Impact of diabetes and bariatric surgery on gastroesophageal reflux disease and patient- reported outcomes.

A cross-sectional study of patients with and without type 2 diabetes, and a randomized study (Oseberg) comparing the short-and medium term effects of gastric bypass and sleeve gastrectomy on gastroesophageal reflux disease and patient-reported outcomes.

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Being a part of this project has taught me how to work and live for the better.

List of abbreviations

AET: Acid exposure time

AGB: Adjustable Gastric Band

BDI: Beck Depression Inventory

BE: Barretts esophagus

BES: Binge Eating Scale

BMI: Body mass index

BPD/DS: Biliopancreatic diversion/duodenal switch

CAN: Cardiovascular Autonomic Neuropathy

CI: Confidence interval

DCI: Distal Contractile Integral

EE: Erosive esophagitis

EGD: Esophago-Gastro-Duodenoscopy

FTQ: Food Tolerance Questionnaire

GERD: Gastroesophageal Reflux Disease

GerdQ: Gastroesophageal reflux disease Questionnaire

GI: the Gastrointestinal tract

GSRS: Gastrointestinal Symptom Rating Scale

GSRS-R: Gastrointestinal Symptom Rating Scale-Reflux part

HbA1c: Glycated hemoglobin

HRM: High-resolution manometry

HRQoL: Health related quality of life

IWQOL-Lite: Impact of Weight on Quality of Life

LES: Lower esophageal sphincter

MCS: Mental component summary

NERD: Non-ersoive reflux disease

Oseberg-study: **O**besity **s**urg**e**ry in Tøns**berg**-study

PCS: Physical component summary

PIP: Pressure inversion point

PRO: Patient-reported outcome

PROMs: Patient-reported outcome measures

QoL: Quality of life

RCT: Randomized controlled trial

RD: Risk Difference

RYGB: Roux-en-Y gastric bypass

SF-36: Short-form 36 health survey

SG: Sleeve gastrectomy

T2D: Type 2 diabetes

TLESRs: Transient Lower Esophageal Sphincter Relaxations

Non-T2D: No type 2 diabetes

WHO: World Health Organization

WRSM: Weight-Related Symptoms Measure

The **O**besity **s**urg**e**ry in Tøns**berg** (**Oseberg**) study, named after the Oseberg ship, a well-preserved Viking ship discovered at the Oseberg farm near Tønsberg in Vestfold county, Norway (Figure below).

Thesis summary

The prevalence of obesity is increasing rapidly, and it has become a major threat to the health of people worldwide. In Norway, approximately 7% of women and 5% of men suffer from severe obesity (BMI≥35 kg/m²) (1).

Together with the increase of obesity, there is also an increase of type 2 diabetes (T2D). Both obesity and T2D are associated with increased risk of gastroesophageal reflux disease (GERD).

Long-standing GERD may lead to serious health problems; for example, esophagitis, which can causes ulcers, strictures, Barrett's esophagus and an increased risk of esophageal adenocarcinoma. People with obesity and T2D may have a higher prevalence of GERD than people with obesity only.

In addition, both obesity and T2D may be associated with reduced health-related quality of life (HRQoL), depression and eating disorders.

The absence of successful non-surgical obesity management tools has lead to an increase in the number of surgical treatment procedures (bariatric surgery). Gastric bypass (RYGB) and sleeve gastrectomy (SG) are the most commonly performed bariatric procedures both in Norway and worldwide. Different studies have shown favorable effects of bariatric surgery on weight loss,

remission of T2D, improvement of GERD and quality of life. The use of SG has increased over the last decade, probably due to its technical simplicity. However, concerns have been raised due to increased incidence of GERD following SG. By contrast, RYGB has been proposed as the surgical treatment of choice for people with obesity and GERD due to its excellent results in terms of weight loss and GERD resolution.

Although both SG and RYGB can be performed safely in patients with obesity and T2D, there are few randomized controlled trials comparing advantages and disadvantages of these methods on GERD and clinically important patient-reported outcomes.

The main aims of this thesis were, first, to assess the impact of T2D on GERD (paper 1), and, second, to compare the effects of SG and RYGB on GERD (paper 2) and clinically important patient-reported outcomes (paper 3). Accordingly, the specific objectives and hypotheses were threefold: First, we aimed to compare the prevalence of GERD in patients with or without T2D, hypothesizing that patients with T2D had a higher prevalence of erosive esophagitis but less GERD symptoms than those without T2D (cross-sectional study, paper 1). Second, we aimed to compare the 1-year effects of SG and RYGB on a number of GERD outcomes, hypothesizing that patients with T2D undergoing SG would have a higher 1-year prevalence of GERD symptoms, erosive esophagitis and pathological acid reflux than those undergoing RYGB (randomized trial, paper 2). Third, we aimed to compare changes in a number of patient-reported outcomes 3 years after RYGB versus SG (randomized trial, paper 3). We hypothesized that RYGB would lead to worsening of gastrointestinal symptoms compared with SG, while SG would increase reflux symptoms, and that larger weight loss after RYGB, as compared with SG, would lead to greater improvements in weight-related symptoms and weight-related quality of life.

Our results showed, first, that the prevalence of erosive esophagitis was high and not significantly different in patients with or without T2D, and the proportion of patients with symptomatic GERD was low independent of the presence or absence of T2D. Second, SG was associated with a

substantially higher 1-year risk of pathological acid reflux and new-onset erosive esophagitis than RYGB. Third, RYGB was associated with a greater 3-year improvement in weight-related quality of life, less reflux symptoms, greater weight loss, and higher diabetes remission rates than SG. On the other hand, changes in symptoms related to abdominal pain, indigestion, diarrhea, dumping, depression and binge eating did not differ between groups.

Our results from paper 1 suggest that the burden of GERD is similar among patients with or without T2D preparing for bariatric surgery, Second, the results from paper 2 suggest that screening for GERD with endoscopy and/or 24-pH monitoring may be indicated after bariatric surgery, regardless of symptoms. Third, the results from paper 3 suggest that patient-reported outcomes can be used in the shared decision making process to inform patients about similarities and differences between expected outcomes after SG and RYGB in patients with T2D. These results may add knowledge to existing policies and guidelines, and may result in more targeted, efficient and personalized treatment, with potential benefits for both individuals and society.

Avhandlingens sammendrag

Fedme er en økende trussel mot folkehelsen. Basert på data fra Tromsø-undersøkelsen, lider omtrent 7 % av kvinnene og 5 % av mennene i Norge av alvorlig fedme (BMI≥35 kg/m²) (1). Fedme øker risikoen for type 2 diabetes (T2D), mens både fedme og T2D øker risikoen for gastroøsofageal reflukssykdom (GØRS). GØRS er definert som en tilstand som utvikler seg når innhold fra magesekken passerer opp i spiserøret (øsofagus) og gir plagsomme symptomer og komplikasjoner. Tilstanden har også negativ innvirkning på helserelatert livskvalitet og kan føre til utvikling av Barretts øsofagus (forstadium til spiserørskreft). Personer med fedme og T2D kan ha en høyere forekomst av GØRS enn personer med fedme alene. Den sterke korrelasjonen mellom vekt og GØRS tyder på at det kan foreligge en årsakssammenheng. Man vet imidlertid lite om hvilken rolle T2D spiller for utvikling av GØRS, hverken når det gjelder objektive refluksfunn eller reflukssymptomer. Konservativ vektreduserende behandling hos pasienter med fedme er ofte utilstrekkelig og mange blir derfor tilbudt en vektreduserende operasjon. Gastrisk bypass (GBP) og sleeve gastrektomi (SG) er to fedmeoperasjoner som begge gir vektreduksjon og bedring av T2D. GBP er en veldokumentert kirurgisk metode, mens SG er en nyere metode som mangler god vitenskapelig dokumentasjon på behandlingseffekt, mekanismer og komplikasjoner hos pasienter med T2D. GBP har i mange år vært det best dokumenterte og mest naturlige kirurgiske behandlingstilbudet til pasienter med T2D eller GØRS. Selv om SG sannsynligvis øker forekomsten og alvorlighetsgraden av GØRS, har den blitt den mest brukte fedmekirurgiske prosedyren både i Norge og på verdensbasis. Det er derfor et stort behov for studier som kan sammenligne effekten av GBP og SG på GØRS. Det er også mangel på studier av god kvalitet og langtidsoppfølging som sammenlikner effektene av GBP og SG på klinisk viktige pasientrapporterte utfall (PROs). Osebergstudien er en trippelblindet randomisert studie som ble igangsatt for å sammenligne effekten av GBP og SG på remisjon av type 2 diabetes (primært endepunkt), men sekundært ønsket studien også å sammenlikne en rekke andre fordeler og ulemper ved disse to operasjonsmetodene.

Formålet med den første studien i dette doktorarbeidet var å sammenligne forekomsten av GØRS hos pasienter med eller uten T2D, med en hypotese om at pasienter med T2D hadde en høyere forekomst av erosiv øsofagitt, men mindre GØRS-symptomer enn de uten T2D (tverrsnittstudie, artikkel 1). For det andre sammenlignet vi 1-årseffektene av SG og GBP på en rekke GØRS-utfall, og vår hypotese var at pasienter med T2D som gjennomgikk SG ville ha en høyere 1-års forekomst av GØRS-symptomer, erosiv øsofagitt og patologisk sur refluks, enn de som gjennomgikk GBP (randomisert studie, Oseberg, artikkel 2). Til slutt sammenlignet vi endringer i en rekke pasientrapporterte utfall (PROs) 3 år etter GBP versus SG (randomisert studie, Oseberg, artikkel 3). Vi antok at GBP ville føre til forverring av mage-tarm symptomer sammenlignet med SG, mens SG ville øke reflukssymptomer. I tillegg antok vi at større vekttap etter GBP, sammenlignet med SG, ville føre til større forbedringer i vektrelaterte symptomer og vektrelatert livskvalitet. Resultatene fra vår første studie viste at prevalensen av erosiv reflukssykdom var høy i men ikke signifikant forskjellig hos pasienter med eller uten T2D, mens andelen av pasienter med symptomatisk GØRS var lav, uavhengig av tilstedeværelse eller fravær av T2D. For det andre, var SG assosiert med en 3 ganger høyere 1-års risiko for patologisk sur refluks og 5 ganger høyere risiko for nyoppstått erosiv øsofagitt enn GBP (47% vs 9%). GBP var derimot assosiert med en større forbedring i vektrelatert livskvalitet, færre reflukssymptomer, større vekttap og høyere diabetesremisjon enn SG, tre år etter operasjonen. Det var ingen statistisk signifikant forskjell mellom gruppene når det gjaldt endringer i symptomer relatert til magesmerter, fordøyelsesbesvær, diaré, dumping, depresjon og overspisingssymptomer. Resultater fra vår første studie tyder på at GØRS prevalens er sammenliknbar hos pasienter med fedme med og uten T2D. Resultater fra første og andre studie tyder på at screening med endoskopi og/eller 24-pH-måling kan være indisert før- og etter fedmekirurgi, uavhengig av om pasienter har symptomer eller ikke. Resultater fra vår tredje studie om pasientrapporterte utfallsmål ville i tillegg kunne belyse fordeler og ulemper mellom begge

operasjonsmetoder når det gjelder livskvalitet og vil i fremtiden kunne gi pasienter og behandlere et bedre grunnlag for valg av operasjonsmetode i behandling av sykelig overvekt.

List of papers

Paper 1

Erosive Esophagitis and Symptoms of Gastroesophageal Reflux Disease in Patients with Morbid Obesity with and without Type 2 Diabetes: a Cross-sectional Study.

Jolanta Lorentzen, Asle W. Medhus, Jens Kristoffer Hertel, Heidi Borgeraas, Tor-Ivar Karlsen, Ronette L. Kolotkin, Rune Sandbu, Daniel Sifrim, Marius Svanevik, Dag Hofsø, Birgitte Seip, Jøran Hjelmesæth.

Obes Surg. 2020 Jul; 30 (7):2667-2675.PMID:32193740 .https://doi.org/10.1007/s11695-020-04545-w

Paper 2

Sleeve Gastrectomy Confers Higher Risk of Gastroesophageal Reflux Disease Than Gastric Bypass: A Randomized Controlled Trial From the Oseberg Reflux Working Group.

Jolanta Lorentzen, Asle W. Medhus, Dag Hofsø, Marius Svanevik, Birgitte Seip and Jøran Hjelmesæth.

Gastroenterology. 2021 Dec;161(6):2044-2046. e4. doi: 10.1053/j.gastro.2021.08.021. Epub 2021 Aug 20. PMID: 34419459.

The Oseberg Reflux working group: Heidi Borgeraas, Jens Kristoffer Hertel, Milada C. Småstuen, Daniel Sifrim, and Rune Sandbu.

Paper 3

Patient-reported outcomes, weight loss and remission of type 2 diabetes 3 years after gastric bypass and sleeve gastrectomy (Oseberg); a single-centre randomised controlled trial.

Marius Svanevik*, Jolanta Lorentzen*, Heidi Borgeraas, Rune Sandbu, Birgitte Seip, Asle Wilhelm Medhus, Jens Kristoffer Hertel, Ronette L. Kolotkin, Milada C. Småstuen, Dag Hofsø and Jøran Hjelmesæth.

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1 Introduction

1.1 Background

Worldwide, approximately 650 million people have obesity (2, 3) and over 400 million people have diabetes (4, 5). Further, the majority (90%) of patients who develop type 2 diabetes (T2D) are suffering from overweight or obesity (6, 7). Gastroesophageal reflux disease (GERD) is a common condition that affects about 13% of the worldwide population and 20% of the adult population in high-income countries (8). It is defined by symptoms such as heartburn and regurgitation or complications such as erosive esophagitis, strictures, Barretts esophagus (BE) and esophageal adenocarcinoma (9). Several studies have shown different risk factors for GERD including obesity (10), diabetes (11), smoking, alcohol and caffeine usage (12). One study with Mendelian randomization suggested causal roles of adiposity, diabetes and cigarette smoking in the development of GERD (8).

Approximately 2 % of the Norwegian adult population suffer from severe obesity defined as BMI≥40 kg/m² or BMI≥35 kg/m² with at least one obesity related comorbidity (3, 13, 14).

In this PhD thesis I chose to use the term “severe obesity ” rather than “morbid obesity” , because the term “severe” is considered less stigmatizing than“morbid” (15). Severe obesity is associated both with reduced quality of life and comorbidities such as e.g. T2D, non-alcoholic fatty liver disease, obstructive sleep apnea and GERD (9, 16-18). The cost for the health care system in Norway related to overweight and obesity is estimated to 68 billion NOK per year (2, 19). In 2004 the Ministry of Health and Care Services in Norway acknowledged severe obesity as a serious public health problem (20) and the Regional Health Authorities were instructed to provide patients with severe obesity an appropriate treatment choice; either non-surgical or surgical. A treatment developed for obesity is now also recommended to treat T2D and the most effective treatment is

bariatric surgery (5, 21) which also has beneficial effects on health related quality of life (HRQoL) (22).

Roux-en-Y-gastric bypass (RYGB) is considered the gold standard procedure in the surgical treatment of severe obesity with beneficial effects on weight loss, remission of T2D and improvement of existing GERD (23). Nevertheless, during the last decade, sleeve gastrectomy (SG) has become the most common bariatric procedure in Norway and worldwide (24). However, one of the concerns related to SG is an increase in the prevalence and severity of GERD following this procedure and long-standing GERD may lead to complications such as severe esophagitis, esophageal strictures, dysplasia and in worst case esophageal cancer (25, 26). In view of this, it has been debated if SG should be offered to patients with preexisting GERD. In clinical practice, making diagnosis of GERD in patients with obesity based on symptoms alone can be challenging since the correlation between GERD symptoms and objective GERD findings is weak (27-30). Patients with severe obesity and T2D may be even more susceptible to asymptomatic erosive esophagitis than patients without T2D (11, 31-33). This PhD thesis aimed, first, to investigate whether patients with T2D scheduled for bariatric surgery had a higher prevalence of GERD than patients without T2D. Second, the thesis aimed to compare the effects of RYGB and SG on prespecified secondary patient -reported outcomes (PROs) and GERD in patients with T2D included in the Oseberg study.

The primary endpoint of this trial, 1 year remission of T2D, has been published (34).

1.2 Obesity

1.2.1 Definition and classification

Obesity is a chronic, progressive disease defined as abnormal or excessive fat accumulation that may impair health (35). Body mass index (BMI) is the most utilized method to diagnose and classify obesity and is defined as weight (in kilogram) divided by height (in meter) squared (36). In adults, The World Health Organization (WHO) classifies BMI ≥25 kg/m² and < 30 kg/m² as being overweight and BMI≥30 kg/m² as obesity (Table 1). Severe obesity is defined as BMI≥40 kg/m² or BMI≥35 kg/m² with at least one obesity related comorbidity, e.g. T2D, hypertension, cardiovascular disease, obstructive sleep apnea, arthritis and cancer (3, 37).

Table 1. BMI chart with obesity classifications adopted from the WHO 1998 report. Contributed by the World Health Organization - "Report of a WHO consultation on obesity. Obesity Preventing and Managing a Global Epidemic."(36)

WHO CLASSIFICATION OF WEIGHT STATUS	
WEIGHT STATUS	BODY MASS INDEX (BMI), kg/m²
Underweight	< 18.5
Normal range	18.5-24.9
Overweight	25.0-29.9
Obese	≥30
Obese class I	30.0-34.9
Obese class II	35.0-39.9
Obese class III	≥40

1.2.2 Pathogenesis of obesity

The pathogenesis of obesity is multifactorial. In an effort to systemize the factors associated with obesity an “Obesity system map”(Foresight Map) was developed in 2007, dividing more than 100 variables into the seven following domains : social psychology, food production, food consumption, individual psychology, physiology, individual physical activity and physical activity environment (19, 38). A wealth of food, low physical activity and several other environmental factors contribute to obesity and interact with a genetic susceptibility and produce a positive energy balance which leads

to overweight (36, 39). More than 1100 independent loci have been identified and may have a relation to obesity (40, 41) (Figure 1).

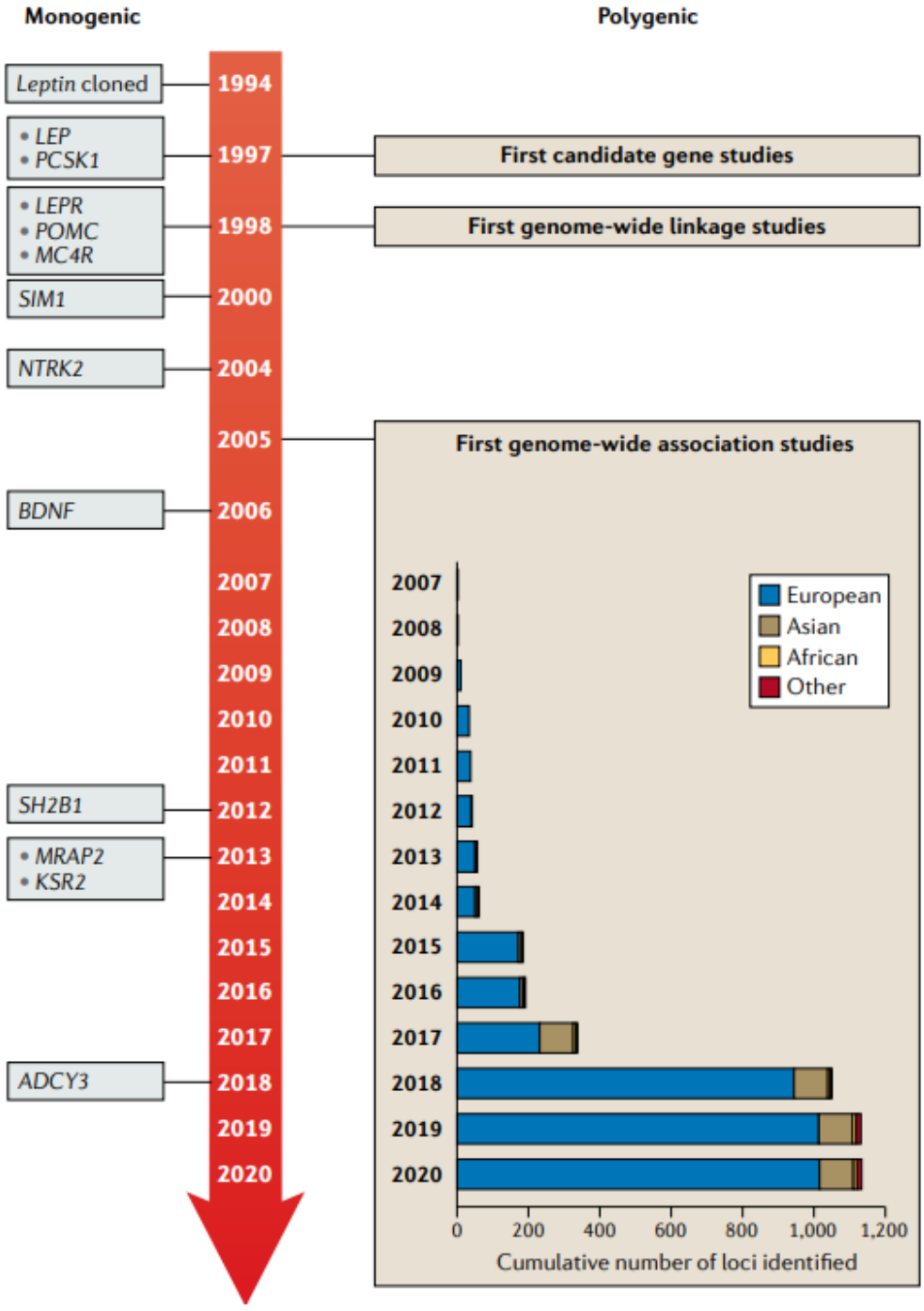


Figure 1. Timeline of key discoveries in obesity genetics. Genes identified for monogenic obesity in a given year are shown on the left. Discoveries made for polygenic obesity are shown on the right, including a cumulative count of newly discovered loci per year and by ancestry, reproduced from Loos et al. with permission (41).
ADCY3, adenylate cyclase 3; BDNF, brain-derived neurotrophic factor; KSR2, kinase suppressor of Ras2; LEP, leptin; LEPR, leptin receptor; MC4R, melanocortin 4 receptor; MRAP2, melanocortin receptor accessory protein 2; NTRK2, neurotrophic receptor tyrosine kinase 2; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, pro-opiomelanocortin;SH2B1, SH2B adaptor protein 1; SIM1, transcription factor 1.

The two major factors that control and interact in the regulation of food intake are the homeostatic and hedonic systems. The homeostatic system consists of the hypothalamus and brainstem and stimulates eating behavior when energy stores are low. The homeostatic pathway controls energy balance. The communication troughout the brain-adipose axis allows balance between energy intake and expenditure. The hedonic system (reward pathway) is mainly located in the corticolimbic areas and can override the homeostatic system during periods of energy abundance by increasing the desire to consume foods that are appetizing (42). Obesity develops when the homeostatic and hedonic system are out of balance (43). Obesity is associated with alterations in hedonic and homeostatic pathways that results in maladaptive patterns of consumption.

Multiple neurotransmitters like serotonin (5-hydroxytryptamine), dopamine, gamma-aminobutyric acid (GABA), glutamate, acetylcholineare may also explain the imbalance between homeostatic and hedonic regulation (42). Interesting, central serotonergic signaling has anorexigenic effect and increases energy expenditure through the stimulation of thermogenesis in the adipose tissue. Both the homeostatic and hedonic systems receive input from multiple signals that have information on energy intake, status and stores. Gut hormones and peptides are regulators which are secreted in response to fasting or exposure to ingested nutrients, may affect eating behavior by promoting satiety or hunger (44, 45). Ghrelin is a gut hormone called hunger hormone because it stimulates appetite. Ghrelin is produceds by enteroendocrine cells in the gastric fundus and its levels increase during fasting and decrease postprandially. The secretion of ghrelin is controlled by the sympathetic nervous system. Obesity is associated with reduced postprandial ghrelin suppression (46, 47). Anorexigenic intestinal hormones like glucagon-like peptid 1(GLP1), peptide YY (PYY) and cholecystokininare secreted in response to food intake and involved in both insulin secretion and satiety. Anorexigenic hormones levels decrease in people with obesity in connection with meal consumption (48-51).

To summarize, the pathophysiology of obesity is multifactorial and involves complex interactions between genetic, hormonal, environmental and psychological factors.

1.2.3 Prevalence of obesity

The prevalence of obesity and obesity related diseases is increasing, with approximatelly 650 million adults (13%) worldwide currently living with obesity (3). It has been hypothesized by the World Obesity Federation that by 2030 approximately 1 in 5 women and 1 in 7 men will have obesity (52) (Table 2). In Norway the prevalence of obesity was found to be 23% in women and men older than 20 years in the Nord-Trøndelag Health study (HUNT) (14), a study from 2017-2019 (2, 14, 53).

Table 2. Estimated global prevalence and numbers of adult with obesity in 2010-2030.

	2010		2025		2030	
Adult obesity prevalence	% adults	number	% adults	number	% adults	number
Obesity (Class I, II and III) BMI ≥30kg/m^2	11.4%	511m	16.1%	892m	17.5%	1,025m
of which, severe obesity (Class II and III) BMI ≥35kg/m^2	3.2%%	143m	5.1%	284m	5.7%	333m
and of these, severe obesity (Class III) BMI ≥40kg/m^2	0.9%	42m	1.7%	93m	1.9%	111m

Source: NCD Risk Factors Collaboration (2017), UN Population Division and World Obesity federation projections.

1.2.4 Obesity treatment strategies

In 2004 the Ministry of Health and Care Services in Norway acknowledged severe obesity to be an increasingly serious public health problem (20, 54). The Regional Health Authorities in South-Eastern Norway decided to provide patients with severe obesity an appropriate treatment choice; either non-surgical or surgical. Treatment of obesity is based on professional support including dietary interventions and/or physical activity, aiming to help people with obesity to improve their health behaviors and lose body weight.

1.2.5 Lifestyle treatment

Lifestyle interventions including modifications of eating behavior and/or physical activity are mandatory in all obesity treatment programs, either alone or supplemented with drugs or bariatric surgery (55). Various weight loss intervention strategies are clearly defined and described in the AHA/ACC/TOS guidelines for the Management of overweight and obesity in adults (56).

The role of physical activity in weight management is to increase activity related energy expenditure and to maintain resting energy expenditure by preserving lean muscle mass. The combination of diet and exercise may result in greater weight-loss (57). Physical activity is most important to prevent weight regain after weight loss (58). Achieving a weight loss of about 5-10% prevents and reduces co-morbidities like T2D and CVD (55). Because many diets have been shown to be effective for short-term weight loss, nutritional advice should be individualized to each patient. To prescribe a diet to achieve reduced calorie intake for individuals with overweight or obesity who would benefit from weight loss is a part of a comprehensive lifestyle intervention. Among others, any of the following methods can be used to reduce food and calorie intake (56):

a. "Prescribe 1,200–1,500 kcal/d for women and 1,500–1,800 kcal/d for men;

b. Prescribe a 500-kcal/d or 750-kcal/d energy deficit;

c.Prescribe one of the evidence-based diets that restricts certain food types (such as high-carbohydrate foods, low-fiber foods, or high-fat foods) in order to create an energy deficit by reduced food intake".

The composition of the ideal weight loss diet is strongly debated. A variety of diets with focus on reduced energy intake have been shown to improve HbA1c levels. The diets include reduced energy/fat intake, portion control, healthy food choices, carbohydrate counting and simplified meal plans (59). Data from randomized controlled trials (RCTs) of long duration support the weight and

health benefits of a low-fat diet, defined as less than or equal to 20% to 30% of total daily calories, however, low carbohydrate diets (>150 g/d) may reduce insulin resistance more than low-fat diets (60-62). In the recent Norwegian scoping review of 11 RCTs on low carb-high fat versus high-carb-low-fat, the authors concluded that use of typical low-carb diet (*starting with CHO ≤20–40 g/d in the first phase or <20% of total energy intake)* during a period of 6-24 months resulted in a larger mean weight loss compared with low-fat diet < 30% of energy as fat (63, 64). Low-carbohydrate diets, which are high in saturated fat, can raise LDL-cholesterol and increase risk of cardiovascular disease. By contrast, a low-carb diet may increase adiponectin, an adipocyte hormone which improves insulin sensitivity and countract atherogenesis (65).

1.2.6 Obesity- pharmacological treatment

Pharmacotherapy can be used as an adjunct to lifestyle interventions and should be considered to help patients achieve targeted weight-loss and health goals as an adjunct to comprehensive lifestyle intervention for individuals who have a BMI greater than or equal to 30 kg/m ^{2} or a BMI greater than or equal to 27 kg/m ^{2} with at least 1 obesity-associated comorbidity (eg, T2D, hypertension, hyperlipidemia, and obstructive sleep apnea) (66).

Four drugs are currently approved and available in Norway for treatment of patients with severe obesity: orlistat, naltrexone-bupropion, liraglutide and semaglutide (67). Orlistat (Xenical) promotes weight loss by inhibiting gastrointestinal lipases, decreasing the absorption of fat from the gastrointestinal tract by about 30% (68, 69). Naltrexone-bupropion (Mysimba) combines the dopamine/norepinephrine reuptake inhibitor bupropion with the opioid antagonist naltrexone. Naltrexone works by autoinhibition of pro-opiomelanocortin neurons in the arcuate nucleus of the hypothalamus. Bupropion increases dopamine at specific places in the brain. The combined effects of naltrexone and bupropion are to reduce appetite. CNS pathways that regulate food intake and body weight are the hypothalamic melanocortin system and the mesolimbic reward system. These

systems are the target of the bupropion and naltrexone combination (69, 70). Treatment with Mysimba leads to approximately 5 % larger weight loss than in the placebo group at 1 year (71).

Liraglutide 3.0 mg daily (Saxenda) is a glucagon-like peptide-1 receptor (GLP-1 receptor) agonist approved for the treatment of obesity. Liraglutide has central (e.g. hypothalamus, brainstem, cortical area) (Figure 2) and gastrointestinal effects. It delays gastric emptying and decreases food intake as well as subjective hunger. Liraglutide also increases insulin release from the pancreas and decreases excessive glucagon release. It has been reported that daily injections of liraglutide 3.0 mg results in on-average 5% larger weight loss than placebo injections after one year (71).

Once-weekly semaglutide 2.4 mg (Wegovy) showed a 12% larger weight loss than placebo after 1 year (72). Qsiva, is an appetite suppressant which combines phentermine/topiramate and has now been approved for marketing in Norway. A number of promising new weight reducing drugs are under development, e.g. tirzepatide (Mounjaro), which is associated with a mean 1-year weight loss of approximately 20% (73, 74). An overview of current pharmacological therapy is shown below in Table 3.

Table 3. Pharmacological treatment-current*

	Approved	Mechanisms of action	Weight loss (% change)	Side effects
Orlistat (Xenical)	1999	Preventing the absorption of ingested fats by inhibiting intestinal lipase	2.6 kg (3.0%)	Bloating, fecal incontinence,malabsorption of fat-soluble vitamins and medications
Phentermine/topiramate (Qsiva)	2012	Phenetermine (appetite suppressant). Topiramate(↑fullness, ↓appetite and↓cravings↑energy expenditure)	8.8 kg (6.8%)	Dizziness,paraesthesia,insomnia,dry mouth, glaucoma,suicidal tendency
Naltrexone/bupropion (Mysimba)	2014	Dopamine and norepinephrine reuptake inhibitor.Promote satiety and inhibit reward system	5.0 kg (4.0%)	Nausea, constipation, vomiting dizziness, dry mouth and headache
Liraglutide (Saxenda)	2014	Glucagon-like peptide-1 (GLP-1) receptor agonist. Slows GI transit, alters glucose homeostasis and↓appetite	5.3 kg (5.4%)	Nausea, vomiting, gallbladder disease, pancreatitis
Semaglutide (Wegovy)	2021	Glucagon-like peptide-1 (GLP-1) receptor agonist ↓in energy intake owing to ↓appetite via effects in the hypothalamus and area postrema of the brain	11.2 kg (12.4 %)	Nausea, diarrhea, constipation, gallbladder related disorders, pancreatitis

* Source: May et al. Ther Adv Endocrinol Metab 2020 (69), Son JW et al. Diabetes Metab J. 2020 (75).

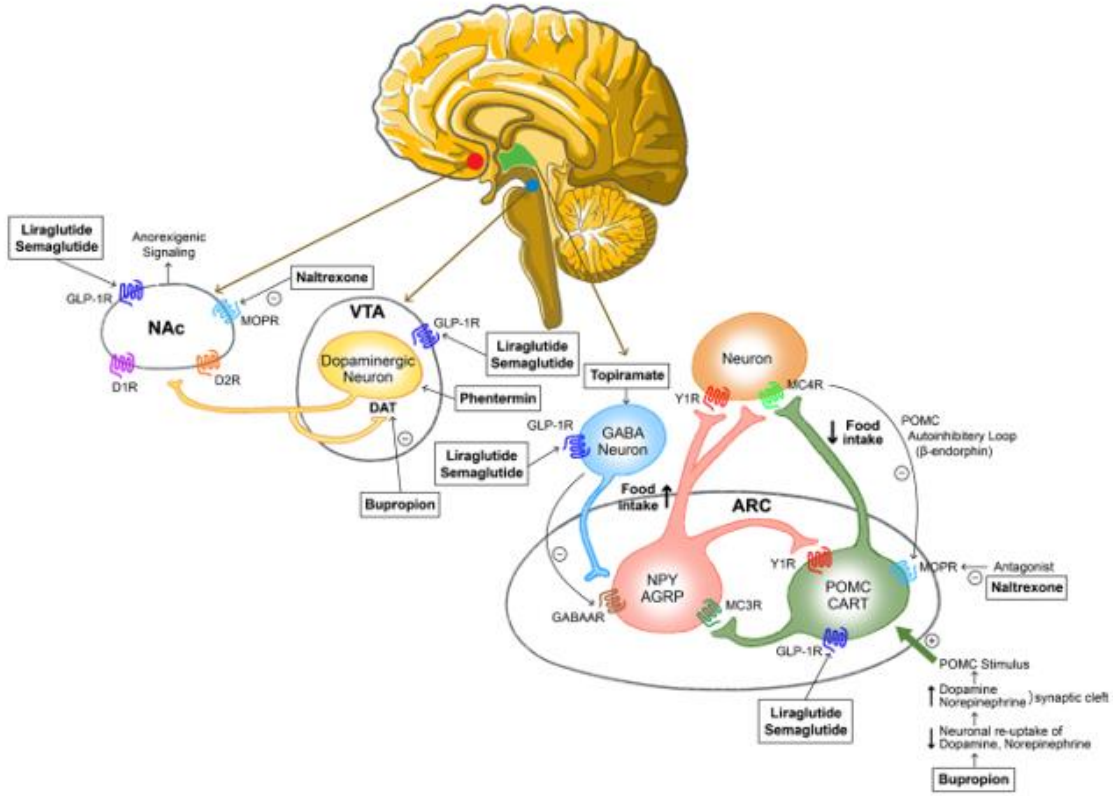


Figure 2. Central mechanisms of anti-obesity drugs, reproduced from Tak et al. with permission(71).
AGRP, agouti-related peptide; ARC, arcuate nucleus; CART, cocaine- and amphetamine-regulated transcript; DAT, dopamine active transporter; D1R, dopamine 1-class receptor; D2R, dopamine 2-class receptor; GABA, gamma-aminobutyric acid; GABAAR, gamma-aminobutyric acid type A receptor; GLP-1R, glucagon-like peptide-1 receptor; MC3R, melanocortin-3 receptor; MC4R, melanocortin-4 receptor; MOPR, μ-opioid receptor; NAc, nucleus accumbens; NPY, neuropeptide Y; POMC, proopio-melanocortin; VTA, ventral tegmental area; Y1R, neuropeptide Y receptor type 1.

1.2.7 Obesity- surgical treatment (bariatric surgery)

People with severe obesity, who respond poorly to intensive lifestyle intervention alone, or in combination with drug therapy, may be appropriate candidates for bariatric surgery.

RYGB and SG are the most used methods within bariatric surgery. RYGB involves a creation of small gastric pouch (25 mL). Further, proximal loop of small intestine anastomoses to the pouch and then an entero-enteroanastomosis makes with an alimentary limb of 120 cm and a bileopancreatic limb of 60 cm. As a result food bypasses most of the stomach, duodenum and jejunum. In the SG

surgery, the stomach is divided along its vertical length creating a sleeve. Approximately 75% of the stomach is removed.

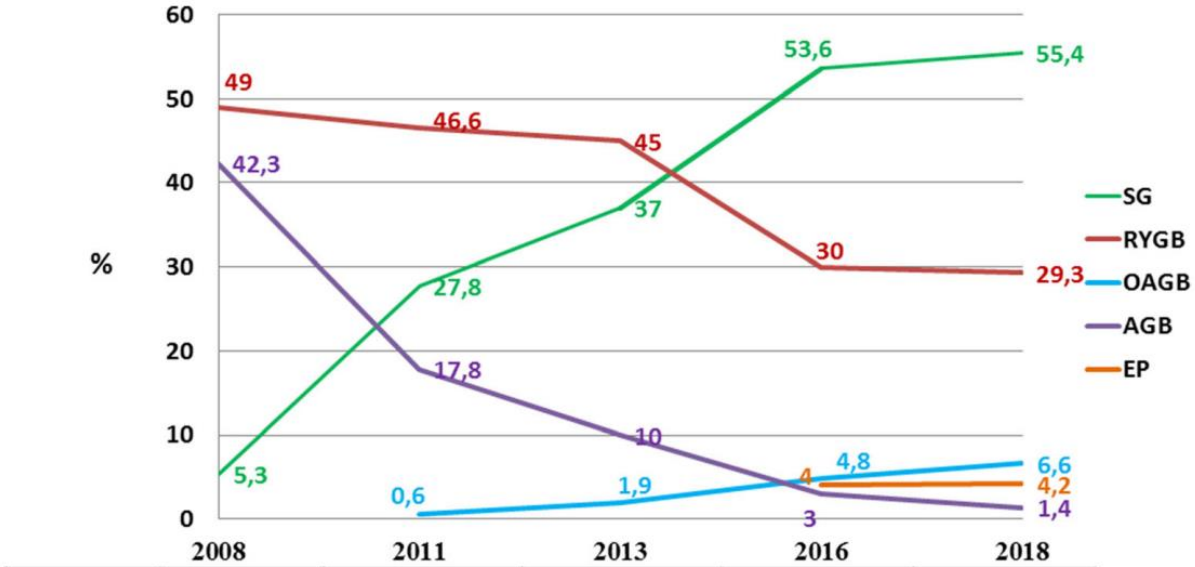
Bariatric surgery induces weight loss through several mechanisms (76). First, both the altered anatomy of the stomach after RYGB and SG, and the bypassing of the duodenum and proximal small intestine after RYGB, give rapid delivery of nutritient to more distal parts of the small intestine which have a high density of enteroendocrine L-cells . These L-cells respond to food (particulalry carbohydrates) with increased production and secretion of GLP-1. GLP-1 reduces appetite and increases the release of insulin by pancreatic beta-cells. The postprandial elevated secretion of anorectic gut peptides may be the most important factor responsible for increase in satiety. In addition to GLP-1, another anorexigenic gut hormone, PYY, is secreted in connection with food intake. There is evidence that the postprandial increases in GLP-1 and PPY after SG are lower than after RYGB, and this might partly explain the difference in weight loss and weight regain between these two procedures (76).

Further, it has been suggested that increased resting energy expenditure may be a contributing mechanism to weight loss after RYGB, but the evidence is conflicting (76). Some recent studies showed resting energy expenditure to variously decrease (77), remain stable (78) or increase (79) within the first year after RYGB . There was no change in total energy consumtion after SG (80).

Bile acids may also have a role in postoperative weight loss, possibly due to increased GLP-1 secretion and the direct association with improved glucose homeostasis. The proposed mechanisms for the beneficial effects of bile acids on glucose homeostasis is due to a decreased hepatic gluconeogenesis and delayed intestinal glucose absorption. Studies have shown that bile acid concentrations in the systemic circulation are increased after RYGB and SG, probably because of of alterations in bile acids transport (76, 81, 82). Third, during obesity, the gut microbiota changes with compositional and functional alterations. These changes have been associated with low-grade inflammation, increased body weight, increased fat mass, and the development of T2D.

Some studies have reported association between gut microbiota and adipose tissue gene regulation (83). Microbiota like Firmicutes and Bacteroidetes have been found to be associated with obesity. Changes in gut microbiota after bariatric surgery are currently being proposed as one the many mechanism explaining beneficial weight loss and remission of T2D. One of the explanatory mechanisms as to why gut microbiota may lead to weight loss might be through the stimulation of GLP-1 secretion via short-chain fatty acids (76, 84).

The types and number of bariatric procedures performed in the world have changed dramatically. The total annual number of procedures has doubled over the last decade, up to almost 700 000 procedures a year (85). This means that more than 100 000 patients with obesity and T2D undergo bariatric surgery every year.The doubling in bariatric procedures is almost entirely due to the introduction of SG. The number of RYGB- operations has been relatively stable. In 2018, the proportion of SG- and RYGB-procedures was 55% and 29%, respectively (Figure 3) (85, 86).



Bariatric procedures (N)	344,221	340,768	468,609	685,874	696,191

Figure 3. Bariatric surgery worldwide from 2008-2018. Reproduced from Angrisani et al.(85) with permission.
AGB, adjustable gastric banding; EP, endoscopic procedures; OAGB, one anastomosis gastric bypass; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy.

RYGB was introduced first as open surgery in the 1960s and as laparoscopic procedure in 1994. Cesar Roux, a Swiss surgeon, was in 1892 the first to perform a Y loop to treat gastric outlet obstruction due to carcinoma or peptic ulcer disease (87). The procedure was adapted in 1967 by Edward Mason, who associated the restrictive effect of the gastric pouch to the reduced bowel absorption of the Roux-en-Y reconstruction and created the first surgical procedure to treat obesity (88). Development of laparoscopic techniques improved operating time significantly and made the procedure safe and effective, wherein a a gastric pouch is created with bypass of the remaining stomach and first segment of small intestine (Figure 4).

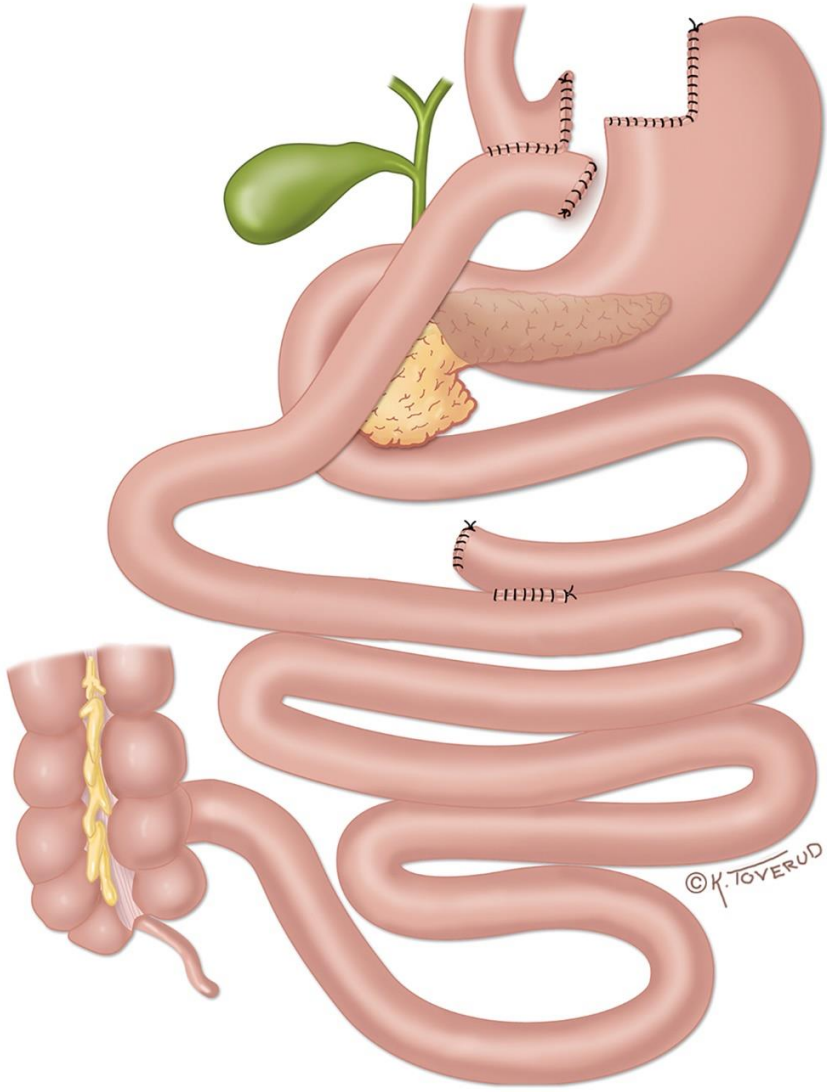


Figure 4. Roux-en-Y gastric bypass by © Kari C. Toverud CMI (certified medical illustrator), with permission.

