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To those who hesitate to seek treatment for obesity.

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ABSTRACT

Background: Metabolic bariatric surgery (MBS) is the most effective treatment of severe obesity, a global epidemic associated with multiple comorbidities. MBS may result in type 2 diabetes (T2D) remission. The Individualized Metabolic Surgery (IMS) score aims to predict the remission and guide procedure selection between the two most common MBS procedures, laparoscopic sleeve gastrectomy (LSG) and Roux-en-Y gastric bypass (LRYGB). The Finnish SLEEVEPASS trial is a randomized multicenter clinical trial with long-term follow-up comparing LSG and LRYG. Severe obesity is associated with low-grade chronic inflammation, which is considered to contribute to the development of comorbidities and increased cancer risk. MBS may cause nutritional deficiencies, and micronutrient supplements are recommended postoperatively.

Aims: The aim of this thesis was to evaluate and compare long-term metabolic and nutritional effects of LSG and LRYGB. Study I aimed to validate the IMS score. Study II assessed the effect of MBS on low-grade chronic inflammation using high-sensitivity C-reactive protein (hs-CRP). Study III evaluated long-term nutritional deficiencies and adherence to micronutrient supplements at 10 years.

Results: IMS score correlated with the probability of T2D remissions, but there was no statistically significant difference between the procedures to guide procedure selection. MBS resulted in long-term decrease in hs-CRP, which correlated with BMI through follow-up. Long-term nutritional deficiencies were rare after MBS. There was a statistically significant difference between LSG and LRYGB in iron deficiency. Adherence to micronutrient supplements was higher in LRYGB group.

Conclusions: IMS score demonstrated strong prediction of T2D remission, but did not facilitate procedure selection. Hs-CRP decreased sustainably after MBS with weight loss as the driving force. Nutritional deficiencies were relatively rare after MBS, except for iron deficiency, which should be monitored, especially after LRYGB and considered in procedure selection.

KEYWORDS: metabolic bariatric surgery, Roux-en-Y gastric bypass, sleeve gastrectomy, type 2 diabetes, IMS score, hs-CRP, nutritional deficiencies

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Kliininen laitos
Kirurgian oppiaine
Gastroenterologinen kirurgia ja urologia
ILMARI SAARINEN: Laparoskooppisen mahalaukun kavennus- ja ohitusleikkauksen pitkäaikaisvaikutukset aineenvaihduntasairauksiin ja ravitsemukseen vaikean lihavuuden kirurgisessa hoidossa
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TIIVISTELMÄ

Tausta: Vaikea lihavuus liitännäissairauksineen on maailmanlaajuinen terveysongelma. Tehokkain hoito vaikeaan lihavuuteen on lihavuuskirurgia, jolla voidaan aikaansaada tyypin 2 diabeteksen (T2D) remissio. Individualized Metabolic Surgery (IMS) -pisteytys pyrkii ennustamaan T2D:n remission todennäköisyyttä ja ohjaamaan valintaa kahden yleisimmän lihavuuskirurgisen leikkausmenetelmän, laparoskooppisten mahalaukun kavennuksen (LSG) ja mahalaukun Roux-en-Y ohitusleikkauksen (LRYGB), välillä. Suomalainen SLEEVEPASS-tutkimus on pitkän aikavälin satunnaistettu kliininen monikeskustutkimus, jossa vertaillaan kavennusta ja ohitusleikkausta. Vaikea lihavuus aiheuttaa kehoon matala-asteisen tulehdustilan, jonka uskotaan vaikuttavan liitännäissairauksien kehittymiseen ja syöpäriskiin. Lihavuusleikkauksen jälkeen potilaat saattavat kärsiä ravintoainepuutoksista ja heille suositellaan pysyvää vitamiinilisien käyttöä.

Tavoitteet: Tämä väitöskirja pyrkii arvioimaan ja vertailemaan LSG:n ja LRYGB:n pitkäaikaisvaikutuksia aineenvaihduntasairauksiin ja ravitsemukseen. Osatyön I tavoitteena oli validoida IMS-pisteytys. Osatyössä II tutkittiin leikkauksien vaikutusta matala-asteiseen tulehdustilaan herkän C-reaktiivisen proteiinin (hs-CRP) avulla. Osatyö III arvioi ravintoainepuutosten yleisyyttä ja vitamiinilisien käyttöä 10 vuoden kohdalla leikkauksesta.

Tulokset: IMS-pisteet olivat selvästi yhteydessä T2D:n remissioon, mutta menetelmien välillä ei ollut eroa. Hs-CRP laski leikkausten jälkeen korreloiden selvästi painonlaskun kanssa. Ravintoaineiden puutokset olivat harvinaisia pitkällä aikavälillä leikkausten jälkeen. Menetelmien välillä oli eroa vain raudanpuutteessa. Vitamiinilisien käyttö oli yleisempää LRYGB-ryhmässä.

Johtopäätökset: IMS-pisteytys ennusti T2D:n remissiota, mutta ei helpottanut menetelmän valintaa. Hs-CRP laski leikkausten jälkeen pitkäaikaisesti painonlaskun myötä. Ravintoaineiden puutokset olivat harvinaisia leikkauksen jälkeen, lukuun ottamatta raudanpuutetta, jota tulisi seuloa etenkin LRYGB:n jälkeen ja huomioida menetelmän valinnassa.

AVAINSANAT: lihavuuskirurgia, mahalaukun kavennusleikkaus, mahalaukun ohitusleikkaus, tyypin 2 diabetes, IMS-pisteytys, hs-CRP, ravintoainepuutokset

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Abbreviations

ADA	American Diabetes Association
AHA	American Heart Association
ANOVA	Analysis of variance
ASMBS	American Society for Metabolic and Bariatric Surgery
AUC	Area under the curve
BMI	Body Mass Index
BPD	Biliopancreatic diversion
BPD-DS	Biliopancreatic diversion with duodenal switch
CI	Confidence interval
CVD	Cardiovascular disease
DS	Duodenal switch
EBMIL	Excess BMI loss
EWL	Excess weight loss
GERD	Gastroesophageal reflux disease
GIP	Glucose dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
HbA1c	Glycated hemoglobin
HDL	High-density lipoprotein
Hs-CRP	High-sensitivity C-reactive Protein
IDF	International Diabetes Federation
IFSO	International Federation for the Surgery of Obesity and Metabolic Disorders
IL-6	Interleukin 6
IMS	Individualized Metabolic Surgery
JIB	Jejunoileal bypass
LAGB	Laparoscopic adjustable gastric banding
LDL	Low-density lipoprotein
Look AHEAD	Look Action for HEAlth in Diabetes
LRYGB	Laparoscopic Roux-en-Y gastric bypass
LSG	Laparoscopic sleeve gastrectomy
MBS	Metabolic bariatric surgery

MASLD	Metabolic dysfunction-associated steatotic liver disease
MASH	Metabolic dysfunction-associated steatohepatitis
NCD-RisC	Non-Communicable Disease Risk Factor Collaboration
OAGB	One anastomosis gastric bypass
OMM	Obesity management medication
OR	Odds ratio
OSAS	Obstructive sleep apnea syndrome
PYY	Peptide YY
RCT	Randomized clinical trial
RL	Reference limit
RYGB	Roux-en-Y gastric bypass
SADI-S	Single-anastomosis duodenoileal bypass with sleeve gastrectomy
SG	Sleeve gastrectomy
SLEEVEPASS	Sleeve vs. Bypass
SM-BOSS	Swiss Multicenter Bypass or Sleeve Study
SOS	Swedish Obese Subjects
T2D	Type 2 diabetes
TNF-alpha	Tumor necrosis factor -alpha
TWL	Total weight loss
VBG	Vertical banded gatroplasty
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 Saarinen I*, Grönroos S*, Hurme S, Peterli R, Helmiö M, Bueter M, Strandberg M, Wölnerhanssen BK, Salminen P. Validation of the individualized metabolic surgery score for bariatric procedure selection in the merged data of two randomized clinical trials (SLEEVEPASS and SM-BOSS). *Surg Obes Relat Dis.* 2023 May;19(5):522-529.

II Saarinen I, Strandberg M, Hurme S, Grönroos S, Juuti A, Helmiö M, Salminen P. Association of high-sensitivity C-reactive protein (hs-CRP) with weight loss after sleeve gastrectomy and Roux-en-Y gastric bypass at 10 years: A secondary analysis of the SLEEVEPASS randomized clinical trial. *Obes. Surg.* 2024 Dec;34(12):4378-4384.

III Saarinen I, Strandberg M, Hurme S, Helmiö M, Grönroos S, Juuti A, Juusela R, Nuutila P, Salminen P. Nutritional deficiencies after sleeve gastrectomy and Roux-en-Y gastric bypass at 10 years: A secondary analysis of the SLEEVEPASS randomized clinical trial. *Br J Surg.* 2025 Jul;112(7):znaf132.

*Equal contribution

1 Introduction

Obesity is a chronic disease characterized by excess body fat. The global number of people with obesity has grown with an alarming speed over the last decades now surpassing one billion (NCD-RisC* 2024). As a developed western country, Finland has a high prevalence of obesity covering over a quarter of adults (THL 2023). People with obesity face stigmatization as they are often viewed as lazy and lacking self-control (Rubino et al. 2020). However, research has shown that obesity is a multifactorial heterogenic disease with genetics, gut microbiota, changes in brain function, and environment contributing to its development (Lin et al. 2021).

Obesity is associated with low-grade chronic inflammation originating from the excess adipose tissue. This pathogenesis includes overexpressed inflammatory cytokines, oxidative stress, and activation of macrophages in adipose tissue (Rohm et al. 2022). Obesity is also related with multiple complications including metabolic, mechanistic, and mental comorbidities (Heymsfield et al. 2017). Type 2 diabetes (T2D) is a classic example of metabolic comorbidity, which has been estimated to derive from obesity in 80% of the cases (Smith et al. 2016). In 2024, T2D was accountable for 9.3% of deaths globally (IDF 2025).

The most effective treatment of obesity is metabolic bariatric surgery (MBS). It is shown to result in greater and more sustainable weight loss than conservative treatment of obesity (Sjöström 2013; Adams et al. 2017; Sarma et al. 2022). In addition, MBS has beneficial effect on comorbidities. Even a complete remission of T2D may be achieved after MBS (Courcoulas et al. 2024; Ikramuddin et al. 2018; Sjöström et al. 2014). Some predictive factors for postoperative T2D remission have been recognized, which has led to development of scoring systems aiming to predict T2D remission. Individualized Metabolic Surgery (IMS) score is one of these systems (Aminian et al. 2017). Along with predicting the remission, the IMS score also aims to guide procedure selection (Aminian et al. 2017).

The chronic low-grade inflammation has also been shown to resolve as a result of MBS. The effect of MBS on inflammation may be assessed with inflammatory markers such as high sensitivity C-reactive protein (hs-CRP) (Askarpour et al. 2019). Research indicates that decrease in inflammatory markers is associated with weight loss but not necessarily with resolution of comorbidities (O'Rourke et al. 2019).

Being an efficient treatment for obesity, MBS has its complications. One of the long-term plausible undesirable consequences is nutritional deficiencies, such as vitamin D, vitamin B12, iron and calcium deficiencies along with protein malnutrition (Stein et al. 2014). To prevent these deficiencies, MBS patients are recommended to use micronutrient supplements postoperatively (Mechanick et al. 2019).

The two most common MBS procedures are laparoscopic sleeve gastrectomy (LSG) and laparoscopic Roux-en-Y gastric bypass (LRYGB). LRYGB is the gold standard operation of MBS (IFSO 2025). In 2014, LSG surpassed LRYGB as the most common technique (Angrisani et al. 2018) gaining its popularity without studies on its long-term outcomes. Today, some long-term results are available and show that also LSG is efficient in long-term with slightly inferior weight loss compared to LRYGB (Uhe et al. 2022; Wölnerhanssen et al. 2021; Salminen et al. 2022). The long-term research comparing LSG and LRYGB are still relatively scarce.

The Finnish SLEEVE vs. byPASS (SLEEVEPASS) trial so far is the largest randomized controlled trial (RCT) comparing LSG and LRYGB with available long-term results (Salminen et al. 2022). Another similar large RCT is the Swiss Multicenter Bypass or Sleeve Study (SM-BOSS) (Peterli et al. 2018). The data of these two RCTs were merged to form the largest randomized cohort in the world (Wölnerhanssen et al. 2021).

This doctoral thesis is based on the SLEEVEPASS trial and the merged data of SLEEVEPASS and SM-BOSS. In this randomized setting, the thesis studies the IMS score as a predictive marker for T2D remission and evaluates whether IMS score facilitates procedure selection. The association of hs-CRP with weight loss and the differences in the effects of LSG and LRYGB on hs-CRP are reported. Lastly, long-term nutritional deficiencies after LSG and LRYGB are compared along with adherence to micronutrient supplements.

2 Review of the Literature

2.1 Obesity

According to World Health Organization (WHO), overweight is defined as body mass index (BMI) greater than or equal to 25 kg/m^2 and obesity as BMI greater than or equal to 30 kg/m^2. People with BMI of 40 kg/m^2 or higher are considered to have severe obesity. WHO recognised obesity as a disease by including it in the International Classification of Diseases in 1948. However, even among medical professionals, the nature of obesity as a disease that needs to be actively treated, is still questioned.

2.1.1 Global obesity epidemic

Obesity, often referred as epidemic, is a growing threat to health globally. From 1990 to 2022, the number of adults with obesity has more than doubled and the number of children and adolescents with obesity has quadrupled. This results in over one billion people living with obesity today. The prevalence of obesity has increased in almost all countries in the world with just a few exceptions in Europe, for example France. So called obesity transition has been seen, as low-income countries formerly struggling with underweight are facing the growing occurrence of obesity (NCD-RisC* 2024).

Based on Finnish Institute for Health and Welfare's (THL) Terve Suomi -study from 2023, obesity is more common in Finland than the global average. A total of 34% of women and 44% of men had overweight. Over one fourth of adults, 30% of women and 27% of men, were living with obesity, and the prevalence of BMI over 35kg/m^2 was 12% in women and 8% in men (THL 2023). The prevalence in children (aged between 2 to 17 years) was 9% in 2022 (Paalanen et al. 2022).

2.1.2 Comorbidities of obesity

Obesity is a risk factor for many other diseases. In other words, obesity contributes to development of these diseases. These diseases are generally referred to as obesity-related comorbidities (Salminen et al. 2024).

2.1.2.1 Type 2 Diabetes (T2D)

One of the most notorious comorbidities of obesity is T2D. Over 80% of T2D is estimated to be caused by obesity, and the risk of a patient with obesity to develop T2D is seven times higher than the risk of an individual with normal weight (Smith et al. 2016). T2D is characterised by insulin resistance which develops through low-grade chronic inflammation caused by excess adipose tissue in obesity. As insulin resistance increases, the pancreatic β-cells seek to compensate by exhilarating the insulin production. Eventually they are unable to fulfil the growing need for insulin and T2D occurs (Klein et al. 2022).

The worldwide prevalence of T2D in adults is around 10.9% containing diagnosed and undiagnosed cases. It is associated with increased mortality, both as a direct cause of death and as an indirect factor through cardiovascular disease and chronic kidney disease. In 2024, T2D led globally to 3.4 million deaths which corresponds to around 9.3% of all deaths (IDF 2025). In Finland, it was estimated that around 429 000 patients suffered from T2D in 2017 (Koponen et al. 2018).

2.1.2.2 Other comorbidities of obesity

2.1.2.2.1 Metabolic comorbidities and increased cancer risk

Along with T2D, obesity is linked to several other chronic metabolic diseases. These comprise cardiovascular disease (CVD), hypertension, hypercholesterolemia and metabolic dysfunction-associated steatotic liver disease (MASLD) (Kloock et al. 2023; Smith et al. 2016). CVD with its complications, myocardial infarction and stroke, is a relevant mediator of obesity-related mortality (Bhaskaran et al. 2018). MASLD may lead to metabolic dysfunction-associated steatohepatitis (MASH) and further to cirrhosis. It also predisposes to hepatocellular carcinoma (Aminian, Al-Kurd, et al. 2021).

Obesity is also associated with several other cancers. These include breast, colon thyroid, esophageal, gastric cardia, liver, pancreatic, renal, endometrial, ovarian and gallbladder cancer, meningioma, melanoma, multiple myeloma and leukemia (Avgerinos et al. 2019; WHO 2022). In addition to increasing risk for cancers, obesity is also associated with greater overall mortality of cancer patients (Petrelli et al. 2021).

People with obesity suffer more frequently from infertility. In women, this is partly mediated by polycystic ovarian syndrome (PCOS), which is associated with obesity (Carson et al. 2021). Obesity-associated male infertility is among others derived from reduced testosterone production and hyperinsulinemia (Leisegang et al. 2021). Recently, obesity has gained attention as an independent risk factor for psoriasis (Griffiths et al. 2021).

2.1.2.2.2 Mechanistic comorbidities

Mechanistic comorbidities of obesity include osteoarthritis, obstructive sleep apnea syndrome (OSAS) and gastroesophageal reflux disease (GERD) (Heymsfield et al. 2017). In obesity, over-weight causes extra burden on the joints especially in lower limbs. This burden may predispose to osteoarthritis which is seen more commonly in patients with obesity (Murphy et al. 2008). Recent research suggests that metabolic changes in obesity also play part in the pathogenesis of osteoarthritis (Sampath et al. 2023).

In OSAS, upper airways collapse during sleep and a pause in breathing occurs. This leads to intermitting oxygen saturation and arousals that disrupt the sleep. Obesity adds mechanical stress in pharyngeal soft tissue. Similarly to osteoarthritis, there is also metabolic link between obesity and OSAS (Kuvat et al. 2020).

Patients with obesity have increased intra-abdominal pressure, which can predispose to GERD. The intra-abdominal pressure may result in hiatal hernia, which in turn compromises the function of the gastroesophageal barrier and enables acidic regurgitation from the stomach (Tack et al. 2018).

2.1.2.2.3 Mental comorbidities

Whilst obesity is associated with numerous somatic conditions, it is also linked to several mental comorbidities. These comprise eating disorders, such as binge eating disorder and bulimia nervosa, as well as depression, bipolar disorder and schizophrenia. The causal mechanisms connecting obesity and mental health are bidirectional. On one hand, obesity may negatively affect body image and self-esteem, which predisposes to mental illnesses. On the other hand, mental health problems are characterized by changes in appetite and over-all daily rhythm, which may result in weight gain (Yu et al. 2023; Kemp et al. 2023). In addition, some medications used in the treatment of mental health problems like mirtazapine and citalopram have weight gain as a side effect (Gill et al. 2020).

