities. (Current Care Guidelines 2013)

Among the pharmacological options for obesity currently available in Finland, orlistat (Xenical®) has been in use for the longest time. The weight-reducing effect is based on inhibition of pancreatic enzymes resulting in reduced intestinal uptake of fat. It has a modest efficacy and the side effects are quite common resulting in compromised treatment compliance. The most common side effects are fatty or oily stools and fecal urgency. In a randomized placebo-controlled study by Richelsen et al, the addition of orlistat to lifestyle interventions was associated with maintenance of an extra 2.4 kg weight loss at three-year follow-up. (Richelsen et al. 2007)

Since the beginning of 2018, there has been a medication combining bupropion and naltrexone (Mysimba®) available on the market in Finland. It affects the energy balance via the central nervous system by reducing appetite and increasing energy expenditure (Greenway et al. 2009). Treatment with Mysimba® has been reported to result in an average of 5% weight reduction after one year treatment, when compared to placebo (Hollander et al. 2013, Greenway et al. 2010, Apovian et al. 2013).

Liraglutide (Victoza®) is a drug that has previously been used for management of T2DM as a subcutaneous injection. It has been made available for obesity treatment since June 2018 in Finland. It has an appetite suppressing effect via brain glucagon-like peptide-1 (GLP-1) receptors. In one study, liraglutide combined with diet and exercise was associated with an average of 8.4 kg weight reduction, compared to 2.8 kg in the placebo group, with a 56-week follow-up time (Pi-Sunyer et al. 2015).

2.3 Operative treatment of obesity

2.3.1 History of bariatric surgery

The first weight-reducing operation dates back to 1952, when a Swedish surgeon Viktor Henriksson reported on resecting 105 cm of the small intestine (Henriksson 1952). Dr Richard Varco at the University of Minnesota is acknowledged as the first to perform jejunoileal bypass (JIB) on a morbidly obese patient in 1953, but he never published this case (Buchwald 2014). In 1954, Kremen, Linner, and Nelson, also from the University of Minnesota, were the first to report of the JIB operation (Kremen et al. 1954). Since the publication of a refined JIB technique by Payne and DeWind in 1969, it became the standard weight-reducing operation for a while. In this technique, 35 cm of proximal jejunum was attached to the terminal ileum 10 cm from the ileocecal valve. (Payne and DeWind 1969) These extremely malabsorptive surgical techniques were highly effective, but induced major adverse effects such as steatorrhea, electrolyte imbalances, vitamin and mineral deficiencies, kidney stones, gas bloat syndrome, steatohepatitis, and progressive liver disease caused by the surgically created short bowel syndrome and bacterial overgrowth in the bypassed small intestine. In many cases the anatomy had to be restored to normal. These problems led to more or less abandoning of the JIB technique in the early 1970s. (Brown et al. 1974, Scott et al. 1971)

Professor Nicola Scopinaro from Genoa explored the possibility to reduce some of the morbidity associated with JIB without compromising the weight-reducing effect. To achieve this, he hypothesized that the terminal ileum must be preserved and the bypassed intestine must have a continuous flow of contents to prevent bacterial overgrowth. To address this hypothesis, he developed the biliopancreatic diversion (BPD) in 1976. (Scopinaro et al. 1980) Marceau and Hess further refined it into BPD with duodenal switch (BPD-DS) in 1998 (Hess and Hess 1998, Marceau et al. 1993). These techniques are described in more detail in chapter 2.3.3.4.

In 1966, Edward E. Mason performed the first gastric bypass operation at the University of Iowa. He was aiming for a weight-loss procedure with less malabsorption than JIB and adding restriction for weight reduction. This operation included horizontal division of the stomach and constructing a loop gastrojejunostomy to the proximal gastric pouch of about 100-150 ml in size. (Mason and Ito 1967) This original technique was modified since and in 1977 Alder described a smaller 50 ml gastric pouch formed by cross-stapling the stomach and introducing the Roux-en-Y reconstruction. This provided more gastric restriction and reduced the risk of anastomotic ulcer. (Alder and Terry 1977) With the introduction of laparoscopic approach in 1994 (Wittgrove et al. 1994), laparoscopic

Roux-en-Y gastric bypass (LRYGB) became the most common bariatric procedure in the world for two decades (Buchwald 2014).

Aiming for a less invasive procedure, various iterations of gastroplasty as a restrictive procedure have been developed since the 1970s. The original version by Printen and Mason in 1973 consisted of a partial horizontal transection of the stomach, leaving a greater curvature conduit and a small connective portion between the gastric parts (Printen and Mason 1973). In 1981, Laws and Piatadosi made the pouch vertical and introduced a silastic ring to support and restrict the opening (Laws and Piantadosi 1981). In 1982, Edward E. Mason described the vertical banded gastroplasty (VBG), with a mesh band through a gastric window to restrict the outlet (Mason 1982). However, the long-term results were disappointing with unsatisfactory weight loss and complications, such as development of gastro-gastric fistulas and enlargement of pouches. The technique was abandoned in the 1990s with the ascendancy of the laparoscopic adjustable gastric banding (LAGB) (Angrisani et al. 2018).

LAGB was first introduced in 1993 (Belachew et al. 1994). As the first laparoscopic less invasive procedure, it gained popularity in the 1990s and early 2000s (Angrisani et al. 2018). Similar to VBG, the mid-term results even up to five years were good, but the long-term results beyond ten years were disappointing due to insufficient weight loss and increasing number of complications such as band erosions and slippages (Suter et al. 2006). Nowadays, LAGB is almost an abandoned procedure in most of the countries in Europe and many patients have been converted to other bariatric procedures. Currently, the majority of the few LAGBs are performed in the US and Australia. (Angrisani et al. 2018)

Laparoscopic sleeve gastrectomy (LSG) was developed as a first-stage operation for high-risk super-obese patients before the definitive bariatric procedure, originally the BPD-DS (Regan et al. 2003). The initial results with LSG were surprisingly promising as it was shown to be effective as a primary operation. However, long-term results exceeding five years are currently still not available. In 2014 LSG became the most commonly performed bariatric operation in the world (Angrisani et al. 2018).

2.3.2 Indications and contraindications for bariatric surgery

Bariatric surgery can be considered for patients with severe or morbid obesity if conservative treatment has failed. In 1991, The National Institutes of Health (NIH) Consensus Development Panel has published recommendations for gastrointestinal surgery for severe obesity (National Institutes of Health conference 1991). These recommendations with minor variations are still followed worldwide including Finland (Table 1). In Finland, age limits are set between 18 and 65 years, but

individual evaluation is possible (Current Care Guidelines 2013). On the other hand, the International Diabetes Federation recommends bariatric surgery for patients with uncontrolled T2DM even with BMI between 30 and 35 kg/m² (Dixon et al. 2011). All contraindications for bariatric surgery are relative and all the pros and cons must be weighed individually as in all surgical treatment.

Table 1. Indications and contraindications for bariatric surgery

Indications	Contraindications
BMI over 40 kg/m² or BMI over 35 kg/m² with obesity related disease - type 2 diabetes mellitus - hypertension - hyperlipidemia - severe osteoarthritis - obstructive sleep apnoea - obesity-induced cardiomyopathy - polycystic ovario syndrome Age between 18-60 years Conservative treatment has failed	Severe eating disorder Severe and active psychiatric disease Drug or alcohol abuse Active ulcer disease Inability to understand instructions

2.3.3 Current most common operative techniques and their mechanisms of effect

2.3.3.1 Laparoscopic Roux-en-Y gastric bypass (LRYGB)

LRYGB has been the most frequently performed bariatric procedure for many years until 2014, when it was surpassed by LSG. In 2016, there were nearly 686 000 bariatric operations performed worldwide, and 30% (approximately 191 000 procedures) of these were LRYGBs. (Angrisani et al. 2018)

Regarding the current standard LRYGB technique, a small gastric pouch (approximately 30 to 50 ml) is created by dividing the upper part of the stomach (Figure 1). The jejunum is anastomosed to the gastric pouch at approximately 50-70 cm distal to the ligament of Treitz. From this gastrojejunal anastomosis, the length of the alimentary limb is measured approximately 150 cm, and a jejunojejunal anastomosis is created between the alimentary and the biliopancreatic limbs. Then the jejunum is transected between the two anastomoses completing the Roux-en-Y configuration. Food is diverted from the gastric pouch directly into the jejunum, thus bypassing the gastric remnant, duodenum and proximal jejunum. In this standard technique, the length of the common channel after the jejunojejunal anastomosis varies depending on the total length of the small intestine, which has a large individual variation. Many surgeons have introduced several variations of this

technique regarding the lengths of the intestinal limbs, with the intention to modify the degree of malabsorption. A longer alimentary limb does not seem to result in significant effect on weight loss (Choban and Flancbaum 2002). Some nonrandomized observational studies have reported better weight loss with a longer biliopancreatic limb (MacLean et al. 2001, Leifsson and Gislason 2005, Nergaard et al. 2014). A randomized controlled trial (RCT) on the subject was published by Homan et al in 2018 (Homan et al. 2018). They compared a standard LRYGB (alimentary limb 150 cm, biliopancreatic limb 75 cm) with a long biliopancreatic limb LRYGB (alimentary limb 75 cm, biliopancreatic limb 150 cm). A significantly better %EWL was achieved with the long biliopancreatic limb LRYGB across the four-year follow-up, but no difference in percent total weight loss (%TWL) was observed after four years. (Homan et al. 2018)

In LRYGB, the amount of food intake is reduced due to the small gastric pouch. The weight reduction is enhanced by changes in the intestinal hormone levels (e.g. GLP-1, peptide YY, anti-incretin factors, and ghrelin) (Yousseif et al. 2014, Korner et al. 2005, Rubino et al. 2010).

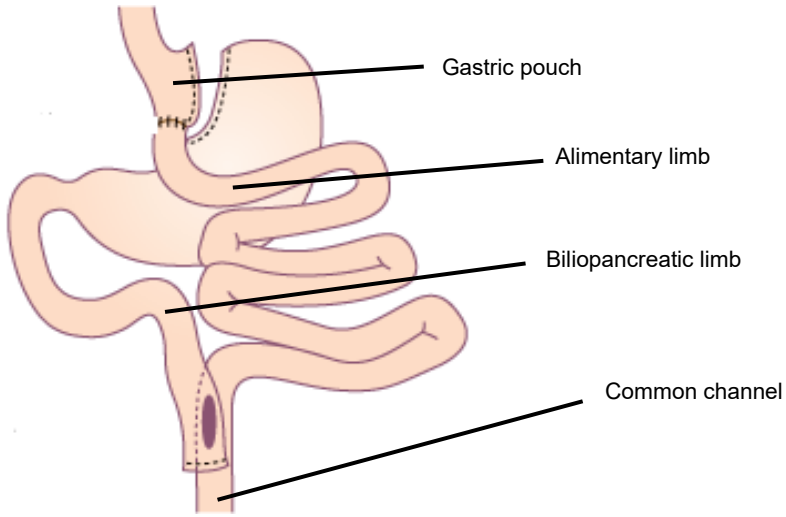

Figure 1. Laparoscopic Roux-en-Y gastric bypass, LRYGB. Picture modified from textbook Surgery (Leppäniemi et al 2018), artist Tiina Ripatti. Reproduced with the permission of the copyright holders.

2.3.3.2 Laparoscopic sleeve gastrectomy (LSG)

LSG has increased rapidly in popularity since its introduction and in 2014 it became the most commonly performed bariatric procedure in the world. In 2016, 54% of all the bariatric operations performed worldwide were LSGs, comprising a total of approximately 340 000 operations. (Angrisani et al. 2018)

LSG is a partial vertical gastrectomy in which the majority of the greater curvature and the whole fundus are resected creating a tubular shaped stomach. Approximately 1/3 of the stomach is preserved including the pylorus and most of the antrum (Figure 2). LSG is considered mainly a restrictive weight-reducing operation by nature, but it also has additional metabolic effects via changes in release of intestinal hormones (GLP-1, peptide YY, cholecystokinin (CCK), and ghrelin) (Yousseif et al. 2014, Mans et al. 2015).

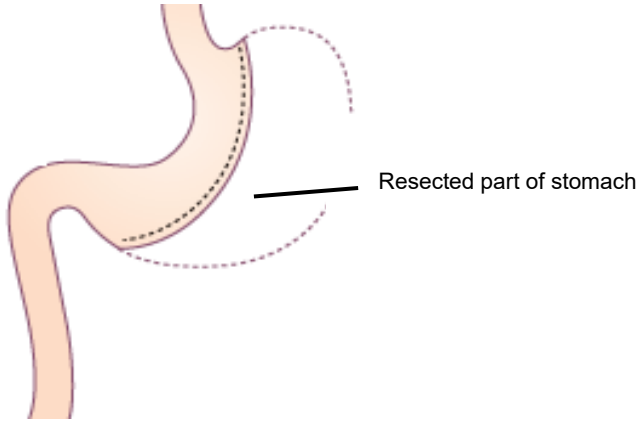

Figure 2. Laparoscopic sleeve gastrectomy, LSG. Picture modified from textbook Surgery (Leppäniemi et al 2018), artist Tiina Ripatti. Reproduced with the permission of the copyright holders.