About 18 % of total bariatric procedures performed from 2011 to 2017 were estimated to be RYGB (5). Several studies have documented the beneficial effects of RYGB on weight loss, remission of T2DM and improvement of existing GERD (23, 89). The creation of a small gastric pouch, the exclusion of the fundus and most parts of the body decreased acid secretion and at the same time reduced gastroesophageal reflux. The Roux-en Y configuration avoids bile reflux (90).

SG was introduced first as open surgery in 1988 and then as laparoscopic technique in 1999 and accounted for 59% of bariatric surgery performed in the years 2011-2017 (5).

SG is purely a restrictive procedure, performed by removing the greater curvature of the stomach, a resection of 80% of the stomach leaving a tube-shaped gastric pouch and the small intestine intact (Figure 5).

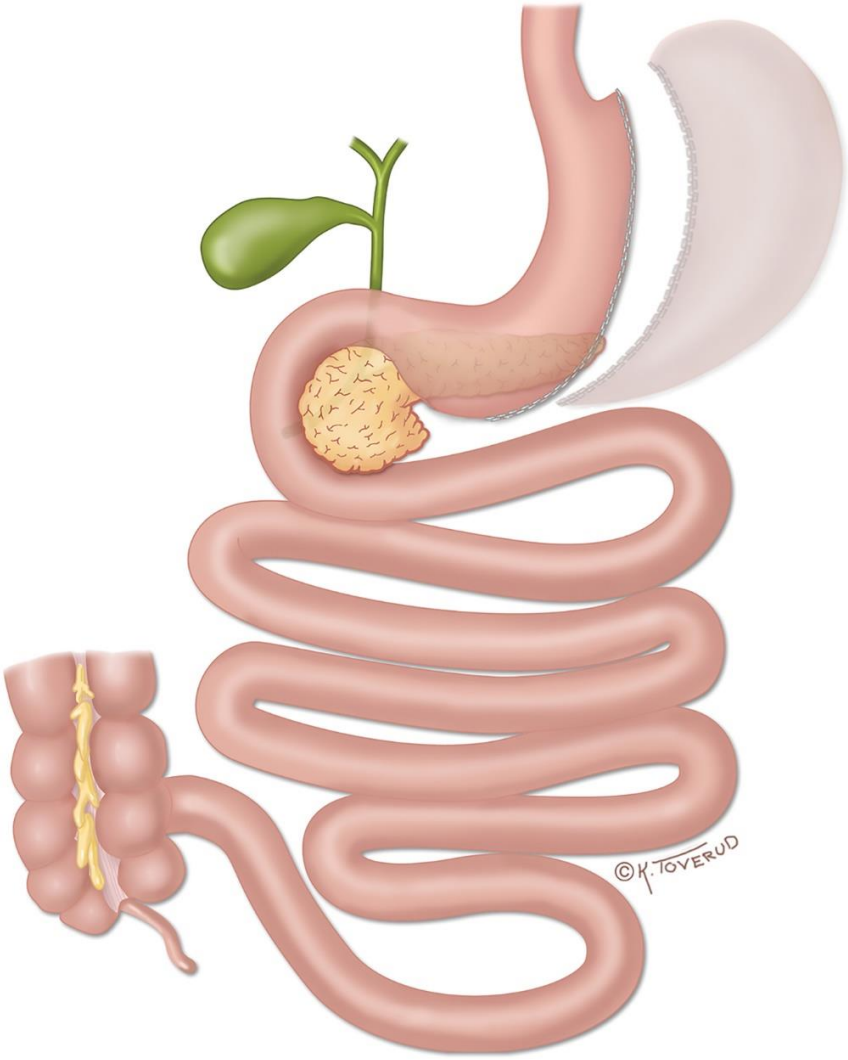


Figure 5. Sleeve gastrectomy by © Kari C. Toverud CMI (certified medical illustrator), with permission.

SGs technical simplicity, the lower incidence of surgical complications, and the fact that the procedure can later be converted to RYGB in case of insufficient weight loss ensures its attractiveness (23). SG also has many advantage such as intact pylorus, no mobilization of the small intestine, no possibility of internal hernation, reduced risk of dumping, no bypass of the small intestine, less malabsorption syndrome and ERCP is still possible. Additionally, SG can still be converted into RYGB if complications occur.

1.3 Type 2 Diabetes (T2D)

1.3.1 Definition, classification, pathogenesis and complications of T2D

The diagnosis of diabetes is made when glycated hemoglobin (HbA1c) is greater than or equal to 48 mmol/mol (6.5%), or fasting blood glucose is greater than or equal to 7.0 mmol/l, or a 2-hour blood glucose is greater than or equal to 11.1 mmol/l after a 75 g oral glucose tolerance test (OGTT) (91). Diabetes mellitus is a group of metabolic disorders characterized by persistent elevated blood glucose levels with disturbances of carbohydrate, fat and protein metabolism which is caused by the absence of or defects in insulin secretion from the pancreatic beta cells. T2D is the most common form of diabetes and accounts for over 90% of all diabetes cases worldwide (92). Important factors in T2D pathogenesis are low insulin production from pancreatic beta-cells and peripheral insulin resistance (55, 93).

Adipose tissue produces non-esterified fatty acids, glycerol, hormones and proinflammatory cytokines which are involved in the development of insulin resistance in people with obesity. When insulin resistance is accompanied by pancreatic beta-cell dysfunction, glycemic control worsens resulting in diabetes. Insulin resistance is the common link associated with obesity and T2D (94, 95).

1.3.2 Type 2 diabetes and obesity

The majority of people who develop T2D have overweight or obesity (6, 96). Women and men with BMI≥35 kg/m² have 93- and 42 times higher risk of developing diabetes, respectively (97, 98). There is a a strong relationship between obesity and T2D due to various pathophysiological mechanisms (5, 95). Pancreatic beta-cells can normally compensate by increasing insulin production to maintain glucose homeostasis, but with an increase in adipose tissue, the combination of declining insulin production and increasing insulin resistance results in the inability of the body to maintain euglycemia and might lead to development of T2D.

1.3.3 Prevalence of type 2 diabetes

The worldwide prevalence of T2D is expected to increase from 171 million people at the start of this century to 380 million people by 2030 with an yearly incidence of about 20.8 million (99) . Similar patterns are seen in Norway. Data from the large Norwegian-population based study, the Nord-Trøndelag Health surveys (HUNT) conducted from 2017-2019, showed a prevalence of T2D of 6.0 % (93), including 0.7% previously undiagnosed diabetes as confirmed by HbA1c equal to or above the diagnostic threshold (48 mmol/mol) (93).

1.3.4 Complications of type 2 diabetes

The medical and socioeconomic burdens of T2D are considerable and primarily caused by microvascular (retinopathy, neuropathy, nephropathy) and macrovascular (cardiovascular disease) complications. The pathogenesis of gastrointestinal symptoms in diabetes is associated with autonomic neuropathy. Esophageal dysmotility is ofen found in patients with diabetic neuropathy. Esophageal transit might be delayed in 35% of patients with T2D (11). Both obesity and T2D are associated with impaired quality of life, impaired gastrointestinal quality of life and a high prevalence of GERD and esophageal motility disorders (11, 94). Higher mortality rates among people with obesity seem to be explained by obesity related co-morbidities such T2D rather than obesity alone (100).

1.3.5 Type 2 diabetes - treatment options

Modern treatment of T2D primarly focuses on weight loss, which improves glycemic control, and quality of life, which may prevent microvascular and macrovascular complications.

First, patients should be counselled to improve their dietary habits and reduce their caloric intake in order to lose weight and improve metabolic control. If lifestyle changes are difficult to achieve, a weight loss drug may be added to make it easier to achieve a sufficient weight loss.

Eventually, bariatric surgery might be indicated in selected patients with severe obesity with insufficient effects of pharmacological weight loss therapy. In people with T2D and obesity even a weight loss of 2-5 % may improve glycemia and reduce or prevent using of anti-diabetic medications (101).

Greater weight loss reduces HbA1c and fasting glucose significantly and may lead to diabetes remission. Glucose lowering drugs are important in order to prevent hyperglycemia. Drugs such as insulin, sulphonylureas and metformin reduce the risk of microvascular complications (102, 103).

Newer medications, such as GLP-1 agonists, have benefical effects on both glycemia and body weight (72). Lifestyle interventions such as low-calorie diet and /or physical activity have also been shown to improve glycemic control (104).

Surgical weight reduction has been the best treatment for patients diagnosed with both severe obesity and T2D (5). Clinical studies demonstrate that bariatric surgery has a superior T2D remission rate and glycemic control when compared with medical therapy (105-107). The most commonly performed procedures which treat both obesity and T2D are SG and RYGB. Therefore, obesity management is an very important factor for treatment of T2D. The American Diabetes Association (ADA) published a consensus statement defining diabetes remission as "*a return of HbA_{1c} to <6.5% (<48 mmol/mol) that occurs spontaneously or following an intervention and that persists for at least 3 months in the absence of usual glucose-lowering pharmacotherapy*"(108).

1.4 Gastroesophageal reflux disease (GERD)

1.4.1 Definition, classification and pathogenesis of GERD

GERD is a condition in which gastric contents flow back (returns) into the esophagus (food pipe), resulting in heartburn, acid regurgitation and damage to the esophageal mucosa. It is defined as a disease when mild symptoms occur more than twice a week or there moderate symptoms more than once a week, according to the Montreal classification (109, 110). GERD is subclassified into esophageal- or extra-esophageal disease. The cardinal symptoms in GERD patients are heartburn and regurgitation (11). GERD includes erosive esophagitis and endoscopy-negative disease, which is called non-erosive reflux disease (NERD). The diagnosis of GERD should ideally be made by integrating the presence of GERD-symptoms with the results of esophagogastroduodenoscopy (EGD) and/or 24-hour pH monitoring (110, 111).

Pathological acid reflux is defined according to the Lyon criteria with *conclusive evidence of pathological acid reflux* as either erosive esophagitis Los Angeles (LA) grade C or D (112), long segment Barrett's esophagus (BE), peptic esophageal stricture or total acid exposure time (AET) >6% (27, 112). The anti-reflux mechanism of the esophagus consists of the lower esophagus sphincter (LES), the angle of His, and the muscle fibers of the diaphragm. The LES is 2 to 4 cm in length of the distal esophagus and consists of contracted circular smooth muscle located within the diaphragm hiatus. Gastroesophageal reflux occurs when gastric content enters the distal esophagus, stimulating the chemoreceptors and causing irritation, which leads to the manifestation of symptoms (113, 114). The main mechanism that leads to physiologic reflux is transient lower esophageal sphincter relaxations (TLESRs). TLESRs is a relaxation occurring without preceding swallowing. Different stimuli such as distension of the stomach after meals may activate TLESRs (114, 115). TLESRs occur also in the upright position. In patients with GERD there is often an increased frequency of TLESRs (116).

In GERD patients, TLESRs are two times more likely to be associated with acid reflux (117).

The pathophysiological mechanisms predisposing to GERD in patients with obesity include obesity related hiatal hernia, especially hiatal hernia greater than 2 cm, higher intra-gastric and intra-abdominal pressure, and decreased LES pressure (10, 118, 119). Increased levels of estrogen, increased production of bile acids and pancreatic enzymes may also contribute to GERD (10, 32, 118, 120). The composition of biliary refluxate, such as conjugated bile acids is a factor that may promote mucosal damage and lead to GERD symptoms and BE.

1.4.2 GERD- prevalence

GERD is common, with a worldwide prevalence of 8–33% (112, 121, 122). A meta-analysis of 19 studies found a prevalence of 14% in people younger than 50 years and 17% in people 50 years or older (9, 123, 124). Patients with obesity *and* T2D have a high prevalence of GERD (10, 30) and may be more susceptible to asymptomatic GERD (11, 31, 125). The Diamond trial showed that the diagnosis of GERD based on symptoms lacks sensitivity and specificity (126).

In general, the frequency and severity of GERD symptoms, especially heartburn, do not associate with degree of esophageal damage (127). According to the Diamond study, the sensitivity and specificity for symptom-based diagnosis of GERD was 63% and 63% by family practitioners and 67% and 70% by gastroenterologists, respectively (126). Questionnaire based diagnosis of GERD identified patients with GERD with only 62% sensitivity and 67% specificity (126). Diagnosis of GERD based on effect of test treatment with the proton pump inhibitors (PPIs) identified patients with GERD with 78% sensitivity and 54 % specificity respectively (128).

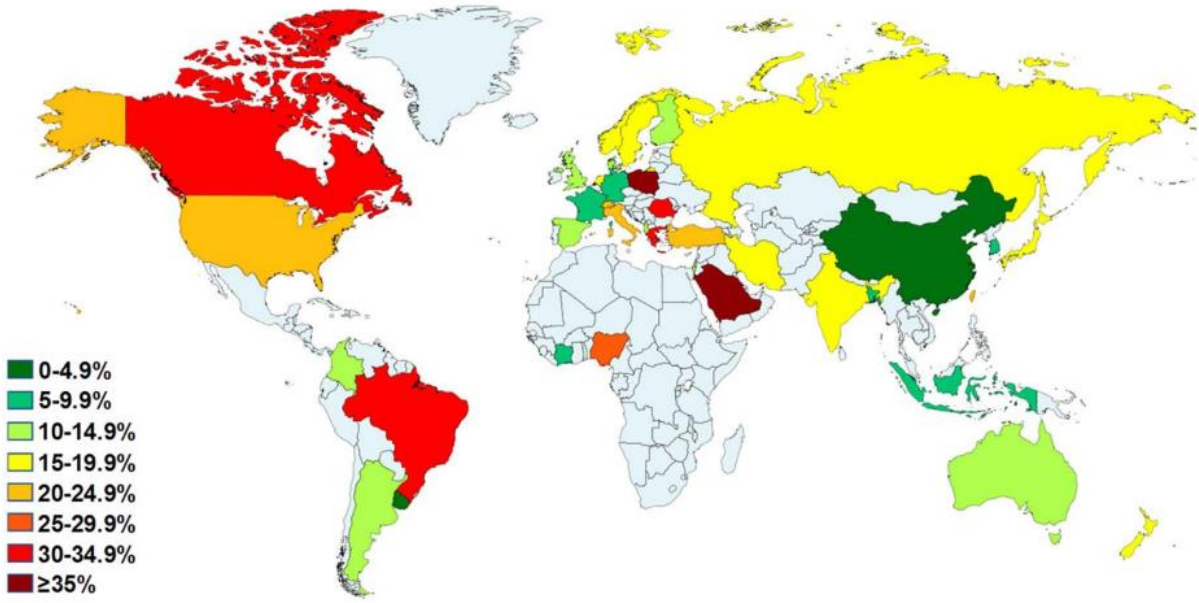


Figure 6. Distribution of GERD prevalence according to country, reproduced from Nirwan et al. (124) with permission.

1.4.3 GERD- complications

Long-standing GERD may cause complications (25, 26). The most common complication of GERD is erosive esophagitis which is a condition with mucosal inflammation in distal esophagus and occurs in 18% to 25% of patients with GERD symptoms (129, 130). Peptic esophageal ulcers and strictures may occur if the acidic exposure to the esophagus results in fibrotic scarring and have a incidence of 7% to 23% in untreated patients (131). BE with a prevalence of about 7%, can lead to esophageal adenocarcinoma, especially the presence of long-segment BE (≥ 3 cm) increases the risk of adenocarcinoma. The risk of adenocarcinoma in patients with BE is 30 to 60 times higher than in the general population (132). A study concluded that people with obesity have a five-fold increased risk of BE and adenocarcinoma in esophagus (133). The global incidence rate of esophageal adenocarcinoma is estimated to be 1.1 cases per 100 000 men and 0.3 per 100 000 women (134).

1.4.4 GERD- treatment options and surveillance

The goal of anti-reflux treatment is to control symptoms, prevent complications and improve quality of life (135). There are many options to treat GERD, including lifestyle modifications, medical- and surgical treatment (135). Lifestyle modifications are the first-line therapy and include elevation of the head of the bed, weight loss, caution with alcohol, caffeine, tobacco and spicy foods. Gastric acid inhibitors with proton pump inhibitors (PPIs) or/and H2 blockers (H2RAs) are at present the mainstay GERD therapy. However, the long-term use of PPIs may increase the risk of hip fractures, pneumonia and diarrhea. In addition, tachyphylaxis can occur with H2RAs after starting treatment, which limits the regular use of these drugs in GERD management (135). Patients with refractory GERD, despite high-dose PPIs and H2Ras, and especially those with hiatal hernia, may all benefit from anti-reflux surgery. There are several surgical options available, like total fundoplication (Nissen type), partial fundoplication (anterior or posterior) and magnetic sphincter augmentation (136). Bariatric procedures like RYGB has also been proposed as treatment option for obesity combined with GERD.

To prevent the progression of BE to adenocarcinoma, endoscopic surveillance is recommended in persons with known BE (114, 134). The ESGE recommends varying surveillance intervals for different BE lengths (137). For patients with an irregular columnar-lined esophagus of < 1 cm, no endoscopic surveillance or biopsies are recommended. For BE ≥1 cm and <3 cm, endoscopic surveillance should be repeated every 5 years. For BE ≥3 cm and < 10 cm endoscopic examination every 3 years is recommended. Patients with BE ≥10 cm should be referred to a expert center.

1.4.5 GERD and obesity

Obesity is an independent risk factor for GERD (120). GERD has been reported in 62% to 73% of patients seeking bariatric surgery (138, 139). El-Serag et al (140) showed that patients with a BMI > 30 kg/m² are 2.5 times more likely to have reflux symptoms and/or erosive esophagitis than those

with a normal BMI. Epidemiological studies demonstrated an increased prevalence of GERD in patients with obesity (141, 142). Prospective screening endoscopy studies evaluating erosive esophagitis in people with obesity are limited and restricted to pre-bariatric surgery populations. Prospective endoscopic studies have documented a high prevalence of erosive esophagitis in people with obesity ranging from 17% to 54% (143, 144). Obesity itself had a carcinogenetic effect that can stimulate cell proliferation and inhibit apoptosis (133). This is why the monitoring of people with obesity, GERD and BE is important for preventing the development of adenocarcinoma. The association of BE with obesity has been shown in the study of Stein et al., who found that for each 5-unit increase in BMI the risk of BE increased by 35% (145). Another study concluded that people with obesity have a five-fold increased risk of BE and adenocarcinoma in esophagus (133). However, no association between obesity and BE has been reported in the study of Lagergren et al. (146). Nevertheless, recent studies have found obesity to be a significant risk factor for GERD and BE with a clear association between BMI and GERD/ BE (133, 147).

1.4.6 GERD and type 2 diabetes

T2D is a risk factor for GERD, and a 40% prevalence of GERD has been found in patients with T2D (11, 141). The pathophysiology of GERD in patients with T2D is multifactorial. It has been hypothesized that motility disorders may play a role (26), e.g. esophageal transit which has an important role in GERD pathogenesis is delayed in 35% of patients with T2D (11). Gastroparesis is commonly observed in patients with diabetic neuropathy and may increase the risk of GERD (148). Acute changes in blood glucose concentration affect gastric emptying, for example, acute hyperglycemia with blood glucose of 15 mmol/l or more decreases the rate of gastric emptying in diabetic patients (149). Moreover, a correlation between diabetic autonomic neuropathy and esophageal dysfunction has been found (11, 148). It is, however, uncertain whether patients with obesity and T2D have a higher risk of of GERD than those without T2D.

A meta-analysis of nine observational studies assessed the association between T2D and GERD in a population of individuals with diabetes compared to controls without diabetes (11). This analysis showed that diabetes was a significant risk factor for the prevalence of GERD. Further, it is well known that GERD symptoms and endoscopic findings are weakly correlated in this group of patients (29, 30, 32, 148).

1.4.7 Bariatric surgery (RYGB and SG) in persons with severe obesity and GERD

Bariatric surgery like SG and RYGB induces a substantial weight loss and is also an effective treatment for T2D (5). Some studies suggest a larger weight loss and approximately 70% remission of T2D one year after RYGB. However, other studies indicate a similar effect of SG and RYGB on weight loss. The choice of bariatric procedure should not be solely based on the effect on weight loss, but also other factors such as preexisting GERD and T2D. Larger weight loss can contribute to improvement of GERD, however, many studies have showed increasing prevalence and severity of GERD following SG and high incidences of "new-onset" GERD after SG, varying from 5 % to 32 % (150-152). In contrast, RYGB is considered an effective anti-reflux procedure independent of weight loss (153, 154).

1.4.8 Esophageal motility disorders (dysmotility) in persons with obesity and diabetes

Esophageal dysmotility is a condition when muscles and the enteric nervous system of the esophagus do not work properly and this may lead to swallowing problems (dysphagia), heartburn and chest pain (155). Esophageal motility disorders in patients with severe obesity has a prevalence between 20% to 61%. The most common dysmotility disorder in patients with severe obesity is hypotensive lower esophageal sphincter (LES) and disturbance in esophageal body contractility such as ineffective esophageal motility (IEM), hypercontractile esophagus)(156). In patients with T2D, esophageal motility disorders occur in up to 63% (157). Esophageal motility disorders can be

related to hyperglycemia, autonomic neuropathy, biomechanical and sensory alterations of the esophagus.

Diabetes may be associated with high amplitude waves, multiphase waves, hypertensive LES, and reduced LES relaxation, which again may cause lower wave amplitude, and a lower peristaltic velocity related to autonomic neuropathy. These changes may result in dysphagia and increased risk of GERD (113, 158).

1.4.9 Esophageal motility disorders and GERD

The GERD-protective mechanism at the esophago-gastric junction consists of the LES, a smooth muscle structure, and of the crural diaphragm, a skeletal muscle structure. These two structures are called the internal and the external LES, respectively. The smooth muscles of the LES consist of clasp and sling fibers (113). Most reflux occurs when LES and the crural diaphragm are anatomically separate and form a so called sliding hiatus hernia.

Esophageal peristalsis is important in order to reduce the volume of the refluxate and the duration of esophageal exposure to gastric contents. Abnormalities in esophageal peristalsis give prolonged exposure of the esophagus to gastric contents, which may lead to GERD symptoms and esophagitis (155). Motility changes of esophagus related to GERD are reduced amplitude of esophageal contractions, fewer peristaltic waves, abnormal peristalsis, decreased velocity of peristalsis and reduced LES pressure (11, 159). Patients with obesity and/or T2D have a high prevalence (40%-70%) of GERD and esophageal motility disorders (10). The high prevalence of GERD in patients with T2D is associated with motility disturbances and LES alterations (160).

The prevalence of motility disorders in patients with obesity and GERD is high and include LES basal pressure alteration, disturbed LES relaxation, ineffective esophageal motility (IEM) and hypercontractile esophagus (10, 160).

1.5 Patient-reported outcomes (PROs)

Patient-reported outcomes (PROs) are defined as "*any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else* "(161, 162). PROs refer to patient-reported: ``1) *disease symptoms or treatment side effects, such as pain, fatigue, or anxiety; 2) functional outcomes such as physical, sexual, social, role, emotional, or cognitive functioning; or 3) multidimensional constructs such as health-related quality of life (HRQoL) or health utility*``(161, 162). The patient experience has a central role for comprehensive assessment of the impact of treatment, e.g. treatment of obesity and self-assessed health status is an important predictor of mortality and morbidity (163).

Health related quality of life (HRQoL) is an important PRO. HRQoL is defined as "*a multidomain concept that represents the patient's general perception of the impact of an illness and its treatment on physical, psychological, and social aspects of life"*(164).

Obesity and type 2 diabetes are associated with impaired HRQoL, depression, eating disorders and gastrointestinal symptoms. One of the earliest references to quality of life is in the Nichomachean Ethics, where Aristotle (384-322 BC) describes QoL as: "*Both the multitude and persons of refinement conceive the good life or doing well to be the same thing as being happy (165).* WHO (1948) declared health to be "*a state of complete physical, mental and social well-being and not merely the absence of disease*" (165). People with obesity suffer from social stigma and discrimination related to their weight, which is associated with negative physical and psychological outcomes like impaired HRQL, depression, anxiety, eating disorders, gastrointestinal symptoms and body image dissatisfaction (17, 166-168). At least one of these diagnoses has been found in 42% of patients with obesity (169-171).

Bariatric surgery, especially RYGB and SG, has beneficial effects on weight loss, diabetes control and HRQoL.

To determine which PROs among people living with obesity were the most important, and to select patient-reported outcome measures that can be chosen for measuring selected PROs, a global

multidisciplinary consensus meeting took place and the following PROs were included: self-esteem, physical health, mental health, social health, stigma, eating, body image, and excess skin (172).

The BARIAtric and metabolic surgery Clinical Trials (BARIACT) study developed a Core outcome set (COS) for bariatric and metabolic surgery in terms of the benefits and adverse events, with overall HRQoL one of the nine selected core outcomes (172, 173). By using PROs in clinical trials, patients can communicate their treatment experiences, which may help patients and doctors to choose the best available treatment by providing the costs and benefits ofdifferent treatments and improve future clinical trial methods. SG and RYGB have beneficial effects on weight loss, diabetes control and HRQoL, but at the potential cost of new-onset or worsening of depression or binge eating problems as well as various side effects including gastrointestinal symptoms, mental health symptoms, dumping syndrome and postprandial hypoglycaemia . Dumping syndrome and other troublesome gastrointestinal symptoms may increase after both SG and RYGB, while reflux symptoms are commonly observed after SG. PROs are secondary outcomes in this thesis. Article III focuses on changes in depression and binge eating problems as well as various side effects including gastrointestinal symptoms, mental health symptoms, dumping syndrome and postprandial hypoglycaemia at 3 years after surgery.

In the literature, dumping syndrome has been reported to occur in approximately 40% of patients after RYGB or SG and is categorized as early or late dumping (174). Early dumping occurs due to a rapid gastric emptying characterized by gastrointestinal and vasomotor symptoms after intake of meals. Bariatric surgery either reduces gastric volume or removes pylorus which results in rapid delivery of food (rapid gastric emptying) to duodenum and small intestine and causes distention and contribute contractions and gastrointestinal symptoms. Another mechanism in early dumping syndrome involves increased release of GI hormones and vasoactive agents such as vasoactive intestinal peptide, incretins GIP and GLP-1, insulin and glucagon (174-176).

Early dumping syndrome is characterized by a combination of gastrointestinal symptoms (pain,

diarrhoea, bloating, nausea) and vasomotor symptoms (sweating, flushing, dizziness, palpitations) within 1 hour after a meal(174, 177). Early dumping syndrome occurs often than late dumping. The pathophysiology of late dumping syndrome is connected to either the hyperinsulinemic response or reactive hypoglycemia. Late dumping occurs up to 3 hours after a meal (174). Rapid delivery of undigested carbohydrates to the small intestine results in high glucose concentrations that induce a hyperinsulinemic response resulting in hypoglycemia. Late dumping occurs up to 3 hours after a meal (174). Late dumping syndrome (sweating, palpitations,hunger, drowsiness/ unconsciousness, tremor, irritability) typically occurs 1 to 3 hours postprandially. Isolated late dumping syndrome with hypoglycemia as the only symptom occurs in about 25% of patients (175). Dumping syndrome is highly associated with reduction in quality of life.

PROs give information about the patient's experience and effectiveness of interventions, and PRO measures (PROMs) are what we call the tools used to collect this information (172). According to the US FAD Administration (2009) the definition of PROMs is ``*Any report of the status of a patient`s health condition that comes directly from the patient, without interpretation of the patient`s response by a clinician or anyone else*``(162). A wide variety of PROMs have been used in obesity treatment research. The International Consortium for Health Outcomes Measurement (ICHOM) and the Core Outcome Measures in Effectiveness Trials (COMET) initiative encourage standardization of outcome measurement in clinical practice and clinical trials (172).

2 Rationale, aims and objectives of the studies

2.1 Paper 1

Rationale

Many studies have confirmed the association between T2D and GERD in the general population (123). The potential association between GERD and T2D in patients with severe obesity is less clear (11), and whether patients with T2D scheduled for bariatric surgery have a higher prevalence of GERD than those without T2D is uncertain. Further, it is well known that GERD symptoms and objective GERD findings are weakly correlated (30), but the relationship between erosive esophagitis and GERD symptoms in patients with and without T2D is not fully examined.

Aims and objectives

First, we aimed to compare the prevalence of GERD symptoms and erosive esophagitis in patients with severe obesity with or without T2D, hypothesizing that patients with T2D scheduled for bariatric surgery had a higher prevalence of erosive esophagitis than patients without T2D. Second, we aimed to assess the correlation between pathological acid reflux, erosive esophagitis and symptoms in patients with or without T2D, hypothesizing that patients with T2D with erosive esophagitis had less GERD symptoms than those without T2D. Third, we assessed whether there was an association between pathological acid reflux and erosive esophagitis in this patient group with obesity and T2D (178, 179).

2.2 Paper 2

Rationale

Weight loss reduces GERD in patients with severe obesity. RYGB may further reduce GERD independent of weight loss (153, 154), while SG may be increase risk of GERD (150, 151). Previous studies assessing GERD after bariatric surgery, especially after SG, were limited due to unclear definition of GERD. It is uncertain whether SG and RYGB affect GERD differently (180).

Aims and objectives

The aim of this paper was to compare the 1-year effects of SG and RYGB on prespecified GERD outcomes such as GERD symptoms (subjective findings) and erosive esophagitis, pathological acid reflux and esophageal motility (objective findings). We hypothesized that patients with T2D undergoing SG would have a higher 1-year prevalence of GERD symptoms, erosive esophagitis and pathological acid reflux than those undergoing RYGB.

2.3 Paper 3

Rationale

Obesity and T2D are associated with impaired health-related quality of life, eating disorders and bothersome symptoms from the gastrointestinal tract. RYGB and SG are effective treatment options for people with severe obesity with T2D, and both methods improve quality of life. However, only two randomized controlled trials have compared the medium- to long-term effects of RYGB and SG on changes in patient-reported outcomes (PROs) (107, 181) and no randomized study of patients with T2D has compared the medium- to long-term effects of the two surgical procedures on patient-reported gastrointestinal symptoms, dumping syndrome, postprandial hypoglycemia or eating disorders.

Aims and objectives

The aim of this paper was to investigate whether RYGB and SG differentially affect patient-reported outcomes, including gastrointestinal symptoms, dumping syndrome, weight-related symptoms, quality of life, depression, binge eating and hedonic hunger, three years after both procedures. First, we hypothesized that RYGB would be associated with a worsening of abdominal pain, indigestion, diarrhoea, and dumping syndrome compared with SG, while SG would be worse regarding reflux symptoms. Second, we hypothesized that larger weight loss after RYGB, as compared with SG, would lead to greater improvements in weight-related symptoms and weight-related quality of life.

3 Materials and Methods

3.1 Trial design and location

The "**O**besity **s**urg**e**ry in Tøns**berg**-study" (the Oseberg-study) is a randomized, triple-blind, single-center trial which primarily aimed to assess the effects of RYGB and SG on complete remission of T2D in the absence of active pharmacologic therapy (34, 182). The primary outcomes of this study have been published (34). A number of prespecified secondary outcomes including patient - reported outcomes (PROs) and GERD are presented and discussed in this thesis. The study was conducted at the Department of Endocrinology, Obesity and Nutrition at Vestfold Hospital Trust, a tertiary care obesity center in Southern Norway between January 2013 and February 2017, when inclusion was finished.

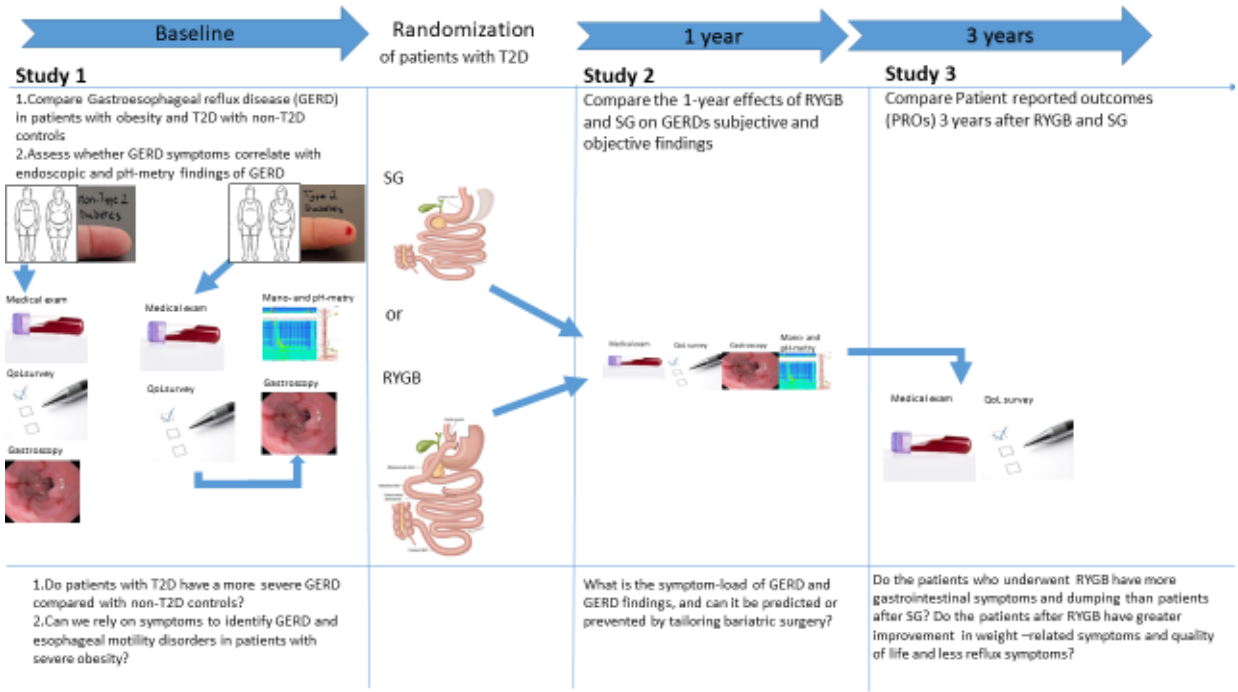


Figure 7. Schematic overview of the studies.
GERD, Gastroesophageal reflux disease; RYGB, Roux-en-Y gastric bypass; SG, Sleeve gastrectomy; T2D, type 2 diabetes.

The overview of participants and study design is shown below in Table 4.

Table 4. Overview of participants and study design.

	Study 1		Study 2	Study 3
Study design	Cross -sectional		RCT	RCT
Diagnosis	Obesity, T2D	Obesity, Non-T2D	Obesity, T2D	Obesity, T2D
Number of participants	124	64	109	109
Age, years (SD)	48.6 (9.4)	43.0 (11.0)	47.7 (9.6)	47.7 (9.6)

Data presented as observed mean (SD) and number (n); Non-T2D, non-type 2 diabetes; RCT, randomized controlled trial; T2D, type 2 diabetes.

3.2 Study participants

The patients were recruited from the waiting list for patients enrolled for treatment and accepted for bariatric surgery. All patients scheduled for bariatric surgery at the center were screened for study eligibility approximately three weeks prior to randomization (baseline).

(The timetable for the patients is shown below in Table 5).

Table 5. Patient schedule at the outpatient clinic.

Schedule	Planned activities
Outpatient clinic gastroenterology	
Day 1: Patients are fasting from midnight and arrive 08.00-09.30 Patient 1 08.30-11.00 Patient 2	1.PROMs questionnaires are filled in at the clinic by patients (Sf-36, IWQOL-Lite,WRSM,BDI,FTQ, PFS, BES, GSRS, GerdQ, The Arts' questionnaire) 2.Esophagogastroduodenoscopy (EGD) 3.Manometry 4.24-hour pH monitoring, closure of the pH probe and information about the questionnaire
Day 2: 12.00 Patient 1 12.10 Patient 2	Removing pH/impedance probe, analyses of findings and final decision if patients are eligible for inclusion

BDI, Beck Depression Inventory; BES, Binge eating scale; FTQ, Food Tolerance Questionnaire; GerdQ, Gastroesophageal Reflux Disease Questionnaire; GSRS, Gastrointestinal Symptom Rating Scale; IWQOL-Lite, Impact of Weight on Quality of Life-Lite; PFS, Power of Food Scale; PROM, patient-reported outcome measures; SF-36, Short-Form 36 Health Survey; WRSM, Weight-Related Symptom Measure.

Eligible participants were adult patients aged 18 or over, with T2D, and BMI ≥ 35 kg/m², or BMI ≥33 kg/m² with previously verified BMI≥35 kg/m².

Between October 15, 2012, and September 1, 2017, 319 consecutive patients with T2D were assessed for eligibility, 194 were excluded and 125 patients were initially enrolled and underwent a baseline examination between January 28, 2013 and February 12, 2018. Further, one patient was excluded due to undetectable c-peptide level on baseline examination, leaving 124 patients to be included.

During the first year of this study, the prevalence of erosive esophagitis was higher than expected, and the potential impact of T2D on these findings was unclear. Therefore, to explore whether the prevalence of GERD was particularly high among patients with T2D, the steering committee decided in 2014 to add a control group of bariatric patients without T2D (182). Participants in the control group were also recruited from the waiting list for bariatric surgery at the Department of Endocrinology, Obesity and Nutrition at Vestfold Hospital Trust.

3.3 Inclusion/exclusion criteria

The inclusion criteria for both groups were age ≥ 18 years and BMI ≥ 35 kg/m2, or BMI ≥33 kg/m2 with previously verified BMI ≥ 35 kg/m2.

T2D was diagnosed in patients with an HbA1c ≥ 6.5% (48 mmol/mol) or use of antidiabetic medications with HbA1c ≥ 6.1 %.

Exclusion criteria were as follows: unable to give informed consent, previous major abdominal surgery (appendectomy, laparoscopic cholecystectomy or gynaecological procedures not included), severe endocrine-, heart-, lung-, liver- and kidney disease, cancer and chronic medical conditions associated with increased risk of peri- and postoperative complications, drug or alcohol addiction, mentalmand psychiatric conditions leading to reduced compliance, pregnancy, severe GERD (LA classification grade C or D, or Barrett's esophagus), hiatal hernia > 5cm, and elevated esophageal pressure [Distal Contractile Integral (DCI) >5000 mm Hg*s*cm] with symptoms of dysphagia and/or painful swallowing and suspected malignancy.

Inclusion criteria for patients without T2D: as above, but HbA1c < 6.5 % and no anti-diabetic medication. Patients were excluded if contraindications for SG were found, and these were: GERD (LA classification grade C and D), BE and/or hiatus hernia > 5cm, and suspected malignancy.

3.4 Sample size calculation and randomization procedure/blinding

The Oseberg-study was powered to detect differences in the primary outcome which was remission of diabetes. With a two-sided 5% significance level and a power of 80%, a sample size of 55 in each group was required, and to allow for drop outs, the sample size was set to 125 patients (182).
In the Oseberg reflux-study where GERD symptoms were assessed in patients with T2D and patients without T2D, to show a mean (SD) clinically meaningful difference of at least 10 GSRS score points between groups with or without T2D (power 80% and alpha 0.05), 44 patients without T2D had to be included. Taking into account possible loss to follow-up and incomplete data, a total of 64 controls without T2D were included.
The participants were randomized using a computerized random number generator (randomization. com) with a 1:1 allocation using blocks sizes of 10. Opaque sealed envelopes were numbered, and a note with the procedure to be conducted, according to the randomization list, was placed inside the envelope. The patients, the study personnel, the primary outcome assessors and follow-up personnel were all blinded to treatment allocation at all visits until the 1-year follow-up. Only authorized staff members had access to the allocation sequence. Neither the investigators responsible for patient recruitment nor clinicians (including endoscopists) who were in contact with the patients had access to the allocation sequence. The allocation for each specific patient was revealed to the surgical staff only, in the operating room on the day of surgery where the surgeon opened the envelope and found the surgical procedure to be conducted. The surgeons did not participate in the patient follow-up.

The esophagogastroduodenoscopy (EGD) was performed by experienced consultants of gastroenterology (endoscopists) at the outpatient clinic, Vestfold Hospital Trust. During the procedure, a picture of lower esophagus sphincter (LES) was taken and erosive esophagitis was graded according to the LA classification. Afterwards, two others experienced endoscopists who did not have access to the patients identification graded erosive esophagitis based on the image of LES taking during the examination.

3.5 Interventions

3.5.1 Bariatric surgery

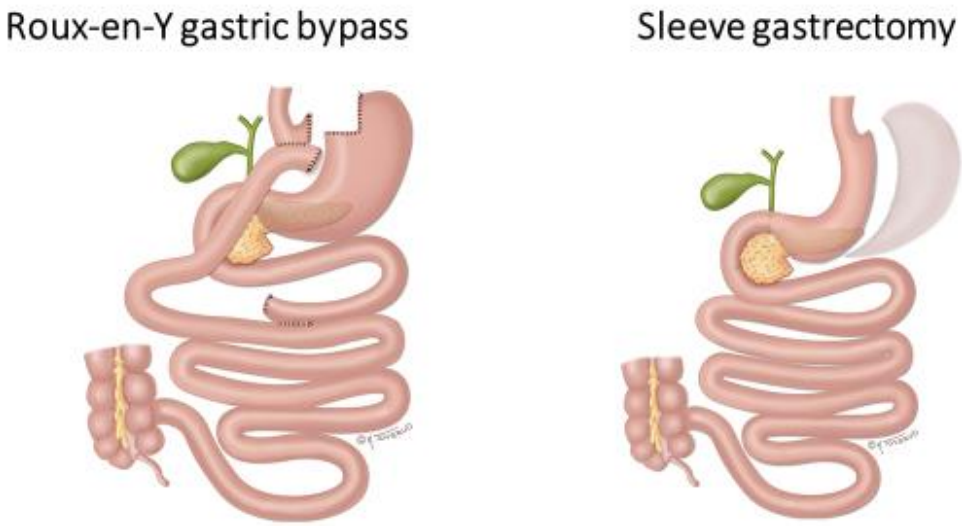


Figure 8. Anatomical differences of gastric bypass (left) and sleeve gastrectomy (right). Illustration by by © Kari C. Toverud CMI (certified medical illustrator), with permission) (183).

All procedures were performed laparoscopically by experienced surgeons. The surgical procedures were standardized and similar in both RYGB and SG (182). The two intervention groups underwent identical pre-and postoperative treatment programs, including a low-energy-diet (less than 1200 kcal/day) during the 2 weeks preceding surgery and a standard 1- year clinical follow-up with participation in group meetings and/or individual counseling at the center (182). In the RYGB the left crus was dissected free and any hiatal hernia was left in situ. The minor curvature was opened at the second vessel.The gastric pouch was created by horizontally stapling the stomach from the minor curvature and then vertically stapling to create a gastric pouch of 25 ml.

The gastrojejunostomy was created using a 45 mm stapler and completed with a running suture.