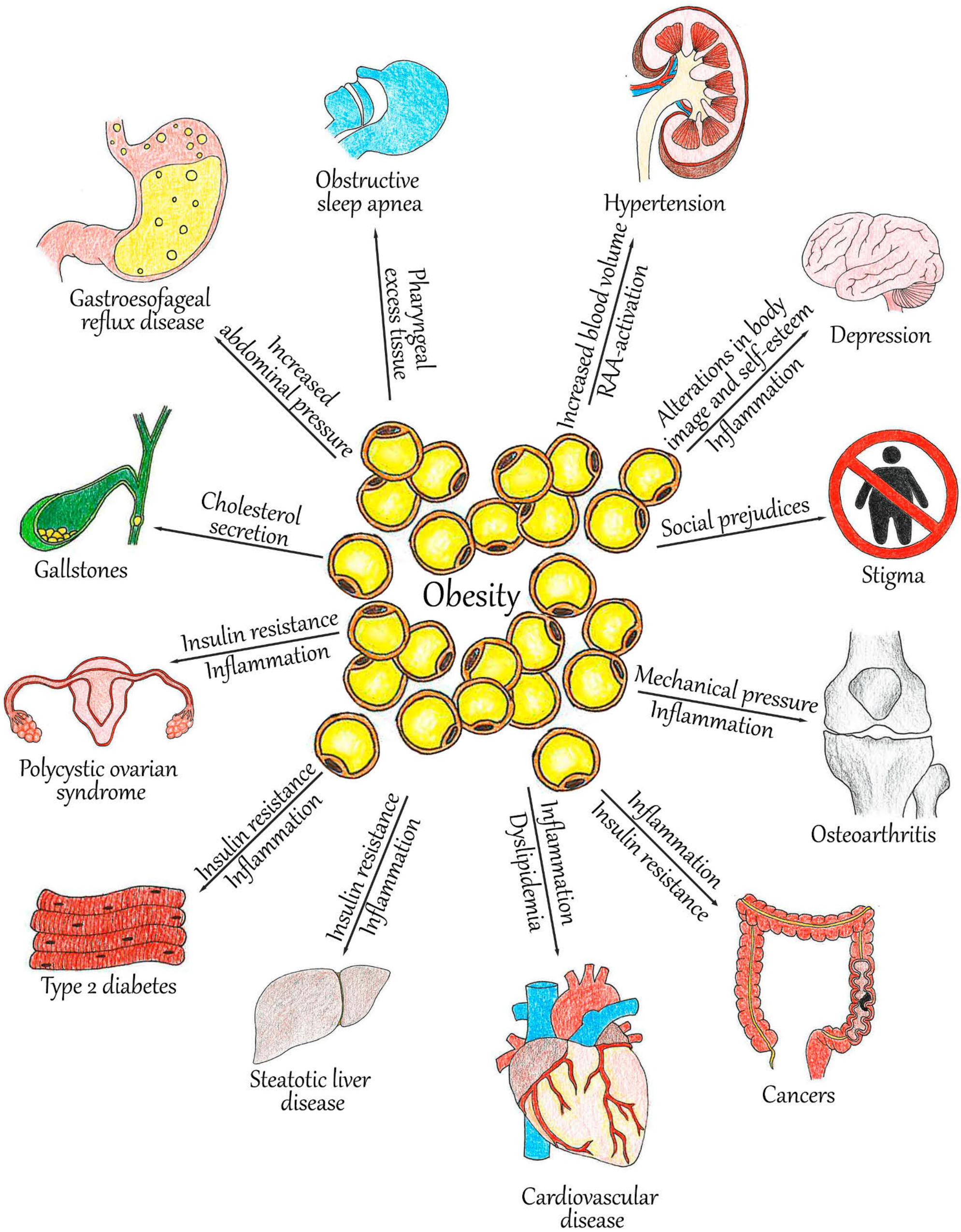

Figure 1. Comorbidities of obesity and the mechanisms behind them. Artwork by Anniina Kananen.

2.1.3 Obesity as a chronic disease

Hippocrates has been quoted as saying that obesity is a disease. (Phillips et al. 2018) WHO came to agree with the "Father of medicine" in 1948. However, it has long remained as the most accepted opinion of both public and healthcare professionals that obesity is a choice made by the individual. Patients with obesity have been seen responsible for their weight gain and preservation. In this paradigm, the only treatment seen necessary to cure obesity, is for the patient to restore their self-control and start eating less (Westbury et al. 2023).

Despite the ongoing popularity of this erroneous narrative, recent research and consensus has confirmed obesity to be a chronic disease (Rubino et al. 2023; Salminen et al. 2024). It has its own genetic and environmental risk factors, tendency to worsen over-time and relapses after successful treatment (Bray et al. 2017). The pathogenesis of obesity is multifactorial including genetics and epigenetics, gut microbiota, cultural and socioeconomical environment. To summarize, the human body regulates eating and energy storage as if there were scarcity of food. In the modern world, food is easily accessible, which leads to improper function of this regulation (Lin et al. 2021; Westbury et al. 2023).

2.1.3.1 Stigma of obesity

Blaming patients for their obesity is associated with the wider concept of obesity stigma. Patients with obesity are often perceived as lacking self-control, lazy, and even stupid. They face discrimination in the workplace, healthcare and society (Pearl 2018). In the media and culture, the stereotype is reinforced by presenting people with obesity as amusing and gluttonous (Heuer et al. 2011). Stigmatization can lead to severe physical and mental harm (Rubino et al. 2020).

It is of essence to recognise and object stigmatization while treating obesity. Stigma can prevent a patient with obesity from seeking treatment. It has been shown that patients who undergo metabolic bariatric surgery are exposed to even stronger stigma and often decide to conceal their surgical status (Hansen et al. 2018).

2.1.3.2 Pathophysiology of obesity and chronic inflammation

Obesity is characterized by positive energy balance, where energy intake is larger than consumption. Over-time the positive energy balance causes accumulation of excess adiposity. The lipids distribute to various parts of the body including subcutaneous tissue, visceral adipose tissue, inner organs and muscles (Heymsfield et al. 2017).

White adipose tissue is not merely an energy storage but an active endocrine organ. It produces hormones and cytokines and participates in metabolism regulation

(Neeland et al. 2019). However, when adipose tissue expands redundantly, it tends to develop a chronic inflammatory state. Several mechanisms have been identified behind this inflammation. In obesity, pro-inflammatory macrophages are found in adipose tissue in larger numbers than in normal-weight individuals. Due to rapid growth of adipocytes and lagging angiogenesis, hypoxia and oxidative stress may occur adding in inflammatory response (Rohm et al. 2022). The inflammation manifests as higher leukocyte count which is seen in patients with obesity (Schwartz et al. 1991; Nieto et al. 1992; Womack et al. 2007). A recent study found that patients with severe obesity had increased low-density neutrophil level (Sanchez-Pino et al. 2022). Furthermore, adipose tissue produces and activates proinflammatory cytokines such as tumor necrosis factor -alpha (TNF-alpha) and interleukin 6 (IL-6) (Ellulu et al. 2017; Lafontan 2005).

2.1.3.2.1 Serum high-sensitivity C-reactive protein (hs-CRP) in obesity

CRP is a commonly used inflammatory marker (Moutachakkir et al. 2017). In obesity, IL-6 upregulates the production of CRP, but the levels remain lower compared to for example those associated with infections (Ganter et al. 1989). Serum hs-CRP test detects smaller differences in concentration at low levels of CRP compared to the standard CRP test and may therefore be used to assess low-grade inflammation. Elevated hs-CRP levels are shown to occur in patients with obesity (Ebrahimi et al. 2016; Mora et al. 2006).

Hs-CRP has also been shown to have a predictive value in obesity-related comorbidities such as CVD (Ridker et al. 1998; Kaptoge et al. 2012) and T2D (Wang et al. 2013). The American Heart Association (AHA) recommends it for clinical evaluation of CVD risk (Arnett et al. 2019). Many studies have shown that elevated hs-CRP may also be an independent risk factor for worsening insulin resistance, de novo T2D and increased mortality of patients with T2D (Wang et al. 2013; Yan et al. 2019; Soinio et al. 2006). However, there are studies suggesting that obesity is the link between hs-CRP and metabolic diseases (Kahn et al. 2006).

2.1.3.3 Nutritional state in patients with obesity

Obesity is associated with micronutritional deficiencies such as vitamin D, vitamin B1, vitamin B12, iron, and magnesium deficiencies. Several underlying mechanisms have been identified. Although patients with obesity have excess energy intake, they often do not gain enough micronutrients due to low nutritional quality of energy dense food. Obesity-related chronic inflammation results in changes in the metabolism and absorption of micronutrients. Regarding vitamin D, lesser outdoor activity and wider distribution in adipose tissue may lead to deficiency (Stein et al. 2014; Kobylińska et al. 2022).

2.2 Conservative treatment of obesity

2.2.1 Lifestyle interventions

The treatment of obesity aims to weight loss. Traditionally this aim has been pursued by making lifestyle interventions. These interventions comprise a wide range of lifestyle counselling, from a general practitioner's recommendation to lose weight to dietary therapy, weight loss groups and behavioural therapy. The core of lifestyle modifications consists of reducing the daily energy intake with changes in diet and eating behaviour and increasing physical activity (Kushner et al. 2014). Still today, lifestyle intervention is recommended as the primary treatment of obesity by national guidelines worldwide (Gaskin et al. 2024; Semlitsch et al. 2019).

Despite being the foundation of obesity treatment guidelines, lifestyle interventions have been shown inefficient, especially at long-term (Adams et al. 2017; Courcoulas et al. 2024; Ikramuddin et al. 2018; Schauer et al. 2017). Although weight loss of approximately 5% can be achieved with lifestyle modifications at 2 years, weight regain is common. At 10-15 years, around 50% of the lost weight is regained (Kheniser et al. 2021). In the Look AHEAD trial, patients achieved 7-10% weight loss at 10 years with intensive lifestyle interventions including group and individual sessions for weight management counseling (first weekly and then with decreasing occurrence). However, no significant effect on cardiovascular mortality was seen (Wing et al. 2013). Naturally, this type of intensive counselling comes with costs and largely occupies healthcare provider resources.

The reasons why lifestyle interventions fail, lie in physiological changes caused by weight loss. Levels of leptin and thyroid hormones decrease which results in increased sense of hunger. Another factor increasing the desire to eat is changes in the autonomic nervous system (sympathetic nervous system deactivates, while parasympathetic activates). Parasympathetic tone also enhances energy restoration. The metabolic functions decelerate, and skeletal muscles work more efficiently, both of which reduce the consumption of energy. These changes make weight loss and especially maintaining the lower weight challenging (Rosenbaum et al. 2023).

2.2.2 Pharmacological treatment of obesity (Obesity management medications, OMMs)

Obesity management medications (OMMs) are used to enhance weight loss and to facilitate preserving reached weight. In recent years, rapid evolution has been seen in pharmacological treatment of obesity, as new and more effective OMMs have entered the market. In general, OMMs can be divided to three groups by their mechanisms of action: intragastrointestinal medications (orlistat), centrally acting medications (naltrexone-bupropion), and nutrient-stimulated hormone (NuSH)-based medications (liraglutide, semaglutide, tirzepatide) (Gudzune et al. 2024).

2.2.2.1 Orlistat

Orlistat blocks the absorption of fat in the small intestine by deactivating lipase enzymes (Gudzune et al. 2024). This orally administered drug has been associated with 3.1% greater weight-lowering effect compared to placebo (Shi et al. 2024). Relatively modest results adjoined with gastrointestinal adverse effects reduce orlistat's popularity (Gudzune et al. 2024).

2.2.2.2 Naltrexone-bupropion

Naltrexone-bupropion is the only purely centrally acting OMM with official indication for obesity treatment in Finland. It is administered via oral route. Naltrexone-bupropion affects by stimulating proopiomelanocortin neurons in brain reducing appetite and food cravings (Gudzune et al. 2024). According to recent meta-analysis of 6 RCTs, naltrexone-bupropion resulted in 4.1% greater weight loss than placebo (Shi et al. 2024).

2.2.2.3 Nutrient-stimulated hormone (NuSH)-based medications

NuSH-based medications have revolutionized the conservative treatment of obesity in the past few years. These include glucagon like peptide-1 receptor agonists (GLP-1 analogues) liraglutide and semaglutide, and GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) agonist tirzepatide. Their effectiveness for weight loss has created a growing demand that results in intermittent supply issues (Gudzune et al. 2024).

Liraglutide and semaglutide were first introduced for T2D treatment. GLP-1 affects pancreatic β-cells by amplifying insulin secretion, but also in the brain by reducing appetite (Gudzune et al. 2024). Liraglutide has been associated with 4.7% greater weight loss compared with placebo. Semaglutide is more effective resulting in weight loss of 11.4% greater than placebo (Shi et al. 2024). Initially liraglutide and semaglutide have been designed to be administered subcutaneously once a week. To date, semaglutide is also available as oral tablet (Knop et al. 2023).

Tirzepatide is the NuSH-based OMM that has latest entered the market. Tirzepatide is a dual agonist of GLP-1 and GIP receptors, which seem to have a synergistic effect in the brain (Gudzune et al. 2024). The weight loss achieved with tirzepatide has been shown 20.9% greater than placebo (Jastreboff et al. 2022). Due to novelty of NuSH-based OMMs, the studies on their effects are scarce and lack long-term follow-up. It has been shown that if the NuSH-therapy is discontinued, weight is often regained (Wilding et al. 2022).

2.2.2.4 Combining surgery and medications

OMMs and MBS are not merely alternatives but may be combined for optimal treatment of obesity. OMMs may be utilized to support the preoperative weight loss particularly in patients with very high BMI (Cohen, Park, et al. 2024). In patients with suboptimal initial response to MBS or recurrent weight gain, OMMs may enhance the treatment outcomes (Miras et al. 2019; Mok et al. 2023). Combining MBS and OMMs is a novel practice and thus far research on the matter remains scarce (Cohen, Park, et al. 2024).

2.3 Metabolic bariatric surgery

2.3.1 Development of metabolic bariatric surgery

Obesity is not only a health problem of the modern world. It has been an ordeal to humans through the course of history and furthermore the cure has been sought. Legend has it, that the Spanish king of Leon, Sancho, after losing his throne due to obesity, had his lips sewed together so that he would have to adhere to liquid diet. The treatment was successful, and Sancho returned to power (Faria 2017). The first modern MBS procedure was performed by Viktor Henriksson in 1952 in Sweden. He resected 105 cm of small bowel to treat a 32-year-old woman with obesity (Henrikson 1994). In the next year 1953, Richard Varco carried out the first jejunoileal bypass (JIB) in the United States. This method was adopted by others among the few who were practicing MBS at the time. Weight loss after these early intestinal bypasses was sufficient, but the patients suffered from malnutrition and its complications as well as diarrhea and dehydration (Phillips et al. 2018).

In 1967, the first gastric bypass was performed by Edward Mason (Mason et al. 1967). Many different versions of this operation were developed until in 1977, Griffen et al. introduced RYGB for obesity. RYGB was shown to be nearly as sufficient regarding weight loss, but had markedly less long-term complications than intestinal bypasses (Griffen et al. 1977) It became the gold standard of MBS.

Although RYGB was less radical than JIB, it also affected the nutritional state of the patients. The interest towards purely restrictive procedures rose. In 1973, the horizontal partial gastroplasty was introduced by Printen and Mason. The technique narrowed the route of food through the stomach without reducing the stomach volume. However, the weight loss was not sufficient as patients were able to increase their food intake gradually. The gastroplasty was further developed by Laws and Piatadosi who made the pouch vertical and added a restrictive silastic ring. After modifications, Mason published the method as vertical banded gastroplasty (VGB). It gained popularity and led to development of laparoscopic gastric banding (LAGB) in the 1990s. (Phillips et al. 2018) The mid-term results of these procedures were relatively good, but in long-term studies showed weight regain and non-tolerable complication rates (Suter et al. 2006). Consequently, the banding procedures have been virtually abandoned (Angrisani et al. 2024).

While some were seeking to invent MBS methods with minimal risk of malabsorption, others looked back to weight loss efficiency of JIB. Biliopancreatic diversion (BPD) was introduced by Scopinaro in 1979 (Scopinaro et al. 1979). This surgery included partial gastrectomy, an anastomosis between distal jejunum and the gastric pouch, and the proximal jejunum anastomosed to the distal ileum. BPD was modified by Hess and Hess and combined with duodenal switch (DS) in 1998. The technique included sleeve gastrectomy, duodenal division, a proximal duodenoileostomy and a common channel of approximately 100cm (Hess et al. 1998).

SG was originally developed as a part of the duodenal switch operation. Michael Gagner performed BPD-DS in two stages for high-risk patients and noticed that they lost weight significantly after the first performed SG. He started performing SG as a stand-alone procedure and it showed to be sufficient (Phillips et al. 2018). SG has become the most performed MBS in the world for its simple technique (Angrisani et al. 2024).

Gastric bypass can also be performed with only one anastomosis (De Luca et al. 2021). This procedure, known as one-anastomosis gastric bypass (OAGB), was introduced in 1997 and has gained popularity especially in the Middle-East (Angrisani et al. 2024). In 2010, the single-anastomosis duodenoileal bypass with sleeve gastrectomy (SADI-S) was published (Sánchez-Pernaute et al. 2010). This operation is a modification of BPD-DS. Both of these procedures have a limited long-term follow-up (Sánchez-Pernaute et al. 2022; Robert et al. 2024; Robert et al. 2019).

A huge advancement in all MBS was the development of laparoscopy in the 1990's (Sundbom 2014). The first laparoscopic RYGB (LRYGB) was performed in 1994 (Wittgrove et al. 1994) and in 2005 laparoscopy surpassed the open technique as the most common MSB approach. Advantages of laparoscopy comprise lower complication rate, faster recovery, shorter hospitalization and cosmetical superiority. Currently, laparoscopy is inbuilt in MBS as it has enabled modern MBS. (Sundbom 2014).

2.3.2 Metabolic bariatric surgery to date

LSG is the most performed MBS procedure worldwide. It surpassed LRYGB in total amount of surgeries in 2014 (Angrisani et al. 2018). In 2021, it covered 58.2% of all MBS. LRYGB is the second most common (26.4%), followed by OABG (7.6%). According to the International Federation of the Surgery for Obesity (IFSO) report from 2021, the total worldwide number of MBS operations was around 600 000 (Angrisani et al. 2024). Naturally the actual number of operations is larger as all operations are not reported.