2.3.3.3 Laparoscopic adjustable gastric banding (LAGB)

LAGB was the second most performed bariatric procedure in the world in 2008, representing about 42% of all procedures. Since then, the technique has been nearly abandoned due to high rates of insufficient weight loss and complication leading to band removal. (Suter et al. 2006) In 2016, there were approximately 19 000 LAGB operations performed in the world representing only about 3% of all the bariatric operations. According to the IFSO Worldwide Survey 2016, most of the LAGB operations still left, were performed in USA, France, Italy and Australia. (Angrisani et al. 2018)

LAGB is a purely restrictive procedure. A tight, adjustable silicone ring is placed around the cardia of the stomach. The silicone ring is connected via a tube to an infusion port placed in the subcutaneous tissue, usually in the middle part of the sternum. The port can be accessed with a syringe and a needle. Injection of saline into the port leads to reduction in the band diameter, resulting in an increased degree of restriction (Figure 3).

Despite being the essence of the LAGB method, adjustability has also been a drawback. To be successful, LAGB requires an extensive follow-up program with continuous fine tuning adjustments and repeated nutritional advice. This requires dedicated health care professionals and considerable resources from the heath care systems.

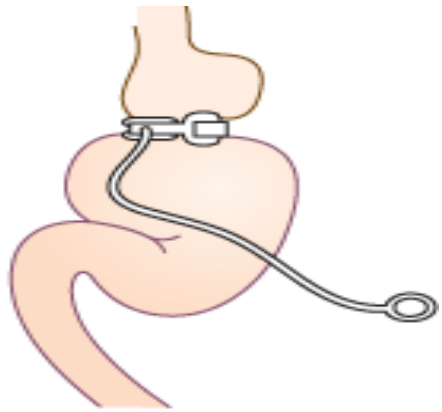

Figure 3. Laparoscopic adjustable gastric banding, LAGB. Picture adapted from textbook Surgery (Leppäniemi et al 2018), artist Tiina Ripatti. Reproduced with the permission of the copyright holders.

2.3.3.4 Other techniques

Despite being the most effective bariatric operations, BPD and BPD-DS have not become commonly used operative techniques (Crea et al. 2011). In recent years their popularity has further decreased, together representing only approximately 0.5% of all operations worldwide. The technical complexity of the procedures compared to other bariatric operations and a higher rate of complications such as malnutrition and steatorrhea have probably played a role.(Angrisani et al. 2018) Nevertheless, BPD and BPD-DS can be considered among the best options for a selected group of patients, such as super-obese (Skogar and Sundbom 2017) and patients with refractory diabetes (Roslin et al. 2015).

In BPD the lower 2/3 of the stomach is resected. The small intestine in transected approximately 200 to 250 cm proximal to the ileocaecal valve, and the distal part of the small bowel is anastomosed to the gastric pouch. The biliopanceatic limb is anastomosed to the distal ileum about 50 cm proximal to the ileocaecal valve, creating a common channel of only 50 cm in length which causes severe malabsorption (Figure 4).

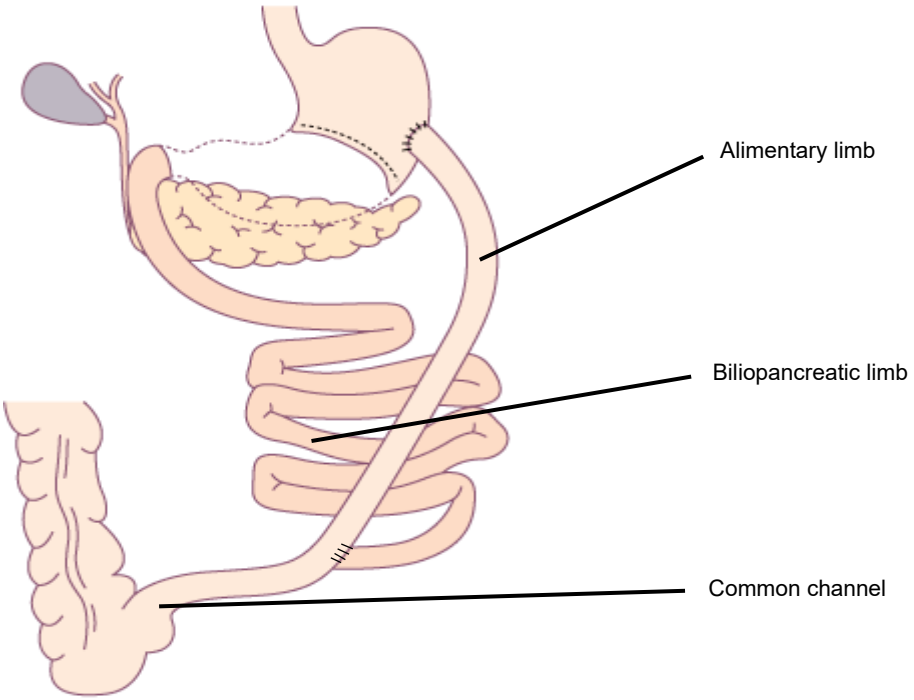

Figure 4. Biliopancreatic diversion, BPD. Picture modified from textbook Surgery (Leppäniemi et al 2018), artist Tiina Ripatti. Reproduced with the permission of the copyright holders.

BPD-DS can be carried out as a single or two-staged operation. As a first step, an LSG is performed. Then as a second step, the duodenum is transected immediately below the pylorus, and the small intestine in transected 250 cm proximal to the ileocaecal valve. Thereafter, the distal part of the small bowel is anastomosed to the proximal part of the duodenum. Finally, the biliopancreatic limb is anastomosed to the ileum about 100 cm prior to the ileocaecal valve, creating a common channel of 100 cm in length (Figure 5).

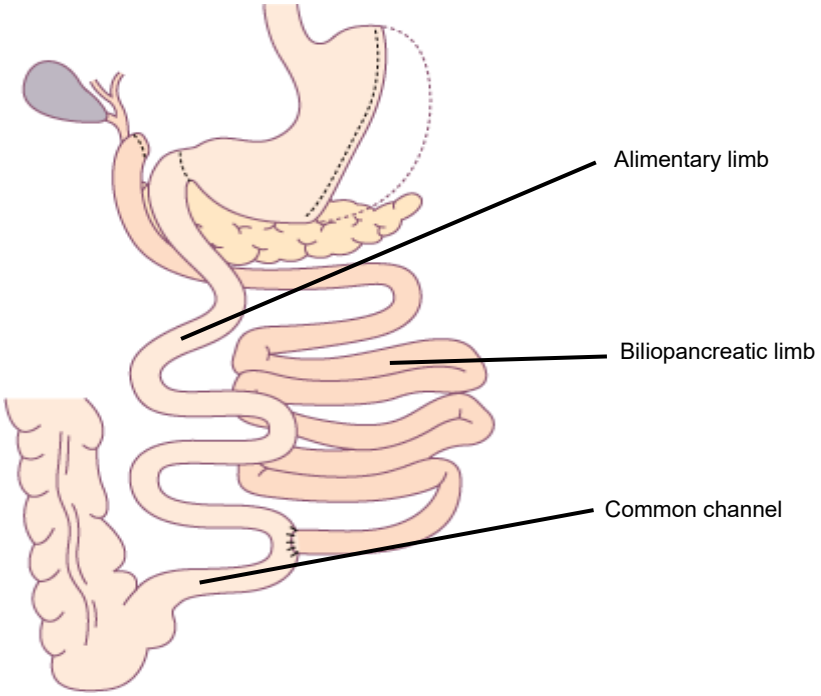

Figure 5. Biliopancreatic diversion with duodenal switch, BPD-DS. Picture modified from textbook Surgery (Leppäniemi et al 2018), artist Tiina Ripatti. Reproduced with the permission of the copyright holders.

The one anastomosis gastric bypass (OAGB) is also known as single anastomosis gastric bypass (SAGB) or mini gastric bypass (MGB). It is a modification of the LRYGB first published in 2001 with a markedly longer BPD-limb (Rutledge 2001). In 2016, this operation constituted 5% of all the bariatric operations worldwide (> 30 000 patients) and it has been growing in popularity (Angrisani et al. 2018) despite lacking sufficient results from long-term follow-up. In this technique, the gastric pouch is created longer than in LRYGB and a small bowel loop 200 cm distal to the ligament of Treitz (the biliopancreatic limb) is anastomosed to the gastric pouch with no enteroenteral anastomosis (Figure 6). Standard LRYGB was compared with OAGB in a French RCT (YOMEGA trial) (Robert et al. 2019). At two-year follow-up, the results were similar regarding %EWL and metabolic improvements. However, higher incidences of diarrhea, steatorrhea, and nutritional adverse events were observed with OAGB, suggesting a malabsorptive effect related to the 200 cm biliopancreatic limb of the procedure (Robert et al. 2019).

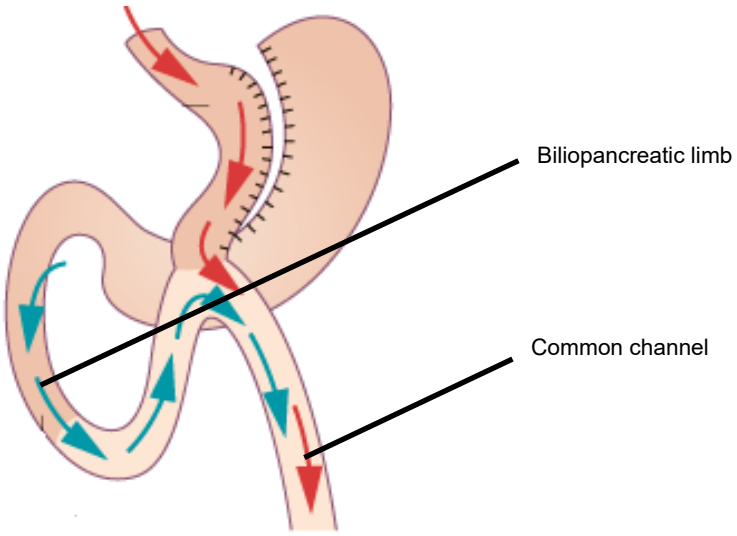

Figure 6. One anastomosis gastric bypass, OAGB. Picture modified from textbook Surgery (Leppäniemi et al 2018), artist Tiina Ripatti. Reproduced with the permission of the copyright holders.

In single-anastomosis duodenoileal bypass (SADI), a LSG is created first, and the duodenum is divided immediately distal of the pylorus. A small bowel loop 200-300 cm proximal to the ileocaecal valve is anastomosed to the duodenum leaving the pylorus intact and no enteroenteral anastomosis (Figure 7). This technique has shown promising results of EWL > 100% at two to three years' follow-up (Sánchez-Pernaute et al. 2010) and has also been used as a second stage operation after failed LSG (Zaveri et al. 2019, Cylke et al. 2018).

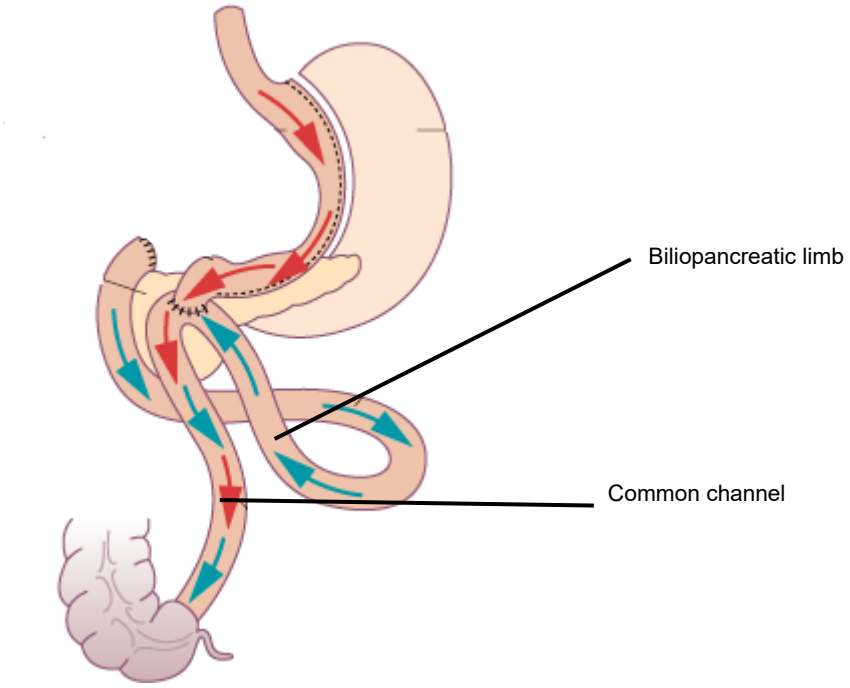

Figure 7. Single-anastomosis duodenoileal bypass, SADI. Picture modified from textbook Surgery (Leppäniemi et al 2018), artist Tiina Ripatti. Reproduced with the permission of the copyright holders.

Laparoscopic greater curvature plication (Fried et al. 2012) and vertically placed removable gastric clip (Jacobs et al. 2017) are two examples of minimally invasive laparoscopic procedures, but so far they have not gained vast popularity and the long-term follow-up results are either disappointing or lacking altogether.

2.3.4 Endoscopic procedures

Several endoscopic bariatric procedures have also been developed. The concept of intra-gastric balloon (IGB) is to endoscopically introduce a saline-containing silicone balloon into the stomach to induce restriction and a feeling of satiety (Mathus-Vliegen and Tytgat 2005). A novel variation of IGB includes a swallowable balloon that does not even require endoscopy at insertion or removal (Jamal et al. 2019). Most often IGB has been advocated for use as a bridge to surgery, i.e. preceding a more definitive bariatric operation (Zerrweck et al. 2012). The potential to reduce complications with such a regimen remains, however, to be demonstrated (Coffin et al. 2017).