An entero-enteroanastomosis was then made 120 cm distal of the gastro-enteroanastomosis by firing one 45 mm white load (Ethicon) or tan (Medtronic, formerly Covidien) and a biliopancreatic limb of 60 cm was made (182), Figure 8.

In the SG the greater curvature was dissected free starting 4–5 cm from the pylorus up to the angle of Hiss. The left crus was visualised and inspected for hiatal hernia. Small sliding hernias and wide hiatus were left in situ. The ventricle was then lifted and any adhesions in the lesser sac divided.

A 35 Fr bougie was used along the lesser curvature guiding the creation of a tubular sleeve with linear staplers. The first two loads were always green (Ethicon) or purple (Covidien), while blue (Ethicon) or tan (Medtronic, formerly Covidien) loads were used for the rest of the ventricle.

The last stapler was placed 5 mm laterally to the angle of Hiss. The staple line was then inspected and secured with clips for additional haemostasis, no oversewing or buttressing material was routinely used. No routine dissection of crura or gastroesophageal junction to evaluate for incipient hiatal hernia were performed, Figure 8.

3.5.2 **Complications after bariatric surgery**

At each study visit patients were asked as to whether they had experienced any adverse events orcomplications. Every complication was retrieved from general practitioner or hospital. Events were registered by the investigator regardless of whether they were deemed relevant to the intervention or not.

3.5.3 Medical treatment

Participants were prescribed a proton pump inhibitor (PPI) for 4 weeks following surgery. The need for further PPI treatment was assessed at each study visit (5-week, 16-week, 34-week, and 1-year)

based on the scores from the Gastroesophageal Reflux Disease Questionnaire (GerdQ) (109, 141). PPI therapy was stopped in patients with no- (GerdQ-score ≤2) or mild (GerdQ score 3-7) symptoms. In patients with severe symptoms (GerdQ-score ≥8) PPI therapy was intensified and patients were referred to a gastroenterologist (182).

3.6 Outcome measures

Prespecified main and secondary outcomes in this part of the Oseberg study were patient-reported outcomes (PROs), GERD-symptoms, erosive esophagitis, pathological acid reflux and esophageal motility. Overview of the outcome measures is shown below in Table 6. All clinical data was recorded on a predesigned clinical research form at all study visits. All clinicians and patients were blinded to the procedure the first year after surgery.

Table 6. Overview of the outcome measures in the studies.

Outcome measures	Study 1	Study 2	Study 3
Gastroesophageal Reflux Disease questionnaire(GerdQ)	x	x	
Gastrointestinal Symptom Rating Scale-Reflux questionnaire (GSRS-R)	x	x	
Gastrointestinal Symptom Rating Scale questionnaire (GSRS)			x
Arts' questionnaire			x
Impact of Weight on Quality of Life-Lite questionnaire (IWQOL-Lite)			x
Weight-Related Symptom Measure (WRSM)			x
Short-Form 36 Health Survey (SF-36) questionnaire			x
Beck Depression Inventory questionnaire (BDI)			x
Food Tolerance Questionnaire (FTQ)			x
Power of Food Scale questionnaire (PFS)			x
Binge Eating Scale (BES)			x
Esophagogastroduodenoscopy	x	x	
24-hour pH monitoring	x*	x	
High-resolution manometry	x*	x	

Non-T2D, non-type 2 diabetes; T2D, type 2 diabetes. *Not measured in patients without diabetes.

3.6.1 Patient-reported outcome measures

PROs were measured by using patient-reported outcome measures (PROMs) which are different validated questionnaires related to surgical procedures (gastrointestinal symptoms, dumping syndrome), weight loss, depression, binge eating, and hedonic hunger.

Gastrointestinal Reflux Disease Questionnaire

The Gastroesophageal Reflux Disease Questionnaire (GerdQ) is used to assess the frequency and severity of GERD (184). It is a validated 6-item questionnaire for GERD and includes four positive predictors (heartburn, regurgitation, sleep disturbances due to heartburn or reflux, and the use of anti-reflux medication) and two negative predictors for GERD (epigastric pain and nausea). The four positive predictor items each score from 0-3, where 0=no day, 1=1 day, 2=2-3 days and 3=4-7 days of the individual item during the previous week. The two negative predictor items score from 3-0, ie in reverse order to the positive predictors, where 0=4-7 days, 1=2-3 days, 2=1 day and 3=no day of the individual item during the previous week.The range of the total score for all six items is between 0 and 18.

A validated Norwegian version of the questionnaire was used in this thesis (185). According to the Diamond study (primary care patients) the prevalence of GERD increases with increasing GerdQ scores (126). In the Diamond study no patients had GERD with scores 0-2. Approximately half (52%) of the patients with a 3-7 score had GERD, whilst 81% of those with a sum score of 8 or above had GERD.

In this thesis, GerdQ was used to identify patients with symptomatic GERD, defined as a score of 8 and higher.

The Gastrointestinal Symptom Rating Scale

The original Gastrointestinal Symptom Rating Scale (GSRS) was first an interview based rating scale but was modified to become a self-administered questionnaire used to measure a wide range of symptoms in upper gastrointestinal diseases (186). The questionnaire is a validated, disease-

specific scale of 15-items that assesses common symptoms of gastrointestinal disorders during the previous 7 days (186, 187). The GSRS has a good internal consistency and reliability and acceptable construct validity and responsiveness in European patient populations (186, 187). It has five dimensions: abdominal pain, diarrhea, indigestion syndrome, obstipation and reflux.

The abdominal pain subscale includes three items (abdominal pain, gastric hunger pain, and nausea), while the reflux subscale includes two items (heartburn and acid regurgitation).

The indigestion subscale collects abdominal distension, borborygmi, and flatulence scores and the diarrhea subscale collects increased frequency of evacuation, loose stools, and urgent need to defecate scores.

The GSRS has a seven-point graded Likert-type scale where 1 represents absence of troublesome symptoms and 7 represents very troublesome symptoms. In this thesis, the sum score was converted to a 0–100 scale in the first and second paper in order to be comparable with other quality of life scales, with scores over or equal to 20 compatible with GERD diagnosis.

The Arts' questionnaire

The Art dumping score measures the severity of dumping symptoms after the ingestion of glucose during the first hour for early dumping symptoms and between 1 and 2 h for late dumping (177). This is a dumping severity score based on symptom-pattern descriptions using a 4-point Likert scale in response to the oral glucose challenge.

Impact of Weight on Quality of Life-Lite (IWQOL-Lite)

The IWQOL-Lite is a valid and reliable obesity-specific quality of life questionnaire that is more sensitive to detecting change over time due to weight loss. This questionnaire was developed in 2001 by RL Kolotkin, and it assesses the impact of weight on quality of life and is validated for use in people with severe obesity (188, 189). For obesity specific quality of life, the validated Norwegian version of IWQOL-Lite was used (190, 191). The IWQOL-Lite is a 31-item, self-reported measure of

weight-related quality of life that provides a total score plus scores on five domains: 1. Physical Function (11 items, e.g. feeling short of breath, getting up from chairs), 2. Self- Esteem (7 items, e.g. afraid of rejection, avoid looking in mirrors), 3. Public distress (5 items, e.g.fitting through aisles, experience ridicule), 4. Sexual Life (4 items, e.g. avoid sexual encounters, difficulty with sexual performance), and 5. Work (4 items, e.g. do not receive recognition, afraid to attend interviews) (188). Participants choose between the answers on the Likert scale from `` always`` true which gives 5 points to ``never true`` which gives 1 point. Higher scores represent better quality of life. Scores were transformed to a 0 to 100 scale to enable comparison of outcomes between scales, where 100 represents the best QoL and 0 represents the worst QoL.

Weight-Related Symptom Measure

The Weight-Related Symptom Measure (WRSM) is a weight-specific, self-report measure containing 20 items; for the presence and distress of weight-related symptoms (shortness of breath, tiredness, sleep problems, sensitivity to cold, increased thirst, increased irritability, back pain, frequent urination, pain in the joints, water retention, foot problems, sensitivity to heat, snoring, increased appetite, leakage of urine, light-headedness, increased sweating, loss of sexual desire, decreased physical stamina, and skin irritation) (192). The distress scores of the symptoms are reported on a six-point Likert scale. The first set assesses whether or not a patient had the specific symptom, and the second set rates the level of the distress with values from zero (not at all) to six (bothers a very great deal). Two sum scores were calculated, an additive sum score of presence of symptoms ranging from 1 to 20 and bothersomeness sum score for all symptoms from 0 to 120 with higher scores indicating a higher symptom burden.

Short-Form 36 Health Survey (SF-36), general questionnaire

In paper 3 we evaluated generic quality of life using the validated Norwegian version of Short-Form 36 Health Survey (SF-36, version 1) (193, 194). The SF-36 v1 was developed in 1990 and version 2 in 1998 by Ware JE and Sherbourne CD. It was developed during the Medical Outcomes study (MOS) to measure generic health concepts relevant across age, disease and treatment groups (195, 196).

The questionnaire has previously been validated in the general Norwegian population (197) and in Norwegian patients with severe obesity (193). The SF-36 questionnaire has been validated for use in patients with obesity scheduled for bariatric surgery in a study from Bahrain (198). Two other studies undertaken in Norway and Italy investigated the validity of the SF-36 in people with severe obesity who received conservative treatment (193, 199). The two summary scales, physical component summary (PCS) and mental component summary (MCS), were found to have adequate validity in people with obesity planning for bariatric surgery. However, the validity of the eight individual domains was less certain, while the authors suggested that PCS and MCS should be the primary endpoints when using the SF-36 in people with severe obesity (193, 198, 200).

The 36 questions are transformed into eight dimensional scores from 0-100 (0= maximum disability, 100=no disability); vitality, physical function, bodily pain, general health, physical role, emotional role, social role and mental health. Higher scores indicate better quality of life.

The 8 subscales are 'physical functioning' (10 items), 'role physical' (4 items), 'bodily pain' (2 items), 'general health' (5 items), 'vitality' (4 items), 'social functioning' (2 items), 'role emotional' (3 items), and 'mental health' (5 items). These 8 subscales result in 2 summary scales; a PCS and an MCS (165). The 'PCS ' consists of 21 items and the 'MCS' of 14 items. These eight dimensional scores from 0-100 (0= maximum disability, 100=no disability).

Beck Depression Inventory

The Beck Depression Inventory (BDI) is a structured, disease specific questionnaire consisting of 21 categories of symptoms and attitudes that describe the behavioral manifestation of depression. This questionnaire assesses the intensity of depressive symptoms. (201). Total scores on the 21-item scale range from 0 to 63, with higher scores indicate greater depressive symptomatology: 0-9 absent or normal, 10-15 s mild mood disturbance, 16-19 borderline clinical depression, 21-30 moderate depression, 31-40 severe depression and >41 extreme depression.

A BDI score of ≥14 was used as a cut-off for clinically significant symptoms of depression (202).

Food Tolerance Questionnaire

The Food Tolerance Questionnaire (FTQ) is an 11-item questionnaire that assesses overall quality of alimentation, timing of food intake, tolerance of different types of food, and frequency of vomiting (203). The questionnaire reports overall satisfaction 1-5, and overall food tolerance, with scores ranging from 0-16, with higher scores representing greater food tolerance.

Power of Food Scale

The Power of Food Scale (PFS) was developed to assess both the psychological impact and respondent's responsiveness to a food- plentiful environment (204). This is a 15-item scale divided into three domains: food being readily available in the environment but not physically present, food is physically present, but not tasted, and food is first tasted but not already consumed. Scores for the aggregate domains were calculated as the mean of those three domain scores.

The PFS is rated on a 5-point Likert scale. This questionnaire was developed as a quantitative measure of appetite related outcomes like hedonic hunger. Hedonic hunger refers to desire or drive to consume foods for the purpose of pleasure and in the absence of physical hunger (205, 206).

Binge Eating Scale

The Binge eating scale (BES) is a 16-item scale that assesses the extent to which people with obesity experience binge-eating problems, including eating in secret, loss of control and guilt following binge eating (207). Scores range between 0-46, with higher scores indicating greater binge eating problems. Cut-off scores have been established to determine binge severity, with "severe" represented by scores >27, "moderate" by scores 18-26, and "mild-none" by scores <17 (208).

The BES was developed in 1982 by Gormally et al. to assess severity of binge eating among persons with obesity, both before and after bariatric procedure (207). It is a valid and useful binge eating screening tool for patients seeking bariatric surgery that will inform clinicians of eating pathology (209). BES values above 17 are suggested to be diagnostic for binge eating disorder (BED) in candidates for bariatric surgery (sensitivity of 94% and a specificity of 76%). BES contemplates two different factors of compulsion: feelings/cognition and behavioral manifestations (209).

3.6.2 Definitions

Weight loss

Weight loss was primarily defined by percent total body weight loss [%TWL= (weight change / initial weight) * 100], but changes in body weight (kg) and BMI were also provided.

Diabetes-remission

Complete or partial remission of T2D were defined as HbA_{1c} of ≤6.0% [42 mmol/mol] or < 6.5% [48 mmol/mol], respectively, both in the absence of active pharmacological therapy or ongoing procedure (210).

Hypoglycemia

Hypoglycemia was defined as a verified blood glucose level of less than 3.9 mmol/l and the presence of typical symptoms and signs of hypoglycemia.

Esophagogastroduodenoscopy, erosive esophagitis

Esophagogastroduodenoscopy (EGD) was performed by experienced endoscopists using Olympus® 180 or 190 gastroscope and a high-quality picture of LES was taken during the procedure at baseline and at 1-year follow-up.

Any anti-reflux medication was discontinued 7 days prior to EGD.

Erosive esophagitis (inflammation or injury to the esophageal mucosa) was graded according to the LA classification by two experienced endoscopists who were blinded for surgical procedure based on the image of the LES (110, 211)(Figure 9 and Table 7). In case of disagreement, the first author and the endoscopists reviewed the case together and reached an agreement.

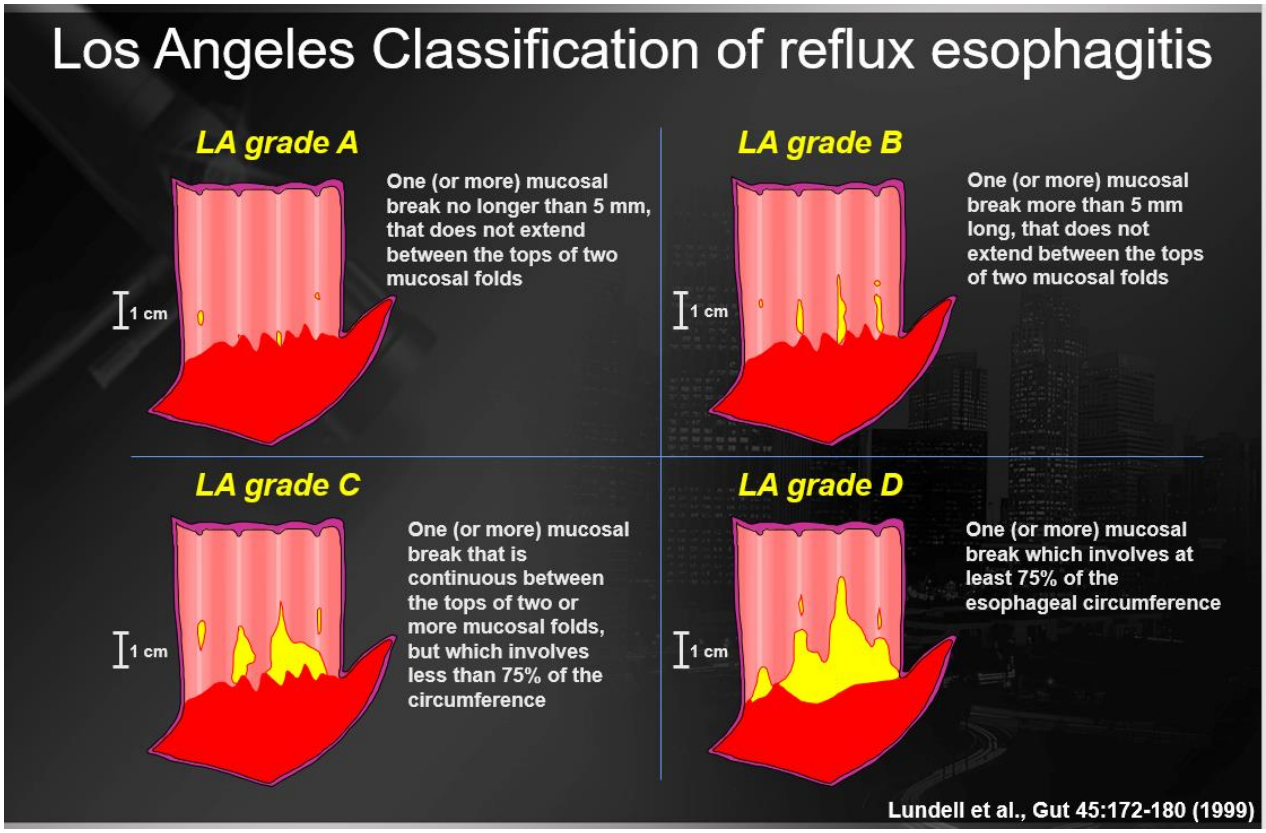


Figure 9. Los Angeles classification of esophagitis. Reproduced from Lundell LR et al. with permission (211).
The LA classification is the endoscopic scoring system used to grade the severity of gastroesophageal reflux disease, GERD. The LA classification divides reflux esophagitis into four categories A to D, where D is the most severe form of GERD.

Table 7. The Los Angeles classification of esophagitis

Grade A	One (or more) mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds
Grade B	One (or more) mucosal break more than 5 mm long that does not extend between the tops of two mucosal folds
Grade C	One (or more) mucosal break that is continuous between the tops of two or more mucosal folds but which involves less than 75% of the circumference
Grade D	One (or more) mucosal break which involves at least 75% of the oesophageal circumference

New-onset GERD

New-onset GERD was defined as finding of erosive esophagitis LA grade A-D/ BE or AET>6% or DeMeester score ≥14.72 at 1-year of follow-up and absence of erosive esophagitis at baseline endoscopy or/and normal AET and DeMeester score at baseline examination.

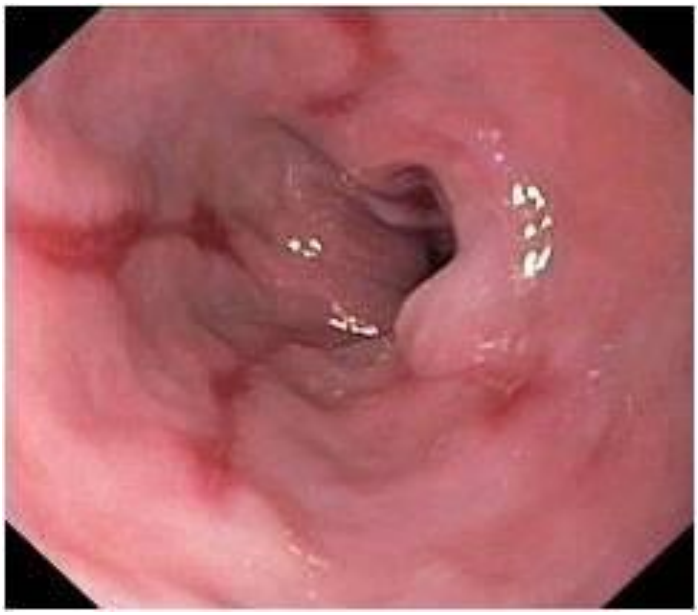


Figure 10. Endoscopic photo of the distal esophagus showing erosive esophagitis (picture from the outpatient clinic of the Gastroenterology Department at Vestfold Hospital Trust, with permission).

Hiatal hernia

Patients with hiatal hernia >5 cm at EGD baseline screening were excluded. Hiatal hernia was measured by EGD longitudinally in centimeters from the LES to the diaphragmatic impression and was defined as hiatal hernia if ≥ 2 cm.

Hiatal hernia was also detected by using high-resolution manometry (HRM) at 1 year follow-up as an axial lower esophageal sphincter-diafragmatic crura (LES- DC) separation was measured longitudinally in centimeters from the LES to the pressure inversion point (PIP) and was defined as hiatal hernia if ≥ 2 cm.

Barrett's esophagus

Barrett's esophagus (BE) is a condition in which the normal squamous epithelium in esophagus is replaced by a metaplastic, columnar epithelium (133). The diagnosis of BE was made by identifying mucosal changes in the distal esophagus by EGD and verified by histological examination of biopsies (by pathologists at Vestfold Hospital Trust) using the Prague classification containing specialized intestinal metaplasia examination (137, 212). A diagnosis of adenocarcinoma was verified in biopsies by pathologists.

Non-erosive reflux disease-definition

Non-erosive reflux disease (NERD) was defined as the presence of typical symptoms of GERD and pathological acid reflux in the absence of visible esophageal mucosal injury on EGD (213).

Remission of GERD-definition

Remission of GERD was defined as absence of GERD-symptoms and discontinuation of GERD-medication.

Ambulatory 24-hour pH monitoring

Ambulatory pH monitoring was performed after 6 hours fasting and 7 days off proton pump inhibitor and H2-blocker, using the Digitrapper™pH-Z Testing System (Medtronic, Minneapolis, USA), Figure 11. The probe was introduced transnasally and the pH sensor placed 5 cm above LES after identification by high-resolution manometry (Manoscan, Medtronic o.s.v.). Patients were asked to follow their normal daily habits, including eating habits, and record upper GI symptoms, meals, medication, and supine position (bedtime only).

The data were recorded by a portable digital data logger for 24 hours, and DeMeester score was calculated using a standard software program (27).

Pathologic acid reflux was diagnosed as DeMeester score ≥ 14.72 (214) or distal esophageal acid exposure time (AET) ≥ 6% (27). The examination with 24-hour pH monitoring was pre-planned and performed only in patients with T2D.

The Lyon GERD Consensus proposes that >80 reflux episodes per 24 hours are abnormal, which is considered an adjunctive measure to be used when AET is inconclusive (ie, AET between 4% and 6%) (27), Figure 12.

Figure 11. Digitrapper™pH-Z Testing System, Medtronic (picture from the outpatient clinic of the Gastroenterology Department at Vestfold Hospital Trust, with permission).

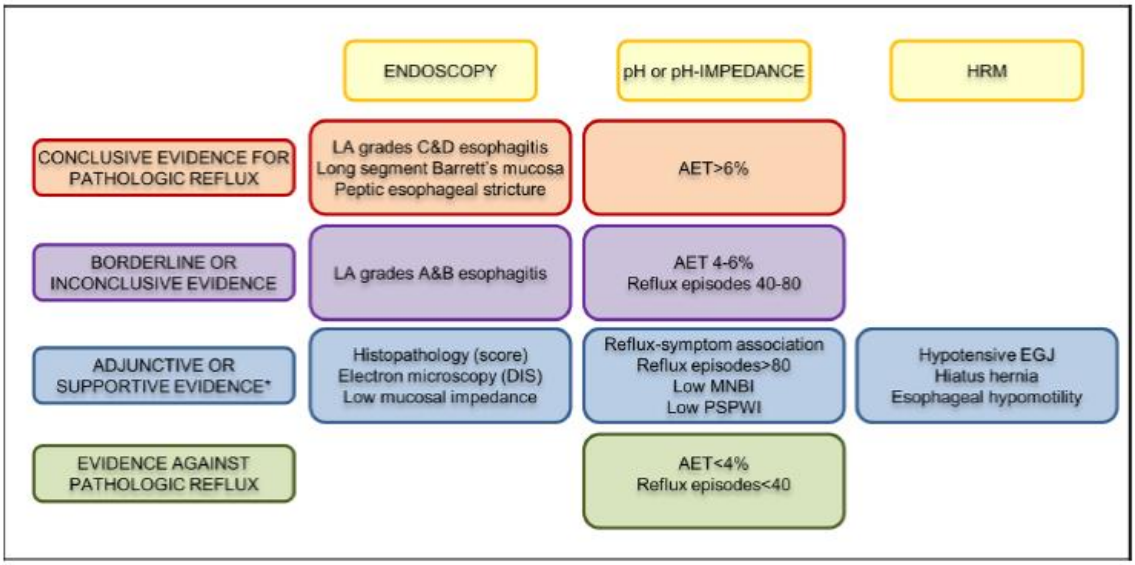


Figure 12.The Lyon consensus reproduced from Gyawali et al. with permission (27).
AET, acid exposure time; DIS, dilated intercellular spaces; EGJ, esophagogastric junction; HRM, High-resolution manometry; LA, Los Angeles classification; MNBI, mean nocturnal baseline impedance; PSPW, postreflux swallow-induced peristaltic wave.

High-resolution manometry, esophageal motility disorders

High-resolution manometry (HRM) R (Medtronic, Minneapolis, USA), including the Chicago classification of esophageal motility disorders (version 3.0) was used to identify motility disorders, (Figure 13). Patients underwent transnasal placement of the manometric catheter in the supine position after at least a 6-hour fast. The catheter was fixed in place by taping it to the nose. The manometric protocol included a 5-min period to assess basal sphincter pressure and 10 water swallows of 5 ml. HRM manometric data were analyzed using ManoView analysis software. Data were corrected for thermal sensitivity of the pressure-sensing elements by ManoView.Two independent investigators manually analyzed all reports. We used the Chicago classification of esophageal motility disorders (version 3.0) to classify motility disorders (27, 31). A diagnosis of dysmotility was registered in patients with either *hypocontractility,* defined as ineffective esophageal motility (IEM) (≥50% ineffective swallows with DCI <450 mmHg/s/cm); *hypercontractility*, defined as jackhammer esophagus (≥20% DCI >8000 mm Hg*cm*s); *hypotensive LES,* defined as median residual pressure <4 mmHg or mean basal pressure <13mmHg; or *hypertensive LES,* defined as median residual pressure >15 mmHg or mean basal pressure>43 mmHg.

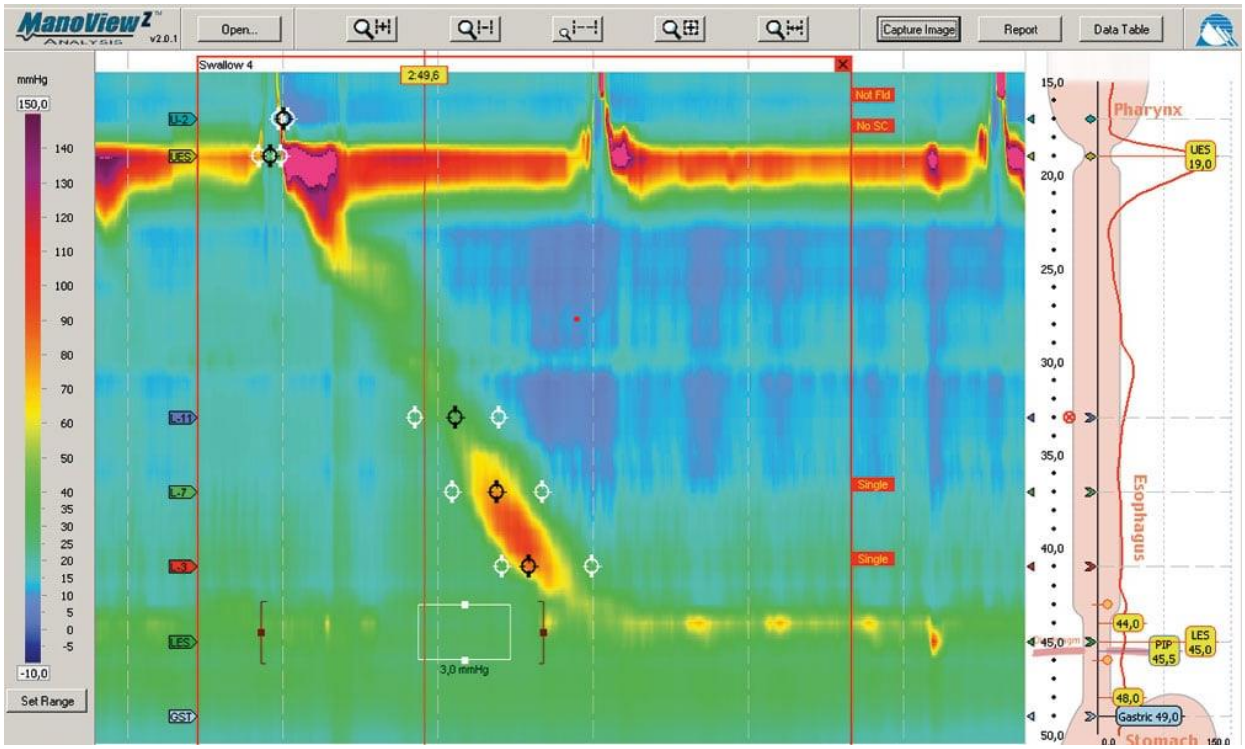


Figure 13. Picture of high-resolution manometry (picture from the outpatient clinic of the Gastroenterology Department at Vestfold Hospital Trust, with permission). LES, Lower esophageal sphincter; PIP, Pressure inversion point; UES, Upper esophageal sphincter.

Gastric emptying rate

An oral paracetamol test was used to calculate intestinal absorption as a measure of gastric emptying rate. Paracetamol was chosen because of easy availability and price. Time to peak paracetamol concentration was used as a marker of gastric emptying rate (215).

A 1 g paracetamol tablet was crushed to powder, dissolved in the glucose solution and ingested by the participants over 5 minutes. Blood samples were drawn before ingestion and 15, 30, and 60 minutes after the combined glucose and paracetamol load. Plasma paracetamol was analyzed on Vitros 5.1 (Ortho-Clinical Diagnostics, Raritan, New Jersey, USA) until 50 October 2017 and thereafter on a Cobas 8000 analyzer (Roche Diagnostics, Mannheim, Germany).

3.7 Statistical analyses

Categorical variables were presented as counts (percentages) or relative risk (RR), and continuous variables were presented as mean values with standard deviations (SD) or 95% confidence intervals (CI). Groups of patients at defined timepoints were compared using chi-square (Fisher`s exact test) or independents sample t-tests as appropriate. All tests were two-sided and p values < 0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS 25 (SPSS Inc., Chicago, IL).

Changes over time were examined with linear mixed models (Paper III). The prespecified secondary outcome variables were measured at baseline,1-year and 3-year follow-up, and analyzed according to intention to treat (ITT) principles. The binary outcomes were analysed using Chi-square and Fisher`s exact test as appropriate and the McNemar test was used to compare changes in proportions. In addition, all PROs were also assessed at the 5-week follow-up. The repeated measures models were not adjusted for potential confounders as there were no baseline differences between the groups. For continuous variables, the estimated means and 95% confidence intervals (CI) at 1-year follow-up were reported. For the binary variables, counts (%) and differences in risks between surgery-groups quantified as risk difference (RD) (95% CI) were reported at 1-year.

All data analyses were performed using IBM SPSS (version 25.0) and STATA version (15.0). P-values <0.05 were considered statistically significant and all tests were two-sided. Since all analyzed variables are considered exploratory, no adjustment for multiple testing was performed (216).

4 Ethics

4.1 Approvals

The project was conducted in adherence to the Helsinki Declaration and was registered at ClinicalTrials.gov with the identifier NCT01778738 and approved by the Regional Committee for

Medical Research Ethics (REK) (ID No. 2012/1427 and 2012/1427 b). Potential candidates for study participation were invited to an information meeting a few months prior to randomization. All patients were informed about the study procedures, benefits and adverse effects prior to inclusion. Written, informed consent was obtained from all included patients and stored appropriately. The participants were informed about their ability to withdraw their consent at any time during the study.

The non-T2D group was handled slightly different as a non-randomized, controlled group. Written, informed consent was obtained from all included patients and stored appropriately. Patients in this group were informed about the study procedure, which was the esophagogastroduodenoscopy, and were involved in making decisions about bariatric treatment options.

4.2 Funding

This work has been supported by grants from Vestfold Hospital Trust and South-Eastern Norway Regional Health Authority. The funders had no role in the study design, data collection, analysis or decision to publish the manuscripts. All authors of the papers declare that they have no conflicts of interest.

5 Summary of results

5.1 Paper 1

Between October 2012 and September 2017, 319 consecutive patients with BMI≥35 kg/m² and T2D were assessed for eligibility, 194 were ineligible, and 125 patients were enrolled. Additionally, one patient was excluded because of undetectable c–peptide level on baseline examination indicating type 1 diabetes. Finally, a total of *124 patients with obesity and T2D*, 81 women, mean (SD) age 48.6 (9.4) years and BMI 42.3 (5.5) kg/m² were included in the study (Table 8). In addition, a total of 210 consecutive patients without T2D scheduled for bariatric surgery were assessed for eligibility, and 81 patients were invited to participate. Out of these 81 patients, 17 declined participation, leaving *64 patients without T2D* to be included in the study, 46 women, mean age 43.0 (11.0) years and BMI 43.0 (5.0) kg/m² (Table 8).

Patients with T2D were on average 6 years older than those without T2D, and a lower proportion of patients with T2DM used nonsteroidal anti-inflammatory drugs as compared with patients without T2D (Table 8). BMI, drinking habits, smoking habits, and the proportion of patients using anti-reflux medication did not differ significantly between groups (Table 8).

Table 8. Demographic and clinical characteristics in candidates for bariatric surgery with or without type 2 diabetes mellitus (T2DM), reproduced from Lorentzen et al. (217) with permission from Springer Nature.

	T2DM (n=124)	Non-T2DM (n=64)	*p* value
Age, years (SD)	48.6 (9.4)	43.0 (11.0)	0.001
Gender, female, no.(%)	81 (65)	46 (72)	0.46
Ethnicity, Caucasian, no. (%)	117 (96)	64 (100)	0.24
Weight, kg (SD)	125.6 (21.8)	127.2 (20.1)	0.63
Body mass index, BMI, kg/m²	42.3 (5.5)	43.0 (5.0)	0.46
Current smoker, no. (%)	14 (11)	4 (6)	0.34
Alcohol consumption (units per week)	0 (0-8)	1 (0-3)	0.13
Use of anti-reflux medication, no. (%)	35 (29)	12 (19)	0.23
Proton pump inhibitors, no. (%)	34 (27)	11 (17)	NA
Histamine receptor antagonists, no. (%)	1 (0.8)	1 (1.6)	NA
Use of NSAID, no. (%)	14 (11)	20 (32)	0.001
Duration of diabetes, years (SD)	6.4 (6.0)	NA	NA
Diabetes complications, no. (%)	13 (12)	NA	NA

First, the prevalence of GERD-symptoms was similarly low in both groups, < 29%, and the prevalence of erosive esophagitis was 58% in the diabetes group versus 47% in the group without diabetes, p=0.16. Second, we did not find any significant correlation between pathological acid reflux, erosive esophagitis and symptoms in either group (68% in diabetes group without symptoms and 80% in non-diabetic group without symptoms). In summary, our results showed that the prevalence of GERD in patients scheduled for bariatric surgery was similar in patients with or without T2D, and the proportion of patients with asymptomatic GERD was high and independent of the presence or absence of T2D.

5.2 Paper 2

A total of 109 patients were randomly assigned and allocated to SG (n=55) or RYGB (n=54). One patient in each group withdrew after surgery, and 107 patients (98%) completed the 1- year follow-up. Mean (SD) age was 47.7 (9.6) years, BMI 42.3 (5.3) kg/m² and 72 patients (66%) were women and 104 (95%) were white (Figure 14).

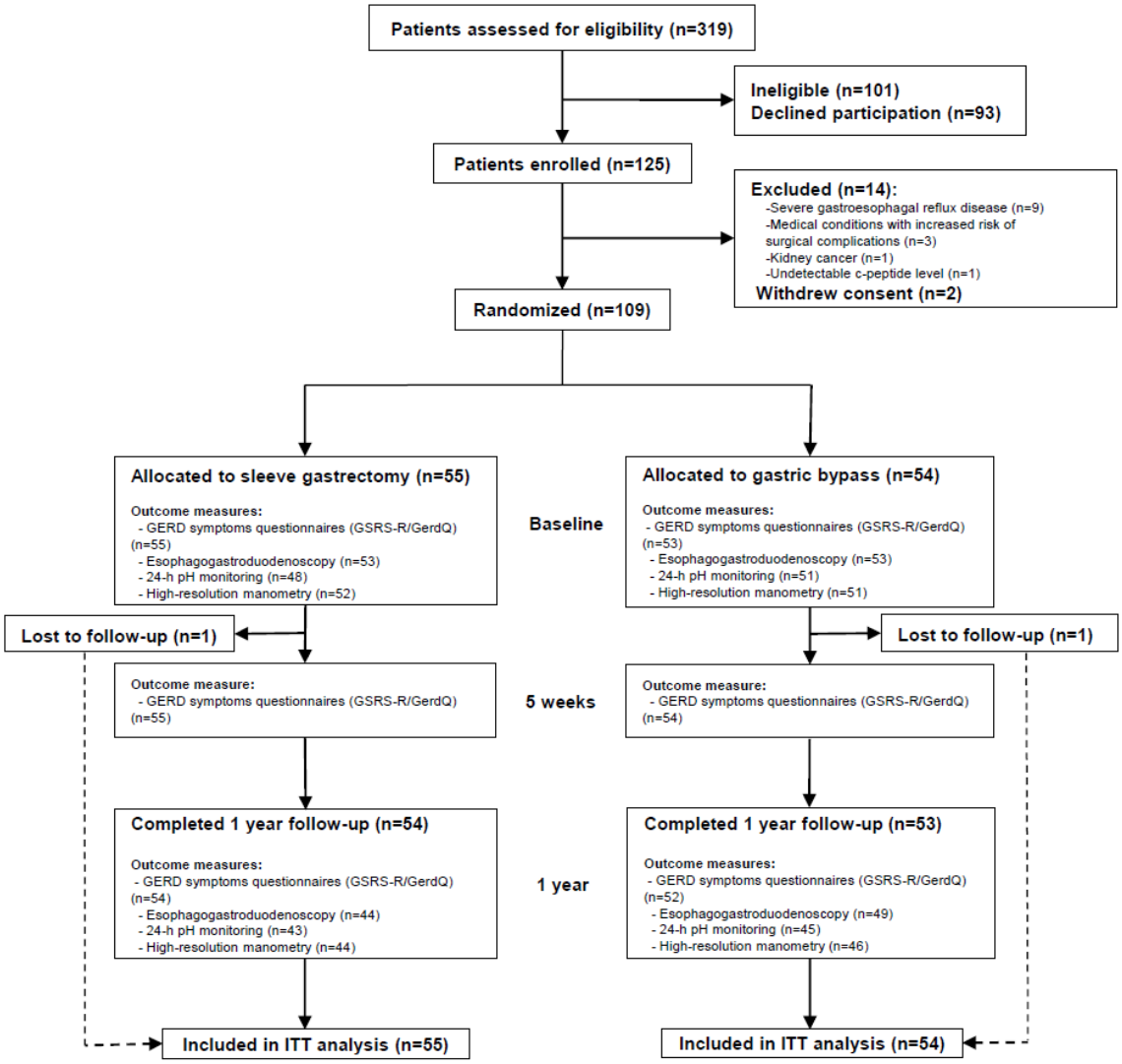


Figure 14. Flow chart showing number of patients included, randomized and analysed at 1 year (from the original full length manuscript submitted to Gastroenterology, June 2021); (the manuscript is included in this thesis).
GERD, Gastroesophageal reflux disease; GerdQ, Gastroesophageal reflux disease Questionnaire; GSRS-R, Gastrointestinal Symptom Rating Scale-Reflux part; ITT analysis, Intention-to-treat analysis.

GERDS symptoms (GSRS-Reflux) were reported by 17% after SG and by 6% after RYGB (risk difference RD 12% [95%CI, -1 to 23%]). GERD symptoms assessed by using GerdQ showed similar

results for both groups. The prevalence of erosive esophagitis was relatively high and similar in both groups, while pathological acid reflux was diagnosed in significantly more patients after SG than after RYGB (49% versus 16% [RD, 33%, CI 15 to 52%]) (Figure 15A).

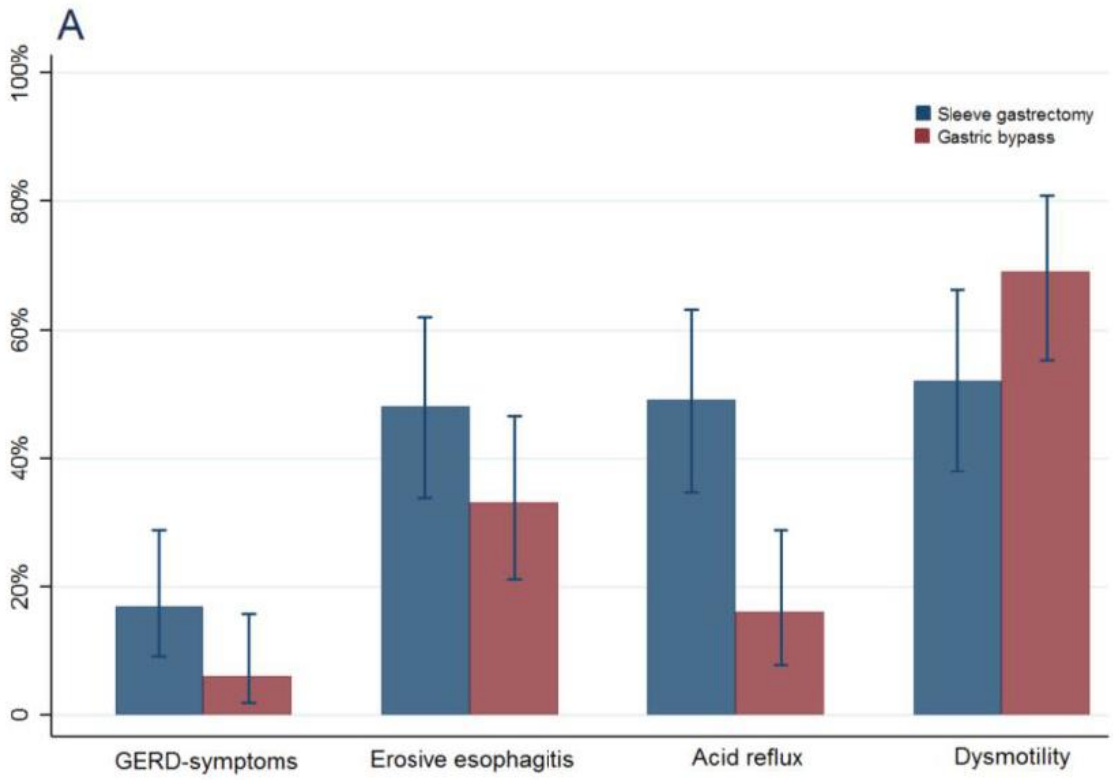


Figure 15A. Proportion of patients with GERD symptoms, erosive esophagitis, pathological acid reflux and dysmotility 1 year after sleeve gastrectomy and gastric bypass. Reproduced from Lorentzen et al. with permission (218).

Seventy-seven percent of patients reported remission of symptoms, with no differences between groups (Figure 15B).

The remission rate of erosive esophagitis was 50% with no difference between groups. By contrast, the remission of pathological acid reflux was 2 times higher after RYGB than after SG, 83% versus 42%. The overall dysmotility remission rate was 29% (Figure 15B).