In 2020-21, the long-lasting increase in numbers of MBS experienced a slight decrease. This is presumed to be a consequence of the COVID-19 pandemic and therefore the growth of MBS is expected to recover. (Angrisani et al. 2024) A noteworthy trend in MBS is the growing popularity of endoscopic procedures that have yet remained marginal. (Angrisani et al. 2024)

2.3.2.1 Indications and contraindications of metabolic bariatric surgery

The guidelines of IFSO and American Society for Metabolic and Bariatric Surgery (ASMBS) recommend MBS to be considered for all patients with BMI over 35kg/m^2 and for T2D patients with BMI over 30kg/m^2. Furthermore, MBS should be considered for patients with BMI over 30kg/m^2 if they have not achieved sufficient weight loss or improvement in comorbidities with conservative treatment. The guidelines do not set any age limit for MBS. While treating older patients, frailty should be considered rather than mere age of the patient. Children and adolescents with BMI over 120% of the 95th percentile and a major comorbidity or a BMI over 140% of the 95th percentile should be considered for MBS. These new guidelines were published in 2022 (Eisenberg et al. 2022).

In Finland, the official indications of MBS are still based on the 1991 guidelines, but the updating of the national guidelines has been initiated in January 2025. MBS may be considered for ages 18-65 years. Based on obesity alone, BMI must exceed 40kg/m^2. In presence of obesity-related comorbidity, the BMI limit is 35kg/m^2. For T2D patients who have not achieved sufficient results with conservative treatment, MBS may be considered for patients with BMI of 30-35 kg/m^2. In addition, the patient must have undergone a 6-month conservative treatment for obesity and achieved a 5% weight loss. MBS may be considered for adolescents of 13-17 years.

2.4 Surgical techniques of LSG and LRYGB

2.4.1 Laparoscopic sleeve gastrectomy (LSG)

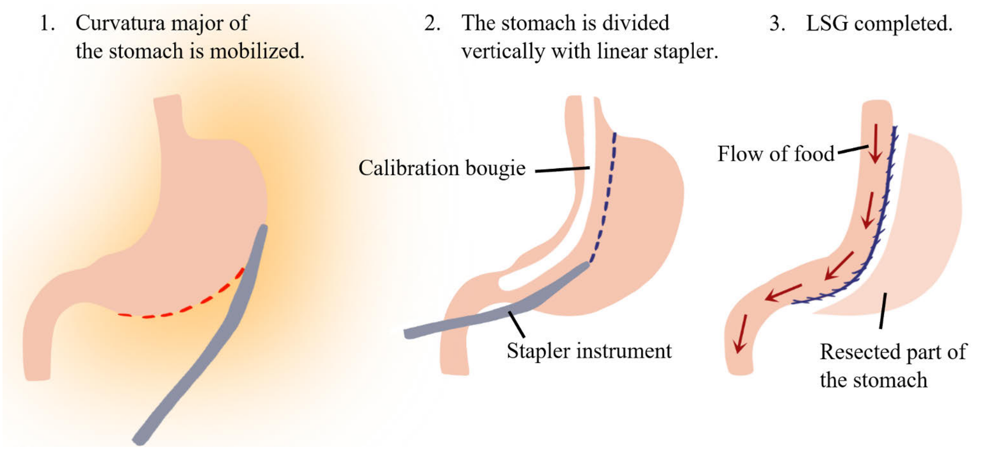

Figure 2. Laparoscopic sleeve gastrectomy. Artwork by Pihla Ranta.

LSG is performed by dividing the stomach vertically and creating a tubular shaped stomach. The pylorus is retained in the procedure. A calibration bougie inserted is commonly used, and the resected part of the stomach is pulled out from the abdomen through a laparoscopic troacar hole.

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

A small gastric pouch is created from the upper part of stomach. Jejunum is divided proximally, and the distal part, called the alimentary limb, is joint with gastrojejunostomy to the pouch. A side-to-side jejunostomy between the proximal biliopancreatic and alimentary limb is constructed. The food flows through gastric pouch to alimentary limb bypassing greatest part of the stomach, duodenum and proximal jejunum. The bile and the pancreatic enzymes flow through the biliopancreatic limb to the junction of the limbs. In the end, the mesenteric defects are closed to avoid internal herniation (Stenberg et al. 2016).

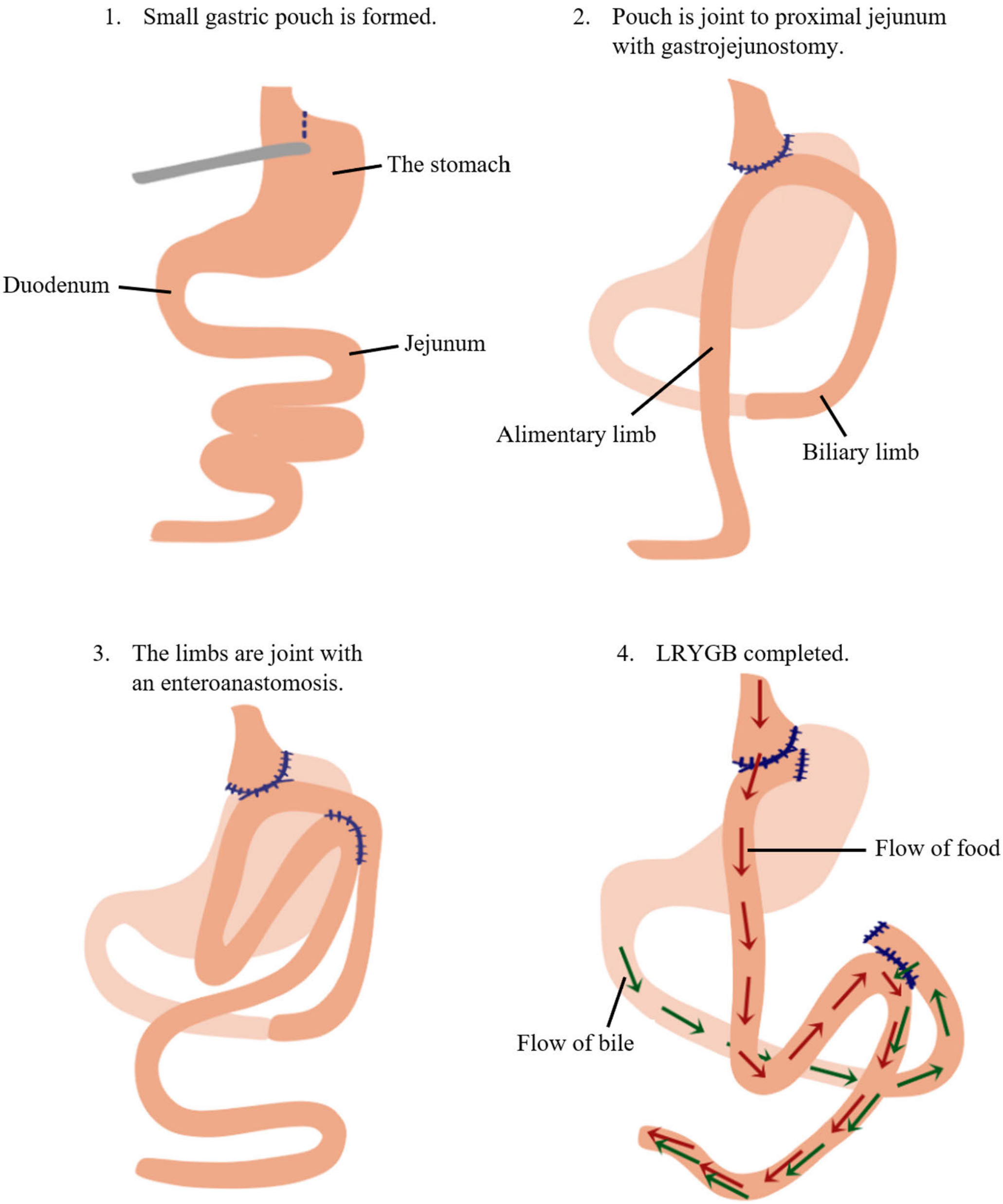

Figure 3. Laparoscopic Roux-en-Y gastric bypass. Artwork by Pihla Ranta.

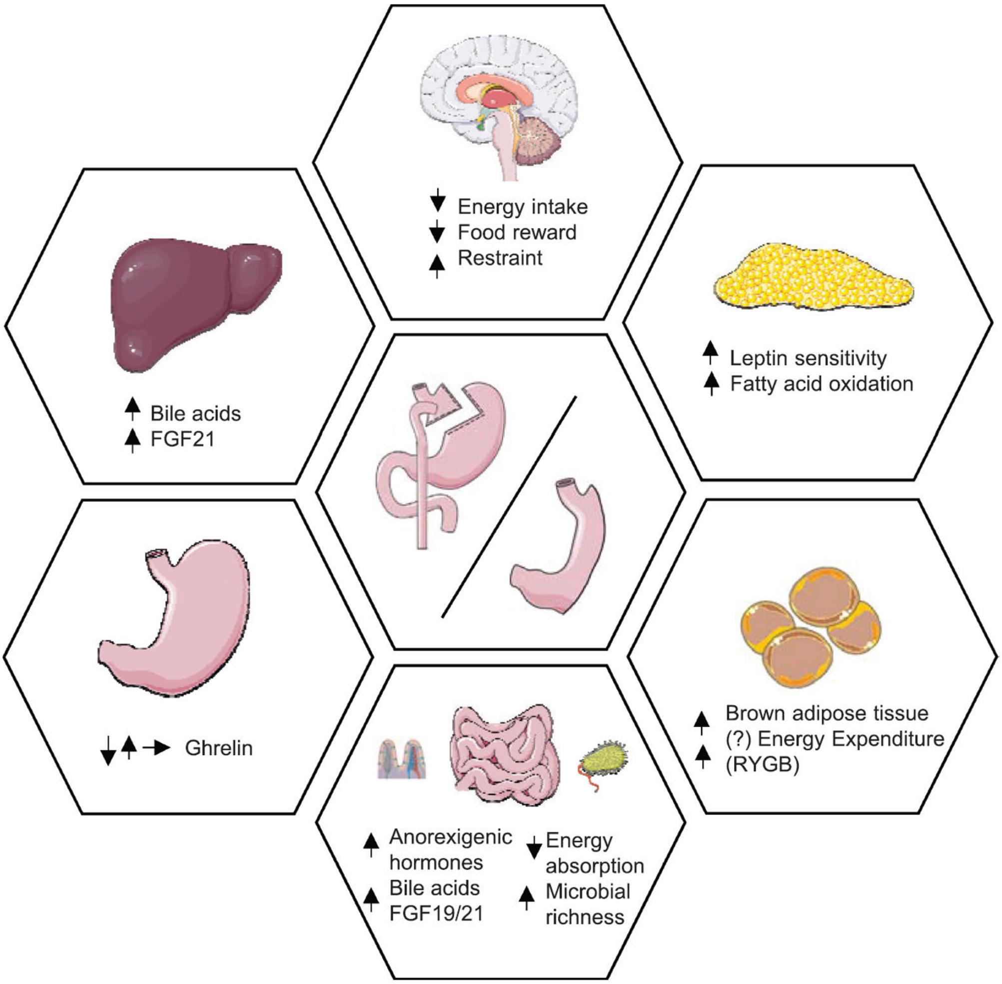

Figure 4. Weight loss mechanisms of LSG and LRYGB. Reproduced with permission from Akalestou E., A. D. Miras, G. A. Rutter and C. W. le Roux. 2022. End Rev. 43(1):19-34.

2.4.3 Mechanisms of weight loss by metabolic bariatric surgery

MBS causes reduced energy intake and weight loss by several mechanisms. The alterations in gastrointestinal tract also lead to lower levels of ghrelin, a hormone which stimulates the feeling of hunger. Simultaneously, levels of gut hormones GLP-1 and Peptide YY (PYY) rise resulting in satiety. These circumstances enable a patient to lose weight without the persistent craving for food. MBS changes eating behaviour by alterations in neural signalling between the gut and the brain. This reduces the rewarding mechanisms in the brain induced by, for example fat and sugar, and may result in decreased proportion of the energy-dense foods in diet. The procedures restrict the amount of consumed food as the volume of the stomach is reduced and the nutrients flow faster to the small intestine. Hypoabsorption of energy rich nutrients is another mechanism of MBS. Apart from previous conception, it is not caused by reduced absorption surface area alone. Alterations in gut microbiota also contribute, as Bacteroidetes increase and Firmicutes decrease, which results in reduced caloric absorption and even greater energy consumption (Alabduljabbar et al. 2023).

2.5 Outcomes of metabolic bariatric surgery

2.5.1 Measures of weight loss outcomes

Weight loss induced by MBS or any other treatment may be measured in different ways. Percentage total weight loss (%TWL) is currently the recommended measure in MBS research. It presents the proportion of the initial total weight that has been lost. Percentage excess weight loss (%EWL) presents the lost proportion of the initial excess weight. However, %EWL is more influenced by initial BMI than %TWL, as it tends to show more modest results for patients with higher BMI and excess weight (Corcelles et al. 2016). %TWL is also easier to understand for patients and healthcare professionals alike (Brethauer et al. 2015). Percentage excess body mass index loss (%EBMIL) describes the decrease in initial excess BMI. Similarly to %EWL, %EBMIL is dependent on initial BMI. Definition of excess BMI (over 25 kg/m^2) is however, more simple than excess weight, as it applies the same numeral limit for all patients (Brethauer et al. 2015).

2.5.2 Weight loss outcomes

Weight loss by MBS is greater and more sustainable than the one achieved with conservative treatment (Courcoulas et al. 2024; Sarma et al. 2022; Adams et al. 2017; Sjöström 2013). The currently used techniques induce a long-term total weight loss (TWL) of around 20-30% (Salminen et al. 2022; Adams et al. 2017; Vitiello et al. 2023; Liagre et al. 2022). Weight achieves its nadir at 1 year after MBS and afterwards a gently sloping slight re-increase is seen (Salminen et al. 2022; Courcoulas et al. 2024; Ikramuddin et al. 2018).

Comparing the weight loss effects of LSG and LRYGB as the most common procedures is naturally under active research. The merged data of the two largest RCTs SLEEVEPASS and SM-BOSS found LSG less effective with excess BMI loss of 55.5% compared to 62.7% achieved with LRYGB at 5 years postoperatively (Wölnerhanssen et al. 2021). The most recent meta-analysis of RCTs and a recently published large RCT show similar results with LRYGB having slightly greater weight loss at 5 years (Uhe et al. 2022; Biter et al. 2024). The 10-year results from the SLEEVEPASS trial also found the excess weight loss not equivalent between LSG and LRYGB, but 8.4% higher after LRYGB.

2.5.3 Comorbidity and mortality outcomes

2.5.3.1 Type 2 diabetes outcomes

The effects of MBS on T2D have been studied thoroughly and the outcomes are very convincing. MBS enhances glycemic control and reduces the need for insulin and other antidiabetic medication. At best, it may result in remission of T2D (Courcoulas et al. 2024; Ikramuddin et al. 2018; Sjöström et al. 2014). Remission is defined by American Diabetes Association (ADA) as glycated hemoglobin (HbA1c) less than 6.5% or 48 mmol/l that persists for at least three months without using any glucose-lowering medications (Riddle et al. 2021).

MBS has been shown to be more effective treatment against T2D than conservative treatment (Courcoulas et al. 2024; Ikramuddin et al. 2018; Sjöström 2013). Therefore, as stated above, the MBS guidelines have lower BMI limits for patients with T2D. In a pooled analysis from 4 RCTs by Courcoulas et al., MBS resulted in 15.5 mmol/l lower HbA1c than conservative treatment at 7 years postoperatively. At 12 years from surgery the HbA1c was 12.0 mmol/l lower than in the conservatively treated group. T2D remission occurred in 18.2% of the MBS patients at 7 years, whereas in the conservative group remission occurred in 6.2% (Courcoulas et al. 2024). A meta-analysis of long-term studies from 2017 had similar results. MBS increased T2D remission, reduced micro- and macrovascular events and mortality compared to conservative treatment (Sheng et al. 2017). It is also known from other studies that in longer follow-up T2D remission and improvement rate decreases (Sjöström 2013). Although a relapse might follow the initial remission after MBS, the glycemic control and need for medications are improved compared to baseline. In other words, the favourable effects of MBS on T2D sustain despite the potential relapse (Aminian et al. 2020).

2.5.3.2 Other comorbidity outcomes

MBS has favourable effects on other comorbidities of obesity, which are superior to conservative treatment. A remission or improvement is seen in dyslipidemia with lower low-density lipoprotein (LDL) and triglyceride levels and higher high-density lipoprotein (HDL) levels. Blood pressure is lower in patients who have undergone MBS (Ikramuddin et al. 2018; Adams et al. 2017). MBS reduces the risk for cardiovascular events and stroke (Sjöström 2013; Tang et al. 2022). Lower-limb osteoarthritis patients have better functionality and less pain after MBS (Eymard et al. 2024). A remission of OSAS may occur following MBS (Peromaa-Haavisto et al. 2024). GERD is a noteworthy comorbidity as it may worsen after LSG and improve after LRYGB. GERD is thus considered as a contraindication for LSG (Salminen et al. 2022). MBS has positive effect on depression, anxiety and eating disorders. However, there is some evidence that risk of self-harm and suicide may increase after MBS (Law et al. 2023). Overall cancer risk is also decreased after MBS (Sjöström 2013; Aminian et al. 2022).

2.5.3.3 Mortality outcomes

MBS has been shown to reduce overall mortality. This effect is particularly strong in T2D patients. In a recent meta-analysis, MBS was associated with 5.1 years longer median life expectancy than conservative treatment of obesity. In T2D patients, the life expectancy was 9.3 years longer than in conservatively treated patients (Syn et al. 2021).

2.6 Prediction of type 2 diabetes remission and procedure selection

2.6.1 T2D remission after LSG and LRYGB

The effects of LSG and LRYGB on T2D remission appear similar. In the meta-analysis by Uhe et al. no difference was seen in T2D remissions at any follow-up points up to 5 years (Uhe et al. 2022). Previous meta-analyses have had similar results (Lee et al. 2021). The merged data of SLEEVEPASS and SM-BOSS showed a complete T2D remission in 24% after LSG and 32% after LRYGB and partial remission in 25% and 24%, respectively, at 5 years with no statistically significant difference (Wölnerhanssen et al. 2021). The recent five-year outcomes of a large Dutch RCT also showed no difference in remissions between the procedures (Biter et al. 2024). However, there are also studies with contradictory results (Hofsø et al. 2019; Aminian, Wilson, et al. 2021). In a large retrospective cohort with 693 LSG and 1362 LRYGB patients, LRYGB resulted in better T2D outcomes (Aminian, Wilson, et al. 2021). In another retrospective study LSG resulted in more late relapses after initial remission compared with LRYGB (Aminian et al. 2020). It would require around 700 enrolled patients in an RCT setting, to detect a 10-percentage point difference in T2D remission between LSG and LRYGB and this is achievable only by international collaboration.