An example of endoscopic gastrointestinal bypass device (EGIBD) is the EndoBarrier®. It is a 60 cm long plastic sheath which extends from the proximal

duodenum to the jejunum, thus mimicking a duodenojejunal bypass. It is a relatively safe procedure but has an up to 20% rate of early removal due to patient intolerance. The ValenTx® is a 120 cm barrier device that extends from the gastroesophageal junction to the jejunum also with a high rate of early removal. The %EWL results for these devices have been 12-40% at three-month follow-up with patients with T2DM not requiring antidiabetic medication while the device was in place. (Majumder and Birk 2013)

New endoscopic suturing devices, such as Apollo OverStitch®, USGI-POSE®, and EndoCinch®, offer the potential to perform sleeve-like restrictive procedures transorally (Majumder and Birk 2013). The durability of this endoscopic gastric plication technique has not been examined (Familiari et al. 2011).

2.3.5 Effects of bariatric surgery

Traditionally, the primary end point of bariatric surgery has been its impact on weight loss. In recent years, other outcomes such as resolution of obesity-related comorbidities and ultimately the patients' improved QOL after surgery have become more recognized. The term metabolic surgery has been taken into use, and it describes the many effects of surgical treatment in addition to just plain weight loss. Regarding these various outcomes, the superiority of bariatric surgery compared to conservative treatment of obesity has been documented in several studies (Adams et al. 2018, Puzziferri et al. 2014, Sjöström 2013).

2.3.5.1 Effect on weight loss

In the surgical literature, weight loss has traditionally been reported as %EWL. It is calculated as (initial weight − follow-up weight)/(initial weight − ideal weight corresponding to BMI 25) × 100%. %EWL reaching ≥ 50% postoperatively is usually considered a good result. Other methods used in the literature for reporting weight loss results include change in BMI (ΔBMI), percent excess BMI loss (%EBMIL), and total absolute weight loss (TWL). The disadvantage of using %EWL is that it doesn't reflect successful weight loss in very high BMI patients. This group of patients may end up with lower %EWL results despite achieving better absolute weight loss than lower BMI patients. Thus outcome reporting standards have been adopted and %TWL, calculated as (initial weight − follow-up weight)/(initial weight) × 100%, is now considered a better outcome measure compared to %EWL and %EBMIL. (Brethauer et al. 2015)

In 2004, Buchwald et al. published a large systematic review and meta-analysis on different bariatric procedures. Overall %EWL for the patients was 61.2%. For

LRYGB, LGB, and BPD or BPD-DS the results were 61.6%, 47.5%, and 70.1%, respectively. (Buchwald et al. 2004)

In a recent meta-analysis of 15 randomized controlled trials (RCTs), long-term outcomes of LSG versus LRYGB were compared (Yang et al. 2019). Five-year follow-up was reached in only five trials (Peterli et al. 2018, Schauer et al. 2017b, Ignat et al. 2017, Zhang et al. 2014, Yang et al. 2019). %EWL at five years was 59.1% after LSG and 69.3% after LRYGB (Yang et al. 2019). In a current nonrandomized cohort study from early 2019, long-term ten-year %EWL results were 56.0% following LRYGB and 53.2% following LSG (Jiménez et al. 2019).

BPD and BPD-DS are considered the most effective bariatric procedures regarding weight loss. In a study published in 2016, BPD resulted in excellent %EWL of 83% at three-year follow-up (Biertho et al. 2016).

2.3.5.2 Effect on obesity related comorbidities

In the often cited meta-analysis by Buchwald et al, bariatric surgery in general had an impressively good effect on all obesity related comorbidities (Buchwald et al. 2004). Surgical treatment of obesity is found to be superior to conservative treatment in reaching glycemic control in patients with T2DM and is associated with a lower risk of macrovascular complications (Brethauer et al. 2013, Chen et al. 2016, Schauer et al. 2017b, Mingrone et al. 2015, Jiménez et al. 2012). The durability of glycemic control after bariatric surgery has also been under investigation. In the Longitudinal Assessment of Bariatric Surgery (LABS) study, among patients with T2DM at baseline, the remission rate at seven years postoperatively was 60.2% after LRYGB and 20.3% after LAGB (Courcoulas et al. 2018). In a cohort study by Fisher et al., 5301 obese patients (BMI $\geq$ 35) with T2DM were matched to 14 934 control patients and followed for macrovascular disease outcomes. Bariatric surgery resulted in lower composite incidence of cerebrovascular and coronary artery events at five years. (Fisher et al. 2018) Preoperative duration of T2DM and level of glycated hemoglobin (HbA1C) have been associated as predictors of glycemic control after LSG and LRYGB (Huang et al. 2018). Besides T2DM, bariatric surgery also reduces the burden of many other obesity-associated comorbidities including hypertension (Schiavon et al. 2018, Buchwald et al. 2004), hyperlipidemia (Buchwald et al. 2004, Mingrone et al. 2015) , stroke and coronary artery disease (Sjöström et al. 2012), heart failure (Aggarwal et al. 2016), OSA (Ashrafian et al. 2015, Buchwald et al. 2004, Greenburg et al. 2009), asthma (Ulrik 2016, van Huisstede et al. 2015), NASH (Lassailly et al. 2015), PCOS and infertility (Skubleny et al. 2016, Milone et al. 2016), urinary incontinence (Subak et al. 2015), and cancer incidence (Sjöström et al. 2009, Schauer et al. 2017a).

2.3.5.3 Effect on obesity related mortality

Bariatric surgery is associated with reduced risk of overall mortality in the obese population (Adams et al. 2007, Telem et al. 2015, Pontiroli and Morabito 2011, Reges et al. 2018). A recent population study from the UK (Moussa et al. 2019) showed that bariatric surgery was associated with significantly reduced risk of all-cause mortality among obese patients with BMI ≥ 35 kg/m² with a hazard ratio (HR) of 0.49 compared to obese controls. This was a case-controlled primary care database analysis including almost 190 000 patients with a median follow-up time of 98 months. (Moussa et al. 2019) In the matched-controlled SOS interventional study, the cumulative overall mortality during a 16-year follow-up was 5.0% in the surgery group and 6.3% in the control group. The unadjusted overall HR for mortality was 0.76 in the surgery group compared to controls and HR adjusted for age, sex, and risk factors was 0.71. (Sjöström et al. 2007) Data from the SOS study has also demonstrated that surgical treatment of obesity results in reduced number of cardiovascular deaths (Sjöström et al. 2012). Adams et al. conducted a large registry data study with a mean follow-up of 12.5 years that showed a 46% lower total cancer mortality rate in the surgery group compared to obese controls, with a HR of 0.54 (Adams et al. 2009). Long-term mortality rates of bariatric patients have been shown to improve significantly regardless of the type of bariatric procedure performed (Telem et al. 2015).

2.3.5.4 Effect on quality of life (QOL)

Obesity has negative consequences on the physical, psychological, and social aspects of QOL, especially among the severely obese. Physical health is impaired due to comorbidities and decreased physical activity. Obesity is also associated with depression, low self-esteem, and eating disorders. Social relations are affected by weight-related stigmatization and shame. (Kushner and Foster 2000, Kolotkin et al. 2001) Many studies have demonstrated that surgery for obesity results in significant and lasting improvements in patient-reported QOL outcomes (Mazer et al. 2017, Hachem and Brennan 2016, Strain et al. 2014, Driscoll et al. 2016, Sarwer et al. 2010). In a systematic review and meta-analysis, bariatric surgery was reported to have a significant positive influence on QOL in general, but with greater influence on physical compared to mental aspects of QOL (Lindekilde et al. 2015).

2.3.5.5 Economic impact of bariatric surgery

Bariatric surgery is considered a cost-effective intervention for obese patients compared with non-surgical interventions (Picot et al. 2009). In the short term, bariatric surgery is more costly than conservative treatment of obesity, but all costs

can be estimated to have been recouped within two years for laparoscopic bariatric surgery patients (Cremieux et al. 2008). In one study, the overall cost of medication was significantly reduced already at one year after surgery, especially for patients with T2DM and OSA (Gesquiere et al. 2014). According to a Finnish cost-utility analysis, non-operative treatment of obesity would cost more to the healthcare system in Finland than surgical treatment after five years following surgery (Mäklin et al. 2011). Bariatric surgery in the Finnish health care system was thoroughly evaluated by the Finnish Office for Health Technology Assessment (FINOHTA) and a report was published in 2009. The results showed that surgical treatment of patients who suffer from morbid obesity gives significant health benefits and reduces costs for the healthcare system. (Ikonen et al. 2009)

2.3.6 Mortality and complications after bariatric surgery

In a meta-analysis published in 2017, based on 38 RCTs and involving 4030 patients, short-term (≤ 30 days) all-cause mortality after bariatric surgery was 0.18% (Cardoso et al. 2017). In this analysis, the specific mortality rates for LRYGB and LSG were 0.18% and 0.24%, respectively. Open surgeries in general were associated with a higher mortality rate (0.31%) than laparoscopic surgeries (0.16%). (Cardoso et al. 2017) Three large non-randomized studies on LSG show the 30-day mortality rates vary from 0.03% to 0.24% (Stroh et al. 2016, Sakran et al. 2016, Young et al. 2015). An analysis based on the Scandinavian Obesity Surgery Registry database included 26 173 patients undergoing primary LRYGB operation for morbid obesity, and showed a 90-day mortality rate of 0.04% (Stenberg et al. 2014). For BPD and BPD-DS the 30-day mortality has been reported to be 1.1% (Buchwald et al. 2007).

A meta-analysis from 2016 found that LSG had fewer early (<30-day) major complications in RCTs than LRYGB (3.4% vs. 7.5%), but no statistically significant differences were observed for minor complications, readmission and reoperation rates, or mortality (Osland et al. 2016). In the SM-BOSS trial, the rate of severe complications (< 30-day) requiring a reoperation was 4.5% after LRYGB and 0.9% after LSG, but the difference was not statistically significant (Peterli et al. 2013).The most typical early (<30-day) complications after LRYGB are bleeding (2.0-2.1%), gastrointestinal leakage or abscess (1.2-1.8%), small bowel obstruction (1.0.-1.1%), anastomotic stricture (0.2-0.3%), and anastomotic ulcer (0.5%) (Stenberg et al. 2014, Alizadeh et al. 2018). After LSG, the typical early postoperative complications include bleeding (0.3-1.0%) and gastrointestinal leakage (0.5-1.2%) (Alizadeh et al. 2018, Dhar et al. 2018, Berger et al. 2016).

Gallstone disease is the most common late complication of bariatric surgery. The incidence of gallstone formation and cholecystectomy ten years after bariatric surgery have been 16–43% and 9-40%, respectively (Melmer et al. 2015). Various

factors may play a role in the development of gallstones following bariatric surgery: rapid weight loss increases the saturation of cholesterol in the bile, changes the mucin concentration in the gallbladder, and the emptying of the gallbladder may be compromised due to anatomical changes following bariatric surgery (Shiffman et al. 1991, Shiffman et al. 1992, Everhart 1993, Bastouly et al. 2009, Iglézias Brandão de Oliveira et al. 2003).

Regarding the late (>30-day) complications after LRYGB, the most important ones include internal herniation of the small bowel (1-16%) (Geubbels et al. 2015, Higa et al. 2011), ulcer at the gastrojejunal anastomosis (0.6-7.6%) (Coblijn et al. 2014, Coblijn et al. 2015), stricture at the gastrojejunal anastomosis (0-15.9%) (Awad et al. 2015, Peifer et al. 2007, Gould et al. 2006), early and late dumping syndrome (5-20%) (Emous et al. 2018, Nielsen et al. 2016), and nutritional deficiencies (3.6-34.6% for various parameters) (Clements et al. 2006). Among the late complications after LSG, the rates of exacerbation of prevalent GERD and new onset ("de novo") reflux have been reported to be 19% and 23%, respectively (Yeung et al. 2019). Other typical late complications after LSG are stenosis of the operated stomach (0.7–4%) (Cottam et al. 2006, Lalor et al. 2008), and nutritional deficiencies (iron 28.6%, folate 12.5%, vitamin B12 15.4%, vitamin D 86% at 4-year follow-up, with poor supplementation maintenance) (Ben-Porat et al. 2017). Early dumping is less common after SG compared to LRYGB, but no differences for late dumping have been reported (Emous et al. 2018).

2.3.7 Revisional surgery after insufficient weight loss

There are no standardized criteria for insufficient weight loss after bariatric surgery. Brethauer et al. suggested "a standardized outcome reporting" after bariatric surgery including weight loss outcomes, but criteria for insufficient weight loss were not included (Brethauer et al. 2015). A systematic review looking at the definition of failure of primary bariatric surgery concluded that in the majority of the studies reviewed failure was not defined, but %EWL below 50% at 18 months was the most frequent definition used for insufficient weight loss (Mann et al. 2015). The majority of patients will regain some of their weight over time. Weight regain quantified as percentage of maximum weight lost has had the best association with most clinical outcomes (King et al. 2018). Revisional surgery is needed in some of the patients with insufficient weight loss or weight regain (Sjöström et al. 2007, Mehaffey et al. 2016). However, standardized outcome criteria for revisional surgery have not yet been established.

In recent years, many conversions from LAGB to other bariatric procedures have been performed. Several studies have addressed the question whether safe revisional surgery should be performed as a one-step or a two-step operation for the band

removal and the redo procedure. In a recent systematic review and meta-analysis (Dang et al. 2016), no differences in the rates of complications, morbidity, and mortality between one-step and two-step revisions for both LRYGB and LSG were found. Regarding insufficient weight loss after LAGB, > 50% EWL was achieved after conversion to both LRYGB and LSG with no significant difference between the groups at five-year follow-up (Angrisani et al. 2017).