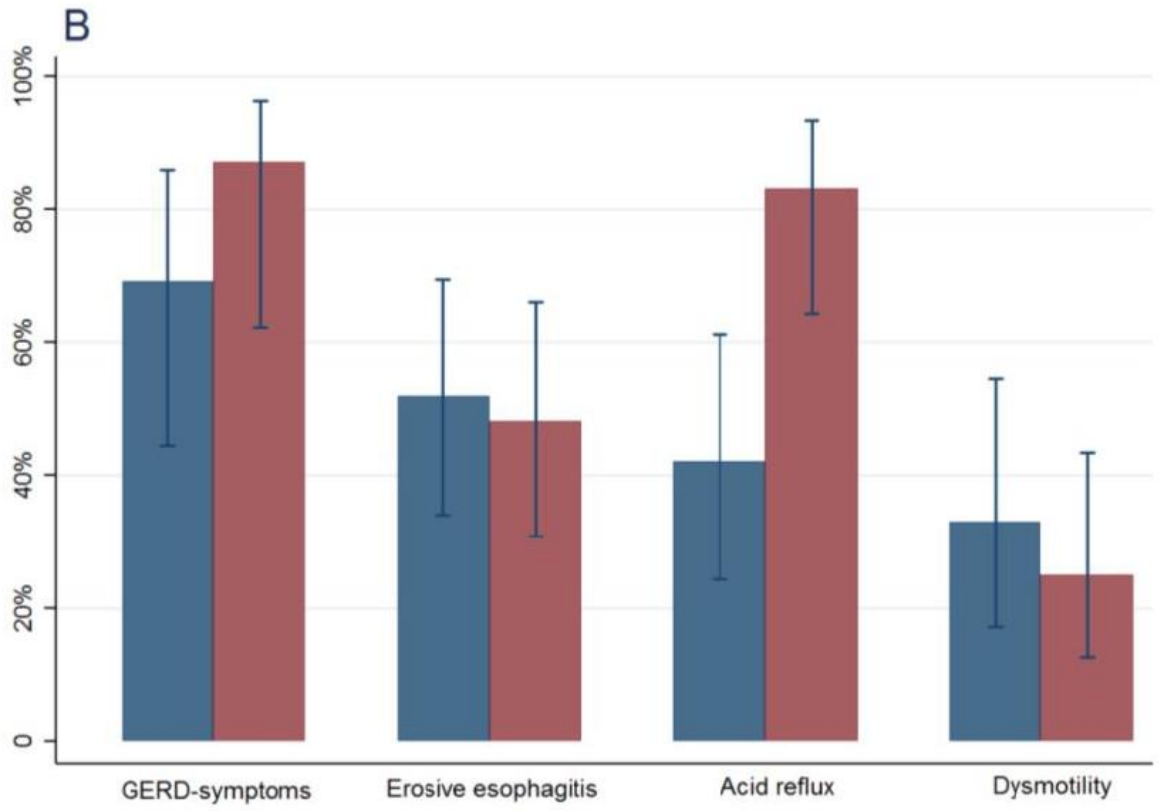


Figure 15B. Proportions of patiets with remission of baseline GERD-symptoms, erosive esophagitis, acid reflux and dysmotility, 1 year after sleeve gastrectomy and gastric bypass. Reproduced from Lorentzen et al. with permission (218).

We found a significantly higher incidence of both new-onset esophagitis and new-onset pathological acid reflux after SG compared with after RYGB (47% versus 9%, RD, 38%, [CI 11 to 65%]) and 41% versus 10% (RD, 31% [CI, 4 to 58%]), respectively (Figure 15C).

The incidence of new-onset dysmotility was 45%, with no differences between groups (Figure 15C).

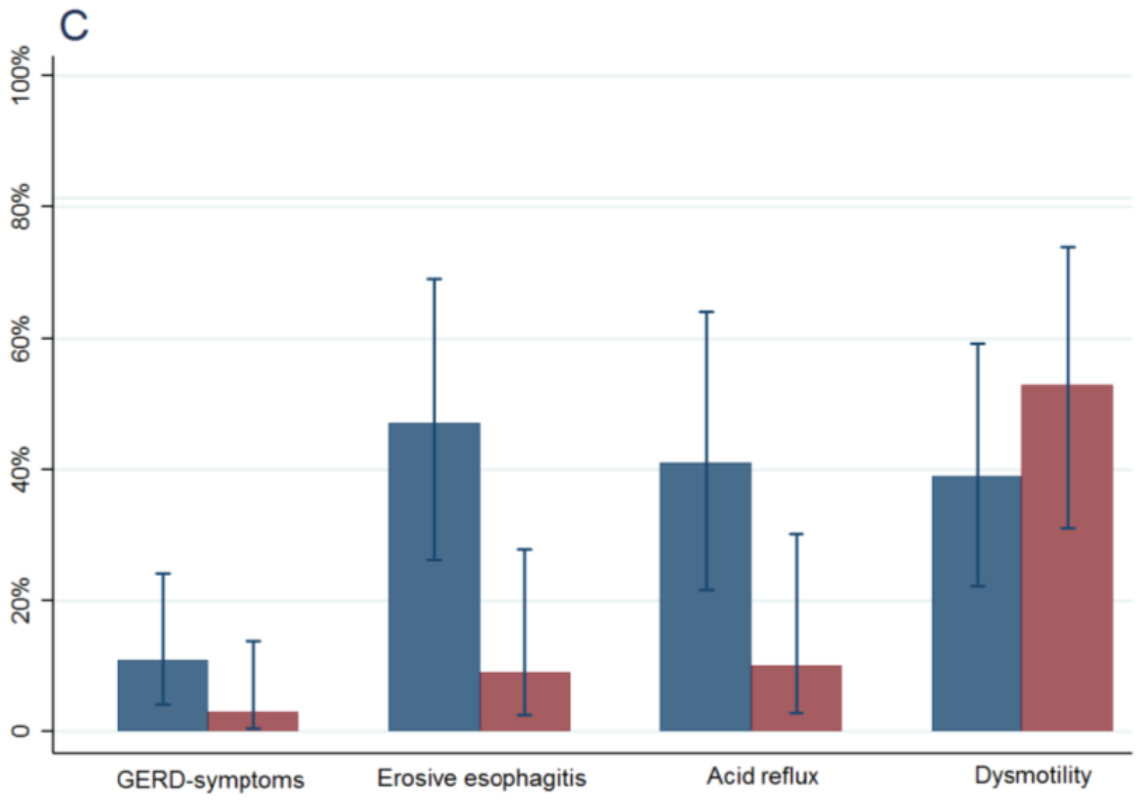


Figure 15C. Incidence of new-onset GERD-symptoms, erosive esophagitis, acid reflux and dysmotility, 1 year after Sleeve gastrectomy and gastric bypass. Reproduced from Lorentzen et al. with permission (218).

There were no associations between presence of a hiatal hernia and erosive esophagitis or pathological acid reflux.

5.3 Paper 3

A total of 109 patients (72 female) with obesity and T2D were included in the analyses. They had a mean age of 47.7 years (SD 9.6), BMI 42.3 kg/m2 (5.3) and median (IQR) HbA1c of 7.9% (6.9–9.0) or 63 mmol/mol (52–75). A total of 54 patients (49.5%) underwent RYGB and 55 patients (50.5%) SG, and after 3 years, 48 and 45 patients attended follow-up (85%), and in addition three patients (total n=96) were contacted by telephone for registration of comorbidities, adverse events, dumping and self-reported weight. Data from all patients (n=109) were included in the mixed model analysis.

The mean GSRS-total, -diarrhoea, -indigestion, -constipation, and -abdominal pain scores did not change 3 years after both SG and RYGB. The mean reflux symptom score (GSRS-reflux) was reduced with 26 % (0.43) after RYGB, with no change after SG, between group difference (95%CI) 0.54 (0.90-0.17). Of 96 patients, 35 (37%) reported one episode of early dumping, while 22 (23%) patients reported late dumping, with no significant difference between groups. Based on the weight related quality of life questionnaire, IWQOL-Lite, RYGB was associated with significantly greater improvements in self-esteem, public distress and physical function scores. The mean IWQOL-Lite total score increased by 48% after SG and 74% after RYGB, between-group difference 9.4 (3.3 to 15.5) points. The number and bothersomeness of weight related symptoms (WRSM) decreased by 24% and 40% after RYGB and 19% and 33% after SG, respectively, with no difference between the groups.

The SF-36 Physical Component Summary score increased by 19% after RYGB and 17% after SG. The Mental Component Summary score increased significantly after SG. With the exception of emotional role (both groups) and mental health (RYGB), both groups showed significant improvements in all domains of the SF 36 subscales, with no significant difference between groups. The mean Beck Depression Inventory symptom score was reduced by 40% after SG and 45% after RYGB and Binge eating symptoms were reduced by 26% after sleeve and 32% after gastric bypass, with no difference between groups. Percentage total body weight loss was significantly higher after RYGB than after SG (mean difference 8.1%, 95% CI 5.6-10.7%). The remission rate of diabetes and

percentage total body weight were significantly greater after RYGB than after SG, 67% vs. 33%, and 25% vs. 17%, respectively.

5.4 Summary of main results

1) The prevalence of GERD was similar in patients scheduled for bariatric surgery with or without T2D (Paper 1)
2) The proportion of patients with asymptomatic GERD was high independent of the presence or absence of T2D (Paper 1)
3) SG was associated with a substantially higher 1-year risk of pathological acid reflux and new-onset erosive esophagitis than RYGB (Paper 2)
4) Most of the patients with esophagitis or pathologic acid reflux were asymptomatic, and the prevalence of GERD symptoms was low in both groups. (Paper 2)
5) RYGB was associated with a greater 3-year improvement in weight-related quality of life (improvement in IWQOL-Lite scores), less reflux symptoms, greater weight loss, and higher probability of diabetes remission than SG (Paper 3).

6 Discussion

6.1 Discussion of results

6.1.1 Relationship between the papers

This thesis comprises the results of a paper investigating the association between T2D and GERD (Paper 1) and two papers assessing the association between GERD symptoms and objective findings (Paper 1 and 2). In addition, one paper compares the 1-year effects of RYGB and SG on GERD (Paper 2), and another paper compares the 3-year effects of RYGB and SG on a number of PROs including GERD symptoms and health-related quality of life (Paper 3).

Obesity and T2D may represent causal risk factors in the development of GERD (8, 120). Further, patients with T2D may be more susceptible to asymptomatic GERD (11). The relationship between GERD symptoms and endoscopic GERD findings in patients with and without T2D has not been fully investigated. GERD may be underdiagnosed in patients with T2D. In Paper 1 we examined the prevalence of GERD in patients with obesity with and without T2D before bariatric surgery. We found the prevalence of GERD-symptoms to be similarly low in both groups(< 29%), while the prevalence of erosive esophagitis was high in both groups (58% versus 47%, p = 0.16). We did not find any significant correlation between pathological acid reflux, erosive esophagitis and symptoms in either group, but there was a strong correlation between erosive esophagitis and pathological acid reflux.

Recent evidence indicates that RYGB may reduce GERD independent of weight loss (153, 154), while SG may increased GERD symptoms and objective GERD findings(151, 219). The results of some previous studies indicate that after bariatric surgery the majority of the patients with GERD may be asymptomatic (150, 180). Interestingly, some studies showed a paradoxal presence of GERD-symptoms after RYGB often considered an ”anti-reflux”procedure (220). However, the impact of RYGB and SG on the evolution of GERD remains to be fully examined. We aimed to

reduce this knowledge gap by comparing validated measures of GERD before and after RYGB and SG. Our results showed that reporting of GERD symptoms was low after both procedures at 1-year follow-up, while the prevalence of erosive esophagitis was relatively high and similar in both groups. In contrast, there was a significantly higher prevalence of pathologic acid reflux and incidence of new-onset GERD after SG. Both obesity and T2D may lead to impaired health-related quality of life (166, 170, 171). Bariatric surgery has beneficial effects on weight loss, diabetes control and quality of life. However, few studies have compared changes in quality of life after RYGB and SG, especially in people with diabetes. Paper 3 adds to our knowledge of changes in quality of life after both surgical methods. The results of paper 3 increase the possibility of individually adapted (tailored) treatment with the best possible effect and the fewest possible side effects.

6.1.2 Paper 1

To our knowledge, this study is the first to compare the prevalence of GERD in patients with and without T2D scheduled for RYGB or SG. Furthermore, it is also the first study to assess the association between GERD symptoms and erosive esophagitis in patients with and without T2D.

In the present study, the proportion of patients with asymptomatic GERD was high independent of the presence or absence of T2D. Likewise, GERD symptoms were not significantly associated with erosive esophagitis and there was no difference between the groups with or without T2D. The majority of patients with erosive esophagitis did not have GERD symptoms, while the majority of those with GERD symptoms had erosive esophagitis. Further, 71% of T2D-patients with pathological acid reflux had erosive esophagitis and 67% of them were asymptomatic.

Our finding of a low number of patients with GERD symptoms is corroborated by some previous studies (30, 221-223) and is partly in agreement with others (224, 225). The high prevalence of asymptomatic patients with erosive esophagitis in both groups might be partly explained by

esophageal hyposensitivity because of obesity, diabetes or both of these conditions (226). Esophageal sensitivity is a major determinant of GERD symptom perception (227). In this study we only evaluated indirect sensitivity by using validated forms like GSRS-R and GerdQ. The epithelial lining in a normal population is thinner in the proximal part of the esophagus than in the distal part. The afferent nerves lie deeper in the lining in distal esophagus. Patients with non-erosive reflux disease (NERD) have a thinner epithelial lining in distal esophagus and the afferent sensory cells are located closer to the lumen. Patients with severe obesity, diabetes and BE have acid hyposensitive esophagus. Some studies have suggested that patients with BE may have a generalized sensory defect in the esophagus, independent of nervous changes which are related to the metaplastic mucosa (228). However, the evidence regarding acid sensitivity in people with obesity and BE is limited.

In our study, four patients with T2D had BE and none of them had GERD symptoms. Patients with BE have lower sensitivity, but sensitivity increases as reflux exposure decreases from erosive disease to non-erosive disease (227). Studies showed that in patients with BE the nociceptive sensory receptors are located more profoundly in the esophageal mucosa, which may partly explain their esophageal hyposensitivity (229).

The proportion of patients with erosive esophagitis in this trial was high in both groups with a numerically higher proportion of patients with erosive esophagitis in the group with T2D. However, the difference was not statistically significant, but since sample size was estimated only for differences in GSRS scores, a type 2 error cannot be eliminated.

Our findings were in accordance with studies that showed a high prevalence of erosive esophagitis in patients with severe obesity (144). The association between GERD symptoms and erosive esophagitis has been shown to be weak in our study as well as in other studies (30, 32, 221). In our trial, 29 of 43 patients (67%) who had both pathological acid reflux and erosive esophagitis were asymptomatic. Three of the 18 patients (17%) with GERD symptoms without erosive esophagitis

had pathologicacid reflux (NERD). These findings support other studies confirming a poor association between GERD symptoms and pathological acid reflux (32, 179, 230).

The duration of reflux exposure is also determined by the presence of hiatal hernia and some authors suggest that hiatal hernia is the main mechanism for reflux (231).

In this study, we found the same proportions of patients with hiatal hernia ≥ 2 cm in both groups [54/123 (44%) for T2D and 28/64 (44%) for the group without T2D)]. However, we found no association between presence of hiatal hernia and pathological acid reflux.

In view of the findings presented in Paper 1, we suggest that EGD and/or 24-hour pH monitoring may be appropriate in the preoperative examination of patients scheduled for bariatric surgery.

6.1.3 Paper 2

By contrast with our hypotheses, the prevalences of GERD symptoms and erosive esophagitis were not higher 1 year after SG than after RYGB. The proportions of patients with GERD symptoms were similarly low in both groups, while the proportion of patients with erosive esophagitis was relatively high in both groups. Nevertheless, in accordance with our hypotheses, the prevalence of pathological acid reflux was three times higher after SG than after RYGB, which was explained by both a lower remission rate and a higher incidence of new-onset acid reflux. The incidence of new-onset esophagitis was five times higher after SG (47% vs 9%).

Before the Oseberg study there was limited research on the effect of SG versus RYGB on GERD.

The prediction of worse GERD control after SG has been a subject of intense interest. Available data suggested a more favorable RYGB effect on GERD than SG.

Larger weight loss can contribute to greater improvement in GERD. However, many studies have reported GERD improvement after RYGB independent of weight loss (153). Even though weight reduction is comparable between RYGB and SG, many studies have showed increasing prevalence

and severity of GERD following SG and a high incidences of new-onset GERD after SG, varying from 5 % to 32 % (150-152, 219). The methodological issues facing many of the studies include that the majority were observational and only few of them had objectively evaluated the presence of GERD by using EDG and/or 24-hour pH- measurement (180, 232-235). The assessment of GERD was therefore limited.

In view of this, the present RCT-study, which is one of few studies with objective evaluation of GERD following SG and RYGB, was carried out. The 109 patients included in this paper are the first patients who participated in the study described in Paper 1.

SG as surgical method is in itself probably the strongest independent predictor of new-onset GERD because of higher intragastric pressure, changes in esophagogastric junction (EGJ) morphology, presence of hiatal hernia, decreased gastric compliance, impaired gastric emptying , reduced LES pressure and removal of gastric fundus.

The gastroesophageal pressure gradient may drive reflux and influences motility. When the gastric pressure is high, it provokes three effects: formation of hernia, creation of a distal resistance which triggers hypercontractility to overcome the resistance, and drive reflux.

In a study of Navarini, post-operative hiatal hernia occurred in most patients after SG and was an independent predictor of GERD (236).

The gastric pouch in RYGB is also tubular, but its fixation due to the gastrojejunal anastomosis might prevent an eventual thoracic migration and formation of hiatal hernia.

In our study, the proportion of patients with a hiatal hernia <5 cm was relatively high after SG, but did not differ significantly between groups. We found no association between endoscopic findings/ pathological acid reflux and hiatal hernia. The lack of association between GERD and hiatal hernia in our study can partly be explained by the small size of detected hiatal hernias. According to some studies, hiatal hernia> 3cm is associated with increasing reflux burden (237).

Patients with hiatal hernias >5 cm were excluded at baseline during the screening procedure.

Several studies reported an association between GERD and esophageal motility disorders. GERD severity and frequence increase based on the type of motility disorders, such as fragmented peristalsis, ineffective esophageal motility (IEM), absent contractility and hypotensive LES (238, 239). However, the relationship between GERD and esophageal motility disorders, especially esophageal body motility impairment is still the matter of investigation. Whether the alteration of peristalsis is a cause or a consequence of GERD is not clear (238).

A hypotensive LES is a predisposing factor for GERD (189,190). However, manometric changes after SG have varied, with some studies demonstrating increased LES pressure and others decreased LES pressure (152, 240-242).

More than half of our patients had esophageal dysmotility at baseline, but the majority with hypertensive LES, and the prevalence did not change after both procedures. The prevalence of hypotensive LES was low in both intervention groups. Some studies showed that hypotensive LES is associated with higher severity of GERD (243). Our results could not confirm this finding.

In addition, both procedures were associated with accelerated rather than impaired gastric emptying. The gastric emptying rate was two times higher after RYGB than SG.

Recent concerns have been raised due to an increased frequency of asymptomatic GERD that occurs after SG. Most patients in this study were asymptomatic despite the fact that they had erosive esophagitis or pathological acid reflux.

The high remission rates of GERD symptoms, erosive esophagitis and acid reflux, after both surgical procedures, are partly explained by the substantial weight loss accompanied by reduced intra-abdominal and intra-gastric pressure, which both are major physiopathological components of GERD (180, 244). Further, both procedures reduce gastric volume (234, 245-247) followed by reduced number of acid producing cells and accelerated gastric emptying (240, 248-250).

Both procedures may prevent the genesis of an acid pocket, a potentially important source of postprandial acid reflux (251, 252).

Our findings are in line with other studies which have demonstrated incidence of new-onset GERD after SG to be between 10% to 23% (253).

Another study examined GERD 1 year after SG using 24 hour pH-measurement, showing a very high percentage of new-onset GERD in 50% of patients and worsening of GERD in 80% of the patients (254).A large RCT trial (150), reported 5-year postoperative GERD remission in 25% of patients after SG compared to 60.4% after RYGB with new-onset GERD in 31.6% and 10.7%, respectively. There are currently no formal guidelines regarding operative method choice in patients with obesity and GERD. RYGB is considered an effective antireflux treatment and "the gold standard procedure", while SG may induce or even worsen GERD. Nevertheless, in this study at 1 year after RYGB there was a high prevalence of erosive esophagitis (33%) (255). In addition, two patients who underwent RYGB had new-onset Barrett`s esophagus, five patients had persistent acid reflux and two patients new-onset acid reflux. None of these patients reported GERD symptoms. Our study confirmed the efficacy of RYGB on GERD symptom resolution in most of the patients. However, 14 % had persistent or new-onset GERD symptoms after RYGB (255).

Santonicola at al. (220) reported similar paradoxal presence of GERD symptoms (24%) 1 year after RYGB. Several mechanisms may explain the occurrence of GERD after RYGB like hiatal hernia, impaired gastric emptying and hypotensive lower esophageal sphincter (LES) (234, 256). However, in contrast to these mechanisms, our study showed no association between the presence of hiatal hernia and pathological acid reflux. This study showed accelerated rather than reduced gastric emptying, and a low prevalence of hypotensive LES (4%) after RYGB. The relatively high prevalence of pathological acid reflux after RYGB might be an indication that not all acid producing parietal cells in the small gastric pouch (25 cc) are excluded.

In addition, at 1 year after RYGB, pathologic acid reflux was diagnosed in 7/52 (13%) of patients (218, 255). Our study provides evidence that in patients with T2D, SG is associated with

a substantially higher risk of pathological acid reflux and new onset esophagitis, most often without reflux symptoms. In view of this, our results suggest that screening with endoscopy and/or 24-pH monitoring may be indicated after bariatric surgery, regardless of symptoms. Our results need verification, but they may in the meantime help patients and clinicians in the shared decision process and tailoring of treatment.

6.1.4 Paper 3

Recent studies have provided strong evidence of a relationship between obesity and patient-reported outcomes (PROs). However, there are limited scientific articles comparing the medium- to long-term PROs after RYGB versus SG a, with few randomized controlled trials (RCTs) conducted. In addition, no randomized study of patients with T2D has compared the medium- to long-term effects of RYGB versus SG regarding symptoms from the gastrointestinal tract, dumping or eating disorders.

Before undertaking this study we conducted multiple searches within the academic literature, identifying only two randomized studies of patients with T2D that have compared the medium to long-term effects of RYGB and SG on PROs (107, 181). None of these studies investigated weight-related quality of life, binge eating or hedonic hunger. The SF-36 and RAND 36 scores in both studies improved similary after RYGB and SG, which was in line with our findings with the exception of emotional role (both groups) and mental health (gastric bypass). To our knowledge, our study is the first RCT to compare the medium-term (3-year) effects of RYGB and SG on predefined secondary PROs, in patients with obesity and T2D.

In our study, at 3 years after surgery, there were improvements in both groups regarding weight-related symptoms and weight-related quality of life. In addition, patients in both groups reported less symptoms of depression and binge eating problems were reduced in both groups.

Corroborating our hypotheses, RYGB was associated with a greater 3-year improvement in weight-related quality of life, greater weight loss, less reflux symptoms and higher diabetes remission than SG. The total gastrointestinal symptom scores (GSRS scores) remained unchanged 3 years after both surgical procedures. These findings reinforce those from the SM-BOSS study (150) and two other studies (200, 257). However, the use of Gastrointestinal Quality of Life Index (GIQLI) scores in the SM-BOSS study made a direct comparison with our results impossible because the gastrointestinal domain was not assessed in the SM-BOSS study.

Our study is also the first RCT-study to compare 3 years incidence of early and late dumping syndrome after RYGB and SG in patients with T2D. We did not find any differencies in the incidence of dumping symptoms between these two procedures.

Symptoms of depression were reduced after both surgical methods in the study of Murphy et al.(181), with these results comparable to our own.

IWQOL-Lite is considered the most important patient-reported outcome measure of self-esteem, according to a consensus of a global multidisciplinary meeting in 2022 (172). Weight-related quality of life measured with the IWQOL-Lite improved significantly more after RYGB according to self-esteem, public distress and physical function. Our results are in contrast with the results from a two-center observational study including patients with severe obesity (12% of patients with diabetes) and showing similar significant long-term improvements in IWQOL-Lite total scores after RYGB and SG (258). All participants in our study had T2D and there was a significantly greater weight loss after RYGB than after SG. The results from our study support previous findings which showed that body weight loss correlated with changes in IWQOL-Lite and improved overall health and especially weight-related quality of life.

The similar improvements in depression- and binge eating symptoms 3 years after both procedures in this thesis are in line with results from a systematic review of 7 observational studies (259).

Problems with hedonic hunger decreased similarly after both procedures, with an observational study reporting the same results (260).

Surgery is associated with many anatomical changes and changes in appetite hormones. Patients who undergo surgical treatment for obesity also modify many aspects of their eating behavior (205).

In this study, PROs improved from baseline to 3 years after both surgical procedures. Significant differences between the procedures, favoring RYGB, were observed in weight-related quality of life, reflux symptoms, weight loss and remission of diabetes. Changes in symptoms related to body weight, abdominal pain, indigestion, diarrhoea, dumping, depression and binge eating did not differ between groups. PROs from this study can be used in the shared decision making process to inform patients about the advantages and disadvantages of these two surgical procedures.

6.2 Methodological consideration

6.2.1 Study design and patient population

The studies in this thesis were designed as a cross-sectional study (Paper 1) and as a randomized, controlled trial (Paper 2 and 3). We included patients with severe obesity and T2D from a tertiary care obesity center in Norway. We have prioritized the patient demographics and characteristics most relevant to our research questions and, accordingly, we chose not to include various comorbidities. The cohort in Paper 1 was bigger than in the RCT-cohort because during the first year of this study the prevalence of erosive esophagitis was higher than expected, with the potential impact of T2D on these findings unclear. Therefore, to explore whether the prevalence of GERD was higher among patients with T2D, the steering committee decided, in 2014, to add a control group of bariatric patients without T2D (182). The sample size was at that point not

determined. To ensure sufficient strength in case of loss to follow-up, a total of 64 control patients without diabetes were included.

6.2.2 Strenghts

This study (Paper 2 and 3) has some strengths. The gold standard study design (RCT) reduced the risk of bias and secured a relatively high validity of the exploratory results, making them potentially relevant for treatment seeking patients with obesity and T2D. Other important strengths of the study are the prespecified secondary outcomes (Study 2 and 3) and the high accuracy of data collection with regards to confounders and clinical endpoints. The outcomes (variables) were measured at the same time for all participants who were selected based on the inclusion and exclusion criteria set. The repeated measures models were not adjusted for possible confounders or potential imbalance at baseline due to the randomized design.

We obtained patient-reported outcome measurements (PROMs) at baseline and multiple time-points (baseline, 5 weeks, 1 year, 2 year and 3 year). In this context, PROMs were able to distinguish between patients who have experienced positive changes over time and those who have experienced negative changes or those who experienced no changes at all, and to estimate accurately the extent of those changes.

One advantage of generic PROMs is that the questionnaires allow comparison of various medical conditions.

An obesity specific PROMs like IWQOL-Lite (20 items) is based on extensive qualitative work with a wider variety of individuals living with obesity and is a reliable and valid measure of weight-related quality of life in this population (261). The IWQOL-Lite has similar psychometric properties in persons with diabetes and obesity compared to persons with no diabetes and obesity (262).

Standardization is important for all surgical procedures. Another strength of this study is the standardization of SG (35 Fr Bougie) and RYGB (25ml pouch, 120 cm Roux-limb and 60cm biliopancreatic limb). Both methods were performed with laparoscopy and identical incisions.

6.2.3 Limitations

This trial had some limitations. The RCT-part of this study was of pragmatic art.

In general, pragmatic randomized studies help clinicians and patients to choose between alternative treatment methods. The generalizability of this study is limited due to the single-centre design. The majority of the patients were also of Caucasian origin (96%) and were women (68%). The comparative groups in Paper 1 were non-matched resulting in groups that differed in age. Patients in the non-T2D group were younger (the mean age 43 y) than patients in the group with T2D (the mean age 48,6 y). In addition, our findings should be interpreted with caution because of small size of the study, and, as such, the findings may not be generalizable to bariatric patients without diabetes (Paper 1). All outcomes were prespecified, however, the high number of analyses increased the risk of false positive results (type 1 error). Sample size calculations were made for the primary end points at 1 year and not for the secondary outcomes. We made sample size calculations at baseline for differences in GSRS scores between the groups with and without diabetes. The EGD describe erosive esophagitis, which is present only in approximately 50% of patients.

The sensitivity rate for detecting GERD by using 24-hour pH monitoring is 92% because of identification of GERD patients with NERD (238). HRM can detect functional esophageal and esophageogastro-junction pathology which may be involved in the pathophysiology of GERD.

Gastroscopy and manometry are examinitions known to cause discomfort. We made sure that no more participants than necessary underwent gastroscopy and manometry.

The examination with 24 hour pH monitoring was performed only in patients with T2D due to capacity issues at the gastroenterological outpatient clinic. Taking that and the small sample size into account, negative findings do not exclude the possibility that important differences between the procedures may exist (type 2 error).

We assessed hiatal hernia at baseline by performing endoscopy, which is a more imprecise means of assessing hernias compared with HRM. HRM is a more objective method for hiatal hernia assessment because the method is independent of the endoscopist and has a sensitivity of 92% and a specificity of 95% for hiatal hernia detection as compared with 73% sensitivity of EGD or radiography alone (263). The HRM method was used in study 2 (paper 2).

In addition, hiatal hernias were not repaired at the time of SG and RYGB. Hiatal hernia repair during the sleeve gastrectomy could have prevented postoperative GERD.

There were no diabetes-specific PROs included in this study (264) and generic PROMs may not be sufficiently sensitive to detect minor treatment effects on diabetes- specific PROs (265).

The heterogeneity and lack of standardization of PROMs limit the ability to make comparisons and to draw conclusions about the impact of bariatric surgery on quality of life (172, 266). After the first year, patients were unblinded and had knowledge of the procedure. We cannot exclude the possibility that this knowledge of procedure type may have influenced how patients reported symptoms.

The results of our study should be considered exploratory and need confirmation in future studies.

6.2.4 Statistics

The Oseberg study was powered to detect differences in the primary outcomes diabetes remission rates and beta-cell function (182). With a two-sided 5% significance level and a power of 80%, a sample size of 55 in each group was required, and to allow for drop outs, the sample size was set to 125 patients (182, 267).

The preplanned secondary outcomes in this trial were assessed in both intention-to-treat and per-protocol populations. Intention-to-treat, whereby all randomized patients are included, is considered the gold standard in statistical analyses of RCTs. The prespecified secondary outcome variables such as EGD and 24 hour pH monitoring were measured at baseline and 1-year, and analyzed according to ITT principles using generalized linear mixed models for repeated measures with identity link (continuous outcomes) and log-link (for binary outcomes). Sample size in this study was calculated for differences in GSRS scores, not for differences in prevalence of erosive esophagitis. The lack of statistical significance could therefore be caused by a type 2 error.

6.2.5 Randomization and blinding

The primary goal of randomization is to reduce selection bias and to minimize possibledifferences between studied group of patients, by balancing known and unknown prognostic factors and possible confounders in preplanned treatment (268). Random assignment permits the use of probability theory to express the likelihood that any difference in outcome between intervention groups reflects pure chance. Randomized controlled trial is accepted as the best design (gold standard) for evaluation of the efficacy of a new method e.g., surgical procedure (268, 269). Randomization eliminates any influence the investigator or participant has on the allocation of treatment (268).

Before randomization, all patient were screened prior to surgery and informed consent was obtained from all the patients.

Another measure to reduce bias is blinding. Blinding reduces detection and performance bias.

Blinding of participants and personnel reduces performance bias(268, 270). The term “triple-blinded” refers to full blinding where the assignment is hidden from participants, study personell and researches analyzing the data.

6.2.6 External validity/generalizability

External validity, also called generalizability, is the extent to which the results can be generalized to other groups/participants different to those who are enrolled in the study (268, 271).

The gold standard study design of this trial (randomized, triple-blinded, study II) reduces the risk of bias and secures a high internal and external validity (generalizability) of the results making them relevant for treatment seeking patient with obesity and T2D.

Patients of Caucasian origin represented 96% of the patients in the T2D group with T2D, while all patients in the non-T2D groupwere Caucasian, with a majority women (68%). As such, the results may therefore not be generalizable to other ethnicities or patient groups.

We have prioritized the inclusion in our analyses of patient demographics and characteristics most relevant to our research questions and, accordingly, chose not to include various comorbidities.

Patients included in Oseberg study were recruited from a tertiary care center treating patients with severe obesity. The specific population of treatment seeking people with obesity entails generalizability only to similar populations.

6.2.7 Ethical consideration

"The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that*, "A physician shall act in the patient's best interest when providing medical care"* (272-274).

Consideration of the subjects must always take precedence over the interests of the researcher, the interests of science and the interests of society, see "Declaration of Helsinki" (274).

This PhD project was conducted in adherence to the Helsinki Declaration, and the OSEBERG study was approved by the Regional Committee for Medical Research Ethics (REK) (ID nr. 2012/1427). This study is registered in ClinicalTrials (Research protocol, Obesity Surgery in Tønsberg, OSEBERG-study, ClinicalTrials.gov NCT01778738).

Moreover, regular patient insurance applies and all the study participants have signed a written informed consent prior to participating in the study. The participants were also informed orally about the study's purpose, confidentiality, voluntary participation and their right to end their involvement at any point. One possible ethical problem that could arise during the study period would be the early revealing of the benefits of RYGB, such that the study would have to be discontinued (275).

To avert that from happening, regular evaluations and complication meetings were held with involved staff, patients representatives and the Oseberg steering group. The evaluations provided feedback to study staff and enabled continuous improvements with a focus on the patients throughout the study period.

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7 Conclusions, implications and future perspectives

The results from the *cross-sectional study* (paper 1) did not confirm our hypotheses regarding potential differences in frequency and intensity of GERD between patient with or without T2D. First, the prevalence of GERD symptoms was generally low and comparable between patients with and without T2D while the prevalence of erosive esophagitis was generally high and comparable between groups. Second, patients with T2D and erosive esophagitis had a similarly low GERD symptom burden as those without T2D and erosive esophagitis. In addition, the results showed no significant associations between pathological acid reflux, erosive esophagitis and GERD symptoms. These results strongly suggest that symptoms are not a reliable indicator of GERD in patients scheduled for bariatric surgery. Accordingly, GERD may be underdiagnosed in patients who are not screened with endoscopy or 24-hour pH-monitoring (acid reflux).

In view of these results, EGD and/or 24-hour pH-monitoring may be appropriate to include in the routine preoperative examination of patients scheduled for bariatric surgery. However, more evidence regarding the beneficial effects of general screening is needed before any specific recommendation about EGD and/or 24 hour pH-monitoring screening before bariatric surgery can be implemented.

The 1-year results from the *randomized controlled study* (paper 2) did not confirm our hypotheses of a higher prevalence of GERD symptoms and erosive esophagitis after SG than after RYGB. However, SG was associated with a significant higher incidence of new-onset esophagitis, and conclusive evidence of pathological acid reflux (Lyon criteria) was three times higher 1 year after SG than after RYGB.

In agreement with our hypotheses, the results of this study confirm the efficacy of RYGB on GERD symptom resolution in most of the patients, however, 14 % of patients treated with RYGB had persistent or new-onset GERD. It is difficult to identify predictors for which patient will develop GERD after SG.

In view of this, the results, if confirmed, suggest that screening with endoscopy and/or 24-hour pH monitoring may be indicated after both SG and RYGB, regardless of symptoms.

These results support the recent Position Statement by the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO), recommending that surveillance with EGD should be undertaken routinely after bariatric surgery, regardless of symptoms (276).

Our findings also support previous research suggesting that bariatric surgery improves quality of life in different domains in both the short- and long-term.

The 3-year results from the *randomized study* in this thesis (paper 3) confirmed our hypothesis that RYGB was associated with a greater improvement in weight-related quality of life than SG. However, in contrast with our hypothesis, the burden of gastrointestinal symptoms such as abdominal pain, indigestion, diarrhoea and dumping syndrome did not differ significantly between groups. In addition, the percentage total body weight loss correlated significantly with changes in IWQOL-Lite, suggesting that weight loss could be a mediator of improved weight-related quality of life.

The new patient reported knowledge favoring RYGB in terms of improvements in weight-related quality of life, reflux burden, weight loss and remission of diabetes, can be applied in the shared decision making when informing patients about the advantages and disadvantages of the two surgical methods.

The results of the three papers in this thesis provide both health services and patients with new knowledge which may influence future guidelines and clinical practice.

References

1. Løvsletten O, Jacobsen BK, Grimsgaard S, Njølstad I, Wilsgaard T, Løchen ML, et al. Prevalence of general and abdominal obesity in 2015-2016 and 8-year longitudinal weight and waist circumference changes in adults and elderly: the Tromsø Study. BMJ Open. 2020;10(11):e038465.
2. vedlegg-sak-086-2008-Rapport - utredning og behandling av sykelig overvekt i spes helsetjenesten - voksne pdf 21 [Internet].
3. WHO. Obesity and overweight. In WHO.2020. Available from: www.who.int/news-room/factsheets/detail/obesity-and-overweight [
4. World Health Organization. Diabetes type 2-Fact sheet:WHO;2021(updated june 2021. Available from:https://www.who.int/health-topics/diabetes#tab=tab 1. 2021 [updated 2021.
5. Affinati AH, Esfandiari NH, Oral EA, Kraftson AT. Bariatric Surgery in the Treatment of Type 2 Diabetes. Curr Diab Rep. 2019;19(12):156.
6. Eckel RH, Kahn SE, Ferrannini E, Goldfine AB, Nathan DM, Schwartz MW, et al. Obesity and type 2 diabetes: what can be unified and what needs to be individualized? Diabetes Care. 2011;34(6):1424-30.
7. Ganz ML, Wintfeld N, Li Q, Alas V, Langer J, Hammer M. The association of body mass index with the risk of type 2 diabetes: a case-control study nested in an electronic health records system in the United States. Diabetol Metab Syndr. 2014;6(1):50.
8. Yuan S, Larsson SC. Adiposity, diabetes, lifestyle factors and risk of gastroesophageal reflux disease: a Mendelian randomization study. Eur J Epidemiol. 2022;37(7):747-54.
9. Maret-Ouda J, Markar SR, Lagergren J. Gastroesophageal Reflux Disease: A Review. Jama. 2020;324(24):2536-47.
10. Hampel H, Abraham NS, El-Serag HB. Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. Annals of internal medicine. 2005;143(3):199-211.
11. Sun XM, Tan JC, Zhu Y, Lin L. Association between diabetes mellitus and gastroesophageal reflux disease: A meta-analysis. World journal of gastroenterology. 2015;21(10):3085-92.
12. Watanabe Y, Fujiwara Y, Shiba M, Watanabe T, Tominaga K, Oshitani N, et al. Cigarette smoking and alcohol consumption associated with gastro-oesophageal reflux disease in Japanese men. Scand J Gastroenterol. 2003;38(8):807-11.
13. Midthjell K, Krüger O, Holmen J, Tverdal A, Claudi T, Bjørndal A, Magnus P. Rapid changes in the prevalence of obesity and known diabetes in an adult Norwegian population. The Nord-Trøndelag Health Surveys: 1984-1986 and 1995-1997. Diabetes Care. 1999;22(11):1813-20.
14. Midthjell K, Lee CM, Langhammer A, Krokstad S, Holmen TL, Hveem K, et al. Trends in overweight and obesity over 22 years in a large adult population: the HUNT Study, Norway. Clin Obes. 2013;3(1-2):12-20.
15. Hjelmesæth J. Overweight or obese – you are not your condition. Tidsskr Nor Laegeforen. 2015;135(16):1473.
16. Carlsson LMS, Sjöholm K, Jacobson P, Andersson-Assarsson JC, Svensson PA, Taube M, et al. Life Expectancy after Bariatric Surgery in the Swedish Obese Subjects Study. N Engl J Med. 2020;383(16):1535-43.

17. Kolotkin RL, Andersen JR. A systematic review of reviews: exploring the relationship between obesity, weight loss and health-related quality of life. Clin Obes. 2017;7(5):273-89.
18. Strain GW, Kolotkin RL, Dakin GF, Gagner M, Inabnet WB, Christos P, et al. The effects of weight loss after bariatric surgery on health-related quality of life and depression. Nutr Diabetes. 2014;4(9):e132.
19. Frood S, Johnston LM, Matteson CL, Finegood DT. Obesity, Complexity, and the Role of the Health System. Curr Obes Rep. 2013;2(4):320-6.
20. Nasjonal faglig retningslinje for forebygging utredning og behandling av overvekt og fedme hos voksne Norwegian directorate of health editor 2011
21. Buchwald H, Oien DM. Metabolic/bariatric surgery Worldwide 2008. Obes Surg. 2009;19(12):1605-11.
22. Castanha CR, Tcbc-Pe Á ABF, Castanha AR, Belo G, Lacerda RMR, Vilar L. Evaluation of quality of life, weight loss and comorbidities of patients undergoing bariatric surgery. Rev Col Bras Cir. 2018;45(3):e1864.
23. Uhe I, Douissard J, Podetta M, Chevallay M, Toso C, Jung MK, Meyer J. Roux-en-Y gastric bypass, sleeve gastrectomy, or one-anastomosis gastric bypass? A systematic review and meta-analysis of randomized-controlled trials. Obesity (Silver Spring). 2022;30(3):614-27.
24. Angrisani L, Santonicola A, Iovino P, Vitiello A, Zundel N, Buchwald H, Scopinaro N. Erratum to: Bariatric Surgery and Endoluminal Procedures: IFSO Worldwide Survey 2014. Obes Surg. 2017;27(9):2290-2.
25. Chai J, Jamal MM. Esophageal malignancy: a growing concern. World journal of gastroenterology. 2012;18(45):6521-6.
26. Iyer PG, Borah BJ, Heien HC, Das A, Cooper GS, Chak A. Association of Barrett's esophagus with type II Diabetes Mellitus: results from a large population-based case-control study. Clin Gastroenterol Hepatol. 2013;11(9):1108-14.e5.
27. Gyawali CP, Kahrilas PJ, Savarino E, Zerbib F, Mion F, Smout A, et al. Modern diagnosis of GERD: the Lyon Consensus. Gut. 2018;67(7):1351-62.
28. Mainie I, Tutuian R, Shay S, Vela M, Zhang X, Sifrim D, Castell DO. Acid and non-acid reflux in patients with persistent symptoms despite acid suppressive therapy: a multicentre study using combined ambulatory impedance-pH monitoring. Gut. 2006;55(10):1398-402.
29. Stanghellini V, Armstrong D, Monnikes H, Bardhan KD. Systematic review: do we need a new gastro-oesophageal reflux disease questionnaire? Aliment Pharmacol Ther. 2004;19(5):463-79.
30. Sakitani K, Suzuki N, Ihara S, Hirata Y, Kawazu S, Iwamoto Y, Koike K. Decline in perception of acid regurgitation symptoms from gastroesophageal reflux disease in diabetes mellitus patients. PloS one. 2018;13(3):e0194466.
31. Horikawa A, Ishii-Nozawa R, Ohguro M, Takagi S, Ohtuji M, Yamada M, et al. Prevalence of GORD (gastro-oesophageal reflux disease) in Type 2 diabetes and a comparison of clinical profiles between diabetic patients with and without GORD. Diabet Med. 2009;26(3):228-33.
32. Heimgartner B, Herzig M, Borbely Y, Kroll D, Nett P, Tutuian R. Symptoms, endoscopic findings and reflux monitoring results in candidates for bariatric surgery. Dig Liver Dis. 2017;49(7):750-6.
33. Madalosso CA, Fornari F, Callegari-Jacques SM, Madalosso CA, Gurski RR. Performance of the Montreal Consensus in the diagnosis of gastroesophageal reflux disease in morbidly obese patients. Obes Surg. 2008;18(6):668-74.