2.6.2 Prediction of type 2 diabetes remission

Predicting the remission and late relapse of T2D preoperatively is under active research. It is essential in selecting the patients who would benefit most from MBS and tailoring the optimal surgical treatment for each patient. Despite its positive impact on T2D, the benefits of MBS need to be weighed against the risks that are present in surgical treatment. Several preoperative factors have been identified that could facilitate assessing the probability of remission.

2.6.2.1 Patient's age and body mass index

Patient's age at the time of surgery is one factor that has been investigated as a predictive factor for T2D remission. Research indicates that the higher the age, the smaller the probability of T2D remission (Park et al. 2016; Souteiro et al. 2017; Wang et al. 2015). Preoperative BMI is a factor associated with more controversial results. On one hand there are studies that have shown BMI to be an independent predictive factor (Dixon et al. 2013; AbdAlla Salman et al. 2022). On the other hand, a meta-analysis by Panunzi et al. showed that baseline BMI did not predict T2D remission (Panunzi et al. 2015). Another meta-analysis by Wang et al. had similar results (Wang et al. 2015).

2.6.2.2 Duration of type 2 diabetes

The preoperative duration of T2D seems to be strongly connected to the likelihood of T2D remission. Shorter duration is associated with remissions and with less late relapses (Wang et al. 2015; Panunzi et al. 2016; AbdAlla Salman et al. 2022; Dixon et al. 2013; Aminian et al. 2020). In a study on LSG patients, a subgroup of patients with preoperative duration of T2D over 5 years had a remission rate of 16% while the remission rate in the whole population was 63% (Aminian et al. 2016).

2.6.2.3 Laboratory markers (glycemic control and β-cell function)

Glycemic control before surgery, usually assessed with HbA1c or fasting glucose, has also been studied as a predictive factor for T2D remission. These laboratory values are often easily available for all T2D patients. Lower HbA1c and fasting glucose seem to predict remission consistently (Wang et al. 2015; Souteiro et al. 2017; Panunzi et al. 2016; Park et al. 2016). Souteiro et al. found that patients who achieved remission had 9.8 mmol/mol lower mean preoperative HbA1c than those who did not (Souteiro et al. 2017).

A more specific laboratory marker for the function of pancreatic β-cells is the C-peptide. It is a by-product of β-cell insulin production, and its concentrations are dependent on the amount of endogenous insulin production. There is strong evidence that higher baseline C-peptide is associated with a higher rate of T2D remissions (Wang et al. 2015; Dixon et al. 2013; Souteiro et al. 2017; Park et al. 2016; AbdAlla Salman et al. 2022).

2.6.2.4 Prescribed medications (insulin and oral anti-diabetic medications)

One way to evaluate the severity of T2D is to investigate the prescribed medications. Usually, the treatment of T2D starts with oral medications like metformin. Insulin is added to treatment when glycemic control is no longer achieved with oral drugs and subcutaneously administered drugs like GLP-1 analogs.

The lower number of oral anti-diabetic medications at the time of operation has indeed been shown to predict greater probability T2D remission and its sustainability in some studies (Aminian et al. 2016; Panunzi et al. 2016; Aminian et al. 2020). Similarly baseline insulin use has been associated with lower remission rate (Wang et al. 2015). However, literature is not unanimous on these matters. For example, in a study by Souteiro et al. the oral medications and insulin use did not predict remission (Souteiro et al. 2017).

2.6.3 Procedure selection based on type 2 diabetes remission predictive score

Predicting T2D remission with different variables has led to question whether the predictors could be utilized in procedure selection. Although the impact of LSG and LRYGB on T2D seems equal on a large-scale, on single patient-level one may be superior to another. In the next chapter, the IMS score, a T2D remission prediction tool that aims to guide procedure selection, is introduced.

2.6.3.1 Individualized Metabolic Surgery (IMS) score

The IMS score was developed by Aminian et al. and published in 2017(Aminian et al. 2017). It is based on a retrospective dataset from Cleveland clinic (Cleveland, USA) with 659 MBS patients. All these patients had T2D preoperatively and had undergone either LSG or LRYGB. This training dataset was used by Aminian et al., to generate a T2D remission prediction model including preoperative variables. Furthermore, for the original publication, it was validated in another retrospective cohort of 241 patients from Hospital Clínic Universitari of Barcelona, Spain (Aminian et al. 2017).

The IMS score includes four preoperative factors: 1) HbA1c (categorized into under or above 7%), 2) number of diabetes medications including oral and injectable drugs including insulin (from 1 to 5), 3) preoperative duration of diabetes (years), and 4) insulin use (categorized into yes or no). With these variables, the model generates a score from 0 to 180. The score distribution is further categorized into three T2D severity stages: mild (≤25), moderate (25-95), and severe (>95) (Aminian et al. 2017).

Based on previous research and their findings in the training dataset, the basic thought of Aminian et al. was the milder the T2D, the greater the odds of remission. They studied the severity stages in terms of procedure selection and found that on the moderate stage, LRYGB led to remission significantly more often than LSG. Therefore, they ended up recommending LRYGB to patients with moderate T2D. In the mild and the severe stages, there was no difference in the remission rate between the procedures. (Aminian et al. 2017).

2.6.3.2 Other type 2 diabetes remission predictive scoring systems

There are several other prediction scores for T2D remission. Other scores, however, do not attempt to guide procedure selection but merely describe the probability of T2D remission.

The ABCD score (first Diabetes Surgery score) was developed by Taiwanese group and published in 2013. It includes four predictive factors: age, BMI, C-peptide, and duration of diabetes (Lee et al. 2013). After the original publication some minor modifications were made by the developers, but the basic idea remained the same (Lee et al. 2015).

The DiaRem score was introduced in 2014. It consists of age, HbA1c, and type of antidiabetic medication (including insulin) (Still et al. 2014). It was further developed by another study group who added duration of T2D and number of medications as variables. This new score was published as Advanced-DiaRem (Ad-DiaRem) score (Aron-Wisnewsky et al. 2017).

In 2018, the DiaBetter score was published. It has HbA1c, duration of T2D, and antidiabetic medication (including insulin) as variables (Pucci et al. 2018). The prediction scores and included variables are shown in **Table 1**.

Table 1. T2D remission prediction scores and included variables.

	ABCD	DIAREM	AD-DIAREM	DIABETTER	IMS
AGE	X	X	X		
BMI	X				
C-PEPTIDE	X				
T2D DURATION	X		X	X	X
HBA1C		X	X	X	X
MEDICATION TYPE		X		X	
INSULIN USE		X	X		X
NUMBER OF OTHER T2D MEDICATIONS			X		X

2.6.3.3 Comparison between IMS score and other scoring systems

The ability of the IMS score to predict T2D remission has been evaluated to be sufficient (Shen et al. 2019; Plaeke et al. 2021; Ghusn et al. 2024). In comparative studies with other scores, the IMS score has generally demonstrated strong performance. In their validation of 11 scoring models, Plaeke et al. found it to be the most accurate (Plaeke et al. 2021). Ghusn et al. showed the IMS score had the highest area under the curve (AUC) compared with DiaRem and Ad-DiaRem scores (Ghusn et al. 2024). Comparisons between the IMS and the ABCD score have shown contradicting results and there is no consensus on their relative superiority (Chen et al. 2018; Ohta et al. 2021).

The parameters in the IMS score have similarity with the ones in DiaRem, Ad-DiaRem and DiaBetter scores. All include preoperative HbA1c and the use of anti-diabetic medications and insulin, that are shown to predict T2D remission (Wang et al. 2015; Panunzi et al. 2016). Furthermore, the IMS, Ad-DiaRem, and DiaBetter scores have duration of T2D as variable, which is strongly associated with T2D remission (Wang et al. 2015; Panunzi et al. 2016; Aminian et al. 2016; AbdAlla Salman et al. 2022). These three scores performed best in a comparative study by Plaeke et al. (Plaeke et al. 2021).

2.7 Obesity-related chronic inflammation after bariatric surgery

Previous research has shown that MBS induces subsiding of obesity-related inflammation. This is demonstrated by decreasing levels of inflammatory markers such as TNF-alpha and IL-6 (Askarpour et al. 2019). Adipose tissue macrophage numbers have also been shown to decrease postoperatively in short-term (Osorio-Conles et al. 2021). Some studies have shown that MBS lowers patient's leukocyte count. The impact was mostly derived from decreasing neutrophil levels (Recarte et al. 2023; Veronelli et al. 2004). More specifically, a recent study associated obesity with elevated level of low-density neutrophils which reduced postoperatively (Sanchez-Pino et al. 2022).

2.7.1 Effect of metabolic bariatric surgery on hs-CRP

MBS has been shown to decrease hs-CRP levels in short-term (Askarpour et al. 2019). There are few studies with longer-term follow-up (Hinerman et al. 2022; Lautenbach et al. 2021). In their retrospective analysis of LRYGB patients, Hinerman et al. showed the decrease to be sustained at 7 years (Hinerman et al. 2022). Lautenbach et al. found no difference in the effect of LSG and LRYGB in a retrospective setting at 4 years. However, long-term studies on the effect of LSG on hs-CRP are lacking (Lautenbach et al. 2021).

Hs-CRP seems to achieve its nadir around 2 years postoperatively (Hinerman et al. 2022; Lautenbach et al. 2021). Many studies have shown a correlation between hs-CRP decrease and weight loss, but not with remission of comorbidities (Lautenbach et al. 2021; O'Rourke et al. 2019; Illán-Gómez et al. 2012). The question whether preoperative hs-CRP predicts weight loss is yet to be determined. O'Rourke et al found no correlation between baseline hs-CRP and weight loss outcomes (O'Rourke et al. 2019).

2.8 Effect of metabolic bariatric surgery on nutritional state

Multiple advantages of MBS have been discussed in previous sections. However, MBS also has disadvantages and some of its effects may not be desirable. While MBS aims to reduce energy intake, it changes the intake of other nutrients as a side-effect. Consequently, one of the complications of MBS is nutritional deficiencies.

2.8.1 Effect on protein and albumin status

Protein malnutrition is associated with MBS, and it may manifest as hypoalbuminemia. Previous studies have found the prevalence of hypoalbuminemia to be 27.9% at 10 years after MBS (Stein et al. 2014). A recent short-term study found no difference in albumin levels after LSG and LRYGB (Javanainen et al. 2018). Previously it was presumed that alterations in the gastrointestinal tract cause malabsorption of protein. However, recent research indicates that protein absorption does not change after MBS or may even accelerate after LRYGB (Mahawar et al. 2017; Svane et al. 2019).

2.8.2 Effect on vitamin D and calcium status

Vitamin D and calcium metabolisms are closely linked and contributing to bone health. Vitamin D and calcium deficiencies may result in bone density loss and increased fracture risk (Khazai et al. 2008). There is some evidence indicating that MBS increases the risk for fractures, but long-term results are lacking (Saad et al. 2022). LSG may result in lower fracture risk compared to LRYGB (Paccou et al. 2020; Saad et al. 2022).

2.8.2.1 Vitamin D

As stated previously, patients with obesity are known to have a greater risk of vitamin D insufficiency and deficiency compared to normal-weight patients and this risk seems to increase after MBS (Giustina et al. 2023; Gao et al. 2023). With postoperative vitamin D supplementation, the risk can be reduced, although deficiency is still frequent (Giustina et al. 2023; Gao et al. 2023; Carlin et al. 2006; Schollenberger et al. 2015). In a recent meta-analysis by Giustina et al., patients undergoing LRYGB had a greater risk of vitamin D deficiency than those undergoing LSG. The meta-analysis consisted mostly of short-term studies (Giustina et al. 2023). In another recent meta-analysis, the prevalence of deficiency after LRYGB was reported up to 42%, and the prevalence seemed to increase over time. However the meta-analysis reported severe heterogeneity in the results (Gao et al. 2023). Regarding LSG, a recent study reported 26.7% prevalence for insufficiency and 8.9% prevalence for deficiency that persisted up to 4 years postoperatively (Fox et al. 2020).

2.8.2.2 Calcium

MBS patients may suffer from postoperative hypocalcemia (Shah et al. 2017; Gasmi et al. 2022; Cao et al. 2023). In their retrospective analysis of 1000 patients, Shah et al. found the prevalence of hypocalcemia to be 3.6% after MBS, 9.3% after LSG and 1.9% after LRYGB. However, they reported presumable selection bias due to the fact that renal insufficiency patients tended to undergo LSG and were thus overrepresented in the LSG group (Shah et al. 2017). A meta-analysis by Cao et al. associated LSG with lower risk for calcium deficiency compared to LRYGB (Cao et al. 2023).

2.8.3 Effect on anemia and related micronutrient status

2.8.3.1 Anemia

MBS patients are known to suffer from anemia (Lewis et al. 2020; Weng et al. 2015; Johansson et al. 2021; Nie et al. 2023). A meta-analysis on LSG studies by Nie et al. found an anemia prevalence of 18% at 5 years after LSG (Nie et al. 2023). In the Swedish Obese Subjects (SOS) study, the anemia prevalence after LRYGB was 17.7% at 20 years. LRYGB was associated with 69% cumulative anemia incidence compared to 24% in the non-surgical control group after 20 years of follow-up (Johansson et al. 2021). No difference in anemia prevalence was found between LSG and LRYGB in a meta-analysis of short-term RCTs (Kwon et al. 2022). At next, we will delve into micronutrient deficiencies contributing to anemia.

2.8.3.2 Iron

Iron deficiency is the most common cause of anemia. It is also prevalent after MBS (Lewis et al. 2020; Weng et al. 2015; Nie et al. 2023; Johansson et al. 2021). Studies on iron deficiency have heterogeneity in applied markers which include serum or plasma iron, transferrin saturation and ferritin. Out of these, ferritin is the one recommended by WHO (WHO 2020). However, ferritin has its limitations, as it might increase due to inflammatory response (Kernan et al. 2017). In the meta-analysis of Nie et al., the prevalence of low ferritin level was 27% at 5 years after LSG. After LRYGB, the combined prevalence of iron deficiency (measured as low transferrin saturation) and anemia at 20 years was 12.3% in the SOS study (Johansson et al. 2021). Sandvik et al. reported a low ferritin prevalence of 23.6% at 10 years after LRYGB (Sandvik et al. 2021). At short-term, no difference in iron deficiency between LSG and LRYGB has been detected by RCTs (Kwon et al. 2022).

2.8.3.3 Vitamin B12

Vitamin B12 deficiency is another cause of anemia. The deficiency has also other unpleasant possible impacts, such as neuropsychiatric symptoms and cutaneous manifestations (Langan et al. 2017). Previous research on LSG indicates that it does not cause vitamin B12 deficiency or at least the risk is small (Lewis et al. 2020; Nie et al. 2023). Nie et al. found the prevalence of deficiency to be 4% both at baseline and 5 years after LSG (Nie et al. 2023). It is known that LRYGB patients have an elevated risk of vitamin B12 deficiency in short- to mid-term (Lewis et al. 2020; Weng et al. 2015; Johansson et al. 2021). However, some studies indicate that the prevalence would decrease over follow-up (Weng et al. 2015; Johansson et al. 2021). In the SOS study, the prevalence of vitamin B12 deficiency increased from 1.7% at baseline to 19.3% at 2 years but thereafter decreased to 2.0% at 20 years (Johansson et al. 2021). Short-term RCTs have shown the prevalence of deficiency to be lower in patients undergoing LSG than LRYGB (Kwon et al. 2022).

2.8.3.4 Folate

The lack of folic acid may result in anemia. It is also an important vitamin in pregnancy as deficiency predisposes lead to neural tube defects in foetus (Slater et al. 2017). Research indicates that LSG and LRYGB do not increase the prevalence of folate deficiency (Nie et al. 2023; Weng et al. 2015; Lewis et al. 2020). In the recent meta-analysis by Kwon et al., there was no difference between the procedures in folate deficiency. However, long-term data on post-bariatric folate deficiency is lacking.

2.8.4 Effect on mineral status

2.8.4.1 Magnesium

Magnesium is a mineral participating in various cellular level functions and its deficiency causes unspecific symptoms like fatigue, muscle cramps, and muscle weakness (Touyz et al. 2024). As stated previously, obesity and T2D are associated with magnesium deficiency (Piuri et al. 2021). The meta-analysis by Cao et al. found that MBS increased magnesium levels. The prevalence of magnesium deficiency in their long-term subgroup was 5.8% after any MBS (Cao et al. 2023).

2.8.4.2 Phosphorus

Phosphorus is required for cellular energy metabolism, synthesis of numerous biomolecules and producing apatite in bone. The deficiency symptoms include bone loss, muscle weakness, neurological symptoms, anemia, and metabolic acidosis (Wagner 2024). Cao et al. found the prevalence of phosphorus deficiency to be 6.7% at long-term after any MBS. The meta-analysis showed that LSG patients seemed to have lower risk for deficiency compared to LRYGB (Cao et al. 2023).

2.8.5 Micronutrient supplementation after metabolic bariatric surgery

To prevent the deficiencies, MBS patients are recommended to use micronutrient supplementation postoperatively. At present, these recommendations include calcium-vitamin D supplementation, vitamin B12 supplementation, multivitamin, and iron supplementation (Mechanick et al. 2019; O'Kane et al. 2020; Bruun et al. 2024). However, research has shown that poor adherence to supplementation after MBS is common at short- and long-term (Bjerkan et al. 2023; Spetz et al. 2022; Schiavo et al. 2017; James et al. 2016). In a large survey study in Netherlands, inconsistent multivitamin use was reported by 15.7% and no use at all by 7.4% regardless of time passed from surgery (Smelt et al. 2021). Bjerkan et al. reported adherence rates of 69% for vitamin D, 95% for vitamin B12, and 74% for multivitamin at 12 years after LRYGB (Bjerkan et al. 2023).

Spetz et al. identified young age, experienced side effects, mental health issues, and no regular medication before MBS as risk factors for poor adherence. They also found that non-adherence increased over time (Spetz et al. 2022). In the study by Smelt et al, the most common patient-reported reasons for poor adherence were forgetfulness, gastrointestinal side-effects and unpleasant taste or smell (Smelt et al. 2021).