Conversion of LSG to LRYGB is usually successful when performed for GERD (Crawford et al. 2017, Parmar et al. 2017). However, there is no evidence that standard LRYGB results in further weight reduction, if weight loss after LSG has been insufficient (Parmar et al. 2017). BPD-DS and its later simplified modification SADI have been suggested as the revisional procedures of choice for insufficient weight loss after LSG (Lee et al. 2019).

Tran et al. investigated the options for revisional surgery after failed LRYGB in a systematic review of techniques and outcomes (Tran et al. 2016). BPD-DS, distal LRYGB, and banding of the gastric pouch resulted in sustained weight loss up to three-year follow-up with acceptable complication rates. On the other hand, revision of the gastric pouch and anastomosis, or revision to endoluminal procedures were not successful. (Tran et al. 2016)

3 Aims

1) To assess the changes in disease-specific quality of life (DSQOL) and health-related quality of life (HRQOL) after LAGB for morbid obesity, and to compare the HRQOL with age and gender standardized general population.
2) To investigate the early (30-day) results regarding operating time and morbidity comparing LSG and LRYGB for morbid obesity.
3) To compare the short-term results of weight loss, resolution of comorbidities and morbidity at six months after LSG and LRYGB for morbid obesity.
4) To determine whether LSG and LRYGB are equivalent for weight loss at five years in patients with morbid obesity, and to compare the two operating techniques for resolution of comorbidities, morbidity, mortality and improvement of QOL.

4 Materials and Methods

4.1 Patients

4.1.1 Study I

From March 2000 to October 2003, 101 consecutive patients operated by LAGB for morbid obesity in Vaasa Central Hospital were included in this study. The operative treatment was set according to standard recommendations for indications and contraindications. The Moorehead-Ardelt QOL questionnaire (Oria and Moorehead 1998) was offered preoperatively to all patients. In addition to this, the 15D QOL questionnaire (Sintonen 2001) was offered preoperatively to the last 79 patients starting approximately one year since the beginning of the study. The QOL was assessed preoperatively and at one and five years postoperatively. In addition to this, the 15D QOL data from the LAGB patients was compared to 15D data from age- and gender- standardized general population.

4.1.2 Studies II-IV (SLEEVEPASS trial)

The SLEEVEPASS trial was carried out at three tertiary referral hospitals (Turku University Hospital, Vaasa Central Hospital, and Helsinki University Hospital). From April 2008 to June 2010, a total of 240 patients enrolled for surgical treatment for morbid obesity were randomized to undergo either LSG or LRYGB.

Inclusion criteria for the study were age 18 to 60 years, BMI greater than 40 kg/m^2 or greater than 35 kg/m^2 with a significant obesity-associated comorbidity, and previous adequate but failed conservative treatment. Exclusion criteria were BMI greater than 60 kg/m^2, significant psychiatric disorder or severe eating disorder, active alcohol or substance abuse, active gastric ulcer disease, severe GERD with a large hiatal hernia, and previous bariatric surgery.

In the SLEEVEPASS trial, all the participating patients went through a thorough preoperative multidisciplinary evaluation according to standard treatment protocol. This was carried out by an endocrinologist, dietician, and surgeon. In addition, a psychiatric evaluation was obtained if considered necessary. The patients were checked for laboratory tests and underwent upper gastrointestinal endoscopy and

abdominal ultrasound examination. Any revealed Helicobacter pylori infection and/or gastric ulcer were treated before surgery. Only symptomatic gallstones were considered an indication for laparoscopic cholecystectomy.

Postoperative outcomes were assessed at 30 days, six months, one, two, three, and five years. Follow-up of the SLEEVEPASS study was planned to continue up to 20 years (7, 10, 15, and 20 years). For every follow-up visit, the patients were evaluated at the outpatient clinic where all prespecified data were thoroughly recorded. Patients lost to follow-up were contacted repeatedly by telephone or mail.

4.2 Methods

4.2.1 Laparoscopic adjustable gastric banding (LAGB)

A small window was created along the avascular layer behind the gastroesophageal junction by blunt dissection using an atraumatic endodissector (Goldfinger®, Ethicon Endo-Surgery). The band (Swedish Adjustable Gastric Band, SAGB, Obtech) was introduced to the retrogastric channel by a loop suture attached to the endodissector and drawn to the correct position. The band was then closed and secured with one suture. A small proximal pouch (approximately 2-4 ml) was created above the band and secured anteriorily by nonabsorbable gastro-gastric sutures. The catheter end of the band was then brought out through one of the trocars, connected to the filling port, and the port was fixed subcutaneously with sutures to the periosteum of the sternum. The band was left empty at the operation and later injected with fluid at the postoperative follow-up visits.

4.2.2 Laparoscopic sleeve gastrectomy (LSG)

Depending on the surgeon's preference, the procedure was carried out 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® (Ethicon Endo-Surgery). The stomach was resected vertically by starting with two sequential 4.8/60-mm green load stapler (Covidien) firings for the antrum. The majority of the antrum was preserved as the resection was initiated 4–6 cm proximal to the pylorus. The rest of the resection was carried out by approximately four sequential 3.5/60-mm blue-load firings. All the staple lines were reinforced (Covidien). The sleeve was created narrow along a 33–35-Fr calibration bougie. The resected stomach was removed through one of the trocar sites by a plastic retrieval bag (EndoCatch®, Covidien). A perioperative methylene blue test was routinely performed after LSG at two of the three hospitals taking part in this study.

4.2.3 Laparoscopic Roux-en-Y gastric bypass (LRYGB)

The procedure was started by creating a small gastric pouch. The lesser curvature was dissected using a Harmonic Scalpel® and the stomach was divided horizontally and vertically with typically two to three linear stapler firings using reinforced 3.5/45 and 3.5/60-mm cartridges with blue loads (Covidien) creating a small pouch. Then the biliopancreatic limb was measured at 50–80 cm distal to the ligamentum of Treitz. An antecolic end-to-side gastrojejunostomy was constructed. Depending on the surgeon's preference, either a 25-mm circular stapler (OrVil®, Covidien) or a 3.5/45-mm blue-load linear stapler (Covidien) was used for this. The omentum was not routinely divided. The jejunal opening in the circular stapler anastomosis was closed with a reinforced 3.5/45-mm blue-load linear stapler firing. The opening in the linear stapler anastomosis was closed with a continuous suture either manually or using EndoStitch® (Covidien). The alimentary limb was measured at 150 cm and a side-to-side jejunojejunostomy was created by a linear stapler using a 2.5/60-mm cartridge with white load. Depending on the surgeon's preference, the opening in the anastomosis was closed 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 methylene blue. The mesenteric defects were not routinely closed.

4.2.4 The Moorehead-Ardelt questionnaire

The Moorehead–Ardelt QOL questionnaire (Oria and Moorehead 1998) is a one-page DSQOL instrument. It includes the following five dimensions: self-esteem, social, sexual, and physical activity, and work capacity. Each dimension is divided into five levels. The total score ranges from -3 to +3 with higher score indicating better QOL. It is relatively simple and patient-friendly and it is commonly used in the evaluation of QOL following bariatric surgery.

4.2.5 The 15D questionnaire

The 15D QOL questionnaire (Sintonen 2001) is a generic and standardized HRQOL instrument. It can be used both as a profile and single index score measure. It includes the following 15 dimensions: breathing, mental function, speech (communication), vision, mobility, usual activities, vitality, hearing, eating, elimination, sleeping, distress, discomfort and symptoms, sexual activity, and depression. Each dimension is divided into five levels. The reliability, validity, sensitivity, discriminatory power, and responsiveness to change have been tested in the Finnish population (Sintonen 2001, Sintonen 1997). A representative sample of Finnish population with the 15D QOL data can be obtained from the National Health

2000 Health Examination Survey (Aromaa and Koskinen 2004). This population was weighted to reflect the age and gender distribution of the patients in study I to enable comparison of HRQOL to general population.

4.2.6 Randomization in SLEEVEPASS trial

The patients in SLEEVEPASS trial were randomized by a closed-envelope method to undergo either LSG or LRYGB with a 1:1 equal allocation ratio. The randomization envelopes were sealed, opaque and sequentially numbered. The shuffled envelopes were sent to each participating hospital. After a clinical decision of proceeding to operative treatment for morbid obesity, the randomization was carried out at the preoperative outpatient clinic visit by opening a sealed envelope containing the information of the assigned randomization group. The treating surgeons in the participating hospitals were responsible for the randomizations and were all part of the study team, i.e. the assessors were not blinded for group allocation.

4.2.7 Outcome measures in SLEEVEPASS trial

Weight loss defined as %EWL was determined as the primary end point. Baseline weight was recorded at the start of the evaluation process for bariatric surgery. The primary end point was originally planned to be assessed at one year follow-up, but was later postponed at five years, as the importance of long-term outcomes after bariatric surgery was better understood. This didn't affect the sample size calculation.

The secondary endpoints were predefined as remission of comorbidities, improvement of DSQOL, overall morbidity and mortality. At the postoperative follow-up visits, the recorded comorbidities (T2DM, hypertension and dyslipidemia) were defined as resolved (no medication), improved (reduction in medications), or persisting (same medication as preoperatively). At five-year follow-up, the remission of T2DM was also analyzed according to the American Diabetes Association (ADA) criteria (Buse et al. 2009) (complete remission defined as glycated hemoglobin (HbA1C) < 6.0% and fasting glucose < 5.6 mmol/l; partial remission defined as HbA1C < 6.5% and fasting glucose 5.6-6.9 mmol/l, both for at least one year's duration in the absence of active pharmacologic therapy). Regarding dyslipidemia, the patients were evaluated for lipid disturbances (total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides (TG)) at all time points. The decision to discontinue medication for dyslipidemia was based on the treating physician's decision using European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines (Catapano et

al. 2011). True remission of dyslipidemia according to these guidelines (LDL < 3.0 mmol/l and no dyslipidemia medications) was assessed at five-year follow-up for the patients with baseline dyslipidemia.

Postoperative complications were classified as major or minor. A modified version of a classification for endoscopic biliary sphincterotomy complications was used (Cotton et al. 1991). Morbidity resulting in reoperation, hospital stay exceeding seven days, need for blood transfusions of four or more units, or death constituted a major complication. All other adverse events in the postoperative period were classified as minor complications. In addition, all late complications recorded between the follow-up points of 30 days and five years after surgery were retrospectively classified according to the Clavien-Dindo classification (Dindo et al. 2004).

4.2.8 Statistical analysis

In study I, continuous variables were described as means and standard deviations. The Moorehead-Ardelt scores were analyzed using a repeated measurements analysis of variance and the Tukey-Kramer method was used to adjust the p-values of pairwise comparisons of time points. The difference between the patients and the population sample in the mean 15D dimension level values and scores were tested using a two-tailed independent samples t-test. The few missing items of data on any dimension of the 15D questionnaire were replaced by predictions from regression models with the other dimensions and age as explanatory variables. A $p<0.05$ was considered statistically significant.

In studies II-IV, sample size calculations were performed for %EWL using an equivalence design. Calculations were based on a test of mean difference between LRYGB and LSG, assuming the mean of 60 and standard deviation of 20 in the LRYGB group. An α level of .05 and power of 90% were used in calculations. The prespecified equivalence margins for the clinical significance of weight loss differences between LRYGB and LSG were −9 to +9 percent units of mean %EWL (DeMaria et al. 2002, Higa et al. 2001, Himpens et al. 2006); the aim was to evaluate the margins based on minimal clinically important difference. Based on these calculations, 108 patients per group were needed, and assuming 10% dropout rate, a total of 240 study patients were planned to be enrolled in the study.

In studies II and III, means, ranges, and standard deviations were used for normally distributed continuous variables and medians and ranges for non-normally distributed continuous variables. Categorical variables were characterized using frequencies and percentages. Associations between categorical variables were statistically tested using Pearson's $\chi 2$ test, and for small frequencies, Fisher's exact test was used. Differences between groups in normally distributed continuous

variables were tested using independent samples t-test, and for non-normally distributed variables, the Mann–Whitney U-test was used. The p-values < 0.05 were considered statistically significant. Statistical analyses were performed using SAS System for Windows ver. 9.2 (SAS Institute, Cary, NC, USA).

In study IV, means and standard deviations were used for continuous variables except for micronutrient concentrations, for which medians and ranges were used. Categorical variables were characterized using frequencies and percentages.

In study IV, equivalence of %EWL between the operations at different time points was evaluated using repeated-measurements analysis of variance (ANOVA). The model included operation, time passed from the operation, center, and diabetes status as independent variables, excess weight at the beginning of the study as a covariate, and interaction of operation and time. At every time point, 95% confidence intervals (CI) for the difference between the study groups were calculated, and equivalence was evaluated using the predefined margins of equivalence (−9 to 9). If the 95% CI of difference is within equivalence margins, the groups are equivalent.

Repeated-measurements ANOVA was used to analyze the dependent variables, i.e. fasting plasma glucose levels and HbA1c values for patients with T2DM and levels of total cholesterol, LDL, HDL, and TG for all patients. All of the models included operation, time, and center as independent variables and also included interaction of operation and time. In the analyses of fasting plasma glucose and HbA1c values, preoperative use of insulin was also included in the model as an independent variable. In the analyses of lipid values, diabetes status was also included in the model as an independent variable. Repeated-measurements ANOVA tests for general differences across time points and, with the test of interaction of operation and time, tests whether the difference between the operations have any differences between the time points. According to the idea of repeated-measurements ANOVA, the difference between the study groups was evaluated separately at four points (0.5, 1, 3, and 5 years) only when the interaction of operation and time was statistically significant. If the interaction was not statistically significant, the results are presented by main-effects operation and time, meaning that mean estimates for operations are calculated across time points and mean estimates for time points are calculated for the whole dataset, not separately for operations. The QOL score was also analyzed using repeated-measurements ANOVA but including only baseline and 5 years in the analysis.