34. Hofso D, Fatima F, Borgeraas H, Birkeland KI, Gulseth HL, Hertel JK, et al. Gastric bypass versus sleeve gastrectomy in patients with type 2 diabetes (Oseberg): a single-centre, triple-blind, randomised controlled trial. The lancet Diabetes & endocrinology. 2019;7(12):912-24.
35. Hofmann B. Obesity as a Socially Defined Disease: Philosophical Considerations and Implications for Policy and Care. Health Care Anal. 2016;24(1):86-100.
36. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser. 2000;894:i-xii, 1-253.
37. Weir CB, Jan A. BMI Classification Percentile And Cut Off Points. StatPearls. Treasure Island (FL): StatPearls Publishing
Copyright © 2022, StatPearls Publishing LLC.; 2022.
38. Kopelman P, Jebb SA, Butland B. Executive summary: Foresight 'Tackling Obesities: Future Choices' project. Obes Rev. 2007;8 Suppl 1:vi-ix.
39. Fawcett KA, Barroso I. The genetics of obesity: FTO leads the way. Trends Genet. 2010;26(6):266-74.
40. Leibel RL. Energy in, energy out, and the effects of obesity-related genes. N Engl J Med. 2008;359(24):2603-4.
41. Loos RJF, Yeo GSH. The genetics of obesity: from discovery to biology. Nat Rev Genet. 2022;23(2):120-33.
42. van Galen KA, Ter Horst KW, Serlie MJ. Serotonin, food intake, and obesity. Obes Rev. 2021;22(7):e13210.
43. Lutter M, Nestler EJ. Homeostatic and hedonic signals interact in the regulation of food intake. J Nutr. 2009;139(3):629-32.
44. Tschöp M, Weyer C, Tataranni PA, Devanarayan V, Ravussin E, Heiman ML. Circulating ghrelin levels are decreased in human obesity. Diabetes. 2001;50(4):707-9.
45. Campos A, Port JD, Acosta A. Integrative Hedonic and Homeostatic Food Intake Regulation by the Central Nervous System: Insights from Neuroimaging. Brain Sci. 2022;12(4).
46. English PJ, Ghatei MA, Malik IA, Bloom SR, Wilding JP. Food fails to suppress ghrelin levels in obese humans. J Clin Endocrinol Metab. 2002;87(6):2984.
47. Shankar K, Takemi S, Gupta D, Varshney S, Mani BK, Osborne-Lawrence S, et al. Ghrelin cell-expressed insulin receptors mediate meal- and obesity-induced declines in plasma ghrelin. JCI Insight. 2021;6(18).
48. Perry B, Wang Y. Appetite regulation and weight control: the role of gut hormones. Nutr Diabetes. 2012;2(1):e26.
49. Izquierdo AG, Crujeiras AB, Casanueva FF, Carreira MC. Leptin, Obesity, and Leptin Resistance: Where Are We 25 Years Later? Nutrients. 2019;11(11).
50. Ard J, Fitch A, Fruh S, Herman L. Weight Loss and Maintenance Related to the Mechanism of Action of Glucagon-Like Peptide 1 Receptor Agonists. Adv Ther. 2021;38(6):2821-39.
51. Steinert RE, Feinle-Bisset C, Asarian L, Horowitz M, Beglinger C, Geary N. Ghrelin, CCK, GLP-1, and PYY(3-36): Secretory Controls and Physiological Roles in Eating and Glycemia in Health, Obesity, and After RYGB. Physiol Rev. 2017;97(1):411-63.
52. World Obesity Atlas 2022. https://dataworldobesityorg/publications/World-Obesity-Atlas-2022-updatedpdf. 2022.
53. https://wwwfhino/nettpub/ncd/overvekt/voksne/. 2017-2021.

54. Styringsdokument. https://www.regjeringen.no/globalassets/upload/hod/bestillerdokumnet/styringsdokument-helse-sor.pdf2004.
55. Heymsfield SB, Wadden TA. Mechanisms, Pathophysiology, and Management of Obesity. N Engl J Med. 2017;376(3):254-66.
56. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. J Am Coll Cardiol. 2014;63(25 Pt B):2985-3023.
57. Muollo V, Rossi AP, Milanese C, Masciocchi E, Taylor M, Zamboni M, et al. The effects of exercise and diet program in overweight people - Nordic walking versus walking. Clin Interv Aging. 2019;14:1555-65.
58. Swift DL, McGee JE, Earnest CP, Carlisle E, Nygard M, Johannsen NM. The Effects of Exercise and Physical Activity on Weight Loss and Maintenance. Prog Cardiovasc Dis. 2018;61(2):206-13.
59. Evert AB, Boucher JL, Cypress M, Dunbar SA, Franz MJ, Mayer-Davis EJ, et al. Nutrition therapy recommendations for the management of adults with diabetes. Diabetes Care. 2013;36(11):3821-42.
60. Westman EC, Feinman RD, Mavropoulos JC, Vernon MC, Volek JS, Wortman JA, et al. Low-carbohydrate nutrition and metabolism. Am J Clin Nutr. 2007;86(2):276-84.
61. Kirkpatrick CF, Bolick JP, Kris-Etherton PM, Sikand G, Aspry KE, Soffer DE, et al. Review of current evidence and clinical recommendations on the effects of low-carbohydrate and very-low-carbohydrate (including ketogenic) diets for the management of body weight and other cardiometabolic risk factors: A scientific statement from the National Lipid Association Nutrition and Lifestyle Task Force. J Clin Lipidol. 2019;13(5):689-711.e1.
62. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation. 2014;129(25 Suppl 2):S102-38.
63. Hjelmesæth J, Sjöberg A. Human body weight, nutrients, and foods: a scoping review. Food Nutr Res. 2022;66.
64. Kirkpatrick CF, Liday C, Maki KC. The Effects of Carbohydrate-Restricted Dietary Patterns and Physical Activity on Body Weight and Glycemic Control. Curr Atheroscler Rep. 2020;22(6):20.
65. Yanai H, Yoshida H. Beneficial Effects of Adiponectin on Glucose and Lipid Metabolism and Atherosclerotic Progression: Mechanisms and Perspectives. Int J Mol Sci. 2019;20(5).
66. Igel LI, Kumar RB, Saunders KH, Aronne LJ. Practical Use of Pharmacotherapy for Obesity. Gastroenterology. 2017;152(7):1765-79.
67. Norsk Legemiddlehåndbok. https://www.legemiddelhandboka.no/T3.7/Tabeller.
68. Tchang BG, Saunders KH, Igel LI. Best Practices in the Management of Overweight and Obesity. Med Clin North Am. 2021;105(1):149-74.
69. May M, Schindler C, Engeli S. Modern pharmacological treatment of obese patients. Ther Adv Endocrinol Metab. 2020;11:2042018819897527.
70. Onakpoya IJ, Lee JJ, Mahtani KR, Aronson JK, Heneghan CJ. Naltrexone-bupropion (Mysimba) in management of obesity: A systematic review and meta-analysis of unpublished clinical study reports. Br J Clin Pharmacol. 2020;86(4):646-67.

71. Tak YJ, Lee SY. Long-Term Efficacy and Safety of Anti-Obesity Treatment: Where Do We Stand? Curr Obes Rep. 2021;10(1):14-30.
72. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med. 2021;384(11):989-1002.
73. Coskun T, Sloop KW, Loghin C, Alsina-Fernandez J, Urva S, Bokvist KB, et al. LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: From discovery to clinical proof of concept. Mol Metab. 2018;18:3-14.
74. Frias JP, Nauck MA, Van J, Kutner ME, Cui X, Benson C, et al. Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial. Lancet. 2018;392(10160):2180-93.
75. Son JW, Kim S. Comprehensive Review of Current and Upcoming Anti-Obesity Drugs. Diabetes Metab J. 2020;44(6):802-18.
76. Akalestou E, Miras AD, Rutter GA, le Roux CW. Mechanisms of Weight Loss After Obesity Surgery. Endocr Rev. 2022;43(1):19-34.
77. Chu L, Steinberg A, Mehta M, O'Kane C, Toulany A, Langer JC, Hamilton JK. Resting Energy Expenditure and Metabolic Adaptation in Adolescents at 12 Months After Bariatric Surgery. J Clin Endocrinol Metab. 2019;104(7):2648-56.
78. Heshka S, Lemos T, Astbury NM, Widen E, Davidson L, Goodpaster BH, et al. Resting Energy Expenditure and Organ-Tissue Body Composition 5 Years After Bariatric Surgery. Obes Surg. 2020;30(2):587-94.
79. Wilms B, Ernst B, Thurnheer M, Schmid SM, Spengler CM, Schultes B. Resting energy expenditure after Roux-en Y gastric bypass surgery. Surg Obes Relat Dis. 2018;14(2):191-9.
80. Hao Z, Townsend RL, Mumphrey MB, Morrison CD, Münzberg H, Berthoud HR. RYGB Produces more Sustained Body Weight Loss and Improvement of Glycemic Control Compared with VSG in the Diet-Induced Obese Mouse Model. Obes Surg. 2017;27(9):2424-33.
81. Kuhre RE, Wewer Albrechtsen NJ, Larsen O, Jepsen SL, Balk-Møller E, Andersen DB, et al. Bile acids are important direct and indirect regulators of the secretion of appetite- and metabolism-regulating hormones from the gut and pancreas. Mol Metab. 2018;11:84-95.
82. Albaugh VL, Banan B, Ajouz H, Abumrad NN, Flynn CR. Bile acids and bariatric surgery. Mol Aspects Med. 2017;56:75-89.
83. Graessler J, Qin Y, Zhong H, Zhang J, Licinio J, Wong ML, et al. Metagenomic sequencing of the human gut microbiome before and after bariatric surgery in obese patients with type 2 diabetes: correlation with inflammatory and metabolic parameters. Pharmacogenomics J. 2013;13(6):514-22.
84. Tolhurst G, Heffron H, Lam YS, Parker HE, Habib AM, Diakogiannaki E, et al. Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2. Diabetes. 2012;61(2):364-71.
85. Angrisani L, Santonicola A, Iovino P, Ramos A, Shikora S, Kow L. Bariatric Surgery Survey 2018: Similarities and Disparities Among the 5 IFSO Chapters. Obes Surg. 2021:1-12.
86. Welbourn R, Hollyman M, Kinsman R, Dixon J, Liem R, Ottosson J, et al. Bariatric Surgery Worldwide: Baseline Demographic Description and One-Year Outcomes from the Fourth IFSO Global Registry Report 2018. Obes Surg. 2019;29(3):782-95.
87. Tham E, Ang SM, Cowan SW, Yeo CJ, Isenberg GA. César Roux-The Mind behind the Roux-en-Y. Am Surg. 2019;85(1):e14-e7.

88. Torgersen Z, Osmolak A, Forse RA. Sleeve gastrectomy and Roux En Y gastric bypass: current state of metabolic surgery. Curr Opin Endocrinol Diabetes Obes. 2014;21(5):352-7.
89. SAGES guideline for clinical application of laparoscopic bariatric surgery. Surg Endosc. 2008;22(10):2281-300.
90. Gorodner V, Viscido G, Signorini F, Obeide L, Moser F. Gastroesophageal reflux disease and morbid obesity: evaluation and treatment. Updates Surg. 2018;70(3):331-7.
91. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022;45(Suppl 1):S17-s38.
92. González EL, Johansson S, Wallander MA, Rodríguez LA. Trends in the prevalence and incidence of diabetes in the UK: 1996-2005. J Epidemiol Community Health. 2009;63(4):332-6.
93. Bjarkø VV, Haug EB, Sørgjerd EP, Stene LC, Ruiz PL, Birkeland KI, et al. Undiagnosed diabetes: Prevalence and cardiovascular risk profile in a population-based study of 52,856 individuals. The HUNT Study, Norway. Diabet Med. 2022;39(6):e14829.
94. Kolotkin RL, Meter K, Williams GR. Quality of life and obesity. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2001;2(4):219-29.
95. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature. 2006;444(7121):840-6.
96. Carbone S, Del Buono MG, Ozemek C, Lavie CJ. Obesity, risk of diabetes and role of physical activity, exercise training and cardiorespiratory fitness. Prog Cardiovasc Dis. 2019;62(4):327-33.
97. Colditz GA, Willett WC, Rotnitzky A, Manson JE. Weight gain as a risk factor for clinical diabetes mellitus in women. Ann Intern Med. 1995;122(7):481-6.
98. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. Diabetes Care. 1994;17(9):961-9.
99. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1211-59.
100. Livingston EH, Ko CY. Effect of diabetes and hypertension on obesity-related mortality. Surgery. 2005;137(1):16-25.
101. Astrup A, Finer N. Redefining type 2 diabetes: 'diabesity' or 'obesity dependent diabetes mellitus'? Obes Rev. 2000;1(2):57-9.
102. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352(9131):837-53.
103. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352(9131):854-65.
104. Wing RR. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. Arch Intern Med. 2010;170(17):1566-75.
105. Jakobsen GS, Småstuen MC, Sandbu R, Nordstrand N, Hofsø D, Lindberg M, et al. Association of Bariatric Surgery vs Medical Obesity Treatment With Long-term Medical Complications and Obesity-Related Comorbidities. Jama. 2018;319(3):291-301.

106. Hofsø D, Nordstrand N, Johnson LK, Karlsen TI, Hager H, Jenssen T, et al. Obesity-related cardiovascular risk factors after weight loss: a clinical trial comparing gastric bypass surgery and intensive lifestyle intervention. Eur J Endocrinol. 2010;163(5):735-45.
107. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Aminian A, Brethauer SA, et al. Bariatric Surgery versus Intensive Medical Therapy for Diabetes - 5-Year Outcomes. N Engl J Med. 2017;376(7):641-51.
108. Riddle MC, Cefalu WT, Evans PH, Gerstein HC, Nauck MA, Oh WK, et al. Consensus Report: Definition and Interpretation of Remission in Type 2 Diabetes. Diabetes Care. 2021;44(10):2438-44.
109. Savarino E, Bredenoord AJ, Fox M, Pandolfino JE, Roman S, Gyawali CP. Expert consensus document: Advances in the physiological assessment and diagnosis of GERD. Nature reviews Gastroenterology & hepatology. 2017;14(11):665-76.
110. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. The American journal of gastroenterology. 2006;101(8):1900-20; quiz 43.
111. Liu L, Li S, Zhu K, Yu W, Wang H, Guo J, Gao H. Relationship between esophageal motility and severity of gastroesophageal reflux disease according to the Los Angeles classification. Medicine (Baltimore). 2019;98(19):e15543.
112. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2013;108(3):308-28; quiz 29.
113. Mittal R, Vaezi MF. Esophageal Motility Disorders and Gastroesophageal Reflux Disease. N Engl J Med. 2020;383(20):1961-72.
114. Mikami DJ, Murayama KM. Physiology and pathogenesis of gastroesophageal reflux disease. Surg Clin North Am. 2015;95(3):515-25.
115. Iwakiri K, Hayashi Y, Kotoyori M, Tanaka Y, Kawakami A, Sakamoto C, Holloway RH. Transient lower esophageal sphincter relaxations (TLESRs) are the major mechanism of gastroesophageal reflux but are not the cause of reflux disease. Dig Dis Sci. 2005;50(6):1072-7.
116. Schneider JH, Küper M, Königsrainer A, Brücher B. Transient lower esophageal sphincter relaxation in morbid obesity. Obes Surg. 2009;19(5):595-600.
117. Mittal RK, Holloway RH, Penagini R, Blackshaw LA, Dent J. Transient lower esophageal sphincter relaxation. Gastroenterology. 1995;109(2):601-10.
118. Pandolfino JE, El-Serag HB, Zhang Q, Shah N, Ghosh SK, Kahrilas PJ. Obesity: a challenge to esophagogastric junction integrity. Gastroenterology. 2006;130(3):639-49.
119. Pandolfino JE, Kwiatek MA, Kahrilas PJ. The pathophysiologic basis for epidemiologic trends in gastroesophageal reflux disease. Gastroenterol Clin North Am. 2008;37(4):827-43, viii.
120. Anggiansah R, Sweis R, Anggiansah A, Wong T, Cooper D, Fox M. The effects of obesity on oesophageal function, acid exposure and the symptoms of gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2013;37(5):555-63.
121. Punjabi P, Hira A, Prasad S, Wang X, Chokhavatia S. Review of gastroesophageal reflux disease (GERD) in the diabetic patient. Journal of diabetes. 2015;7(5):599-609.
122. El-Serag HB, Sweet S, Winchester CC, Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut. 2014;63(6):871-80.

123. Eusebi LH, Ratnakumaran R, Yuan Y, Solaymani-Dodaran M, Bazzoli F, Ford AC. Global prevalence of, and risk factors for, gastro-oesophageal reflux symptoms: a meta-analysis. Gut. 2018;67(3):430-40.
124. Nirwan JS, Hasan SS, Babar ZU, Conway BR, Ghori MU. Global Prevalence and Risk Factors of Gastro-oesophageal Reflux Disease (GORD): Systematic Review with Meta-analysis. Sci Rep. 2020;10(1):5814.
125. Kristo I, Paireder M, Jomrich G, Felsenreich DM, Fischer M, Hennerbichler FP, et al. Silent Gastroesophageal Reflux Disease in Patients with Morbid Obesity Prior to Primary Metabolic Surgery. Obes Surg. 2020;30(12):4885-91.
126. Dent J, Vakil N, Jones R, Bytzer P, Schoning U, Halling K, et al. Accuracy of the diagnosis of GORD by questionnaire, physicians and a trial of proton pump inhibitor treatment: the Diamond Study. Gut. 2010;59(6):714-21.
127. Richter JE, Rubenstein JH. Presentation and Epidemiology of Gastroesophageal Reflux Disease. Gastroenterology. 2018;154(2):267-76.
128. Numans ME, Lau J, de Wit NJ, Bonis PA. Short-term treatment with proton-pump inhibitors as a test for gastroesophageal reflux disease: a meta-analysis of diagnostic test characteristics. Ann Intern Med. 2004;140(7):518-27.
129. Ronkainen J, Aro P, Storskrubb T, Johansson SE, Lind T, Bolling-Sternevald E, et al. High prevalence of gastroesophageal reflux symptoms and esophagitis with or without symptoms in the general adult Swedish population: a Kalixanda study report. Scandinavian journal of gastroenterology. 2005;40(3):275-85.
130. Zagari RM, Fuccio L, Wallander MA, Johansson S, Fiocca R, Casanova S, et al. Gastro-oesophageal reflux symptoms, oesophagitis and Barrett's oesophagus in the general population: the Loiano-Monghidoro study. Gut. 2008;57(10):1354-9.
131. Pregun I, Hritz I, Tulassay Z, Herszényi L. Peptic esophageal stricture: medical treatment. Dig Dis. 2009;27(1):31-7.
132. Cossentino MJ, Wong RK. Barrett's esophagus and risk of esophageal adenocarcinoma. Semin Gastrointest Dis. 2003;14(3):128-35.
133. Veugelers PJ, Porter GA, Guernsey DL, Casson AG. Obesity and lifestyle risk factors for gastroesophageal reflux disease, Barrett esophagus and esophageal adenocarcinoma. Dis Esophagus. 2006;19(5):321-8.
134. Coleman HG, Xie SH, Lagergren J. The Epidemiology of Esophageal Adenocarcinoma. Gastroenterology. 2018;154(2):390-405.
135. Chen J, Brady P. Gastroesophageal Reflux Disease: Pathophysiology, Diagnosis, and Treatment. Gastroenterol Nurs. 2019;42(1):20-8.
136. Wilson H, Mocanu V, Sun W, Dang J, Jogiat U, Kung J, et al. Fundoplication is superior to medical therapy for Barrett's esophagus disease regression and progression: a systematic review and meta-analysis. Surg Endosc. 2022;36(4):2554-63.
137. Weusten B, Bisschops R, Coron E, Dinis-Ribeiro M, Dumonceau JM, Esteban JM, et al. Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. Endoscopy. 2017;49(2):191-8.
138. Bou Daher H, Sharara AI. Gastroesophageal reflux disease, obesity and laparoscopic sleeve gastrectomy: The burning questions. World journal of gastroenterology. 2019;25(33):4805-13.

139. Merrouche M, Sabate JM, Jouet P, Harnois F, Scaringi S, Coffin B, Msika S. Gastro-esophageal reflux and esophageal motility disorders in morbidly obese patients before and after bariatric surgery. Obes Surg. 2007;17(7):894-900.
140. El-Serag HB, Graham DY, Satia JA, Rabeneck L. Obesity is an independent risk factor for GERD symptoms and erosive esophagitis. Am J Gastroenterol. 2005;100(6):1243-50.
141. Iovino P, Angrisani L, Galloro G, Consalvo D, Tremolaterra F, Pascariello A, Ciacci C. Proximal stomach function in obesity with normal or abnormal oesophageal acid exposure. Neurogastroenterol Motil. 2006;18(6):425-32.
142. Murray L, Johnston B, Lane A, Harvey I, Donovan J, Nair P, Harvey R. Relationship between body mass and gastro-oesophageal reflux symptoms: The Bristol Helicobacter Project. International journal of epidemiology. 2003;32(4):645-50.
143. Sharara AI, Rustom LBO, Bou Daher H, Rimmani HH, Shayto RH, Minhem M, et al. Prevalence of gastroesophageal reflux and risk factors for erosive esophagitis in obese patients considered for bariatric surgery. Dig Liver Dis. 2019;51(10):1375-9.
144. Mora F, Cassinello N, Mora M, Bosca M, Minguez M, Ortega J. Esophageal abnormalities in morbidly obese adult patients. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2016;12(3):622-8.
145. Stein DJ, El-Serag HB, Kuczynski J, Kramer JR, Sampliner RE. The association of body mass index with Barrett's oesophagus. Alimentary pharmacology & therapeutics. 2005;22(10):1005-10.
146. Lagergren J, Bergstrom R, Nyren O. No relation between body mass and gastro-oesophageal reflux symptoms in a Swedish population based study. Gut. 2000;47(1):26-9.
147. Smith KJ, O'Brien SM, Smithers BM, Gotley DC, Webb PM, Green AC, Whiteman DC. Interactions among smoking, obesity, and symptoms of acid reflux in Barrett's esophagus. Cancer Epidemiol Biomarkers Prev. 2005;14(11 Pt 1):2481-6.
148. Gatopoulou A, Papanas N, Maltezos E. Diabetic gastrointestinal autonomic neuropathy: current status and new achievements for everyday clinical practice. European journal of internal medicine. 2012;23(6):499-505.
149. Koch CA, Uwaifo GI. Are gastrointestinal symptoms related to diabetes mellitus and glycemic control? Eur J Gastroenterol Hepatol. 2008;20(9):822-5.
150. Peterli R, Wölnerhanssen BK, Peters T, Vetter D, Kröll D, Borbély Y, et al. Effect of Laparoscopic Sleeve Gastrectomy vs Laparoscopic Roux-en-Y Gastric Bypass on Weight Loss in Patients With Morbid Obesity: The SM-BOSS Randomized Clinical Trial. Jama. 2018;319(3):255-65.
151. Gagner M, Hutchinson C, Rosenthal R. Fifth International Consensus Conference: current status of sleeve gastrectomy. Surg Obes Relat Dis. 2016;12(4):750-6.
152. Rebecchi F, Allaix ME, Giaccone C, Ugliono E, Scozzari G, Morino M. Gastroesophageal reflux disease and laparoscopic sleeve gastrectomy: a physiopathologic evaluation. Ann Surg. 2014;260(5):909-14; discussion 14-5.
153. Pallati PK, Shaligram A, Shostrom VK, Oleynikov D, McBride CL, Goede MR. Improvement in gastroesophageal reflux disease symptoms after various bariatric procedures: review of the Bariatric Outcomes Longitudinal Database. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2014;10(3):502-7.
154. De Groot NL, Burgerhart JS, Van De Meeberg PC, de Vries DR, Smout AJ, Siersema PD. Systematic review: the effects of conservative and surgical treatment for obesity on gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2009;30(11-12):1091-102.

155. Helm JF, Dodds WJ, Pelc LR, Palmer DW, Hogan WJ, Teeter BC. Effect of esophageal emptying and saliva on clearance of acid from the esophagus. N Engl J Med. 1984;310(5):284-8.
156. Jaffin BW, Knoepflmacher P, Greenstein R. High prevalence of asymptomatic esophageal motility disorders among morbidly obese patients. Obes Surg. 1999;9(4):390-5.
157. Kong MF, Horowitz M, Jones KL, Wishart JM, Harding PE. Natural history of diabetic gastroparesis. Diabetes Care. 1999;22(3):503-7.
158. Faraj J, Melander O, Sundkvist G, Olsson R, Thorsson O, Ekberg O, Ohlsson B. Oesophageal dysmotility, delayed gastric emptying and gastrointestinal symptoms in patients with diabetes mellitus. Diabet Med. 2007;24(11):1235-9.
159. Gokturk S, Akyuz F, Arici S, Alpaslan B, Ormeci A, Soyer OM, et al. Gastroesophageal Reflux in Asymptomatic Patients with Diabetes: An Impedance Study Diabetes, Obesity and Gastroesophageal Reflux. Exp Clin Endocrinol Diabetes. 2020;128(1):52-8.
160. Rubenstein JH, Morgenstern H, McConell D, Scheiman JM, Schoenfeld P, Appelman H, et al. Associations of diabetes mellitus, insulin, leptin, and ghrelin with gastroesophageal reflux and Barrett's esophagus. Gastroenterology. 2013;145(6):1237-44.e1-5.
161. Weldring T, Smith SM. Patient-Reported Outcomes (PROs) and Patient-Reported Outcome Measures (PROMs). Health Serv Insights. 2013;6:61-8.
162. Mercieca-Bebber R, King MT, Calvert MJ, Stockler MR, Friedlander M. The importance of patient-reported outcomes in clinical trials and strategies for future optimization. Patient Relat Outcome Meas. 2018;9:353-67.
163. DeSalvo KB, Bloser N, Reynolds K, He J, Muntner P. Mortality prediction with a single general self-rated health question. A meta-analysis. J Gen Intern Med. 2006;21(3):267-75.
164. Patrick DL, Burke LB, Powers JH, Scott JA, Rock EP, Dawisha S, et al. Patient-reported outcomes to support medical product labeling claims: FDA perspective. Value Health. 2007;10 Suppl 2:S125-37.
165. Ware JE KM. SF-36 Physical and Mental Health Summary Scales: A Manual for Users of Version 1, 2ndWare JE, Kosinski M: SF-36 Physical and Mental Health Summary Scales: A Manual for Users of Version 1, 2001.
166. Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BW, Zitman FG. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatry. 2010;67(3):220-9.
167. Onyike CU, Crum RM, Lee HB, Lyketsos CG, Eaton WW. Is obesity associated with major depression? Results from the Third National Health and Nutrition Examination Survey. Am J Epidemiol. 2003;158(12):1139-47.
168. Spahlholz J, Baer N, König HH, Riedel-Heller SG, Luck-Sikorski C. Obesity and discrimination - a systematic review and meta-analysis of observational studies. Obes Rev. 2016;17(1):43-55.
169. Lin HY, Huang CK, Tai CM, Lin HY, Kao YH, Tsai CC, et al. Psychiatric disorders of patients seeking obesity treatment. BMC Psychiatry. 2013;13:1.
170. Ul-Haq Z, Mackay DF, Fenwick E, Pell JP. Meta-analysis of the association between body mass index and health-related quality of life among adults, assessed by the SF-36. Obesity (Silver Spring). 2013;21(3):E322-7.
171. Egede LE, Zheng D. Independent factors associated with major depressive disorder in a national sample of individuals with diabetes. Diabetes Care. 2003;26(1):104-11.

172. de Vries CEE, Terwee CB, Al Nawas M, van Wagensveld BA, Janssen IMC, Liem RSL, et al. Outcomes of the first global multidisciplinary consensus meeting including persons living with obesity to standardize patient-reported outcome measurement in obesity treatment research. Obes Rev. 2022;23(8):e13452.
173. Coulman KD, Hopkins J, Brookes ST, Chalmers K, Main B, Owen-Smith A, et al. A Core Outcome Set for the Benefits and Adverse Events of Bariatric and Metabolic Surgery: The BARIACT Project. PLoS Med. 2016;13(11):e1002187.
174. van Beek AP, Emous M, Laville M, Tack J. Dumping syndrome after esophageal, gastric or bariatric surgery: pathophysiology, diagnosis, and management. Obes Rev. 2017;18(1):68-85.
175. Ukleja A. Dumping syndrome: pathophysiology and treatment. Nutr Clin Pract. 2005;20(5):517-25.
176. Tack J. Gastric motor disorders. Best Pract Res Clin Gastroenterol. 2007;21(4):633-44.
177. Tzovaras G, Papamargaritis D, Sioka E, Zachari E, Baloyiannis I, Zacharoulis D, Koukoulis G. Symptoms suggestive of dumping syndrome after provocation in patients after laparoscopic sleeve gastrectomy. Obes Surg. 2012;22(1):23-8.
178. Conchillo JM, Schwartz MP, Selimah M, Samsom M, Sifrim D, Smout AJ. Acid and non-acid reflux patterns in patients with erosive esophagitis and non-erosive reflux disease (NERD): a study using intraluminal impedance monitoring. Dig Dis Sci. 2008;53(6):1506-12.
179. Martinez SD, Malagon IB, Garewal HS, Cui H, Fass R. Non-erosive reflux disease (NERD)--acid reflux and symptom patterns. Aliment Pharmacol Ther. 2003;17(4):537-45.
180. Gu L, Chen B, Du N, Fu R, Huang X, Mao F, et al. Relationship Between Bariatric Surgery and Gastroesophageal Reflux Disease: a Systematic Review and Meta-analysis. Obes Surg. 2019;29(12):4105-13.
181. Murphy R, Plank LD, Clarke MG, Evennett NJ, Tan J, Kim DDW, et al. Effect of Banded Roux-en-Y Gastric Bypass Versus Sleeve Gastrectomy on Diabetes Remission at 5 Years Among Patients With Obesity and Type 2 Diabetes: A Blinded Randomized Clinical Trial. Diabetes Care. 2022;45(7):1503-11.
182. Borgeraas H, Hjelmesaeth J, Birkeland KI, Fatima F, Grimnes JO, Gulseth HL, et al. Single-centre, triple-blinded, randomised, 1-year, parallel-group, superiority study to compare the effects of Roux-en-Y gastric bypass and sleeve gastrectomy on remission of type 2 diabetes and beta-cell function in subjects with morbid obesity: a protocol for the Obesity surgery in Tonsberg (Oseberg) study. BMJ open. 2019;9(6):e024573.
183. Hofsø D, Aasheim ET, Søvik TT, Jakobsen GS, Johnson LK, Sandbu R, et al. [Follow-up after bariatric surgery]. Tidsskr Nor Laegeforen. 2011;131(19):1887-92.
184. Jonasson C, Wernersson B, Hoff DA, Hatlebakk JG. Validation of the GerdQ questionnaire for the diagnosis of gastro-oesophageal reflux disease. Alimentary pharmacology & therapeutics. 2013;37(5):564-72.
185. Jonasson C, Moum B, Bang C, Andersen KR, Hatlebakk JG. Randomised clinical trial: a comparison between a GerdQ-based algorithm and an endoscopy-based approach for the diagnosis and initial treatment of GERD. Alimentary pharmacology & therapeutics. 2012;35(11):1290-300.
186. Dimenas E, Glise H, Hallerback B, Hernqvist H, Svedlund J, Wiklund I. Well-being and gastrointestinal symptoms among patients referred to endoscopy owing to suspected duodenal ulcer. Scand J Gastroenterol. 1995;30(11):1046-52.

187. Revicki DA, Wood M, Wiklund I, Crawley J. Reliability and validity of the Gastrointestinal Symptom Rating Scale in patients with gastroesophageal reflux disease. Qual Life Res. 1998;7(1):75-83.
188. Kolotkin RL, Crosby RD, Kosloski KD, Williams GR. Development of a brief measure to assess quality of life in obesity. Obes Res. 2001;9(2):102-11.
189. Kolotkin RL, Crosby RD, Williams GR. Assessing weight-related quality of life in obese persons with type 2 diabetes. Diabetes Res Clin Pract. 2003;61(2):125-32.
190. Aasprang A, Våge V, Fløtlo TN, Hegland PA, Kolotkin R, Natvig GK, Andersen JR. Patient-reported quality of life with obesity - development of a new measurement scale. Tidsskr Nor Laegeforen. 2019;139(11).
191. A A. Reliability and validity of the Norwegian version of Impact of Weight on Quality of Life questionnaire. Obes Facts 2016.
192. Patrick DL, Bushnell DM, Rothman M. Performance of two self-report measures for evaluating obesity and weight loss. Obes Res. 2004;12(1):48-57.
193. Karlsen TI, Tveitå EK, Natvig GK, Tonstad S, Hjelmesæth J. Validity of the SF-36 in patients with morbid obesity. Obes Facts. 2011;4(5):346-51.
194. Ware JE, Jr. SF-36 health survey update. Spine (Phila Pa 1976). 2000;25(24):3130-9.
195. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-83.
196. Hays RD, Sherbourne CD, Mazel RM. The RAND 36-Item Health Survey 1.0. Health Econ. 1993;2(3):217-27.
197. Loge JH, Kaasa S. Short form 36 (SF-36) health survey: normative data from the general Norwegian population. Scand J Soc Med. 1998;26(4):250-8.
198. Al Amer R, Al Khalifa K, Alajlan SA, Al Ansari A. Analyzing the Psychometric Properties of the Short Form-36 Quality of Life Questionnaire in Patients with Obesity. Obes Surg. 2018;28(8):2521-7.
199. Corica F, Corsonello A, Apolone G, Lucchetti M, Melchionda N, Marchesini G. Construct validity of the Short Form-36 Health Survey and its relationship with BMI in obese outpatients. Obesity (Silver Spring). 2006;14(8):1429-37.
200. Coulman KD, Blazeby JM. Health-Related Quality of Life in Bariatric and Metabolic Surgery. Curr Obes Rep. 2020;9(3):307-14.
201. Richter P, Werner J, Heerlein A, Kraus A, Sauer H. On the validity of the Beck Depression Inventory. A review. Psychopathology. 1998;31(3):160-8.
202. von Glischinski M, von Brachel R, Hirschfeld G. How depressed is "depressed"? A systematic review and diagnostic meta-analysis of optimal cut points for the Beck Depression Inventory revised (BDI-II). Qual Life Res. 2019;28(5):1111-8.
203. Suter M, Calmes JM, Paroz A, Giusti V. A new questionnaire for quick assessment of food tolerance after bariatric surgery. Obes Surg. 2007;17(1):2-8.
204. Cappelleri JC, Bushmakin AG, Gerber RA, Leidy NK, Sexton CC, Karlsson J, Lowe MR. Evaluating the Power of Food Scale in obese subjects and a general sample of individuals: development and measurement properties. Int J Obes (Lond). 2009;33(8):913-22.
205. Espel-Huynh HM, Muratore AF, Lowe MR. A narrative review of the construct of hedonic hunger and its measurement by the Power of Food Scale. Obes Sci Pract. 2018;4(3):238-49.

206. Lowe MR, Butryn ML, Didie ER, Annunziato RA, Thomas JG, Crerand CE, et al. The Power of Food Scale. A new measure of the psychological influence of the food environment. Appetite. 2009;53(1):114-8.
207. Gormally J, Black S, Daston S, Rardin D. The assessment of binge eating severity among obese persons. Addict Behav. 1982;7(1):47-55.
208. Marcus MD, Wing RR, Lamparski DM. Binge eating and dietary restraint in obese patients. Addict Behav. 1985;10(2):163-8.
209. Grupski AE, Hood MM, Hall BJ, Azarbad L, Fitzpatrick SL, Corsica JA. Examining the Binge Eating Scale in screening for binge eating disorder in bariatric surgery candidates. Obes Surg. 2013;23(1):1-6.
210. Buse JB, Caprio S, Cefalu WT, Ceriello A, Del Prato S, Inzucchi SE, et al. How do we define cure of diabetes? Diabetes Care. 2009;32(11):2133-5.
211. Lundell LR, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut. 1999;45(2):172-80.
212. Alvarez Herrero L, Curvers WL, van Vilsteren FG, Wolfsen H, Ragunath K, Wong Kee Song LM, et al. Validation of the Prague C&M classification of Barrett's esophagus in clinical practice. Endoscopy. 2013;45(11):876-82.
213. Savarino E, Zentilin P, Savarino V. NERD: an umbrella term including heterogeneous subpopulations. Nature reviews Gastroenterology & hepatology. 2013;10(6):371-80.
214. Liu S, Xu M, Yang J, Qi H, He F, Zhao X, et al. Research on Gastroesophageal Reflux Disease Based on Dynamic Features of Ambulatory 24-Hour Esophageal pH Monitoring. Computational and mathematical methods in medicine. 2017;2017:9239074.
215. Borgeraas H, Hjelmesæth J, Birkeland KI, Fatima F, Grimnes JO, Gulseth HL, et al. Single-centre, triple-blinded, randomised, 1-year, parallel-group, superiority study to compare the effects of Roux-en-Y gastric bypass and sleeve gastrectomy on remission of type 2 diabetes and β-cell function in subjects with morbid obesity: a protocol for the Obesity surgery in Tønsberg (Oseberg) study. BMJ Open. 2019;9(6):e024573.
216. Li G, Taljaard M, Van den Heuvel ER, Levine MA, Cook DJ, Wells GA, et al. An introduction to multiplicity issues in clinical trials: the what, why, when and how. Int J Epidemiol. 2017;46(2):746-55.
217. Lorentzen J, Medhus AW, Hertel JK, Borgeraas H, Karlsen TI, Kolotkin RL, et al. Erosive Esophagitis and Symptoms of Gastroesophageal Reflux Disease in Patients with Morbid Obesity with and without Type 2 Diabetes: a Cross-sectional Study. Obes Surg. 2020;30(7):2667-75.
218. Lorentzen J, Medhus AW, Hofsø D, Svanevik M, Seip B, Hjelmesæth J. Sleeve Gastrectomy Confers Higher Risk of Gastroesophageal Reflux Disease Than Gastric Bypass: A Randomized Controlled Trial From the Oseberg Reflux Working Group. Gastroenterology. 2021;161(6):2044-6.e4.
219. Ali M, El Chaar M, Ghiassi S, Rogers AM. American Society for Metabolic and Bariatric Surgery updated position statement on sleeve gastrectomy as a bariatric procedure. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2017;13(10):1652-7.
220. Santonicola A, Ruggiero L, Palma R, Angrisani L, Iovino P. Gerd symptoms after laparoscopic Roux-en-Y gastric bypass: an emerging scenario. Int J Obes (Lond). 2022;46(5):1076-8.

221. Sharaf RN, Weinshel EH, Bini EJ, Rosenberg J, Sherman A, Ren CJ. Endoscopy plays an important preoperative role in bariatric surgery. Obes Surg. 2004;14(10):1367-72.
222. Kase H, Hattori Y, Sato N, Banba N, Kasai K. Symptoms of gastroesophageal reflux in diabetes patients. Diabetes Res Clin Pract. 2008;79(2):e6-7.
223. Suter M, Dorta G, Giusti V, Calmes JM. Gastro-esophageal reflux and esophageal motility disorders in morbidly obese patients. Obes Surg. 2004;14(7):959-66.
224. Ortiz V, Ponce M, Fernandez A, Martinez B, Ponce JL, Garrigues V, Ponce J. Value of heartburn for diagnosing gastroesophageal reflux disease in severely obese patients. Obesity (Silver Spring, Md). 2006;14(4):696-700.
225. Kristo I, Paireder M, Jomrich G, Felsenreich DM, Nikolic M, Langer FB, et al. Modern Esophageal Function Testing and Gastroesophageal Reflux Disease in Morbidly Obese Patients. Obes Surg. 2019;29(11):3536-41.
226. Frokjaer JB, Andersen SD, Ejskaer N, Funch-Jensen P, Arendt-Nielsen L, Gregersen H, Drewes AM. Gut sensations in diabetic autonomic neuropathy. Pain. 2007;131(3):320-9.
227. Tack J, Pandolfino JE. Pathophysiology of Gastroesophageal Reflux Disease. Gastroenterology. 2018;154(2):277-88.
228. Falk GW, Jacobson BC, Riddell RH, Rubenstein JH, El-Zimaity H, Drewes AM, et al. Barrett's esophagus: prevalence-incidence and etiology-origins. Ann N Y Acad Sci. 2011;1232:1-17.
229. Woodland P, Shen Ooi JL, Grassi F, Nikaki K, Lee C, Evans JA, et al. Superficial Esophageal Mucosal Afferent Nerves May Contribute to Reflux Hypersensitivity in Nonerosive Reflux Disease. Gastroenterology. 2017;153(5):1230-9.
230. Gokturk S, Akyuz F, Arici S, Alpaslan B, Ormeci A, Soyer OM, et al. Gastroesophageal Reflux in Asymptomatic Patients with Diabetes: An Impedance Study Diabetes, Obesity and Gastroesophageal Reflux. Exp Clin Endocrinol Diabetes. 2018.
231. Wilson LJ, Ma W, Hirschowitz BI. Association of obesity with hiatal hernia and esophagitis. Am J Gastroenterol. 1999;94(10):2840-4.
232. Rebecchi F, Allaix ME, Patti MG, Schlottmann F, Morino M. Gastroesophageal reflux disease and morbid obesity: To sleeve or not to sleeve? World J Gastroenterol. 2017;23(13):2269-75.
233. Del Genio G, Tolone S, Limongelli P, Brusciano L, D'Alessandro A, Docimo G, et al. Sleeve gastrectomy and development of "de novo" gastroesophageal reflux. Obes Surg. 2014;24(1):71-7.
234. Li J, Lai D, Wu D. Laparoscopic Roux-en-Y Gastric Bypass Versus Laparoscopic Sleeve Gastrectomy to Treat Morbid Obesity-Related Comorbidities: a Systematic Review and Meta-analysis. Obes Surg. 2016;26(2):429-42.
235. Tutuian R. Obesity and GERD: pathophysiology and effect of bariatric surgery. Curr Gastroenterol Rep. 2011;13(3):205-12.
236. Navarini D, Madalosso CAS, Tognon AP, Fornari F, Barão FR, Gurski RR. Predictive Factors of Gastroesophageal Reflux Disease in Bariatric Surgery: a Controlled Trial Comparing Sleeve Gastrectomy with Gastric Bypass. Obes Surg. 2020;30(4):1360-7.
237. Rengarajan A, Bolkhir A, Gor P, Wang D, Munigala S, Gyawali CP. Esophagogastric junction and esophageal body contraction metrics on high-resolution manometry predict esophageal acid burden. Neurogastroenterol Motil. 2018;30(5):e13267.