Measuring adherence has its challenges. Self-reported data on adherence is subjective and the estimations on one’s own adherence may be overoptimistic. Data from prescription or reimbursement records is objective but may be difficult to obtain (Osterberg et al. 2005; Anghel et al. 2019). For example, in Finland, many of the micronutrient supplements are not reimbursed resulting in insufficient records as patients do not necessarily renew their prescriptions.

3 Aims

This doctoral thesis focuses on long-term effects after LSG and LRYGB regarding T2D and procedure selection, low-grade chronic inflammation, the prevalence of nutritional deficiencies, and the adherence to micronutrient supplements. The specific aims of the present study were:

1. To validate the IMS score and to assess whether it facilitates procedure selection and predicts remission of T2D for patients with severe obesity and T2D.

2. To evaluate the association of hs-CRP with weight loss at 10 years after LSG and LRYGB and to determine the feasibility of hs-CRP as a potential predictive marker for MBS weight loss outcomes.

3. To compare the prevalence of nutritional deficiencies and assess the adherence to micronutrient supplements at 10 years after LSG and LRYGB.

4 Patients and methods

4.1 Patients

4.1.1 The SLEEVEPASS trial

The SLEEVEPASS trial was initiated in 2008. It was implemented at three hospitals (Turku, Vaasa and Helsinki) in Finland involving 240 patients. Between March 2008 and June 2010, these patients were randomized to undergo either LSG or LRYGB. Randomization was executed with closed-envelope method with 1:1 allocation ratio. The SLEEVEPASS was the first largescale RCT comparing LSG and LRYGB.

Eligibility criteria comprised age 18 to 60 years, BMI greater than 40 kg/m^2 or greater 35 kg/m^2 with a significant obesity-associated comorbidity, and previous failed adequate conservative treatment of obesity. Exclusion criteria comprised BMI greater than 60 kg/m^2, significant psychiatric or eating disorder, active alcohol or substance abuse, active gastric ulcer disease, severe gastroesophageal reflux with a large hiatal hernia, and previous MBS.

Preoperatively, the patients were evaluated by a multidisciplinary team (an endocrinologist, a dietitian, and a surgeon). Psychiatric evaluation was performed when necessary. In addition, the patients underwent upper gastrointestinal endoscopy, abdominal ultrasound, and laboratory tests. Helicobacter pylori infection associated gastric ulcer disease and symptomatic gallstones were treated if diagnosed.

The patients received micronutrient supplementation recommendations postoperatively. These included oral multivitamin, oral calcium-vitamin D, and oral or intramuscular vitamin B12 supplementations. Iron supplementation was recommended only if iron deficiency was diagnosed.

4.1.2 The SLEEVEPASS and SM-BOSS trials merged

As mentioned, the SLEEVEPASS trial was the first largescale LSG and LRYGB -comparing RCT. Another similar RCT is the SM-BOSS trial with 225 patients. The patients were enrolled between 2007 and 2011 in four MBS centres in Switzerland. The SM-BOSS had the same inclusion criteria as the SLEEVEPASS trial. The exclusion criteria included previous bariatric surgery, contraindications for major gastrointestinal surgery, large hiatal hernia, severe symptomatic gastroesophageal reflux disease despite medication, history of inflammatory bowel disease, need for endoscopic follow-up of duodenum, and expected dense adhesions at the level of the small bowel.

Raw patient-level data of SLEEVEPASS and SM-BOSS trials were combined, and the results were standardised. Additional data was collected on T2D (preoperative duration of T2D and number of T2D medications).

4.2 Methods

4.2.1 Surgical techniques

4.2.1.1 LSG

The LSG included mobilizing of the stomach and dividing it into resected and preserved parts in an order preferred by the surgeon. The mobilization was performed by dissecting the short gastric vessels upward until the angle of His with Harmonic Scalpel™ (Ethicon Endo-Surgery, Cincinnati, OH, USA). The longitudinal resection of the stomach was executed along a 33-35 Fr calibration bougie using linear staplers (Covidien, Mansfield, MA, USA). The resection was initiated 4–6 cm proximal to the pylorus to preserve the majority of the antrum. At first, two sequential 4.8/60mm green-load firings were used for the antrum. Then, the resection was completed with sequential 3.5/60-mm blue-load firings (four on average) with all the staple lines reinforced.

4.2.1.2 LRYGB

To perform the LRYGB, a small gastric pouch (20–40 ml) was formed by dissecting along the lesser curvature using a Harmonic Scalpel™ and then dividing the stomach horizontally and vertically with linear staplers using reinforced 3.5/45 and 3.5/60mm (blue loads). The biliopancreatic limb was measured with graspers at 50–80 cm (50cm in SM-BOSS) distal to the ligament of Treitz. An antecolic end-to-side gastrojejunostomy was constructed as either a 25-mm circular stapler anastomosis (OrVilTM, Covidien) or a 3.5/45-mm blue-load linear stapler anastomosis depending on the surgeon’s preference. The omentum was not routinely transected. 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 running suture either manually or using EndoStitch™

(Covidien). The alimentary limb was measured with graspers 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. The opening in the anastomosis was closed depending on the surgeon's preference with either running suture or by using two reinforced 3.5/60-mm linear stapler firings with blue loads. The gastrojejunostomy was checked for leaks with a methylene blue test performed via a bougie while clamping the jejunal part of the anastomosis. The resulting mesenteric defects were not routinely closed at the time of the surgery.

4.2.2 Long-term follow-up

The predefined follow-up points of the SLEEVEPASS trial were 6 months, 1 year, 3 years, and 5 years. Since then, the follow-up has continued at 7 and 10 years and is planned to extend to 15 to 20 years. The 10-year follow-up was completed January 27th, 2021.

4.2.3 SLEEVEPASS primary endpoint

Weight loss, defined as percentage excess weight loss (%EWL), was the primary endpoint of the SLEEVEPASS trial. %EWL was calculated as (preoperative weight − follow-up weight) / (preoperative weight − ideal weight for BMI 25) × 100% (Brethauer et al. 2015). The primary endpoint was predefined to be evaluated at five years after surgery (Salminen et al. 2018). At 10 years, weight loss was measured additionally as percentage total weight loss (%TWL [preoperative weight – follow-up weight/preoperative weight x 100]) and as percentage excess BMI loss (%EBMIL) (Salminen et al. 2022).

4.2.4 IMS score calculations (Study I)

To conduct Study I, IMS score was calculated for patients with preoperative T2D in the merged RCT data of the SLEEVEPASS and the SM-BOSS. Calculations were based on four independent factors predicting the postoperative remission of T2D: the duration of T2D, the number of diabetes medications, insulin use, and glycemic control (glycated hemoglobin level, HbA1c < 7%). According to calculated scores, the patients were categorized into three T2D severity stages: mild (IMS ≤ 25), moderate (25 < IMS ≤ 95), and severe (IMS > 95) (Aminian et al. 2017). In each stage, the T2D remission rate was assessed at 5 years. Long-term T2D remission was defined according to the ADA consensus statement at the time of 5-year follow-up as HbA1c < 6.5%, fasting blood glucose 126 mg/dl, and off T2D medications at 5 years or more after surgery (Buse et al. 2009). In addition, changes in BMI and

%TWL were analyzed in T2D severity stages. Change in BMI was used to enable comparison with the original IMS score article (Aminian et al. 2017).

4.2.5 Hs-CRP measurements (Study II)

For Study II, CRP values were assayed with serum high-sensitivity CRP test (S-uCRP or S-hs-CRP) from blood samples collected from the trial patients preoperatively and at 6 months, 1, 3, 5, 7, and 10 years. The vast majority of the available values were from the patient cohort at Turku University hospital and a minority from Helsinki University Hospital. Hs-CRP tests were not included in the laboratory tests taken at Vaasa central hospital. The patients with available preoperative control value were included in the analysis. All hs-CRP values ≥ 25 were considered as signs of an acute infection or autoimmune disease activation and were therefore excluded from the analyses. Weight loss was defined as %TWL.

4.2.6 Nutritional outcomes (Study III)

4.2.6.1 Laboratory measurements

As mentioned, the 10-year follow-up of the SLEEVEPASS trial was completed in January 2021. The patients went through blood tests including the following nutritional measurements: serum or plasma 25-hydroxyvitamin D (S-25-D or P-25-D), serum or plasma ionized calcium (S-Ca-Ion or P-Ca-Ion), serum or plasma vitamin B12 (S-B12-Vit or P-B12-Vit), blood hemoglobin (B-Hb), plasma ferritin (P-Ferrit), plasma albumin (P-Alb), plasma magnesium (P-Mg) and plasma phosphorus (P-Pi). The reference values and ranges used by local laboratories were applied as follows: vitamin D deficient <25 nmol/l, insufficient 25-50 nmol/l, sufficient 50-75 nmol/l, and recommended 75-120 nmol/l. The reference range for ionized calcium was 1.15-1.30 mmol/l. The vitamin B12 reference range was 145-570 pmol/l. Anemia was defined as low hemoglobin with the following hemoglobin reference ranges: 117-155 g/l for women and 134-167 g/l for men. Iron status was measured using plasma ferritin with the reference ranges of 15-125 µg/l for women and 20-195 µg/l for men. For albumin, the reference range was 36-45 g/l, and for magnesium 0.71-0.94 mmol/l. For phosphorus, the reference range was 0.76-1.41 mmol/l for women, 0.71-1.53 mmol/l for men aged 18 to 49 years, and 0.71-1.23 mmol/l for men aged 50 years or older.

4.2.6.2 Questionnaire on supplement use

Questionnaires on micronutrient supplementation were collected from the patients. The included supplements were: multivitamin, calcium-vitamin D, vitamin B12, and iron. Per oral and intramuscular vitamin B12 supplements were not allocated. The questionnaire is included in the Appendices section of this dissertation.

4.2.7 Statistical analysis

In principle, all the analyses were conducted according to modified intention-to-treat, where the patients who never underwent surgery were excluded. In study III, the prevalence of nutritional deficiencies was additionally analyzed per-protocol. In the per-protocol analysis, the LSG patients who underwent conversion to LRYGB were analyzed in LRYGB group, and conversions to other procedures were excluded. Continuous variables were described as means with standard deviations (SD) or, if the data were skewed, as medians with 25th (Q1) and 75th (Q3) percentiles. Categorical variables were characterized using frequencies and percentages and tested using Pearson’s Chi Squared test or Fisher´s exact test when appropriate.

In study I, Non-parametric Kruskal-Wallis –test was used to test differences in continuous baseline variables between the IMS T2D severity stages. To enable comparison with the original publication, Pearson’s Chi Squared test was used to compare the remission rates of T2D between the operations separately in three severity stages, and one-way analysis of variance (ANOVA) was used to evaluate the differences in BMI between the severity stages separately in two operations. In addition, logistic regression analysis was used to evaluate the effect of T2D severity stage, operation, and percentage total weight loss (%TWL) on T2D remission. In contrast to the original article, %TWL was used in the model to represent the weight loss instead of change in BMI. In the severe T2D stage, there was no remission after LRYGB operation, and thus, the severe stage and the moderate stage were combined for the first reported model. The first model included T2D severity stage (severe and moderate stages combined), operation, %TWL, and interaction of severity stage and operation. The final model included only the main effects of T2D severity stage (original variable with three categories) and operation, because using this simple model enabled the use of severity stage with original categories. The results of logistic regression models were quantified using odds ratios (OR) with 95% confidence intervals (95% CIs). Missing observations were excluded from the analyses.

In study II, linear mixed models suitable for repeated measures were used to evaluate the differences between time-points and operations in hs-CRP. The final model included operation, time, BMI, and interaction of operation and time. The interaction of operation and time was not statistically significant, and therefore, the results are presented using main effects of operation and time. The results were quantified using model-based estimates with 95% confidence intervals (95% CI). Values of hs-CRP were not normally distributed, and logarithmic transformation was used in the analyses. The estimates were transformed back to the original scale. Tukey-Kramer-method was used to correct p-values of pairwise comparisons between the timepoints. The correlations between continuous variables were evaluated using Spearman's rank-order correlation coefficient.

In Study III, the difference between procedures and the effect of calcium-vitamin D supplement to the prevalence of vitamin D insufficiency was analyzed using logistic regression analysis including main effects of procedure and supplement use, and interaction of procedure and supplement use. In the analysis, the insufficiency prevalence was compared with the joint prevalence of sufficient and recommended level. The final model included only main effects, because interaction was not statistically significant. Results are presented using odds ratios (OR) with 95% confidence intervals (CI). The difference in mean vitamin B12 was evaluated using 2-way analysis of variance (ANOVA) with main effects of procedure and supplement use, and interaction of procedure and supplement use. If interaction was not statistically significant, the results were reported using main effects. Results of ANOVA were reported using least squares mean estimates with 95% CIs. Normality assumption was evaluated visually and using Kolmogorov-Smirnov-test. For vitamin B12, logarithmic transformation was used to achieve normality, and back-transformed least squares mean estimates were reported.

In all analyses, two-tailed p-values less than 0.05 were considered statistically significant. Statistical analyses were performed using SAS software, version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

4.2.8 Ethics

Both SLEEVEPASS and SM-BOSS study protocols were approved by the ethics committees of each participating hospital. The trials were designed in accordance with the principles of the Declaration of Helsinki and registered at the clinical trials registry of the National Institutes of Health at Clinicaltrials.gov (SLEEVEPASS NCT00793143; SM-BOSS NCT00356213). All patients gave written informed consent.

To ethically conduct a randomized study comparing two surgical procedures requires that both procedures have been proven safe. The idea of this type of study is to investigate whether the procedures are similarly effective or if one is better than the other. This implies that there is no strong evidence supporting one of the procedures. If one was known to be substantially more efficient, it would be unethical to not provide it for all patients. Randomizing surgical procedures is different than randomizing medication as drugs can often be easily switched if it is redeemed best for the patient. Surgical procedure however, should always aim to be nonrecurring. Although conversions are possible and sometimes necessary, every reoperation has risks.

5 Results

5.1 Study I: Validation of the IMS score for bariatric procedure selection in the merged data of SLEEVEPASS and SM-BOSS trials

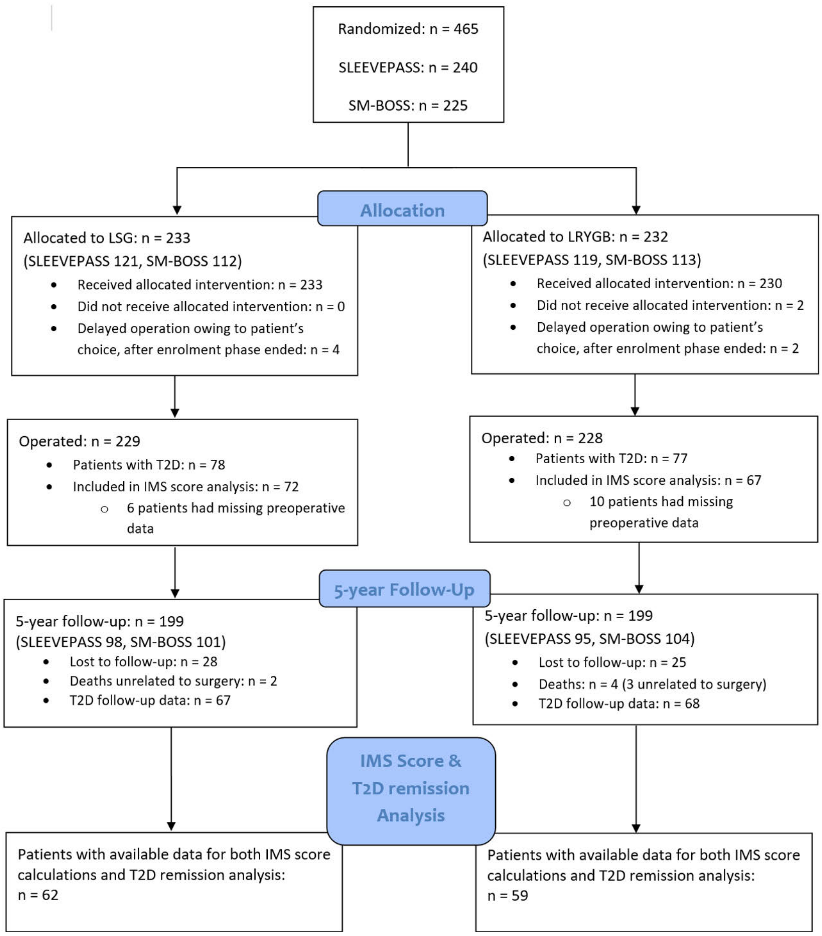

Figure 5. Flow diagram of the patients in the merged data of SLEEVEPASS and SM-BOSS included in study I. Reproduced with the permission of the copyright holders from the original study I.

A total of 155 patients had T2D at baseline, and out of these 139 (89.7%) had necessary preoperative data for IMS calculations. At 5 years, 135 patients with T2D (87.1%) were available for follow-up. The T2D remission rates were: 49.3% (33/67) after LSG, and 55.8% (38/68) after LRYGB (p=0.418). The flow of the patients is presented in **Figure 5**, and the baseline characteristics of the study patients are described in **Table 2**.

Table 2. Baseline characteristics of the patients in study I categorized by original study and operation. Reproduced with the permission of the copyright holders from the original study I.

	SM-BOSS	SLEEVEPASS	LSG	LRYGB
AGE (YEARS), MEAN (SD)	47.9 (10.3)	51.6 (8.1)	50.4 (8.9)	50.2 (9.2)
SEX: FEMALE/MALE, FREQUENCY (%)	30/24 (55.6%)	62/39 (61.4%)	43/35 (55.1%)	49/28 (63.6%)
BODY MASS INDEX, BMI (KG/M^2), MEAN (SD)	44.7 (10.3)	46.9 (6.2)	46.1 (6.2)	46.1 (6.0)
PREOPERATIVE DURATION OF T2D (YEARS), MEDIAN (Q_1-Q_3)	1.0 (0.5-7.0)	5.0 (2.0-8.0)	5.0 (1.1-7.5)	4.0 (1.0-7.0)
NO T2D MEDICATION, N (%)	17/44 (38.6%)	0/100 (0.0%)	9/75 (12.0%)	8/69 (11.6%)
1 T2D MEDICATION, N (%)	22/44 (50.0%)	51/100 (51.0%)	32/75 (42.7%)	41/69 (59.4%)
2 T2D MEDICATIONS, N (%)	5/44 (11.1%)	40/100 (40.0%)	31/75 (41.3%)	14/69 (20.3%)
3 T2D MEDICATIONS, N (%)	0/44 (0.0%)	8/100 (8.0%)	3/75 (4.0%)	5/75 (7.3%)
4 T2D MEDICATIONS, N (%)	0/44 (0.0%)	1/100 (1.0%)	0/75 (0.0%)	1/69 (1.5%)
INSULIN USE, N (%)	10/54 (18.5%)	32/101 (31.7%)	24/78 (30.7%)	18/77 (23.4%)
GLYCATED HEMOGLOBIN, HBA1C (%), MEDIAN (Q_1-Q_3)	6.8 (6.1-7.9)	6.6 (6.3-7.2)	6.7 (6.3-7.5)	6.6 (6.1-7.7)
GLYCEMIC CONTROL (HBA1C<7%), N (%)	31/51 (60.8%)	67/101 (66.3%)	51/77 (66.2%)	47/75 (62.7%)

5.1.1 IMS score calculations

The 139 patients with available preoperative data for calculating the IMS score were distributed among T2D severity stages as follows: 41/139 (29.5%) into mild stage, 77/139 (55.4%) into moderate stage, and 21/139 (15.1%) into severe stage. The baseline characteristics of the study patients according to severity stage are shown in **Table 3**.