Normality of the residuals of the models was evaluated visually and using the Kolmogorov-Smirnov test. For skewed variables (HbA1C, fasting glucose, HDL, and TG), logarithmic transformation was used to achieve normality. The results were quantified using least squares mean (95% CI) estimates and difference (95% CI) between operations. When logarithmic transformation was used for analyses, estimates were transformed to the original scale, but for those variables differences

are not presented, because back-transformed estimates for difference represent the ratio of group means, not the difference. For categorical variables, differences between study groups were evaluated using Pearson $\chi 2$ or Fisher exact test. Post hoc analyses included BMI for the whole study group and %EWL and BMI in patients with diabetes. All post hoc analyses were performed using repeated-measurements ANOVA as described above. Differences between groups at the five-year point regarding vitamin deficiencies in the whole study group were evaluated using the Mann-Whitney U-test.

P-values for multiple comparisons were adjusted using the step-down Bonferroni method of Holm. Analyses were performed according to the intention-to-treat population, i.e. all patients were analyzed in their original intervention group, and missing data were excluded from the analyses. Because of missing values at least at one time point (60/240 patients (25%)), a sensitivity analysis using multiple imputation was performed for the primary outcome (%EWL). Multivariate imputation by fully conditional specification method was performed. The predictive mean matching method was used to construct ten imputed datasets, and repeated-measurements ANOVA was performed for each. The results of these sensitivity analyses were compared with the original analysis of %EWL.

Two-sided p-values < 0.05 were considered statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc), and all figures were drawn with R version 3.2.0 (R Foundation for Statistical Computing).

4.2.9 Ethics

Study I was approved by the Ethics Committee of Vaasa Healthcare District. SLEEVEPASS trial (studies II-IV) was approved by the Ethics Committee of Turku University Hospital and all participating hospitals. The patients were thoroughly informed of both of the operative techniques at the preoperative outpatient clinic visits. However, at the time of enrollment, there was no long-term data on LSG available. A written informed consent was obtained from all patients at the outpatient clinic by the study group surgeon. SLEEVEPASS trial was registered at clinicaltrials.gov (NCT00793143).

5 Results

5.1 QOL after LAGB for morbid obesity (I)

Preoperatively, the mean age of the 101 patients was 43 years (range 23-66, SD 10.7) and 75% were female. The mean preoperative BMI was 46.3 kg/m² (range 36.3-66.6, SD 6.3). Of the 101 patients enrolled in this study, 71 (70%) suffered from at least one of the common comorbidities associated with morbid obesity, such as T2DM, hypertension, OSA or arthrosis. Four procedures (4%) had to be converted from laparoscopy to open operation. During the five-year follow-up, seven patients (7%) went through revision laparoscopy because of band leakage and a total of 13 patients (13%) had to have their band removed. The mean %EWL was 37.3% (SD 16.5) at one-year follow-up and 57.9% (SD 31.1) at five years.

The preoperative DSQOL scores were significantly improved on all five domains of the Moorehead-Ardelt questionnaire at one-year follow-up but no significant further change was seen after that until the five-year follow up (Table 2).

Table 2. Moorehead-Ardelt quality of life scores preoperatively, and at 1, and 5 years after laparoscopic adjustable gastric banding (LAGB). Reproduced with the permission of the copyright holders.

Dimensions	Score range	Preoperative group (n=95)	1-year postoperative group (n=73)	5-year postoperative group (n=63)	P-values*
Self-esteem	-1 to +1	-0.01 (0.39)	0.44 (0.37)	0.40 (0.43)	<0.01, <0.01, 0.43
Physical	-0.5 to +0.5	0.14 (0.23)	0.29 (0.19)	0.30 (0.19)	<0.01, <0.01, 0.96
Social	-0.5 to +0.5	-0.23 (0.23)	0.07 (0.23)	0.13 (0.25)	<0.01, <0.01, 0.22
Labor	-0.5 to +0.5	-0.04 (0.26)	0.15 (0.25)	0.19 (0.25)	<0.01, <0.01, 1.00
Sexual	-0.5 to +0.5	-0.03 (0.30)	0.09 (0.24)	0.08 (0.33)	0.04, 0.05, 0.87
Total score	-3 to +3	-0.17 (1.08)	1.04 (0.90)	1.10 (1.16)	<0.01, <0.01, 0.94

Values are means (standard deviation), 95% confidence intervals. *P-values derived from the differences between the preoperative group and the 1-year postoperative group, between the preoperative group and the 5-year postoperative group, and between the two postoperative groups, in that order.

Of the 15 different dimensions recorded in the 15D HRQOL questionnaire, a significant improvement was seen in the dimensions of moving, breathing, sleeping, usual activities, depression, distress, vitality and sexual activity at one-year follow-up compared to preoperative values. A significant worsening was seen in the dimension of eating at one year. The improvements at one-year follow-up also remained at five years except for the dimensions of sleeping and distress. The one-year worsening of eating was no longer evident at five-year follow-up. At one year after surgery, HRQOL had improved in a statistically significant manner as indicated by the mean total 15D score (0.836 vs. 0.900 for preoperative vs. one-year follow-up, respectively, $p < 0.001$). This improvement was maintained until five years after surgery (mean total 15D score 0.899, preoperative vs. five-year follow-up $p < 0.001$), and there was no difference in the total 15D scores between the one-year and five-year assessments ($p = 0.262$). Despite these improvements, HRQOL of the bariatric patients remained at a lower level when compared with the age- and gender-standardized general population (Figure 8).

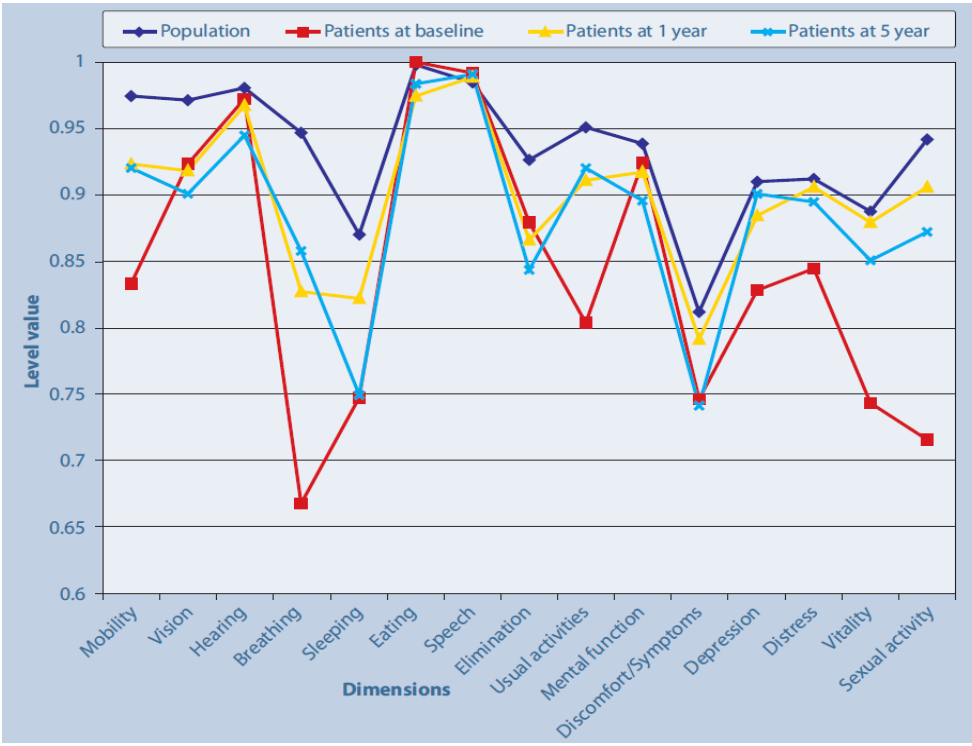

Figure 8. 15D quality of life score profiles of patients before, and at 1, and 5 years after laparoscopic adjustable gastric banding (LAGB) compared with the age- and gender-standardized general population. Reproduced with the permission of the copyright holders.

5.2 Comparison of outcomes of LSG and LRYGB in the treatment of morbid obesity: the SLEEVEPASS randomized clinical trial (studies II-IV)

Among the 240 patients randomized in the SLEEVEPASS trial, 69.6% were women, the mean age was 48 years (range 23-67, SD 9), and the mean baseline BMI was 45.9 kg/m² (range 35-66, SD 6.0). Baseline characteristics are presented in Table 3. There were no differences in demographic characteristics between the two study groups regarding sex, age, BMI, and obesity-related comorbidities.

Table 3. Baseline characteristics of the patients in the SLEEVEPASS trial. Reproduced with the permission of the copyright holders.

Characteristics	LSG (n= 121)	LRYGB (n= 119)
Age, mean (SD), years	48.5 (9.6)	48.4 (9.3)
Sex, No. (%)		
Women	87 (71.9)	80 (67.2)
Men	34 (28.1)	39 (32.8)
Weight, mean (SD), kg	130.1 (21.5)	134.9 (22.5)
BMI, mean (SD), kg/m²	45.5 (6.2)	46.4 (5.9)
Type 2 diabetes, 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, mean (SD)*	0.10 (0.94)	0.12 (1.12)
Hospitals participating in the study, No.		
Turku	40	40
Vaasa	40	40
Helsinki	41	39

Abbreviations: LSG = Laparoscopic sleeve gastrectomy, LRYGB = Laparoscopic Roux-en-Y gastric bypass, BMI = Body mass index, QOL = Quality of life. * Score range -3 to +3, with higher score indicating better QOL

Two patients in the LRYGB group were excluded from the study after the randomization, resulting in a total of 238 patients operated. In addition, one patient in the LRYGB group was converted to LSG during the operation due to technical difficulties, but was analyzed in the original randomized group according to intention-to-treat analysis. Of the 240 patients originally randomized, 193 (80.4%) completed the five-year follow-up. The flow of the participants through the trial is shown in Figure 9.

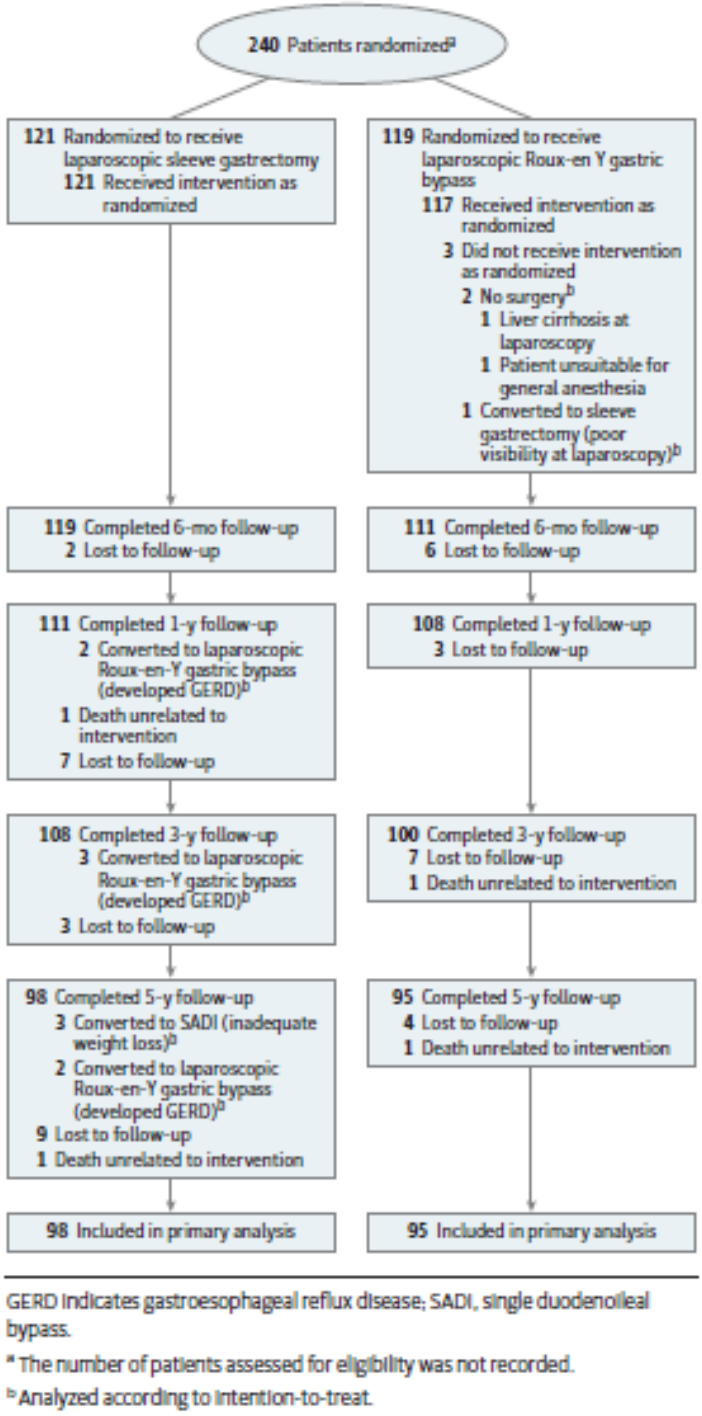

Figure 9. Flow of participants through the SLEEVEPASS trial. Reproduced with the permission of the copyright holders.