238. Balla A, Meoli F, Palmieri L, Corallino D, Sacchi MC, Ribichini E, et al. Manometric and pH-monitoring changes after laparoscopic sleeve gastrectomy: a systematic review. Langenbecks Arch Surg. 2021;406(8):2591-609.
239. Reddy CA, Baker JR, Lau J, Chen JW. High-Resolution Manometry Diagnosis of Ineffective Esophageal Motility Is Associated with Higher Reflux Burden. Dig Dis Sci. 2019;64(8):2199-205.
240. Ardila-Hani A, Soffer EE. Review article: the impact of bariatric surgery on gastrointestinal motility. Aliment Pharmacol Ther. 2011;34(8):825-31.
241. Petersen WV, Meile T, Küper MA, Zdichavsky M, Königsrainer A, Schneider JH. Functional importance of laparoscopic sleeve gastrectomy for the lower esophageal sphincter in patients with morbid obesity. Obes Surg. 2012;22(3):360-6.
242. Ashrafi D, Osland E, Memon MA. Bariatric surgery and gastroesophageal reflux disease. Ann Transl Med. 2020;8(Suppl 1):S11.
243. Savarino E, Gemignani L, Pohl D, Zentilin P, Dulbecco P, Assandri L, et al. Oesophageal motility and bolus transit abnormalities increase in parallel with the severity of gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2011;34(4):476-86.
244. Suter M. Gastroesophageal Reflux Disease, Obesity, and Roux-en-Y Gastric Bypass: Complex Relationship-a Narrative Review. Obes Surg. 2020;30(8):3178-87.
245. Laffin M, Chau J, Gill RS, Birch DW, Karmali S. Sleeve gastrectomy and gastroesophageal reflux disease. Journal of obesity. 2013;2013:741097.
246. Signorini F, Olguín S, Viscido G, Obeide L, Moser F. Esophagitis evolution after sleeve gastrectomy or gastric bypass in consecutive cases. Surg Endosc. 2020;34(10):4330-5.
247. Signorini F, Viscido G, Bocco MCA, Obeide L, Moser F. Impact of Gastric Bypass on Erosive Esophagitis and Barret's Esophagus. Obes Surg. 2020;30(4):1194-9.
248. Yeung KTD, Penney N, Ashrafian L, Darzi A, Ashrafian H. Does Sleeve Gastrectomy Expose the Distal Esophagus to Severe Reflux?: A Systematic Review and Meta-analysis. Ann Surg. 2020;271(2):257-65.
249. Engevik AC, Kaji I, Goldenring JR. The Physiology of the Gastric Parietal Cell. Physiol Rev. 2020;100(2):573-602.
250. Yao X, Forte JG. Cell biology of acid secretion by the parietal cell. Annu Rev Physiol. 2003;65:103-31.
251. Herbella FA, Vicentine FP, Del Grande JC, Patti MG, Arasaki CH. Postprandial proximal gastric acid pocket in patients after Roux-en-Y gastric bypass. J Gastrointest Surg. 2010;14(11):1742-5.
252. Mitchell DR, Derakhshan MH, Robertson EV, McColl KE. The Role of the Acid Pocket in Gastroesophageal Reflux Disease. J Clin Gastroenterol. 2016;50(2):111-9.
253. Juodeikis Ž, Brimas G. Long-term results after sleeve gastrectomy: A systematic review. Surg Obes Relat Dis. 2017;13(4):693-9.
254. Georgia D, Stamatina T, Maria N, Konstantinos A, Konstantinos F, Emmanouil L, et al. 24-h Multichannel Intraluminal Impedance PH-metry 1 Year After Laparocopic Sleeve Gastrectomy: an Objective Assessment of Gastroesophageal Reflux Disease. Obes Surg. 2017;27(3):749-53.
255. Lorentzen J, Medhus AW, Hofsø D, Svanevik M, Seip B, Hjelmesæth J. Letter to the Editor regarding the article «Gerd symptoms after laparoscopic Roux-en-Y gastric bypass: an emerging scenario» by Antonella Santonicola, Luigi Ruggiero, Rossella Palma, Luigi Angrisani

and Paola Iovino. International Journal of Obesity (2022) 46:1076–1078. International Journal of Obesity. 2022;46(10):1936-7.
256. Lewis KH, Callaway K, Argetsinger S, Wallace J, Arterburn DE, Zhang F, et al. Concurrent hiatal hernia repair and bariatric surgery: outcomes after sleeve gastrectomy and Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2021;17(1):72-80.
257. Kolotkin RL, Crosby RD, Gress RE, Hunt SC, Adams TD. Two-year changes in health-related quality of life in gastric bypass patients compared with severely obese controls. Surg Obes Relat Dis. 2009;5(2):250-6.
258. Nielsen HJ, Nedrebø BG, Fosså A, Andersen JR, Assmus J, Dagsland VH, et al. Seven-year trajectories of body weight, quality of life and comorbidities following Roux-en-Y gastric bypass and sleeve gastrectomy. Int J Obes (Lond). 2022;46(4):739-49.
259. Wu F, Shi F, Fu X, Du N, Chen B, Zhou X. Laparoscopic sleeve gastrectomy versus Roux-en-Y gastric bypass for quality of life: a systematic review and meta-analysis. Surg Obes Relat Dis. 2020;16(11):1869-76.
260. Makaronidis JM, Pucci A, Adamo M, Jenkinson A, Elkalaawy M, Batterham RL. Impact of sleeve gastrectomy compared to Roux-en-y gastric bypass upon hedonic hunger and the relationship to post-operative weight loss. Intern Emerg Med. 2022;17(7):2031-8.
261. Kolotkin RL, Williams VSL, Ervin CM, Williams N, Meincke HH, Qin S, et al. Validation of a new measure of quality of life in obesity trials: Impact of Weight on Quality of Life-Lite Clinical Trials Version. Clin Obes. 2019;9(3):e12310.
262. Colquitt JL, Picot J, Loveman E, Clegg AJ. Surgery for obesity. Cochrane Database Syst Rev. 2009(2):Cd003641.
263. Weijenborg PW, van Hoeij FB, Smout AJ, Bredenoord AJ. Accuracy of hiatal hernia detection with esophageal high-resolution manometry. Neurogastroenterol Motil. 2015;27(2):293-9.
264. Langendoen-Gort M, Groeneveld L, Prinsen CAC, Beulens JW, Elders PJM, Halperin I, et al. Patient-reported outcome measures for assessing health-related quality of life in people with type 2 diabetes: A systematic review. Rev Endocr Metab Disord. 2022;23(5):931-77.
265. Fontaine KR, Barofsky I. Obesity and health-related quality of life. Obes Rev. 2001;2(3):173-82.
266. Raaijmakers LC, Pouwels S, Thomassen SE, Nienhuijs SW. Quality of life and bariatric surgery: a systematic review of short- and long-term results and comparison with community norms. Eur J Clin Nutr. 2017;71(4):441-9.
267. Dmitrienko A, D'Agostino RB, Sr. Multiplicity Considerations in Clinical Trials. N Engl J Med. 2018;378(22):2115-22.
268. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. International journal of surgery. 2012;10(1):28-55.
269. Hariton E, Locascio JJ. Randomised controlled trials - the gold standard for effectiveness research: Study design: randomised controlled trials. Bjog. 2018;125(13):1716.
270. Monaghan TF, Agudelo CW, Rahman SN, Wein AJ, Lazar JM, Everaert K, Dmochowski RR. Blinding in Clinical Trials: Seeing the Big Picture. Medicina (Kaunas). 2021;57(7).
271. Steckler A, McLeroy KR. The importance of external validity. Am J Public Health. 2008;98(1):9-10.
272. Lov om medisinsk og helsefaglig forskning(Helseforskningsloven) LOV-2008-06-20-44.

273. Norge, helseinformasjon Mn. Helsepersonelloven og pasient- og brukerrettighetsloven : med forskrifter : lov om helsepersonell m.v., vedtatt 2. juli 1999 nr. 64 : lov om pasient- og brukerrettigheter, vedtatt 2. juli 1999 nr. 63. Oslo: MEDLEX norsk helseinformasjon; 2012.
274. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. Jama. 2013;310(20):2191-4.
275. Lov om behandling av etikk og redelighet i forskning [forskningsetikkloven]. LOV-2006-06-30-56 (2007).
276. Brown WA, Johari Halim Shah Y, Balalis G, Bashir A, Ramos A, Kow L, et al. IFSO Position Statement on the Role of Esophago-Gastro-Duodenal Endoscopy Prior to and after Bariatric and Metabolic Surgery Procedures. Obes Surg. 2020;30(8):3135-53.

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ORIGINAL CONTRIBUTIONS

Erosive Esophagitis and Symptoms of Gastroesophageal Reflux Disease in Patients with Morbid Obesity with and without Type 2 Diabetes: a Cross-sectional Study

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Abstract

Background Type 2 diabetes (T2DM) is associated with gastroesophageal reflux disease (GERD) in the general population, but the relationship between these conditions in candidates for bariatric surgery is uncertain. We compared the prevalence of GERD and the association between GERD symptoms and esophagitis among bariatric candidates with and without T2DM.

Methods Cross-sectional study of baseline data from the Oseberg study in Norway. Both groups underwent gastroduodenoscopy and completed validated questionnaires: Gastrointestinal Symptom Rating Scale and Gastroesophageal Reflux Disease Questionnaire. Participants with T2DM underwent 24-h pH-metry.

Results A total of 124 patients with T2DM, 81 women, mean (SD) age 48.6 (9.4) years and BMI 42.3 (5.5) kg/m^2, and 64 patients without T2DM, 46 women, age 43.0 (11.0) years and BMI 43.0 (5.0) kg/m^2, were included. The proportions of patients reporting GERD-symptoms were low (< 29%) and did not differ significantly between groups, while the proportions of patients with esophagitis were high both in the T2DM and non-T2DM group, 58% versus 47%, $p = 0.16$. The majority of patients with esophagitis did not have GERD-symptoms (68–80%). Further, 55% of the patients with T2DM had pathologic acid reflux. Among these, 71% also had erosive esophagitis, whereof 67% were asymptomatic.

Conclusions The prevalence of GERD was similar in bariatric patients with or without T2DM, and the proportion of patients with asymptomatic GERD was high independent of the presence or absence of T2DM. Accordingly, GERD may be underdiagnosed in patients not undergoing a preoperative endoscopy or acid reflux assessment.

Trial Registration Clinical Trials.gov number NCT01778738

Keywords Gastroesophageal reflux disease (GERD) · Erosive esophagitis · Heartburn · Acid regurgitation · Acid reflux · Type 2 diabetes mellitus · Obesity · Bariatric surgery

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Introduction

Gastroesophageal reflux disease (GERD) is common with a worldwide prevalence of 8–33% [1–4], and GERD symptoms have been reported in up to 73% of bariatric surgery candidates [5, 6]. GERD develops when the reflux of acid gastric content causes troublesome symptoms and/or mucosal damage [7] and is associated with increased risk of esophageal strictures, Barrett's esophagus, and esophageal adenocarcinoma [8].

Obesity is an independent risk factor for GERD [9], partly due to obesity related hiatal hernia [10, 11], decreased lower esophageal sphincter (LES) resting pressure [9], and higher intragastric pressure [10, 12]. Type 2 diabetes mellitus (T2DM) is associated with GERD independent of body weight [2, 13].

Patients with T2DM may be more susceptible to both GERD symptoms and asymptomatic erosive esophagitis [14, 15]. However, whether patients with T2DM scheduled for bariatric surgery have a higher prevalence of GERD than those without T2DM is uncertain. Further, it is well known that GERD symptoms and endoscopic findings are weakly correlated [16–19] but the relationship between esophagitis and GERD symptoms in patients with or without T2DM has not been well investigated [10, 20]. In addition, few previous studies have assessed the association between esophageal acid exposure and reflux symptoms or erosive esophagitis in subjects with severe obesity [10, 21, 22].

We aimed, first, to compare the prevalence of GERD symptoms and erosive esophagitis among patients with or without T2DM scheduled for bariatric surgery, hypothesizing a higher prevalence of GERD among patients with T2DM; second, to assess whether erosive esophagitis was associated with GERD symptoms within both groups; and, third, to assess the associations between pathologic acid reflux, erosive esophagitis, and GERD symptoms in patients with T2DM.

Materials and Methods

Trial Design

This is a cross-sectional analysis of baseline data on GERD from the Oseberg study, an ongoing, randomized, triple-blind, single-center trial, which primarily aims to assess the effects of gastric bypass and sleeve gastrectomy on remission of T2DM [23, 24].

During the first year of this study, the prevalence of erosive esophagitis was higher than expected, and the potential impact of T2DM on these findings was unclear. Therefore, to explore whether the prevalence of GERD was particularly high among patients with T2DM, the steering committee decided, in 2014, to add a control group of bariatric patients without T2DM [23].

Settings

The study was conducted at the Morbid Obesity Centre at Vestfold Hospital Trust, a tertiary care obesity center in Southern Norway between January 2013 and February 2018.

Participants

All patients scheduled for bariatric surgery at the center were screened for study eligibility. The inclusion criteria for both groups were age ≥ 18 years and BMI ≥ 35 kg/m^2, or BMI ≥ 33 kg/m^2 with previously verified BMI ≥ 35 kg/m^2.

T2DM was diagnosed in those with an HbA1c ≥ 6.5% (48 mmol/mol) or use of antidiabetic medications. Exclusion criteria were previous major abdominal surgery, chronic medical conditions associated with increased risk of peri- and postoperative complications, drug or alcohol addiction, mental and psychiatric conditions leading to reduced compliance, pregnancy, and previously known severe gastroesophageal reflux disease (Los Angeles classification grade C or D, or Barrett's esophagus).

Outcomes

Prespecified secondary outcomes of the Oseberg study and the main outcomes of this analysis were GERD symptoms, erosive esophagitis, and pathologic acid reflux.

GERD Symptom Questionnaires

The Gastroesophageal Reflux Disease Questionnaire (GerdQ) [25] is a validated 6-item questionnaire for reflux disease and includes four positive predictors for GERD (heartburn, regurgitation, sleep disturbances due to heartburn or reflux, and the use of over the counter medication) and two negative predictors for GERD (epigastric pain and nausea). The range of the total score for all six items is between 0 and 18. A validated Norwegian version of the questionnaire [26] was used. GerdQ was defined as positive when the score was ≥ 8 points.

The Gastrointestinal Symptom Rating Scale (GSRS) is a 15-item scale that assesses common symptoms of gastrointestinal disorders [27, 28]. The GSRS Reflux subscale includes two items: heartburn and acid regurgitation. Each item is scored from zero to six, where higher scores indicate greater severity of symptoms. The GSRS in European patient populations has a good internal consistency and reliability and acceptable construct validity and responsiveness [27, 28]. The sum score was converted to a 0–100 scale to be comparable with other quality of life scales. GSRS Reflux was defined as positive when the score was ≥ 20 points.

Erosive Esophagitis

Esophagogastroduodenoscopy (EGD) was performed by experienced endoscopists using Olympus® 180 or 190 gastroscope. Anti-reflux medication was discontinued 7 days prior to EGD. Erosive esophagitis was graded according to the Los Angeles (LA) classification [29, 30] by two experienced endoscopists who were unaware of surgical procedure, based on the image of the lower esophageal sphincter (LES). In case of disagreement, the first author and the endoscopists reviewed the case together and reached an agreement. Hiatal hernia was measured longitudinally in centimeters from the LES to the diaphragmatic impression and was defined as hiatal hernia if ≥ 2 cm.

A diagnosis of Barrett's esophagus or adenocarcinoma was verified in biopsies. Non-erosive reflux disease (NERD) was defined as the presence of typical symptoms of GERD in the absence of visible esophageal mucosal injury on EGD and the presence of pathologic acid reflux [31].

Ambulatory 24-h pH-Metry

Ambulatory pH-metry was performed after 6 h fasting and 7 days off proton pump inhibitor and H2 blocker, using the Digitrapper™ pH-Z Testing System, Medtronic, Minneapolis, USA.

The probe was introduced transnasally and placed 5 cm above LES after verification with high-resolution manometry. Patients were asked to follow their normal daily habits, including eating habits, and record upper GI symptoms, meals, medication, and supine position (bedtime only). The data were recorded by a portable digital data logger for 24 h, and DeMeester score was calculated using a standard software program [16]. Pathologic acid reflux was diagnosed as DeMeester score ≥ 14.72 [32] or distal esophageal acid exposure time (AET) ≥ 6% [11, 16]. The examination with 24-h pH-metry was preplanned and performed only in patients with T2DM.

Sample Size

A total of 120 subjects with T2DM were planned to be included in the Oseberg study [23].

To show a mean (SD) clinically meaningful difference of at least 10 [20] GSRS score points between groups with or without T2DM (power 80% and alpha 0.05), at least 44 patients without T2DM had to be included. Taking into account possible loss to follow-up and incomplete data, a total of 64 controls without T2DM were included.

Blinding

The patients, study staff, endoscopists, and the primary outcome assessor were blinded to treatment allocation, and the surgeons did not participate in the follow-up.

Statistical Methods

Descriptive data are presented as mean (SD), median (range), or number (%). Between-group comparisons were analyzed with independent samples *t* test, and chi-squared tests for continuous and categorical variables as appropriate. All tests were two-sided and p values < 0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS 25 (SPSS Inc., Chicago, IL).

Results

Between October 15, 2012, and September 1, 2017, 319 consecutive patients with T2DM were assessed for eligibility, 194 were excluded, and 125 patients were initially enrolled and underwent a baseline examination between January 28, 2013, and February 12, 2018 (Fig. 1). Further, one patient was excluded due to undetectable c-peptide level on baseline examination, leaving 124 patients to be included (Fig. 1). A total of 210 consecutive patients without T2DM scheduled for bariatric surgery between January 2016 and January 2018 were assessed for eligibility, 81 patients were invited to participate, and 64 patients were included (Fig. 1b).

Patients with T2DM were on average 6 years older than those without T2DM, and a lower proportion of patients with T2DM used nonsteroidal anti-inflammatory drugs as compared with patients without T2DM (Table 1). Body mass index, drinking habits, smoking habits, and the proportion of patients using anti-reflux medication did not differ significantly between groups (Table 1).

GERD Symptoms

The GSRS and GerdQ questionnaires were completed by 97% of patients. The proportion of patients with reflux symptoms did not differ significantly between those with or without T2DM: GSRS (28% versus 18%, $p = 0.12$) and GerdQ (14% versus 18%, $p = 0.53$) (Table 2).

Esophagogastroduodenoscopy Findings

With the exception of one patient with T2DM, all patients underwent esophagogastroduodenoscopy (EGD). The proportion of patients with esophagitis did not differ significantly between patients with or without T2DM (58% versus 47%, $p = 0.16$) (Table 2). The majority of patients with findings had

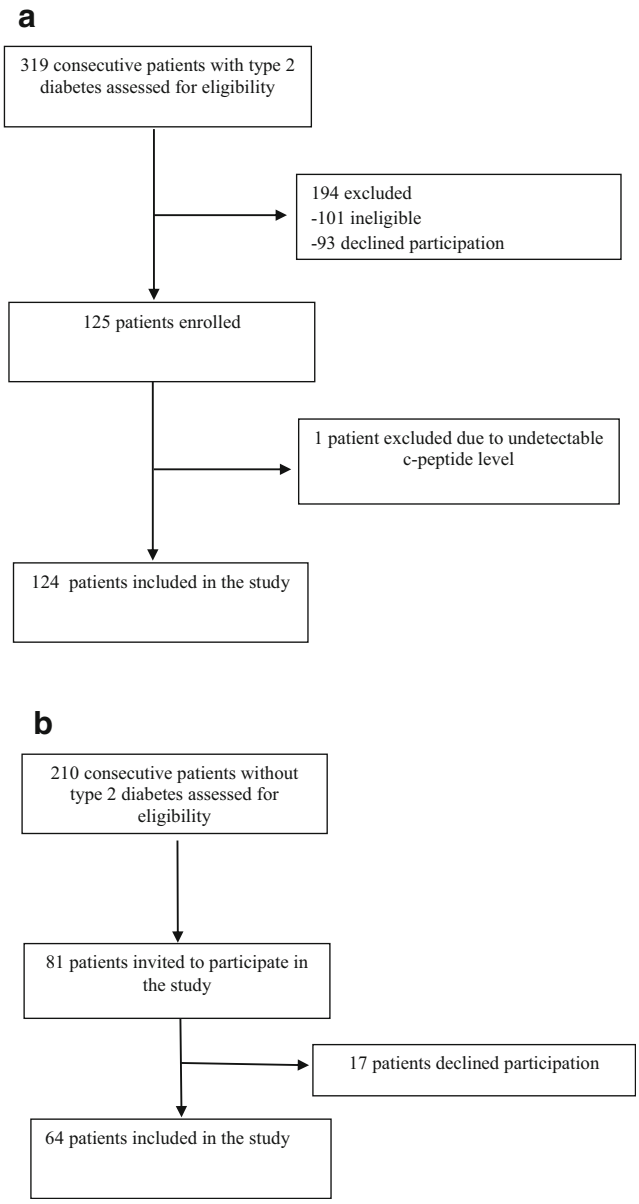

Fig. 1 **a** Flow chart of patients with type 2 diabetes mellitus. **b** Flow chart of patients without type 2 diabetes mellitus

less advanced erosive esophagitis (Los Angeles grades A and B), and few patients had more advanced esophagitis (Los Angeles grades C ($n = 3$) and D ($n = 2$)). Four patients with T2DM had Barrett's esophagus. Hiatal hernias were diagnosed in 44% of the patients in both groups (Table 2), and the majority of patients with hiatal hernia had erosive esophagitis, 36 (67%) patients in the T2DM group and 23 (82%) patients in the non-T2DM group.

Association Between Erosive Esophagitis and GERD Symptoms

GERD symptoms were not significantly associated with erosive esophagitis among patients with or without T2DM (Table 3). Notably, the majority of patients with esophagitis did not have GERD symptoms (68–80%), while the majority of patients with GERD symptoms had esophagitis (Table 3). Both questionnaires had low sensitivities (0.20–0.33) for diagnosing endoscopic esophagitis in both groups, while their respective specificities were higher (0.76–0.94) (Table 4). Accordingly, the predictive values of negative tests were low in both groups, while the positive predictive value of GerdQ was relatively high (Table 4).

24-h pH-Metry

A total of 114 out of 124 (92%) patients with T2DM completed the 24-h pH monitoring out of whom 111 completed questionnaires and 113 underwent EGD. Pathologic acid reflux was diagnosed in 63 patients (55%) with DeMeester score ≥ 14.72 including 48 patients (42%) with AET ≥ 6% (Table 5). Twenty of 65 T2DM patients with erosive esophagitis did not have pathologic acid reflux (Table 5), but one of these patients had borderline GERD.

Further, 45 of 63 patients (71%) with pathologic acid reflux had erosive esophagitis. In addition, 29 of 43 patients (67%) who had both pathological acid reflux and erosive esophagitis were asymptomatic. Three of the 18 patients (17%) with GERD symptoms without erosive esophagitis had pathologic acid reflux (NERD).

Discussion

The results from the present analysis of baseline data from the Oseberg study did not confirm our hypothesis of a higher prevalence of GERD among bariatric patients with T2DM compared with those without T2DM. Further, the proportions of patients with GERD symptoms were relatively low in both groups (< 29%), while approximately half the patients in both groups had esophagitis. In addition, in agreement with previous studies [10, 19, 33], we found no significant association between GERD symptoms and erosive esophagitis in neither group. Notably, the majority of patients (both groups) with esophagitis did not have GERD symptoms. In addition, more than half of the patients with T2DM had pathologic acid reflux, and the majority of these patients also had asymptomatic esophagitis.

Possible Mechanisms and Explanations

Taking into account that obesity and T2DM are independent predictors of GERD [9, 14, 34, 35], we expected a higher prevalence of GERD symptoms and esophagitis among patients with obesity and T2DM than in those with obesity only. T2DM may increase the risk of esophagitis due to reduced amplitude of esophageal contractions, fewer peristaltic waves,

Table 1 Demographic and clinical characteristics in candidates for bariatric surgery with or without type 2 diabetes mellitus (T2DM)

	T2DM ($n = 124$)	Non-T2DM ($n = 64$)	p value
Age, years (SD)	48.6 (9.4)	43.0 (11.0)	0.001[a]
Gender, female, no. (%)	81 (65)	46 (72)	0.46[b]
Ethnicity, Caucasian, no. (%)	117 (96)	64 (100)	0.24[b]
Weight, kg (SD)	125.6 (21.8)	127.2 (20.1)	0.63[a]
Body mass index (BMI), kg/m^2 (SD)	42.3 (5.5)	43.0 (5.0)	0.46[a]
Current smoker, no. (%)	14 (11)	4 (6)	0.34[b]
Alcohol consumption (units per week)	0 (0–8)	1 (0–3)	0.13[b]
Use of anti-reflux medication, no. (%)	35 (29)	12 (19)	0.23[b]
Proton pump inhibitors, no. (%)	34 (27)	11 (17)	NA
Histamine receptor antagonists, no. (%)	1 (0.8)	1 (1.6)	NA
Use of NSAID, no. (%)*	14 (11)	20 (32)	0.001[b]
Duration of diabetes, years (SD)	6.4 (6.0)	NA	NA
Diabetes complications, no. (%)**	13 (12)	NA	NA

Data are presented as observed mean (SD), median (range), or no. (%) of patients

[a]Independent samples t test

[b] Chi-squared test

*NSAID used due to self-reported comorbidities like skeletal-muscle and arthritis disorders

**Retinopathy, neuropathy, or nephropathy (albuminuria)

decreased velocity of peristalsis, reduced lower esophageal sphincter pressure, and abnormal gastroesophageal reflux [14, 36–39]. Notably, the numerical proportion of patients with esophagitis in the group with T2DM was higher than in the group without T2DM, but since sample size was calculated for differences in GSRS scores, we cannot rule out that the lack of statistical significance could be caused by a type 2 error.

Table 2 GERD symptoms, endoscopic findings, and 24-h ambulatory pH-metry among bariatric candidates with or without type 2 diabetes mellitus (T2DM)

	T2DM ($n = 123$)	Non-T2DM ($n = 64$)	p value
GSRS-R score ≥ 20, no. (%)*	34 (28)	11 (18)	0.17[b]
GerdQ score ≥ 8, no. (%)*	17 (14)	11 (18)	0.68[b]
GSRS-R score, mean (SD) *	13.2 (16.9)	9.0 (14.0)	0.09[a]
GerdQ score, mean (SD)*	6.3 (1.84)	6.3 (1.62)	0.91[a]
Esophagitis, no. (%)**	71 (58)	30 (47)	0.21[b]
LA grade A, no. (%)	41 (33)	18 (28)	0.64
LA grade B, no. (%)	27 (22)	10 (16)	
LA grade C, no. (%)	2 (2)	1 (2)	
LA grade D, no. (%)	1 (0.8)	1 (1.6)	
Barrett's esophagus, no. (%)	4 (3)	0	0.36
Hiatal hernia ≥ 2 cm, no. (%)	54 (44)	28 (44)	1.0[b]
Hiatal hernia ≥ 5 cm, no. (%)	4 (3)	0	0.14[b]
Peptic ulcer, no. (%)	7 (6)	8 (13)	0.18[b]
DeMeester score, mean (SD)***	24 (22)	NA	NA
pH < 4, % of time (AET) (SD)***	6.42 (6.61)	NA	NA

Data are presented as observed mean (SD) or no. (%) of patients

[a]Independent samples t test

[b] Chi-squared test

AET = distal esophageal acid exposure time

[*] T2DM $n = 120$, non-T2DM $n = 62$

[**] T2DM $n = 123$, non-T2DM $n = 64$

[***] T2DM $n = 114$

Table 3 Association between erosive esophagitis (any grade) and GERD symptoms among bariatric candidates with or without T2DM

			Erosive esophagitis					
			T2DM group ($n = 120$)			Non-T2DM group ($n = 62$)		
			Yes ($n = 69$)	No ($n = 51$)	p value	Yes ($n = 28$)	No ($n = 34$)	p value
GERD symptoms	GSRS Reflux ≥ 20	Yes no. (%)	22 (32)	12 (24)	0.42[a]	6 (21)	5 (15)	0.72[a]
		No no. (%)	47 (68)	39 (76)		22 (79)	29 (85)	
	GerdQ ≥ 8	Yes no. (%)	14 (20)	3 (6)	0.05[a]	8 (29)	3 (9)	0.09[a]
		No no. (%)	55 (80)	48 (94)		20 (71)	31 (91)	

Data are presented as no. (%) of patients

[a]Chi-squared test

The high prevalence of asymptomatic GERD (erosive esophagitis) in both groups might be partly explained by esophageal hyposensitivity due to obesity, diabetes, or both [40]. To our knowledge, the cause of esophageal hyposensitivity in patients with obesity and/or diabetes is unknown. However, it has been shown that in patients with Barrett's esophagus who often are hyposensitive to acid reflux, the nociceptive sensory nerves are located more profound in the esophageal mucosa [41]. Accordingly, it can be speculated whether the subjects included in the present study may have deep sensory nerves, which may partly explain their esophageal hyposensitivity, but this was not assessed in the present study.

Comparison with Other Studies

To the best of our knowledge, our study is the first to compare the prevalence of GERD symptoms and erosive esophagitis among bariatric patients with or without T2DM. However, our finding of a low frequency of GERD symptoms confirms the results of previous studies of patients with morbid obesity [33, 35, 42] and a study of patients with diabetes [43].

Table 4 Sensitivity, specificity, positive predictive value, and negative predictive value of GSRS ≥ 20 and GerdQ ≥ 8 for detection of endoscopic esophagitis among bariatric candidates with or without T2DM

	GSRS Reflux		GerdQ	
	T2DM	Non-T2DM	T2DM	Non-T2DM
Sensitivity	0.33	0.21	0.20	0.28
Specificity	0.76	0.85	0.94	0.91
Positive predictive value	0.65	0.55	0.82	0.72
Negative predictive value	0.45	0.57	0.46	0.60

In addition, our results are in accordance with previous studies among bariatric surgery candidates which have documented a high prevalence of erosive esophagitis [6, 44].

Our findings differ from the results in two previous studies which reported a high percentage of GERD symptoms among patients with morbid obesity [5, 45], but a low percentage of erosive esophagitis. However, these studies are not comparable with ours because they included younger patients and used self-reported gastrointestinal symptoms or other types of questionnaires than GerdQ and GSRS to assess GERD symptoms.

Our findings of a high prevalence of asymptomatic GERD in patients with and without T2DM partly confirm previous studies, both from the general population and in populations with T2DM and/or obesity [22, 46]. The association between GERD symptoms, as assessed by the validated questionnaires, and erosive esophagitis has been shown to be weak by others [10, 19, 33]. Our findings also support other studies demonstrating a poor association between GERD symptoms and pathologic acid reflux [10, 47], suggesting that most acid reflux events may be asymptomatic in patients with severe obesity. In line with the high frequency of asymptomatic esophagitis and acid reflux, only three patients had NERD in our study.

Interestingly, 20 of 65 T2DM patients with erosive esophagitis did not have pathologic acid reflux, and only one of these had borderline GERD. This finding is in contrast with Kristo et al. [46], who reported a high proportion of borderline GERD among patients with esophagitis. In addition, duodeno-gastroesophageal reflux of bile may partly explain our findings of erosive esophagitis in patients without acid reflux [48], but bile reflux was not assessed in the present study.

Our study has some limitations. Most patients were of Caucasian origin, with a majority of women (68%), and the results may not be generalizable to other ethnicities. The comparative groups were non-matched, resulting in groups that

Table 5 Association between pathologic acid reflux, GERD symptoms, and esophagitis among bariatric candidates with T2DM

			Pathological acid reflux (DeMeester score)			Pathological acid reflux (AET)		
			No reflux (< 14.72)	Reflux (≥ 14.72)	*p* value	No reflux (< 6%)	Reflux (≥ 6%)	*p* value
GERD symptoms	GSRS Reflux ≥ 20	Total	49	62		64	47	
		Yes no. (%)	13 (27)	19 (31)	0.79[a]	17 (27)	15 (32)	0.69[a]
		No no. (%)	36 (73)	43 (69)		47 (73)	32 (68)	
	GerdQ ≥ 8	Yes no. (%)	5 (10)	10 (16)	0.53[a]	7 (11)	8 (17)	0.52[a]
		No no. (%)	44 (90)	52 (84)		57 (89)	39 (83)	
Erosive esophagitis		Total	50	63		65	48	
		Yes no. (%)	20 (41)	45 (71)	0.002[a]	32 (49)	33 (69)	0.06[a]
		No no. (%)	30 (59)	18 (29)		33 (51)	15 (31)	

Data are presented as number (%) of patients

AET = distal esophageal acid exposure time

[a]Chi-squared test

differed in age and use of NSAIDs. Increasing age is a risk factor for GERD, and older patients may underreport reflux symptoms [49].

Conclusion

Our results suggest that the prevalence of GERD in patients scheduled for bariatric surgery is similar in patients with or without T2DM and that the proportion of patients with asymptomatic GERD is high independent of the presence or absence of diabetes. Accordingly, GERD may be underdiagnosed in patients not undergoing a preoperative endoscopy or acid reflux assessment.

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Compliance with Ethical Standards

The study was registered in an international trial register (Clinical Trials.gov) https://clinicaltrials.gov/ct2/show/NCT01778738, and a protocol paper has been published previously [23].

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval The study protocol was approved by the Regional Committees for Medical and Health Research Ethics in Norway (ref: 2012/1427/REK Sør-Øst B). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all participants included in the study.

References

1. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2013;108(3):308–28. quiz 29
2. Punjabi P, Hira A, Prasad S, et al. Review of gastroesophageal reflux disease (GERD) in the diabetic patient. J Diab. 2015;7(5):599–609.
3. Gyawali CP, de Bortoli N, Clarke J, et al. Indications and interpretation of esophageal function testing. Ann N Y Acad Sci. 2018;1434(1):239–53.
4. El-Serag HB, Sweet S, Winchester CC, et al. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut. 2014;63(6):871–80.
5. Merrouche M, Sabate JM, Jouet P, et al. Gastro-esophageal reflux and esophageal motility disorders in morbidly obese patients before and after bariatric surgery. Obes Surg. 2007;17(7):894–900.
6. Bou Daher H, Sharara AI. Gastroesophageal reflux disease, obesity and laparoscopic sleeve gastrectomy: the burning questions. World J Gastroenterol. 2019;25(33):4805–13.

7. Savarino E, Bredenoord AJ, Fox M, et al. Expert consensus document: advances in the physiological assessment and diagnosis of GERD. Nat Rev Gastroenterol Hepatol. 2017;14(11):665–76.
8. Dulai GS, Guha S, Kahn KL, et al. Preoperative prevalence of Barrett's esophagus in esophageal adenocarcinoma: a systematic review. Gastroenterology. 2002;122(1):26–33.
9. Anggiansah R, Sweis R, Anggiansah A, et al. The effects of obesity on oesophageal function, acid exposure and the symptoms of gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2013;37(5):555–63.
10. Heimgartner B, Herzig M, Borbely Y, et al. Symptoms, endoscopic findings and reflux monitoring results in candidates for bariatric surgery. Dig Liver Dis. 2017;49(7):750–6.
11. Wilson LJ, Ma W, Hirschowitz BI. Association of obesity with hiatal hernia and esophagitis. Am J Gastroenterol. 1999;94(10): 2840–4.
12. Pandolfino JE, El-Serag HB, Zhang Q, et al. Obesity: a challenge to esophagogastric junction integrity. Gastroenterology. 2006;130(3): 639–49.
13. Iyer PG, Borah BJ, Heien HC, et al. Association of Barrett's esophagus with type II diabetes mellitus: results from a large population-based case-control study. Clin Gastroenterol Hepatol. 2013;11(9): 1108–14.e5.
14. Sun XM, Tan JC, Zhu Y, et al. Association between diabetes mellitus and gastroesophageal reflux disease: a meta-analysis. World J Gastroenterol. 2015;21(10):3085–92.
15. Horikawa A, Ishii-Nozawa R, Ohguro M, et al. Prevalence of GORD (gastro-oesophageal reflux disease) in type 2 diabetes and a comparison of clinical profiles between diabetic patients with and without GORD. Diabet Med. 2009;26(3):228–33.
16. Gyawali CP, Kahrilas PJ, Savarino E, et al. Modern diagnosis of GERD: the Lyon Consensus. Gut. 2018;67(7):1351–62.
17. Mainie I, Tutuian R, Shay S, et al. Acid and non-acid reflux in patients with persistent symptoms despite acid suppressive therapy: a multicentre study using combined ambulatory impedance-pH monitoring. Gut. 2006;55(10):1398–402.
18. Stanghellini V, Armstrong D, Monnikes H, et al. Systematic review: do we need a new gastro-oesophageal reflux disease questionnaire? Aliment Pharmacol Ther. 2004;19(5):463–79.
19. Sakitani K, Suzuki N, Ihara S, et al. Decline in perception of acid regurgitation symptoms from gastroesophageal reflux disease in diabetes mellitus patients. PLoS One. 2018;13(3):e0194466.
20. Madalosso CA, Fornari F, Callegari-Jacques SM, et al. Performance of the Montreal Consensus in the diagnosis of gastroesophageal reflux disease in morbidly obese patients. Obes Surg. 2008;18(6): 668–74.
21. Ronkainen J, Aro P, Storskrubb T, et al. High prevalence of gastroesophageal reflux symptoms and esophagitis with or without symptoms in the general adult Swedish population: a Kalixanda study report. Scand J Gastroenterol. 2005;40(3):275–85.
22. Ortiz V, Ponce M, Fernandez A, et al. Value of heartburn for diagnosing gastroesophageal reflux disease in severely obese patients. Obesity. 2006;14(4):696–700.
23. Borgeraas H, Hjelmesaeth J, Birkeland KI, et al. Single-Centre, triple-blinded, randomised, 1-year, parallel-group, superiority study to compare the effects of Roux-en-Y gastric bypass and sleeve gastrectomy on remission of type 2 diabetes and beta-cell function in subjects with morbid obesity: a protocol for the obesity surgery in Tonsberg (Oseberg) study. BMJ Open. 2019;9(6):e024573.
24. Hofso D, Fatima F, Borgeraas H, et al. Gastric bypass versus sleeve gastrectomy in patients with type 2 diabetes (Oseberg): a single-centre, triple-blind, randomised controlled trial. Lancet Diabetes Endocrinol. 2019;7(12):912–24.
25. Jonasson C, Wernersson B, Hoff DA, et al. Validation of the GerdQ questionnaire for the diagnosis of gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2013;37(5):564–72.
26. Jonasson C, Moum B, Bang C, et al. Randomised clinical trial: a comparison between a GerdQ-based algorithm and an endoscopy-based approach for the diagnosis and initial treatment of GERD. Aliment Pharmacol Ther. 2012;35(11):1290–300.
27. Dimenas E, Glise H, Hallerback B, et al. Well-being and gastrointestinal symptoms among patients referred to endoscopy owing to suspected duodenal ulcer. Scand J Gastroenterol. 1995;30(11): 1046–52.
28. Revicki DA, Wood M, Wiklund I, et al. Reliability and validity of the Gastrointestinal Symptom Rating Scale in patients with gastroesophageal reflux disease. Qual Life Res. 1998;7(1):75–83.
29. Vakil N, van Zanten SV, Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol. 2006;101(8): 1900–20. quiz 43
30. Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut. 1999;45(2):172–80.
31. Savarino E, Zentilin P, Savarino V. NERD: an umbrella term including heterogeneous subpopulations. Nat Rev Gastroenterol Hepatol. 2013;10(6):371–80.
32. Liu S, Xu M, Yang J, et al. Research on gastroesophageal reflux disease based on dynamic features of ambulatory 24-hour esophageal pH monitoring. Comput Math Methods Med. 2017;2017: 9239074.
33. Sharaf RN, Weinshel EH, Bini EJ, et al. Endoscopy plays an important preoperative role in bariatric surgery. Obes Surg. 2004;14(10):1367–72.
34. Argyrou A, Legaki E, Koutserimpas C, et al. Risk factors for gastroesophageal reflux disease and analysis of genetic contributors. World J Clin Cases. 2018;6(8):176–82.
35. El-Serag H. Role of obesity in GORD-related disorders. Gut. 2008;57(3):281–4.
36. Wang X, Pitchumoni CS, Chandrarana K, et al. Increased prevalence of symptoms of gastroesophageal reflux diseases in type 2 diabetics with neuropathy. World J Gastroenterol. 2008;14(5):709–12.
37. Lee SD, Keum B, Chun HJ, et al. Gastroesophageal reflux disease in type II diabetes mellitus with or without peripheral neuropathy. J Neurogastroenterol Motil. 2011;17(3):274–8.
38. Gatopoulou A, Papanas N, Maltezos E. Diabetic gastrointestinal autonomic neuropathy: current status and new achievements for everyday clinical practice. Eur J Intern Med. 2012;23(6):499–505.
39. Krishnan B, Babu S, Walker J, et al. Gastrointestinal complications of diabetes mellitus. World J Diabetes. 2013;4(3):51–63.
40. Frokjaer JB, Andersen SD, Ejskaer N, et al. Gut sensations in diabetic autonomic neuropathy. Pain. 2007;131(3):320–9.
41. Woodland P, Shen Ooi JL, Grassi F, et al. Superficial esophageal mucosal afferent nerves may contribute to reflux hypersensitivity in nonerosive reflux disease. Gastroenterology. 2017;153(5):1230–9.
42. Suter M, Dorta G, Giusti V, et al. Gastro-esophageal reflux and esophageal motility disorders in morbidly obese patients. Obes Surg. 2004;14(7):959–66.
43. Kase H, Hattori Y, Sato N, et al. Symptoms of gastroesophageal reflux in diabetes patients. Diabetes Res Clin Pract. 2008;79(2):e6–7.
44. Mora F, Cassinello N, Mora M, et al. Esophageal abnormalities in morbidly obese adult patients. Surg Obes Relat Dis. 2016;12(3): 622–8.
45. Tolone S, Limongelli P, del Genio G, et al. Gastroesophageal reflux disease and obesity: do we need to perform reflux testing in all candidates to bariatric surgery? Int J Surg. 2014;12(Suppl 1): S173–7.
46. Kristo I, Paireder M, Jomrich G, et al. Modern esophageal function testing and gastroesophageal reflux disease in morbidly obese patients. Obes Surg. 2019;29(11):3536–41.

47. Gokturk S, Akyuz F, Arici S, et al. Gastroesophageal reflux in asymptomatic patients with diabetes: an impedance study diabetes, obesity and gastroesophageal reflux. Exp Clin Endocrinol Diabetes. 2018.
48. Tack J, Koek G, Demedts I, et al. Gastroesophageal reflux disease poorly responsive to single-dose proton pump inhibitors in patients without Barrett's esophagus: acid reflux, bile reflux, or both? Am J Gastroenterol. 2004;99(6):981–8.
49. Johnson DA, Fennerty MB. Heartburn severity underestimates erosive esophagitis severity in elderly patients with gastroesophageal reflux disease. Gastroenterology. 2004;126(3):660–4.

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Sleeve Gastrectomy Confers Higher Risk of Gastroesophageal Reflux Disease Than Gastric Bypass: A Randomized Controlled Trial From the Oseberg Reflux Working Group

Obesity is associated with increased intra-abdominal pressure, impaired gastric emptying, and decreased lower esophageal sphincter (LES) pressure, all factors predisposing for gastroesophageal reflux disease (GERD).[1] Furthermore, autonomic neuropathy in diabetes may increase the risk of GERD because of abnormal peristalsis and reduced LES pressure. Accordingly, patients with obesity and/or type 2 diabetes have a high prevalence of GERD and esophageal motility disorders. Weight loss reduces acid reflux. In addition, Roux-en-Y gastric bypass (RYGB) is considered an effective antireflux procedure, whereas sleeve gastrectomy (SG) may induce or worsen GERD.[2] Previous studies assessing GERD after SG were limited by unclear definitions of GERD, and it is unclear whether SG and RYGB affect GERD differently.[2] Therefore, we aimed to compare the 1-year effects of SG and RYGB on prespecified secondary GERD outcomes from the randomized controlled Oseberg trial (Supplementary Methods),[3] hypothesizing that those who underwent SG would have a higher 1-year risk of subjective and objective measures of GERD.

One hundred twenty-five patients with severe obesity and type 2 diabetes were enrolled. Sixteen patients were excluded or withdrew consent, leaving 109 patients allocated to SG (n = 55) or RYGB (n = 54); 107 patients (98%) completed the 1-year follow-up.[3,4] Mean age was 47.7 years (SD, 9.6), mean body mass index was 42.3 kg/m^2 (SD, 5.3), and 72 (66%) were women. At baseline, patient demographics, clinical characteristics,[4] and gastrointestinal outcome measures were similar between groups (Supplementary Table 1). Twenty-nine percent of patients had GERD symptoms (Gastrointestinal Symptom Rating Scale-Reflux [GSRS-R] score $\geq$ 20), whereas more than half had erosive esophagitis (58%), pathologic acid reflux (DeMeester score $\geq$ 14.72 [56%]), esophageal dysmotility (54%), or a small ($\geq$1 cm and $<$5 cm) hiatal hernia (62%).

At the 1-year follow-up, the prevalence of GERD symptoms was higher in the SG group than in the RYGB group (GSRS-R score $\geq$ 20, 17% vs 6%, P = .070; Gastroesophageal Reflux Disease Questionnaire score $\geq$ 8, 13% vs 2%, P = .026) (Figure 1*A*, Supplementary Table 2). Three of eight patients with GSRS-R $\geq$ 20 had pathologic acid reflux. Remission of symptoms was reported by 77%, whereas 7% reported new-onset symptoms, with no between-group differences (Figure 1*B* and *C*).