Table 3. Baseline characteristics of patients categorized by T2D severity. Reproduced with the permission of the copyright holders from the original study I.

	MILD (N=41)		MODERATE (N=77)		SEVERE (N=21)	
	LSG (N=19)	LRYGB (N=22)	LSG (N=41)	LRYGB (N=36)	LSG (N=12)	LRYGB (N=9)
AGE (YEARS), MEAN (SD)	46.4 (9.2)	50.6 (11.0)	52.2 (8.0)	49.2 (8.0)	51.8 (8.0)	52.5 (9.7)
SEX: FEMALE/MALE, N (%)	12/7 (63.2%)	15/7 (68.2%)	24/17 (58.5%)	22/14 (61.1%)	5/7 (41.7%)	7/2 (77.8%)
BODY MASS INDEX (KG/M^2), MEAN (SD)	47.6 (6.4)	47.8 (5.7)	46.1 (6.4)	46.8 (6.4)	42.6 (6.0)	43.8 (6.2)
GLYCATED HEMOGLOBIN, HBA1C (%), MEDIAN (Q_1-Q_3)	6.2 (5.8-6.7)	6.1 (5.7-6.5)	6.7 (6.4-7.0)	6.8 (6.2-7.7)	8.6 (7.4-9.7)	8.7 (8.2-9.7)
PREOPERATIVE DURATION OF T2D (YEARS), MEDIAN (Q_1-Q_3)	1.0 (0.5-1.5)	1.0 (0.5-1.0)	5.0 (4.0-7.0)	5.0 (4.0-7.0)	11.0 (8.0-20.5)	15.0 (13.0-26.0)
NO T2D MEDICATION, N (%)	7/19 (36.8%)	8/22 (36.4%)	1/41 (2.4%)	0/36 (0.0%)	0/12 (0.0%)	0/9 (0.0%)
1 T2D MEDICATION, N (%)	12/19 (63.2%)	14/22 (63.6%)	19/41 (46.3%)	22/36 (61.1%)	0/12 (0.0%)	4/9 (44.4%)
2 T2D MEDICATIONS, N (%)	0/19 (0.0%)	0/22 (0.0%)	20/41 (48.8%)	10/36 (27.8%)	10/12 (83.3%)	3/9 (33.3%)
3 T2D MEDICATIONS, N (%)	0/19 (0.0%)	0/22 (0.0%)	1/41 (2.4%)	4/36 (11.1%)	2/12 (16.67%)	1/9 (11.1%)
4 T2D MEDICATIONS, N (%)	0/19 (0.0%)	0/22 (0.0%)	0/41 (0.0%)	0/36 (0.0%)	0/12 (0.0%)	1/9 (11.1%)
INSULIN USE, N (%)	0/19 (0.0%)	0/22 (0.0%)	10/41 (24.4%)	7/36 (19.4%)	12/12 (100.0%)	9/9 (100.0%)
GLYCEMIC CONTROL (HBA1C<7%), N (%)	18/19 (94.7%)	22/22 (100.0%)	8/41 (68.3%)	19/36 (52.8%)	1/12 (8.3%)	1/9 (11.1%)

5.1.2 T2D remission rates by operation and severity stage

There were altogether 121 patients that had the necessary data on preoperative factors for IMS score calculation and T2D remission at 5 years. Of these, 52.6% (63/121) had complete remission of T2D at 5 years. The remission rates in each severity stage were 86.5% (32/37) in the mild stage, 43.9% (29/66) in the moderate stage, and 11.1% (2/18) in the severe stage ($p<0.001$). The mild stage had the highest likelihood for T2D remission (mild versus moderate OR, 8.3; 95% CI, 2.8–24.0; $p<0.001$ and mild versus severe OR, 52.2; 95% CI, 9.0–302.3; $p<0.001$). The moderate and the severe stages also differed statistically significantly in the odds for T2D remission (OR, 6.3, 95% CI, 1.3–29.8; $p<0.020$).

The remission rates according to T2D severity stage and operation are presented in **Table 4**. In the logistic regression analysis for T2D remission, interaction of severity stage (severe and moderate stages combined), and operation was not statistically significant (p=0.524). Therefore, no further analyses were performed to test the difference between the operations separately in the severity stages.

Table 4. T2D remission rates on severity stages according to operation. Reproduced with the permission of the copyright holders from the original study I.

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

*Fisher's exact test.

5.1.3 Weight loss by operation and severity stage

The BMI change at 5 years differed statistically significantly between severity stages in patients who underwent LRYGB (p=0.043). The greatest BMI loss was in the mild stage. Regarding LSG patients, there were no statistically significant differences (p=0.454) in the BMI change between the T2D severity categories. The change in BMI from baseline to 5 years after LSG or LRYGB according to T2D severity is shown in **Table 5**. The overall effect of %TWL on T2D remission was statistically significant (p=0.001) and greater %TWL was associated with greater odds for remission (OR, 1.1; 95% CI, 1.0–1.2).

Table 5. BMI at baseline and at 5 years by severity stage and operation. Reproduced with the permission of the copyright holders from the original study I.

BMI, MEAN (SD)	LRYGB				LSG			
	Mild	Moderate	Severe	P*	Mild	Moderate	Severe	P*
BASELINE	47.8 (5.7)	46.8 (6.4)	43.8 (6.2)	0.275	47.6 (6.4)	46.1 (6.4)	42.9 (6.0)	0.137
5 YEARS	33.25 (5.5)	34.8 (6.1)	35.1 (5.0)	0.586	36.6 (6.4))	37.6 (5.9)	33.3 (6.7)	0.172
CHANGE FROM BASELINE	-14.6 (6.1)	-11.6 (4.2)	-10.0 (3.5)	0.043	-11.0 (5.6)	-9.3 (4.1)	-10.4 (4.5)	0.454

*One-way analysis of variance.

5.2 Study II: Association of hs-CRP with weight loss after LSG and LRYGB at 10 years: A secondary analysis of the SLEEVEPASS trial

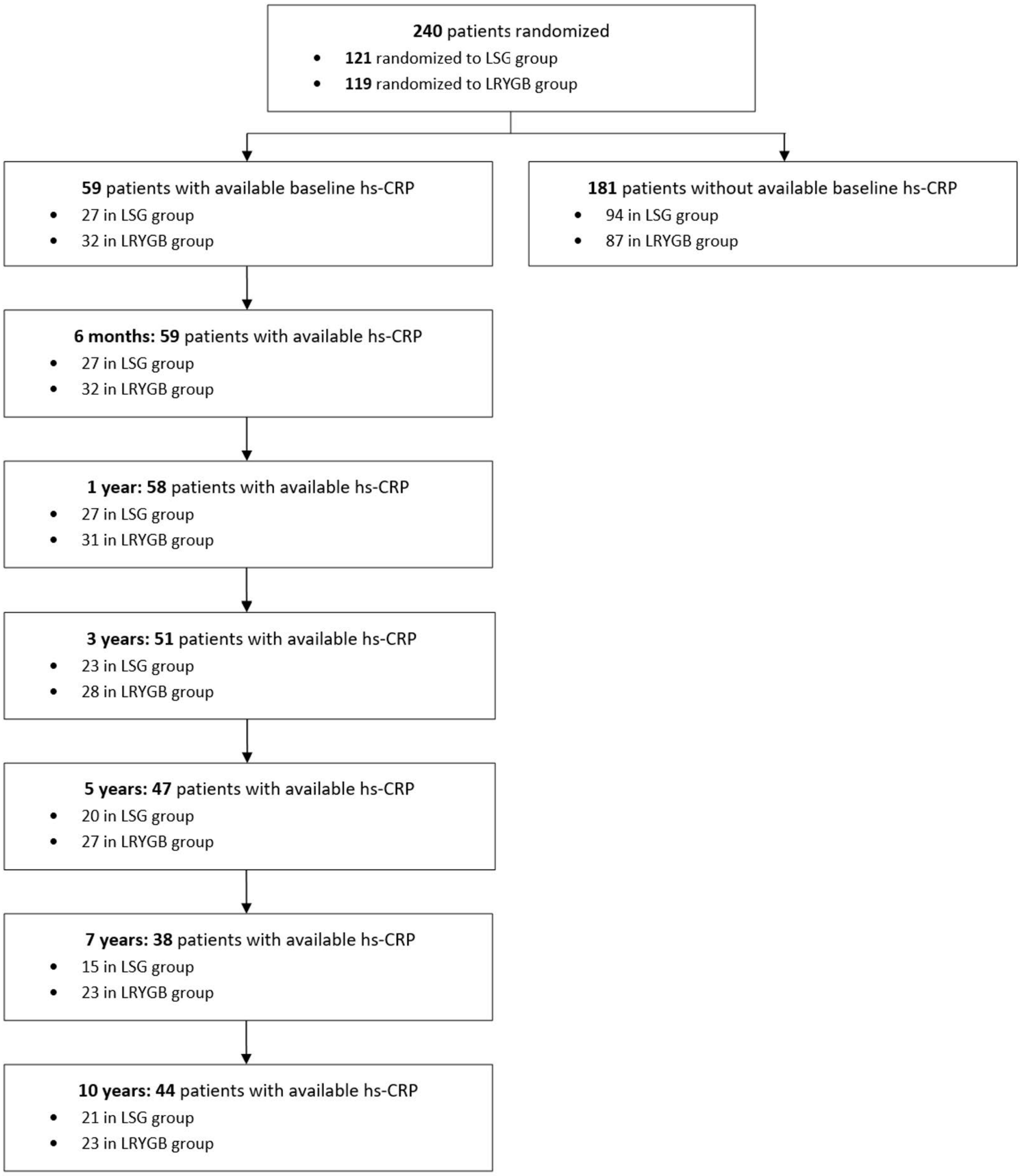

Figure 6. Flow of patients in Study II. Reproduced with the permission of the copyright holders from the original study II.

Out of 240 SLEEVEPASS study patients, 59 (24,6%) had available baseline hs-CRP value (56 at Turku University hospital, 3 patients at Helsinki University hospital). Of these, 27 were randomized to LSG and 32 to LRYGB. The flow of patients is presented in **Figure 6**, and the baseline characteristics of the patients included in study II are shown in **Table 6**.

Table 6. Baseline characteristics of the patients with available hs-CRP at baseline. Reproduced with the permission of the copyright holders from the original study II.

	LSG	LRYGB	ALL INCLUDED PATIENTS	EXCLUDED PATIENTS	P INCLUDED VS. EXCLUDED
N	27	32	59	181	NA
AGE (YEARS), MEAN (SD)	46.7 (8.6)	47.2 (10.1)	47.0 (9.4)	48.9 (9.3)	0.945†
FEMALE, N (%)	18/27 (66.7%)	20/32 (62.5%)	38/59 (64.4%)	129/181 (71.3%)	0.332*
MALE, N (%)	9/27 (33.3%)	12/32 (37.5%)	21/59 (35.6%)	52/181 (28.7%)	0.332*
BODY MASS INDEX, BMI (KG/M^2), MEAN (SD)	47.3 (5.9)	48.9 (7.8)	48.2 (7.0)	47.8 (6.9)	0.896†
T2D, N (%)	13/27 (48.2%)	15/32 (46.9%)	28/59 (47.5%)	73/181 (40.3%)	0.364*
BLOOD PRESSURE MEDICATION, N (%)	15/27 (55.6%)	24/32 (75.0%)	39/59 (66.1%)	131/181 (72.4%)	0.410*
HIGH LDL / CHOLESTEROL MEDICATION, N (%)	7/27 (25.9%)	11/32 (34.4%)	18/59 (30.5%)	66/181 (36.5%)	0.436*
CPAP-TREATED OSAS, N (%)	5/27 (18.5%)	10/32 (31,3%)	15/59 (25.4%)	48/181 (26.5%)	0.134*
HS-CRP (MG/L), MEDIAN (Q_1-Q_3)	5.5 (2.7-8.2)	4.0 (2.8-5.5)	4.2 (2.8-7.0)	NA	NA

*Fisher's exact test
†Analysis of variance

5.2.1 Hs-CRP through 10 years after LSG and LRYGB

Table 7. Mean hs-CRP at follow-up points and the effects of operation and time. Reproduced with the permission of the copyright holders from the original study II.

<table>
<tr><th colspan="5">ALL STUDY PATIENTS</th></tr>
<tr><th>FOLLOW-UP POINT</th><th colspan="2">Hs-CRP (mg/mL), mean estimate (95% CI)*</th><th>P compared to baseline†</th><th>P compared to 3 years†</th></tr>
<tr><td>BASELINE</td><td colspan="2">2.06 (1.48-2.86)</td><td>NA</td><td>0.043</td></tr>
<tr><td>6 MONTHS</td><td colspan="2">1.92 (1.49-2.48)</td><td>0.999</td><td>0.002</td></tr>
<tr><td>1 YEAR</td><td colspan="2">1.42 (1.09-1.85)</td><td>0.518</td><td>0.680</td></tr>
<tr><td>3 YEARS</td><td colspan="2">1.14 (0.87-1.49)</td><td>0.043</td><td>NA</td></tr>
<tr><td>5 YEARS</td><td colspan="2">1.81 (1.38-2.38)</td><td>0.994</td><td>0.026</td></tr>
<tr><td>7 YEARS</td><td colspan="2">1.90 (1.42-2.56)</td><td>0.999</td><td>0.023</td></tr>
<tr><td>10 YEARS</td><td colspan="2">1.38 (1.05-1.81)</td><td>0.286</td><td>0.858</td></tr>
<tr><th colspan="5">OPERATION COMPARISON (OVER TIME)</th></tr>
<tr><th></th><th></th><th>Main effect of operation*</th><th>Main effect of time*</th><th>Operation*time interaction*</th></tr>
<tr><td>LSG</td><td>2.5 (1.48-3.4)</td><td rowspan="2"><0.001</td><td rowspan="2">0.001</td><td rowspan="2">0.540</td></tr>
<tr><td>LRYGB</td><td>1.0 (0.8-1.4)</td></tr>
</table>

*Linear mixed models were used. Results were adjusted for BMI. Logarithmic transformation was used in the analyses and estimates were transformed back to the original scale. †Tukey-Kramer -method

At baseline, hs-CRP was the highest (mean estimate 2.06, 95% CI 1.48-2.86). There was a decrease after surgery, and hs-CRP reached its lowest point at 3 years (mean estimate 1.14mg/L, 95% CI 0.87-1.49). Hs-CRP differed statistically significantly between the follow-up points ($p<0.001$). Compared to baseline, there was a statistically significant difference in hs-CRP only at 3 years ($p=0.043$). After 3 years, hs-CRP increased until 7 years (mean estimate 1.90mg/L, 95% CI 1.42-2.56). From 7 to 10 years, a slight decrease was seen (mean estimate 1.38mg/L, 95% CI 1.05-1.81).

There was no statistically significant difference between the operations in hs-CRP change over time (operation*time interaction $p=0.540$). Hs-CRP decreased after both procedures, but it was higher through the whole 10-year follow-up in LSG group (main effect of operation $p<0.001$). Results were adjusted for BMI to enable the evaluation of the effect of operation. The hs-CRP over time with effect of operation and time are presented in **Table 7**, and the hs-CRP trajectory through 10 years of follow-up is presented in **Figure 7**.

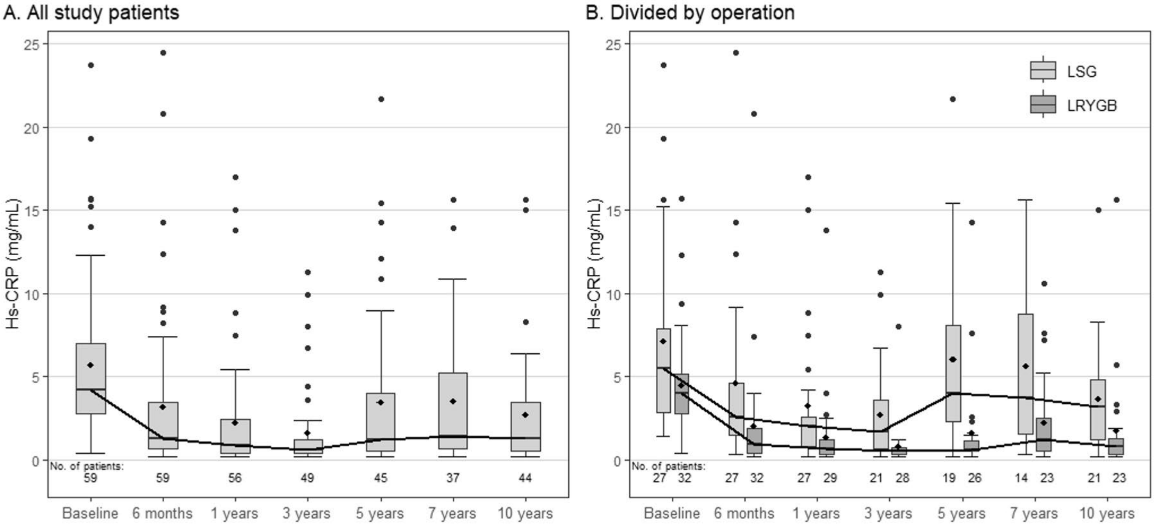

Figure 7. Hs-CRP through 10-year follow-up. Reproduced with the permission of the copyright holders from the original study II. The lower and upper hinges correspond to the first and third quartiles (the 25th and 75th percentiles) and whiskers indicate smallest observation greater than or equal to lower hinge - 1.5* IQR and largest observation less than or equal to upper hinge + 1.5* IQR. Dots indicate outliers.

5.2.2 Association of hs-CRP with weight loss

At 10 years, a greater %TWL had statistically significant correlation with lower 10-year-hs-CRP (Spearman correlation -0.558, p<0.001). The preoperative hs-CRP correlated statistically significantly with preoperative BMI (Spearman correlation 0.282, p=0.030). At 10 years, there was also a statistically significant correlation between hs-CRP and the present BMI (Spearman correlation 0.490, p=0.001).