5.2.1 The early 30-day results of the SLEEVEPASS study (II)

The median operating time in the LSG group of 66 min (range 40-188) was significantly shorter than that in the LRYGB group of 94 min (range 52-195) ($p < 0.001$). The median length of hospital stay was four days in both study groups (LSG, range 1-22 days; LRYGB, range 3-16 days). The overall 30-day morbidity was 13.2% in the LSG group and 26.5% in the LRYGB group ($p = 0.010$). The rate of minor complications was lower after LSG (7.4%) compared to LRYGB (17.1%) ($p = 0.023$). The difference between the major complication rates was not statistically significant (LSG 5.8%, LRYGB 9.4%, $p = 0.292$). All the major and minor 30-day complications are presented in detail in Table 4.

Table 4. Early (<30-day) complications after laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass. Reproduced with the permission of the copyright holders.

Complication category and type	LSG (n=121)	LRYGB (n=117)	P value
Minor complications, No (%)			
Bleeding	3 (2.5)	2 (1.7)	
Intra-abdominal infection/infection of unknown origin	2 (1.7)	8 (6.8)	
Pneumonia	1 (0.8)	6 (5.1)	
Superficial wound infection	2 (1.7)	3 (2.6)	
Trocar site pain	1 (0.8)		
Dehydration		1 (0.9)	
Total	**9 (7.4)**	**20 (17.1)**	**0.02**
Major complications, No (%)			
Bleeding	3 (2.5)	7 (6.0)	
Intra-abdominal infection/infection of unknown origin	1 (0.8)	3 (2.6)	
Pneumonia	1 (0.8)		
Bowel perforation	1 (0.8)		
Torsion of enteroanastomosis		1 (0.9)	
Outlet obstruction	1 (0.8)		
Total	**7 (5.8)**	**11 (9.4)**	**0.29**
Overall morbidity	**16 (13.2)**	**31 (26.5)**	**0.01**

Abbreviations: LSG = Laparoscopic sleeve gastrectomy; LRYGB = Laparoscopic Roux-en-Y gastric bypass

5.2.2 Weight-loss and remission of comorbidities at six-month follow-up of the SLEEVEPASS study (III)

The mean %EWL at six-month follow-up was 49.2% (range 10.7-94.8, SD 17.3) after LSG and 52.9% (range 18.2-85.9, SD 15.2) after LRYGB with no statistical difference between the study groups (p = 0.086). No differences were found regarding resolution of obesity related comorbidities at six months. T2DM was resolved or improved in 84.3% of patients after LSG and 93.3% after LRYGB (p = 0.585). The corresponding results for hypertension were 76.8% and 81.9% (p = 0.707) and for dyslipidemia 64.1% and 69.0% (p = 0.485).

5.2.3 Five-year follow-up of the SLEEVEPASS study (IV)

Weight loss

At five years, the estimated mean %EWL was 49% (95% CI, 45-52) after LSG and 57% (95% CI, 53-61) after LRYGB. The model-based estimate of mean %EWL was 8.2 percentage units (95% CI, 3.2-13.2) higher in the LRYGB group than in the LSG group at five-year follow-up, as presented in Table 5. The groups were, thus, not equivalent based on the predefined margins of equivalence of -9 to 9. The difference in mean %EWL between LSG and LRYGB groups did not meet the criteria of equivalence at any of the registered time points of six months and one, three and five years. LRYGB resulted in statistically greater weight loss than LSG at five years, but the difference was not clinically significant.

Across the follow-up, the change in BMI was significantly different between LSG and LRYGB groups (p < 0.001 for operation x time interaction). At five years, the mean estimate of BMI was 1.1 (95% CI, -0.5 to 2.6) units lower following LRYGB, but there was no statistically significant difference between the operations (p = 0.54). Regarding patients with T2DM, there was also no difference in the mean estimate of BMI (p = 0.29), which was 2.1 (95% CI, -0.2 to 4.5) units lower after LRYGB compared with LSG. For patients with T2DM, the study groups were not equivalent regarding %EWL at any of the time points. At five-year follow-up, the estimate of mean %EWL was 11.7% (95% CI, 3.7-19.7) lower in patients after LSG than LRYGB. These results are shown in Table 5, and Figures 10, and 11.

Table 5. Excess weight loss mean differences and body mass index model-based means for the whole study group and for patients with diabetes after laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass at baseline and at 5 years. Reproduced with the permission of the copyright holders.

		Baseline	5y
EWL (%), mean difference between LRYGB and LSG (95% CI)*†			
All patients			8.2 (3.2 to 13.2)
Patients with diabetes			11.7 (3.7 to 19.7)
BMI (kg/m²), model based mean (95% CI)°† [n]			
All patients	Operation *time: p<0.001		
LSG		47.3 (46.2 to 48.3) [121]	36.5 (35.4 to 37.6) [98]
LRYGB		48.4 (47.3 to 49.5) [119]	35.4 (34.3 to 36.5) [95]
Difference		-1.1 (-2.6 to 0.40)	1.1 (-0.5 to 2.6)
P-value			0.179
Patients with diabetes	Operation *time: p<0.001		
LSG		46.3 (44.7 to 47.9) [52]	36.6 (35.0 to 38.3) [41]
LRYGB		47.4 (45.8 to 49.0) [49]	34.5 (32.8 to 36.1) [41]
Difference		-1.1 (-3.4 to 1.1)	2.1 (-0.2 to 4.5)
P-value			0.072
EWL = excess weight loss = (initial weight – follow-up weight) : (initial weight – ideal weight for BMI 25kg/m²)			
LSG = laparoscopic sleeve gastrectomy, LRYGB = laparoscopic Roux-en-Y gastric bypass, BMI = body mass index			
* In EWL equivalence design was used in the analyses and equivalence margins were set from -9 to +9			
° In BMI superiority design was used in the analysis			
† Repeated measurements ANOVA			
All the results are adjusted for center and diabetes status.			

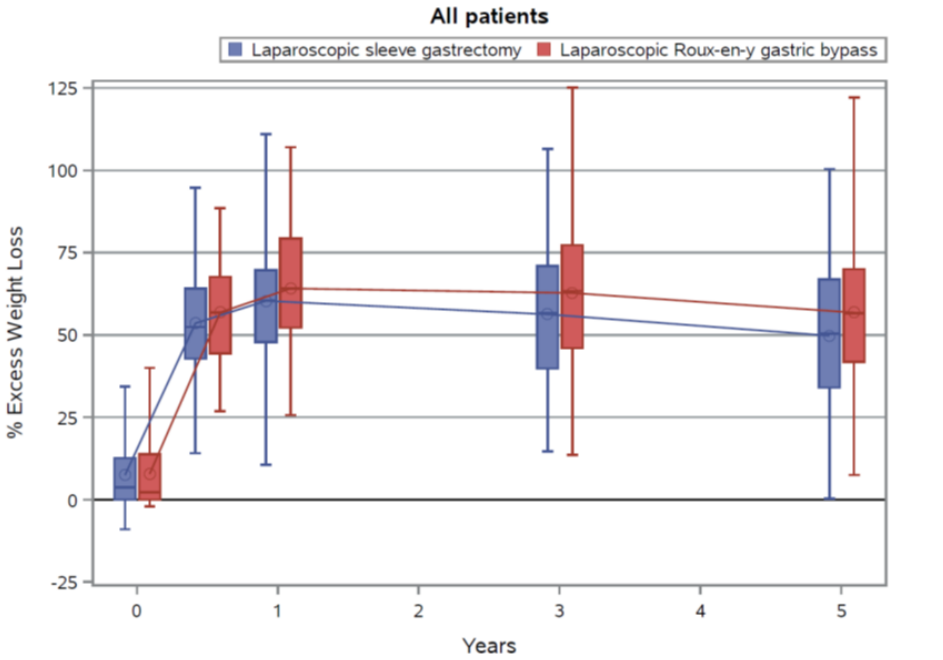

Figure 10. Percent excess weight loss (%EWL) for the whole study group after laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass over the 5-year follow-up. %EWL at baseline represents preoperative weight loss between day of randomization and day of surgery. Lower and upper borders of boxes indicate 25th and 75th quartiles, respectively; lower and upper ends of error bars indicate minimum and maximum values, respectively; horizontal lines in boxes indicate median values; dots indicate mean values. Reproduced with the permission of the copyright holders.

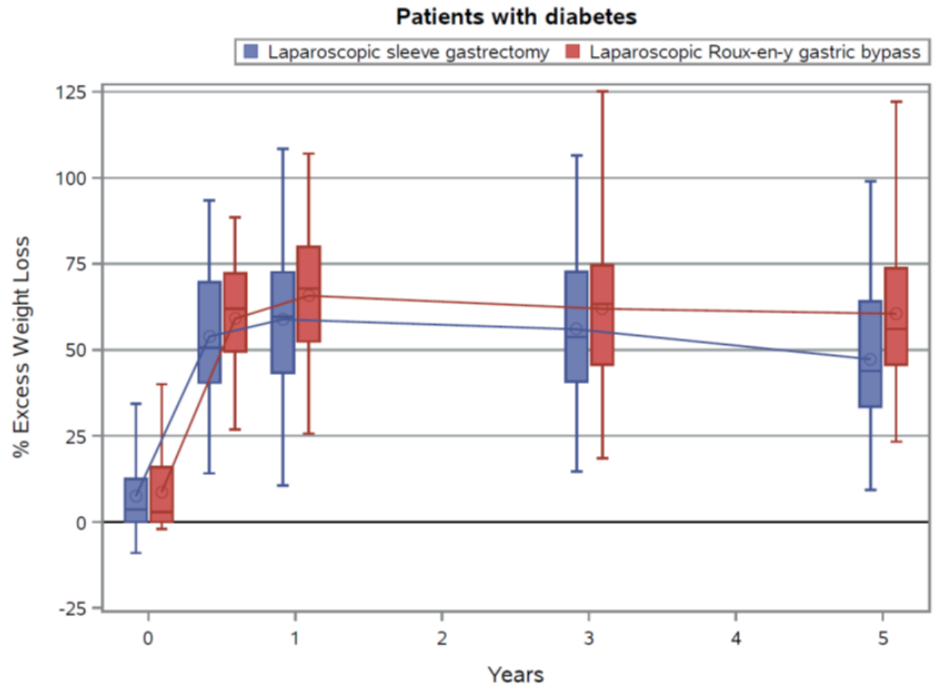

Figure 11. Percent excess weight loss (%EWL) for patients with diabetes after laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass over the 5-year follow-up. %EWL at baseline represents preoperative weight loss between day of randomization and day of surgery. Lower and upper borders of boxes indicate 25th and 75th quartiles, respectively; lower and upper ends of error bars indicate minimum and maximum values, respectively; horizontal lines in boxes indicate median values; dots indicate mean values. Reproduced with the permission of the copyright holders.

Remission of T2DM

At five years postoperatively, the difference in T2DM remission was not significant between the study groups ($p > 0.99$). There was complete remission in 5/41 patients (12%) in the LSG group and 10/40 (25%) in the LRYGB group. Improved glycemic control was seen in both study groups at five years compared with baseline. The mean estimated fasting plasma glucose level was 7.5 (95% CI, 6.9-8.2) mmol/l in the LSG group and 6.7 (95% CI, 6.1-7.3) mmol/l in the LRYGB group with no statistically significant difference ($p = 0.052$). There was no difference between the study groups regarding HbA1C, the mean estimated value during the follow-up time of five years was 6.6% (95% CI, 6.4-6.8) in the LSG group and 6.6% (95% CI, 6.4-6.8) in the LRGB group ($p = 0.93$).

Remission of other comorbidities

At five-year follow-up, 14/30 patients (47%) in the LSG group and 24/40 (60%) in the LRYGB group had discontinued their dyslipidemia medications; 6/30 patients (20%) in the LSG group and 2/40 (5%) in the LRYGB group needed less medications; and no change was seen in 10/30 patients (33%) in the LSG group and 14/40 (35%) in the LRYGB group ($p = 0.15$). For the whole study group, there was no statistically significant difference ($p = 0.053$) in total cholesterol values at five years between the study groups: 4.9 (95% CI, 4.7-5.0) mmol/l for the LSG group and 4.6 (95% CI, 4.5-4.8) mmol/l for the LRYGB group. Also, there was no difference in the HDL values: 1.4 (95% CI, 1.3-1.4) mmol/l for the LSG group and 1.4 (95% CI, 1.3-1.5) mmol/l for the LRYGB group ($p = 0.79$). LDL values were significantly lower ($p = 0.02$) in the LRYGB group at five-year follow-up compared with the LSG group: 2.5 (95% CI, 2.3-2.6) mmol/l and 2.7 (95% CI, 2.6-2.9) mmol/l, respectively. The mean estimates of TG values across time were 1.2 (95% CI, 1.2-1.3) mmol/l for the LSG group and 1.2 (95% CI, 1.1-1.2) mmol/l for the LRYGB group with no statistically significant difference between the study groups ($p = 0.18$). Regarding the 38 patients who had discontinued their dyslipidemia medication, 22 had true remission (LDL < 3.0 mmol/l and no dyslipidemia medications) at five years postoperatively. For the LSG group, true remission was reached by 6/30 patients (20%) and for the LRYGB group 16/40 patients (40%).

At five years after the operation, 20/68 patients (29%) in the LSG group and 37/73 (51%) in the LRYGB group had discontinued their hypertension medications; 24/68 (35%) in the LSG group and 22/73 (30%) in the LRGB group needed less medications; and no change in the hypertension medications was detected in 24/68 (35%) and 14/73 (19%) patients, respectively ($p = 0.02$).

Quality of life

At five-year follow-up, the Moorehead-Ardelt questionnaire was used for DSQOL analysis. Mean Moorehead-Ardelt QOL total scores were 0.85 (SD, 1.08) for the LSG group and 0.76 (SD, 1.01) for the LRYGB group. The change in QOL did not differ significantly between the study groups ($p = 0.70$ for operation x time interaction). The difference in QOL between the groups was not statistically significant ($p = 0.85$), but total QOL score increased statistically significantly by 0.7 (95% CI, 0.6-0.9) units from baseline until the follow-up at five years ($p < 0.001$).