Erosive esophagitis was diagnosed in 48% of SG patients and 33% of RYGB patients (risk difference [RD], 15%; 95% confidence interval [CI], −5% to 35%) (Figure 1*A*, Supplementary Table 2). Most patients with esophagitis were asymptomatic (GSRS-R $<$ 20): 17 of 21 SG patients and 15 of 16 RYGB patients. The esophagitis remission rate was 50%, with no difference between groups (Figure 1*B*). The incidence of new-onset esophagitis was 47% after SG and 9% after RYGB (RD, 38%; 95% CI, 11%–65%) (Figure 1*C*).

The proportion of patients with either *pathologic acid reflux* or *conclusive evidence of pathologic acid reflux* was 3 times higher after SG versus RYGB: 49% vs 16% (RD, 33%; 95% CI, 15%–52%) and 32% vs 11% (RD, 21%; 95% CI, 4%–37%), respectively (Figure 1*A*, Supplementary Table 2). Most patients with pathologic acid reflux were asymptomatic (GSRS-R $<$ 20): 18 of 21 SG patients and 7 of 7 RYGB patients. The remission rate of pathologic acid reflux was 2 times higher after RYGB than after SG, 83% vs 42% (RD, 42%; 95% CI, 17%–66%) (Figure 1*B*). By contrast, the incidence of new-onset pathologic acid reflux was 4 times higher after SG than after RYGB, 41% vs 10% (RD, 31%; 95% CI, 4%–58%) (Figure 1*C*).

Sixty-one percent of patients had at least 1 finding of *esophageal dysmotility*, with no difference between groups (Figure 1*A*, Supplementary Table 2). The most frequent abnormality was hypertensive LES. The mean basal and residual LES pressures were within the normal ranges in both groups, and no patients reported dysphagia or chest pain. Overall, the dysmotility remission rate was 29% and the incidence of new-onset dysmotility 45%, with no differences between groups (Figure 1*B* and *C*).

The proportion of patients with hiatal hernia or treated with antireflux medication tended to be higher in the SG group at 1 year (Supplementary Table 2). There was no association between the presence of a hiatal hernia and erosive esophagitis or pathologic acid reflux. The gastric emptying rate (time to peak paracetamol concentration) was significantly slower after SG when compared with RYGB but increased after both procedures (Supplementary Table 2).

To our knowledge, this is the first randomized controlled study to compare the prevalence, remission, and incidence of GERD after SG versus RYGB using a combination of validated questionnaires, 24-hour pH monitoring, high-resolution manometry, and esophagogastroduodenoscopy. Patients who underwent SG had a substantially higher 1-year risk of gastroesophageal acid reflux and new-onset esophagitis than those who underwent RYGB, and most patients with esophagitis or acid reflux were asymptomatic. Our results support the recent International Federation for the Surgery of Obesity and Metabolic Disorders Position Statement recommending that surveillance with esophagogastroduodenoscopy should be undertaken routinely after bariatric surgery, regardless of symptoms.[5]

Abbreviations used in this paper: **GERD, gastroesophageal reflux disease; GSRS-R, Gastrointestinal Symptom Rating Scale-Reflux; LES, lower esophageal sphincter; RD, risk difference; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy.**

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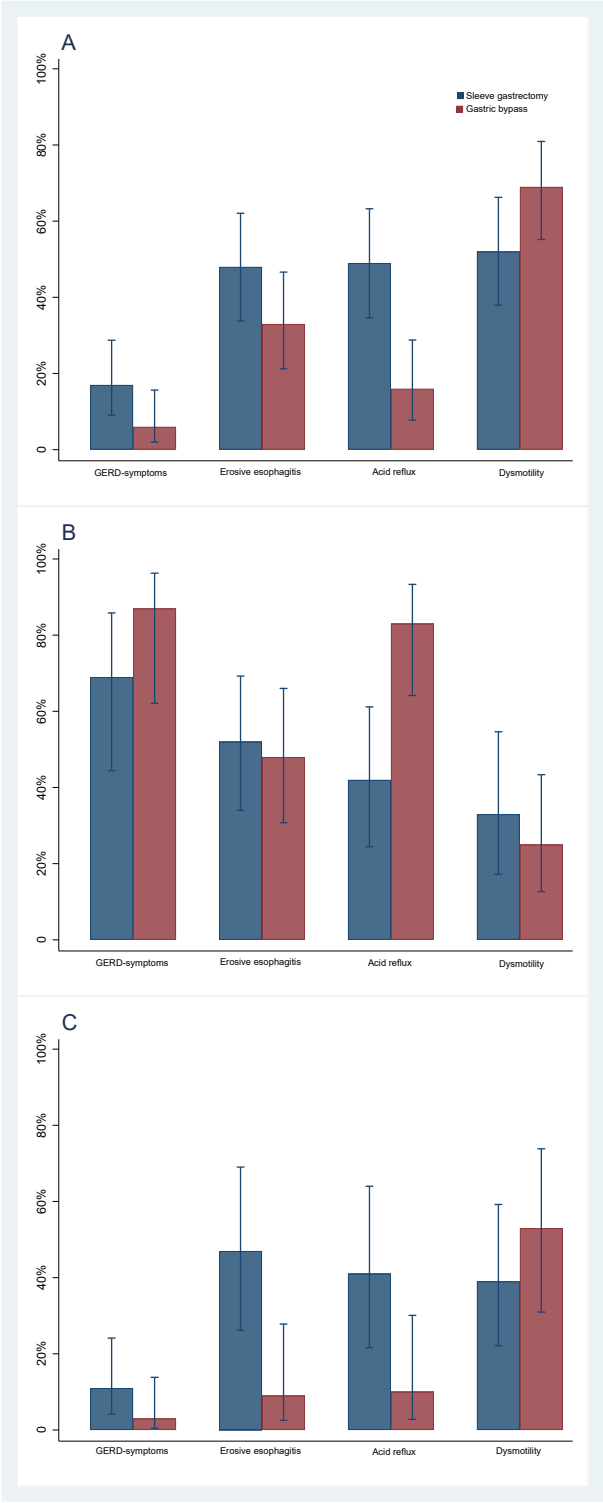

Figure 1. (*A*) Proportions of patients with GERD symptoms (GSRS $\geq$ 20), erosive esophagitis, pathologic acid reflux (DeMeester $\geq$ 14.72), and dysmotility 1 year after sleeve gastrectomy (*blue bars*) and gastric bypass (*red bars*). (*B*) Proportions of patients with remission of baseline GERD symptoms, erosive esophagitis, pathologic acid reflux, and dysmotility 1 year after sleeve gastrectomy (*blue bars*) and gastric bypass (*red bars*). (*C*) Proportions of patients with new-onset GERD symptoms, erosive esophagitis, pathologic acid reflux, and dysmotility 1 year after sleeve gastrectomy (*blue bars*) and gastric bypass (*red bars*).

One recent meta-analysis demonstrated that both RYGB and SG were effective in treating self-reported GERD, with RYGB showing a better effect.[2] Our study expands on these findings, adding new evidence that RYGB seems to be superior to SG at treating patients with asymptomatic GERD.[2]

Increased acid reflux after SG has been explained by reduced gastric compliance, hypotensive LES,[6] or hiatal hernia.[7] However, although hiatal hernia tend to be more frequent after SG than after RYGB (Supplementary Table 2), we found no association between the presence of a hiatal hernia and erosive esophagitis or pathologic acid reflux. In addition, the prevalence of hypotensive LES was low in both groups.

The generally high remission rates of GERD may partly be explained by the substantial weight loss accompanied by reduced intra-abdominal and intragastric pressure,[2] reduced number of acid-producing cells,[7] and accelerated gastric emptying.[8] All these changes were most pronounced after RYGB.

More than half the patients had esophageal dysmotility at baseline and at 1 year, but none reported dysphagia or chest pain. These findings indicate that abnormalities of high-resolution manometry have uncertain clinical relevance in this group of patients.

This short-term (1-year) analysis of mainly white participants with type 2 diabetes was not powered for prespecified secondary outcomes, limiting the generalizability of the results.[3] The 5-year-follow up results from this ongoing study (the Oseberg trial) will be published when available.[3]

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org and at https://doi.org/10.1053/j.gastro.2021.08.021.

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References

1. Hampel H, et al. Ann Intern Med 2005;143:199–211.
2. Gu L, et al. Obes Surg 2019;29:4105–4113.
3. Borgeraas H, et al. BMJ Open 2019;9:e024573.
4. Hofso D, et al. Lancet Diabetes Endocrinol 2019;7:912–924.
5. Brown WA, et al. Obes Surg 2020;30:3135–3153.
6. Guzman-Pruneda FA, et al. J Gastrointest Surg 2021; 25:542–550.
7. Li J, et al. Obes Surg 2016;26:429–442.
8. Ardila-Hani A, et al. Aliment Pharmacol Ther 2011; 34:825–831.

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Conflicts of interest
The authors disclose no conflicts.

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Supplementary Methods

The Oseberg study is an ongoing, randomized (1:1), triple-blinded, single-center trial conducted at a tertiary care center in Norway.[1] Primary outcomes, methods, and study protocol have been published.[1,2] The study protocol was approved by the Regional Committees for Medical and Health Research Ethics (2012/1427/REK sør-øst B).

Eligible participants were consecutive adult patients with type 2 diabetes and a body mass index $\geq$ 35 kg/m^2. Exclusion criteria, relevant for this analysis, were severe GERD (Los Angeles classification grade C or D, or Barrett's esophagus), hiatal hernia $>$ 5 cm, or elevated esophageal pressure (distal contractile integral $>$ 5000 mm Hg/s/cm) with symptoms of dysphagia and/or painful swallowing.

Surgical procedures were standardized as previously described.[1] For RYGB, a 25-mL gastric pouch was created with an alimentary limb of 120 cm and a biliopancreatic limb of 60 cm. For SG, a 35-Fr bougie was used along the lesser curvature for calibration of the gastric tube with no routine staple-line reinforcement. The 2 intervention groups underwent identical pre- and postoperative treatment programs.[1] Participants were prescribed a proton pump inhibitor (PPI) the first 4 weeks after surgery. The Gastroesophageal Reflux Disease Questionnaire (GerdQ)[3] was used to evaluate treatment with a PPI at 5 weeks, 16 weeks, 34 weeks, and 1 year. PPI therapy was stopped, or considered stopped, in patients with no or mild symptoms (GerdQ score $<$ 8). In patients with severe symptoms (GerdQ score $\geq$ 8), PPI therapy was intensified, and referral to a gastroenterologist was considered.[1]

The prespecified secondary outcomes of GERD symptoms, erosive esophagitis, acid reflux, and esophageal motility were assessed at baseline (3 weeks before surgery) and 1 year after surgery.[1] The Gastrointestinal Symptom Rating Scale (GSRS)[4] and GerdQ[3] were used to assess GERD symptoms.[4] The GSRS-Reflux (GSRS-R) subscales heartburn and acid regurgitation have a high reliability and acceptable construct validity in European patient populations, and GerdQ is a validated 6-item questionnaire for diagnosing reflux disease.

Esophagogastroduodenoscopy was performed by experienced endoscopists using an Olympus 180 or 190 gastroscope to take a high-quality picture of the LES (excluding the gastroesophageal junction). Any antireflux medication was discontinued 7 days before esophagogastroduodenoscopy. Erosive esophagitis was diagnosed according to the Los Angeles classification[5] by 2 other experienced endoscopists unaware of the surgical procedure based on the image of the LES. In case of disagreement, the first author and the endoscopists reviewed the case together and reached an agreement. The diagnosis of Barrett's esophagus was based on identification of mucosal changes in the distal esophagus by esophagogastroduodenoscopy using the Prague classification verified by histologic examination of biopsies (by pathologists at Vestfold Hospital Trust) demonstrating intestinal metaplasia.[6]

Ambulatory 24-hour pH monitoring was performed after 6 hours of fasting and 7 days off antireflux medication, using the Digitrapper pH-Z Testing System (Medtronic, Minneapolis, MN). Data were recorded by a portable digital data logger for 24 hours, and acid exposure time and DeMeester scores were calculated using a standard software program. Acid exposure time was defined by the time percentage of esophageal pH $<$ 4 during 24-hour pH monitoring. Pathologic acid reflux was defined if the DeMeester score $\geq$ 14.72, whereas conclusive evidence of pathologic acid reflux was defined according to the Lyon criteria (either erosive esophagitis Los Angeles grade C or D, or Barrett's esophagus, or increased total acid exposure time $>$ 6% regardless of typical GERD symptoms).[7]

The manometric protocol included a 30-second period to assess basal lower sphincter pressure and 10 swallows of 5 mL of water. Manometric data were analyzed using ManoView analysis software (Medtronic). The Chicago classification (version 3.0) was used to identify motility disorders.[8] Two independent investigators manually analyzed all patients with esophageal pressure topography. Data were corrected for thermal sensitivity of the pressure-sensing elements. The reference values for LES pressures were mean basal LES pressure 13–43 mm Hg and median residual LES pressure 4–15 mm Hg.

Dysmotility was registered as hypocontractility, defined as ineffective esophageal motility ($\geq$50% ineffective swallows); hypercontractility, defined as jackhammer esophagus ($\geq$20% distal contractile integral $>$8000 mm Hg*cm*s); hypotensive LES, defined as median residual pressure $<$ 4 mm Hg or mean basal pressure $<$ 13 mm Hg; or hypertensive LES, defined as median residual pressure $>$15 mm Hg or mean basal pressure $>$ 43 mm Hg.

Patients with hiatal hernia $>$ 5 cm at endoscopy screening were excluded. The presence or absence of small hiatal hernia ($\geq$1 cm and $<$5 cm) was estimated by high-resolution manometry before and 1 year after surgery. Time to peak and maximal paracetamol concentrations were used as markers of gastric emptying rate.[1]

The Oseberg study was powered to detect differences in the primary outcome remission of diabetes, and the sample size was set to 125 patients.[1] Patients were randomized and allocated (1:1 ratio) to either RYGB or SG using a computerized random number generator with block sizes of 10.[1] All study personnel, patients, and assessors (gastroenterologists) of the prespecified secondary outcome measures were blinded to allocations.[1]

Baseline characteristics are reported as means (SD), medians (interquartile range), or counts (percentages). Outcome variables were measured at baseline, 5 weeks (GERD symptoms only), and 1 year and analyzed according to intention-to-treat principles using generalized linear mixed models for repeated measures with identity link (continuous outcomes) and logit link (for binary outcomes). The repeated-measures models were not adjusted for potential confounders, because there were no baseline differences between the groups. For continuous outcomes, the estimated means and 95% CIs at the 1-year follow-up are reported. For the binary outcomes, we report counts (%) and differences in risks between surgery groups quantified

as RD (95% CI) at 1 year. The CIs for binomial proportions depicted in bar plots were calculated using the Wilson score method. All data analyses were performed using IBM SPSS (version 25.0) and STATA version (15.0). A $P < .05$ was considered statistically significant, and all tests were 2-sided. Because all analyzed outcomes are considered exploratory, no adjustment for multiple testing was performed.

Supplementary References

1. Borgeraas H, et al. BMJ Open 2019;9:e024573.
2. Hofso D, et al. Lancet Diabetes Endocrinol 2019;7:912–924.
3. Jonasson C, et al. Aliment Pharmacol Ther 2013;37:564–572.
4. Dimenas E, et al. Scand J Gastroenterol 1995;30:1046–1052.
5. Lundell LR, et al. Gut 1999;45:172–180.
6. Alvarez Herrero L, et al. Endoscopy 2013;45:876–882.
7. Gyawali CP, et al. Gut 2018;67:1351–1362.
8. Kahrilas PJ, et al. Neurogastroenterol Motil 2015;27:160–174.

Supplementary Table 1. Baseline Demographics and Clinical Characteristics

	Sleeve gastrectomy (n = 55)	Gastric bypass (n = 54)
Sex		
Male	23 (42)	14 (26)
Female	32 (58)	40 (74)
Mean age, y (SD)	47.1 (10.2)	48.2 (8.9)
White ethnicity	53 (96)	51 (94)
Mean body mass index, kg/m^2 (SD)	42.1 (5.3)	42.4 (5.4)
Diabetes		
Mean duration, y (SD)	6.3 (5.5)	6.6 (6.5)
Median HbA1c, % (interquartile range)	7.9 (6.9-9.9)	7.6 (6.8-8.5)
Medication	50 (91)	46 (85)
Antireflux medication	11 (20)	17 (31)
Current smoker	4 (7)	7 (13)
GERD symptoms		
Mean GSRS-R score (SD)	13.8 (15.9)	12.4 (17.4)
GSRS-R score $\geq$ 20	16/55 (29)	15/53 (28)
Mean GerdQ score (SD)	6.4 (2.1)	6.0 (1.4)
GerdQ score $\geq$ 8	7/55 (13)	5/53 (9)
Erosive esophagitis		
Total esophagitis	31/53 (58)	30/53 (57)
Los Angeles grade A	19/53 (36)	21/53 (40)
Los Angeles grade B	12/53 (23)	9/53 (17)
Acid reflux		
Mean acid exposure time (SD)	5.4 (4.5)	6.3 (5.6)
Acid exposure time $>$ 6%	19/48 (40)	20/51 (39)
Mean DeMeester score (SD)	20.6 (16.1)	24.3 (21.5)
Pathologic acid reflux (DeMeester score $\geq$ 14.72)	27/48 (56)	28/51 (55)
Mean number of acid reflux episodes (SD)	86 (56)	91 (68)
Esophageal motility		
Mean LES basal pressure, mm Hg (SD)	34.3 (13.8)	35.8 (13.6)
Mean LES residual pressure, mm Hg (SD)	13.3 (8.0)	12.3 (6.9)
Mean amplitude, mm Hg (SD)	102.8 (48.0)	119.3 (56.8)
Mean distal contractile integral, mm Hg*cm*s (SD)	2910 (2170)	3293 (2137)
Esophageal dysmotility		
Total dysmotility	26/52 (50)	30/51 (59)
Ineffective esophageal motility	1/52 (2)	3/51 (6)
Jackhammer esophagus	6/52 (12)	8/51 (16)
Hypotensive LES	1/52 (2)	4/51 (8)
Hypertensive LES	23/52 (44)	20/51 (39)
Hiatal hernia[a]	34/52 (65)	30/51 (59)
Gastric emptying rate		
Mean maximum concentration of paracetamol, mmol/L (SD)	66 (22)	69 (20)
Mean time to peak paracetamol, min (SD)	50 (17)	54 (20)

Values are n or n/N (%) unless otherwise defined.
[a]All hiatal hernias $\geq$ 1 cm and $<$5 cm.

Supplementary Table 2. GERD Symptoms, Esophagitis, Acid Reflux, and Esophageal Motility at 1-Year Follow-up

	Sleeve gastrectomy (n = 55)	Gastric bypass (n = 54)	Between-group difference/RD (95% CI)	*P*
GERD symptoms				
Mean GSRS-R score	9.8 (6.0–13.6)	3.7 (–0.1 to 7.6)	6.0 (0.7–11.4)	.028
GSRS-R score ≥ 20	9 (17)	3 (6)	0.12 (–0.01 to 0.23)	.070
Mean GerdQ score	6.0 (5.5–6.6)	5.6 (5.1–6.1)	0.4 (–0.3 to 1.2)	.27
GerdQ score ≥ 8	7 (13)	1 (2)	0.11 (0.01–0.21)	.026
Erosive esophagitis				
Total	21 (48)	16 (33)	0.15 (–0.05 to 0.35)	.14
Los Angeles grade A	17 (39)	13 (27)	–0.00 (–0.26 to 0.25)	.98
Los Angeles grade B	3 (7)	1 (2)	Not analyzed[a]	NA
Barrett's esophagus	1 (2)	2 (4)	Not analyzed[a]	NA
Acid reflux				
Mean acid exposure time	5.4 (3.9–7.0)	2.8 (1.3–4.3)	2.7 (0.5–4.8)	.015
Acid exposure time > 6%	13 (30)	5 (11)	0.19 (0.03–0.36)	.023
Mean DeMeester score	22.6 (16.6–28.6)	10.3 (4.50–16.2)	12.3 (3.9–20.6)	.004
Pathologic acid reflux (DeMeester score ≥ 14.72)	21 (49)	7 (16)	0.33 (0.15–0.52)	<.001
Conclusive evidence pathologic acid reflux[b]	14 (32)	5(11)	0.21 (0.04-0.37)	.014
Mean number of acid reflux episodes	80 (64–97)	45 (29–62)	35 (12–58)	.003
Esophageal motility				
Mean LES basal pressure, mm Hg	34.1 (30.1–38.2)	34.5 (30.5–38.5)	–0.3 (–6.0 to 5.4)	.91
Mean LES residual pressure, mm Hg	11.2 (9.2–13.3)	11.0 (9.0–13.0)	0.2 (–2.7 to 3.0)	.90
Mean amplitude, mm Hg	103.7 (89.7–117.6)	116.2 (102.4–130.0)	–12.5 (–32.2 to 7.1)	.21
Mean distal contractile integral, mm Hg*cm*s	2658 (2071–3245)	2994 (2416–3573)	–336 (–1160 to 488)	.42
Esophageal dysmotility				
Total dysmotility	23 (52)	32 (70)	–0.17 (–0.37 to 0.03)	.088
Ineffective esophageal motility	4 (9)	3 (7)	0.03 (–0.09 to 0.14)	.65
Jackhammer esophagus	5 (11)	6 (13)	–0.02 (–0.15 to 0.12)	.81
Hypotensive LES	4 (9)	9 (20)	–0.10 (–0.25 to 0.04)	.15
Hypertensive LES	14 (32)	21 (46)	–0.14 (–0.34 to 0.06)	.17
Antireflux medication	12 (22)	5 (9)	0.13 (–0.01 to 0.26)	.065
Mean body mass index, kg/m^2	32.4 (31.1–33.7)	30.3 (28.9–31.6)	2.1 (0.2–4.0)	.029
Hiatal hernia[c]	21/44 (48)	15/49 (31)	0.15 (–0.04 to 0.35)	.13
Gastric emptying rate				
Maximum concentration of paracetamol, mmol/L	90 (82–99)	150 (142–159)	–60 (–72 to –48)	<.0001
Time to peak paracetamol, min	32 (28–36)	15 (11–20)	17 (10–23)	<.0001

Values in parentheses are percents or 95% CIs. NA, not analyzed.
[a]Not sufficient statistical power.
[b]Either erosive esophagitis Los Angeles grade C or D, or Barrett's esophagus, or increased total acid exposure time (>6%), regardless of typical GERD symptoms.
[c]All hiatal hernias ≥ 1 cm and <5 cm.

III

Title:
Patient-reported outcomes, weight loss and remission of type 2 diabetes 3 years after gastric bypass and sleeve gastrectomy (Oseberg); a single-centre randomised controlled trial.

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Abstract

Background

Little is known about the comparative effects of various bariatric procedures on patient-reported outcomes. We compared the 3-year effects of gastric bypass and sleeve gastrectomy on a number of patient-reported outcome measures in the Oseberg study.

Methods

Single-centre, randomised trial of patients with obesity and type 2 diabetes allocated (1:1) to gastric bypass or sleeve gastrectomy. Randomisation was performed with a computerised random number generator and a block size of 10. Study personnel, patients and the primary outcome assessor were blinded to allocations for 1 year. Primary clinical outcome was 1-year remission of diabetes, and prespecified secondary outcomes reported here were 3-year changes in various clinically important patient-reported outcomes, weight loss and diabetes remission, analysed as intention to treat. This trial is ongoing, closed to recruitment and is registered with ClinicalTrials.gov, NCT01778738.

Findings

Between Oct 15, 2012 and Sept 1, 2017, 109 patients were randomly assigned to gastric bypass (n=54) or sleeve gastrectomy (n=55), with 93 (85%) patients completing 3-year follow-up.

As compared with sleeve gastrectomy, gastric bypass was associated with a greater improvement in weight-related quality of life (IWQOL-Lite), between group difference 9.4 [95% CI 3.3 to 15.5], less reflux symptoms (GSRS), between group difference -0.54 [95%CI, -1.00 to -0.07]; 8% greater total body weight loss [25% vs 17%] and a higher probability of diabetes remission [67% vs 33%], risk ratio 2·00 (1·27 to 3·14). Five patients reported postprandial hypoglycaemia in the third year after gastric bypass versus none after sleeve-gastrectomy (p=0.059). Symptoms of abdominal pain, indigestion, diarrhoea, dumping syndrome, depression, binge eating and hedonic hunger did not differ between groups.

Interpretation

At 3 years, gastric bypass was superior to sleeve gastrectomy regarding weight related quality of life, reflux symptoms, weight loss and remission of diabetes, while symptoms of abdominal pain, indigestion, diarrhoea, dumping, depression and binge eating did not differ between groups. This new patient-reported knowledge can be used in the shared decision-making process to inform patients about similarities and differences between expected outcomes after the two surgical procedures.

Funding

Morbid Obesity Centre, Vestfold Hospital Trust.

Introduction

Patient-reported outcomes refer to the patients' subjective views on disease symptoms, treatment side effects and other aspects of functional status and quality of life. Obesity and type 2 diabetes are associated with impaired health-related quality of life (HRQoL), depression, eating disorders and gastrointestinal symptoms[1].

Bariatric surgery, mainly gastric bypass and sleeve gastrectomy, has beneficial effects on weight loss, diabetes control and HRQoL, but at the potential cost of new-onset or worsening of depression or binge eating problems as well as various side effects including gastrointestinal symptoms, mental health symptoms, dumping syndrome and postprandial hypoglycaemia[2] . Early dumping syndrome is characterized by a combination of gastrointestinal symptoms (pain, diarrhoea, bloating, nausea) and vasomotor symptoms (sweating, flushing, dizziness, palpitations) within 1 hour after a meal. Late dumping syndrome (sweating, palpitations, hunger, drowsiness/ unconsciousness, tremor, irritability) typically occurs 1 to 3 hours postprandially[3]. Other troublesome gastrointestinal symptoms may increase after both gastric bypass[4] and sleeve gastrectomy[5], while reflux symptoms are commonly observed after sleeve gastrectomy[5].

Only two high-quality randomised controlled trials have compared the medium- to long-term effects of gastric bypass and sleeve gastrectomy on changes in patient-reported outcomes [6,7], assessing only generic HRQoL[6,7] and symptoms of depression[7]. Further, to our knowledge, no randomised study of patients with type 2 diabetes has compared the medium- to long-term

effects of the two surgical procedures on patient-reported gastrointestinal symptoms, dumping syndrome, postprandial hypoglycaemia or eating disorders.

The Oseberg study is a randomised, parallel-group, single-centre trial including patients with severe obesity and type 2 diabetes, conducted at a public tertiary obesity center in Norway. The primary clinical outcome (remission of type 2 diabetes) has been published previously; confirming the superiority of gastric bypass compared with sleeve gastrectomy[8]. In addition, 1-year results showed no changes in gastrointestinal pain, indigestion, constipation, or diarrhoea after gastric bypass or sleeve gastrectomy, while both binge eating problems and hedonic hunger declined similarly after both procedures[9].

The primary objective of this analysis was to compare in patients with type 2 diabetes the 3-year effects of sleeve gastrectomy and gastric bypass on patient-reported outcomes including gastrointestinal symptoms, dumping syndrome, weight-related symptoms, quality of life, depression, binge eating and hedonic hunger. We firstly hypothesized that gastric bypass would be associated with a worsening of gastrointestinal symptoms (abdominal pain, indigestion, diarrhoea) and dumping syndrome when compared with sleeve gastrectomy, while sleeve gastrectomy would be associated with a worsening of reflux symptoms. Secondly, we hypothesized that larger weight loss after gastric bypass would lead to greater improvements in weight-related symptoms and weight-related quality of life.

Methods

Trial design

The Oseberg study is a randomised, parallel-group, single-centre trial at Vestfold Hospital Trust in Tønsberg, Norway. Patients with severe obesity and type 2 diabetes were randomised and allocated (1:1) to Roux-en-Y gastric bypass or sleeve gastrectomy. The study protocol was approved by the Regional Committees for Medical and Health Research Ethics in Norway (2012/1427/REK sør-øst B) and the 1-year results and protocol have been published previously[8]. This study is registered in ClinicalTrials.gov (NCT01778738).

Participants

Inclusion criteria were age ≥18 years, current BMI ≥33.0 kg/m^2 with previously verified BMI ≥35.0 kg/m^2 and type 2 diabetes. Diabetes was diagnosed if glycated haemoglobin was ≥6.5% [48 mmol/mol] or by the use of anti-diabetic medications with glycated haemoglobin ≥6.1% [43 mmol/mol]). Key exclusion criteria were previous major abdominal surgery, cancer, severe medical conditions associated with increased risk of complications, drug or alcohol addiction, pregnancy and severe gastro-esophageal reflux disease[10]. All patients provided written informed consent.

Interventions

The two intervention groups received identical pre- and post-operative treatment, including a low-calorie diet (<1200 kcal/day) during the 2 weeks preceding surgery. After surgery, patients were assessed at 5 weeks, 16 weeks, 34 weeks, 1 year, 2 years and 3 years. Both groups were

prescribed identical vitamin and mineral supplementations, which were adjusted according to specific predefined algorithms[10]. Sleeve gastrectomy (35 Fr Bougie) and gastric bypass (25ml pouch, 120 cm Roux-limb and 60cm biliopancreatic limb) were performed laparoscopically using identical skin incisions as previously described [8,10].

Outcomes

All outcomes in this analysis are predefined secondary outcomes from the Oseberg-study, of which the primary clinical endpoint was remission of diabetes at 1 year. The secondary outcomes include, first, changes in patient-reported outcomes and second, weight loss and remission of diabetes at 3 years. All patient-reported outcome questionnaires were completed by the patients on a digital tablet at baseline, 5 weeks, 1 year, 2 years and 3 years after surgery. Participants were examined for symptoms of dumping and hypoglycaemia in clinical interviews based on questionnaires in the case report forms. In addition, clinical and laboratory assessments were performed 16 weeks and 34 weeks after surgery.

Gastrointestinal symptoms

The 15-item gastrointestinal symptom rating scale (GSRS) was used to evaluate severity of 5 different gastrointestinal symptoms experienced during the previous week[11]. The GSRS is scored on a seven-point Likert scale from no discomfort (1) to very severe discomfort (7) and breaks down into five dimensions; abdominal pain, reflux, diarrhoea, indigestion and constipation. Higher scores indicate greater severity of symptoms.

Dumping syndrome and postprandial hypoglycaemia

Late and early dumping were assessed and reported using the Arts' questionnaire[12], with hypoglycaemic events recorded at all time points. Postprandial hypoglycaemia was defined as a verified blood glucose level of less than 3.9 mmol/l and the presence of typical symptoms and signs of hypoglycaemia. All patients were specifically asked whether they had experienced hypoglycaemic symptoms such as perspiration, palpitations, tremor, irritability, anxiety, headache, hunger, confusion, seizures or unconsciousness, since the last visit.

Impact of Weight on Quality of Life - Lite (IWQOL-Lite)

The IWQOL-Lite is a 1-week recall validated 31-item, self-report measure of weight-related quality of life that provides a total score plus scores on five domains (Physical Function, Self-Esteem, Sexual Life, Public Distress and Work)[13]. Scores are transformed to a 0 to 100 scale, where 100 represents the best HRQOL. The IWQOL-Lite has similar psychometric properties, including factor structure, in persons with diabetes plus obesity compared to persons with no diabetes and obesity[14].

Weight-Related Symptom Measure

This 20-item measure assesses the presence and bothersomeness of distinct weight-related symptoms using 4-week recall[15]; shortness of breath, tiredness, sleep problems, sensitivity to cold, increased thirst, increased irritability, back pain, frequent urination, pain in the joints, water retention, foot problems, sensitivity to heat, snoring, increased appetite, leakage of urine,

light-headedness, increased sweating, loss of sexual desire, decreased physical stamina and skin irritation. Two summary scores are calculated (symptom presence and symptom bothersomeness), where higher scores indicate higher symptom presence/distress.

Short Form Health Survey 36 (SF 36)

Generic HRQoL was evaluated using the 4-week recall 36 item Short-Form Health Survey (SF-36 v.1).[16] There are eight dimensional scores: vitality, physical function, bodily pain, general health, physical role, emotional role, social role and mental health. The dimensional scores are combined into two norm-based summary scores: Physical Component Summary (PCS) and Mental Component Summary (MCS). Higher scores indicate better HRQoL.

Beck Depression Inventory

This is a 21-item scale that assesses depressive symptoms during the previous week[17]. Higher scores indicate greater depressive symptomatology. A score of ≥14 has been used as a cut off for clinically significant symptoms of depression[18]

Power of Food Scale

This 15-item scale assesses the psychological impact of highly palatable food in a food-abundant environment [19]. It measures appetitive drive for food, rather than its consumption. Higher scores represent higher hedonic hunger.

Binge Eating Scale

This 16-item scale assesses the behavioural, cognitive and emotional symptoms associated with binge eating[20]. Higher scores indicate greater binge eating symptomatology. A score of >17 has been established to determine a significant binge eating severity in bariatric surgery candidates [21].

Adverse effects

Complications were assessed at all clinical visits and patient records were obtained from other institutions if needed to classify type of adverse event.

Remission of diabetes

Complete remission of diabetes was defined as HbA1c ≤6.0% (42 mmol/mol) with no medication, and partial remission as HbA1c<6.5% (48 mmol/mol) with no medication[22].

Sample size

The Oseberg-study was powered (significance level to 5% and power to 80%) to detect differences in diabetes remission rates (n=110) or changes in beta cell function (n=100)[8,10]. No formal sample size calculation was performed for secondary outcomes.

Randomisation

Patients were randomised and allocated (1:1 ratio) to either sleeve gastrectomy or gastric bypass using a computerised random number generator with block sizes of 10. All study personnel, patients and the primary outcome assessor were blinded to allocations until the blinding was lifted at one year [8,10].

Statistical analysis

For all analyses (except per protocol), the participants were included in the group to which they were randomised. Binary outcomes (observed categorical outcomes) were analysed using Fisher`s exact test, and the McNemar test was used to compare changes in proportions. Continuous outcomes were analysed with linear mixed effects models for repeated measures, using an unstructured covariance matrix. The linear mixed models contained fixed effect for treatment group, time as a discrete variable, a treatment x time interaction and a random intercept. Based on the mixed models, we estimated mean point estimates (with 95% confidence intervals) for all time points, change from baseline until 3 years and estimated difference in change between groups. Missing data points were not imputed.

The potential independent effects of clinically relevant variables (type of surgery, sex, weight change and diabetes remission) on changes in patient-reported outcomes were modelled as fixed effects in an exploratory multiple linear regression analysis, using a backward stepwise elimination approach with a cut-off of $p>0.10$ (i.e. the variable with the largest p-value was eliminated and the model was run again in an iterative manner until only variables with $p<0.1$ were retained in the model). All tests were two-sided and significance level was set to 0.05. The analyses were considered exploratory, thus no corrections for multiple testing were performed. STATA software, version 15.0 was used to perform linear mixed effects models and risk ratios for all binary outcomes (RRs) with 95% CI. Other statistical analyses were performed using SPSS software, version 26.0.

Role of the funding source

The study is organised and financed by the Morbid Obesity Centre, Vestfold Hospital Trust, Tønsberg, Norway. Five authors (MS, DH, HB, JL and JH) had independent access to the data, with all authors vouching for data completeness, accuracy and for the fidelity of the trial to the protocol.

RESULTS

Patient flow and recruitment

Between October 15, 2012 and September 1, 2017, 319 consecutive patients with type 2 diabetes scheduled for bariatric surgery were assessed for eligibility, of whom 109 patients were randomly assigned to sleeve gastrectomy (n=55) or gastric bypass (n=54)[8]. After 3 years, 48 and 45 patients attended follow-up (85%), and in addition three patients (total n=96) were contacted by telephone for registration of comorbidities, adverse events, dumping and self-reported weight (figure 1). Data from all patients (n=109) were included in the mixed model analysis, including one patient who was converted from sleeve gastrectomy to gastric bypass after 2 years. Baseline demographics, characteristics, and patient-reported outcome measures were similar between groups (table 1). Patient-reported outcome measures showed a good internal consistency with a Cronbach's alpha > 0.8 for all scores except for the subscales GSRS abdominal pain and SF-36 vitality which both had a Cronbach's alpha > 0.7.

Patient-reported outcome measures possibly related to surgical procedure

The mean GSRS-total, diarrhoea -, indigestion, -constipation, and -abdominal pain scores remained largely unchanged 3 years after both surgeries (table 2, figure 2A), and only one patient (in the sleeve gastrectomy group) had an increase in the total score of 2 or more (suppl figure 1A and B). By contrast, the mean reflux symptom score was reduced by 0.43 (26%) after gastric bypass, between group difference (95% CI) 0.54 (0.17 to 0.90) (table 2, figure 2A). During the third year of follow-up, 16/48 (33%) patients after sleeve gastrectomy, and 19/48 (40%) after gastric bypass reported at least one episode of early dumping, while 10/48 (21%)

patients after sleeve gastrectomy, and 12/48 (25%) after gastric bypass reported at least one episode of late dumping, with no significant difference between groups (figure 2B).

Five (12%) patients reported at least one verified episode of postprandial hypoglycaemia during the third year after gastric bypass compared with none after sleeve gastrectomy, p=0.059 (figure 2B, supplementary table 1).

Patient-reported outcome measures possibly related to weight loss

The mean IWQOL-Lite total score increased by 48% after sleeve gastrectomy and 74% after gastric bypass, between-group difference 9.4 (3.3 to 15.5) points (figure 2C, table 2), with significantly greater improvements in the subscales self-esteem, public distress and physical function after gastric bypass compared with sleeve gastrectomy (supplementary table 2, figure 2C).

A total of 38/47 (81%) and 41/45 (91%) in the sleeve gastrectomy- and gastric bypass group, respectively, had a meaningful change in the IWQOL-lite total score of 12 points or more from baseline to 3 years (p=0.23) (table 2).

The number and bothersomeness of weight-related symptoms (WRSM) decreased by 19% and 33% after sleeve gastrectomy and 24% and 40% after gastric bypass, respectively, with no difference between groups (table 2, figure 2D). Further, the bothersomeness of several specific weight-related symptoms (e.g. shortness of breath, snoring, sweating, decreased physical stamina) declined significantly in both groups, while both groups experienced increased sensitivity to cold (supplementary figure 2).

The SF-36 Physical Component Summary score increased by 17% after sleeve gastrectomy and 19% after gastric bypass, while the Mental Component Summary score only increased significantly after sleeve gastrectomy, both with no difference between groups (table 2). With the exception of emotional role (both groups) and mental health (gastric bypass), both groups showed significant improvements in all domains of the SF 36 subscales, with no significant between-group differences (supplementary table 2).

Depression, binge eating and hedonic hunger

The mean Beck Depression Inventory symptom score was reduced by 40% after sleeve gastrectomy and 45% after gastric bypass (table 2, figure 2D). The proportion of patients with a clinically relevant depression score (≥14) was reduced from 26/55 (47%) to 7/47 (15%) after sleeve gastrectomy (p=0.0042), and from 21/54 (39%) to 9/44 (21%) after gastric bypass (p=0.092), with no statistical differences between the groups at 3 years.

Binge eating symptoms were reduced by 26% after sleeve and 32% after gastric bypass, with no difference between groups (table 2, figure 2D). However, the proportion of patients with a symptom score >17 did not change significantly between baseline and 3-year follow-up; from 8/55 (15%) to 4/47 (9%) (p=0.63) after sleeve gastrectomy and from 10/54 (19%) to 5/44 (11%) (p=0.51) after gastric bypass.

Both groups experienced moderate reductions in total Power of Food Scale scores from baseline (table 2), as well as reductions of all subscale scores (supplementary table 2), with no significant differences between the groups.

Weight loss and remission of diabetes

Percentage total body weight loss was significantly higher after gastric bypass than after sleeve gastrectomy (mean difference 8.1%, 95% CI 5.6-10.7%) (table 2, figure 2D/3A).

The proportion of patients with complete remission of diabetes was substantially higher 3 years after gastric bypass than after sleeve gastrectomy 30/45 (67%) vs 16/48 (33%), RR (95%CI) 2.00 (1.27 to 3.14), p=0.0018, whereas the proportions with partial remission of diabetes did not differ significantly 32/45 (71%) vs 26/48 (54%), RR 1.31 (0.95 to 1.80), p=0.13 (Figure 3B). When excluding the one patient who was converted from sleeve gastrectomy to gastric bypass after 2 years, the results were broadly unchanged: RR (95% CI) was 2.09 (1.31 to 3.33) for complete remission and 1.34 (0.96 to 1.85) for partial remission. HbA_{1c} was significantly reduced after both procedures, with no significant difference between groups (mean difference -1.0 mmol/mol, 95%CI -5.1 to 3.1 mmol/mol, p=0.65).

Complications and harms

The total number of adverse events from 6 weeks up to 3 years after surgery was 57 after sleeve gastrectomy and 52 after gastric bypass (supplementary table 3). The largest groups of adverse events included infectious (n=10 vs n=10), gastrointestinal (n=11 vs n=10), and cardiovascular (n=8 vs n=8) complications. One patient who underwent sleeve gastrectomy was converted to gastric bypass due to insufficient weight loss, whereas one gastric bypass patient was re-

operated due to small bowel obstruction. A total of four patients, two in each group, underwent cholecystectomy due to symptomatic gallbladder stones. There were no deaths.

Associations of weight change and diabetes remission with changes in patient-reported outcomes

Percentage total body weight loss, but not remission of diabetes, was significantly associated with changes in the IWQOL-Lite total score ($p<0.001$) (supplementary table 4). Further, percentage total body weight loss was associated with reduction in binge eating scores ($p=0.018$). Neither weight loss nor diabetes remission was associated with weight-related symptoms, generic health-related quality of life or depressive symptoms.

Discussion

Patients with type 2 diabetes and severe obesity randomised to either sleeve gastrectomy or gastric bypass reported substantial improvements in weight-related symptoms and weight-related quality of life, as well as reduced symptoms of depression and binge eating during the 3-year period after surgery. In line with our hypotheses, as compared with sleeve gastrectomy, gastric bypass was associated with greater weight loss, greater improvement in weight-related quality of life (IWQOL-Lite), less reflux symptoms (GSRS) and higher likelihood of diabetes remission. However, by contrast with our hypotheses, the burden of gastrointestinal symptoms such as abdominal pain, indigestion, diarrhoea and dumping syndrome did not differ significantly between groups.

The Oseberg study is, to our knowledge, the first randomised trial of patients with type 2 diabetes to compare medium-term effects of gastric bypass and sleeve gastrectomy on self-reported gastrointestinal symptoms as assessed by a validated questionnaire, demonstrating that the total gastrointestinal symptom scores remained unchanged 3 years after both surgical procedures. However, our findings add evidence to the results of a randomised trial of 100 patients with unknown diabetes status showing no changes in the gastrointestinal domain symptom scores in the Gastrointestinal Quality of Life Index (GIQLI) 3 to 5 years after sleeve gastrectomy or gastric bypass[23] Apparently by contrast, the SM-BOSS trialists reported similar increases in the GIQLI 3 and 5 years after gastric bypass and sleeve gastrectomy, although the authors did not specifically assess the gastrointestinal symptom domain, making any comparison with our results impossible[24,25]. However, our findings partly contrast with those

from two recent observational studies of patients with or without diabetes which demonstrated significant increases in both the total GSRS symptom score and the subscales constipation and abdominal pain 2 years after gastric bypass and sleeve gastrectomy [4,5]. This discrepancy may partly be explained by different populations (particularly with regards to diabetes prevalence), different sample size and slightly different follow-up time.