5.2.3 Hs-CRP as a predictive marker for metabolic bariatric surgery outcomes

The baseline hs-CRP level did not correlate statistically significantly with %TWL at 10 years (Spearman correlation -0.152, p=0.299). To same extent, the hs-CRP change in the first 6 months postoperatively had no statistically significant correlation with the 10-year-%TWL (Spearman correlation 0.167, p=0.254).

5.3 Study III: Nutritional deficiencies after LSG and LRYGB at 10 years: A secondary analysis of the SLEEVEPASS trial

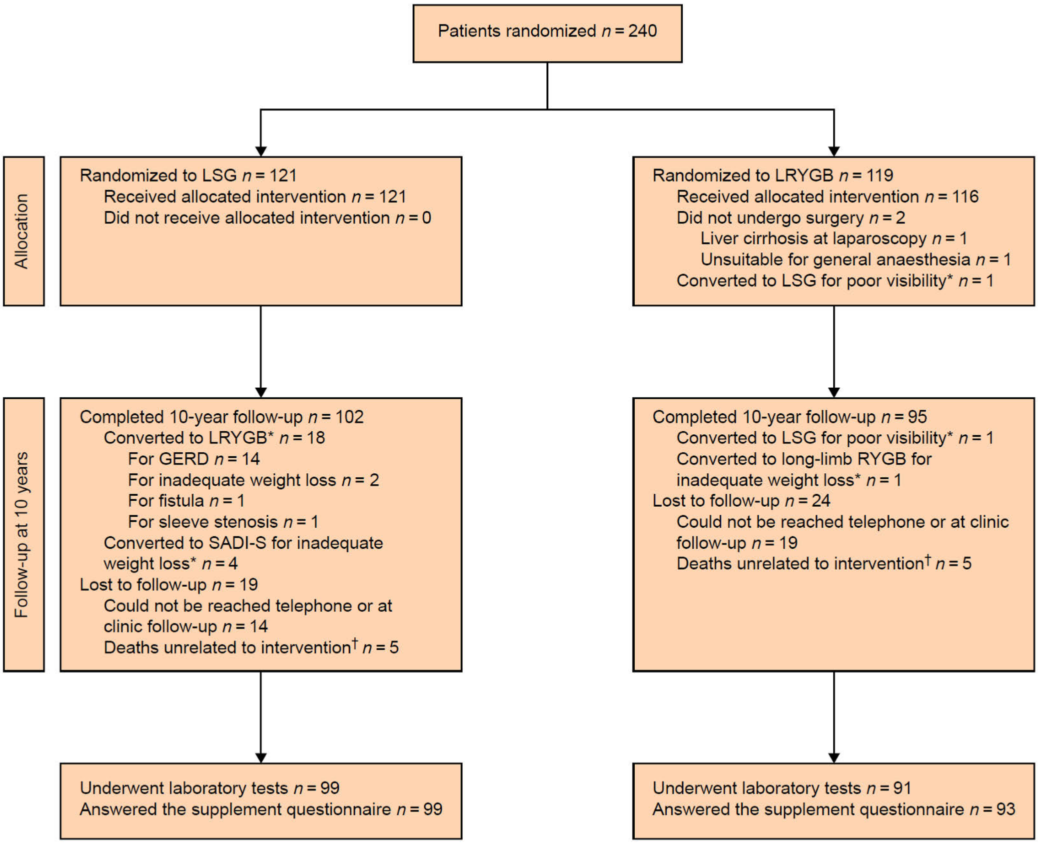

Figure 8. The flow of patients in study III. Reproduced with the permission of the copyright holders from the original study III.
[a]Analyzed according to intention-to-treat.
[b]The specific causes of death were: 1 traffic incident, 1 drowning, 1 ketoacidosis, 1 pulmonary embolism, 1 uterine cancer, 1 cholangiocarcinoma, 1 lung cancer, 1 pancreatic cancer, and 2 alcohol overdoses.

The patient flow of study III is presented in **Figure 8**. Of the 240 patients enrolled in the SLEEVEPASS trial, 2 patients never underwent surgery, and during the 10-year follow-up, there were 10 deaths unrelated to surgery. Out of the remaining 228 patients, 197 (86.4%) were available for 10-year follow-up and out of these, 190 patients (83.3%) underwent laboratory tests and 192 (84.2%) answered the supplement questionnaire. The baseline characteristics of the patients are described in **Table 8**. The number of laboratory results available at 10 years are described in **Table 9**.

Table 8. The baseline characteristics of the patients in the SLEEVEPASS trial. Reproduced with the permission of the copyright holders of the original study (Salminen et al. 2022).

	LSG	LRYGB
Female, N (%)	87 (71.9)	80 (67.2)
Male, N (%)	34 (28.1)	39 (32.8)
Age (Years), Mean (Sd)	48.5 (9.6)	48.4 (9.3)
Weight (Kg), Mean (Sd)	130.1 (21.5)	134.9 (22.5)
BMI (Kg/M^2), Mean (Sd)	45.5 (6.2)	46.4 (5.9)
T2D, N (%)	52 (43.0)	49 (41.2)
Hypertension, N (%)	83 (68.6)	87 (73.1)
Dyslipidemia, N (%)	39 (32.2)	45 (37.8)
Hospitals participating in the study		
Turku	40	40
Vaasa	40	40
Helsinki	41	39

Table 9. The number of laboratory results available at 10 years with means and medians. Reproduced with the permission of the copyright holders from the original study III.

	ALL STUDY PATIENTS		LSG		LRYGB		P
	N	Mean (SD) / Median (Q_1, Q_3)	N	Mean (SD) / Median (Q_1, Q_3)	N	Mean (SD) / Median (Q_1, Q_3)	
VITAMIN D (NMOL/L), MEAN (SD)	178	75.3 (22.3)	94	77.6 (24.0)	84	72.6 (19.9)	0.132*
CALCIUM, (MMOL/L), MEAN (SD)	175	1.23 (0.05)	92	1.24 (0.05)	83	1.23 (0.04)	0.095*
VITAMIN B12 (PMOL/L), MEDIAN (Q_1, Q_3)	91	396 (271, 513)	46	386 (282, 471)	45	433 (253, 543)	0.609†
HEMOGLOBIN (G/L), MEAN (SD)	189	135.2 (14.3)	91	136.8 (15.0)	98	133.5 (13.4)	0.119*
FERRITIN (µG/L), MEDIAN (Q_1, Q_3)	58	28.0 (15.0, 62.0)	29	34.0 (20.0, 54.0)	29	20.0 (12.0, 117.0)	0.397†
MAGNESIUM (MMOL/L), MEAN (SD)	178	0.84 (0.09)	93	0.83 (0.09)	85	0.85 (0.1)	0.176*
PHOSPHORUS (MMOL/L), MEAN (SD)	166	1.03 (0.15)	88	1.00 (0.14)	78	1.06 (0.15)	0.011*
ALBUMIN (G/L), MEAN (SD)	184	37.8 (3.4)	97	37.8 (3.05)	87	37.8 (3.9)	0.930*

*Paired t-test
†Mann-Whitney U test

The nutrient levels categorized by reference range and the prevalence of nutritional deficiencies are presented in detail in **Table 10**. The per-protocol analysis results are shown in the corresponding table (**Appendix 2**). The results were similar to the intention-to-treat analysis except for iron deficiency. The use of micronutritional supplements is described in **Table 11**. LSG patients had lower overall adherence to supplements [70/99 (70.7%) vs 83/93 (89.3%), p=0.002].

Table 10. Nutrient values categorized by reference ranges at 10 years. Reproduced with the permission of the copyright holders from the original study III.

	ALL STUDY PATIENTS	LSG	LRYGB	P*
VITAMIN D (NMOL/L)	**N (%)**	**N (%)**	**N (%)**	
<25	0/178 (0.0)	0/94 (0.0)	0/84 (0.0)	
25-50	19/178 (10.7)	10/94 (10.6)	9/84 (10.7)	
51-74	73/178 (41.0)	35/94 (37.2)	38/84 (45.2)	0.413
75-120	80/178 (44.9)	44/94 (46.8)	36/84 (42.9)	
>120	6/178 (3.4)	5/94 (5.3)	1/84 (1.2)	
CALCIUM (MMOL/L)				
<1.15	4/175 (2.3)	3/92 (3.3)	1/83 (1.2)	
1.15-1.30	163/175 (93.1)	82/92 (89.1)	81/83 (97.6)	0.088
>1.3	8/175 (4.6)	7/92 (7.6)	1/83 (1.2)	
VITAMIN B12 (PMOL/L)				
<145	2/91 (2.2)	2/46 (4.6)	0/45 (0.0)	
145-570	71/91 (78.0)	37/46 (80.4)	34/45 (75.6)	0.240
>570	18/91 (19.8)	7/46 (15.2)	11/45 (24.4)	
HEMOGLOBIN (G/L)				
UNDER RL	30/189 (15.9)	15/98 (15.3)	15/91 (16.5)	
WITHIN RLS	155/189 (82.0)	80/98 (81.6)	75/91 (82.4)	0.783
OVER RL	4/189 (2.1)	3/98 (3.1)	1/91 (1.1)	
FERRITIN (µG/L)				
UNDER RL	16/58 (27.6)	4/29 (13.8)	12/29 (41.4)	
WITHIN RLS	35/58 (60.3)	23/29 (79.3)	12/29 (41.4)	0.017
OVER RL	7/58 (12.1)	2/29 (6.9)	5/29 (17.2)	
ALBUMIN (G/L)				
<36	47/184 (25.5)	25/97 (25.8)	22/87 (25.3)	
36-45	134/184 (72.8)	70/97 (72.2)	64/87 (73.6)	>0.999
>45	3/184 (1.6)	2/97 (2.1)	1/87 (1.2)	
MAGNESIUM (MMOL/L)				
<0.71	10/178 (5.6)	6/93 (6.5)	4/85 (4.7)	
0.71-0.94	152/178 (85.4)	80/93 (86.0)	72/85 (84.0)	0.770
>0.94	16/178 (9.0)	7/93 (7.5)	9/85 (10.6)	
PHOSPHORUS, (MMOL/L)				
UNDER RL	4/166 (2.4)	3/88 (3.4)	1/78 (1.3)	
WITHIN RLS	159/166 (95.8)	84/88 (95.5)	75/78 (96.2)	0.606
OVER RL	3/166 (1.8)	1/88 (1.1)	2/78 (2.6)	

* Fisher's exact test
Abbreviations: RL; Reference limit

Table 11. Descriptives of micronutritional supplement use. Reproduced with the permission of the copyright holders from the original study III.

SUPPLEMENT	ALL STUDY PATIENTS	LSG	LRYGB	P*
MULTIVITAMIN, FREQUENCY (%)	116/191 (60.7)	50/98 (51.0)	66/93 (71.0)	0.005
CALCIUM-VITAMIN D, FREQUENCY (%)	130/191 (68.1)	58/98 (59.2)	72/97 (77.4)	0.008
VITAMIN B12, FREQUENCY (%)	80/190 (42.1)	28/97 (28.9)	52/93 (55.9)	<0.001
IRON, FREQUENCY (%)	17/189 (9.0)	4/96 (4.2)	13/93 (14.0)	0.022

*Fisher's exact test

5.3.1 Vitamin D

The prevalence of vitamin D insufficiency did not differ statistically significantly between LSG and LRYGB at 10 years [10/94 (10.6%) vs 9/84 (10.7%), OR 0.7; 95% CI 0.3 to 2.0; respectively, p=0.545]. Patients adherent to calcium-vitamin D supplement had statistically significantly less vitamin D insufficiency than non-adherent patients [8/121 (6.6%) vs 11/54 (20.4%), OR 0.3; 95% CI 0.1 to 0.7; p=0.008]. The effect of supplementation on insufficiency prevalence did not differ statistically significantly between the procedures (operation*supplementation interaction p=0.340). The descriptives of vitamin D and calcium levels by adherence to supplements are shown in **Table 12**.

Table 12. Vitamin D and calcium levels by adherence to calcium-vitamin D supplement. Reproduced with the permission of the copyright holders from the original study III.

	ALL STUDY PATIENTS, N (%)		LSG, N (%)		LRYGB, N (%)	
	Non-adherent	Adherent	Non-adherent	Adherent	Non-adherent	Adherent
VITAMIN D, NMOL/L						
MEAN (SD)	68.3 (24.0)	77.5 (19.9)	72.7 (25.8)	79.0 (20.7)	58.8 (16.3)	76.3 (19.4)
CATEGORIZED BY RLS						
25-50	11/54 (20.4)	8/121 (6.6)	6/37 (16.2)	4/55 (7.3)	5/17 (29.4)	4/66 (6.1)
51-74	25/54 (46.3)	47/121 (38.8)	16/37 (43.2)	19/55 (34.1)	9/17 (52.9)	28/66 (42.4)
75-120	16/54 (29.6)	64/121 (52.9)	13/37 (35.1)	31/55 (56.4)	3/17 (17.7)	33/66 (50.0)
>120	2/54 (3.7)	2/121 (1.7)	2/37 (5.4)	1/55 (1.8)	0/17 (0.0)	1/66 (1.5)
CALCIUM, MMOL/L						
<1.15	1/50 (2.0)	2/121 (1.7)	1/34 (2.9)	1/56 (1.8)	0/16 (0.0)	1/65 (1.5)
1.15-1.30	46/50 (92.0)	115/121 (95.0)	30/34 (88.2)	51/56 (91.1)	16/16 (100.0)	64/65 (98.5)
>1.3	3/50 (6.0)	4/121 (3.3)	3/34 (8.8)	4/56 (7.1)	0/16 (0.0)	0/65 (0.0)

5.3.2 Vitamin B12

The estimated mean vitamin B12 after LSG was 372 pmol/l (95% CI 302 to 459 pmol/l) and 379 pmol/l (95% CI 318 to 444 pmol/l) after LRYGB (p=0.939). There was no difference in the mean estimate of vitamin B12 in patients adherent to vitamin B12 supplements compared with non-adherent patients [398 pmol/l (95%CI 322 to 493 pmol/l) vs. 351 pmol/l (95% CI 299 to 412 pmol/l), respectively, p=0.348)]. There was no statistically significant difference in the effect of supplement use between the procedures (operation*supplementation interaction p=0.120). The descriptives of vitamin B12 level by adherence to supplements are shown in **Table 13**.

Table 13. Vitamin B12 level by adherence to supplement. Reproduced with the permission of the copyright holders from the original study III.

	ALL STUDY PATIENTS, N (%)		**LSG, N (%)**		**LRYGB, N (%)**	
VITAMIN B12, PMOL/L	**Non-adherent**	**Adherent**	**Non-adherent**	**Adherent**	**Non-adherent**	**Adherent**
MEDIAN (Q1, Q3)	365 (271, 459)	472 (273, 667)	389 (298, 1326)	377 (243, 510)	303 (227, 429)	505 (273, 669)
CATEGORISED BY RLS						
<145	1/51 (2.0)	1/37 (2.7)	1/35 (2.9)	1/8 (12.5)	0/16 (0.0)	0/29 (0.0)
145-570	44/51 (86.3)	24/37 (64.9)	29/35 (82.7)	5/8 (62.5)	15/16 (93.8)	19/29 (65.5)
>570	6/51 (11.8)	12/37 (32.4)	5/35 (14.3)	2/8 (25.0)	1/16 (6.25)	10/29 (34.5)

5.3.3 Anemia and iron

There was no statistically significant difference in anemia prevalence presented by low hemoglobin between the procedures [15/98 (15.3%) after LSG vs. 15/91 (16.5%) after LRYGB, p=0.783]. After LSG, the prevalence of iron deficiency measured by ferritin level was statistically significantly lower compared with LRYGB [4/29 (13.8%) vs. 12/29 (41.4%), p=0.017]. In the per protocol analysis (**Appendix 2**), the difference was not statistically significant [LSG 3/20 (15.0%) vs. LRYGB 12/37 (32.4%), p=0.283]. The median ferritin level was 34 µg/l (Q1 20µg/l, Q3 54 µg/l) in LSG group and 20 µg/l (Q1 12 µg/l, Q3 117 µg/l) in LRYGB group (p=0.397). There was no statistically significant association between ferritin deficiency and anemia (p=0.283).

6 Discussion

6.1 IMS score in MBS procedure selection and predicting T2D remission

In study I, the IMS score performed well in predicting T2D remission. A higher IMS score indicating a more severe T2D correlated with decreased probability of remission. However, the present study did not show statistically significant differences in remission rate between LSG and LRYGB at any of the severity stages suggesting that IMS score may not be feasible for aiding procedure selection.

To our knowledge, study I is the only validation of the IMS score within a randomized setting. There is contradiction between this study and the original IMS score paper. Aminian et al. found that LRYGB had superior remission rate in patients with moderate IMS score at 5 years recommending LRYGB for these patients (Aminian et al. 2017). The original study used retrospective data and thus selection bias may have occurred. In study I, the randomized setting mitigates selection bias.

Similarly to our study I, a retrospective study by Chen et al. showed no difference in T2D remissions between the procedures in moderate stage. They speculated that their study might have been affected by Asian ethnicity and lower preoperative BMI (Chen et al. 2018). Ethnicity and baseline BMI in the merged data of SLEEVEPASS and SM-BOSS (Wölnerhanssen et al. 2021) used in study I are more similar to the original IMS dataset (Aminian et al. 2017).

In another retrospective study by Ohta et al., LSG had more T2D remissions than LRYGB in moderate severity stage. Their analysis showed that BPD-DS was the most effective treatment of moderate T2D (Ohta et al. 2021).

In line with study I, IMS score has been found accurate in predicting T2D remission by many other studies (Plaeke et al. 2021; Shen et al. 2019; Ghusn et al. 2024). The present study did not find statistically significant difference in overall T2D remissions between LSG and LRYGB. This is in line with the most recent meta-analysis of RCTs comparing the two procedures (Uhe et al. 2022) and the large RCT by Biter et al (Biter et al. 2024). However, larger long-term RCTs or individual patient data meta-analysis are required to assess this with sufficient statistical power.

The effect of weight loss on T2D remission was analysed with both change in BMI and TWL%. Change in BMI comparison between the severity stages was applied by the original IMS article (Aminian et al. 2017). However, TWL% is currently the recommended measure of weight loss and therefore it was used in our advanced model. Our result does not support the association between weight loss and T2D remission adding to the contradictive literature on the matter (Panunzi et al. 2015; Wang et al. 2015; Dixon et al. 2013; AbdAlla Salman et al. 2022).