Morbidity between 30 days and five years

All the late complications between 30 days and five years postoperatively are presented in detail in Table 6. During this follow-up, the overall morbidity rate was

19% (n = 23) for LSG and 26% (n = 31) for LRYGB with no statistically significant difference (p = 0.19) between the study groups. There was no treatment-related mortality during the follow-up of five years.

Table 6. Complications between 30 days and 5 years after laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass. Reproduced with the permission of the copyright holders.

Complication category and type	LSG n=121	LRYGB n=119	P value
Minor complications, No (%)			
Vomiting/dehydration		3 (2.5)	
Gastroesophageal reflux	11 (9.1)		
Ulcer/ Srticture at gastrojejunal anastomosis	2 (1.7)*	6 (5.0)	
Dumping		3 (2.5)	
Nonspecific abdominal pain		1 (0.8)	
Total	**13 (10.7)**	**13 (10.9)**	**0.96**
Major complications, No (%)			
Gastroesophageal reflux	7 (5.8)		
Intestinal herniation		17 (14.3)	
Incisional hernia	3 (2.5)	1 (0.8)	
Total	**10 (8.3)**	**18 (15.1)**	**0.10**
Overall morbidity	**23 (19.0)**	**31 (26.0)**	

Abbreviations: LSG = Laparoscopic sleeve gastrectomy; LRYGB = Laparoscopic Roux-en-Y gastric bypass. * LSG converted to LRYGB, analysis according to intention-to-treat.

Nutritional deficiencies

All the patients were routinely prescribed multivitamins and calcium/vitamin D supplementation. Other supplementations were prescribed at the postoperative control visits when needed. At five-year follow-up, micronutrient concentrations including vitamin D, vitamin B12, albumin and folate were analyzed regardless of possible vitamin supplementation. There were no statistically significant differences in any of the median micronutrient levels between LSG and LRYGB ($p > 0.05$).

6 Discussion

6.1 QOL after LAGB for morbid obesity (study I)

Several studies have shown that QOL improves significantly after surgical treatment of morbid obesity (Muller et al. 2008, Kolotkin et al. 2009, Karlsson et al. 2007, Hammoud et al. 2009, Folope et al. 2008, Dziurowicz-Kozlowska et al. 2005). The results of our study confirm these findings and show that both DSQOL and HRQOL improve significantly after one year from LAGB and that these improvements are maintained up to five years after surgery. However, despite this sustainable improvement, HRQOL after LAGB was inferior compared to the level of HRQOL of the age- and gender-standardized general population.

6.2 Comparison of LSG and LRYGB in the treatment of morbid obesity (studies II-IV)

In the SLEEVEPASS trial including 240 morbidly obese patients randomized to undergo either LSG or LRYGB, criteria for equivalence in terms of the primary endpoint of %EWL at five years were not met between the two procedures. LRYGB resulted in greater %EWL at five years than LSG, but the CI for the difference extended the predefined equivalence margins of -9 to +9 percent units, and therefore no conclusions about clinical superiority of weight loss after LRYGB could be drawn. Importantly, both LSG and LRYGB were associated with sustained weight loss at long term, with a mean %EWL of 49% and 57%, respectively. There were no statistically significant differences between LSG and LRYGB regarding the secondary outcomes remission of T2DM and dyslipidemia, improvement of QOL, and overall morbidity. However, LRYGB resulted in better remission of hypertension than LSG, defined by the use of antihypertensive medication.

Obesity and the related comorbidities are chronic diseases mandating assessment of the effectiveness of different bariatric procedures at long-term follow-up (Puzziferri et al. 2014). In this study, the weight loss was higher after LRYGB even though the difference was not statistically significant at five-year follow-up. In three relatively recent meta-analyses, a greater weight loss was found to result after LRYGB compared to LSG (Shoar and Saber 2017, Li et al. 2016, Chang et al. 2014).

However, these meta-analyses included mainly nonrandomized studies without appropriate controls. Similar findings of somewhat superior weight loss after LRYGB were reported in most of the RCTs, but these trials are limited either by the small number of enrolled patients (Ignat et al. 2017, Karamanakos et al. 2008, Kehagias et al. 2011, Zhang et al. 2014) or by different primary outcome (Schauer et al. 2017b) compromising assessment of differences between LRYGB and LSG. On the other hand, in the Swiss Multicenter Bypass or Sleeve Study (SM-BOSS), where the study protocol was quite similar to the SLEEVEPASS trial, no significant difference in %EBMIL between LSG and LRYGB was found at five years (Peterli et al. 2018).

The variation in definitions for reporting weight loss outcomes after bariatric surgery must be taken into account. When this trial was designed in 2007, the standard of bariatric surgery outcome reporting was %EWL. Currently, new outcome reporting standards have been adopted and the preferred means of reporting weight loss after bariatric surgery include more than one weight loss outcome as they all have their benefits and limitations, i.e. it is recommended to report all of the different parameters including %EWL, %EBMIL, and %TWL. The outcome measure of %EWL is useful as a standard reporting parameter across populations, as it allows for comparison of individuals with varying initial weights and excess weights. The disadvantage of using %EWL is that it doesn't reflect successful weight loss in very high BMI patients. This group of patients may end up with lower %EWL results despite achieving better absolute weight loss than lower BMI patients. Similar to %EWL, %EBMIL is dependent on initial weight measurements that can vary and be inconsistent. In different studies, initial weight can mean anything from measurements taken months before surgery to a measurement taken on the day of surgery with no established standard. The benefit of using %TWL is that it is easy to measure and comprehend by both physicians and patients. The limitation of using %TWL is that in the setting of variable clinically ideal and initial weights, the data can be clinically misleading. A heavier patient with more excess weight needs to lose more weight than a less heavy patient to reach a similar clinical impact and approach a normal weight range. (Brethauer et al. 2015)

In general, bariatric surgery is shown to be superior to conservative medical therapy for treatment of T2DM (Schauer et al. 2017b, Courcoulas et al. 2015, Halperin et al. 2014, Ikramuddin et al. 2013). In other randomized trials, there are better T2DM remission rates associated with LRYGB than LSG, at least in the long term (Yu et al. 2015, Wang et al. 2015, Yang et al. 2015, Keidar et al. 2013, Osland et al. 2017). In this trial, no statistically significant differences in remission rates of T2DM could be shown between the two procedures up to five-year follow-up. However, the SLEEVEPASS trial was not powered to detect differences for T2DM remission. In a similar way, the SM-BOSS trial (Peterli et al. 2018) and the

STAMPEDE trial (Schauer et al. 2017b) both showed no significant differences in T2DM control between LSG and LRYGB, but they both were also underpowered for detecting differences regarding this outcome. The overall remission rate of T2DM was higher in the SM-BOSS trial than in this trial (Peterli et al. 2018). This could be attributable to possible differences in patient demographics and severity of the disease, such as preoperative T2DM duration. A longer duration of T2DM at baseline is associated with worse outcomes in remission rates after bariatric surgery (Sjöström et al. 2014, Dixon et al. 2013).

In the SLEEVEPASS trial, LRYGB resulted in significantly higher rates of remission of hypertension than LSG at five years assessed by use of antihypertension medication. However, medication use is not an objective outcome for detecting hypertension as medication adherence may be suboptimal and it does not provide objective evidence of normotension (Lauffenburger et al. 2017). Similarly, based on medication use, there was no significant difference in the remission rates for dyslipidemia between the LSG and LRYGB groups. The measured LDL values were significantly lower at five years after LRYGB, while the total cholesterol, HDL, and TG values showed no differences between the study groups. These findings are consistent with observations in other studies, including the SM-BOSS trial (Peterli et al. 2018).

QOL improved significantly after both LSG and LRYGB during the five-year follow-up compared with baseline, and there were no significant differences between the study groups. These findings are in accordance with previous literature (Rubino et al. 2016).

6.3 Limitations of the studies

The main limitation in study I was the missing data concerning possible improvement of obesity related comorbidities postoperatively and their potential association to changes in reported QOL. This was mainly due to insufficient recording of information at the postoperative follow-up visits, and the information could not be obtained retrospectively from the patient records. In addition, no analysis of changes in QOL in relation to weight loss was performed. The comparatively low number of patients with data on 15D QOL questionnaire can be considered a further limitation of this study.

The randomized SLEEVEPASS trial (studies II-IV) also has several limitations. First, at the initiation of the study in 2008, only a small number of bariatric operations (n=430) were performed in the whole country that year. Since then, the number of annual operations in Finland has been growing but reached a plateau during the recent few years. There were no hospitals specialized in bariatric surgery and none of the study hospitals could be considered a high-volume center. However, despite

the limited experience from bariatric surgery at the initiation of this study, all of the operating surgeons participating in this study were experienced laparoscopic surgeons. This individual and institutional learning curve effect may have a role in the relatively high number of reoperation rates for both LSG and LRYGB when compared with other studies (Chang et al. 2014), but the effect does not bias the group comparison.

An additional limitation of studies II-IV is the fact that information on patients not included in the SLEEVEPASS trial were not properly recorded. However, as the subjects participating in the study included most of the patients undergoing bariatric surgery at the study hospitals during the study enrollment period, the trial population can be considered representative of the average bariatric surgery population.

A randomized clinical trial is always limited by the original statistical setting. In the SLEEVEPASS trial, we used the equivalence approach with predefined equivalence margins. However, at the time of study initiation, there was very little data on the long-term results after LSG. Based on this, the predefined equivalence margins had to be set somewhat arbitrarily, which may have an effect on the assessment of clinical importance of %EWL.

A further limitation is the fact that this study is underpowered for detecting differences in remission rates of T2DM between LSG and LRYGB. Even though no significant differences between the study groups were found up to five-year follow-up, no firm conclusions can be drawn from the present study. In addition, sufficient information regarding duration of T2DM at baseline was lacking at the 5-year follow-up, but has since then been retrieved retrospectively. This represents a limitation of the study, because T2DM duration has been shown to predict long-term postoperative remission (Brethauer et al. 2013, Jiménez et al. 2012).

Obesity in itself is known to be a major risk factor for GERD symptoms, with an odds ratio of 1.73 (Eusebi et al. 2018). This increased risk of GERD is also a drawback of LSG (Arman et al. 2016, DuPree et al. 2014). It can be either exacerbation of prevalent disease at baseline or new onset (“de novo”) GERD. Severe reflux can make the patients depend permanently upon proton pump inhibitor (PPI) medication and worsen their QOL. In addition, reflux can lead to esophagitis and Barrett’s esophagus, which in turn represents a potential risk factor for the development of esophageal adenocarcinoma (Drahos et al. 2016). Depending on the length of the Barrett’s segment and the grade of dysplasia, the yearly incidence of development of Barrett adenocarcinoma varies from 0.3% to 2.4% (Anaparthy et al. 2013). The potential progress from LSG induced GERD to actual malignancy in the distal esophagus takes undoubtedly several years to develop and can therefore only be identified by studies with longer follow-up and endoscopic surveillance. In recent studies, Barrett mucosa has been shown to develop in up to 17% of asymptomatic patients after LSG operation. However, most of these patients displayed non-

dysplastic Barrett´s with only gastric (Type II) metaplasia and not intestinal (Type III) metaplasia (Felsenreich et al. 2017, Genco et al. 2017). However, there are still many discrepancies between different studies regarding the rates of development of Barrett's esophagus after LSG as well as after bariatric surgery in general (Oor et al. 2016).

Insufficient assessment of prevalent GERD preoperatively is a major limitation of this study. Upper gastrointestinal endoscopy was performed on all patients before surgery, and severe GERD with large hiatal hernia was considered an exclusion criteria according to the study protocol. However, use of preoperative PPI medication was not properly recorded, there was no thorough standardized evaluation of the endoscopic findings, and no validated GERD symptom or DSQOL questionnaire was offered to the patients. In this study, 6% (n=7) of the patients in the LSG group underwent conversion from LSG to LRYGB for severe GERD, which was the most common reason for late reoperation in the LSG group. In addition, 9% (n=11) of the patients operated by LSG required daily PPI medication at five-year follow-up. A more standardized preoperative assessment of GERD might have resulted in better patient selection and avoiding the reoperations for GERD after LSG. However, at the time of the study initiation the concept of possible LSG associated GERD was not yet as clear as it is today.

The fact that mesenteric defects were not routinely closed in the LRYGB operations at the time of this study represents also a limitation. In the LRYGB group, the most frequent reason for late reoperation was suspicion of internal hernia in 14% (n=17) of the patients. This complication rate was markedly higher than the rate of 0.3-6% in other studies (Ortega et al. 2013, Dogan et al. 2015). The incidence of internal hernias following LRYGB would likely have been reduced by closure of the mesenteric defects at the primary operation (Stenberg et al. 2016, Stenberg et al. 2017, Aghajani et al. 2017). This procedure is currently performed routinely, but it was not standard practice at the time of the set-up of the study.

The rate of reoperations for major late complications was similar following LSG and LRYGB in this study, but the types of complications were different. Currently, at least some of these reoperations can be avoided by improved patient selection in LSG and by closure of the mesenteric defects in LRYGB.

Approximately 20% of the patients randomized in the study were lost to follow-up at five years, which might be considered a limitation. On the other hand, a follow-up rate of 80% at 5 years is comparatively high and can therefore be considered a strength of the trial. Moreover, the drop-out rates were similar in LSG and LRYGB groups and multiple-imputation analysis suggested that there was little risk for bias based on the patients lost to follow-up.