To our knowledge, this is the first randomised clinical trial to compare the medium-term incidence of early and late dumping syndrome after sleeve gastrectomy and gastric bypass in patients with type 2 diabetes. However, our results confirm and add evidence to recent cross-sectional studies not distinguishing between patients with or without diabetes, which suggested that dumping syndrome may be nearly as common after sleeve gastrectomy as after gastric bypass[26]. Early and late dumping were defined as the presence of at least one of several symptoms using the Arts Questionnaire. We did not distinguish between these symptoms, and it is therefore possible that the character of both early and late dumping may differ between the two surgical treatments. Although we did not find any significant difference in the incidence of verified postprandial hypoglycaemia between the surgical procedures during the last year of follow-up, postprandial hypoglycaemia was reported by 5 patients after gastric bypass versus none after sleeve gastrectomy.

Only two randomised studies of patients with type 2 diabetes have compared the medium- to long-term effects of sleeve gastrectomy and gastric bypass on patient-reported outcomes[6,7], but none of these examined weight-related quality of life, binge eating problems or hedonic hunger.

Nevertheless, we confirmed their main results showing that generic HRQoL (SF 36 or RAND 36) improved similarly after both surgical procedures[6,7]. Further, although Murphy et al. compared the effects of sleeve gastrectomy and banded gastric bypass, which may not be directly comparable with our results, we confirmed their finding that symptoms of depression improved similarly after both surgical procedures.

The present findings represent the first RCT based evidence to indicate that, in patients with type 2 diabetes, gastric bypass is superior to sleeve gastrectomy in improving weight related quality of life as measured with the IWQOL-Lite, a reliable and valid measure of weight-related quality of life[13]. We found clinically important differences in changes in the total score and in the subscales self-esteem, public distress and physical function favouring gastric bypass (figure 3A, supplementary table 2).

Our results partly contrast with both those from a recent observational trial of bariatric patients showing similar increases in the IWQOL-Lite total scores 2 years after sleeve gastrectomy and gastric bypass[27], as well as a recent, two-center observational study from Norway including 12% of patients with diabetes which reported significant long-term improvements in generic (SF-36) and obesity specific (IWQOL-Lite) quality of life, with no significant differences between groups[28]. The discrepancy between the results by Monpellier et al. and the present study may be explained by a substantial and similar weight loss (≥30%) in the two groups of patients and a majority of patients without diabetes in the former study, as compared with a significantly larger weight loss after gastric bypass (25%) versus sleeve gastrectomy (17%) in our study of patients with type 2 diabetes. This notion is supported by our finding that percentage total body

weight loss correlated significantly with changes in IWQOL-Lite, suggesting that weight loss may be the main mediator of improved weight-related quality of life.

According to a global multidisciplinary consensus meeting, self-esteem was considered the most important patient-reported outcome by people living with obesity, and IWQOL-Lite was selected as the most appropriate patient-reported outcome measure of self-esteem[28]. In view of this, it might be of particular interest for patients with type 2 diabetes to be informed that our results indicate that self-esteem may be increased by approximately 50% 3 years after sleeve gastrectomy versus 100% after gastric bypass (supplementary table 2). Other long-term RCTs including patients with or without diabetes used other assessment tools for disease specific quality of life including Moorehead-Ardelt Quality of Life Questionnaire II, GIQLI or BAROs, making it difficult to compare their results[29].

Our findings of similar 3-year reductions in depression symptoms and binge eating problems after sleeve gastrectomy and gastric bypass add evidence to both the results of a systematic review showing that 6 out of 7 observational studies reported a reduction in depression symptoms during 3 years after gastric bypass (n=5) or sleeve gastrectomy (n=2), as well as two out of four studies showing a reduction in binge eating symptoms after gastric bypass (n=2), banding (n=1) or sleeve gastrectomy (n=1). In addition, we report similar reductions in hedonic hunger 3 years after gastric bypass and sleeve gastrectomy, which is in keeping with a 6-month observational study which reported a significant and similar 6-month reduction in total scores after both surgical procedures[30], and which is confirming and adding medium-term evidence of

our 1-year results[9]. Importantly, both depression and binge eating problems may worsen after an initial short-term improvement and longer-term follow-up is needed.

Our study has a number of limitations. First, the generalisability is limited by the single-centre design and the inclusion of mainly white patients. Second, sample size calculations were performed for the primary end points at 1 year, and, as such, our 3-year results must be considered exploratory. Moreover, as the sample size is relatively low, negative findings do not exclude the possibility that unrevealed and possibly important differences between the procedures may exist (type 2 error). Third, no diabetes-specific patient-reported outcome measures were administered, leaving some of the differences with regards to the effect of diabetes remission unexplored[31]. In addition, although all outcomes were prespecified, the number of analyses was high, increasing the risk of type 1 errors. Given the exploratory nature of the multiple regression analyses of the potential effect of diabetes remission and weight loss on patient-reported outcomes, we cannot exclude any time-varying confounding of these variables on patient-reported outcomes during the 3-year follow up. Finally, patients were unblinded after 1 year, and we cannot exclude that this could impact some patient-reported outcomes. Major strengths of the study are the randomised design and the prespecified secondary patient-reported outcomes.

The results of our exploratory analyses of secondary PROs need confirmation in adequately powered randomised controlled studies, preferably with PROs as primary outcomes.

As compared with sleeve gastrectomy, gastric bypass was associated with greater 3-year improvement in weight-related quality of life, less reflux symptoms, greater weight loss, and higher diabetes remission rates. By contrast, changes in symptoms related to body weight, abdominal pain, indigestion, diarrhoea, dumping, depression and binge eating did not differ between groups. This new patient-reported knowledge can be used in the shared decision-making process to inform patients about similarities and differences between expected outcomes after the two surgical procedures.

Data Sharing Statement:
Access to data collected from this study, including de-identified individual-participant data, will be made available following publication upon e-mail request to the corresponding author (masvan@siv.no). After approval of a proposal, data will be shared with investigators whose proposed use of the data has been approved by the Oseberg steering committee, according to the consent given by the participants and Norwegian laws and legislations.

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Author contributions:
DH and JH conceived the study and are the principal investigators. MS, JL, HB, RS, BS, AWM, JKH, RLK, MCS, DH, and JH contributed to the design and overlooked the study conduct. MS, JL, HB, and JH wrote the original draft manuscript. MCS was responsible for the statistical analyses. All authors contributed to writing the manuscript, critically participated in interpretation of the data, reviewed the manuscript for intellectual content and approved the final version of the manuscript.

Five authors (MS, DH, HB, JL and JH) had independent access to the data, with all authors vouching for data completeness, accuracy and for the fidelity of the trial to the protocol.

Declaration of interest:

AWM receives an unrestricted research grant from Takeda to his institution.
RK receives royalties from Duke University for the IWQOL-Lite.
DH has received payment for lectures from Eli Lilly and is a member of the national Diabetes forum board.
All other authors (MS, JB, JL, RS, BS, JKH, MCS, and JH) have declared no competing interest.

REFERENCES:

1 Dixon JB. The effect of obesity on health outcomes. *Mol Cell Endocrinol* 2010; **316**: 104–8.

2 Capristo E, Panunzi S, Gaetano AD, *et al.* Incidence of Hypoglycemia After Gastric Bypass vs Sleeve Gastrectomy: A Randomized Trial. *J Clin Endocrinol Metabolism* 2017; **103**: 2136–46.

3 Scarpellini E, Arts J, Karamanolis G, *et al.* International consensus on the diagnosis and management of dumping syndrome. *Nat Rev Endocrinol* 2020; **16**: 448–66.

4 Chahal-Kummen M, Blom-Høgestøl IK, Eribe I, Klungsøyr O, Kristinsson J, Mala T. Abdominal pain and symptoms before and after Roux-en-Y gastric bypass. *Bjs Open* 2019; **3**: 317–26.

5 Chahal-Kummen M, Nordahl M, Våge V, Blom-Høgestøl I, Kristinsson JA, Mala T. A prospective longitudinal study of chronic abdominal pain and symptoms after sleeve gastrectomy. *Surg Obes Relat Dis* 2021; **17**: 2054–64.

6 Schauer PR, Bhatt DL, Kirwan JP, *et al.* Bariatric Surgery versus Intensive Medical Therapy for Diabetes - 5-Year Outcomes. *New England Journal of Medicine* 2017; **376**: 641–51.

7 Murphy R, Plank LD, Clarke MG, *et al.* Effect of Banded Roux-en-Y Gastric Bypass Versus Sleeve Gastrectomy on Diabetes Remission at 5 Years Among Patients With Obesity and Type 2 Diabetes: A Blinded Randomized Clinical Trial. *Diabetes Care* 2022; **45**: 1503–11.

8 Hofsø D, Fatima F, Borgeraas H, *et al.* Gastric bypass versus sleeve gastrectomy in patients with type 2 diabetes (Oseberg): a single-centre, triple-blind, randomised controlled trial. *Lancet Diabetes Endocrinol* 2019; **7**: 912–24.

9 Barstad LH, Johnson LK, Borgeraas H, *et al.* Changes in dietary intake, food tolerance, hedonic hunger, binge eating problems, and gastrointestinal symptoms after sleeve gastrectomy compared with after gastric bypass; 1-year results from the Oseberg study—a randomized controlled trial. *Am J Clin Nutrition* 2023; **117**: 586–98.

10 Borgeraas H, Hjelmesaeth J, Birkeland KI, *et al.* Single-centre, triple-blinded, randomised, 1-year, parallel-group, superiority study to compare the effects of Roux-en-Y gastric bypass and sleeve gastrectomy on remission of type 2 diabetes and β-cell function in subjects with morbid obesity: a protocol for the Obesity surg ery in Tøns berg(Oseberg) study. *BMJ Open* 2019; **9**: e024573-11.

11 Svedlund J, Sjödin I, Dotevall G. GSRS—A clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. *Digestive diseases and sciences* 1988; **33**: 129–34.

12 Arts J, Caenepeel P, Bisschops R, *et al.* Efficacy of the Long-Acting Repeatable Formulation of the Somatostatin Analogue Octreotide in Postoperative Dumping. *Clin Gastroenterol H* 2009; **7**: 432–7.

13 Kolotkin RL, Crosby RD, Kosloski KD, Williams GR. Development of a Brief Measure to Assess Quality of Life in Obesity. *Obes Res* 2001; **9**: 102–11.

14 Kolotkin RL, Crosby RD, Williams GR. Assessing weight-related quality of life in obese persons with type 2 diabetes. *Diabetes Res Clin Pr* 2003; **61**: 125–32.

15 Patrick DL, Bushnell DM, Rothman M. Performance of Two Self-Report Measures for Evaluating Obesity and Weight Loss*. *Obesity research* 2004; **12**: 48–57.

16 Ware J, Snoww K, MA K, BG G. SF36 Health Survey: Manual and Interpretation Guide. 1993; **30**.

17 Beck AT, Steer RA, Brown GK. Manual for the beck depression inventory-II. 1996; **1**: 10–1037.

18 Glischinski M von, Brachel R von, Hirschfeld G. How depressed is "depressed"? A systematic review and diagnostic meta-analysis of optimal cut points for the Beck Depression Inventory revised (BDI-II). *Qual Life Res* 2019; **28**: 1111–8.

19 Cappelleri JC, Bushmakin AG, Gerber RA, *et al.* Evaluating the Power of Food Scale in obese subjects and a general sample of individuals: development and measurement properties. *International journal of obesity (2005)* 2009; **33**: 913–22.

20 Gormally J, Black S, Daston S, Rardin D. The assessment of binge eating severity among obese persons. *Addictive behaviors* 1982; **7**: 47–55.

21 Grupski AE, Hood MM, Hall BJ, Azarbad L, Fitzpatrick SL, Corsica JA. Examining the Binge Eating Scale in Screening for Binge Eating Disorder in Bariatric Surgery Candidates. *Obes Surg* 2013; **23**: 1–6.

22 Buse JB, Caprio S, Cefalu WT, *et al.* How Do We Define Cure of Diabetes? *Diabetes Care* 2009; **32**: 2133–5.

23 Ignat M, Vix M, Imad I, *et al.* Randomized trial of Roux-en-Y gastric bypass versus sleeve gastrectomy in achieving excess weight loss. *Brit J Surg* 2017; **104**: 248–56.

24 Peterli R, Wölnerhanssen BK, Vetter D, *et al.* Laparoscopic Sleeve Gastrectomy Versus Roux-Y-Gastric Bypass for Morbid Obesity—3-Year Outcomes of the Prospective Randomized Swiss Multicenter Bypass Or Sleeve Study (SM-BOSS). *Ann Surg* 2017; **265**: 466–73.

25 Peterli R, Wölnerhanssen BK, Peters T, *et al.* Effect of Laparoscopic Sleeve Gastrectomy vs Laparoscopic Roux-en-Y Gastric Bypass on Weight Loss in Patients With Morbid Obesity. *JAMA* 2018; **319**: 255–11.

26 Ahmad A, Kornrich DB, Krasner H, *et al.* Prevalence of Dumping Syndrome After Laparoscopic Sleeve Gastrectomy and Comparison with Laparoscopic Roux-en-Y Gastric Bypass. *Obes Surg* 2019; **29**: 1506–13.

27 Monpellier VM, Antoniou EE, Aarts EO, Janssen IMC, Jansen ATM. Improvement of Health-Related Quality of Life After Roux-en-Y Gastric Bypass Related to Weight Loss. *Obes Surg* 2017; **27**: 1168–73.

28 Nielsen HJ, Nedrebø BG, Fosså A, *et al.* Seven-year trajectories of body weight, quality of life and comorbidities following Roux-en-Y gastric bypass and sleeve gastrectomy. *Int J Obesity* 2022; **46**: 739–49.

29 Wu F, Shi F, Fu X, Du N, Chen B, Zhou X. Laparoscopic sleeve gastrectomy versus Roux-en-Y gastric bypass for quality of life: a systematic review and meta-analysis. *Surg Obes Relat Dis* 2020; **16**: 1869–76.

30 Makaronidis JM, Pucci A, Adamo M, Jenkinson A, Elkalaawy M, Batterham RL. Impact of sleeve gastrectomy compared to Roux-en-y gastric bypass upon hedonic hunger and the relationship to post-operative weight loss. *Intern Emerg Med* 2022; **17**: 2031–8.

31 Langendoen-Gort M, Groeneveld L, Prinsen CAC, *et al.* Patient-reported outcome measures for assessing health-related quality of life in people with type 2 diabetes: A systematic review. *Rev Endocr Metabolic Disord* 2022; : 1–47.

Figure legends

Figure 1. Flowchart

Figure 2. (A) Percent change in GSRS scores from baseline to 3 years. (B) Proportion of patients reporting at least one episode of early dumping, late dumping or postprandial hypoglycaemia over 3-year follow-up. (C) Percent change in IWQOL-Lite total score and subscale scores from baseline to 3 years. (D) Percent total body weight loss over 3-year follow-up, percent change in weight related symptom measure (WRSM) symptom bothersomeness score, WRSM number of symptoms, Beck depression inventory (BDI) symptom score and binge eating scale symptom score from baseline to 3 years.

Figure 3. (A) Percent total body weight-loss over 3-year follow-up. (B) Proportion of patients with remission of type 2 diabetes over 3-year follow-up.

Supplementary figure 1. (A) Change in GSRS total score from baseline to 3 years in the sleeve gastrectomy group. (B) Change in GSRS total score from baseline to 3 years in the gastric bypass group.

Supplementary figure 2. Changes in weight related symptom measure (WRSM) sub-scores from baseline to 3 years.

1: Shortness of breath, 2: Tiredness, 3: Sleep problems, 4: Sensitivity to cold, 5: Increased thirst, 6: Increased irritability, 7: Back pain, 8: Frequent urination, 9: Pain in the joints, 10: Water retention, 11: Foot problems, 12: Sensitivity to heat, 13: Snoring, 14: Increased appetite, 15: Leakage of urine, 16: Lightheadedness, 17: Increased sweating, 18: Loss of sexual desire, 19: Decreased physical stamina, 20: Skin irritation.

Table 1. Baseline characteristics and patient reported outcome measures

	Sleeve gastrectomy n=55	**Gastric bypass n=54**
Sex		
Women	32 (58%)	40 (74%)
Men	23 (42%)	14 (26%)
Age, years	47·1 (10·2)	48·2 (8·9)
White ethnicity	53 (96%)	51 (94%)
BMI, kg/m²	42·1 (5·3)	42·4 (5·4)
Body weight, kg	126·7 (21·4)	124·4 (23·2)
Duration of diabetes, years	6·3 (5·5)	6·6 (6·5)
HbA1c, %	7·9 (6·9-9·9)	7·6 (6·8-8·5)
HbA1c, mmol/mol	63 (52-85)	60 (51-70)
Diabetes medication	50 (91%)	46 (85%)
Patient Reported Outcome Measures		
Gastrointestinal Symptom Rating Scale (GSRS, total)	2·0 (0·8)	2·1 (0·7)
Diarrhea	2·0 (1·0)	2·1 (1·0)
Indigestion	2·5 (1·2)	2·4 (0·9)
Constipation	1·9 (1·3)	1·8 (0·9)
Abdominal pain	1·9 (0·8)	2·0 (0·9)
Reflux	1·6 (1·0)	1·6 (0·9)
Impact of Weight on Quality of Life-Lite (IWQOL-Lite, total)	54·2 (18·7)	48·4 (16·4)
Short-Form Health Survey 36 (SF-36)		
Physical Component Summary (PCS)	39·9 (10·0)	41·8 (7·3)
Mental Component Summary (MCS)	43·5 (8·9)	46·2 (7·3)
Weight-Related Symptom Measure (WRSM)		
Number of symptoms	15·0 (4·4)	15·2 (4·1)
Symptom bothersomeness score	45·9 (20·9)	43·8 (19·5)
Beck Depression Inventory (BDI)	14·4 (10·1)	12·6 (8·2)
Binge Eating Scale (BES)	11·1 (6·1)	11·0 (6·3)
Power of Food Scale (PFS)	2·6 (0·9)	2·3 (0.7)

Observed baseline data are n (%), mean (SD).

Table 2· Changes in Patient Reported Outcome Measures, body weight and diabetes status

	Sleeve gastrectomy (n=55)	Gastric bypass (n=54)	Between group difference (95% CI) or RR (95%CI)	p value
Gastrointestinal Symptom Rating Scale, symptom scores*				
GSRS Total scores				
Baseline	2.05 (1.84 to 2.26)	2.06 (1.85 to 2.27)	··	··
3 years	1.96 (1.75 to 2.18)	1.97 (1.75 to 2.19)	0.005 (-0.30 to 0.31)	0.98
Change from baseline	-0.09 (-0.27 to 0.10)	-0.09 (-0.28 to 0.10)	-0.005 (-0.27 to 0.26)	0.97
Diarrhea				
Baseline	1·96 (1·69 to 2·22)	2·09 (1·81 to 2·36)	··	··
3 years	1·56 (1·28 to 1·85)	1·97 (1·67 to 2·27)	0·42 (0·01 to 0·83)	0·045
Change from baseline	-0·40 (-0·69 to -0·10)	-0·11 (-0·41 to 0·19)	0·29 (-0·13 to 0·71)	0·18
Indigestion				
Baseline	2·54 (2·26 to 2·82)	2·45 (2·17 to 2·73)	··	··
3 years	2·28 (2·00 to 2·57)	2·53 (2·23 to 2·82)	0·24 (-0·17to 0·66)	0·25
Change from baseline	-0·26 (-0·54 to 0·02)	0·08 (-0·21 to 0·36)	0·34 (-0·06 to 0·74)	0·099
Constipation				
Baseline	1·90 (1·59 to 2·21)	1·80 (1·49 to 2·11)	··	··
3 years	1·97 (1·66 to 2·30)	1·78 (1·46 to 2·11)	-0·19 (-0·65 to 0·27)	0·41
Change from baseline	0·07 (-0·24 to 0·39)	-0·02 (-0·34 to 0·31)	-0·09 (-0·55 to 0·36)	0·69
Abdominal Pain				
Baseline	1·94 (1·70 to 2·18)	2·04 (1·81 to 2·28)	··	··
3 years	2·10 (1·85 to 2·35)	1·90 (1·65 to 2·16)	-0·20 (-0·56 to 0·16)	0·27
Change from baseline	0·16 (-0·09 to 0·41)	-0·14 (-0·40 to 0·12)	-0·30 (-0·67 to 0·06)	0·099
Reflux				
Baseline	1·57 (1·34 to 1·81)	1·63 (1·39 to 1·87)	··	··
3 years	1·68 (1·43 to 1·93)	1·20 (0·95 to 1·45)	-0·48 (-0·83 to -0·12)	0·0080
Change from baseline	0·11 (-0·15 to 0·37)	-0·43-(-0·69 to -0·16)	-0·54 (-0·90 to -0·17)	0·0045
Weight-related quality of life (IWQOL-Lite Total)				
Baseline	54·2 (49·5 to 58·8)	48·4 (43·7 to 53·1)	··	··
3 years	80·6 (75·8 to 85·5)	84·3 (79·4 to 89·2)	3·7 (-3·2 to 10·6)	0·30
Change from baseline	26·4 (22·2 to 30·7)	35·9 (31·5 to 40·2)	9·4 (3·3 to 15·5)	0·0024
Proportion of patients with change ≥12 points	38 (81)	41 (91)	1·13 (0·95 to 1·33)	0.23
Weight-related symptom bothersomeness score (WRSM)				
Baseline	45·9 (41·3 to 50·5)	43·8 (39·2 to 48·5)	··	··
3 years	30·7 (25·8 to 35·5)	26·1 (21·2 to 31·0)	-4·6 (-11·5 to 2·3)	0·19
Change from baseline	-15·2 (-19·8 to -10·7)	-17·7 (-22·3 to -13·2)	-2·5 (-8·9 to 3·9)	0·45
Weight-related number of symptoms (WRSM)				
Baseline	15.0 (13.7 to 16.4)	15.2 (13.8 to 16.5)	··	··
3 years	11.9 (10.5 to 13.3)	11.5 (10.1 to 12.8)	-0.4 (-2.4 to 1.5)	0.65
Change from baseline	-3.1 (-4.3 to -1.9)	-3.7 (-4.9 to -2.5)	-0.6 (-2.3 to 1.1)	0.51
SF-36 Physical Component Summary				
Baseline	39·9 (37·6 to 42·1)	41·8 (39·5 to 44·1)	··	··

3 years	46·7 (44·4 to 49·1)	49·6 (47·2 to 52·0)	2·86 (-0·5 to 6·2·)	0·096
Change from baseline	6·8 (4·7 to 9·0)	7·8 (5·5 to 10·0)	0·9 (-2·2 to 4·0)	0·57
SF-36 Mental Component Summary				
Baseline	43·5 (41·1 to 45·9)	46·2 (43·8 to 48·6)	··	··
3 years	47·1 (44·6 to 49·6)	48·6 (46·1 to 51·2)	1·5 (-2·0 to 5·1)	0·40
Change from baseline	3·5 (1·1 to 5·9)	2·4 (-0·05 to 4·8)	-1·2 (-4·6 to 2·3)	0·50
Beck Depression Inventory, symptom score†				
Baseline	14·4 (12·2 to 16·5)	12·6 (10·5 to 14·8)	··	··
3 years	8·5 (6·3 to 10·7)	7·0 (4·7 to 9·2)	-1·6 (-4·7 to 1·6)	0·34
Change from baseline	-5·8 (-7·8 to -4·0)	-5·7 (-7·6 to -3·7)	0·18 (-2·5 to 2·9)	0·90
Clinical depression at baseline	26 (47)	21 (39)	··	··
Clinical depression at 3 years	7 (15)	9 (21)	1·4 (0·6 to 3·4)	0·59
Binge Eating Scale, symptom score†				
Baseline	11·1 (9·5 to 12·7)	11·0 (9·4 to 12·7)	··	··
3 years	8·2 (6·5 to 9·9)	7·5 (5·8 to 9·3)	-0·7 (-3·1 to 1·7)	0·58
Change from baseline	-2·9 (-4·5 to -1·3)	-3·5 (-5·2 to -1·8)	-0·6 (-3·0 to 1·7)	0·59
Clinical binge eating baseline	8 (15)	10 (19)	··	··
Clinical binge eating at 3 year	4 (9)	5 (11)	1·3 (0·4 to 4·7)	0·73
Power of Food Scale, symptom score†				
Baseline	2·6 (2·4 to 2·8)	2·3 (2·1 to 2·5)	··	··
3 years	2·1 (1·9 to 2·3)	1·9 (1·7 to 2·1)	-0·2 (-0·5 to 0·1)	0·17
Change from baseline	-0·5 (-0·7 to -0·3)	-0·4 (-0·6 to -0·2)	0·1 (-0·2 to 0·4)	0·63
Bodyweight and BMI‡				
Bodyweight, kg				
Baseline	126·7 (121·3 to 132·0)	124·4 (119·0 to 129·7)	··	··
3 years	104·7 (99·4 to 110·1)	92·9 (87·4 to 98·4)	-11·8 (-19·5 to -4·2)	0·0025
Change from baseline	-21·9 (-24·3 to -19·6)	-31·5 (-33·9 to -29·0)	-9·5 (-12·9 to -6·1)	<0·0001
Total body weight loss, %	17·2 (15·4 to 19·0)	25·3 (23·4 to 27·1)	8·1 (5·6 to 10·7)	<0·0001
BMI, kg/m^2				
Baseline	42·1 (40·7 to 43·5)	42·4 (41·0 to 43·8)	··	··
3 years	34·8 (33·4 to 36·2)	31·7 (30·3 to 33·2)	-3·0 (-5·0 to -1·0)	0·0028
Change from baseline	-7·3 (-8·1 to -6·5)	-10·7 (-11·5 to -10·0)	-3·4 (-4·5 to -2·3)	<0·0001
Diabetes remission and glucose homeostasis‡				
Complete remission (HbA_{1c} ≤6·0% with no diabetes medications), n (%)	16 (33)	30 (67)	2·00 (1·27 to 3·14)	0·0018
Partial remission (HbA_{1c} <6·5% with no diabetes medications), n (%)	26 (54)	32 (71)	1·31 (0·95 to 1·80)	0·13
HbA_{1c}, %				
Baseline	8·4 (8·1 to 8·7)	7·9 (7·6 to 8·2)	··	··
3 years	6·7 (6·4 to 7·0)	6·1 (5·8 to 6·4)	-0·6 (-1·0 to -0·1)	0·011
Change from baseline	-1·7 (-2·0 to -1·4)	-1·8 (-2·0 to -1·5)	-0·1 (-0·5 to 0·3)	0·65
HbA_{1c}, mmol/mol				
Baseline	68·2 (64·8 to 71·5)	62·8 (59·5 to 66·2)	··	··
3 years	49·7 (46·2 to 53·1)	43·3 (39·9 to 46·8)	-6·3 (-11·2 to -1·4)	0·011
Change from baseline	-18·5 (-21·4 to -15·6)	-19·5 (-22·4 to -16·5)	-1·0 (-5·1 to 3·1)	0·65
Diabetes medication (Reviewer #4, Comment #3)				

Baseline	50 (91)	46 (85)	··	··
3 years	17 (35)	7 (16)	0·44 (0·20 to 0·96)	0·035
Use of insulin				
Baseline	12 (22)	11 (20)	··	··
3 years	6 (13)	4 (9)	0·71 (0·21 to 2·36)	0·74

Outcome variables are reported as mean (95% CI) and between-group differences (95% CI) for continuous variables (linear mixed models) and n (%) and crude RRs (95% CI) for categorical variables (p values calculated using fishers exact test). All outcomes were analysed according to randomisation group. RR=risk ratio. *Data are missing for 8 (15%) patients in the sleeve gastrectomy group 10 (19%) patients in the gastric bypass group at 3 years. † Data are missing for 9 (16%) patients in the sleeve gastrectomy group 10 (19%) patients in the gastric bypass group at 3 year.· ‡ Data are missing for 7 (13%) patients in the sleeve gastrectomy group 9 (17%) patients in the gastric bypass group at 3 years.

Figure 1

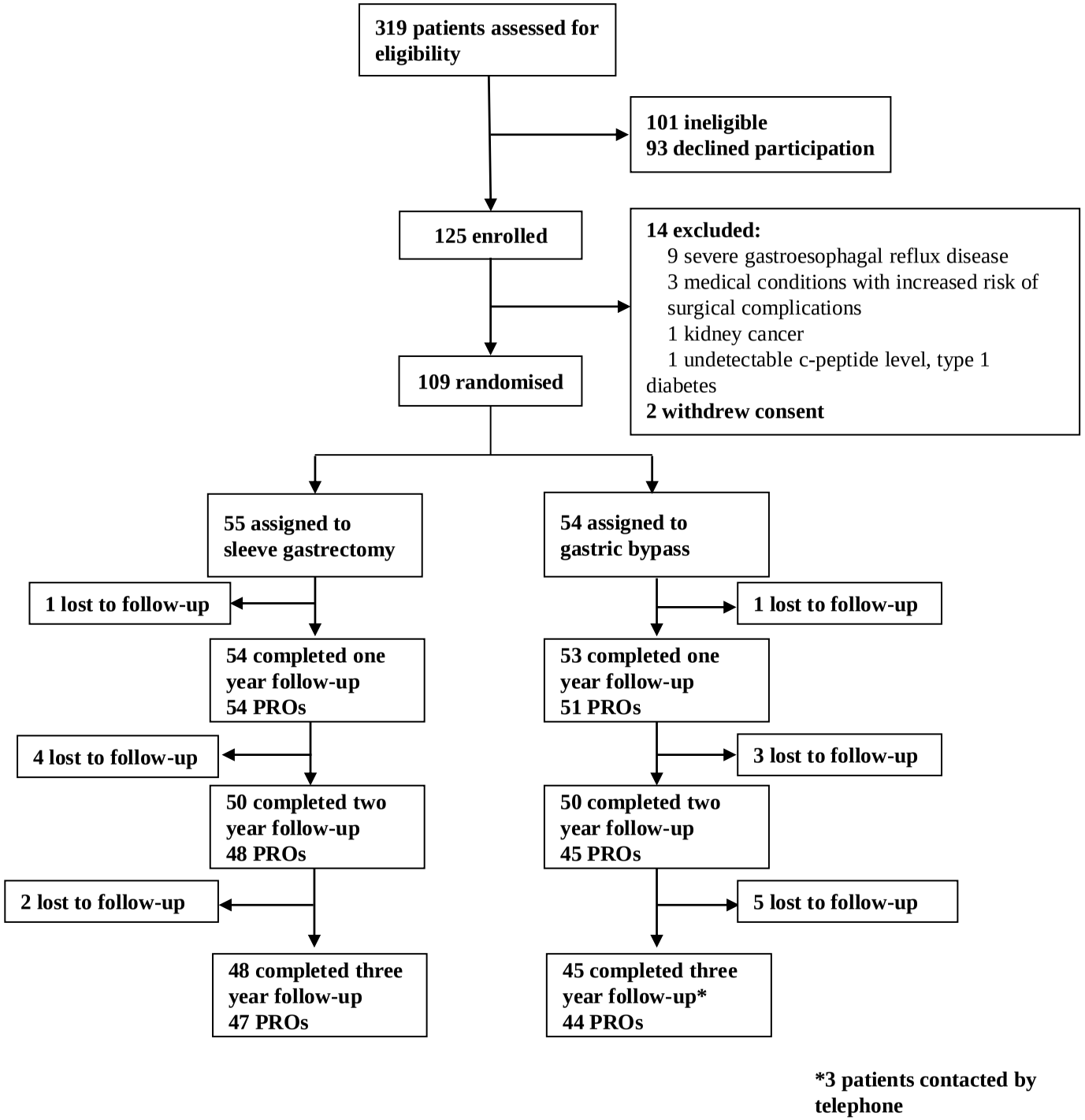
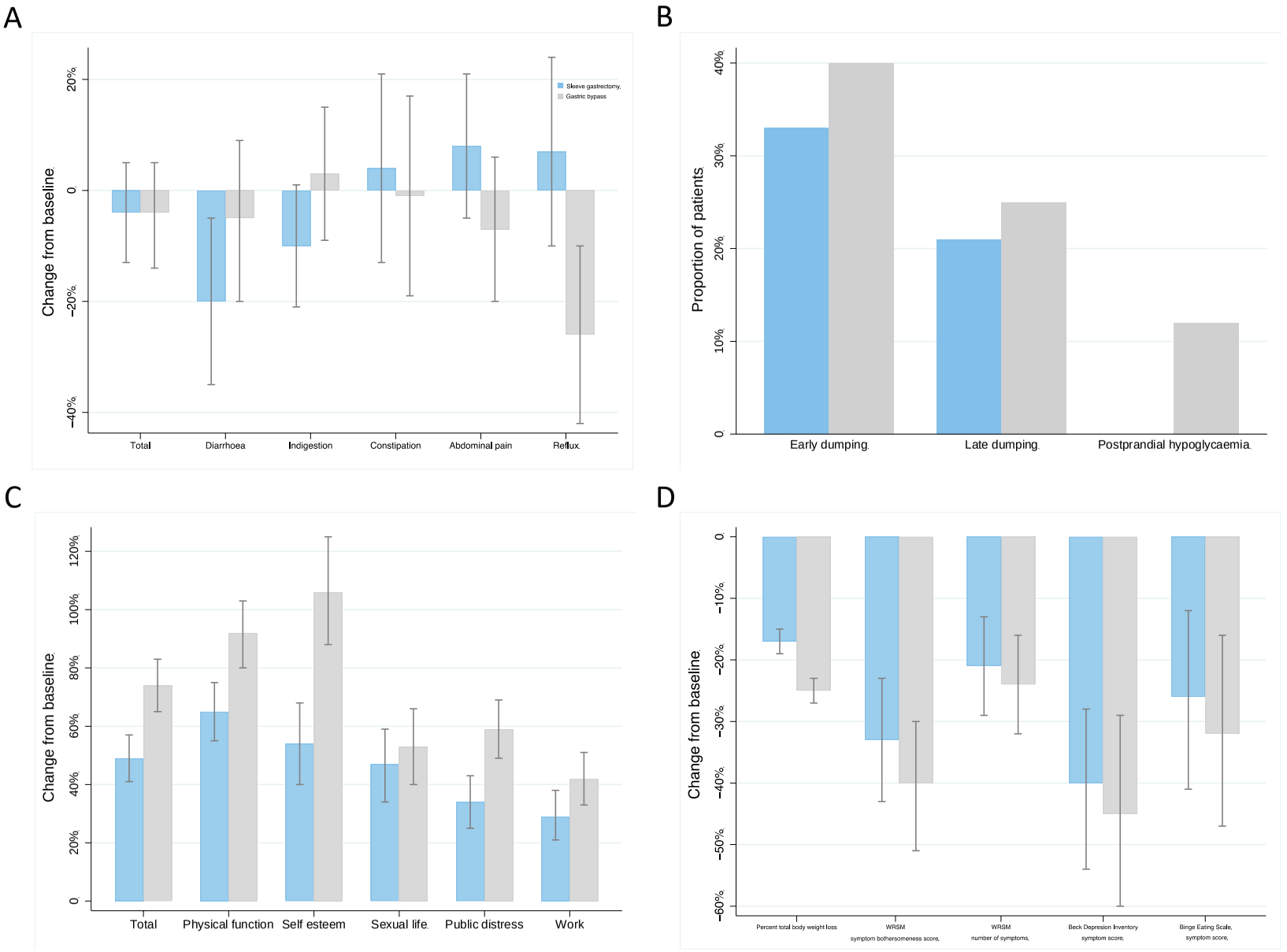

319 patients assessed for eligibility
101 ineligible
93 declined participation
125 enrolled
14 excluded:
9 severe gastroesophagal reflux disease
3 medical conditions with increased risk of surgical complications
1 kidney cancer
1 undetectable c-peptide level, type 1 diabetes
2 withdrew consent
109 randomised
55 assigned to sleeve gastrectomy
54 assigned to gastric bypass
1 lost to follow-up
1 lost to follow-up
54 completed one year follow-up
54 PROs
53 completed one year follow-up
51 PROs
4 lost to follow-up
3 lost to follow-up
50 completed two year follow-up
48 PROs
50 completed two year follow-up
45 PROs
2 lost to follow-up
5 lost to follow-up
48 completed three year follow-up
47 PROs
45 completed three year follow-up*
44 PROs
*3 patients contacted by telephone

Figure 2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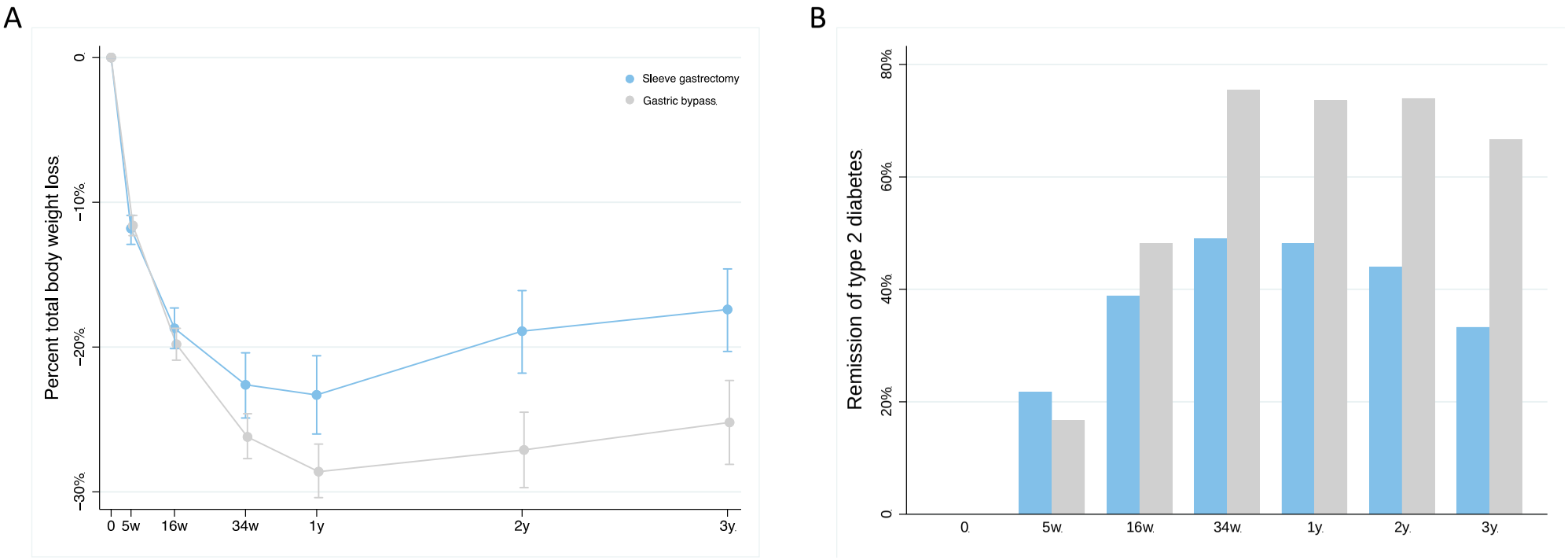
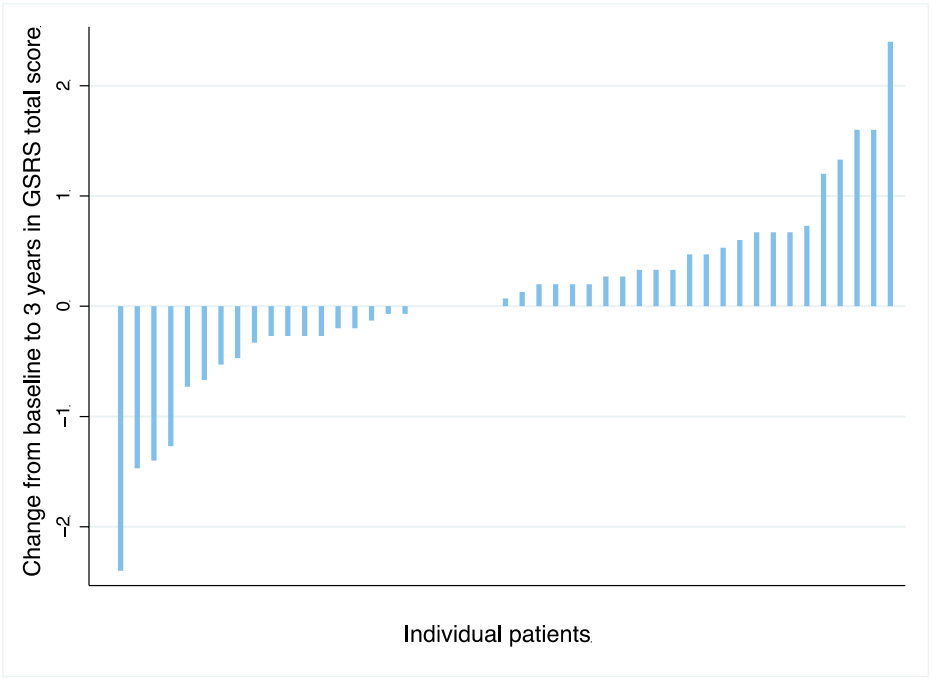
Change from baseline
20%
0
−20%
−40%
Sleeve gastrectomy
Gastric bypass
Total
Diarrhoea
Indigestion
Constipation
Abdominal pain
Reflux
B
Proportion of patients
40%
30%
20%
10%
0
Early dumping
Late dumping
Postprandial hypoglycaemia
C
Change from baseline
120%
100%
80%
60%
40%
20%
0
Total
Physical function
Self esteem
Sexual life
Public distress
Work
D
Change from baseline
0
−10%
−20%
−30%
−40%
−50%
−60%
Percent total body weight loss
WRSM
symptom bothersomeness score
WRSM
number of symptoms
Beck Depresion Inventory
symptom score
Binge Eating Scale
symptom score

Figure 3


A
Percent total body weight loss
0
−10%
−20%
−30%
Sleeve gastrectomy
Gastric bypass
0
5w
16w
34w
1y
2y
3y
B
Remission of type 2 diabetes
0
20%
40%
60%
80%
0
5w
16w
34w
1y
2y
3y

Supplementary figure 1

A



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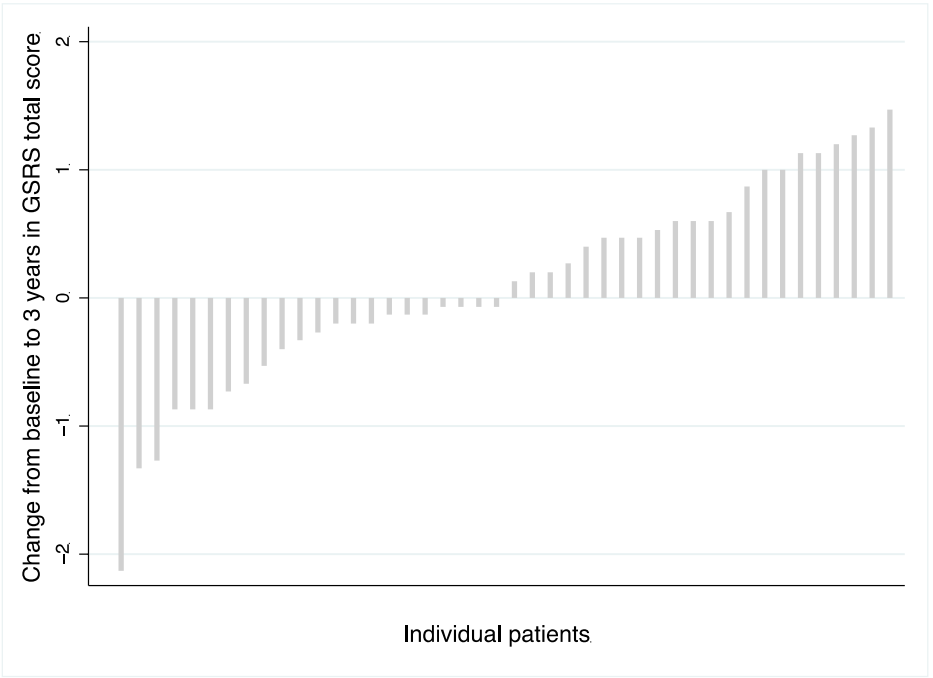

Supplementary figure 2