6.2 Association of hs-CRP with weight loss and clinical applicability of hs-CRP

In study II, hs-CRP decreased after MBS and remained low up to 10 years postoperatively. Hs-CRP was the lowest at 3 years with a statistically significant difference to baseline. There was no statistically significant difference in hs-CRP change over time between LSG and LRYGB. Hs-CRP correlated statistically significantly with BMI both at baseline and at 10 years. Additionally, hs-CRP correlated statistically significantly with greater %TWL at 10 years. Baseline hs-CRP and hs-CRP change in the first 6 months (rapid weight loss period) after surgery did not correlate statistically significantly with %TWL at 10 years.

In line with study II, previous studies have reported sustainable long-term improvement in hs-CRP level at 4-7 years. They found hs-CRP to reach its nadir at 2 years postoperatively, which we interpret to be concurrent with our result regarding different follow-up protocols (Lautenbach et al. 2021; Hinerman et al. 2022). The strong correlation between hs-CRP and BMI before and after surgery has also been found by previous studies. This indicates that weight loss is the driving force behind the resolving inflammation (O'Rourke et al. 2019; Lautenbach et al. 2021; Illán-Gómez et al. 2012). Furthermore, the amount of adipose tissue seems to have a key role in determining the grade of inflammation (Rohm et al. 2022; Kahn et al. 2006).

To our knowledge, study II is the first RCT comparing the effect of LSG and LRYGB on hs-CRP. At baseline, hs-CRP levels were higher in the LSG group, and the difference persisted through follow-up. BMI-adjusted operation*time interaction did not show any statistically significant difference. A retrospective study found a similar result with no difference between LSG and LRYGB (Lautenbach et al. 2021).

In study II, the baseline hs-CRP did not show predictive power over %TWL at 10 years. One previous study found a low correlation between higher baseline hs-CRP and greater weight loss at 3 years. However, they interpreted this correlation to have no clinical relevance (O'Rourke et al. 2019). To same extent, we investigated the hs-CRP change during the first 6 postoperative months as a predictive factor for long-term outcome of surgery, but there was no correlation. Based on the results of this study, the applicability of hs-CRP as a prognostic tool for MBS outcomes is very limited.

6.3 Nutritional deficiencies after LSG and LRYGB

In study III, long-term micro- and macronutritional deficiencies were relatively rare after LSG and LRYGB. The deficiency rates after the two procedures were similar for vitamin D, calcium, and vitamin B12. Iron deficiency, defined as low ferritin, was common and statistically significantly higher after LRYGB compared to LSG. However, ferritin deficiency was not associated with anemia.

This study found a lower prevalence of vitamin D insufficiency (10.7%) than the 42% reported by a recent meta-analysis of LRYGB studies. The meta-analysis reported major heterogeneity in the studies and definitions of vitamin D deficiency (Gao et al. 2023). Another recent meta-analysis found vitamin D deficiency to be less common after LSG, which is in contrast with study III. However, in this meta-analysis only 2 out of 24 included studies were RCTs and had only short- to mid-term follow-up (Giustina et al. 2023). In concurrence with our result, a retrospective study found the prevalence of hypocalcemia after MBS to be 3.6%. They found a higher deficiency prevalence after LSG than LRYGB (9.3% vs 1.9%) but interpreted this difference as a result of selection bias as renal insufficiency patients were overrepresented in LSG group (Shah et al. 2017).

The prevalence of vitamin B12 deficiency (2.2%) in the present study is in line with previous reports showing a prevalence of 2% at 10-20 years after LRYGB (Johansson et al. 2021; Karefylakis et al. 2015). A recent meta-analysis of LSG studies showed the prevalence of vitamin B12 deficiency to remain unchanged (4%) from baseline to 5 years (Nie et al. 2023). Study III is in contrast with a recent meta-analysis of ten RCTs, which found LRYGB patients to have a greater risk for vitamin B12 deficiency than LSG patients (Kwon et al. 2022). However, the studies in this meta-analysis had mostly short-term follow-up (Kwon et al. 2022), and previous research indicates that vitamin B12 deficiency prevalence peaks at 2-3 years after LRYGB before decreasing again (Weng et al. 2015; Johansson et al. 2021). It may be possible that anatomical and physiological alterations of LRYGB cause more fluctuation in vitamin B12 level, and over-time, the metabolism adapts to new circumstances.

Study III is in concurrence with previous long-term studies regarding the prevalence of anemia measured by hemoglobin levels (Johansson et al. 2021; Nie et al. 2023; Sandvik et al. 2021). Similarly in line with the present study, the recent meta-analysis found no difference in anemia prevalence between LSG and LRYGB (Kwon et al. 2022). The prevalence of low ferritin after LSG in study III (13.8%) was remarkably lower than the one reported by the recent meta-analysis (27%) (Nie et al. 2023). In the LRYGB group of the present study, the prevalence of ferritin deficiency was considerably higher (41.4%) compared to the prevalence of iron deficiency in many previous studies (Lewis et al. 2020; Weng et al. 2015; Johansson et al. 2021; Karefylakis et al. 2015; Sandvik et al. 2021). One retrospective study had a high prevalence of low ferritin after LRYGB (37.5%) concurrent with this study (Monaco-Ferreira et al. 2017). Study III is in contrast with the recent meta-analysis which did not show difference in iron deficiency between LSG and LRYGB (Kwon et al. 2022). The results of the present study did not find correlation between anemia and ferritin deficiency, although some studies indicate that anemia after MBS is caused by iron deficiency (Johansson et al. 2021; Nie et al. 2023; Karefylakis et al. 2015). In study III, the availability of ferritin values was somewhat low reducing the sample size. This might affect the findings on ferritin level. On the other hand, iron supplement use was less common in the LSG group than in the LRYGB group. Because iron supplements were recommended only for patients with diagnosed iron deficiency, this supports the result that deficiency was more frequent after LRYGB. Based on study III, the risk for iron deficiency at long-term follow-up should be considered while selecting the MBS procedure especially in treatment of patients with other risk factors for iron deficiency, e.g., women of fertile age. Furthermore, LRYGB patients should be monitored closely for iron deficiency.

6.4 Adherence to micronutrient supplements

The overall adherence to prescribed nutritional supplements in study III was low compared to previous short-term studies (Spetz et al. 2022; Schiavo et al. 2017; James et al. 2016). There is some short-term evidence that adherence decreases over time (Spetz et al. 2022; Schiavo et al. 2017; Modi et al. 2013). This effect, amplified by the longer follow-up, is likely the most important reason for the low adherence in this study, even despite the high follow-up rate and RCT design. In the present study, LSG patients had lower adherence to all supplements than LRYGB patients. Previous research on the matter is scarce (Spetz et al. 2022; Smelt et al. 2021), and further research is required to investigate this phenomenon.

Study III found the adherence to calcium-vitamin D supplementation similar to a recent long-term study on adherence in LRYGB patients (Bjerkan et al. 2023). Concurrently with the results of the present study, previous studies have found higher vitamin D levels in adherent patients (Giustina et al. 2023; Bjerkan et al. 2023; Carlin et al. 2006; Schollenberger et al. 2015). Regarding vitamin B12 supplementation, the adherence in study III (42%) was substantially lower compared to the recent retrospective report (95%). They also found that adherent patients had higher vitamin B12 levels which is in contrast with our study (Bjerkan et al. 2023). In the questionnaire of the present study, oral and intramuscular vitamin B12 supplementation were not differentiated. However, presumably most of the patients had intramuscular supplementation, which is not affected by the alterations of gastrointestinal tract.

The low adherence to micronutritional supplements did not result in high prevalence of deficiencies. On the contrary, the deficiencies were rare overall. Regarding the deficiencies with very low prevalence, for example vitamin B12 and calcium, the necessity of supplementation may be questioned. As long-term research is scarce, the supplementation guidelines (Mechanick et al. 2019; O'Kane et al. 2020; Bruun et al. 2024) are not yet based on hard evidence. Further research is needed to particularize the risk of deficiencies and need for supplementation.

6.5 Strengths and limitations

This thesis, based on the data of the SLEEVEPASS RCT, has several strengths. First, the RCT setting and the multicenter and multisurgeon design add generalisability of the results. Second, the SLEEVEPASS trial has a complete 10-year follow-up and it is, to our knowledge, the first LSG and LRYGB comparing RCT to reach this goal. The follow-up rate at 10 years was 85%, which is very high.

The SLEEVEPASS trial also has limitations. At the time of the enrolment in 2008-2010, the number of annual MBS procedures in Finland was quite low. This may have resulted in a learning curve effect, which, however, concerns both procedures equally. Another limitation is that the excluded patients were not recorded adequately. This bias, in turn, is mitigated by the small numbers of MBS in Finland, as majority of the patients were included in the study to achieve the predefined number of patients.

This thesis is limited by the sample size of the studies. Study I is limited by the number of T2D patients even in the merged data of two large RCTs (SLEEVEPASS and SM-BOSS) lacking sufficient power to detect clinically significant differences in T2D remission rate between LSG and LRYGB. On the other hand, to our knowledge, this merged data is still the largest randomized cohort comparing the two procedures in treatment of severe obesity and T2D. Study II and III are also limited by the small sample size, which is due to a simple human error of non-adherence to study protocol laboratory test follow-up resulting in a large proportion of missing laboratory values. Selection bias is, however, very unlikely, as the non-inclusion of these tests was made by mistake.

In study II, all the results may be affected by the small number of hs-CRP values. Firstly, the small sample size did not allow a sufficient evaluation of the association between hs-CRP and comorbidities and mortality. Secondly, the higher baseline hs-CRP in patients randomized to LSG group is also probably a consequence of the small sample size. Thirdly, the hs-CRP at 3 years was the only one to differ statistically significantly from baseline and other follow-up points. As mentioned, the trajectory of hs-CRP in our study is similar to previous studies (Hinerman et al. 2022; Lautenbach et al. 2021).

In study III, the sample size limitation is present especially in ferritin and iron deficiency. The number of nutritional values at baseline was unfortunately low despite being a predefined secondary outcome. The number of preoperative values did not allow a comparison of deficiency prevalence between baseline and 10 years. Vitamin B12 deficiency was evaluated using serum vitamin B12, which is not currently recommended as the optimal test for deficiency. However, all the reference studies used it as well, which facilitates comparison between different available studies. Results on folate are lacking due to a couple of reasons. Folate deficiency was measured as red blood cell folate which is not in concurrence with the current recommendations. In addition, there was some laboratory technical issues which resulted in the folate results not being available at 10 years. A major limitation in study III is the fact that adherence to supplements was evaluated only by questionnaires. In order to enhance the precision of the results, self-reported data should be combined with objective data from prescription or reimbursement records (Osterberg et al. 2005; Spetz et al. 2022; Anghel et al. 2019).

6.6 Future aspects

Obesity is an ever growing threat to health of humankind (NCD-RisC* 2024). While highly effective (Adams et al. 2017; Sjöström 2013; Courcoulas et al. 2024), MBS remains a rarely utilized remedy for this increasingly significant problem (Angrisani et al. 2024). The increase in number of surgeries turned to decline during the COVID-19 pandemic (Angelo et al. 2023), and the challenge is to restore them to pre-pandemic levels and maintain the growth further.

A more tailored procedure selection is one of the key goals of future MBS research. Current research has shown the differences between the effects of LSG and LRYGB to be relatively small. However, optimizing the primary surgical method choice is of essence to optimize surgical treatment. This calls for a functioning algorithm to facilitate the procedure selection. It should include multiple factors like weight loss and comorbidity remission, GERD, iron deficiency, and overall surgical risk.

The relationship between low-grade inflammation and obesity is a complex one and requires further research. Currently, the clinical importance is relatively unclear, but investigating the inflammation adds our understanding of metabolic diseases and lays foundation for the development of future treatment modalities. For example, there is some evidence that anti-inflammatory drugs may enhance glycemic control and prevent CVD complications (Rohm et al. 2022). Chronic inflammation is also considered to contribute in obesity related cancer-risk (Berger 2014). Thus, the treatment of metabolic diseases is not the only one to potentially benefit from inflammation research.

The risk for nutritional deficiencies is extremely important to consider in MBS. The patients live with their altered anatomy and physiology for the rest of their lives and similarly the nutritional deficiency risk sustains. The nutritional state itself in terms of laboratory values is not the key point for the patients. It is the effects and the symptoms of the potential deficiencies like fatigue, fractures and muscle mass loss, weakened immune system, and neurological symptoms. In the future, we will have more and more patients with 20 or 30 years from their MBS. Elderly people who have undergone MBS in their 20s. What will their nutritional state be? What is the prevalence of the consequences of long-term deficiencies? Are there differences between LSG and LRYGB? These questions, of course, may be expanded to encompass all the effects of MBS.

Today, the effective treatment of obesity does not consist merely of laparoscopic MBS. NuSH-based OMMs are a reckoned alternative resulting in good weight loss (Shi et al. 2024; de Mesquita et al. 2023). The current problems of these medications comprise high prizes and supply disruption. Over time, these problems are likely to solve. In addition, permanent usage is required to maintain sufficient weight loss (Gudzune et al. 2024). The future studies will show the impacts of long-term OMM use, which yet remain unknown. Another interesting front of advancement are the endoscopic MBS procedures. Through further development these mini-invasive techniques may become more common. They could be considered for patients with greater surgical and anesthesia risks (Simons et al. 2024). In the future, the different surgical methods and OMMs will form a new whole of obesity treatment that offers each patient individually tailored single or combination of optimal treatments (Cohen, Busetto, et al. 2024; Cohen, Park, et al. 2024). Individual tailoring is important also for long-term follow-up as the results on nutritional deficiencies highlight.

While discussing treatment options of obesity, one must keep in mind that the ultimate goal is to stop the spreading of obesity epidemic. This requires political will to reduce the risk factors of obesity at society level. We can never entirely escape our biology that has developed for different circumstances of food supply, but we can alter the society in a way that reduces the risk of obesity. A change of culture is needed, and it starts with providing information on obesity as a disease, that should be prevented and treated. The stigmatization of the people with obesity must be put to an end. A more practical and solution-oriented approach adopted by the public will pave the way for the necessary reform.

7 Conclusions

This doctoral thesis results in following conclusions:

1. The IMS score was able to predict T2D remission after MBS. However, it did not facilitate procedure selection between LSG and LRYGB as no differences were detected between the procedures in any of the IMS severity stages.
2. MBS resulted in long-term hs-CRP decrease demonstrating the reduction of the chronic inflammation mediated by substantial and sustainable weight loss. There were no differences in hs-CRP between LSG and LRYGB, but the study was limited by the small sample size. Hs-CRP was not feasible as a predictive marker for MBS weight-loss outcomes.
3. Long-term micronutrient deficiencies were rare after MBS. There were no differences in vitamin D, B12, or calcium deficiency rates after LSG and LRYGB. Iron deficiency was more common and frequent after LRYGB, which needs to be taken into consideration in procedure selection and follow-up. Adherence to micronutrient supplements was lower after LSG than LRYGB.

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Appendix 1. Questionnaire on nutritional supplement use

Patient number

____

Date

____

Follow-up point

____

Weight at 10 years

____

City

Turku

Vaasa

Helsinki

Original type of surgery

Sleeve

Bypass

Conversion?

No

Yes

If converted, to what type of surgery?

Sleeve

Bypass

Other

Converted to what other?

____

If converted, how long is it from conversion?

____

Why was conversion performed?

____

Other comments on conversion:

____

Calcium-Vitamin D supplement in use?

No

Yes

B12-vitamin supplement in use?

No

Yes

Iron supplement in use?

No

Yes

Which kind of iron supplement?

Peroral

Intramuscular

Intravenous

Multivitamin supplement in use?

No

Yes

Appendix 2. Per-protocol analysis: nutrient values categorized by reference ranges at 10 years

	ALL STUDY PATIENTS	LSG	LRYGB	P VALUE*
VITAMIN D (NMOL/L)				
<25	0/175 (0.0)	0/79 (0.0)	0/96 (0.0)	
25-50	19/175 (10.9)	8/79 (10.1)	11/96 (11.5)	
51-74	71/175 (40.6)	27/79 (34.2)	44/96 (45.8)	0.139
75-120	79/175 (45.1)	39/79 (46.4)	40/96 (41.7)	
>120	6/175 (3.4)	5/79 (6.3)	1/96 (1.0)	
CALCIUM (MMOL/L)				
<1.15	4/172 (2.3)	3/76 (4.0)	1/96 (1.0)	
1.15-1.30	160/172 (93.0)	69/76 (90.8)	91/96 (94.8)	0.415
>1.3	8/172 (4.7)	4/76 (5.3)	4/96 (4.2)	
VITAMIN B12 (PMOL/L)				
<145	2/90 (2.2)	1/44 (2.3)	1/46 (2.2)	
145-570	70/90 (78.0)	36/44 (81.8)	34/46 (73.9)	0.713
>570	18/90 (20.0)	7/44 (15.9)	11/46 (23.9)	
HEMOGLOBIN (G/L)				
UNDER RL	29/186 (15.6)	13/82 (15.9)	16/104 (15.4)	
WITHIN RLS	153/186 (82.3)	66/82 (80.5)	87/104 (83.7)	0.783
OVER RL	4/186 (2.2)	3/82 (3.7)	1/104 (1.0)	
FERRITIN (µG/L)				
UNDER RL	15/57 (27.6)	3/20 (15.0)	12/37 (32.4)	
WITHIN RLS	35/57 (60.3)	15/20 (75.0)	20/37 (54.1)	0.283
OVER RL	7/57 (12.1)	2/20 (10.0)	5/37 (13.5)	
ALBUMIN (G/L)				
<36	47/181 (26.0)	23/81 (28.4)	24/100 (24.0)	
36-45	131/181 (72.4)	56/81 (69.1)	75/100 (75.0)	0.582
>45	3/181 (1.7)	2/81 (2.5)	1/100 (1.0)	
MAGNESIUM (MMOL/L)				
<0.71	10/175 (5.7)	6/77 (7.8)	4/98 (4.1)	
0.71-0.94	149/175 (85.1)	66/77 (85.7)	83/98 (84.7)	0.375
>0.94	16/175 (9.1)	5/77 (6.5)	11/98 (11.2)	
PHOSPHORUS (MMOL/L)				
UNDER RL	4/163 (2.5)	2/73 (2.7)	2/90 (2.2)	
WITHIN RLS	156/163 (95.7)	70/73 (95.9)	86/90 (95.6)	>0.999
OVER RL	3/163 (1.8)	1/73 (1.4)	1/90 (2.2)	

*Fisher's exact test

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