6.4 Future perspectives

LSG and LRYGB are the most commonly performed bariatric operations worldwide (Angrisani et al. 2018). They both result in good metabolic outcomes with high safety and good QOL (Nickel et al. 2017). However, these two procedures have different profiles regarding typical complications and causes for possible revisional surgery. One size does not fit all, and the optimal metabolic procedure is not the same for every patient. The aim in the future should be in tailoring a personalized prognostic algorithm to select the appropriate procedure for a given patient. Future research should concentrate on individual patient characteristics, such as BMI, comorbidities, other relevant conditions, and possibly genetic factors that could provide a composite endpoint score to guide optimal operation selection.

Both LSG and LRYGB still need to be prospectively evaluated over an even longer period of time to further understand the long-term outcomes of these procedures. This is highlighted by the LSG induced GERD and Barrett's esophagus, which require long-term follow-up with endoscopic surveillance. Health care professionals responsible for treating bariatric patients should make an effort to improve the patients' adherence to follow-up and compliance with prescribed supplementations. It is also a reality that sometimes one bariatric operation is not sufficient for one patient in the course of several years. Revisional surgery may be needed for insufficient weight loss, weight regain, or complications from the original procedure. Obesity must be regarded a chronic disease that requires long-term follow-up also after bariatric surgery with readiness to treat upcoming issues according to best clinical practices.

7 Conclusions

On the basis of the present investigations the following conclusions can be drawn:

1) DSQOL and HRQOL improve significantly after LAGB. This QOL improvement is maintained at five-year follow-up although QOL does not reach the level of the general population.
2) At 30-day postoperative analysis, LSG is associated with shorter operating time and fewer minor complications compared to LRYGB.
3) At six months postoperatively, weight loss, resolution of comorbidities and complication rates do not differ between LSG and LRYGB.
4) At five years postoperatively, LSG compared with LRYGB do not meet criteria for equivalence in terms of %EWL. Although LRYGB was associated with greater %EWL, the difference was not statistically significant, based on the prespecified equivalence margins. LRYGB resulted in higher rates of hypertension remission than LSG, but there were no differences in remission of T2DM and dyslipidemia, morbidity, mortality and improvement of QOL at five years.

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Mika Helmiö

Appendices

Appendix 1. The 15D questionnaire.

TERVEYTEEN LIITTYVÄN ELÄMÄNLAADUN KYSELYLOMAKE (15D©)

Ohje: Lukekaa ensin läpi huolellisesti kunkin kysymyksen kaikki vastausvaihtoehdot. Merkitkää sitten rasti (x) sen vaihtoehdon kohdalle, joka **parhaiten kuvaa nykyistä terveydentilaanne**. Menetelkää näin kaikkien kysymysten 1-15 kohdalla. Kustakin kysymyksestä rastitetaan siis yksi vaihtoehto.

KYSYMYS 1. Liikuntakyky

1 ( ) Pystyn kävelemään normaalisti (vaikeuksitta) sisällä, ulkona ja portaissa.
2 ( ) Pystyn kävelemään vaikeuksitta sisällä, mutta ulkona ja/tai portaissa on pieniä vaikeuksia.
3 ( ) Pystyn kävelemään ilman apua sisällä (apuvälinein tai ilman), mutta ulkona ja/tai portaissa melkoisin vaikeuksin tai toisen avustamana.
4 ( ) Pystyn kävelemään sisälläkin vain toisen avustamana.
5 ( ) Olen täysin liikuntakyvytön ja vuoteenoma.

KYSYMYS 2. Näkö

1 ( ) Näen normaalisti eli näen lukea lehteä ja TV:n tekstejä vaikeuksitta (silmälaseilla tai ilman).
2 ( ) Näen lukea lehteä ja/tai TV:n tekstejä pienin vaikeuksin (silmälaseilla tai ilman).
3 ( ) Näen lukea lehteä ja/tai TV:n tekstejä huomattavin vaikeuksin (silmälaseilla tai ilman).
4 ( ) En näe lukea lehteä enkä TV:n tekstejä ilman silmälaseja tai niiden kanssa, mutta näen kulkea ilman opasta.
5 ( ) En näe kulkea oppaatta eli olen lähes tai täysin sokea.

KYSYMYS 3. Kuulo

1 ( ) Kuulen normaalisti eli kuulen hyvin normaalia puheääntä (kuulokojeella tai ilman).
2 ( ) Kuulen normaalia puheääntä pienin vaikeuksin.
3 ( ) Minun on melko vaikea kuulla normaalia puheääntä, keskustelussa on käytettävä normaalia kovempaa puheääntä.
4 ( ) Kuulen kovaakin puheääntä heikosti; olen melkein kuuro.
5 ( ) Olen täysin kuuro.

KYSYMYS 4. Hengitys

1 ( ) Pystyn hengittämään normaalisti eli minulla ei ole hengenahdistusta eikä muita hengitysvaikeuksia.
2 ( ) Minulla on hengenahdistusta raskaassa työssä tai urheillessa, reippaassa kävelyssä tasamaalla tai lievässä ylämäessä.
3 ( ) Minulla on hengenahdistusta, kun kävelen tasamaalla samaa vauhtia kuin muut ikäiseni.
4 ( ) Minulla on hengenahdistusta pienenkin rasituksen jälkeen, esim. peseytyessä tai pukeutuessa.
5 ( ) Minulla on hengenahdistusta lähes koko ajan, myös levossa.

15D©/Harri Sintonen

KYSYMYS 5. Nukkuminen

1 ( ) Nukun normaalisti eli minulla ei ole mitään ongelmia unen suhteen.
2 ( ) Minulla on lieviä uniongelmia, esim. nukahtamisvaikeuksia tai satunnaista yöheräilyä.
3 ( ) Minulla on melkoisia uniongelmia, esim. nukun levottomasti tai uni ei tunnu riittävältä.
4 ( ) Minulla on suuria uniongelmia, esim. joudun käyttämään usein tai säännöllisesti unilääkettä, herään säännöllisesti yöllä ja/tai aamuisin liian varhain.
5 ( ) Kärsin vaikeasta unettomuudesta, esim. unilääkkeiden runsaasta käytöstä huolimatta nukkuminen on lähes mahdotonta, valvon suurimman osan yöstä.

KYSYMYS 6. Syöminen

1 ( ) Pystyn syömään normaalisti eli itse ilman mitään vaikeuksia.
2 ( ) Pystyn syömään itse pienin vaikeuksin (esim. hitaasti, kömpelösti, vavisten tai erityisapuneuvoin).
3 ( ) Tarvitsen hieman toisen apua syömisessä.
4 ( ) En pysty syömään itse lainkaan, vaan minua pitää syöttää.
5 ( ) En pysty syömään itse lainkaan, vaan minulle pitää antaa ravintoa letkun avulla tai suonensisäisesti.

KYSYMYS 7. Puhuminen

1 ( ) Pystyn puhumaan normaalisti eli selvästi, kuuluvasti ja sujuvasti.
2 ( ) Puhuminen tuottaa minulle pieniä vaikeuksia, esim. sanoja on etsittävä tai ääni ei ole riittävän kuuluva tai se vaihtaa korkeutta.
3 ( ) Pystyn puhumaan ymmärrettävästi, mutta katkonaisesti, ääni vavisten, sammaltaen tai änkyttäen.
4 ( ) Muilla on vaikeuksia ymmärtää puhettani.
5 ( ) Pystyn ilmaisemaan itseäni vain elein.

KYSYMYS 8. Eritystoiminta

1 ( ) Virtsarakkoni ja suolistoni toimivat normaalisti ja ongelmitta.
2 ( ) Virtsarakkoni ja/tai suolistoni toiminnassa on lieviä ongelmia, esim. minulla on virtsaamisvaikeuksia tai kova tai löysä vatsa
3 ( ) Virtsarakkoni ja/tai suolistoni toiminnassa on melkoisia ongelmia, esim. minulla on satunnaisia virtsanpidätysvaikeuksia tai vaikea ummetus tai ripuli.
4 ( ) Virtsarakkoni ja/tai suolistoni toiminnassa on suuria ongelmia, esim. minulla on säännöllisesti "vahinkoja" tai peräruiskeiden tai katetroinnin tarvetta.
5 ( ) En hallitse lainkaan virtsaamista ja/tai ulostamista.

KYSYMYS 9. Tavanomaiset toiminnot

1 ( ) Pystyn suoriutumaan normaalisti tavanomaisista toiminnoista (esim. ansiotyö, opiskelu, kotityö, vapaa-ajan toiminnot).
2 ( ) Pystyn suoriutumaan tavanomaisista toiminnoista hieman alentuneella teholla tai pienin vaikeuksin.
3 ( ) Pystyn suoriutumaan tavanomaisista toiminnoista huomattavasti alentuneella teholla tai huomattavin vaikeuksin tai vain osaksi.
4 ( ) Pystyn suoriutumaan tavanomaisista toiminnoista vain pieneltä osin.
5 ( ) En pysty suoriutumaan lainkaan tavanomaisista toiminnoista.

10. Henkinen toiminta

1 ( ) Pystyn ajattelemaan selkeästi ja johdonmukaisesti ja muistini toimii täysin moitteettomasti.
2 ( ) Minulla on lieviä vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai muistini ei toimi täysin moitteettomasti
3 ( ) Minulla on melkoisia vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai minulla on jonkin verran muistinmenetystä
4 ( ) Minulla on suuria vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai minulla on huomattavaa muistinmenetystä
5 ( ) Olen koko ajan sekaisin ja vailla ajan tai paikan tajua

KYSYMYS 11. Vaivat ja oireet

1 ( ) Minulla ei ole mitään vaivoja tai oireita, esim. kipua, särkyä, pahoinvointia, kutinaa jne.
2 ( ) Minulla on lieviä vaivoja tai oireita, esim. lievää kipua, särkyä, pahoinvointia, kutinaa jne.
3 ( ) Minulla on melkoisia vaivoja tai oireita, esim. melkoista kipua, särkyä, pahoinvointia, kutinaa jne.
4 ( ) Minulla on voimakkaita vaivoja tai oireita, esim. voimakasta kipua, särkyä, pahoinvointia, kutinaa jne.
5 ( ) Minulla on sietämättömiä vaivoja ja oireita, esim. sietämätöntä kipua, särkyä, pahoinvointia, kutinaa jne.

KYSYMYS 12. Masentuneisuus

1 ( ) En tunne itseäni lainkaan surulliseksi, alakuloiseksi tai masentuneeksi.
2 ( ) Tunnen itseni hieman surulliseksi, alakuloiseksi tai masentuneeksi.
3 ( ) Tunnen itseni melko surulliseksi, alakuloiseksi tai masentuneeksi.
4 ( ) Tunnen itseni erittäin surulliseksi, alakuloiseksi tai masentuneeksi.
5 ( ) Tunnen itseni äärimmäisen surulliseksi, alakuloiseksi tai masentuneeksi.

KYSYMYS 13. Ahdistuneisuus

1 ( ) En tunne itseäni lainkaan ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
2 ( ) Tunnen itseni hieman ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
3 ( ) Tunnen itseni melko ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
4 ( ) Tunnen itseni erittäin ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
5 ( ) Tunnen itseni äärimmäisen ahdistuneeksi, jännittyneeksi tai hermostuneeksi.

KYSYMYS 14. Energisyys

1 ( ) Tunnen itseni terveeksi ja elinvoimaiseksi.
2 ( ) Tunnen itseni hieman uupuneeksi, väsyneeksi tai voimattomaksi.
3 ( ) Tunnen itseni melko uupuneeksi, väsyneeksi tai voimattomaksi.
4 ( ) Tunnen itseni erittäin uupuneeksi, väsyneeksi tai voimattomaksi, lähes "loppuun palaneeksi".
5 ( ) Tunnen itseni äärimmäisen uupuneeksi, väsyneeksi tai voimattomaksi, täysin "loppuun palaneeksi".

KYSYMYS 15. Sukupuolielämä

1 ( ) Terveydentilani ei vaikeuta mitenkään sukupuolielämääni.
2 ( ) Terveydentilani vaikeuttaa hieman sukupuolielämääni.
3 ( ) Terveydentilani vaikeuttaa huomattavasti sukupuolielämääni.
4 ( ) Terveydentilani tekee sukupuolielämäni lähes mahdottomaksi.
5 ( ) Terveydentilani tekee sukupuolielämäni mahdottomaksi.

Appendix 2. The Moorehead-Ardelt questionnaire.

LEIKKAUSHOITOON JA LEIKKAUKSEN JÄLKEISEEN SEURANTAAN TULEVIEN SAIRAALLOISEN LIHAVIEN POTILAIDEN ELÄMÄNLAATUA KARTOITTAVA KYSELYKAAVAKE

Voitteko yleisesti ottaen
Erittäin huonosti Huonosti Aika hyvin Hyvin Erittäin hyvin

Tuletteko toimeen sosiaalisessa kanssakäymisessä
Erittäin huonosti Huonosti Aika hyvin Hyvin Erittäin hyvin

Pystyttekö osallistumaan liikunnallisiin tapahtumiin
Erittäin huonosti Huonosti Aika hyvin Hyvin Erittäin hyvin

Onko työkykynne Teidän mielestänne
Erittäin huono Huono Aika hyvä Hyvä Erittäin hyvä

Onko Teidän kiinnostuksenne seksiin
Erittäin huono Huono Aika hyvä Hyvä Erittäin hyvä

Onko Teillä jokin seuraavista sairauksista
Verenpainetautia
Astma
Diabetes
Masennusta
Rasitusperäisiä nivelkipuja
Uniapnea
Jokin muu sairaus, mikä?_____

Lääkitys, mikä?_____
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